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Otology and Neurotology

Hsc
Home Study Course

Home Study Course

Section 8
April 2017

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY
FOUNDATION

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Empowering otolaryngologist-head and neck surgeons to deliver the best patient care

THE
HOME STUDY COURSE
IN
OTOLARYNGOLOGY — HEAD AND NECK SURGERY

April 2017

SECTION 8

Otology and Neurotology

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Section 8 exam deadline: June, 12, 2017
Expiration Date: August 4, 2017; CME credit not available after that date

Introduction
The Home Study Course is designed to provide relevant and timely clinical information for physicians in training and current practitioners in otolaryngology - head and neck surgery. The course, spanning four sections, allows participants the opportunity to explore current and cutting edge perspectives within each of the core specialty areas of otolaryngology.

The **Selected Recent Material** represents primary fundamentals, evidence-based research, and state of the art technologies in otology and neurotology. The scientific literature included in this activity forms the basis of the assessment examination.

The number and length of articles selected are limited by editorial production schedules and copyright permission issues, and should not be considered an exhaustive compilation of knowledge on otology and neurotology.

The **Additional Reference Material** is provided as an educational supplement to guide individual learning. This material is not included in the course examination and reprints are not provided.

Needs Assessment
AAO-HNSF's education activities are designed to improve healthcare provider competence through lifelong learning. The Foundation focuses its education activities on the needs of providers within the specialized scope of practice of otolaryngologists. Emphasis is placed on practice gaps and education needs identified within eight subspecialties. The *Home Study Course* selects content that addresses these gaps and needs within all subspecialties.

Target Audience
The primary audience for this activity is physicians and physicians-in-training who specialize in otolaryngology-head and neck surgery.

Outcomes Objectives

The participant who has successfully completed this section should be able to:

1. Use diagnostic criteria for vestibular migraine and management options.
2. Review the diagnostic criteria and medical and surgical management options for Ménière's disease.
3. Discuss the radiologic evaluation essential to rule out treatable pathologies causing pulsatile tinnitus.
4. Manage and treat fungal and bacterial malignant otitis externa.
5. Evaluate the recurrence rate after cholesteatoma surgery and the use of diffusion-weighted MRI in diagnosing recurrence.
6. Discuss the hearing outcome results of the U.S. Hybrid L trial and understand candidacy criteria and hearing preservation outcomes.
7. Describe the potential benefits of the Baha Attract system for patients with mixed and conductive hearing losses.
8. Articulate the hearing rehabilitative options for patients with single-sided deafness (SSD) and the superior benefits obtained with cochlear implant when compared to CROS and BAHA systems.
9. Recognize that there is no difference in hearing in noise between the CROS and BAHA systems.
10. Agree that stereotactic radiation is an effective treatment for intracranial and intratemporal facial nerve schwannomas.
11. Relate the advantages of the middle fossa approach for the management of facial nerve paralysis after trauma.
12. Explain the use of electroneuronography to determine the need for surgical intervention in acute facial palsy.
13. Review the typical clinical otologic findings in temporal bone fractures in children.

Medium Used

The Home Study Course is available in electronic or print format. The activity includes a review of outcomes objectives, selected scientific literature, and a online self-assessment examination.

Method of Physician Participation in the Learning Process

The physician learner will read the selected scientific literature, reflect on what they have read, and complete the online self-assessment exam. After completing this section, participants should have a greater understanding of otology and neurotology, as well as useful information for clinical application.

Estimated time to complete this activity: 40.0 hours

Accreditation Statement

The American Academy of Otolaryngology—Head and Neck Surgery Foundation (AAO-HNSF) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation

The AAO-HNSF designates this enduring material for 40.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim credit commensurate with the extent of their participation in the activity.

ALL PARTICIPANTS must achieve a post-test score of 70% or higher for a passing completion to be recorded and a transcript to be produced. Residents; results will be provided to the Training Program Director.

PHYSICIANS ONLY: In order to receive *Credit* for this activity **a post-test score of 70% or higher is required**. Two retest opportunity will automatically available if a minimum of 70% is not achieved.

Disclosure

The American Academy of Otolaryngology Head and Neck Surgery/Foundation (AAO-HNS/F) supports fair and unbiased participation of our volunteers in Academy/Foundation activities. All individuals who may be in a position to control an activity's content must disclose all relevant financial relationships or disclose that no relevant financial relationships exist. All relevant financial relationships with commercial interests[1] that directly impact and/or might conflict with Academy/Foundation activities must be disclosed. Any real or potential conflicts of interest[2] must be identified, managed, and disclosed to the learners. In addition, disclosure must be made of presentations on drugs or devices, or uses of drugs or devices that have not been approved by the Food and Drug Administration. This policy is intended to openly identify any potential conflict so that participants in an activity are able to form their own judgments about the presentation.

[1] A "Commercial interest" is any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

[2] "Conflict of interest" is defined as any real or potential situation that has competing professional or personal interests that would make it difficult to be unbiased. Conflicts of interest occur when an individual has an opportunity to affect education content about products or services of a commercial interest with which they have a financial relationship. **A conflict of interest depends on the situation and not on the character of the individual.**

2016-17 Section 8 OTOLOGY AND NEUROTOLOGY FACULTY

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Consulting Fee: Cochlear Americas

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Brad Kesser, MD, Chair, Otology & Neurotology Education Committee	Disclosure: Royalty: Nasco, Inc
Mark L. Bennett, MD, Chair elect, Otology & Neurotology Education Committee	Disclosure: Leadership Role: Oticon.

This 2016-17 Section 8 Home Study Course includes discussion of off-label uses of the following drugs and devices which have not been approved by the United States Food and Drug Administration:

Name of Drug(s) or Device(s)	**Nature of Off-label Discussion**
Cochlear Implant	Use of CI for single -sided deafness; not-approved FDA indication

Disclaimer

The information contained in this activity represents the views of those who created it and does not necessarily represent the official view or recommendations of the American Academy of Otolaryngology – Head and Neck Surgery Foundation.

June 12, 2017: Suggested section 8 Exam submission deadline**; course closes August 4, 2017.**

EVIDENCE BASED MEDICINE

The AAO-HNSF Education Advisory Committee approved the assignment of the appropriate level of evidence to support each clinical and/or scientific journal reference used to authenticate a continuing medical education activity. Noted at the end of each reference, the level of evidence is displayed in this format: **[EBM Level 3]**.

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)	
Level 1	Randomized[1] controlled trials[2] or a systematic review[3] (meta-analysis[4]) of randomized controlled trials[5].
Level 2	Prospective (cohort[6] or outcomes) study[7] with an internal control group or a systematic review of prospective, controlled trials.
Level 3	Retrospective (case-control[8]) study[9] with an internal control group or a systematic review of retrospective, controlled trials.
Level 4	Case series[10] without an internal control group (retrospective reviews; uncontrolled cohort or outcome studies).
Level 5	Expert opinion without explicit critical appraisal, or recommendation based on physiology/bench research.

Two *additional ratings* to be used for articles that do not fall into the above scale. Articles that are informational only can be rated N/A , and articles that are a review of an article can be rated as Review. All definitions adapted from Glossary of Terms, Evidence Based Emergency Medicine at New York Academy of Medicine at www.ebem.org.

[1] A technique which gives every patient an equal chance of being assigned to any particular arm of a controlled clinical trial.
[2] Any study which compares two groups by virtue of different therapies or exposures fulfills this definition.
[3] A formal review of a focused clinical question based on a comprehensive search strategy and structure critical appraisal.
[4] A review of a focused clinical question following rigorous methodological criteria and employing statistical techniques to combine data from independently performed studies on that question.
[5] A controlled clinical trial in which the study groups are created through randomizations.
[6] This design follows a group of patients, called a "cohort", over time to determine general outcomes as well as outcomes of different subgroups.
[7] Any study done forward in time. This is particularly important in studies on therapy, prognosis or harm, where retrospective studies make hidden biases very likely.
[8] This might be considered a randomized controlled trial played backwards. People who get sick or have a bad outcome are identified and "matched" with people who did better. Then, the effects of the therapy or harmful exposure which might have been administered at the start of the trial are evaluated.
[9] Any study in which the outcomes have already occurred before the study has begun.
[10] This includes single case reports and published case series.

OUTLINE
Section 8 Otology and Neurotology
April 2017

I. Vestibular Disorders

A. Migraine and vertigo
B. Ménière's disease
C. Pulsatile tinnitus

II. External Auditory Canal and Middle Ear

A. Acute otitis externa
B. Cholesteatoma

III. Hearing Loss

A. Sensorineural hearing loss
B. Conductive and mixed hearing loss
C. Single-sided deafness

IV. Temporal Bone/Skull Base

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B. Skull base and ear trauma

V. Facial Nerve

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Selected Recent Materials - Reproduced in this Study Guide

SECTION 8: OTOLOGY and NEUROTOLOGY
APRIL 2017

Goebel JA. 2015 Equilibrium Committee Amendment to the 1995 AAO-HNS Guidelines for the Definition of Ménière's Disease. *Otolaryngol Head Neck Surg*. 2016; 154(3):403-404. EBM level 5.....34-35

Summary: This article presents an expert opinion regarding the evolving definition of Ménière's disease, and describes the amendment to the 1995 AAO-HNS criteria for diagnosis of Ménière's disease.

Gürkov R, Pyykö I, Zou J, Kentala E. What is Ménière's disease? A contemporary re-evaluation of endolymphatic hydrops. *J Neurol*. 2016; 263 Suppl 1:S71-S81. EBM level 5.....36-46

Summary: This is a narrative review of pathophysiology, clinical features, and diagnostic criteria for Ménière's disease. The authors review the gadolinium-based MRI diagnosis of endolymphatic hydrops and discuss the grading system. They propose a new classification of hydropic disorder of inner ear.

Rah YC, Han JJ, Park J, et al. Management of intractable Ménière's disease after intratympanic injection of gentamicin. *Laryngoscope*. 2015; 125(4):972-978. EBM level 4.....47-53

Summary: This study is a retrospective case review on management of intractable Ménière's disease after intratympanic injection of gentamicin (ITG). Class A and B control was achieved by ITG in 90% of patients. Exploratory tympanotomy and gentamicin application (ETG) over the round and oval windows had a 71% success rate of class A outcome in patients who failed ITG. Labyrinthectomy and vestibular neurectomy were still needed in select patients who failed all other therapeutic modalities.

Sood AJ, Lambert PR, Nguyen SA, Meyer TA. Endolymphatic sac surgery for Ménière's disease: a systematic review and meta-analysis. *Otol Neurotol*. 2014; 35(6):1033-1045. EBM level 3a.....54-66

Summary: This study is a systematic review and meta-analysis of endolymphatic sac surgery in Ménière's disease from 1970 to 2013. Endolymphatic sac decompression and/or shunt, with or without silastic, was equally effective long term in over 75% of patients who failed medical therapy for vertigo of Ménière's disease. The authors found that once the sac is opened, inserting silastic into the sac does not improve vertigo control and may diminish audition.

C. Pulsatile tinnitus

Ahsan SF, Seidman M, Yaremchuk K. What is the best imaging modality in evaluating patients with unilateral pulsatile tinnitus? *Laryngoscope*. 2015; 125(2):284-285. EBM level 5.....67-68

Summary: This article is a review of five previous journal articles presenting evaluation methods for patients with pulsatile tinnitus. The authors review and identify the different methods of evaluation and their sensitivity and specificity for diagnosis, and include an evaluation tree for workup of pulsatile tinnitus.

Summary: This article is a review series of radiologic evaluation of pulsatile tinnitus. The authors review previous articles describing anatomical abnormalities including tumors and percentages seen in previous studies. Included is an evaluation tree describing the workup of pulsatile tinnitus and images of anatomical abnormalities.

Summary: This is a retrospective evaluation of patients with diagnosis codes of both migraine and pulsatile tinnitus. Of the 145 patients evaluated with both diagnoses, patients with objective tinnitus were excluded from evaluation, leaving 16 patients for evaluation. Patients were prescribed a migraine diet +/- migraine prophylaxis. Patients were then evaluated for improvement in tinnitus and headaches. The majority of patients received improvement with the diet whereas the medication made little difference, but this may be due to the fact that these patients were more severe cases. The study highlights the importance of treatment modalities, but doesn't describe complications.

II. External Auditory Canal and Middle Ear

A. Acute otitis externa

Summary: This is a retrospective chart review of 20 patients with malignant otitis externa (MOE) treated at a tertiary care institution between 1995 and 2012. Forty-five percent of patients had culture-positive *Pseudomonas aeruginosa*, and 15% grew methicillin-resistant *Staphylococcus aureus* (MRSA). Signs and symptoms were similar across groups. However, all *P. aeruginosa* patients had diabetes, but only 33% of MRSA patients were diabetic. Patients with MRSA required on average 4.7 more weeks of therapy with antibiotics versus non-MRSA patients. The study highlights the evolving pathogens in MOE even in nondiabetic patients.

Summary: This is a review article on malignant otitis externa (MOE) treatment, outcome, and prognostic factors from an Asian perspective. The authors performed a retrospective chart review from 2006 to 2011 on 19 MOE patients who received 6 weeks of intravenous ceftazidime combined with oral fluoroquinolone. They did not discuss concurrent topical therapy. Disease resolved in 63% of patients, and mortality was 21%. Age, diabetic control, time delay in diagnosis, cranial nerve involvement, and inflammatory markers were not predictors of prognosis. Erythrocyte sedimentation rate and C reactive protein levels correlated with disease activity and were used to monitor progress. Clivus involvement implied persistent disease. Sixty-three percent of cultures were positive, usually *Pseudomonas aeruginosa*, and 33% of isolates were multi-drug resistant. Culture-directed therapy did not affect outcome.

Tarazi AE, Al-Tawfiq JA, Abdi RF. Fungal malignant otitis externa: pitfalls, diagnosis, and treatment. *Otol Neurotol*. 2012; 33(5):769-773. EBM level 4.....94-98

Summary: This study reviews literature on malignant otitis externa (MOE), including fungal infections, and reports the findings as a series of case presentations on patients with *Aspergillus* MOE. Oral voriconazole was found to be a viable alternative treatment to intravenous vancomycin and amphotericin B. The authors discuss pitfalls, diagnosis, and treatment of MOE associated with *Pseudomonas aeruginosa* as well as to fungi.

B. Cholesteatoma

Crowson MG, Ramprasad VH, Chapurin N, et al. Cost analysis and outcomes of a second-look tympanoplasty-mastoidectomy strategy for cholesteatoma. *Laryngoscope*. 2016; 126(11):2574-2579. EBM level 4.....99-104

Summary: This article examines a single institution's experience managing patients with cholesteatoma through an intact canal wall tympanoplasty with mastoidectomy. The authors explore differences in hearing outcomes, disease recidivism, and overall costs between patients undergoing a single-stage surgical procedure and a second-look operative approach. Hearing outcomes were similar between these groups, while costs were considerably lower with the single-stage group and disease recidivism was higher for the group undergoing a second-look procedure. The article stresses the need for individualizing the approach based on the level of disease present at the time of the initial surgery.

Kerckhoffs KG, Kommer MB, van Strien TH, et al. The disease recurrence rate after the canal wall up or canal wall down technique in adults. *Laryngoscope*. 2016; 126(4):980-987. EBM level 3.....105-112

Summary: This is a systematic review article that examines the literature on the topic of disease recidivism following canal wall up and canal wall down mastoidectomy for acquired cholesteatoma. The article highlights the variability in the available literature, but demonstrates that recidivistic disease is more likely in canal wall up mastoidectomy techniques. While both canal wall up and canal wall down techniques are associated with recidivistic disease, residual cholesteatoma is more common in canal wall up techniques, while recurrent disease is more common in canal wall down techniques.

Migirov L, Wolf M, Greenberg G, Eyal A. Non-EPI DW MRI in planning the surgical approach to primary and recurrent cholesteatoma. *Otol Neurotol*. 2014; 35(1):121-125. EBM level 4.....113-117

Summary: This article assesses the accuracy of non-echo planar, diffusion-weighted MRI for assessing primary and recurrent/residual cholesteatoma in a cohort of 50 patients. The authors compared preoperative MRI findings with intraoperative findings to determine the degree of accuracy, with a finding of 98% concordance.

III. Hearing Loss

A. Sensorineural hearing loss

Summary: Twenty-seven patients with mixed, conductive, and single-sided hearing loss who received the Baha Attract System were studied for 9 months. Patient benefit, soft-tissue status, device retention, and safety were monitored. Results demonstrated significant improvement in audibility and speech understanding in noise and quiet when compared to preoperative unaided hearing.

Summary: This article discusses U.S. trials for the Cochlear Nucleus Hybrid L24 implant at ten investigational sites. The study included 50 patients with low-frequency hearing intact. Mean improvements in consonant-nucleus-consonant and AzBio were seen in nearly all patients. Hearing preservation rate (as defined as any measurable hearing) at 6 months was 66%.

B. Conductive and mixed hearing loss

Summary: This is a prospective cohort study evaluating the audiological outcomes in patients with conductive/mixed hearing loss who underwent vibroplasty surgery using three different coupling techniques (direct to round window [RW], soft-tissue RW coupling, and stapes/incus coupling). Patients with soft tissue interposed between the floating mass transducer and RW showed the poorest coupling efficiency. Direct RW coupling was significantly better than with soft-tissue RW coupling. Vibroplasty directly to the ossicular chain provided the best coupling efficiency outcomes.

Summary: This article is a systematic review of the utility of CT in the diagnosis of otosclerosis in patients with conductive hearing loss. In patients with a strong clinical suspicion of otosclerosis, the positive and negative predictive value of CT is relatively high. In patients with a low suspicion for otosclerosis, positive and negative predictive values of CT were much lower. CT imaging for conductive hearing loss is only recommended for suspected pathology other than otosclerosis when preparing for middle ear surgery.

C. Single-sided deafness

Finbow J, Bance M, Aiken S, et al. A comparison between wireless CROS and bone-anchored hearing devices for single-sided deafness: a pilot study. *Otol Neurotol*. 2015; 36(5):819-825. EBM level 2.....148-154

Summary: This study compared outcomes with a wireless contralateral routing of signal (CROS) hearing aid to those with a bone-anchored hearing device (BAHD) in patients with single-sided deafness. A within-subject design was used to compare the two devices with regard to head shadow effect reduction, speech perception in quiet and noise, and self-assessment questionnaires. Results showed no significant difference between the two devices on either objective or subjective outcome measures.

Sladen DP, Frisch CD, Carlson ML, et al. Cochlear implantation for single-sided deafness: a multicenter study. *Laryngoscope*. 2017; 127(1):223-228. EBM level 4.....155-160

Summary: This article is a multicenter retrospective review of a cohort of pediatric and adult patients who underwent cochlear implantation for single-sided deafness of a variety of etiologies. Pre- and postoperative testing was performed using both word and sentence testing in quiet in the implanted ear alone, and sentence recognition in noise in the binaural condition. Word and sentence scores for the implanted ear alone improved significantly by 3 months postoperatively, while speech recognition in noise in the binaural condition did not change significantly. The majority of patients reported reduction in tinnitus in the implanted ear.

Zeitler DM, Dorman MF, Natale SJ, et al. Sound source localization and speech understanding in complex listening environments by single-sided deaf listeners after cochlear implantation. *Otol Neurotol*. 2015; 36(9):1467-1471. EBM level 2.....161-165

Summary: This article investigates sound localization ability and speech comprehension in complex noise environments in patients who had unilateral cochlear implantation for single-sided deafness (SSD) as compared to three control groups: normal hearing (NH) young adults, NH older adults, and bilateral cochlear implant (BCI) users. All SSD-CI users showed poorer-than-normal sound localization, typically performing as well as BCI subjects, with some subjects localizing close to the 95th percentile of NH listeners. Speech understanding was significantly improved in ambient noise with signal presented to the CI ear in the SSD-CI listeners.

IV. Temporal Bone/Skull Base

A. Temporal bone and skull base lesions

McRackan TR, Wilkinson EP, Brackmann DE, Slattery WH. Stereotactic radiosurgery for facial nerve schwannomas: meta-analysis and clinical review. *Otol Neurotol*. 2015; 36(3): 393-398. EBM level 3.....166-171

Summary: In this thorough meta-analysis, 10 studies are included comprising 45 patients with at least a 2-year follow up. Of these patients, 93% had tumor control, 67% had stable facial nerve function, 21% had improved function, and 13% had worsened facial nerve function. Hearing results are not as favorable. The authors conclude that stereotactic radiosurgery is an effective and reasonable option for treating facial schwannomas, though hearing loss is a substantial risk.

Wanna GB, Sweeney AD, Haynes DS, Carlson ML. Contemporary management of jugular paragangliomas. *Otolaryngol Clin North Am*. 2015; 48(2):331-341. EBM level 3.....172-182

Summary: This is a well-written, comprehensive review of jugular paragangliomas, discussing epidemiology, clinical presentation, genetics, and management. The extensive experience at the Otology Group of Vanderbilt is discussed.

Wise SC, Carlson ML, Tveiten ØV, et al. Surgical salvage of recurrent vestibular schwannoma following prior stereotactic radiosurgery. *Laryngoscope*. 2016; 126(11):2580-2586. EBM level 3.....183-189

Summary: This article presents a case-control study of 37 patients who underwent surgical resection of sporadic vestibular schwannoma following failed radiation therapy. Controls were patients who underwent primary microsurgery without having received prior radiation. Complications are reported. At follow up, 73% had satisfactory facial nerve function (HBI-II), which was not different from controls. However, a significantly higher percentage of patients had less-than-complete resection.

B. Skull base and ear trauma

Cannon RB, Thomson RS, Shelton C, Gurgel RK. Long-term outcomes after middle fossa approach for traumatic facial nerve paralysis. *Otol Neurotol*. 2016; 37(6):799-804. EBM level 4.....190-195

Summary: This article examines the long-term facial nerve outcomes after a middle fossa approach for traumatic facial paralysis. Patients with both intact and irreversibly injured facial nerves were included. Using the House-Brackmann facial nerve grading system, facial nerve outcomes are provided at 1 year following surgical intervention, with all patients achieving at least a grade III result.

Medina M, Di Lella F, Di Trapani G, et al. Cochlear implantation versus auditory brainstem implantation in bilateral total deafness after head trauma: personal experience and review of the literature. *Otol Neurotol*. 2014; 35(2):260-270. EBM level 4.....196-206

Summary: This article examines hearing outcomes in patients treated with cochlear implants after bilateral temporal bone fractures with hearing loss. Open-set word recognition was obtained in patients undergoing primary cochlear implant placement, and the article identifies the advantage of this technique over auditory brainstem implantation in posttraumatic hearing loss, regardless of fracture location/etiology (with the exception of loss of cochlear nerve continuity).

Schell A, Kitsko D. Audiometric outcomes in pediatric temporal bone trauma. *Otolaryngol Head Neck Surg*. 2016; 154(1):175-180. EBM level 4.....207-212

Summary: This article reviews the hearing outcomes of pediatric patients who sustained temporal bone fractures during a 13-year period. A distinction between otic capsule–sparing and otic capsule–violating fractures is made, based on CT findings, and this serves as a basis for comparing the observed hearing results. While otic capsule–violating fractures were associated with severe hearing loss, most cases with otic capsule–sparing fractures demonstrated near-normal hearing by 6 weeks post-injury.

Waissbluth S, Ywakim R, Al Qassabi B, et al. Pediatric temporal bone fractures: a case series. *Int J Pediatr Otorhinolaryngol*. 2016; 84:106-109. EBM level 4.....213-216

Summary: This article provides a retrospective review of all pediatric patients who presented with temporal bone fractures during a 14-year period at a tertiary referral center. It discusses the typical otologic clinical findings in pediatric patients with temporal bone fracture and highlights commonly observed concomitant fractures/injuries.

V. Facial Nerve

Lee DH. Clinical efficacy of electroneurography in acute facial paralysis. *J Audiol Otol*. 2016; 20(1):8-12. EBM level 5.....217-221

Summary: This article is a wonderful summary of facial paralysis and describes tests used for studying facial paresis including electromyography, electroneurography (ENoG), nerve excitability testing, and the maximal stimulatory test. It further describes facial nerve injury, classification systems, and expected test results. This paper spends the majority of effort on describing ENoG and its utility. While a review article, it is deeply insightful and a great comprehensive summary article that highlights various testing modalities.

2016-17 SECTION 8 ADDITIONAL REFERENCES

Adunka OF, Giardina CK, Formeister EJ, et al. Round window electrocochleography before and after cochlear implant electrode insertion. *Laryngoscope*. 2016; 126(5):1193-1200.

Albu S, Amadori M, Babighian G. Predictors of hearing preservation in the management of labyrinthine fistulas positioned on the semicircular canals. *Ann Otol Rhinol Laryngol*. 2013; 122(8):529-534.

Angeli SI, Abouyared M, Snapp H, Jethanamest D. Utricular dysfunction in refractory benign paroxysmal positional vertigo. *Otolaryngol Head Neck Surg*. 2014; 151(2): 321-327.

Arndt S, Prosse S, Laszig R, et al. Cochlear implantation in children with single-sided deafness: does aetiology and duration of deafness matter? *Audiol Neurotol*. 2015; 20 Suppl 1:21-30.

Arslan HH, Satar B, Yildizoglu U, et al. Validity of late-term electroneurography in Bell's palsy. *Otol Neurotol*. 2014; 35(4):656-661.

Atef AM, Hamouda MM, Mohamed AH, Fattah AF. Topical 5-fluorouracil for granular myringitis: a double-blinded study. *J Laryngol Otol*. 2010; 124(3):279-284.

Baráth K, Schuknecht B, Monge Naldi A, et al. Detection and grading of endolymphatic hydrops in Ménière disease using MR imaging. *AJNR Am J Neuroradiol*. 2014; 35(7):1387-1392.

Bausch B, Wellner U, Peyre M, et al. Characterization of endolymphatic sac tumors and von Hippel-Lindau disease in the International Endolymphatic Sac Tumor Registry. *Head Neck*. 2016; 38 Suppl 1:E673-E679.

Bosman AJ, Snik AF, Hol MK, Mylanus EA. Evaluation of a new powerful bone-anchored hearing system: a comparison study. *J Am Acad Audiol*. 2013; 24(6):505-513.

Buchman CA, Dillon MT, King ER, et al. Influence of cochlear implant insertion depth on performance: a prospective randomized trial. *Otol Neurotol*. 2014; 35(10):1773-1779.

Cannon RB, Gurgel RK, Warren FM, Shelton C. Facial nerve outcomes after middle fossa decompression for Bell's palsy. *Otol Neurotol*. 2015; 36(3):513-518.

Channer GA, Herman B, Telischi FF, et al. Management outcomes of facial nerve tumors: comparative outcomes with observation, CyberKnife, and surgical management. *Otolaryngol Head Neck Surg*. 2012; 147(3):525-530.

Choe WJ, Kim JH, Park SY, Kim J. Electromyographic response of facial nerve stimulation under different levels of neuromuscular blockade during middle-ear surgery. *J Int Med Res*. 2013; 41(3):762-770.

Choi JW, Park YH. Facial nerve paralysis in patients with chronic ear infections: surgical outcomes and radiologic analysis. *Clin Exp Otorhinolaryngol*. 2015; 8(3):218-223.

Contrera KJ, Betz J, Li L, et al. Quality of life after intervention with a cochlear implant or hearing aid. *Laryngoscope*. 2016; 126(9):2110-2115.

Dedhia K, Kitsko D, Sabo D, Chi DH. Children with sensorineural hearing loss after passing the newborn hearing screen. *JAMA Otolaryngol Head Neck Surg*. 2013; 139(2):119-123.

Dornhoffer JL, Friedman AB, Gluth MB. Management of acquired cholesteatoma in the pediatric population. *Curr Opin Otolaryngol Head Neck Surg*. 2013; 21(5):440-445.

Dubach P, Mantokoudis G, Caversaccio M. Ear canal cholesteatoma: meta-analysis of clinical characteristics with update on classification, staging and treatment. *Curr Opin Otolaryngol Head Neck Surg*. 2010; 18(5):369-376.

Ernst A, Todt I, Wagner J. Safety and effectiveness of the Vibrant Soundbridge in treating conductive and mixed hearing loss: a systematic review. *Laryngoscope*. 2016; 126(6):1451-1457.

Espahbodi M, Sweeney AD, Lennon KJ, Wanna GB. Facial nerve stimulation associated with cochlear implant use following temporal bone fractures. *Am J Otolaryngol*. 2015; 36(4):578-582.

Gerdes T, Salcher RB, Schwab B, et al. Comparison of audiological results between a transcutaneous and a percutaneous bone conduction instrument in conductive hearing loss. *Otol Neurotol*. 2016; 37(6):685-691.

Hansen MR, Gantz BJ, Dunn C. Outcomes after cochlear implantation for patients with single-sided deafness, including those with recalcitrant Ménière's disease. *Otol Neurotol*. 2013; 34(9):1681-1687.

Herasym K, Bonaparte JP, Kilty S. A comparison of Locacorten-Vioform and clotrimazole in otomycosis: a systematic review and one-way meta-analysis. *Laryngoscope*. 2016; 126(6):1411-1419.

Janssen RM, Hong P, Chadha NK. Bilateral bone-anchored hearing aids for bilateral permanent conductive hearing loss: a systematic review. *Otolaryngol Head Neck Surg*. 2012; 147(3):412-422.

Kantner C, Gürkov R. Characteristics and clinical applications of ocular vestibular evoked myogenic potentials. *Hear Res*. 2012; 294(1-2):55-63.

Künzel J, Iro H, Hornung J, et al. Function-preserving therapy for jugulotympanic paragangliomas: a retrospective analysis from 2000 to 2010. *Laryngoscope.* 2012; 122(7):1545-1551.

Labadie RF, Noble JH, Hedley-Williams AJ, et al. Results of postoperative, CT-based, electrode deactivation on hearing in prelingually deafened adult cochlear implant recipients. *Otol Neurotol*. 2016; 37(2):137-145.

Lempert T. Vestibular migraine. *Semin Neurol*. 2013; 33(3):212-218.

Lenarz T, James C, Cuda D, et al. European multi-centre study of the Nucleus Hybrid L24 cochlear implant. *Int J Audiol*. 2013; 52(12):838-848.

Lenarz T, Verhaert N, Desloovere C, et al. A comparative study on speech in noise understanding with a direct acoustic cochlear implant in subjects with severe to profound mixed hearing loss. *Audiol Neurootol*. 2014; 19(3):164-174.

Lim HJ, Kim YT, Choi SJ, et al. Efficacy of 3 different steroid treatments for sudden sensorineural hearing loss: a prospective, randomized trial. *Otolaryngol Head Neck Surg*. 2013; 148(1):121-127. Erratum. *Otolaryngol Head Neck Surg*. 2013; 148(6):1064.

Lingam RK, Khatri P, Hughes J, Singh A. Apparent diffusion coefficients for detection of postoperative middle ear cholesteatoma on non-echo-planar diffusion-weighted images. *Radiology*. 2013; 269(2):504-510.

Maes IH, Cima RF, Anteunis LJ, et al. Cost-effectiveness of specialized treatment based on cognitive behavioral therapy versus usual care for tinnitus. *Otol Neurotol*. 2014; 35(5):787-795.

Marchioni D, Mattioli F, Alicandri-Ciufelli M, Presutti L. Prevalence of ventilation blockages in patients affected by attic pathology: a case-control study. *Laryngoscope*. 2013; 123(11):2845-2853.

Masterson L, Rouhani M, Donnelly NP, et al. Squamous cell carcinoma of the temporal bone: clinical outcomes from radical surgery and postoperative radiotherapy. *Otol Neurotol*. 2014; 35(3):501-508.

Matsuoka AJ, Harris JP. Autoimmune inner ear disease: a retrospective review of forty-seven patients. *Audiol Neurotol*. 2013; 18(4):228-239.

Mertens G, Kleine Punte A, De Ridder D, van de Heyning P. Tinnitus in a single-sided deaf ear reduces speech reception in the nontinnitus ear. *Otol Neurotol*. 2013; 34(4):662-666.

McRackan TR, Gifford RH, Kahue CN, et al. Cochlear implantation in Ménière's disease patients. *Otol Neurotol*. 2014; 35(3):421-425.

Mick P, Kwachi I, Lin FR. The association between hearing loss and social isolation in older adults. *Otolaryngol Head Neck Surg*. 2014; 150(3):378-384.

Mion M, Bovo R, Marchese-Ragona R, Martini A. Outcome predictors of treatment effectiveness for fungal malignant external otitis: a systematic review. *Acta Otorhinolaryngol Ital*. 2015; 35(5):307-313.

Mohamad SH, Khan I, Hussain SS. Is cartilage tympanoplasty more effective than fascia tympanoplasty? A systematic review. *Otol Neurotol*. 2012; 33(5):699-705.

Moore BC, Popelka GR. Preliminary comparison of bone-anchored hearing instruments and a dental device as treatments for unilateral hearing loss. *Int J Audiol*. 2013; 52(10):678-686.

Niesten ME, Hamburg LM, Silverman JB, et al. Superior canal dehiscence length and location influences clinical presentation and audiometric and cervical vestibular-evoked myogenic potential testing. *Audiol Neurotol*. 2014; 19(2):97-105.

Rosenfeld RM, Schwartz SR, Cannon CR, et al. Clinical practice guideline: acute otitis externa executive summary. *Otolaryngol Head Neck Surg*. 2014; 150(2):161-168.

Sajisevi M, Weissman JL, Kaylie DM. What is the role of imaging in tinnitus? *Laryngoscope*. 2014; 124(3):583-584.

Sanna M, Fois P, Pasanisi E, et al. Middle ear and mastoid glomus tumors (glomus tympanicum): an algorithm for the surgical management. *Auris Nasus Larynx*. 2010; 37(6):661-668.

Schilder AG, Burton MJ, Eby TL, Rosenfeld RM. Cochrane Corner: amplification with hearing aids for patients with tinnitus and co-existing hearing loss. *Otolaryngol Head Neck Surg*. 2014; 150(6): 915-918.

Schoeff S, Nicholas B, Mukherjee S, Kesser BW. Imaging prevalence of sigmoid sinus dehiscence among patients with and without pulsatile tinnitus. *Otolaryngol Head Neck Surg*. 2014; 150(5):841-846.

Schwartz MS, Kari E, Strickland BM, et al. Evaluation of the increased use of partial resection of large vestibular schwannomas: facial nerve outcomes and recurrence/regrowth rates. *Otol Neurotol*. 2013; 34(8):1456-1464.

Semaan MT, Gilpin DA, Hsu DP, et al. Transmastoid extradural-intracranial approach for repair of transtemporal meningoencephalocele: a review of 31 cases. *Laryngoscope*. 2011; 121(8):1765-1772.

Setty P, D'Andrea KP, Stucken EZ, et al. Endoscopic resection of vestibular schwannomas. *J Neurol Surg B Skull Base*. 2015; 76(3):230-238.

Shah A, Ayala M, Capra G, et al. Otologic assessment of blast and nonblast injury in returning Middle East-deployed service members. *Laryngoscope*. 2014; 124(1):272-277.

Sismanis A. Pulsatile tinnitus: contemporary assessment and management. *Curr Opin Otolaryngol Head Neck Surg*. 2011; 19(5):348-357.

Stevens SM, Rizk HG, McIlwain WR, et al. Association between lateral skull base thickness and surgical outcomes in spontaneous CSF otorrhea. *Otolaryngol Head Neck Surg*. 2016; 154(4):707-714.

Tarabichi M, Nogueira J, Marchioni D, et al. Transcanal endoscopic management of cholesteatoma. *Otolaryngol Clin North Am.* 2013; 46(2):107-130.

Távora-Vieira D, De Ceulaer G, et al. Cochlear implantation improves localization ability in patients with unilateral deafness. *Ear Hear*. 2015; 36(3):e93-e98.

van de Heyning P, Muehlmeier G, Cox T, et al. Efficacy and safety of AM-101 in the treatment of acute inner ear tinnitus−a double-blind, randomized, placebo-controlled phase II study. *Otol Neurotol*. 2014; 35(4):589-597.

Vivas EX, Mccall A, Raz Y, et al. ICP, BMI, surgical repair, and CSF diversion in patients presenting with spontaneous CSF otorrhea. *Otol Neurotol*. 2014; 35(2):344-347.

Wanna GB, Noble JH, Carlson ML, et al. Impact of electrode design and surgical approach on scalar location and cochlear implant outcomes. *Laryngoscope*. 2014; 124 Suppl 6:S1-S7.

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RESEARCH ARTICLE

Benign Paroxysmal Positional Vertigo after Dental Procedures: A Population-Based Case-Control Study

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Data Availability Statement: This study used data from the National Health Insurance Research Database (NHIRD) in Taiwan. The dataset was managed by the National Health Research Institutes (NHRI). Requests for the data could be sent to the Center for Biomedical Resources of NHRI (Email: nhird@nhri.org.tw), and data will be available upon request to all interested researchers through reviewing and approving by the NHRI.

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Abstract

Background

Benign paroxysmal positional vertigo (BPPV), the most common type of vertigo in the general population, is thought to be caused by dislodgement of otoliths from otolithic organs into the semicircular canals. In most cases, however, the cause behind the otolith dislodgement is unknown. Dental procedures, one of the most common medical treatments, are considered to be a possible cause of BPPV, although this has yet to be proven. This study is the first nationwide population-based case-control study conducted to investigate the correlation between BPPV and dental manipulation.

Methods

Patients diagnosed with BPPV between January 1, 2007 and December 31, 2012 were recruited from the National Health Insurance Research Database in Taiwan. We further identified those who had undergone dental procedures within 1 month and within 3 months before the first diagnosis date of BPPV. We also identified the comorbidities of the patients with BPPV, including head trauma, osteoporosis, migraine, hypertension, diabetes, hyperlipidemia and stroke. These variables were then compared to those in age- and gender-matched controls.

Results

In total, 768 patients with BPPV and 1536 age- and gender-matched controls were recruited. In the BPPV group, 9.2% of the patients had undergone dental procedures within 1 month before the diagnosis of BPPV. In contrast, only 5.5% of the controls had undergone dental treatment within 1 month before the date at which they were identified ($P = 0.001$).

Competing Interests: The authors have declared that no competing interests exist.

After adjustments for demographic factors and comorbidities, recent exposure to dental procedures was positively associated with BPPV (adjusted odds ratio 1.77; 95% confidence interval 1.27–2.47). This association was still significant if we expanded the time period from 1 month to 3 months (adjusted odds ratio 1.77; 95% confidence interval 1.39–2.26).

Conclusions

Our results demonstrated a correlation between dental procedures and BPPV. The specialists who treat patients with BPPV should consider dental procedures to be a risk factor, and dentists should recognize BPPV as a possible complication of dental treatment.

Introduction

Benign paroxysmal positional vertigo (BPPV) is the most common form of vertigo in the general population with a lifetime prevalence of 2.4%[1]. It is thought to be caused by dislodgement of otoliths from otolithic organs into the semicircular canals. BPPV can be directly induced by head trauma[2] and other inner ear disorders such as vestibular neuritis[3]. However, most etiologies of BPPV are unclear. The potential risk factors for idiopathic BPPV include old age, bed rest[4], migraine[5], osteoporosis[6], and vascular risk factors[1]. In addition, iatrogenic BPPV induced by specific types of surgery[7, 8] has also been observed.

Dental procedures are considered to be a possible cause of BPPV, and even the most common iatrogenic cause[9]. However, previous studies on the correlation between BPPV and dental work have been mostly case reports or case series[10–14], and this study is the first nationwide population-based case-control study conducted to investigate the correlation between BPPV and dental procedures.

Materials and Methods

Database

This population-based case-control study used data from the National Health Insurance Research Database (NHIRD) in Taiwan. The NHIRD contains records of approximately 23 million enrollees dating back to March 1995, representing almost 99% of the total population in Taiwan. We reviewed records from the Longitudinal Health Insurance Database (LHID) which includes claims data for 1 million enrollees randomly selected from all beneficiaries of the National Health Insurance program. The medical records included in the LHID include those from as far back as 1996 and are updated annually. In order to ensure confidentiality, the enrollees' personal information is scrambled using anonymous identification numbers. Patient consent is not required to access the NHIRD. This study was approved by the Institutional Review Board of the Buddhist Taichung Tzu Chi General Hospital, Taiwan (REC104-11). We extracted data based on International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) codes.

Study Sample

Patients aged 20 years or older who were diagnosed with BPPV (ICD-9-CM: 386.11) between January 1, 2007 and December 31, 2012 were enrolled. The diagnosis of BPPV was mostly established by board-certified otolaryngologists or neurologists after assessing the medical history of the patients and the results of Dix-Hallpike or supine roll tests. In order to increase the diagnostic accuracy, the patients who were diagnosed with BPPV at least three times in out-

patient department follow-up visits or who were hospitalized with BPPV as the primary diagnosis were enrolled as the case group. We excluded the patients who had other vertigo-related diagnoses (ICD-9-CM: 078.81, 386.0–386.10, 386.12–386.9, 780.4) to avoid misdiagnoses of BPPV. The index date was defined as the first diagnosis date of BPPV during the inclusion period for each patient.

We randomly selected individuals without vertigo-related diagnoses (ICD-9-CM: 078.81, 386.0–386.9, 780.4) during the same period from the database as the control group, and matched them with the case patients at a control-to-case ratio of 2:1 according to exact age and gender.

Study Variables

The patients who had previously received any dental procedure were defined as having undergone a dental procedure, and we then identified those who had undergone the procedure within 1 month and within 3 months before the index date. Dental procedures were further classified into five groups: dental scaling, prosthodontics, endodontics, oral surgery, and periodontics.

Covariates

We extracted the demographic information of each participant, including age, gender, socioeconomic status, urbanization, and geographic region. We also the identified the following comorbidities of BPPV within 6 months before the index date: head trauma (ICD-9-CM: 800–804, 850–854), osteoporosis (ICD-9-CM: 733.0X), migraine (ICD-9-CM: 346), hypertension (ICD-9-CM: 401–405), diabetes mellitus (ICD-9-CM: 250) hyperlipidemia (ICD-9-CM: 272.0–272.4), and ischemic or hemorrhagic stroke (ICD-9-CM: 430–434). In addition, Charlson Comorbidity Index Score (CCIS)[15] was computed to represent a range of comorbid status.

Statistics

Data management and statistical analysis were performed using SAS 9.2 software (SAS Institute, Cary, NC). The $\chi 2$ test was used to compare the history of dental procedures, demographic data, and comorbidities between the BPPV and control groups. Odds ratios (ORs) and related 95% confidence intervals (CIs) were calculated to examine the correlations between a history of dental procedures and BPPV using multivariate logistic regression analysis after adjusting for demographic factors and comorbidities. We also use multivariate logistic regression analysis to investigate the associations between different dental procedures and BPPV. A two-sided probability value less than 0.05 was considered to be statistically significant.

Results

Table 1 shows the baseline characteristics of the study subjects. In total, 768 patients with BPPV and 1536 age- and gender-matched controls were recruited in this study. The mean age (± SD) of the participants was 57±15 years, and 62.9% of them were female. In terms of comorbidities, CCIS was significant higher in the BPPV group ($P<0.001$); in addition, hypertension, hyperlipidemia, and migraine were significantly more prevalent in the BPPV group than in the controls ($P<0.05$). The prevalence rates of head trauma, stroke and diabetes were higher in the BPPV group than in the control group, but the differences did not reach statistical significance due to a low 6-month prevalence rate. More than half of the study population lived in un-

Table 1. Baseline characteristics.

Characteristics	BPPV group	Control group	*P*-value
Patient no.	768	1536	
Mean age, years (±SD)	57±15	57±15	0.365
CCIS (Mean±SD)	0.6±1.1	0.4±0.9	<0.001
Gender			NA
Male	285(37.1)	570(37.1)	
Female	483(62.9)	966(62.9)	
Comorbidities			
Hypertension	229(29.8)	322(21.0)	<0.001
Hyperlipidemia	88(11.5)	115(7.5)	0.002
Head trauma	11(1.4)	11(0.7)	0.096
Osteoporosis	13(1.7)	28(1.8)	0.824
Migraine	14(1.8)	7(0.5)	0.001
Stroke	17(2.2)	26(1.7)	0.384
Diabetes mellitus	76(9.9)	133(8.7)	0.330
Socioeconomic status			0.451
Low SES	360(46.9)	747(48.6)	
Moderate SES	261(34.0)	482(31.4)	
High SES	147(19.1)	307(20.0)	
Urbanization			0.356
Urban	248(32.3)	467(30.4)	
Un-urban	520(67.7)	1069(69.6)	
Geographic region			0.007
Northern Taiwan	499(65.0)	1083(70.5)	
Southern Taiwan	269(35.0)	453(29.5)	

BPPV = benign paroxysmal positional vertigo; CCIS = Charlson Comorbidity Index Score; SES = socioeconomic status

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urbanized areas, however socioeconomic status and the level of urbanization were not significantly associated with BPPV.

Table 2 shows comparisons of dental procedures between the BPPV group and control group. In the BPPV group, 9.2% of the patients had received dental procedures within 1 month before the diagnosis of BPPV. In contrast, only 5.5% of the controls had undergone dental treatment within 1 month before the index date. The rate of dental procedures was significantly higher in the BPPV group than in the control group ($P = 0.001$). When we expanded the time period from 1 month to 3 months, the rate of dental procedures was still significantly higher in the BPPV patients than in the controls (18.8% vs. 11.7%, $P<0.001$).

Table 2. Comparison of dental procedures between patients with and without benign paroxysmal positional vertigo.

Characteristics	BPPV group	Control group	*P*-value
Dental procedure within 1 month before the index date			0.001
Yes	71(9.2)	84(5.5)	
No	697(90.8)	1452(94.5)	
Dental procedure within 3 months before the index date			<0.001
Yes	144(18.8)	179(11.7)	
No	624(81.3)	1357(88.3)	

BPPV = benign paroxysmal positional vertigo

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Table 3. Odds ratios for benign paroxysmal positional vertigo with regards to dental procedures and comorbidities.

Variable	BPPV	
	Crude OR(95% CI)	Adjusted OR*(95% CI)
Dental procedure		
Within 1 month	1.76(1.27–2.45)	1.77(1.27–2.47)
Within 3 months	1.75(1.38–2.22)	1.77(1.39–2.26)
Comorbidities		
Hypertension	1.60(1.32–1.95)	1.63(1.29–2.04)
Hyperlipidemia	1.60(1.19–2.14)	1.46(1.06–1.99)
Head trauma	2.02(0.87–4.67)	1.87(0.79–4.44)
Osteoporosis	0.93(0.48–1.80)	0.85(0.43–1.68)
Migraine	4.06(1.63–10.09)	4.23(1.68–10.67)
Stroke	1.32(0.71–2.44)	1.07(0.56–2.05)
Diabetes mellitus	1.16(0.86–1.56)	0.90(0.65–1.25)

BPPV = benign paroxysmal positional vertigo; OR = odds ratio; CI = confidence interval

*Adjusted for age, gender, hypertension, hyperlipidemia, head trauma, osteoporosis, migraine, stroke, diabetes, socioeconomic status, urbanization and geographical region.

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Table 3 presents the results of multivariate logistic regression analysis after adjusting for demographic factors and comorbidities. Compared to the subjects who did not receive dental procedures within 1 month before the index date, the adjusted OR (aOR) of BPPV was 1.77 (95% CI 1.27–2.47) for those who did undergo a dental procedure within 1 month before the index date. This association was still significant for those who underwent a dental procedure within 3 months (aOR 1.77; 95% CI 1.39–2.26). Hypertension (aOR 1.63; 95% CI 1.29–2.04), hyperlipidemia (aOR 1.46; 95% CI 1.06–1.99) and migraine (aOR 4.23; 95% CI 1.68–10.67) were independent risk factors significantly associated with BPPV.

Table 4 lists the ORs for the risks associated with different kinds of dental procedures for BPPV diagnosed within 1 month. Three of the five procedures significantly increased the risk of BPPV, including prosthodontics (aOR 1.61; 95% CI 1.01–2.59), oral surgery (aOR 2.24; 95% CI 1.41–3.56), and periodontics (aOR 3.35; 95% CI 1.99–5.63). The other two procedures also tended to increase the risk of BPPV, but without statistical significance.

Discussion

This study demonstrates that dental procedures are a modest risk factor for BPPV, with a 1.77-fold higher odds of BPPV for those receiving dental treatment than for those without undergoing a procedure regardless of whether the diagnosis of BPPV was within 1 month or 3 months of the procedure. Although a few studies have reported on BPPV after dental therapy, most have been case reports or case series[9, 11, 13] and not systemic studies. Our study is the first population-based study to confirm a correlation between BPPV and dental procedures. In addition, most previous reports have focused on the tapping effect of osteotomes, a tool used in dental procedures[12, 14]. For example, the only previously reported control trial compared the risk of BPPV between the use of mallet and screwable osteotomes[10], whereas our results show that the risk of BPPV is increased with multiple kinds of common dental procedures such as prosthodontics, oral surgery, and periodontics.

The risk factors for BPPV can be categorized as vascular and mechanical. Among the vascular factors, migraine has been strongly associated with BPPV, with the prevalence of migraine

Table 4. Odds ratios for benign paroxysmal positional vertigo associated with different kinds of dental procedures.

Variable	1-month risk of BPPV	
	Crude OR(95% CI)	Adjusted OR*(95% CI)
Without dental procedures	1	1
Dental scaling	1.43(0.93–2.21)	1.42(0.91–2.21)
Prosthodontics	1.61(1.01–2.56)	1.61(1.01–2.59)
Endodontics	1.35(0.63–2.88)	1.36(0.63–2.93)
Oral surgery	2.15(1.36–3.40)	2.24(1.41–3.56)
Periodontics	3.36(2.01–5.61)	3.35(1.99–5.63)

BPPV = benign paroxysmal positional vertigo; OR = odds ratio; CI = confidence interval

*Adjusted for age, gender, hypertension, hyperlipidemia, head trauma, osteoporosis, migraine, stroke, diabetes, socioeconomic status, urbanization and geographical region.

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in patients with BPPV reported to be twice that of controls[5]. Vasospasm or extravasation in the inner ear may be the underlying pathophysiology. Hypertension, diabetes and hyperlipidemia, which are causes of atherosclerosis, have also been reported to be predisposing factors for BPPV[1, 16]. Mechanical factors are also important, however. In addition to head trauma [2], which has been recognized to be a direct cause of BPPV, bed rest in a specific position and intensive body shaking have both been associated with the development of BPPV. Gyo reported that prolonged bed rest may cause loosening of otoconia which then contributes to BPPV[4]. In addition, the direction of otolith dislodgement often corresponds to the direction on which side the patient prefers to lie. In terms of vibratory impact, BPPV following mountain biking[17] or after using a whole body vibration training plate[18] has been reported. On the basis of the results of this study, we suggest that dental procedures are also a mechanical cause of BPPV, regardless of a vibratory or positional effect.

The precise pathophysiology of dental procedure-induced BPPV is unknown. One hypothesis is that the vibratory or percussive tools applied in dental therapy directly induce BPPV. Although the vibratory and percussive impacts are restricted to the oral cavity, the energy conveyed via bone may enter labyrinths and result in loosening and dislodgement of otoliths. Another hypothesis suggests that repeated sitting up and lying down during dental treatment, sometimes with a head position below the horizon, may displace otoliths thereby inducing BPPV.

If the mechanical effects of dental procedures induce BPPV immediately, the date of a diagnosis of BPPV should be close to the date of dental therapy with an interval of less than 1 month. However, when we expanded the time period from 1 month to 3 months, the OR of BPPV did not decrease. Therefore, we suggest that dental procedures sometimes just initially loosen otoconia, and then dislodgement of otoliths may be delayed for days, weeks or even months.

There are several limitations to this study. First, this study is a retrospective analysis using data from the LHID, so we cannot ensure the accuracy of the diagnoses of BPPV. In order to eliminate the effect of this natural limitation of a database, we tried to reduce the diagnostic uncertainty as far as possible by excluding the patients whose BPPV diagnosis was only recorded in one or two out-patient department follow-up visits, and excluded the patients with multiple diagnoses of vestibular disorders. Inevitably these exclusion criteria made us miss the patients who were only treated in one or two sessions and the patients who actually had multiple vestibular disorders. Second, a few dental procedures which are not covered by the National

Health Insurance program such as dental implantation and orthodontics were not included in our analysis. Third, according to the LHID, the index date of the BPPV group was the first date of a diagnosis of BPPV during the inclusion period for each patient. Therefore, we cannot exclude the possibility that some patients already had BPPV before undergoing dental therapy. Changing position during dental therapy may just highlight the symptoms of BPPV, prompting the patients to seek medical care. However, we assumed that the likelihood of this was low, because the symptoms of BPPV are readily detected by the patients themselves during sleep and during daily activities or exercise. In addition, if most cases of BPPV were pre-existing before dental treatment, the 1-month OR for BPPV would be much higher than the 3-month OR, which was not the case.

Conclusions

This study demonstrates a correlation between dental procedures and BPPV. The finding not only clarifies the mechanical pathophysiology of BPPV, but also provides important clinical clues. We suggest that specialists who treat BPPV should ask about dental procedures when taking the patient's history, and emphasize the importance of dental care to avoid frequent dental procedures for high-risk patients. In addition, dentists should recognize that BPPV is one of the complications of dental treatment, be able to identify it, and refer these patients to suitable specialists.

Author Contributions

Conceived and designed the experiments: TC YL H. Chung WL. Performed the experiments: TC YL PS H. Chuang H. Chung WL. Analyzed the data: H. Chung. Contributed reagents/materials/analysis tools: H. Chung. Wrote the paper: TC H. Chung WL.

References

1. von Brevern M, Radtke A, Lezius F, Feldmann M, Ziese T, Lempert T, et al. Epidemiology of benign paroxysmal positional vertigo: a population based study. J Neurol Neurosurg Psychiatry. 2007; 78(7):710–5. Epub 2006/12/01. doi: 10.1136/jnnp.2006.100420 PMID: 17135456; PubMed Central PMCID: PMC2117684.
2. Gordon N. Post-traumatic vertigo, with special reference to positional nystagmus. Lancet. 1954; 266 (6824):1216–8. Epub 1954/06/12. PMID: 13164358.
3. Baloh RW, Honrubia V, Jacobson K. Benign positional vertigo: clinical and oculographic features in 240 cases. Neurology. 1987; 37(3):371–8. Epub 1987/03/01. PMID: 3822129.
4. Gyo K. Benign paroxysmal positional vertigo as a complication of postoperative bedrest. Laryngoscope. 1988; 98(3):332–3. Epub 1988/03/01. doi: 10.1288/00005537-198803000-00019 PMID: 3343883.
5. Ishiyama A, Jacobson KM, Baloh RW. Migraine and benign positional vertigo. Ann Otol Rhinol Laryngol. 2000; 109(4):377–80. Epub 2000/04/25. PMID: 10778892.
6. Vibert D, Kompis M, Hausler R. Benign paroxysmal positional vertigo in older women may be related to osteoporosis and osteopenia. Ann Otol Rhinol Laryngol. 2003; 112(10):885–9. Epub 2003/11/01. PMID: 14587980.
7. Kansu L, Aydin E, Gulsahi K. Benign paroxysmal positional vertigo after nonotologic surgery: case series. Journal of maxillofacial and oral surgery. 2015; 14(Suppl 1):113–5. Epub 2015/04/04. doi: 10.1007/s12663-012-0356-8 PMID: 25838683; PubMed Central PMCID: PMC4379224.
8. Nigam A, Moffat DA, Varley EW. Benign paroxysmal positional vertigo resulting from surgical trauma. J Laryngol Otol. 1989; 103(2):203–4. Epub 1989/02/01. PMID: 2926270.
9. Chiarella G, Leopardi G, De Fazio L, Chiarella R, Cassandro C, Cassandro E. Iatrogenic benign paroxysmal positional vertigo: review and personal experience in dental and maxillo-facial surgery. Acta Otorhinolaryngol Ital. 2007; 27(3):126–8. Epub 2007/09/22. PMID: 17883189; PubMed Central PMCID: PMC2640043.

10. Sammartino G, Mariniello M, Scaravilli MS. Benign paroxysmal positional vertigo following closed sinus floor elevation procedure: mallet osteotomes vs. screwable osteotomes. A triple blind randomized controlled trial. Clin Oral Implants Res. 2011; 22(6):669–72. Epub 2010/11/09. doi: 10.1111/j.1600-0501.2010.01998.x PMID: 21054553.

11. Chiarella G, Leopardi G, De Fazio L, Chiarella R, Cassandro E. Benign paroxysmal positional vertigo after dental surgery. Eur Arch Otorhinolaryngol. 2008; 265(1):119–22. Epub 2007/07/25. doi: 10.1007/s00405-007-0397-7 PMID: 17647006.

12. Penarrocha M, Garcia A. Benign paroxysmal positional vertigo as a complication of interventions with osteotome and mallet. Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons. 2006; 64(8):1324; author reply Epub 2006/07/25. doi: 10.1016/j.joms.2006.02.024 PMID: 16860237.

13. Saker M, Ogle O. Benign paroxysmal positional vertigo subsequent to sinus lift via closed technique. Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons. 2005; 63(9):1385–7. Epub 2005/08/27. doi: 10.1016/j.joms.2005.05.296 PMID: 16122608.

14. Penarrocha M, Perez H, Garcia A, Guarinos J. Benign paroxysmal positional vertigo as a complication of osteotome expansion of the maxillary alveolar ridge. Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons. 2001; 59(1):106–7. Epub 2001/01/11. doi: 10.1053/joms.2001.19307 PMID: 11152180.

15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987; 40(5):373–83. Epub 1987/01/01. PMID: 3558716.

16. Cohen HS, Kimball KT, Stewart MG. Benign paroxysmal positional vertigo and comorbid conditions. ORL J Otorhinolaryngol Relat Spec. 2004; 66(1):11–5. Epub 2004/04/23. doi: 10.1159/000077227 PMID: 15103195.

17. Vibert D, Redfield RC, Hausler R. Benign paroxysmal positional vertigo in mountain bikers. Ann Otol Rhinol Laryngol. 2007; 116(12):887–90. Epub 2008/01/26. PMID: 18217506.

18. Amir I, Young E, Belloso A. Self-limiting benign paroxysmal positional vertigo following use of whole-body vibration training plate. J Laryngol Otol. 2010; 124(7):796–8. Epub 2009/12/17. doi: 10.1017/S0022215109992441 PMID: 20003605.

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REVIEW

Vestibular migraine: the most frequent entity of episodic vertigo

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Abstract Vestibular migraine (VM) is the most common cause of episodic vertigo in adults as well as in children. The diagnostic criteria of the consensus document of the International Bárány Society for Neuro-Otology and the International Headache Society (2012) combine the typical signs and symptoms of migraine with the vestibular symptoms lasting 5 min to 72 h and exclusion criteria. Although VM accounts for 7 % of patients seen in dizziness clinics and 9 % of patients seen in headache clinics it is still underdiagnosed. This review provides an actual overview on the pathophysiology, the clinical characteristics to establish the diagnosis, the differential diagnosis, and the treatment of VM.

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Introduction

Symptoms of vertigo and headache are frequently observed by clinical neurologists. Since 1984 several studies have investigated the association of vestibular symptoms and migraine in adults [1–7]. Various terms have been used to describe this combination including migraine-associated vertigo, migraine-associated dizziness, migraine-related vestibulopathy, migrainous vertigo, and benign paroxysmal vertigo. To our knowledge, Dieterich and Brandt were the first to use the term 'vestibular migraine' (VM) [4]. VM is now the accepted name for vestibular symptoms that are causally related to migraine. The International Headache Society and the International Bárány Society for Neurootology have developed a consensus document with diagnostic criteria for VM [8]. This diagnosis was included in the appendix of the new international classification of headache disorders (ICHD)-3 beta version of headache classification as an emerging entity needing further research [9].

Diagnostic criteria

The criteria for VM combine the typical signs and symptoms of migraine with the exclusion criteria of other disorders that also elicit vestibular signs (Table 1). As in migraine without aura, a diagnosis of VM mainly depends on the patient history, for so far there are no clinically useful biomarkers. The criteria of the consensus paper

Table 1 Vestibular migraine diagnostic criteria [8, 9]

A. At least five episodes fulfilling criteria C and D
B. A current or past history of migraine without aura or migraine with aura
C. Vestibular symptoms of moderate or severe intensity, lasting 5 min to 72 h
D. At least 50 % of episodes are associated with at least one of the following three migrainous features
Headache with at least two of the following four characteristics
Unilateral location
Pulsating quality
Moderate or severe intensity
Aggravation by routine physical activity
Photophobia and phonophobia
Visual aura
E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder

(Table 1) follow those established by Neuhauser and co-workers and validated during the last years for both 'VM' and 'probable VM' [5]. A positive predictive value of 85 % was found in a follow-up study conducted over 9 years [10]. The diagnosis described in the ICHD-3 beta version of the International Headache Society [9] closely approximates the criteria of migraine but requires that the vestibular symptoms last 5 min to 72 h for the diagnosis of VM.

Epidemiology and demographic factors

Case-controlled studies support the clinical association of migraine and vertigo revealing that migraine is more common in patients with vertigo than in age- and sex-matched controls [5, 11] and, also, that vertigo is more common in patients with migraine than in controls [1, 7, 12, 13].

Vestibular migraine is considered the most common cause of recurrent spontaneous vertigo attacks. It has a lifetime prevalence of about 1 % and a 1-year prevalence of 0.9 % in the general population [14] and accounts for about 7 % of patients seen in dizziness clinics and 9 % of patients seen in migraine clinics [5]. Nevertheless, it is still underdiagnosed. A recent study in a tertiary vertigo center found that the referring doctors had suspected only 1.8 % of the young patients to have VM, whereas a diagnosis was made in 20.2 % [15]. VM occurs 1.5 to 5 times more often in women than in men [3–5]. It has been proposed that VM has a genetic cause, namely an autosomal dominant pattern of inheritance with decreased penetrance in men [16].

While VM can develop at any age [2–4], it generally affects persons with a long-established history of migraine [4, 5]. It is diagnosed with an average delay of 8.4 years after the first onset of migraine [17]. The migraine attacks can be replaced by isolated vertigo attacks in post-menopausal women [18].

Epidemiological data confirm that migraine-related syndromes are also the most common cause of vertigo and dizziness in children [19, 20]. If the vertigo attacks in childhood take a monosymptomatic course without headache, they are called "benign paroxysmal vertigo in childhood". The latter represents VM with aura but without headache. VM is with 39 % the most frequent form of vertigo in children followed by psychogenic/functional dizziness in 21 % [19]. The pediatric migraine variant of "benign paroxysmal vertigo in childhood" is characterized by brief attacks of vertigo associated with nystagmus that begin between the first and fourth year of life, last only seconds to minutes, and disappear spontaneously within a few years. It is benign and treatable. There are frequent transitions to other forms of migraine with and without aura.

Clinical characteristics

Symptoms

Spontaneous vertigo has been reported to occur in 21–83 % [2–4], positional vertigo and dizziness in 17–65 % [1, 4, 21], and head motion intolerance in 31–77 % of patients with VM [2, 3]. In a large population study based on telephone interviews, 67 % of the participants with VM reported spontaneous rotational vertigo, whereas 24 % had positional vertigo [14]. Vertigo has also been induced by moving visual objects [22]. In addition, in a study in a headache clinic the most common additional symptoms were unsteadiness (91 %), balance problems (82 %), and vertigo (57 %) [23]; these are vestibular symptoms that do not fulfill the diagnostic criteria of the International Bárány Society for VM [24].

Attack duration can vary from seconds to days [4, 5, 21]; however, the diagnostic criteria for VM require a 5-min minimum. Attacks lasting 5 to 60 min and fulfilling typical aura criteria were found in only 10–30 % of VM patients [4, 5], i.e., most patients did not meet the IHC criteria. An association of vestibular symptoms and headache is frequently seen, but it varies from patient to patient and from attack to attack, even in the same patient. Vertigo can precede or occur during or after headache [3, 5]. While less than 50 % have both symptoms in every attack, about 6 % report isolated vertigo attacks that alternate with migrainous headache symptoms [5]. Along with vertigo, patients may mention photophobia, phonophobia, osmophobia, visual and other auras that are relevant for a confirmation of the diagnosis. Auditory symptoms like hearing

disturbances, tinnitus, and aural pressure have been found in 38 % of patients, but hearing is usually only mildly and transiently affected [1, 3, 21, 25].

Clinical examination in the symptom-free interval

If a neurological examination is performed between the episodes, in the symptom-free interval, the findings are generally normal. However, central vestibular ocular motor abnormalities occur in 8.6 to 66 % of the patients [1–4, 26, 27] including gaze-induced nystagmus, saccadic pursuit, central positional nystagmus, dysmetric or slow saccades [4, 28]. A recent study showed that interictal ocular motor abnormalities increase over time, occurring in 16 to 41 % of patients during a follow-up of 5.5 to 11 years. The most frequent abnormality was central positional nystagmus [28].

Unilateral peripheral vestibular signs such as canal paresis have been reported in 8 to 22 % [1–4, 26, 27] and bilateral vestibular failure in up to 11 % [1, 3, 26]. Mild cochlear loss involving low frequencies has been documented in 3 to 12 % [1, 3, 29] and mild bilateral sensorineural hearing loss in 18 % in a follow-up study conducted over 9 years as a mean [28].

During the acute attack more patients (70 %) developed pathological nystagmus with either spontaneous or positional nystagmus [30]. Such findings made during the acute attack represent signs of a central vestibular dysfunction in 50 % and of a peripheral vestibular dysfunction in 15 %; the site of involvement was unclear in 35 %. Hearing was not affected in these patients [30].

Neurophysiological testing

Vestibular migraine is a clinical diagnosis. Laboratory tests such as posturography, measurements of vestibular evoked myogenic potentials (VEMPs) and subjective visual vertical (SVV) have been used in different studies, but the results have been inconsistent. An increased postural sway was documented by posturography [26, 27]. Some studies reported that VEMPs were absent, delayed [31–33], or reduced in amplitude [31, 34, 35]. In contrast, other studies revealed symmetrical VEMPs with normal latencies and amplitudes [36, 37]. The measurements of SVV did not differ from those recorded in healthy controls [38].

Pathophysiology

The mechanisms underlying vestibular dysfunction that are related to migraine still need further study and clarification. One explanation proposed is a parallel activation of vestibular and cranial nociceptive pathways [39–42]. Experimental studies have demonstrated that trigeminal and vestibular ganglion cells share neurochemical properties and express serotonin, capsaicin, and purinergic receptors [39, 43]. Nociceptive and vestibular afferents with neurochemical similarities converge in brainstem structures like the parabrachial nucleus, the raphe nuclei, and the locus coeruleus. All of these structures play an important role in modulating the sensitivity of pain pathways. They are also involved in the formation of anxiety responses, thus explaining some aspects of the comorbidity of balance disorders, anxiety, and migraine [41].

The cortical regions activated by vestibular stimulation in human functional imaging studies include those also involved in pain perception, for example, the posterior and anterior insula, the orbitofrontal cortex, and the cingulate gyrus [44–46]. A recent functional imaging study of two VM patients reported that the metabolism of the temporo-parietal-insular areas and bilateral thalami increased during the attack [45]. The cause was ascribed to increased activation of the vestibulo-thalamo-cortical pathways. Additional bilateral cerebellar activation was thought to be due to an adaptive process that suppresses the hyperactive vestibular system. A concurrent decrease in metabolism in the occipital cortex [47] was interpreted to represent the well-known reciprocal inhibition that occurs between the visual and vestibular systems [48]. A reciprocal inhibition of sensory cortex areas is typically involved in the intact sensory interaction occurring during vestibular stimulation [44, 48]. In an fMRI study of 12 right-handed VM patients during cold caloric stimulation a typical pattern of BOLD signal changes in temporo-parietal areas was found in the interictal interval as well as in patients with migraine without aura and in healthy controls [49]. In comparison to both control groups VM patients showed a significantly increased thalamic activation, the magnitude of which was positively correlated with the frequency of VM attacks. An increase of activity in the bilateral ventral-anterior thalamus was also seen in the FDG-PET during the VM attack compared to healthy controls at rest (personal communication, Fig. 1). Thus, the bilateral thalamus seems to play an important role in VM.

A voxel-based morphometric MRI study revealed that gray matter volume was reduced in areas associated with pain and visual and vestibular processing, i.e., in the superior, inferior and middle temporal gyri and in the mid cingulate, dorsolateral prefrontal, insula, parietal and occipital cortices. These areas possibly represent the pathoanatomic connection between the pain and the vestibular systems in migraine [50]. Thus, all these findings of the imaging studies indicate that there is a strong overlap of the vestibular and pain pathways at brainstem, thalamic, and cortical levels.

Reciprocal connections between the trigeminal and vestibular nuclei were identified in the one human study

that has been performed [51]. It showed that trigeminal activation produced nystagmus in patients with migraine but not in healthy controls. This was attributed to a lowered threshold for signal transmission between the two systems. Various studies have discussed this feature, which indicates an increased vestibular excitability (hyperexcitability). Such an increase can include increased motion sensitivity, even motion sickness [52]; decreased suppression of the otoacoustic emissions [53]; and reduced perceptual thresholds of dynamic head movements [54]. The mechanisms underlying these changes still remain unclear.

Apart from central mechanisms an inner ear involvement may explain some cochlear and peripheral vestibular findings recorded in certain patients. Trigeminovascular reflex-mediated vasodilatation of cranial blood vessels and subsequently plasma extravasation causing meningeal inflammation are the key features of pain in migraine [55]. The trigeminovascular system also innervates the inner ear [56]. In line with this hypothesis, Koo and Balaban demonstrated a protein extravasation in the inner ear and meningeal tissues in a murine migraine model [57].

Similarities with other paroxysmal disorders that often present with both migraine and vertigo, for example, familial hemiplegic migraine and episodic ataxia type 2, have been reported to be associated with mutations in the calcium channel gene CACNA1A [58], and defects of the ion channels have also been discussed to play a role in VM [4]. So far, however, it has not been possible to identify a genetic defect in the same region [59, 60].

In summary, migraine-related vestibular disorders like VM may be caused by enhanced excitability occurring during the processing of sensory information, which is due to a genetic susceptibility. The enhanced excitation induces interactions of vestibular and pain pathways on several levels, from the inner ear to the thalamus and cortical level.

Differential diagnosis/comorbidity

Ménière's disease is the main differential diagnosis. At an early stage of the disease it may be difficult to differentiate Ménière's disease from VM if aural symptoms are absent in Ménière's disease. Even with the presence of aural symptoms it may be difficult since auditory symptoms like hearing disturbances, tinnitus, and aural pressure have also been found in 38 % of VM patients [1, 3, 21, 25]. To complicate matters, several studies have pointed to a link between Ménière's disease and VM. The prevalence of migraine in patients with Ménière's disease is reported to be twice as high as in healthy subjects, and the most reliable differentiating feature is the low-frequency hearing loss in Ménière's disease [61]. A retrospective study showed that 13 % of patients fulfilled the criteria for both disorders, thus making the differential diagnosis even more complicated [25]. Indeed, an inner ear MR imaging study applying gadolinium-based contrast agent transtympanically showed an cochlear and vestibular endolymphatic hydrops in four of 19 VM patients (21 %) who presented

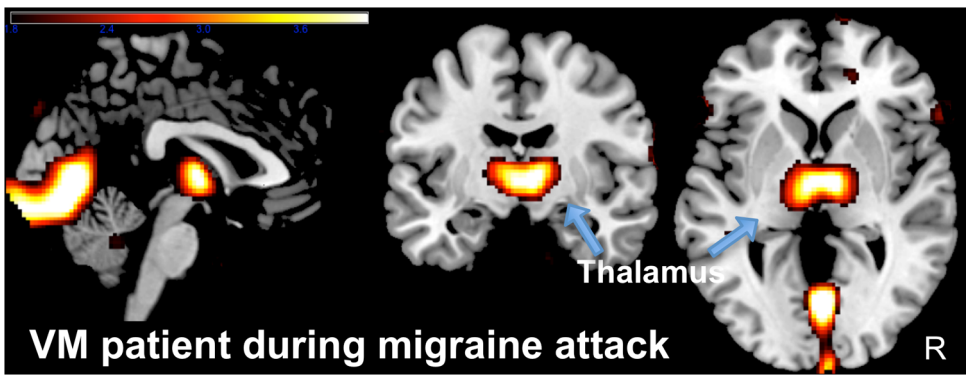

Fig. 1 To analyze the cerebral blood glucose utilization during an actual VM attack a FDG-PET was performed in a 35-year-old patient suffering from VM according to the consensus criteria [8, 9] (ECAT Exact PET Scanner, Siemens/CTI, Knoxville, USA, with a 18F-fluorodeoxyglucose [FDG]-tracer in a three-dimensional acquisition mode). During the attack the patient presented with a central positional nystagmus beating oblique (up- and leftward) and increasing in different head/body positions (supine, left ear down, right ear down). Both, nystagmus and vertiginous sensation, persisted for 72 h and resolved spontaneously without any ongoing vestibular or ocular motor dysfunction. In addition, a structural T_1-weighted MRI (MPRAGE sequence, 180 slices, slice thickness = 1 mm, image matrix = 256^2, TR = 9.7 ms, TE = 4 ms) was acquired in a clinical 1.5 T scanner (Siemens Vision, Erlangen, Germany). The PET image was spatially normalised using the structural MRI data and a proportional scaling was performed to adjust for differences in tracer dosage and uptake time. A two-sample t test was computed with respect to a healthy, age-matched reference sample ($n = 12$) acquired on the same scanner under identical conditions (supine, eyes closed). During the attack the patient showed an increased cerebral glucose metabolism bilaterally in the ventral-anterior thalamus compared to healthy volunteers at rest ($p < 0.001$ uncorrected). The thalamic response was localized to the prefrontal thalamic projection zone [87]. The scale reflects the z score (personal communication: C. Best, Marburg, and P. zu Eulenburg, Mainz, Germany)

with auditory symptoms [62]. This can either be explained by a coincidence of Ménière's disease and VM or by the hypothesis that the hydrops is the consequence of a inner ear damage due to VM. Ménière's disease and VM have also been considered part of a broad spectrum of disorders having a possible common genetic basis [63].

Benign paroxysmal positional vertigo (BPPV), for example, must also be considered in the differential diagnosis in those patients presenting with positional vertigo attacks, because BPPV is also commonly associated with migraine [64, 65].

Anxiety is a common comorbidity of migraine [66] and is frequently associated with vestibular disorders, especially with VM [67]. To define this association a new disorder named MARD (migraine–anxiety-related dizziness) has been proposed [68].

Treatment

Only a few randomized controlled clinical studies have been conducted on the specific treatment of VM: during the attack or as prophylaxis. Two of these studies addressed the use of triptans for *attack therapy* [69, 70]. One study showed that 38 % of patients with VM attacks (3 of 8 episodes) benefitted from 5 mg zolmitriptan, whereas only 22 % in the placebo group (2 of 9 episodes) showed a positive effect. Unfortunately, the validity of this study is limited due to its large confidence intervals and the small number of patients ($n = 10$), who reported only 17 attacks [69]. The other double-blind, randomized, placebo-controlled study with rizatriptan vs. placebo measured how motion sickness responded to a complex vestibular stimulus. Twenty-five migraineurs with or without migraine-related dizziness participated (23 females; aged 21–45 years, 31.0 ± 7.8 years). Thirteen of the 15 subjects who experienced vestibular-induced motion sickness showed a decrease in motion sickness after taking rizatriptan compared to placebo ($p < 0.02$). However, this positive effect was not observed after exposure to more provocative vestibular stimuli. It was suggested that rizatriptan reduces vestibular-induced motion sickness by influencing serotonergic vestibular-autonomic projections [70].

Prophylactic treatment was analyzed recently in The Cochrane Collaboration [71] for randomized controlled trials in adults with the diagnosis of VM or probable VM according to the Bárány Society/International Headache Society criteria. Only 1 out of 558 studies could be identified which was based on the new criteria for VM and had adequate study conditions. This study comparing metoprolol and placebo is still ongoing [72]. Since none of the available studies to date are adequate, most therapeutic recommendations for the prophylactic treatment of VM are nowadays based on the therapy guidelines for migraine with and without aura. Therapeutic approaches that refer specifically to VM are found in case reports, retrospective cohort studies, and open-label trials.

A large retrospective cohort evaluation of 100 patients (median age 47 years, range 21–72 years) compared VM patients with and without prophylactic migraine treatment [73]. All patients on prophylactic treatment showed a decrease of duration, intensity, and frequency of episodic vertigo as well as its associated features ($p < 0.01$). The drugs taken were metoprolol (49 patients, 69 %; median dose 150 mg) or propranolol (31 %; median dose 160 mg), valproic acid (6 patients, 8 %; median dose 600 mg), topiramate (6 patients, 8 %; median dose 50 mg), butterbur extract (4 patients, 5 %; median dose 50 mg), lamotrigine (3 patients, 4 %; median dose 75 mg), amitriptyline (2 patients; 100 mg and 75 mg), flunarizine (1 patient; 5 mg), or magnesium (3 patients; median dose 400 mg). The group not receiving prophylactic therapy but instead following a modified lifestyle showed a reduction of only vertigo intensity [73]. Another retrospective study that included 100 patients with migraine-associated dizziness also reported a positive effect of migraine prophylaxis [74]. A third retrospective cohort included 33 patients with recurrent vertiginous attacks and migraine [75]: the attack frequency was completely reduced in 19 patients (57.6 %), reduced by over 50 % in 8 (24.2 %), and reduced by less than 50 % in 5 (15.2 %); there was no reduction in one patient. In this study 12 patients took propranolol, 11 received clonazepam, seven flunarizine, two metoprolol, and another two patients amitriptyline [75].

Smaller cohorts have reported on the effects of single drugs for migraine prophylaxis. *Sodium valproate* did not relieve the vestibular symptoms in a group of 12 patients with VM, but had a considerable effect on migraine headache in eight [76]. In this group the horizontal vestibulo-ocular reflex (VOR) was evaluated with the sinusoidal harmonic acceleration test at 0.01, 0.02, 0.04, 0.08, and 0.16 Hz using a computerized rotatory chair system. No abnormalities were found in VOR gain, phase, or asymmetry for any frequency. These normal VOR measurements contrasted with the repeated complaints by seven patients (58 %) of vertigo, dizziness, and unsteadiness, which valproate treatment did not improve [76].

Cinnarizine was tested in a retrospective, single-center, open-label investigation on VM and migraine associated with vertigo [77]. The study included 24 patients with VM (23 women, 1 man) and 16 patients with basilar-type migraine (12 women, 4 men). The patients' ages ranged from 18 to 54 years (mean 30 years). The mean frequency of vertigo and also the mean frequency, duration, and intensity of migraine headaches per month were significantly reduced after 3 months of cinnarizine therapy (all $p < 0.001$) [77].

This interesting data will have to be reconfirmed in a large-scale, randomized, controlled clinical trial.

Flunarizine was tested for the treatment of migraine without aura and the treatment of vertigo in two large open-label post-marketing studies [78, 79]. In both conditions flunarizine showed considerable efficacy compared to propranolol for migraine headache or betahistine for vertigo. However, both studies did not specifically include patients with VM and thus the efficacy of flunarizine for this condition remains unproven. The only randomized controlled trial of one tertiary academic center compared the effects of flunarizine in 48 VM patients over 12 weeks with those receiving 16 mg betahistine and vestibular exercises [80]. The flunarizine treatment decreased the frequency of vertiginous episodes ($p = 0.010$), and the severity of vertigo improved ($p = 0.046$). However, frequency and severity of headache were not significantly different in the two treatment groups. Side effects of flunarizine were weight gain and somnolence [80]. A retrospective chart study evaluated the effects of flunarizine and propranolol in another 61 patients with VM. Flunarizine patients ($n = 30$) showed a 68 % responder rate for VM symptoms ($p < 0.001$), while patients on propranolol ($n = 31$) had an improvement rate of 73 % ($p < 0.001$) [81].

One trial reported successfully treating migraine auras, isolated auras, and to a lesser extent migraine-associated headaches with *lamotrigine* [82]. Another retrospective, open-label study demonstrated moderate efficacy of 100 mg lamotrigine in 19 VM patients (13 women, 6 men) over 3–4 months [83]. Vertigo frequency was reduced from 18.1 to 5.4 (average per month), headache frequency decreased from 8.7 to 4.4, but this was not statistically significant. Consequently, lamotrigine may primarily reduce vestibular symptoms but headache only to a less extent [83]. Lamotrigine was also reported useful in three patients with basilar-type migraine over 5 years [84].

An interesting study investigated the combination of effects resulting from the abstinence from *caffeine* and treatment with topiramate and nortriptyline in 34 VM patients [85]. The symptoms were improved in 14 % of the patients who had abstained from caffeine. In comparison, topiramate reduced symptoms in 25 % of patients and nortriptyline reduced dizziness in 46 % of the patients ($p = 0.007$). Thus, 75 % of VM patients had a measurable and meaningful benefit from these therapeutic interventions; consequently they did not switch to other treatments [85].

Less established medications in migraine treatment such as benzodiazepines, selective serotonin reuptake inhibitors (SSRI), pizotifen, dothiepin, acetazolamide, and behavioral modification including special diets were reported to have positive effects on VM [75]. However, a clear therapeutic recommendation for the specific treatment of VM cannot be easily drawn from these data. Moreover, it must be taken into account that inconsistent definitions of VM were used in many of these studies especially in the older ones, so that the examined cohorts were quite heterogeneous. The new diagnostic criteria will eliminate this obvious shortcoming in the future and lead to more comparable, better quality studies.

Vestibular rehabilitation training proved effective in VM patients as add-on treatment to medical therapy or as a stand-alone treatment option [86]. Thirty-six patients (VM = 20, vestibular impairment = 16) with daily vestibular symptoms participated in a 9-week vestibular rehabilitation program. Each patient attended five therapy sessions over 6 months. While the VM group demonstrated poorer subjective performance at therapy onset, both groups benefitted equally from rehabilitation. The same degree of improvement was observed in the migraine group regardless of the medication regime. Thus, vestibular rehabilitation training may be effective in VM regardless of the medical prophylactic therapy used [86]. This agrees with the well-known positive effect of physical activity on the reduction of migraine attack frequency. However, a study with a controlled design is still needed for VM.

The *future perspectives* of both clinical and basic science studies investigating the pathophysiological mechanisms of VM are promising. Understanding the neurochemical organization of the vestibular, nociceptive, and cognitive pathways and their interactions will provide realistic strategies for treatment of the disorder. Further research is needed to clarify the probable genetic mechanisms leading to greater susceptibility. Multicenter randomized controlled treatment trials based on pathophysiology must now be designed on the basis of the recently established diagnostic criteria.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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References

1. Kayan A, Hood JD (1984) Neuro-otological manifestations of migraine. Brain 107:1123–1142
2. Cutrer FM, Baloh RW (1992) Migraine-associated dizziness. Headache 32:300–304

3. Cass SP, Furman JM, Ankerstjerne K, Balaban C, Yetişer S, Aydogan B (1997) Migraine-related vestibulopathy. Ann Otol Rhinol Laryngol 106:182–189
4. Dieterich M, Brandt T (1999) Episodic vertigo related to migraine. J Neurol 246:883–892
5. Neuhauser H, Leopold M, von Brevern M, Arnold G, Lempert T (2001) The interrelations of migraine, vertigo and migrainous vertigo. Neurology 56:436–441
6. Reploeg MD, Goebel JA (2002) Migraine-associated dizziness: patient characteristics and management options. Otol Neurotol 23:364–371
7. Vukovic V, Plavec D, Galinovic I, Lovrencić-Huzjan A, Budisić M, Demarin V (2007) Prevalence of vertigo, dizziness, and migrainous vertigo in patients with migraine. Headache 47:1427–1435
8. Lempert T, Olesen J, Furman J, Waterston J, Seemungal B, Carey J, Bisdorff A, Versino M, Evers S, Newman-Toker D (2012) Vestibular migraine: diagnostic criteria. J Vest Res 22:167–172
9. International Headache Society Classification Subcommittee (2013) The international classification of headache disorders. 3rd edition (beta version). Cephalalgia 33:629–808
10. Radtke A, Neuhauser H, von Brevern M, Hottenrott T, Lempert T (2011) Vestibular migraine-validity of clinical diagnostic criteria. Cephalalgia 31:906–913
11. Lee H, Sohn SI, Jung DK, Cho YW, Lim JG, Yi SD, Yi HA (2002) Migraine and isolated recurrent vertigo of unknown cause. Neurol Res 24:663–665
12. Kuritzky A, Ziegler DK, Hassanein R (1981) Vertigo, motion sickness and migraine. Headache 21:227–231
13. Akdal G, Ozge A, Ergör G (2013) The prevalence of vestibular symptoms in migraine or tension-type headache. J Vestib Res 23:101–106
14. Neuhauser HK, Radtke A, von Brevern M, Feldmann M, Lezius F, Ziese T, Lempert T (2006) Migrainous vertigo: prevalence and impact on quality of life. Neurology 67:1028–1033
15. Geser R, Straumann D (2012) Referral and final diagnoses of patients assessed in an academic vertigo center. Front Neurol 3:Article 169
16. Oh AK, Lee H, Jen JC, Corona S, Jacobson KM, Baloh RW (2001) Familial benign recurrent vertigo. Am J Med Genet 100:287–291
17. Thakar A, Anjaneyulu C, Deka RC (2001) Vertigo syndromes and mechanisms in migraine. J Laryngol Otol 115:782–787
18. Lempert T, Neuhauser H, Daroff RB (2009) Vertigo as a symptom of migraine. Ann N Y Acad Sci 1164:242–251
19. Batu ED, Anlar B, Topcu M, Turanli G (2015) Vertigo in childhood: a retrospective series of 100 children. Eur J Paed Neurol 19:226–232
20. Jahn K, Langhagen T, Heinen F (2015) Vertigo and dizziness in children. Curr Opin Neurol 28:78–82
21. Johnson GD (1998) Medical management of migraine-related dizziness and vertigo. Laryngoscope 108:1–28
22. Waterston J (2004) Chronic migrainous vertigo. J Clin Neurosci 11:384–388
23. Cohen JM, Bigal ME, Newman LC (2011) Migraine and vestibular symptoms—identifying clinical features that predict "vestibular migraine". Headache 51:1393–1397
24. Bisdorff A, Von Brevern M, Lempert T, Newman Toker DE (2009) Classification of vestibular symptoms: towards an international classification of vestibular disorders. J Vest Res 19:1–13
25. Neff BA, Staab JP, Eggers SD, Carlson ML, Schmitt WR, Van Abel KM, Worthington DK, Beatty CW, Driscoll CL, Shepard NT (2012) Auditory and vestibular symptoms and chronic subjective dizziness in patients with Ménière's disease, vestibular migraine, and Ménière's disease with concomitant vestibular migraine. Otol Neurotol 33:1235–1244
26. Teggi R, Colombo B, Bernasconi L, Bellini C, Comi G, Bussi M (2009) Migrainous vertigo: results of caloric testing and stabilometric findings. Headache 49:435–444
27. Celebisoy N, Gökçay F, Sirin H, Biçak N (2008) Migrainous vertigo: clinical, oculographic and posturographic findings. Cephalalgia 28:72–77
28. Radtke A, von Brevern M, Neuhauser H, Hottenrott T, Lempert T (2012) Vestibular migraine: long-term follow-up of clinical symptoms and vestibulo-cochlear findings. Neurology 79:1607–1614
29. Battista RA (2004) Audiometric findings of patients with migraine-associated dizziness. Otol Neurotol 25:987–992
30. von Brevern M, Zeise D, Neuhauser H, Clarke AH, Lempert T (2005) Acute migrainous vertigo: clinical and oculographic findings. Brain 128:365–374
31. Baier B, Stieber N, Dieterich M (2009) Vestibular-evoked myogenic potentials in vestibular migraine. J Neurol 256:1447–1454
32. Boldingh MI, Ljøstad U, Mygland A, Monstad P (2011) Vestibular sensitivity in vestibular migraine: vEMPs and motion sickness susceptibility. Cephalalgia 31:1211–1219
33. Hong SM, Park DC, Yeo SC, Cha CI (2008) Vestibular evoked myogenic potentials with benign paroxysmal positional vertigo involving each semicircular canal. Am J Otolaryngol 29:184–187
34. Roceanu A, Allena M, De Pasqua V, Bisdorff A, Schoenen J (2008) Abnormalities of the vestibulo-collic reflex are similar in migraineurs with and without vertigo. Cephalalgia 28:988–990
35. Murofushi T, Ozeki H, Inoue A, Sakata A (2009) Does migraine-associated vertigo share a common pathophysiology with Meniere's disease? Study with vestibular-evoked myogenic potential. Cephalalgia 29:1259–1266
36. Taylor RL, Zagami AS, Gibson WP, Black DA, Watson SR, Halmagyi MG, Welgampola MS (2012) Vestibular evoked myogenic potentials to sound and vibration: characteristics in vestibular migraine that enable separation from Meniere's disease. Cephalalgia 32:213–225
37. Kandemir A, Çelebisoy N, Köse T (2013) Cervical vestibular evoked myogenic potentials in primary headache disorders. Clin Neurophysiol 124:779–784
38. Kandemir A, Çelebisoy N, Köse T (2014) Perception of verticality in patients with primary headache disorders. Int Adv Otol 10:138–143
39. Balaban CD (2011) Migraine, vertigo and migrainous vertigo: links between vestibular and pain mechanisms. J Vestib Res 21:315–321
40. Furman JM, Balaban CD (2015) Vestibular migraine. Ann NY Acad Sci 1343:90–96
41. Balaban CD, Jacob RG, Furman JM (2011) Neurologic bases for comorbidity of balance disorders, anxiety disorders and migraine: neurotherapeutic implications. Expert Rev Neurother 11:379–394
42. Furman JM, Marcus DA, Balaban CD (2013) Vestibular migraine: clinical aspects and pathophysiology. Lancet Neurol 12:706–715
43. Ahn SK, Balaban CD (2010) Distribution of 5-HT1B and 5-HT1D receptors in the inner ear. Brain Res 1346:92–101
44. Dieterich M, Brandt T (2008) Functional brain imaging of peripheral and central vestibular disorders. Brain 131:2538–2552
45. Fasold O, von Brevern M, Kuhberg M, Ploner CJ, Villringer A, Lempert T, Wenzel R (2002) Human vestibular cortex as identified with caloric stimulation in functional magnetic resonance imaging. Neuroimage 17:1384–1393
46. Bucher SF, Dieterich M, Wiesmann M, Weiss A, Zink R, Yousry TA, Brandt T (1998) Cerebral functional magnetic resonance imaging of vestibular, auditory, and nociceptive areas during galvanic stimulation. Ann Neurol 44:120–125

47. Shin JH, Kim YK, Kim HJ, Kim JS (2014) Altered brain metabolism in vestibular migraine: comparison of interictal and ictal findings. Cephalalgia 34:58–67
48. Brandt T, Bartenstein P, Janek A, Dieterich M (1998) Reciprocal inhibitory visual-vestibular interaction: visual motion stimulation deactivates the parieto-insular vestibular cortex. Brain 121:1749–1758
49. Russo A, Marcelli V, Esposito F, Corvino V, Marcuccio L, Giannone A, Conforti R, Marciano E, Tedeschi G, Tessitore A (2014) Abnormal thalamic function in patients with vestibular migraine. Neurology 82:2120–2126
50. Obermann M, Wurthmann S, Steinberg BS, Theysohn N, Diener HC, Naegel S (2014) Central vestibular system modulation in vestibular migraine. Cephalalgia 34:1053–1061
51. Marano E, Marcelli V, Di Stasio E, Bonuso S, Vacca G, Manganelli F, Marciano E, Perretti A (2005) Trigeminal stimulation elicits a peripheral vestibular imbalance in migraine patients. Headache 45:325–331
52. Lewis RF, Priesol AJ, Nicoucar K, Lim K, Merfeld DM (2011) Abnormal motion perception in vestibular migraine. Laryngoscope 121:1124–1125
53. Murdin L, Premachandra P, Davies R (2010) Sensory dysmodulation in vestibular migraine: an otoacoustic emission suppression study. Laryngoscope 120:1632–1636
54. Lewis RF, Priesol AJ, Nicoucar K, Lim K, Merfeld DM (2011) Dynamic tilt thresholds are reduced in vestibular migraine. J Vestib Res 21:323–330
55. Moskowitz MA (2007) Pathophysiology of headache-past and present. Headache 47:58–63
56. Vass Z, Shore SE, Nuttall AL, Miller JM (1998) Direct evidence of trigeminal innervation of the cochlear blood vessels. Neuroscience 84:559–567
57. Koo JW, Balaban CD (2006) Serotonin-induced plasma extravasation in the murine inner ear: possible mechanism of migraine-associated inner ear dysfunction. Cephalalgia 26:1310–1319
58. Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, Lamerdin JE, Mohrenweiser HW, Bulman DE, Ferrari M, Haan J, Lindhout D, van Ommen GJ, Hofker MH, Ferrari MD, Frants RR (1996) Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca^{2+} channel gene CACNL1A4. Cell 87:543–552
59. Kim JS, Yue Q, Jen JC, Nelson SF, Baloh RW (1998) Familial migraine with vertigo: no mutations found in CACNA1A. Am J Med Genet 79:148–151
60. von Brevern M, Ta N, Shankar A, Wiste A, Siegel A, Radtke A, Sander T, Escayg A (2006) Migrainous vertigo: mutation analysis of the candidate genes CACNA1A, ATP1A2, SCN1A, and CACNB4. Headache 46:1136–1141
61. Radtke A, Lempert T, Gresty MA, Brookes GB, Bronstein AM, Neuhauser H (2002) Migraine and Ménière's disease: is there a link? Neurology 59:1700–1704
62. Gürkov R, Kantner C, Strupp M, Flatz W, Krause E, Ertl-Wagner B (2014) Endolymphatic hydrops in patients with vestibular migraine and auditory symptoms. Eur Arch Otorhinolaryngol 271:2661–2667
63. Cha YH, Kane MJ, Baloh RW (2008) Familial clustering of migraine, episodic vertigo, and Ménière's disease. Otol Neurotol 29:93–96
64. Ishiyama A, Jacobson KM, Baloh RW (2000) Migraine and benign positional vertigo. Ann Otol Rhinol Laryngol 109:377–380
65. Lempert T, Leopold M, von Brevern M, Neuhauser H (2000) Migraine and benign positional vertigo. Ann Otol Rhinol Laryngol 109:1176
66. Smitherman TA, Kolivas ED, Bailey JR (2013) Panic disorder and migraine: comorbidity, mechanisms, and clinical implications. Headache 53:23–45
67. Eckhardt-Henn A, Best C, Bense S, Breuer P, Diener G, Tschan R, Dieterich M (2008) Psychiatric comorbidity in different organic vertigo syndromes. J Neurol 255:420–428
68. Furman JM, Balaban CD, Jacob RG, Marcus DA (2005) Migraine-anxiety related dizziness (MARD): a new disorder? J Neurol Neurosurg Psychiatry 76:1–8
69. Neuhauser H, Radtke A, von Brevern M, Lempert T (2003) Zolmitriptan for treatment of migrainous vertigo: a pilot randomized placebo-controlled trial. Neurology 60:882–883
70. Furman JM, Marcus DA, Balaban CD (2011) Rizatriptan reduces vestibular-induced motion sickness in migraineurs. J Headache Pain 12:81–88
71. Maldonado FM, Birdi JS, Irving GJ, Murdin L, Kivekäs I, Strupp M (2015) Pharmacological agents for the prevention of vestibular migraine (Review). Cochrane Libr Issue 6:1–35
72. Strupp M (2008) Prophylactic treatment of vestibular migraine with metoprolol: a double-blind, placebo-controlled trial. https://www.controlled-trials.com/ISRCTN72824329-2009
73. Baier B, Winkenwerder E, Dieterich M (2009) "Vestibular migraine": effects of prophylactic therapy with various drugs. A retrospective study. J Neurol 256:436–442
74. Bikhazi P, Jackson C, Ruckenstein MJ (1997) Efficacy of antimigrainous therapy in the treatment of migraine-associated dizziness. Am J Otol 18:350–354
75. Maione A (2006) Migraine-related vertigo: diagnostic criteria and prophylactic treatment. Laryngoscope 116:1782–1786
76. Gordon CR, Kuritzky A, Doweck I, Spitzer O, Shupak A, Hering R (1993) Vestibulo-ocular reflex in migraine patients: the effect of sodium valproate. Headache 33:129–132
77. Taghdiri F, Togha M, Razeghi Jahromi S, Refaeian F (2014) Cinnarizine for the prophylaxis of migraine associated vertigo: a retrospective study. SpringerPlus 3:231
78. de Bock GH, Eelhart J, van Marwijk HW, Tromp TP, Springer MP (1997) A postmarketing study of flunarizine in migraine and vertigo. PWS 19:269–274
79. Verspeelt J, De Locht P, Amery WK (1996) Postmarketing study of the use of flunarizine in vestibular vertigo and in migraine. Eur J Clin Pharmacol 51:15–22
80. Lepcha A, Amalanathan S, Augustine AM, Tyagi AK, Balraj A (2014) Flunarizine in the prophylaxis of migrainous vertigo: a randomized controlled trial. Eur Arch Otorhinolaryngol 271:2931–2936
81. Van Ombergen A, Van Rompaey V, Van de Heyning P, Wuyts F (2015) Vestibular migraine in an otolaryngology clinic: prevalence, associated symptoms, and prophylactic medication effectiveness. Otol Neurotol 36(1):133–138
82. Lampl C, Katsarava Z, Diener H-C, Limmroth V (2005) Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura. J Neurol Neurosurg Psychiatry 76:1730–1732
83. Bisdorff AR (2004) Treatment of migraine related vertigo with lamotrigine, an observational study. Bull Soc Sci Med Grand Duche Luxemb 2:103–108
84. Cologno D, d'Onofrio F, Castriota O et al (2013) Basilar-type migraine patients responsive to lamotrigine: a 5-year follow-up. Neurol Sci 34(Suppl 1):S165–S166
85. Mikulec AA, Faraji F, Kinsella LJ (2012) Evaluation of the efficacy of caffeine cessation, nortriptyline, and topiramate therapy in vestibular migraine and complex dizziness of unknown etiology. Am J Otolaryngol 33:121–127
86. Vitkovic J, Winoto A, Rance G, Dowell R, Paine M (2013) Vestibular rehabilitation outcomes in patients with and without vestibular migraine. J Neurol 260:3039–3048
87. Behrens TE, Johansen-Berg H, Woolrich MW et al (2003) Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci 6(7):750–757

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Original Investigation

Development of a Statistical Model for the Prediction of Common Vestibular Diagnoses

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IMPORTANCE Treatment of patients with vestibular disorders can be complex, requires lengthy clinic visit time, and uses greater clinical resources for diagnosis. A pre-encounter intake questionnaire may predict the most common disorders, allowing for more efficient allocation of resources and use of clinicians.

OBJECTIVE To develop a statistical model for predicting vestibular diagnoses, prior to clinical evaluation, from an intake questionnaire.

DESIGN, SETTING, AND PARTICIPANTS Retrospective review of 414 consecutive new vestibular patient intake questionnaires (September 2012 through January 2014) and associated medical records with performance of logistic regression analyses and development of predictive models (July 2013 through May 2015).

INTERVENTIONS Use of a vestibular intake questionnaire for triaging of new patients with complaints of dizziness.

MAIN OUTCOMES AND MEASURES Predictors for the diagnosis of benign paroxysmal positional vertigo (BPPV), Ménière's disease, and vestibular migraine.

RESULTS Of the 414 questionnaires analyzed, 381 (92%) had clinician information necessary to define a final diagnosis. Patients were 34% male and had a mean (range) age of 57 (19-91) years. Of the diagnoses, 183 (48%) were ear related (including 103 BPPV and 49 Meniere's disease), 141 (37%) neurological (including 109 vestibular migraine), 36 (9%) medical, 8 (2%) of psychological origin, 46 (12%) of unknown etiology, and 33 (9%) other causes. The diagnosis of BPPV could be predicted from 4 variables with a sensitivity of 79% and specificity of 65%. The diagnosis of Ménière's disease could be predicted from 5 variables with a sensitivity of 81% and specificity of 85%. The diagnosis of vestibular migraine could be predicted from 4 variables with a sensitivity of 76% and specificity of 59%.

CONCLUSIONS AND RELEVANCE A pre-encounter history questionnaire can provide useful diagnostic information for common vestibular disorders. This can help direct appointment scheduling to improve clinical efficiency, time to intervention, and use of resources. Further refinement may enable the use of shorter questionnaires or screening algorithms.

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Dizziness is among the most common chief complaints among patients presenting to frontline clinicians.[1,2] Whereas dizziness is a symptom with many causes, evaluation by an otolaryngologist is commonly recommended. Treatment of patients with vestibular disorders is complex, requires additional clinic time, and uses greater resources (eg, videonystagmography [VNG], rotary chair). Many patients are found not to have otologic disease, leading to patient and clinician frustration and delays in diagnosis.

Patient history plays a critical role in the evaluation of vestibular complaints.[3,4] The nature of the dizziness (ie, vertigo, lightheadedness, imbalance), the temporal pattern of the dizziness (ie, single episode, recurrent), the duration of attacks (ie, seconds, hours), and associated symptoms (ie, hearing loss, headache) can identify otologic vs nonotologic disease, and even a specific diagnosis.[5] Physical examination may help establish a vestibular diagnosis but often has normal results. Similarly, vestibular testing may be useful in establishing a diagnosis but requires a narrow differential diagnosis for correct test selection and interpretation of test results.[3]

A questionnaire focusing on key elements of the history may provide adequate information for development of a narrow differential diagnosis prior to the office visit.[4,6] Our program began using a vestibular disorders intake questionnaire in September 2012. This 10-page questionnaire was designed as a quality improvement measure to provide more efficient and timely care to patients. The results of the questionnaire have been used to direct appointments (eg, to physician, vestibular therapist, nurse practitioner, neurologist) and to inform choice of testing (eg, VNG, rotary chair, posturography, vestibular evoked myogenic potentials [VEMPs]). Subjectively this appears to have improved clinical efficiency but places time burden on administrative and clinical staff to manage this system.

We performed data analyses of the triage questionnaire. This study used 414 consecutive patient questionnaires for descriptive analyses and predictive model building. Results of this study may be generalized to practice management for allocating resources and improving efficiency of patient evaluation.

Methods

Approval was obtained from the Medical College of Wisconsin institutional review board. Informed consent was waived due to the retrospective nature of this study. This project analyzes a clinically used intake questionnaire specifically designed to triage new patients with vestibular disorders.

Questionnaire

The questionnaire was developed at Mayo Clinic and was modified slightly before being implemented in our institution. A total of 162 data variables were captured from each questionnaire. The questionnaire captures demographic information including medical, family, and social history, and current medication use. There are sections that focus on:

1. The nature of the dizziness perception. This includes a series of check boxes to describe the dizziness, and questions as to the onset, duration, and frequency of spells (episodes), triggers for spells, and the relationship of spells to motion.
2. Headache, migraine, and migraine-associated symptoms.
3. Otologic problems including hearing loss, tinnitus, aural pressure, otalgia, and otorrhea.
4. Prior tests and results including audiograms, imaging, VEMPs, VNG, rotary chair, cardiac Holter monitors, tilt table testing, and so forth.

Predictive Model Development

The development of predictive models for the diagnosis of benign paroxysmal positional vertigo (BPPV), Ménière's disease, and vestibular migraine incorporated an initial data set for identifying key variables for further data collection and a large data set for predictive model building. The initial group consisted of 212 consecutive new patient intake questionnaires. All variables and fields were collected from these questionnaires for analysis. We initially tried to develop models using all available variables, but this resulted in complex algorithms with unsatisfactory sensitivity and specificity. By repetitively narrowing the data set, and checking for improvements in sensitivity and specificity, we identified a set of factors with strong correlation with specific diseases. A subsequent 202 consecutive questionnaires were then interrogated for this narrow set of variables. These variables from the combined 414 questionnaires were then analyzed to build the statistical models for diagnosis predictions.

Statistical Analysis

The initial data set was screened to identify variables using 3 criteria: (1) significant ($P < .05$) association with the 3 diagnoses, (2) sufficient number of observations (≥5 per cell after cross-tabulation with the outcome), and (3) clinical importance and relevance. All variables were converted into dichotomous form (ie, 0 = absent; 1 = present).

The final data set had information on 414 individuals, of which 381 were ultimately fully evaluable (see Results). Logistic regression analyses were performed to build parsimonious predictive models with model variables significant at $P < .05$. All 2-way interactions between significant model variables were investigated for statistical significance. A forward stepwise variable selection procedure was used. The 3 final parsimonious models included only variables significant at the $P < .02$ level, more stringent than the initially planned significance cutoff of .05. The receiver operating characteristic (ROC) curve, area under ROC curve, sensitivity, and specificity at selected cutoffs (ie, linear predictor [LP] values) were assessed using 10-fold cross-validation.

The statistical analysis was performed using the open-source software R, version 3.1.1 (http://www.r-project.org). Two-tailed Wald tests were used for statistical significance testing.

Results

Of the 414 questionnaires analyzed, 381 had clinical information necessary to define a final diagnosis (**Figure**). Of these, 183

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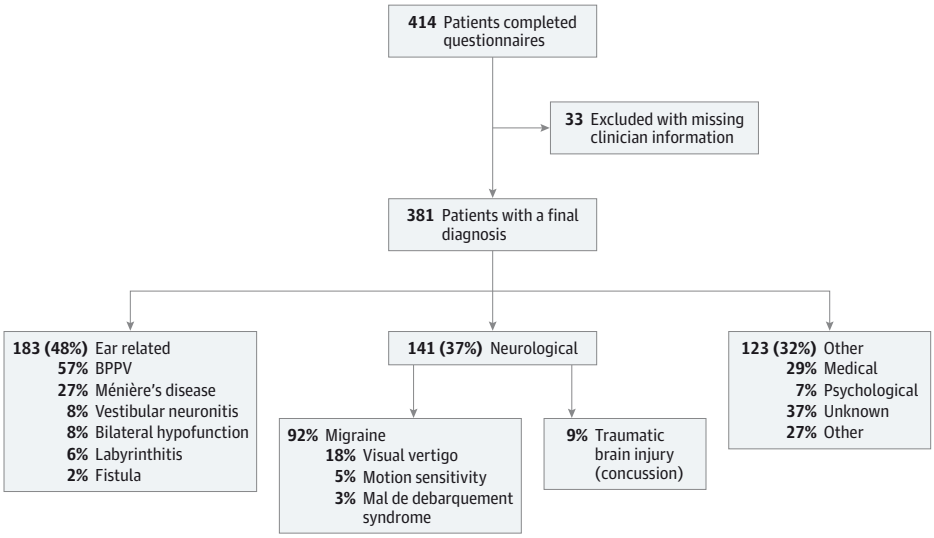
Figure. Distribution of Diagnoses



Distribution of diagnoses among participants who completed a vestibular intake questionnaire and underwent subsequent clinical assessment. Percentages may exceed 100% owing to multiple diagnoses.

(48%) were ear related, 141 (37%) neurological, 36 (9%) considered medical, 8 (2%) believed to be of psychological origin, 46 (12%) of unknown etiology, and 33 (9%) of other causes. Of those deemed ear related, the majority were BPPV (57%), followed by Ménière's disease (27%), vestibular neuronitis (8%), bilateral hypofunction (8%), labyrinthitis (6%), and labyrinthine fistula (perilymph fistula or superior semicircular canal dehiscence) (2%).

Of the 141 patients with conditions judged to be neurological, 118 had a specific diagnosis. These consisted of migraine (92%) and traumatic brain injury/postconcussive syndrome (9%). Thirty-three patients with migraine were further classified as having visual vertigo (23 [70%]), severe motion sensitivity (7 [21%]), and mal de debarquement syndrome (3 [9%]). Nonneurological medical diagnoses (9% of total) included orthostasis and cardiogenic causes, and represented 28% and 44% of this category, respectively.

BPPV

A total of 103 patients had BPPV. All were seen and evaluated by a clinician to confirm the BPPV diagnosis. In some patients, symptoms had resolved by the time of evaluation, but a clinically obtained history, rather than just the questionnaire, suggested BPPV as the definitive diagnosis.

As expected, 78% of those with BPPV indicated that lying down and/or rolling in bed was a trigger compared with 32% of those without BPPV ($P < .001$). Similarly, 78% of those with BPPV described their dizziness as vertigo compared with 57% of those with other diagnoses ($P < .001$). Reported duration of attacks was also significantly different, with 48% of patients with BPPV indicating a duration of seconds whereas only 19% of those without BPPV indicated a duration of seconds ($P < .001$).

Those with BPPV were more likely to say that the dizziness was not continuous ($P = .01$) and that it occurred when they moved ($P = .04$). Those without BPPV were more likely to indicate that automobile rides or loud sounds were triggers than those with BPPV ($P = .002$ and $P < .001$, respectively). Stress as a trigger was also significantly more prevalent in those without BPPV ($P = .003$). Those with BPPV were less likely to exhibit hearing loss than those with other diagnoses, 42% to 61% ($P = .005$).

Ménière's Disease

There were 49 patients evaluated in the clinic with confirmed Ménière's disease meeting probable or definite criteria.[7,8] Those with Ménière's disease, compared with those without, were more likely to describe their dizziness as vertigo, 86% to 59% ($P < .001$). They also were most likely to indicate duration of attacks as minutes to hours, with 75% choosing this option.

Hearing loss is a hallmark of Ménière's disease, and 96% of the patients with Ménière's disease indicated that they had documented hearing loss compared with only 49% of those without Ménière's disease ($P < .001$). Fluctuating hearing also strongly favored patients with Ménière's disease, with 46% noting changes in hearing as opposed to only 6% of patients with other disorders ($P < .001$).

Vestibular Migraine

A total of 109 patients were ultimately believed to have vestibular migraine. Diagnosis was based on clinical impression, which generally follows defined diagnostic criteria for vestibular migraine.[9,10] As expected, those with vestibular migraine had a higher likelihood of self-reporting migraine than those with other vestibular conditions, 42% to 22% ($P < .001$). Photophobia with a headache was reported in 80% of those with a diagnosis of vestibular migraine compared with 37% of those with other conditions ($P < .001$). Similarly, other migraine symptoms also showed increased prevalence in those with vestibular migraine such as history of headache with nausea and vomiting ($P = .007$), unilateral headache ($P = .02$), and throbbing headache ($P = .008$).

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Table. Variables Used in the Predictive Model Building

	Variables Used in Predictive Models		
	Coefficient	*P* Value	Comment
BPPV			
Lying down/rolling over	1.87	<.001	Hallmark of BPPV
Vertigo	0.92	.003	Consistent with BPPV
LOS			
Minutes to hours	−0.98	<.001	Negative predictor; distinguish from Ménière's disease
Days,<week	−1.11	.02	Negative predictor; distinguish from vestibular migraine
Vertigo and LOS: days to weeks	−1.84	.002	Negative predictor; distinguish from vestibular migraine
Ménière's disease			
Vertigo	1.78	<.001	Consistent with Ménière's disease
Documented hearing loss	3.22	<.001	Note this is documented; not subjective
LOS: minutes to hours	1.40	<.001	Hallmark of Ménière's disease attacks
Tinnitus			
Right	2.04	<.001	Unilateral tinnitus
Left	1.52	<.001	Unilateral tinnitus
Vestibular migraine			
History of migraine	0.98	.003	Consistent with vestibular migraine diagnostic definition
Photophobia	1.06	<.001	Consistent with history of migraine
LOS: seconds	−0.86	.01	Negative predictor; distinguish from BPPV
Automobile rides	0.94	.003	Visual vertigo and motion sickness; consistent with vestibular migraine
Migraine and automobile rides	−1.24	.02	Correction factor due to strength of having both descriptors together

Abbreviations: BPPV, benign paroxysmal positional vertigo; LOS, length of spell.

There was a significantly higher response that visual and motion stimuli could trigger dizziness in patients with vestibular migraine. Automobile rides ($P < .001$), reading ($P = .001$), going through aisles and/or tunnels ($P = .003$), and turning when walking ($P = .002$) were all more commonly noted as triggers. In addition, stress ($P = .03$) and association with menstrual cycle ($P = .01$) were slightly more common in those believed to have vestibular migraine.

Predictive Model Building

BPPV

The variables predicting BPPV related to triggers for dizziness, the nature of the dizziness, and the timing of spells. In particular, having dizziness described as vertigo and indicating lying down and/or rolling over as the main trigger were the strongest positive predictors. The other main predictors were related to duration of spells (**Table**).

The questionnaire had 4 check boxes for duration of spells: (1) seconds to minutes, (2) minutes to hours but less than 24 hours, (3) days but less than a week, and (4) days, and can be continuously for weeks. A patient with BPPV would be expected to choose category 1, and indeed this was selected by 48% of patients with BPPV. However, 33% chose minutes to hours and approximately 10% chose each of the longer durations. As such, duration of seconds to minutes was not a positive predictor on its own. Therefore, the model uses longer-duration spells to negatively affect the predictive formula, thus strengthening the relationship between short spells and BPPV. The formula identified for the linear predictor (LP) of BPPV is thus,

$$\text{LP} = -2.19 + 1.87 \times (\text{Lying Down or Rolling Over}) + 0.92 \times (\text{Vertigo}) - 0.98 \times (\text{LOS: Minutes to Hours}) - 1.11 \times (\text{LOS: Days}) - 1.84 \times (\text{Vertigo}) \times (\text{LOS: Days to Weeks}).$$

In this formula, if the variable is present it is replaced by "1" and if not present replaced by "0." For example, if the patient indicates dizziness with rolling over, vertigo, and spells lasting days, the formula computes as LP = −2.19 + 1.87 + 0.92 − 1.11, which equals −0.51. The LP is then transformed into an estimated probability of BPPV with the following formula:

$$\Pr(\text{BPPV}) = \exp(\text{LP})/[1 + \exp(\text{LP})].$$

For example, LP = −0.51 translates into a probability estimate of BPPV equal to 0.375. Cross-validation of this model confirmed good predictive properties with an area under the curve (AUC) of 0.76. At LP greater than or equal to 0.2, the cross-validated sensitivity for BPPV is 0.79 and specificity for BPPV is 0.65.

Ménière's Disease

Positive predictors for Ménière's disease included classification of the dizziness as vertigo and indicating a length of spell lasting minutes to hours. A strong predictor relating to hearing loss was having a documented history of hearing loss, in contrast to a perception of hearing loss. Furthermore, having unilateral tinnitus, in contrast to bilateral tinnitus or no tinnitus, was a strong predictive variable. Tinnitus in the right ear only was a slightly stronger predictor than tinnitus in the left ear. The resultant formula for the linear predictor of Ménière's disease is thus,

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LP = −7.08 + 1.78 × (Vertigo) + 3.22 × (Documented Hearing Loss) + 1.40 × (LOS: Minutes to Hours) + 2.04 × (Tinnitus: Right Ear Only) + 1.52 × (Tinnitus: Left Ear Only).

Cross-validation of this model confirmed an ROC curve with AUC of 0.86. At LP greater than or equal to 0.15, the cross-validated sensitivity for Ménière's disease is 0.81 and cross-validated specificity for Ménière's disease is 0.85.

Vestibular Migraine

The nature of the dizziness was not a predictive variable for vestibular migraine. Patients with vestibular migraine noted many forms of dizziness including vertigo (69%), wooziness (60%), imbalance (70%), faint (57%), swimming sensation (34%), pulsion (23%), and other (9%).

The positive predictors for vestibular migraine related to a history of migraine, migraine aura symptoms, and motion sensitivity, which is frequently found in patients with migraine.[11] Thus, the variables "Diagnosis of Migraine" and "Photophobia With Headaches" were both significantly related to vestibular migraine in contrast to other conditions. Also, selecting automobile rides as a trigger for attacks of dizziness was a strong positive predictor.

The effect of having a diagnosis of migraine and dizziness with automobile rides together skewed the balance between sensitivity and specificity in the model and required a negative correction factor if both were present. A negative predictor was also the indication that attacks last seconds. The final linear predictor for vestibular migraine is thus,

LP = −1.84 + 0.98 × (History of Migraine) − 0.86 × (LOS: Seconds) + 1.06 × (Photophobia) + 0.94 × (Automobile Rides) − 1.24 × (Migraine) × (Automobile Rides).

Cross-validation of this model confirmed good predictive properties with AUC of 0.65. At LP greater than or equal to 0.25, cross-validated sensitivity for vestibular migraine is 0.76 and cross-validated specificity for vestibular migraine is 0.59. Given the often vague or varied complaints of dizziness in vestibular migraine, it is expected that the specificity would be lower compared with other disorders.

Discussion

The efficacy of any questionnaire relies on accuracy in completing the form. The majority of patients were comprehensive in addressing all fields, but some were cursory. In these cases, an advanced practice nurse prescriber with training in vestibular disorders called the patient for further detail. Some of these cases seem to reflect patient attitude that the questionnaire is a formality to obtaining a physician appointment rather than a useful diagnostic tool.

Effectiveness of the questionnaire is also dependent on patient interpretation of the questions. For example, a number of patients with BPPV chose the prompt that dizziness lasts for days to weeks. We interpret this as a failure to distinguish between individual episodes and the period of time during which they have episodes. This confusion has been previously noted.[5] This suggests that questionnaires may need follow-up questions to clarify answers or rigorous study to validate each field. Reliability may be improved with an electronic questionnaire using branching logic to ask additional questions if needed to clarify answers.[12]

It is not clear whether the high association of some variables in this study is specific to the form in which they are presented to the patient. For example, the variable "lying down/rolling in bed" was a strong positive predictor of BPPV but was presented as a check box within a list of 17 potential triggers. Zhao and colleagues,[6] using a questionnaire that primarily asked yes/no questions, also found that dizziness with lying down was a strong predictor of BPPV. Similarly, they found BPPV negatively associated with long attacks, vestibular migraine positively associated with light sensitivity, and Ménière's disease positively associated with unilateral hearing loss or tinnitus. Whereas this may suggest good concordance with the present study, they also identified many variables that differed from those in this report. Therefore, the manner of presentation of the question may play a role in the utility of the questionnaire to predict specific conditions.

The strongest model was that predicting the diagnosis of Ménière's disease. Similar high sensitivity and specificity have been found with other questionnaires for Ménière's disease.[13] This may reflect the strong association of hearing loss and tinnitus with Ménière's disease.[7] These conditions are easily recognized by patients and thus the data collection for these variables may be more accurate. Furthermore, the diagnostic criteria for Ménière's disease include these conditions, thus increasing the probability of Ménière's disease when present.[7]

In contrast to Ménière's disease, the model for predicting vestibular migraine had comparable sensitivity but low specificity. This may reflect the varied clinical nature of vestibular migraine and the weaker diagnostic criteria.[10,14] For example, patients with vestibular migraine often describe dizziness as an "off" sensation that may be poorly interrogated by the questionnaire. Migraine is also significantly underdiagnosed,[15,16] and therefore a key diagnostic criterion for vestibular migraine may be absent from many questionnaires. Furthermore, by means of written history, subtle distinctions that would enable vestibular migraine to be distinguished from persistent postural and perceptual dizziness can be missed. In fact, this study categorized visual vertigo and motion sensitivity as forms of vestibular migraine, which has been our traditional clinical practice, but which may be better considered to be persistent postural and perceptual dizziness (aka chronic subjective dizziness).[17-19]

Limitations of this study include the use of a single center with the reliance on clinical impression, rather than strict diagnostic criteria, to obtain final vestibular diagnoses. A multicenter study with additional clinicians can better reflect the general clinical experience as regards these disorders. Statistically, we performed validation on the same data set as the model building. The internal cross-validation (10-fold cross-validation) partially addressed the validation issue but is not as robust as validation of the predictive models on external, or separately collected, data.

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The goal of initiating a quality improvement project was to alter the clinical practice paradigm for vestibular disorders away from a physician-centric model. Barriers to this are patient and clinician acceptance of a potential nonphysician-based assessment and treatment encounter, limited evidence demonstrating efficacy and efficiency of such a program, and uncertainty in key areas of the clinical pathway used for guiding decision making. The results of this study can provide evidence for patients and referring clinicians as to the diagnostic accuracy of pre-encounter questionnaires and the potential improvement in clinical efficiency. Clinical efficiency is becoming an important metric used to evaluate clinician quality. Time to next appointment, enough time spent with the patient, and clinic on-time performance are all metrics being used by health care systems to measure the quality of services. Structured systems for triaging patients into those requiring a physician evaluation vs ancillary clinicians have been effective. In a primary care setting, access to the practice increased by almost 30% and more than 80% of patients triaged to a nonphysician clinician did not need to follow-up with a physician.[20] Similarly, using a structured questionnaire as support for medical decision making for viral respiratory infection showed that military medics could reduce the need for physician referrals by 37%.[21]

Conclusions

The outcomes in this study have been used in our institution to improve access by using ancillary clinicians. For example, patients with BPPV can be seen within 1 week for vestibular therapy without waiting for a physician appointment. A similar triage model involving vestibular disorders has shown high patient satisfaction, likely due to simultaneous evaluation and treatment.[22] In our practice, patients with substantial headache component and prediction of vestibular migraine are offered neurological consultation as a best first assessment. Freeing the otolaryngologist's schedule from nonotologic patients with vestibular disorders may allow faster access for those predicted to have Ménière's disease or other otologic conditions.

ARTICLE INFORMATION

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Study concept and design: Friedland.
Acquisition, analysis, or interpretation of data: Friedland, Tarima, Erbe, Miles.
Drafting of the manuscript: Friedland, Tarima.
Critical revision of the manuscript for important intellectual content: Friedland, Tarima, Erbe, Miles.
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REFERENCES

1. Crespi V. Dizziness and vertigo: an epidemiological survey and patient management in the emergency room. *Neurol Sci*. 2004;25(suppl 1):S24-S25.

2. Maarsingh OR, Dros J, Schellevis FG, van Weert HC, Bindels PJ, Horst HE. Dizziness reported by elderly patients in family practice: prevalence, incidence, and clinical characteristics. *BMC Fam Pract*. 2010;11:2.

3. Bakhit M, Heidarian A, Ehsani S, Delphi M, Latifi SM. Clinical assessment of dizzy patients: the necessity and role of diagnostic tests. *Glob J Health Sci*. 2014;6(3):194-199.

4. Kentala E, Rauch SD. A practical assessment algorithm for diagnosis of dizziness. *Otolaryngol Head Neck Surg*. 2003;128(1):54-59.

5. Newman-Toker DE. Symptoms and signs of neuro-otologic disorders. *Continuum (Minneap Minn)*. 2012;18(5 Neuro-otology):1016-1040.

6. Zhao JG, Piccirillo JF, Spitznagel EL Jr, Kallogjeri D, Goebel JA. Predictive capability of historical data for diagnosis of dizziness. *Otol Neurotol*. 2011;32(2):284-290.

7. Lopez-Escamez JA, Carey J, Chung WH, et al. Diagnostic criteria for Menière's disease. *J Vestib Res*. 2015;25(1):1-7.

8. Thorp MA, Shehab ZP, Bance ML, Rutka JA; AAO-HNS Committee on Hearing and Equilibrium. The AAO-HNS Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Menière's disease: have they been applied in the published literature of the last decade? *Clin Otolaryngol Allied Sci*. 2003;28(3):173-176.

9. Furman JM, Balaban CD. Vestibular migraine. *Ann N Y Acad Sci*. 2015;1343(1):90-96.

10. Lempert T, Olesen J, Furman J, et al. Vestibular migraine: diagnostic criteria. *J Vestib Res*. 2012;22(4):167-172.

11. Eggers SD, Neff BA, Shepard NT, Staab JP. Comorbidities in vestibular migraine. *J Vestib Res*. 2014;24(5-6):387-395.

12. Goldbloom RB, Kim RK, Hodder-Malloy C, et al. Design and reliability of pediatric HealthQuiz: preliminary report of a comprehensive, computerized, self-administered child health assessment. *Clin Pediatr (Phila)*. 1999;38(11):645-654.

13. López-Escámez JA, López-Nevot A, Gámiz MJ, Moreno PM. Effectiveness of a structured questionnaire for diagnosis of Menière's disease in the first visit. *Acta Otorhinolaryngol Belg*. 2000;54(4):451-458.

14. Radtke A, Neuhauser H, von Brevern M, Hottenrott T, Lempert T. Vestibular migraine—validity of clinical diagnostic criteria. *Cephalalgia*. 2011;31(8):906-913.

15. Arroyo-Quiroz C, Kurth T, Cantu-Brito C, Lopez-Ridaura R, Romieu I, Lajous M. Lifetime prevalence and underdiagnosis of migraine in a population sample of Mexican women. *Cephalalgia*. 2014;34(13):1088-1092.

16. Diamond ML. The role of concomitant headache types and non-headache co-morbidities in the underdiagnosis of migraine. *Neurology*. 2002;58(9)(suppl 6):S3-S9.

17. Bittar RS, Lins EM. Clinical characteristics of patients with persistent postural-perceptual dizziness. *Braz J Otorhinolaryngol*. 2015;81(3):276-282.

18. Ruckenstein MJ, Staab JP. Chronic subjective dizziness. *Otolaryngol Clin North Am*. 2009;42(1):71-77, ix.

19. Staab JP. Chronic subjective dizziness. *Continuum (Minneap Minn)*. 2012;18(5 Neuro-otology):1118-1141.

20. Thorn J, Maun A, Bornhöft L, et al. Increased access rate to a primary health-care centre by introducing a structured patient sorting system developed to make the most efficient use of the personnel: a pilot study. *Health Serv Manage Res*. 2010;23(4):166-171.

21. Golan D, Zagetzki M, Vinker S. Acute respiratory infections: can a non-physician practitioner triage and treat patients by using an algorithm? experience in a military primary care clinic. *Isr Med Assoc J*. 2005;7(9):578-582.

22. Kasbekar AV, Mullin N, Morrow C, Youssef AM, Kay T, Lesser TH. Development of a physiotherapy-led balance clinic: the Aintree model. *J Laryngol Otol*. 2014;128(11):966-971.

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A Systematic Review of Diuretics in the Medical Management of Ménière's Disease

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Abstract

Objective. (1) Review evidence for the use of oral diuretic medications in the management of Ménière's disease. (2) Analyze therapy-related hearing and vertigo outcomes.

Data Sources. Literature was obtained through directed searches of MEDLINE, EMBASE, Web of Science, EBSCO Host, Cochrane Reviews, and linked citations through seminal papers. We searched independent electronic databases for articles that reported the use of diuretics in patients with Ménière's disease.

Review Methods. All articles of level 4 evidence or higher, per the Oxford Centre for Evidence-Based Medicine, were included with no limit for number of patients, duration of therapy, or follow-up period. Two independent investigators reviewed the articles for inclusion eligibility. Outcomes were tabulated, including subjective or quantitative measures of hearing, tinnitus, vertigo episode frequency, and medication adverse effects.

Results. Nineteen articles were included from 1962 to 2012 from 11 countries. Twelve retrospective case series, 4 randomized controlled trials, 2 case-control trials, and 1 prospective case series were identified. Six studies investigated isosorbide; 5, hydrochlorothiazide; 2, acetazolamide; 2, chlorthalidone; and 1 each of betahistine, hydrochlorothiazide, chlorthalidone, acetazolamide, hydrochlorothiazide-triamterene, and nimodipine. Eight (42.1%) studies reported hearing outcomes improvement. Fifteen (79.0%) studies reported vertigo outcomes improvement. Ten (52.6%) studies reported no side effects, and 4 studies (21.1%) reported abdominal discomfort. No significant morbidity or mortality was reported in any study.

Conclusion. Multiple low evidence–level studies report that oral diuretic therapy may be beneficial in the medical management of Ménière's disease. Improvement in vertigo episode frequency was consistently reported, with less convincing evidence for improvement in hearing outcomes.

Keywords

Ménière's disease, diuretics, conservative therapy, medical management

Ménière's disease (MD) or syndrome is a relatively common condition of the inner ear that may affect up to 190 per 100,000 people in the United States.[1] Prevailing theories on its pathogenesis point to endolymphatic hydrops as one derangement responsible for producing dysfunction within the cochlea and peripheral vestibular apparatus. While the exact pathophysiology remains unknown, it is held by many that hydrops of the endolymph within the labyrinth is contributory.[2] It is believed that during an acute attack, pressure within the scala media increases to a critical point where either a ''stretch'' or rupture of Reissner's membrane ensues.[3,4] This event results in admixture of endolymph and perilymph leading to disruption of the ionic gradient, ultimately producing the classic symptoms of fluctuating hearing loss, tinnitus, and aural fullness.

As firm evidence of a unifying pathogenic mechanism is lacking, MD has proven difficult to successfully manage. Options for therapy range from low-salt diet restriction and diuretics to benzodiazepine and steroid regimens for acute attacks. Invasive surgical procedures are considered in refractory cases. Despite the widespread use of diuretics for this condition, limited evidence for its efficacy has been demonstrated in published literature. An excellent systematic review of the effect of diuretic treatment in MD patients was published in 2006 and subsequently updated in 2010.[5] The authors found that there were no trials of high enough quality to meet the standards for their systematic review.

Clinical recommendations and guidelines are best supported by data and evidence generated through high-quality

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investigations. The standard for high-quality studies is a well-executed randomized controlled trial (RCT).[6] Planning and executing an RCT with sufficient power is an expensive and time-consuming undertaking. As a result, a significant proportion of the medical literature evaluating therapy efficacy takes the form of retrospective or prospective cohort analyses. These studies are ranked lower in evidence quality[6]; however, they may represent the only data available.

Considering the historical lack of RCTs in the evaluation of diuretics for MD with no additional systematic review available for data since the Cochrane Review update in 2010,[5] we saw an opportunity to further investigate the use of diuretics in MD. The goal of this systematic review is to evaluate the reported efficacy of oral diuretic therapy in the treatment of MD for adult patients as reported over the past 10 years. Specifically, we aim to determine if diuretic therapy produces improvement in hearing and vestibular outcomes.

Methods

This study was reviewed by the Duke University Medical Center Institutional Review Board (IRB) and deemed to be exempt from full review. Our systematic review protocol was designed in accordance with the PRISMA-P 2015 guidelines (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols).[7]

The core search question for this systematic review was to evaluate the reported efficacy of diuretic therapy in the treatment of MD in the past 10 years. We sought to examine studies including any oral diuretic in adult patients, including reported hearing outcomes, vestibular symptom outcomes, diuretic side effects, and complications of therapy. Inclusion criteria were ''Meniere's disease'' or ''endolymphatic hydrops,'' with 'and' Boolean logic to combine with ''diuretics-osmotic,''''diuretics,'' and ''diuretics-potassium sparing.'' No restrictions were placed on publication country origin or language. Exclusion criteria included studies with medical therapy other than diuretics, as well as review, guideline, commentary, and letter publication types.

On December 16, 2014, a search of EBSCOhost, EMBASE, Web of Science, and the Cochrane Reviews Database was completed with inclusion keywords of ''Meniere Disease'' or ''Endolymphatic hydrops,'' with 'and' or 'or' Boolean logic as appropriate to combine with ''Diuretics-Osmotic,''''Diuretics,'' and ''Diuretics-Potassium Sparing.'' Exclusion criteria were set to exclude review, guidelines, commentary, and letter publication types. A PubMed search was also completed with the strategy of *''Therapy/Broad[filter] AND ((''diuretics''[Pharmacological Action] OR ''diuretics''[MeSH Terms] OR ''diuretics''[All Fields]) AND (''meniere disease''[MeSH Terms] OR (''meniere''[All Fields] AND ''disease''[All Fields]) OR ''meniere disease''[All Fields] OR (''meniere's''[All Fields] AND ''disease''[All Fields]) OR ''meniere's disease''[All Fields])) AND Clinical Trial[ptyp]. Publication types: clinical trial, comparative study, controlled clinical trial, multi-center study, observational study, randomized controlled trial.''*

With the assistance of a Canadian Medical Association reference librarian, an OVID MEDLINE (1946 to November [week 3] 2014) search was completed on December 17, 2014, with the following search strategy: *1) endolymphatic hydrops/ or meniere disease/ or vertigo/; 2) ((labyrinth* or aural or endolymphatic) adj3 (syndrome or vertigo or hydrop*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]; 3) exp Diuretics/ or diure*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier; 4) (1 or 2) and 3; 5) limit 4 to yr=''2004 –Current.''*

Study entries from the above searches were consolidated into one spreadsheet and duplicates removed. Entries were then systematically screened to remove entries with no abstract available, letter or correspondence publication type, or irrelevance to the core search question. Full text articles were obtained, and 2 independent reviewers (M.G.C., A.P.) appraised the articles to exclude review, case report, qualitative survey, basic science, or diagnostic testing publication types. A data extraction spreadsheet was created with headings for title, author, year of publication, country of origin, size of study patient population, study type, diagnosis, diagnostic criteria, intervention, follow-up duration, outcome measures, hearing outcomes, vestibular symptom outcomes, diuretic side effects, complications of therapy, and study conclusion. The studies were appraised according to the Oxford Centre for Evidence-Based Medicine's Level of Evidence grading system.[6]

As the outcome measurements were heterogeneous, a meaningful quantitative analysis was impossible. We performed a qualitative analysis of hearing and vestibular outcomes described for each study to determine if clinical benefit was evident, and we aggregated these results to generate an overall impression.

Results

In sum, 439 studies were identified with our search strategy and subsequently analyzed for possible inclusion (**Figure 1**); 122 duplicate studies were removed. Eleven abstracts were excluded, as no abstract body was available; 1 was a letter to the editor; and 1 was not related to diuretics in the treatment of MD. The full-text articles for the 306 remaining studies were obtained. A total of 287 full texts were excluded, including review articles, case reports, qualitative surveys, and basic science study designs. Thirty-five articles described the use of diuretics with MD; however, the discussion was in the context of the development of new diagnostic tests and not treatment related.

Nineteen studies qualified for inclusion in our systematic review (**Table 1**). Twelve (63.2%) were retrospective case series; 4 (21.1%), RCTs; 2 (10.5%), case-control; and 1 (5.3%), prospective case series. According to the Oxford Centre for Evidence-Based Medicine's Level of Evidence

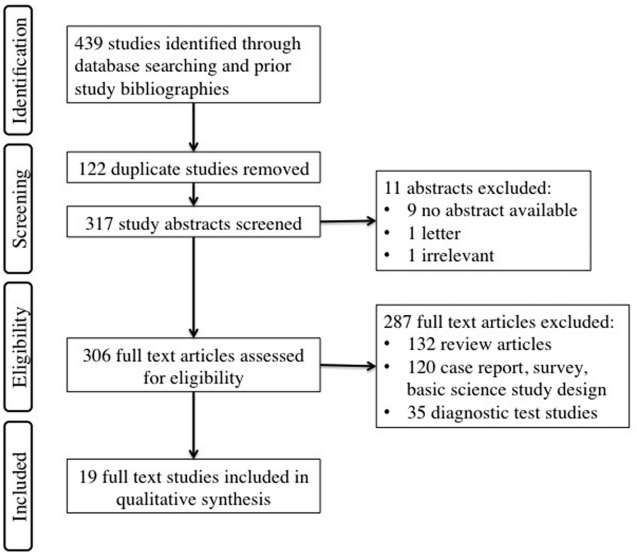

Figure 1. PRISMA-P[7] flow diagram for evaluation of identified studies.

grading system, 13 (68.4%) were classified as level 4; 2 (10.5%), level 1a; 2 (10.5%), level 3b; and 2 (10.5%), level 2b. The most common study country of origin was Japan (n = 6, 31.6%), followed by Sweden (4, 21.1%), and 1 each (5.3%) of England, Germany, Hungary, Italy, Mexico, Netherlands, South Korea, Turkey, and the United States. The diagnostic and reporting criteria varied. The most common criteria set used was the American Academy of Otolaryngology—Head and Neck Surgery Committee on Hearing and Equilibrium guidelines (n = 4), followed by the 1972 American Academy of Ophthalmology and Otolaryngology criteria (n = 3) and the Japan Society for Equilibrium Research for MD guidelines (n = 3). The remainder reported a constellation of symptoms and various diagnostic tests as inclusion criteria for MD.

Eight medications with diuretic properties were analyzed. Six (31.6%) studies investigated isosorbide, 5 (26.3%) hydrochlorothiazide, 2 (10.5%) acetazolamide, 2 (10.5%) chlorthalidone, and 1 (5.3%) each of betahistine or hydrochlorothiazide, chlorthalidone-acetazolamide, hydrochlorothiazide-triamterene, and nimodipine. Betahistine does not have known diuretic properties but was included, as it was a treatment arm in a study investigating hydrochlorothiazide. The dosing, therapy duration, and follow-up period varied widely (**Table 2**). The outcome measurements varied from unstructured reports of symptomology, ancillary testing (electrocochleography, glycerol tests, vestibular testing), and audiology variables to formal reporting of accepted guidelines, including the 1985 Academy of Otolaryngology—Head and Neck Surgery Committee on Hearing and Equilibrium guidelines, 1972 American Academy of Ophthalmology and Otolaryngology standards, and the Japan Society for Equilibrium Research for MD guidelines (**Table 3**).

Eight studies (42.1%) reported a degree of objective hearing improvement. Six (31.6%) reported mixed hearing results, while the remainder demonstrated no or inconclusive hearing results (**Table 4**). Fifteen (79.0%) studies reported improvement in vertigo symptoms, with 2 (10.5%) reporting mixed results and 2 (10.5%) reporting no vertigo outcomes (**Table 5**). Ten (52.6%) studies reported no side effects as a result of therapy. Three (15.8%) studies specifically reported abdominal discomfort, and the remainder reported different constellations of side effects (**Table 6**).

Discussion

MD is a common condition with occasionally debilitating symptoms. As the pathophysiology is not well understood, devising effective therapeutic strategies has been a challenging task. Acute symptom exacerbations can be treated with benzodiazepine and steroid regimens. Physicians may offer more invasive procedures for refractory cases, including medical labyrinthectomy with transtympanic gentamicin injections, endolymphatic sac decompression, surgical labyrinthectomy, and surgical vestibular nerve section. Combinations of low-salt diet restriction and oral diuretics have largely been used as maintenance therapy. Despite the use of diuretics for MD, literature reviews have consistently demonstrated lack of evidence of effectiveness. The Cochrane Group published a thorough systematic review of diuretic efficacy in MD patients in 2006 and an update in 2010; however, no RCTs met their rigorous standards for a systematic review.[5] We realized an opportunity to broaden inclusion criteria to all study designs beyond RCTs to evaluate the potential benefits of diuretic therapy.

We found 19 studies of Level of Evidence 4 or higher, per the Oxford Centre for Evidence-Based Medicine, with considerable heterogeneity in patient population, study design, diuretic type and dosage, follow-up time, and outcomes. Level of Evidence 4 includes studies that are either case series or poor-quality cohort and case-control studies. This heterogeneity precluded formal meta-analysis. Only 4 RCTs were included in our review.[8-11] One RCT directly compared hydrochlorothiazide with betahistine with no placebo arm, and both were found to improve vertigo.[10] Betahistine does not have known diuretic properties but was included, as it was a treatment arm in comparison with hydrochlorothiazide. One RCT with a placebo arm investigated Dyazide (hydrochlorothiazide and triamterene) and found significant improvements in vestibular symptoms but not in hearing or tinnitus.[11] Another RCT with a placebo arm investigated hydrochlorothiazide and found statistically significant improvements in both hearing loss and vestibular symptoms but no significant improvement in tinnitus.[8] Last, a low-quality RCT compared isosorbide with 2 control compounds—methyl acid dihydroergotoxine and vitamin B3—and found significant improvements in headache and tinnitus.[9] The remainder of the studies were retrospective case series,[12-23] case-control studies,[24,25] and 1 prospective case series.[26]

As the studies analyzed are of mostly ''low'' quality with heterogeneous methods for reporting outcomes, caution must be exercised in drawing conclusions from the

Table 1. Characteristics of the Included Studies.

Study Title	Author (Year)	Country	Patients, n	Study Type	Diagnostic Criteria
"Treatment of Meniere's Disease with Hydrochlorothiazide"	Norell and Stahle (1962)[18]	Sweden	57	RCS	Internal/independent criteria
"Experiences with Acetazolamid Therapy Applied in Our Clinic to Patients Suffering from Ménière's Disease for More Than 8 Years"	Varga et al (1966)[22]	Hungary	60	RCS	Internal/independent criteria
"Meniére's Disease and Hydrochlorothiazide (Dichlotride®): A Critical Analysis of Symptoms and Therapeutic Effects"	Klockhoff and Lindblom (1967)[8]	Sweden	30	RCT with placebo	Internal/independent criteria
"Diuretic Treatment of Meniere Disease: Long-Term Results with Chlorthalidone"	Klockhoff et al (1974)[16]	Sweden	34	RCS	Not reported
"Long-term Therapy of Meniere's Disease: Comparison of the Effects of Betahistine Dihydrochloride and Hydrochlorothiazide"	Petermann et al (1982)[10]	Germany	32	RCT, no placebo	Internal/independent criteria
"Treatment of Meniere's Disease with Isosorbide"	Kitahara et al (1982)[9]	Japan	102	RCT with controls	Internal/independent criteria
"Menière's Disease and Isosorbide as an Oral Hyperosmotic Agent"	Yamazaki et al (1982)[23]	Japan	21	RCS	Japan Society for Equilibrium Research for Ménière's disease
"Oral Acetazolamide in Meniere's Disease"	Brookes and Booth (1984)[12]	England	14	RCS	1972 AAOO Ménière's guidelines
"Use of a Diuretic (Dyazide®) in the Treatment of Méniere's Disease"	van Deelen and Huizing (1986)[11]	Netherlands	33	RCT with placebo	Internal/independent criteria
"Long-term Effect of Acetazolamide and Chlorthalidone on the Hearing Loss of Meniere's Disease"	Corvera and Corvera (1989)[24]	Mexico	192	Case-control	Internal/independent criteria
"Evaluation of a Three-Stage Management Program for Meniere's Disease"	Raivio et al (1989)[20]	Sweden	104	RCS	1972 AAOO Ménière's guidelines
"Diuretic and Diet Effect on Meniere's Disease Evaluated by the 1985 Committee on Hearing and Equilibrium Guidelines"	Santos et al (1993)[21]	US	54	RCS	1985 AAO-HNS guidelines
"Effects of Isosorbide in Patients with Meniere's Disease"	Kanda et al (1993)[14]	Japan	32	RCS	1985 AAO-HNS guidelines
"Effect of Isosorbide on Hearing Loss due to Endolymphatic Hydrops"	Kakigi et al (1995)[26]	Japan	103	RCS	Japan Society for Equilibrium Research Society for Ménière's Disease
"Efficacy of Long-term Administration of Isosorbide for Meniere's Disease"	Nozawa et al (1995)[19]	Japan	30	RCS	1972 AAOO Ménière's guidelines
"Use of Nimodipine in the Medical Treatment of	Lassen et al (1996)[17]	Italy	12	RCS	1972 AAOO Ménière's guidelines

(continued)

Table 1. (continued)

Study Title	Author (Year)	Country	Patients, n	Study Type	Diagnostic Criteria
Ménière's Disease: Clinical Experience"					
"Effects of Long-term Treatment with Osmotic Diuretics on Symptoms and Electro-cochleogram in Meniere's Disease"	Kitahara et al (2004)[15]	Japan	7	RCS	Japan Society for Equilibrium Research for Ménière's disease
"Hearing and Dizziness in Patients with Definite Meniere's Disease after the Long Term Use of Diuretics"	Chung et al (2010)[13]	South Korea	27	RCS	1995 AAO-HNS guidelines
"Are Thiazides Effective on Hypertensive Vertigo? A Preliminary Study"	Eryaman et al (2012)[25]	Turkey	24	Case-control	Internal/independent criteria

Abbreviations: AAO-HNS, American Academy of Otolaryngology—Head and Neck Surgery; AAOO, American Academy of Ophthalmology and Otolaryngology; RCS, retrospective case series; RCT, randomized controlled trial.

Table 2. Medication Regimen and Follow-up of the Included Studies.

Study	Medication	Regimen	Follow-Up
Norell and Stahle (1962)[18]	Hydrochlorothiazide	Day 1-4: 25 mg TID; days 5-21: 15-25 mg BID	6 mo
Varga et al (1966)[22]	Acetazolamide	Day 1: 500 mg, with 250 mg TID; day 2: 250 mg QID; days 3-13: 250 mg TID	10 d, 6 mo, 1 y, 5 y
Klockhoff and Lindblom (1967)[8]	Hydrochlorothiazide	25 mg TID, 6 d/wk	2 y
Klockhoff et al (1974)[16]	Chlorthalidone	Salt restriction, 50 or 100 mg daily; in some exceptional cases, doses of 150 or 200 mg were administered for short periods	5 y
Petermann et al (1982)[10]	Betahistine dihydrochloride or hydrochlorothiazide	Betahistine: 8 mg TID; hydrochlorothiazide: 25 mg TID	9 mo
Kitahara et al (1982)[9]	Isosorbide	30 mL TID for 1 wk, then 20 mL TID for 2 wk, then 15-mL dose TID for an indefinite period	6 mo
Yamazaki et al (1982)[23]	Isosorbide	70 mL TID for 1 wk	4 mo
Brookes and Booth (1984)[12]	Acetazolamide	250 mg daily or 500 mg sustained-release preparation	Up to 9 mo
van Deelen and Huizing (1986)[11]	"Dyazide" (50 mg, triamterene; 25 mg, hydrochlorothiazide)	First 3 d of each period: 2 capsules daily; during the remaining period, 2 capsules every second day	17 wk
Corvera and Corvera (1989)[24]	Chlorthalidone or acetazolamide	Chlorthalidone: 50-100 mg every other day; acetazolamide: 500-750 mg daily, 5 d/wk	Chlorthalidone group, 5-13.4 y; acetazolamide range, 5-7.8 y; control group, 5-24.1 y

(continued)

Table 2. (continued)

Study	Medication	Regimen	Follow-Up
Raivio et al (1989)[20]	Chlorthalidone	50 mg daily for at least 3 mo	26.5 mo
Santos et al (1993)[21]	Hydrochlorothiazide with or without triamterene HCl	Sodium restriction and initial starting dose of 50 mg/d but ranging 25-100 mg/d; triamterene used in <15%	Vertigo symptoms: 24 mo; hearing: 22 and 74 mo
Kanda et al (1993)[14]	Isosorbide	90 mL daily for 4 wk; during exacerbation, a 120-mL dose was administered for short periods; dose reduction by 30-60 mL/d depending on degree of improvement	24 mo
Kakigi et al (1995)[26]	Isosorbide	40 mL BID, 2 wk; 30 mL BID, 2 wk; 25 mL BID, 2 wk; 15 mL BID, 2 wk	8 wk
Nozawa et al (1995)[19]	Isosorbide	120 mL daily, tapered stepwise weekly to 60 mL until the 4th week, then individually tapered	26.5 mo
Lassen et al (1996)[17]	Nimodipine	30 mg BID	27 mo
Kitahara et al (2004)[15]	Isosorbide	90 mL per day for >1 y	31.7 mo
Chung et al (2010)[13]	Hydrochlorothiazide	Low-sodium diet (<1500 mg/d) and hydrochlorothiazide (50 mg daily)	2, 4, 6, and 8 y; mean follow-up, 52.4 mo
Eryaman et al (2012)[25]	Hydrochlorothiazide	Once daily for minimum 3 wk	3 wk

Abbreviations: BID, twice daily; TID, 3 times daily; QID, 4 times daily.

Table 3. Outcomes Measures and Study Quality of the Included Studies.

Study	Outcome Measures	Hearing Result	Vertigo Result	Side Effects	Study Quality
Norell and Stahle (1962)[18]	Symptomatology, PTA	In 31 with length of disease <2 y, hearing improvement noted in 57%, while in 26 with length of disease >2 y hearing improvement obtained in only 27%	75% of cases "diminution of or freedom from giddiness was noted"	2 with nausea, diarrhea, abdominal pain	4
Varga et al (1966)[22]	Symptomatology, PTA	After 5 y, 24 of 60 hearing improved, 38 of 60 tinnitus improved	47 of 60 vertigo "fits" improved	None reported	4
Klockhoff and Lindblom (1967)[8]	Symptomatology, PTA	16 of 26 tinnitus improved but not significant ($P > .1$); 18 of 26 had hearing loss improved	15 of 26 had improvement in vertigo; 5 of 26 patients resolved vertigo	Fatigue	1a
Klockhoff et al (1974)[16]	Symptomatology, PTA	18 had reduction of the hearing loss and tinnitus	26 of 34 of an "extent that was of definite clinical value"	Dry mouth, thirst, hypokalemia, weight loss, fatigue	4

(continued)

Table 3. (continued)

Study	Outcome Measures	Hearing Result	Vertigo Result	Side Effects	Study Quality
Petermann et al (1982)[10]	Symptomatology, PTA	Slight improvement of hearing only during the first 3 mo of treatment	6 of 7 during the first 3 mo of treatment noted improvement in vertigo frequency	Hypokalemia, hyperuricemia	2b
Kitahara et al (1982)[9]	Symptomatology	None reported	Improved dizziness in 71%, tinnitus in 72%, and headache in 92%	5 of 51 with abdominal discomfort	2b
Yamazaki et al (1982)[23]	Symptomatology, PTA, ECoG	2 had hearing improvement, 2 had hearing loss	In 18 of 20 who experienced relief, attack of vertigo did not occur in 12 (63%) and vertigo relieved in 6 (31%)	None reported	4
Brookes and Booth (1984)[12]	Symptomatology, PTA	3 of 13 noted gains but could be clearly substantiated in only 1	Symptomatic improvement in the Ménière's symptoms reported by only 4 of 13	Side effects in 6 of 13 (46.2%); paraesthesias in 12 of 13; 4 with headaches, 3 with drowsiness, 1 with chest tightness	4
van Deelen and Huizing (1986)[11]	Symptomatology, PTA	No positive effect on hearing	Significant decrease of vertigo	None reported	1a
Corvera and Corvera (1989)[24]	PTA	In short term (2-6 wk), decrease of average hearing loss observed with both chlorthalidone and acetazolamide; in the long term (>5 y), no preventive effect on deterioration of the hearing loss	Not assessed	None reported	3b
Raivio et al (1989)[20]	PTA, glycerol test, and electronystagmography with caloric testing	In 58 of 104 cases (55.8%), the "treatment was effective"	In 46 of 104 (44.2%), the vertigo was not under control	2 with disabling hypotension	4
Santos et al (1993)[21]	1985 CHE reporting guidelines, PTA	Hearing improved in 35%, unchanged in 29%, worse in 22%, and could not be classified by CHE guidelines in 14%	Vertigo control complete or substantial in 79%, limited or insignificant in 19%, and worse in 2%	None reported	4
Kanda et al (1993)[14]	1985 CHE reporting guidelines, PTA	Improvement in 7 of 32 (22%); hearing deterioration (>10-dB loss) in 13 patients (41%); good control of tinnitus by in 21%	Vestibular symptoms in 80% of patients improved	None reported	4
Kakigi et al (1995)[26]	PTA	57 (39.3%) of 145 ears showed hearing	None reported	None reported	4

(continued)

Table 3. (continued)

Study	Outcome Measures	Hearing Result	Vertigo Result	Side Effects	Study Quality
		improvement >10 dB			
Nozawa et al (1995)[19]	1972 CHE reporting guidelines, PTA	Hearing improved in 6 of 30 (20%), remained unchanged in 18 of 30 (60%), and became worse in 6 of 30 (20%); tinnitus disappeared in 5 of 30 (16.7%) and improved in 10 of 30 (33.3%); effectiveness rate for tinnitus was 50% (15 of 30 patients)	Definitive episodes were successfully controlled in 15 of 20 (75%); of 10 who were given drug intermittently, definitive episodes were successfully controlled in 6 of 10 (60%; according to the AAOO) and 7 of 10 (70%; according to AAO-HNS criteria)	Some patients complained of abdominal discomfort	4
Lassen et al (1996)[17]	1972 CHE reporting guidelines, PTA	Hearing stabilized or improved in 7 of 12 (58%)	Vertigo symptoms well controlled in 8 of 12 (67%)	1 with gastrointestinal upset,	4
Kitahara et al (2004)[15]	Japan Society for Equilibrium Research for Ménière's disease, ECoG	Hearing unchanged in 71%, hearing worsened in 29%	29% complete control of vertigo, 42% improved vertigo. 50% normalization of ECoG	None reported	4
Chung et al (2010)[13]	Dizziness Handicap Inventory, PTA	Hearing improved in 33.3% of 2-y group, 26.7% of 4-y group, 20% of 6-y group, and 16.7% of the 8-y group; initial hearing preserved in 59.3%, 63.3%, 50%, and 16.7% in each group; hearing preserved or improved in 70%-92% of 2, 4, and 6-y groups, but 4 (66.7%) showed aggravation in 8-y group	A significant change in Dizziness Handicap Inventory score and prominent changes observed in functional scores	None reported	4
Eryaman et al (2012)[25]	EEVS, VHQ, vestibular testing (oculomotor, Dix-Hallpike, calorics)	Not reported	Significant decrease in score of EEVS and VHQ at 3 wk compared to baseline	None reported	3b

Abbreviations: AAO-HNS, American Academy of Otolaryngology—Head and Neck Surgery; AAOO, American Academy of Ophthalmology and Otolaryngology; CHE, Committee on Hearing and Equilibrium; ECoG, electrocochleography; EEVS, European Evaluation of Vertigo Scale; PTA, pure tone average; VHQ, Vertigo Handicap Questionnaire.

aggregated results. A majority of these studies reported improvement in vestibular symptoms or vertigo, with less than half reporting improvement in hearing. The mechanisms of action for the diuretics reviewed vary (**Table 7**), but a common theme involves regulation or modulation of ion transport across membranes. The pathophysiology of MD is

Table 4. Hearing Results from Included Studies.

Reported Hearing Result	n (%)
Hearing improvement	8 (42.1)
Mixed hearing results	6 (31.6)
No hearing improvement or worsened	2 (10.5)
No result reported	2 (10.5)
Inconclusive hearing result	1 (5.3)

Table 5. Vertigo Outcomes Results from Included Studies.

Reported Vertigo Symptoms	n (%)
Improvement in vertigo	15 (79.0)
Mixed vertigo results	2 (10.5)
No result reported	2 (10.5)

Table 6. Therapy Side Effects Reported from Included Studies.

Therapy Side Effects	n (%)
None reported	10 (52.6)
Abdominal discomfort	3 (15.8)
Abdominal discomfort, nausea, diarrhea	1 (5.3)
Dry mouth, thirst, hypokalemia, weight loss, fatigue	1 (5.3)
Fatigue	1 (5.3)
Hypokalemia and hyperuricemia	1 (5.3)
Hypotension	1 (5.3)
Paraesthesias, headaches, chest tightness	1 (5.3)

hotly debated, but the contribution of endolymphatic hydrops to MD symptomatology remains a prevailing theory. If the symptoms of MD are related to endolymphatic hydrops, then plausible mechanisms of symptom relief with diuretic agents could include reduction of the hydrops and/or reversal of ion gradient aberrations that result in disruption of vestibular and auditory physiology. Investigation of calcium homeostasis of the endolymph in guinea pigs has shown that calcium is transported into the endolymph of cochlea and out of endolymph in the saccule and utricle.[27] The authors purport the possibility that endolymphatic hydrops may arise from disturbance in calcium flow rather than changes in endolymph volume.[27] One of the main regulators of the electrochemical gradient within the cochlea is the stria vascularis. This structure is also central to the production of endolymph. In temporal bone studies, relative ischemia of the stria vascularis has been demonstrated in patients with a history of MD.[28,29] Whether this observation is the result or cause of hydrops remains to be determined, but these findings serve as additional evidence that dysregulation of the electrochemical gradient may be a pathophysiologic mechanism. To further characterize if diuretic therapy has any direct benefit in treating MD, demonstration of attenuation of endolymphatic hydrops or the modulation of electrochemical mediators is needed.

The dosing and duration of therapy varied widely in this review. Static dosing, tapering, and up-titration methods were all used. The rationale for these dosing strategies was not made clear. The outcomes reporting was heterogeneous with either internal or arbitrary measures or the use of consensus guidelines, including the Japan Society for Equilibrium Research for MD,[30] the 1972 American Academy of Ophthalmology and Otolaryngology Committee on Hearing and Equilibrium guidelines,[31] and the 1985 or 1995 American Academy of Otolaryngology—Head and Neck Surgery Committee on Hearing and Equilibrium guidelines.[32,33] Diuretic therapy for MD appears to be well tolerated. Ten (52.6%) studies reported no side effects, and 4 studies (21.1%) reported abdominal discomfort. No significant morbidity or mortality was reported in any study.

As with other conditions faced by otolaryngologists, diuretic therapies for MD are often initiated as first-line therapy, despite only low-level evidence to justify their use. To compound the uncertainty created by the lack of existing evidence, there is likely little impetus for institutions and pharmaceutical companies to pursue elaborate and well-funded multicenter RCTs to evaluate the use of generic diuretics to treat patients with MD. Clinicians are then confronted with a challenge to appraise the existing literature and tailor therapy to suit the individual patient. If clinicians observe strict adherence to the strength of evidence as the basis for which clinical decisions are made, the efficacy of diuretics in the treatment of MD could be described as speculative at best. However, in situations where a large body of low-level evidence exists with a lack of affirmative high-level evidence, we should not preclude the use of such therapies. If we do, little will be left in our armamentarium.

Our systematic review has limitations to note. Inherent to the design of our review, we purposefully included literature of ''lesser'' quality than RCTs. In doing so, we have exposed our conclusions to potential bias and error inherent to study designs of less rigor. RCTs are the gold standard in prospective study design, owing to their ability to limit bias and account for confounding variables. The downsides of RCTs are the resources and expenses associated with their proper execution. In an era of intense competition for research funding, it is not practical to develop, fund, and execute RCTs to evaluate every therapeutic for every condition. This reality leaves investigators few options other than to sort and compile clinical observations with imperfect data from disparate sources to arrive at conclusions on therapy efficacy. Another limitation to our conclusions is the lack of standardization of diuretic type, dosing, and duration of therapy. Our review identified 8 medications with diuretic properties with varying treatment regimens. The lack of therapy standardization prevents us from making an inference on the efficacy of specific pharmacologic mechanisms of action.

Table 7. Mechanisms of Action for Selected Diuretic Agents.[a]

Agent	Mechanism of Action
Acetazolamide	Reversible inhibition of the enzyme carbonic anhydrase resulting in reduction of hydrogen ion secretion at renal tubule and an increased renal excretion of sodium, potassium, bicarbonate, and water. Decreases production of aqueous humor and inhibits carbonic anhydrase in the central nervous system to retard abnormal and excessive discharge from its neurons.
Chlorthalidone	Sulfonamide-derived diuretic that inhibits sodium and chloride reabsorption in the cortical-diluting segment of the ascending loop of Henle.
Hydrochlorothiazide	Inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions.
Isosorbide	Osmotic diuretic with properties similar to those of mannitol.
Nimodipine	Nimodipine is a dihydropyridine calcium channel blocker that has the general properties of nifedipine, which includes vasodilatation, with reduced peripheral resistance, blood pressure, and afterload; increased coronary blood flow; and a reflex increase in heart rate. Additional evidence suggests a diuretic action of calcium channel blockers through interference with renal and extrarenal systems involved in the regulation of physiologic fluid and electrolyte balance.[35]
Triamterene	Blocks epithelial sodium channels in the late distal convoluted tubule and collecting duct, which inhibits sodium reabsorption from the lumen. This effectively reduces intracellular sodium, decreasing the function of Na+/K+ ATPase, leading to potassium retention and decreased calcium, magnesium, and hydrogen excretion.

[a]Source: Lexicomp,[34] unless otherwise stated.

The natural history of MD is highly variable, which can make it difficult to discern differences between treatment and therapeutic effects. The natural history of an individual patient would be difficult to take into account when analyzing data from interventions, but this factor may explain the variation seen in the outcomes reported in the studies we reviewed. Moreover, we cannot ascertain the percentage of patients who experience spontaneous symptom improvement without the use of diuretic therapy. The natural history of MD lends itself to spontaneous recovery from symptoms without any intervention. Only 2 of our sources were RCTs in design with a placebo as control.[8,11] Patients in these placebo groups did experience symptom improvement, although this was not significant in either RCT. Last, we suspect that publication bias may also explain the relative frequency of positive results reported by the compiled studies in this review. It is probable that studies with negative results either have not been submitted or were not accepted for publication.

Conclusion

Multiple low-evidence-level studies report that oral diuretic therapy may be beneficial in the medical management of MD. If feasible, placebo-controlled studies will be required to further substantiate these claims. Improvement in vertigo episode frequency was often reported, with less convincing evidence for improvement in hearing outcomes. These conclusions are mitigated by multiple limitations, including the natural history of MD, study design, and the possibility of publication bias. Further investigation of the pathophysiology of MD will be essential for providing tailored direction for established and new therapies. Attention will need to be paid to the natural history of MD to determine true treatment effects.

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Author Contributions

Matthew G. Crowson, project design, data collection, data analysis, manuscript preparation, drafting, final approval, accountability for all aspects of the work; **Aniruddha Patki**, Project design, Data analysis, drafting, final approval, accountability for all aspects of the work; **Debara L. Tucci**, Project design, drafting, final approval, accountability for all aspects of the work

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References

1. Harris JP, Alexander TH. Current-day prevalence of Meniere's syndrome. *Audiol Neurootol*. 2010;15:318-322.
2. American Academy of Otolaryngology—Head and Neck Foundation. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. *Otolaryngol Head Neck Surg*. 1995;113:181-185.
3. Gibson WP. Hypothetical mechanism for vertigo in Meniere's disease. *Otolaryngol Clin North Am*. 2010;43:1019-1027.

4. Paparella MM. Pathogenesis of Meniere's disease and Meniere's syndrome. *Acta Otolaryngol Suppl*. 1984;406:10-25.
5. Thirlwall AS, Kundu S. Diuretics for Meniere's disease or syndrome. *Cochrane Database Syst Rev*. 2006:CD003599.
6. OCEBM Levels of Evidence Working Group. *Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document)*. Oxford, UK: Oxford Centre Evidence-Based Medicine; 2011.
7. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015; 349:g7647.
8. Klockhoff I, Lindblom U. Meniére's disease and hydrochlorothiazide (Dichlotride®): a critical analysis of symptoms and therapeutic effects. *Acta Otolaryngol*. 1967;63:347-365.
9. Kitahara M, Takeda T, Yazawa Y, et al. Treatment of Meniere's disease with isosorbide. *ORL J Otorhinolaryngol Relat Spec*. 1982;44:232-238.
10. Petermann W, Mulch G. Long-term therapy of Meniere's disease: comparison of the effects of betahistine dihydrochloride and hydrochlorothiazide. *Fortschr Med*. 1982;100:431-435.
11. van Deelen G, Huizing E. Use of a diuretic (Dyazide®) in the treatment of Méniere's disease. *ORL J Otorhinolaryngol Relat Spec*. 1986;48:287-292.
12. Brookes GB, Booth JB. Oral acetazolamide in Meniere's disease. *J Laryngol Otol*. 1984;98:1087-1095.
13. Chung SW, Cho CH, Han GC. Hearing and dizziness in patients with definite Meniere's disease after the long term use of diuretics. *J Int Adv Otology*. 2010;6:188-194.
14. Kanda K, Watanabe Y, Shojaku H, et al. Effects of isosorbide in patients with Meniere's disease. *Acta Otolaryngol Suppl*. 1993;504:79-81.
15. Kitahara T, Takeda N, Koizuka I, et al. Effects of long-term treatment with osmotic diuretics on symptoms and electrocochleogram in Meniere's disease. *Equilibrium Research*. 2004;63:237-241.
16. Klockhoff I, Lindblom U, Stahle J. Diuretic treatment of Meniere disease: long-term results with chlorthalidone. *Arch Otolaryngol*. 1974;100:262-265.
17. Lassen LF, Hirsch BE, Kamerer DB. Use of nimodipine in the medical treatment of Ménière's disease: clinical experience. *Otol Neurotol*. 1996;17:577-580.
18. Norell I, Stahle J. Treatment of Meniere's disease with hydrochlorothiazide. *Acta Otolaryngol*. 1962;54:447-456.
19. Nozawa I, Nakayama H, Hashimoto K, et al. Efficacy of long-term administration of isosorbide for Meniere's disease. *ORL J Otorhinolaryngol Relat Spec*. 1995;57:135-140.
20. Raivio M, Bunne M, Jorgensen B. Evaluation of a three-stage management program for Meniere's disease. *Am J Otol*. 1989; 10:443-446.
21. Santos PM, Hall RA, Snyder JM, et al. Diuretic and diet effect on Meniere's disease evaluated by the 1985 Committee on Hearing and Equilibrium guidelines. *Otolaryngol Head Neck Surg*. 1993;109:680-689.
22. Varga G, Miriszlai E, Szabó LZ. Experiences with acetazolamid therapy applied in our clinic to patients suffering from Ménière's disease for more than 8 years. *J Laryngol Otol*. 1966;80:250-269.
23. Yamazaki T, Imoto T, Hayashi N, Watanabe S, Kozaki H, Abe T. Menière's disease and isosorbide as an oral hyperosmotic agent (author's transl) [in German]. *Arch Otorhinolaryngol*. 1982;234:97-104.
24. Corvera J, Corvera G. Long-term effect of acetazolamide and chlorthalidone on the hearing loss of Meniere's disease. *Am J Otol*. 1989;10:142-145.
25. Eryaman E, Gokcan G, Parmaksiz E, et al. Are thiazides effective on hypertensive vertigo? A preliminary study. *Kulak Burun Bogaz Ihtis Derg*. 2012;22:219-224.
26. Kakigi A, Takeda T, Saito H, et al. Effect of isosorbide on hearing loss due to endolymphatic hydrops. *Acta Otolaryngol Supp*. 1995;519:223-226.
27. Salt AN, Inamura N, Thalmann R, et al. Calcium gradients in inner ear endolymph. *Am J Otolaryngol*. 1989;10:371-375.
28. Kariya S, Cureoglu S, Fukushima H, et al. Vascular findings in the stria vascularis of patients with unilateral or bilateral Meniere's disease: a histopathologic temporal bone study. *Otol Neurotol*. 2009;30:1006-1012.
29. Masutani H, Takahashi H, Sando I. Stria vascularis in Meniere's disease: a quantitative histopathological study. *Auris Nasus Larynx*. 1992;19:145-152.
30. Watanabe I. Ménière's disease. *ORL J Otorhinolaryngol Relat Spec*. 1980;42:20-45.
31. Committee on Hearing and Equilibrium. Report of Subcommittee on Equilibrium and Its Measurement. Meniere's disease: criteria for diagnosis and evaluation of therapy for reporting. *Trans Am Acad Ophthalmol Otolaryngol*. 1972;76: 1462-1464.
32. American Academy of Otolaryngology—Head and Neck Foundation. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. *Otolaryngol Head Neck Surg*. 1995;113:181-185.
33. Pearson BW, Brackmann DE. Committee on Hearing and Equilibrium guidelines for reporting treatment results in Meniere's disease. *Otolaryngol Head Neck Surg*. 1985;93:579-581.
34. Lexicomp Online.Hudson, OH: Lexi-Comp, Inc; 2015.
35. Barrett RJ, Wright KF, Taylor DR, et al. Cardiovascular and renal actions of calcium channel blocker chemical subgroups: a search for renal specificity. *J Pharm Pharmacol*. 1988;40: 408-14.

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Commentary

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2015 Equilibrium Committee Amendment to the 1995 AAO-HNS Guidelines for the Definition of Ménière's Disease

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Ménière's disease is a disorder of the inner ear that causes attacks of vertigo and hearing loss, tinnitus, aural fullness in the involved ear. Over the past 4 decades, the Equilibrium Committee of the AAO-HNS has issued guidelines for diagnostic criteria, with the latest version being published in 1995. These criteria were reviewed in 2015 by the Equilibrium Committee, and revisions were approved at the recent meeting of the committee at the 2015 AAO-HNSF Annual Meeting. The following commentary outlines the amended and approved criteria.

Keyword

Ménière's disease diagnosis

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Ménière's disease (MD) was first described in 1861 by Prosper Ménière, and it consists of the clinical combination of recurrent attacks of vertigo accompanied by aural fullness, tinnitus, and fluctuating hearing loss. Although no singular etiology for MD has been discovered, the association of clinical symptoms during life and the finding of endolymphatic hydrops on postmortem temporal bone examination have led to the view that the hearing loss and vertigo in MD are associated with abnormal endolymph production and/or resorption. Nevertheless, there remains no singular clinical test for MD, and making the diagnosis rests with identification of key clinical features.

In the past, numerous efforts have been made to produce a consensus statement regarding the diagnosis of MD. In 1974, the Japanese Society for Equilibrium Research proposed criteria for diagnosing MD, which were not published. The American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) followed with a series of published guideline statements in 1972, with subsequent revisions in 1985 and 1995.[1] At present, the AAO-HNS recognizes 4 diagnostic categories for MD: certain, definite, probable, and possible (**Table 1**). Moreover, the nature and documentation of fluctuating hearing loss are broadly defined.

Recently, the Barany Society has initiated an attempt to develop internationally accepted definitions for a variety of vestibular disorders. The Classification Committee of the Barany Society was formed to develop the International Classification of Vestibular Disorders to standardize terminology for reporting and research purposes regarding vestibular signs and symptoms, vestibular syndromes, and specific vestibular diseases. With regard to MD, a multinational collaboration was formed among the Equilibrium Committee of the AAO-HNS, the Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology, the Korean Balance Society, and the Barany Society to further refine the definition of MD and explore potential etiologies. Under the direction of Jose A. Lopez-Escamez, MD, PhD, a consensus document was created on published in 2015.[2] This document outlines the committee's recommendations with regard to diagnostic criteria for MD and discusses potential etiologies and associations with alternative diagnoses, including vestibular migraine and transient ischemia. In this document, only 2 categories of MD—definite and probable—are recognized and the characteristics of each category defined (**Table 2**). At the 2015 AAO-HNSF Annual Meeting in Dallas, the Equilibrium Committee reviewed and approved the modified definitions of MD as an amendment to the 1995 MD guidelines. The major differences between the new and old definitions are as follows: (1) the elimination of the ''certain'' and ''possible'' MD categories, (2) the requirement for audiometrically documented low- to mid-tone fluctuating loss

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Table 1. 1995 AAO-HNS Guidelines for Diagnosis of Ménière's Disease.[1]

Certain	Definite Ménière's disease, plus histopathologic confirmation of hydrops
Definite	Two or more definitive spontaneous episodes of vertigo 20 min or longer
	Audiometrically documented hearing loss on at least 1 occasion
	Tinnitus or aural fullness in the treated ear
	Other causes excluded
Probable	One definitive episode of vertigo
	Audiometrically documented hearing loss on at least 1 occasion
	Tinnitus or aural fullness in the treated ear
	Other causes excluded
Possible	Episodic vertigo of the Ménière's type without documented hearing loss or
	Sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definitive episodes
	Other causes excluded

Table 2. Amended 2015 Criteria for Diagnosis of Menière's Disease.

Definite	Two or more spontaneous episodes of vertigo, each lasting 20 min to 12 h
	Audiometrically documented low- to midfrequency sensorineural hearing loss in 1 ear, defining the affected ear on at least 1 occasion before, during, or after 1 of the episodes of vertigo
	Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear
	Not better accounted for by another vestibular diagnosis
Probable	Two or more episodes of vertigo or dizziness, each lasting 20 min to 24 h
	Fluctuating aural symptoms (hearing, tinnitus, or fullness) in the affected ear
	Not better accounted for by another vestibular diagnosis

in the affected ear only in the ''definite'' category, and (3) a defined range of vertigo duration. The committee did not address additional topics in the International Classification of Vestibular Disorders document regarding etiology or therapy and felt that a more thorough review of the entire disease process via a clinical practice guideline would be more appropriate.

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References

1. Committee on Hearing and Equilibrium. Guidelines for the diagnosis and evaluation of therapy in Menière's disease. *Otolaryngol Head Neck Surg*. 1995;113:181-185.
2. Lopez-Escamez JA, Carey J, Chung WH, et al. Diagnostic criteria for Ménière's disease. *J Vestib Res*. 2015;25;1-7.

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REVIEW

What is Menière's disease? A contemporary re-evaluation of endolymphatic hydrops

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Abstract Menière's disease is a chronic condition with a prevalence of 200–500 per 100,000 and characterized by episodic attacks of vertigo, fluctuating hearing loss, tinnitus, aural pressure and a progressive loss of audiovestibular functions. Over 150 years ago, Prosper Menière was the first to recognize the inner ear as the site of lesion for this clinical syndrome. Over 75 years ago, endolymphatic hydrops was discovered as the pathologic correlate of Menière's disease. However, this pathologic finding could be ascertained only in post-mortem histologic studies. Due to this diagnostic dilemma and the variable manifestation of the various audiovestibular symptoms, diagnostic classification systems based on clinical findings have been repeatedly modified and have not been uniformly used in scientific publications on Menière's disease. Furthermore, the higher level measures of impact on quality of life such as vitality and social participation have been neglected hitherto. Recent developments of high-resolution MR imaging of the inner ear have now enabled us to visualize in vivo endolymphatic hydrops in patients with suspected Menière's disease. In this review, we summarize the existing knowledge from temporal bone histologic studies and from the emerging evidence on imaging-based evaluation of patients with suspected Menière's disease. These indicate that endolymphatic hydrops is responsible not only for the full-blown clinical triad of simultaneous attacks of auditory and vestibular dysfunction, but also for other clinical presentations such as "vestibular" and "cochlear Menière's disease". As a consequence, we propose a new terminology which is based on symptomatic and imaging characteristics of these clinical entities to clarify and simplify their diagnostic classification.

Keywords Menière's disease · Endolymphatic hydrops · Magnetic resonance imaging · Diagnosis · Classification

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Introduction

Prosper Menière reported in 1861 that vertigo, balance and hearing diseases reflected a lesion of the inner ear [1]. Previously, dizziness and balance diseases had been attributed to "apoplectiform cerebral congestion", and the anatomical structures of the inner ear were only considered with respect to sound perception. As a director of the first school for the deaf-mute in Paris, Prosper Menière undoubtedly saw many patients with the combination of deafness and vertigo. However, the role of the inner ear in maintaining balance and orientation was largely unknown at that time. The combination of his clinical experience with this patient group and his knowledge of Flourens' seminal work on the effects of semicircular canal ablation

in pigeons allowed him to recognize the inner ear as the site of lesion.

The cardinal symptoms of Menière's disease (MD) form a disease entity consisting of episodic vertigo, fluctuant hearing loss and tinnitus. The patients also complain of fullness in the ear, gait problems, postural instability, drop attacks and nausea. MD is a chronic illness affecting about 190 per 100,000 patients in a US health claims database, but in population-based studies a prevalence of as high as 513/100,000 has been reported [2]. In 1937, the discovery of endolymphatic hydrops (EH) in human temporal bones by British and Japanese researchers [3, 4] revealed the pathologic counterpart of the clinical syndrome described by Prosper Menière. EH is a distension of the endolymphatic space of the inner ear into areas that are normally occupied by the perilymphatic space. It most often occurs in the cochlear duct and the sacculus but may also involve the utricle and the semicircular canals [5]. Analysis of temporal bone specimens has shown variability of the presence of EH [6] and Salt and Plontke [7] questioned whether the presence of post-mortem EH is either essential or specific to MD. Recent developments of gadolinium chelate (GdC)-enhanced MRI after transtympanic injection of the contrast agent provide a tool for separately visualizing endolymphatic and perilymphatic spaces with gadolinium chelate (GdC) as the contrast agent [8]. With these new imaging techniques, EH can be demonstrated in vivo and can be used to confirm the diagnosis.

In this article, we shall summarize important recent developments in the evaluation of EH in MD and discuss the future impact of these insights on its classification.

Evidence from human temporal bone studies

Morita et al. [9] examined 53 temporal bones and quantified endolymphatic hydrops in patients with Menière's disease: the collective endolymphatic volume of the cochlear duct, saccule and utricle amounted to 64 µl in comparison to 20 µl in healthy subjects. Therefore, the very tightly controlled minuscule endolymphatic fluid space of the inner ear is enlarged by more than 200 % in MD! Of all the hitherto known pathologic changes in MD patients, this change clearly has the highest magnitude.

However, in order to obtain clues that help us to understand (1) what is the pathophysiologic consequence of EH? and (2) what events lead to the development of EH?, other pathologic changes that are found in MD patients have to be considered as well.

Nageris et al. [10] described a related phenomenon: the displacement of the basilar membrane towards the scala tympani in the apical cochlear regions. In MD patients' temporal bones, there was a significant correlation between the severity of EH and the basilar membrane displacement. The reason why this phenomenon was found only in the apical portion of the cochlea is probably the larger width and higher elasticity of the basilar membrane compared to the basal cochlear regions and the lack of a supporting bony structure of the apical Lamina spiralis. This feature is a consequence of EH that has severe functional consequences, since the basilar membrane and its specific biomechanic properties are an essential part of the mechanoelectrical transfer function of the hearing system.

Other morphologic changes that have been observed in MD give not such a clear picture. Unfortunately, the research on inner ear pathology has not been systematically promoted for a long time. Until 1995, examinations of only 100 cases of MD have been published worldwide, and many of those were based on insufficient clinical information. Often, a vestibular fibrosis is observed, with the formation of band-like fibrous structures. These may create a connection between the stapes footplate and the utricular macula, which in turn could be an explanation for the Hennebert sign (occurrence of vertigo when static pressure is applied to the ear canal) [11]. Within the endolymphatic sac (ELS), an increased amount of intraluminal precipitate, consisting of glycoproteins secreted by the ELS, has been demonstrated [12]. Furthermore, ultrastructural evidence suggests that glycoprotein synthesis in the rough endoplasmatic reticulum and Golgi complexes is hyperactive in MD patients [13]. Accumulation of Glycoproteins in the ELS could by its osmotic effect interfere with inner ear homeostasis and contribute to EH formation.

Electron microscopy studies revealed minimal changes of the cochlear hair cells: fusion of stereocilia and displacement of outer hair cells towards the basilar membrane, with loss of contact to the cuticular plate [14, 15], a phenomenon, which by itself may disable the cochlear amplifier function of the outer hair cells and, therefore, lead to hearing loss.

Further findings are a neural fiber loss in the spiral osseus lamina [16] and a reduced number of afferent nerve endings and afferent synapses at the basis of inner and outer hair cells [15]. Tsuji et al. could show a significant reduction of type II hair cells in all five vestibular end organs and of vestibular ganglion neurons [17]. Another recent study on 39 temporal bones found a marked loss of neurons of the spiral ganglion, in both the ipsilateral and contralateral ear in patients with unilateral MD [18]. A similar magnitude of loss of cochlear inner and outer hair cells was found (about 70 %). The stria vascularis, which can be regarded as the "power plant" of inner ear homeostasis, was found to be atrophic (reduced in area) and suffering from a reduced blood vessel density [19].

In summary, besides EH, several degenerative changes could be observed in the audiovestibular periphery of MD patients, especially in the afferent vestibular and cochlear

ganglia and nerves. However, these findings do not yet allow for definitive conclusions on the sequence of pathophysiologic events during the development and progress of the disease.

Relationship between histologically proven EH and clinical definite Menière's disease

Despite the development of several animal models of EH, none of these models displays the typical phenotype observed in human MD patients: paroxysmal audiovestibular events plus chronic-progressive loss of inner ear functions. Therefore, we shall concentrate on evidence from human patients when considering the relationship between EH and clinical MD in patients.

In a recent review, Foster et al. [20] analyzed all published articles that have reported on temporal bones with EH and/or on temporal bones of patients with clinically suspected MD. This resulted in a total of 3707 temporal bone specimens. Of these, 165 cases had been reported to fulfill the AAO-HNS 1995 criteria. Two of these studies were specifically designed to explore the relationship of EH to MD that meets the AAO-HNS 1995 criteria, and found EH in 100 % of MD cases [6, 21]. 163 of the temporal bones from definite MD patients in this review (98.8 %) had EH in at least one ear. Only two of 165 cases had been classified as MD without EH, and these cases were mentioned incidentally in a single study of strial changes in the contralateral ear of MD patients. Foster et al. communicated with the authors of that study [18] and report that both cases were diagnosed before the AAO-HNS 1995 criteria, and that their clinical presentation was not described so it is impossible to verify whether they fulfilled the AAO-HNS criteria during their lifetime. None of these cases can be used to refute the primary finding of the Merchant study that EH and MD are found in association with 100 % of cases when the current definition of MD is strictly applied.

This indicates that it is virtually certain that EH is present in at least 1 temporal bone in a person who meets current MD criteria. The authors conclude that EH is unlikely to be just an epiphenomenon of MD, because the association is perfect: every case with MD according to the AAO-HNS criteria showed EH. It seems, therefore, that EH is necessary but not sufficient for the display of the full symptom triad of MD.

Diagnostic criteria: evolution of the current criteria for assessment of Menière's disease

Symptom-based classification methods have been used to make the diagnosis [22]. In the diagnostic work up, mainly vertigo character and type, associated hearing loss and tinnitus or aural fullness are taken into consideration. Indeed, in a taxonomic investigation of patients with vertigo, after exclusion of neurological and middle ear conditions, head trauma and ototoxicity, Hinchcliffe [23] found that those with 'classical' Menière's disease (meeting the ''definite MD' definition below) fell in a single nosological entity with all the other cases of vertigo. He later argued that MD included 'formes frustes', where the triad of symptoms is not complete [24]. Diagnostically confirmed cases represent only a limited proportion of individuals with the disease, as reflected in the variability between prevalence studies [2, 25].

The nomenclature of "cochlear" or "vestibular" MD was coined by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) in 1972 [26] and was abandoned with the 1985 [27] and 1995 [22] updates of the AAO-HNS criteria as there was insufficient evidence that these mono-symptomatic diseases share the same pathophysiology with MD. The revised AAO-HNS criteria [22] define 'Possible MD' as episodic vertigo or fluctuating hearing loss. 'Probable MD' consists of one attack of rotatory vertigo lasting at least 20 min together with tinnitus and documented hearing loss. 'Definite MD' consists of two or more spontaneous episodes of vertigo 20 min or longer with tinnitus and documented hearing loss. 'Certain MD' is diagnosed by additional histological verification of EH in the inner ear. To define the condition clinically, the existing AAO-HNS classification is often unhelpful as the latency of joint presentation of the cardinal complaints may take up to 10 years [28]. General practitioners, otolaryngologists and audio-vestibular physicians face a challenge in making the diagnosis of MD. The symptoms can be variable, occur over different time spans and the hearing loss can recover before audiometric measurements are made [22].

Recently, the Classification Committee of the Bárány Society formulated diagnostic criteria for MD jointly with several national and international organizations [29]. The classification includes two categories: definite MD and probable MD. The diagnosis of definite MD is based on clinical criteria and requires the observation of an episodic vertigo syndrome associated with low- to medium-frequency sensorineural hearing loss and fluctuating aural symptoms (hearing, tinnitus and/or fullness) in the affected ear. Duration of vertigo episodes is limited to a period between 20 min and 12 h. Probable MD is a broader concept defined by episodic vestibular symptoms (vertigo or dizziness) associated with fluctuating aural symptoms occurring in a period from 20 min to 24 h. These definitions unfortunately do not help the clinician in defining MD. One interesting difference is that the proposed definition does not include endolymphatic hydrops that was the original finding in the disease.

Recent novel imaging methods have made it possible to visualize EH with gadolinium contrasted 3T MRI. The AAO-HNS (1995) criteria [22] include EH as landmark to define certain MD. Recently, Nakashima et al. [30] suggested that the inner ear of all patients with suspected MD should be imaged and the classification as definite MD should include MRI evidence of EH. The authors propose that also monosymptomatic ears with EH could be treated as MD in the same way as in the 1972 AAO-HNS classification, which recognized vestibular MD and cochlear MD as one disease entity among the umbrella of MD [26]. Supporting this idea, Pyykkö et al. [28] reported that in about 20 % of the patients with MD it can take more than 5 years and in 10 % even more than 10 years before cochlear and vestibular symptoms will coincide.

To conclude, we propose that diagnosis of MD should be based on the presence of EH in addition to symptoms and that also monosymptomatic patients with EH be regarded as 'certain' MD cases. MRI investigations should be made more frequently in assessing MD than hitherto.

Clinical features of Menière's disease

Although the cardinal symptoms of vertigo, hearing loss and tinnitus are generally well acknowledged by physicians, MD patients often complain also of pressure or fullness in the ear, gait problems, postural instability, Tumarkin attacks and nausea [31, 32]. To determine the severity of the impact on the patients' quality of life, several symptom-specific scoring instruments have been developed. Such rating scales are, e.g., the Hearing Disability and Handicap Scale [33, 34], the Vertigo Handicap Index [35], and the International Tinnitus Inventory [36]. A MD-specific indicator is the MD Patient Oriented Severity Index (MDPOSI) [37]. Some of these have been developed to evaluate changes in the natural course or therapeutic effects, such as MDPOSI. The symptom-specific instruments seem to more accurately reflect changes in control of vertigo in MD over time than do, e.g., general Quality of Life (QoL) instruments [32]. These indicators seem to be capable of describing changes in the activity of the disease and are used in the validation of the efficacy of the treatment [38, 39]. In addition, it seems that personal trait measured as sense of coherence, attitude and mood are important determinants for the impact of MD [32, 39, 40]. Stephens et al. [41] pointed out that anxiety, as a mood disorder, will reflect expectations, environmental demands and attitudes. They showed that the level of anxiety correlated with the Sense of Coherence [40].

However, the personal factors, uncertainty of life and environmental factors have not been included in the different complaint-oriented impact classifications. In this regard, the International Classification of Function group (ICF, WHO 2001) [42] has developed a system encompassing many different aspects of the disease, which can be used as explanatory framework. This framework allows a better understanding of the impact of the illness and what consequences it has on general well-being and, therefore, may help to alleviate these impacts. Social participation which is included in the ICF is a vital part of life in human behavior that forms the core construct of the level of activities enabling goal-directed behavior. When establishing treatment strategies, ICF includes two most important additional topics: own attitudes and personal contextual factors, as pointed out by Wade [43].

In MD, ICF brings in some important elements of activity limitations such as fatigue and car driving that were reported only in an open-set questionnaire. It also brings in the work-related items that can be severe and impact greatly on the quality of life in MD, as well as specific participation restrictions, such as problems in shopping, doing household work, performing sport activities and gardening [44]. Among personal contextual factors, the restrictions in life and uncertainty are also important [44]. These items were reflected in anxiousness which was one of the most significant factors correlating with the quality of life [32].

In several instruments measuring quality of life such as 15-D, SF-36 as well as in the perception of 'wellness' changes in vitality has been reported in MD [45]. About 70 % of the subjects with MD had reduced vitality [46]. Reduction of vitality correlated with increased anxiety, reduction of quality of life and with several items describing participation restrictions. The reduction in vitality seems to be a consequence of the condition (in this case vestibular dysfunction) rather than a causative factor for MD [32, 47, 48]. Although personality trait was associated with anxiety and vitality, the personality trait was regarded as a modifying factor for the condition. The relatively minor role of the personality trait in quality of life and disease-specific impact has been documented earlier [39, 48, 49]. Van Cruissen et al. [47] indicated that the psychological profile of MD patients seems comparable to patients with other chronic conditions.

To summarize, MD causes restrictions in a very broad spectrum of personal activities as well as in contextual factors and is characterized by reduced vitality and uncertainty of control of life. The restricted formulation of complaints in current classifications does not explain the individual constraints caused by the illness. The condition may lead to restrictions and limitations that are not directly related to the disease at first glance [44]. There are very few reports in the literature describing the complaints associated with fatigue and especially social isolation [38, 48]. The assumption that healing an impaired function

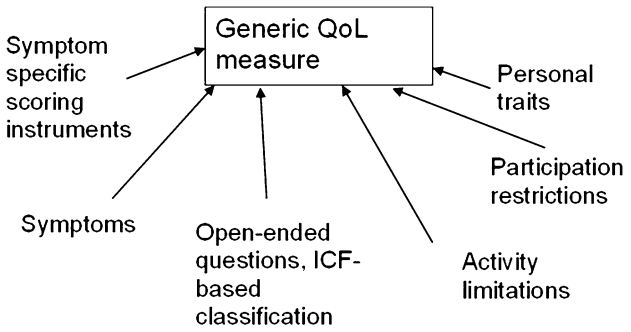

Fig. 1 Different approaches used to analyze the impacts of Menière's Disorder all of which influence generic measures of quality of life (QoL). The disease-specific model can be built from impairments caused by symptoms, open-ended questions, activity limitations or participation restriction (modified from [32]). All these different measures display specific aspects of QoL but are not interchangeable with the outcome of generic QoL instruments

alone would restore the full health in patients with MD is erroneous, since the social participation forms the core construct to achieve any goal-directed behavior [40, 50]. We, therefore, encourage future studies in MD to include the above-mentioned measures of health (Fig. 1), especially vitality and its association with social and personal isolation and to apply holistic therapeutic efforts in MD.

Evidence from MR imaging in humans

Recent developments of 3 T MR imaging provide a tool for visualizing EH with gadolinium chelate (GdC) as the contrast agent. Following the development of separate visualization of the endo- and perilymphatic compartments by Zou et al. [8], Naganawa et al. [51] and Nakashima et al. [52, 53] developed specific algorithms using Fluid Attenuation Inversion Recovery sequences (FLAIR) that will demonstrate minute amounts of contrast agent in the inner ear [54]. Later, they demonstrated that 3-D recovery turbo spin echo with real reconstruction (3D-real IR) showed higher contrast between the non-enhanced endolymph and the surrounding bone [55]. With the new imaging techniques, EH can be demonstrated in vivo and can confirm the diagnosis. Recently, it has been demonstrated that EH can differently affect cochlear and vestibular compartments and cause different complaints [28]. The value of EH imaging in the differential diagnosis has been shown for the example of patients with clinically suspected vestibular migraine [56]. Furthermore, EH could be demonstrated to progress over time [57] during the disease course, and to be correlated with the deterioration of cochlear, saccular and hSCC function [58–61]. However, the association between clinical symptoms and EH is not uniform in each patient, as hearing can be relatively well preserved despite prominent endolymphatic hydrops. Nakashima et al. [62] and Fiorino et al. [63] have demonstrated, with MRI, that EH was present in all living patients with definite MD.

The classification of the degree of endolymphatic hydrops is performed separately for the vestibulum and the cochlea, based on previously documented criteria [64]. The normal limit of ratio of the endolymphatic area over the vestibular fluid space (sum of the endolymphatic and perilymphatic area) is 33 % and any increase in the ratio would be indicative of EH. According to these criteria, *mild EH* in the vestibule covers the ratio of 34–50 % and significant *EH* covers the ratio of more than 50 % in the vestibule. Examples of mild and significant vestibular EH are given in Fig. 2. The respective evaluation of the ratio of the endolymphatic area in the cochlea is correlated to the displacement of Reissner's membrane. Normally, the Reissner's membrane remains in situ and is shown as a straight border between the endolymph containing scala media and the perilymph containing scala vestibuli. Mild EH displays an extrusion of the Reissner's membrane towards the scala vestibuli and results in an area enlargement of the scala media while not exceeding the area of the scala vestibuli. Significant EH causes an increase of the scala media with an area larger than that of the scala vestibuli. Based on previous MRI studies in normal subjects, Nakashima et al. suggested 33 % as the upper limit for the enlargement of endolymphatic space of the vestibule [64]. The normal values that we use have been recently confirmed by other researchers [63, 65].

For clinical MR imaging of endolymphatic hydrops, two alternative routes of GdC application may be used: intravenous (i.v.) or intratympanic (i.t.). After microscopically controlled application of GdC into the middle ear cavity, it enters the inner ear via the round and oval windows (Fig. 3). The benefit in i.t. delivery is that it achieves higher GdC concentrations—with a significantly lower total administration dosage—than i.v. delivery and the pathology is easier to recognize. However, the i.t. application is off-label, and in our hands about 5–10 % of patients have insufficient GdC uptake from the middle ear. I.t. administration of GdC reduces the risk of systemic toxicity, although it may potentially cause local irritation and toxicity [66, 67]. Current clinical data, however, reveal no evidence of ototoxicity after i.t. application [68–70]. If the clinical presentation suggests a disturbance of the blood–labyrinth barrier, e.g., due to inflammatory processes, this requires i.v. application of GdC to visualize this pathology. In their most recent imaging techniques of the inner ear, Naganawa and Nakashima [70–72] used i.v. administration of GdC with subtraction technique in 3T MRI. With a single dose of i.v. GdC, EH was visualized at 4 h post-injection in humans.

The development of dynamic imaging techniques of the inner ear has provided two important new insights into MD: (1) the cochlear and vestibular compartments can be

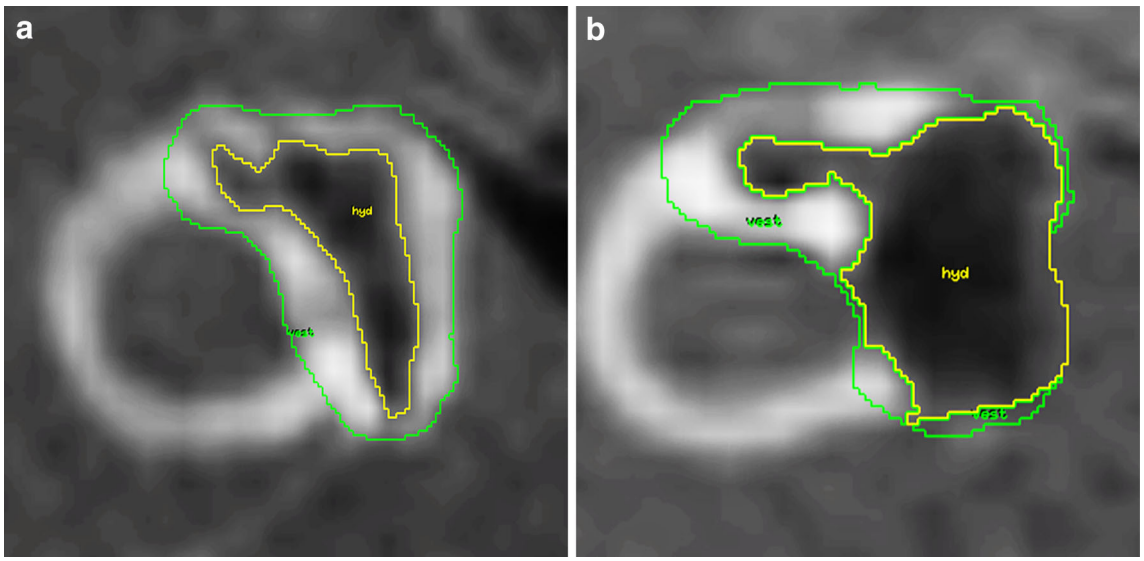

Fig. 2 Assessment of vestibular endolymph space in a right inner ear using regions of interest (ROI). The outer ROI defines the cross-sectional area of the vestibulum at the level of the horizontal semicircular canal ("vest"). The inner ROI defines the endolymphatic space inside the vestibulum ("hyd"). **a** The vestibular endolymph ratio in this patient is 0.35, corresponding to mild EH. **b** The vestibular endolymph ratio in this patient is 0.64, corresponding to significant EH (Figure reproduced from [61])

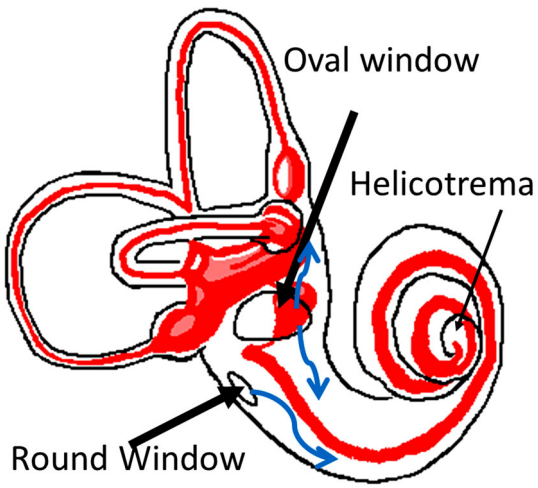

Fig. 3 Entry of intratympanically applied drugs into the inner ear perilymph space (*white*) via the round and oval windows. Endolymph space is marked in *red*

differently affected. (2) EH is very often present in the "asymptomatic contralateral ears" [28, 53]. It has been well known since long that in typical unilateral MD, the incidence of symptomatic and functional involvement of the contralateral ear increases almost linearly with the length of observation, resulting in bilaterality rate of almost 50 % at 30 years after onset of unilateral MD [92]. Initial clinically bilateral presentations of MD, however, are rare. With the advent of endolymphatic hydrops imaging, we now find that even in clinically unilateral MD, the proportion of contralateral hydropic changes of the inner ear is surprisingly high, and was reported to reach 65 % of clinically "asymptomatic contralateral ears" in an average MD population [28]. This would indicate that MD is a systemic disease. In a recent study, EH was present in 190 out of 205 ears (93 %) with symptoms attributable to MD [28]. Table 1 demonstrates that EH occurs more frequently in the vestibule than the cochlea but most commonly the EH was found in both cochlea and vestibule.

Of equally great interest are the findings on EH in other disease entities of the inner ear. The great advantage of these imaging data over the autopsy data is the much more detailed clinical description and the perfect temporal association between the EH and the clinical symptoms.

Table 2 summarizes the currently published imaging data on patients that have not been clinically classified as definite MD cases. This emerging new body of evidence allows for some first observations:

The patients with fluctuating low frequency hearing loss very often have EH, and there is a tendency towards more apically located cochlear EH. These are analogous to the "cochlear MD" entity as defined by the AAO-HNS 1972 guidelines. On the other hand, a pure sudden sensorineural hearing loss (not affecting the low frequencies) seems not to be clearly associated with EH. For the other patient groups, with less typical presentations, however, there are two different entities emerging: those with EH and those without EH (Table 3).

In contrast to the "cochlear MD", the patients with "vestibular MD" show more variability, but still a significant portion of them has EH. A probable explanation for

Table 1 Endolymphatic hydrops in patients with symptoms associated with Menière's disorder classified with the AAO-HNS as possible, probable and definite Menière's disorder (205 ears with symptoms) and also in 45 contralateral ears without symptoms are included

Symptom/diagnosis	EH in cochlea only	EH in vestibule only	EH in both	Total with EH
Possible MD ($n = 122$)	8	43	57	108
Probable MD ($n = 15$)	2	4	8	14
Definite MD ($n = 68$)	1	4	63	68
Total ($n = 250$)	11	51	136	219

Cochlea and vestibule are analyzed separately. Table modified from Pyykko et al. [28]

Table 2 Summary of published reports of EH in patients that were not clinically classified as definite Meniére's disease

Entity	*N*	With EH (%)	Remarks	References
FLFSNHL	1	1 (100 %)		[73]
	8	6 (80 %)		[74]
	56 ears	38 cochlear EH, 44 vestibular EH	No. of patients with EH not given	[75]
	1	1 (100 %)		[76]
	1	1 (100 %)		[77]
	3	3 (100 %)		[78]
	43	40 (93 %)		[28]
	8	8 (100 %)	All had EH in Cochlea and Vestibulum. The two cases with severe vestibular EH had absent VEMP	[79]
	5	5 (100 %)		[80]
ALFSNHL	1	1 (100 %)		[81]
	2	2 (100 %)	Both had EH in the apical cochlear regions	[82]
RPV	64	31 (48 %)	All patients had horizontal Nystagmus during attacks	[83]
	3	0 (0 %)		[74]
	1	0 (0 %)		[84]
	56	29 cochlear EH, 47 vestibular EH	No. of patients with EH not given	[75]
	2	1 (50 %)		[85]
	2	2(100 %)	EH was more pronounced in Vestibulum in all 3 cases	[78]
	17	15 (88 %)		[28]
SSNHL+V	7	4 (57 %)	Average hearing loss was 90 dB.	[86]
SSNHL	8	2 (25 %)	EH in Cochlea and Vestibulum. MRI at 2 and 11 months after SSNHL. Interpreted as DEH cases	[87]
	4	0 (0 %)		[74]
	1	0 (0 %)	HL was 68 dB	[85]
hSCC malformation	11	9 (82 %)	6 cases had severe EH	[88]
DEH	11	8		[74]
	7	7 (100 %)	Most had EH in both Cochlea and Vestibulum	[89]
	2	2 (100 %)		[82]
	1	1 (100 %)		[85]
	5	5 (100 %)		[90]
	2	2 (100 %)		[80]
VS	13	4 (31 %)	Only the vestibulum could be analyzed	[91]
LVAS	1	1 (100 %)		[85]

N number of patients, *FLSNHL* Fluctuating low frequency sensorineural hearing loss, *ALFSNHL* acute low frequency sensorineural hearing loss, *RPV* recurrent peripheral vestibulopathy, *SSNHL+V* sudden sensorineural hearing loss with vertigo, *SSNHL* sudden sensorineural hearing loss, *hSCC* horizontal semicircular canal, *DEH* delayed endolymphatic hydrops, *VS* vestibular schwannoma, *LVAS* large vestibular aquaeduct syndrome

Table 3 Proposed terminology for inner ear diseases related to endolymphatic hydrops, based on clinical and imaging findings

Proposed new terminology	Old terminology	Other terms
Primary hydropic ear disease (PHED)		
Cochleovestibular type	Definite MD SSNHL+V	Typical MD
Cochlear type	Cochlear MD ALFSNHL	FLFSNHL
Vestibular type	Vestibular MD	RPV, Forme fruste
Secondary hydropic ear disease (SHED)		
Cochlear/vestibular/cochleovestibular type, associated with:	Secondary MD	Menière syndrome
VS		
LVAS		
Labyrinthitis, meningitis		
Noise induced hearing loss		
Trauma		
Congenital hearing loss	DEH	
Inner ear malformation		
…		

FLSNHL fluctuating low frequency sensorineural hearing loss, *ALFSNHL* acute low frequency sensorineural hearing loss, *RPV* recurrent peripheral vestibulopathy, *SSNHL+V* sudden sensorineural hearing loss with vertigo, *DEH* delayed endolymphatic hydrops, *VS* vestibular schwannoma, *LVAS* large vestibular aquaeduct syndrome

this observation is the fact that—in contrast to the "cochlear MD" group which is defined by the very specific audiometric finding of fluctuating hearing levels predominantly in the low frequencies—in this "vestibular MD" group there has not yet been identified a distinctive vestibular phenotype. In analogy to the "cochlear MD", it is possible that a predominantly vestibular EH phenotype could be a certain pattern of abnormalities within the different vestibular function tests. A similar phenomenon linked to EH is well described in definite MD patients: whereas the caloric vestibular response is declining relatively early in the disease course, the vestibuloocular reflex as assessed by the head impulse test is remarkably well preserved until the rather late stages of the disease. This constellation is in stark contrast with, e.g., the entity of vestibular neuritis, where both tests are regularly pathologic. Whether a distinctive vestibular phenotype pattern is also present in "vestibular MD" still remains to be determined. Large-scale studies in this only recently recognized specific clinical and morphological entity are not yet available, but will likely promote our understanding of MD and EH in the future.

Proposed new terminology based on clinical and imaging findings

Based on the above-mentioned evidence, in order to simplify and clarify the terminology for patients with symptoms formerly described in various ways, e.g., "cochlear MD", "vestibular MD", "forme fruste", "atypical MD", "monosymptomatic MD", and in order to enable a description more closely related to the underlying pathology, we propose a new terminology for these clinical entities.

In this system, two main categories of inner ear disease with underlying EH are recognized: Primary Hydropic Ear Disease (PHED) and Secondary Hydropic Ear Disease (SHED). PHED includes not only the definite MD patients, but also the other clinical entities with the clinical phenotype formerly described as "cochlear MD" or "vestibular MD". The individual symptomatologic differentiation is described by the addition of "cochlear" or "vestibular" or "cochleovestibular type". This category (PHED) is characterized by the absence of any evident cause for the EH, i.e., a condition or preceding event that is likely to have a significant contribution to the formation of EH. If, in contrast, such a condition, e.g., tumors, malformations, infections, noise or other traumas that affect the inner ear can be identified in the patient, then the second category of SHED should be used. We are aware that high-resolution inner ear imaging is presently not available in all institutions. Therefore, the annotations of "suspected" and "certain" should be used, depending on the confirmation of EH in the individual patient by MR imaging.

Examples would be: "a 45-year-old patient with certain PHED of the vestibular type." Or "a 20-year-old patient with suspected SHED of the audiovestibular type associated with LVAS".

Especially for the entity of so-called "recurrent peripheral vestibulopathy"/"vestibular MD", which is still

an only vaguely defined clinical presentation, we expect that the addition of EH to the description of these patients will add important pathological information and help to define the vestibular phenotype of these patients. Furthermore, and even more important for the development of new therapeutic strategies, this proposed new classification may lead to an earlier identification of EH during the disease course, since health practitioners will likely be more aware of EH as the potential underlying pathology in patients that do not (yet) display the full-blown triad of MD symptoms. Therefore, therapeutic interventions may be possible earlier in the disease course, hopefully increasing the chance of halting or even reversing the further progression of EH.

Conclusion

Recent studies have shown that the description of functional impairments in MD restricted to vertigo, hearing loss and tinnitus as pure symptoms do not sufficiently reflect the wide-ranging impact on quality of life that MD patients are facing. Therefore, personal factors and measures of activity and vitality should be included in future studies.

The milestone development of MR imaging of endolymphatic hydrops supports the central role of endolymphatic hydrops in the pathology of MD, and confirms the same result from temporal bone studies. It has improved the differential diagnosis in suspected MD and warrants the discussion about a new pathology-based description of clinical entities that display various symptoms of inner ear dysfunctions due to endolymphatic hydrops.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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References

1. Atkinson M (1961) Meniere's original papers reprinted with an English translation with commentaries and biographical sketch. Acta Otolaryngo (Stockh) 162:1–78
2. Havia M, Kentala E, Pyykko I (2005) Prevalence of Meniere's disease in general population of Southern Finland. Otolaryngol Head Neck Surg 133(5):762–768
3. Hallpike CS, Cairns H (1938) Observations on the pathology of Menière's syndrome. Proc R Soc Med 31:1317–1336
4. Yamakawa K (1938) Über die pathologische Veränderung bei einem Menière-Kranken. Proceedings of 42nd Annual Meeting Oto-Rhino-Laryngol Soc Japan. J Otolaryngol Soc Jpn 4:2310–2312
5. Merchant SN, Rauch SD, Nadol JB Jr (1995) Meniere's disease. Eur Arch Otorhinolaryngol 252(2):63–75
6. Merchant SN, Adams JC, Nadol JB Jr (2005) Pathophysiology of Meniere's syndrome: are symptoms caused by endolymphatic hydrops? Otol Neurotol 26(1):74–81
7. Salt AN, Plontke SK (2010) Endolymphatic hydrops: pathophysiology and experimental models. Otolaryngol Clin North Am 43:971–983
8. Zou J, Pyykko I, Bjelke B, Dastidar P, Toppila E (2005) Communication between the perilymphatic scalae and spiral ligament visualized by in vivo MRI. Audiol Neuro-Otol 10(3):145–152
9. Morita N, Kariya S, Farajzadeh Deroee A, Cureoglu S, Nomiya S, Nomiya R, Harada T, Paparella MM (2009) Membranous labyrinth volumes in normal ears and Meniere disease: a three-dimensional reconstruction study. Laryngoscope 119(11):2216–2220
10. Nageris B, Adams JC, Merchant SN (1996) A human temporal bone study of changes in the basilar membrane of the apical turn in endolymphatic hydrops. Am J Otol 17(2):245–252
11. Nadol JB Jr (1977) Positive Hennebert's sign in Meniere's disease. Arch Otolaryngol 103(9):524–530
12. Ikeda M, Sando I (1984) Endolymphatic duct and sac in patients with Meniere's disease. A temporal bone histopathological study. Ann Otol Rhinol Laryngol 93(6 Pt 1):540–546
13. Wackym PA, Linthicum FH Jr, Ward PH, House WF, Micevych PE, Bagger-Sjoback D (1990) Re-evaluation of the role of the human endolymphatic sac in Meniere's disease. Otolaryngol Head Neck Surg 102(6):732–744
14. Kimura RS, Ota CY, Schuknecht HF, Takahashi T (1976) Electron microscopic cochlear observations in bilateral Meniere's disease. Ann Otol Rhinol Laryngol 85(6 Pt 1):791–801
15. Nadol JB Jr, Thornton AR (1987) Ultrastructural findings in a case of Meniere's disease. Ann Otol Rhinol Laryngol 96(4): 449–454
16. Spoendlin H, Balle V, Bock G, Bredberg G, Danckwardt-Lilliestrom N, Felix H, Gleeson M, Johnsson LG, Luciano L, Rask-Andersen H et al (1992) Multicentre evaluation of the temporal bones obtained from a patient with suspected Meniere's disease. Acta Otolaryngol Suppl 499:1–21
17. Tsuji K, Velazquez-Villasenor L, Rauch SD, Glynn RJ, Wall C 3rd, Merchant SN (2000) Temporal bone studies of the human peripheral vestibular system. Meniere's disease. Ann Otol Rhinol Laryngol Suppl 181:26–31
18. Kariya S, Cureoglu S, Fukushima H, Kusunoki T, Schachern PA, Nishizaki K, Paparella MM (2007) Histopathologic changes of contralateral human temporal bone in unilateral Meniere's disease. Otol Neurotol 28(8):1063–1068
19. Kariya S, Cureoglu S, Fukushima H, Nomiya S, Nomiya R, Schachern PA, Nishizaki K, Paparella MM (2009) Vascular findings in the stria vascularis of patients with unilateral or bilateral Meniere's disease: a histopathologic temporal bone study. Otol Neurotol 30(7):1006–1012
20. Foster CA, Breeze RE (2013) Endolymphatic hydrops in Meniere's disease: cause, consequence, or epiphenomenon? Otol Neurotol 34(7):1210–1214
21. Rauch SD, Merchant SN, Thedinger BA (1989) Menieres syndrome and endolymphatic hydrops—double-blind temporal bone study. Ann Oto Rhinol Laryn 98(11):873–883
22. AAO-HNS (1995) Committee on hearing and equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. American Academy of Otolaryngology-Head

and Neck Foundation, Inc. Otolaryngol Head Neck Surg 113(3):181–185
23. Hinchcliffe R (1967) An attempt to classify the primary vertigos. J Laryngol Otol 81:849–857
24. Hinchcliffe R (1973) Ménière's syndrome. Recent advances in otolaryngology. In: Ransome J, Holden H, Bull TR (eds). Churchill Livingstone, Edinburgh, vol 12, pp 127–143
25. Alexander TH, Harris JP (2010) Current epidemiology of Meniere's syndrome. Otolaryngol Clin North Am 43(5):965–970
26. Committee on Hearing and Equilibrium (1972) Report of Subcommittee on Equilibrium and its Measurement. Meniere's disease: criteria for diagnosis and evaluation of therapy for reporting. Trans Am Acad Ophthalmol Otolaryngol 76:1462–1464
27. Pearson BW, Brackmann DE (1985) Committee on Hearing and Equilibrium guidelines for reporting treatment results in Meniere's disease. Otolaryngol Head Neck Surg 93(5):579–581
28. Pyykko I, Nakashima T, Yoshida T, Zou J, Naganawa S (2013) Meniere's disease: a reappraisal supported by a variable latency of symptoms and the MRI visualisation of endolymphatic hydrops. BMJ Open 3(2). doi:10.1136/bmjopen-2012-001555
29. Lopez-Escamez JA, Carey J, Chung WH, Goebel JA, Magnusson M, Mandala M, Newman-Toker DE, Strupp M, Suzuki M, Trabalzini F, Bisdorff A (2015) Diagnostic criteria for Meniere's disease. J Vestib Res 25(1):1–7
30. Nakashima T NS, Pyykko I, Poe D (2015) New outlook on Meniere's disease. Nature rewiews. Accepted for publication
31. Pyykko I, Ishizaki H, Kaasinen S, Aalto H (1994) Intratympanic gentamicin in bilateral Meniere's disease. Otolaryngol Head Neck Surg 110(2):162–167
32. Levo H, Stephens D, Poe D, Kentala E, Rasku J, Pyykko I (2012) EuroQol 5D quality of life in Meniere's disorder can be explained with symptoms and disabilities. Int J Rehabil Res 35(3):197–202
33. Hètu R, Getty L, Beaudry J, Philibert L (1994) Attitudes towards co-workers affected by occupational hearing loss I: questionnaire development and inquiry. Br J Audiol 28(6):299–311
34. Noble W, Atherley GR (1970) The Hearing measurement scale: a questionnaire for the assessment of auditory disability. J Auditory Res 10(3):229–250
35. Yardley L, Putman J (1992) Quantitative analysis of factors contributing to handicap and distress in vertiginous patients: a questionnaire study. Clin Otolaryngol 17(3):231–236
36. Kennedy V, Chéry-Croze S, Stephens D, Kramer S, Thai-Van H, Collet L (2005) Development of the International Tinnitus Inventory (ITI): a patient-directed problem questionnaire. Audiol Med 3(4):228–237
37. Green JD Jr, Verrall A, Gates GA (2007) Quality of life instruments in Meniere's disease. Laryngoscope 117(9):1622–1628
38. Hagnebo C, Melin L, Larsen HC, Lindberg P, Lyttkens L, Scott B (1997) The influence of vertigo, hearing impairment and tinnitus on the daily life of Meniere patients. Scand Audiol 26(2):69–76
39. Soderman AC, Bagger-Sjoback D, Bergenius J, Langius A (2002) Factors influencing quality of life in patients with Meniere's disease, identified by a multidimensional approach. Otol Neurotol 23(6):941–948
40. Ketola S, Levo H, Rasku J, Pyykkö I, Kentala E (2014) The sense of coherence in patients with Menière's disorder. Auris Nasus Larynx 41(3):244–248
41. Stephens D, Kentala E, Varpa K, Pyykko I (2007) Positive experiences associated with Menière's disorder. Otol Neurotol 28(7):982–987
42. Levo H, Stephens D, Poe D, Kentala E, Pyykko I (2010) Use of ICF in assessing the effects of Meniere's disorder on life. Ann Otol Rhinol Laryngol 119(9):583–589
43. Wade DT, Halligan P (2003) New wine in old bottles: the WHO ICF as an explanatory model of human behaviour. Clin Rehabil 17(4):349–354
44. Levo H, Stephens D, Poe D, Kentala E, Pyykko I (2010) Use of ICF in assessing the effects of Menière's disorder on life. Ann Otol Rhinol Laryngol 119(9):583–589
45. Foottit J, Anderson D (2012) Associations between perception of wellness and health-related quality of life, comorbidities, modifiable lifestyle factors and demographics in older Australians. Australas J Ageing 31(1):22–27
46. Levo HSD, Kentala E, Rasku J, Pyykkö I (2013) Fatigue in meniere's disease. Hear Bal Commun 11(4):191–197
47. van Cruijsen N, Jaspers JP, van de Wiel HB, Wit HP, Albers FW (2006) Psychological assessment of patients with Meniere's disease. Int J Audiol 45(9):496–502
48. Kirby SE, Yardley L (2009) Cognitions associated with anxiety in Meniere's disease. J Psychosom Res 66(2):111–118
49. Stephens D, Pyykkö I, Kentala E, Levo H, Rasku J (2012) The effects of Menière's disorder on the patient's significant others. Int J Audiol 51(12):858–863
50. Wade D (2006) Why physical medicine, physical disability and physical rehabilitation? We should abandon Cartesian dualism. Clin Rehabil 20(3):185–190
51. Naganawa S, Sugiura M, Kawamura M, Fukatsu H, Sone M, Nakashima T (2008) Imaging of endolymphatic and perilymphatic fluid at 3T After intratympanic administration of gadolinium-diethylene-triamine pentaacetic acid. Am J Neuroradiol 29(4):724–726
52. Nakashima T, Naganawa S, Sugiura M, Teranishi M, Sone M, Hayashi H, Nakata S, Katayama N, Ishida IM (2007) Visualization of endolymphatic hydrops in patients with meniere's disease. Laryngoscope 117(3):415–420
53. Naganawa S, Nakashima T (2014) Visualization of endolymphatic hydrops with MR imaging in patients with Meniere's disease and related pathologies: current status of its methods and clinical significance. Jpn J Radiol 32(4):191–204
54. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T (2010) Visualization of endolymphatic hydrops in Meniere's disease with single-dose intravenous gadolinium-based contrast media using heavily T(2)-weighted 3D-FLAIR. Magn Reson Med Sci 9(4):237–242
55. Naganawa S, Satake H, Kawamura M, Fukatsu H, Sone M, Nakashima T (2008) Separate visualization of endolymphatic space, perilymphatic space and bone by a single pulse sequence; 3D-inversion recovery imaging utilizing real reconstruction after intratympanic Gd-DTPA administration at 3 Tesla. Eur Radiol 18(5):920–924
56. Gürkov R, Kantner C, Strupp M, Flatz W, Krause E, Ertl-Wagner B (2014) Endolymphatic hydrops in patients with vestibular migraine and auditory symptoms. Eur Arch Otorhinolaryngol 271(10):2661–2667
57. Jerin C, Krause E, Ertl-Wagner B, Gurkov R (2014) Longitudinal assessment of endolymphatic hydrops with contrast-enhanced magnetic resonance imaging of the labyrinth. Otol Neurotol 35(5):880–883
58. Gürkov R, Flatz W, Ertl-Wagner B, Krause E (2013) Endolymphatic hydrops in the horizontal semicircular canal: a morphologic correlate for canal paresis in Ménière's disease. Laryngoscope 123(2):503–506
59. Gürkov R, Flatz W, Louza J, Strupp M, Krause E (2011) In vivo visualization of endolyphatic hydrops in patients with Meniere's disease: correlation with audiovestibular function. Eur Arch Otorhinolaryngol 268(12):1743–1748
60. Gürkov R, Flatz W, Louza J, Strupp M, Ertl-Wagner B, Krause E (2012) Herniation of the membranous labyrinth into the horizontal semicircular canal is correlated with impaired caloric response in Meniere's disease. Otol Neurotol 33(8):1375–1379
61. Gürkov R, Flatz W, Louza J, Strupp M, Ertl-Wagner B, Krause E (2012) In vivo visualized endolymphatic hydrops and inner ear

functions in patients with electrocochleographically confirmed Meniere's disease. Otol Neurotol 33(6):1040–1045
62. Nakashima T, Naganawa S, Teranishi M, Tagaya M, Nakata S, Sone M, Otake H, Kato K, Iwata T, Nishio N (2010) Endolymphatic hydrops revealed by intravenous gadolinium injection in patients with Meniere's disease. Acta Otolaryngol 130(3): 338–343
63. Fiorino F, Pizzini FB, Beltramello A, Mattellini B, Barbieri F (2011) Reliability of magnetic resonance imaging performed after intratympanic administration of gadolinium in the identification of endolymphatic hydrops in patients with Meniere's disease. Otol Neurotol 32(3):472–477
64. Nakashima T, Naganawa S, Pyykko I, Gibson WP, Sone M, Nakata S, Teranishi M (2009) Grading of endolymphatic hydrops using magnetic resonance imaging. Acta Otolaryngol 560:5–8
65. Liu F, Huang W, Wang Z, Chen Q, Liu X, Li S, Wang S (2011) Noninvasive evaluation of endolymphatic space in healthy volunteers using magnetic resonance imaging. Acta Otolaryngol 131(3):247–257
66. Pyykko I, Zou J, Poe D, Nakashima T, Naganawa S (2010) Magnetic resonance imaging of the inner ear in Meniere's disease. Otolaryngol Clin North Am 43(5):1059–1080
67. Zou J, Pyykko I, Bretlau P, Klason T, Bjelke B (2003) In vivo visualization of endolymphatic hydrops in guinea pigs: magnetic resonance imaging evaluation at 4.7 tesla.[Erratum appears in Ann Otol Rhinol Laryngol. 2005 Sep;114(9):738]. Ann Otol Rhinol Laryngol 112 (12):1059–1065
68. Louza J, Krause E, Gurkov R (2013) Audiologic evaluation of Meniere's disease patients one day and one week after intratympanic application of gadolinium contrast agent: our experience in sixty-five patients. Clin Otolaryngol 38(3):262–266
69. Louza J, Krause E, Gurkov R (2015) Hearing function after intratympanic application of gadolinium-based contrast agent: a long-term evaluation. Laryngoscope 125(10):2366–2370
70. Louza JP, Flatz W, Krause E, Gurkov R (2012) Short-term audiologic effect of intratympanic gadolinium contrast agent application in patients with Menière's disease. Am J Otolaryngol 33(5):533–537
71. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T (2013) Imaging of Ménière's disease after intravenous administration of single-dose gadodiamide: utility of multiplication of MR cisternography and HYDROPS image. Magn Reson Med Sci 12(1):63–68
72. Naganawa S, Yamazaki M, Kawai H, Bokura K, Iida T, Sone M, Nakashima T (2014) MR imaging of Ménière's disease after combined intratympanic and intravenous injection of gadolinium using HYDROPS2. Magn Reson Med Sci 13(2):133–137
73. Fukuoka H, Tsukada K, Miyagawa M, Oguchi T, Takumi Y, Sugiura M, Ueda H, Kadoya M, S-i Usami (2010) Semi-quantitative evaluation of endolymphatic hydrops by bilateral intratympanic gadolinium-based contrast agent (GBCA) administration with MRI for Meniere's disease. Acta Otolaryngol 130(1):10–16
74. Katayama N, Yamamoto M, Teranishi M, Naganawa S, Nakata S, Sone M, Nakashima T (2010) Relationship between endolymphatic hydrops and vestibular-evoked myogenic potential. Acta Otolaryngol 130(8):917–923
75. Kato M, Sugiura M, Shimono M, Yoshida T, Otake H, Kato K, Teranishi M, Sone M, Yamazaki M, Naganawa S, Nakashima T (2013) Endolymphatic hydrops revealed by magnetic resonance imaging in patients with atypical Meniere's disease. Acta Otolaryngol 133(2):123–129
76. Miyagawa M, Fukuoka H, Tsukada K, Oguchi T, Takumi Y, Sugiura M, Ueda H, Kadoya M, Usami S (2009) Endolymphatic hydrops and therapeutic effects are visualized in 'atypical' Meniere's disease. Acta Otolaryngol 129(11):1326–1329
77. Naganawa S, Satake H, Iwano S, Fukatsu H, Sone M, Nakashima T (2008) Imaging endolymphatic hydrops at 3 tesla using 3D-FLAIR with intratympanic Gd-DTPA administration. Magn Reson Med Sci 7(2):85–91
78. Naganawa S, Yamazaki M, Kawai H, Bokura K, Sone M, Nakashima T (2012) Visualization of endolymphatic hydrops in Meniere's disease after single-dose intravenous gadolinium-based contrast medium: timing of optimal enhancement. Magn Reson Med Sci 11(1):43–51
79. Teranishi M, Naganawa S, Katayama N, Sugiura M, Nakata S, Sone M, Nakashima T (2009) Image evaluation of endolymphatic space in fluctuating hearing loss without vertigo. Eur Arch Oto-Rhino-L 266(12):1871–1877
80. Yamamoto M, Teranishi M, Naganawa S, Otake H, Sugiura M, Iwata T, Yoshida T, Katayama N, Nakata S, Sone M, Nakashima T (2010) Relationship between the degree of endolymphatic hydrops and electrocochleography. Audiol Neuro-Otol 15(4): 254–260
81. Hornibrook J, Coates M, Goh A, Gourley J, Bird P (2012) Magnetic resonance imaging for Meniere's disease: correlation with tone burst electrocochleography. J Laryngol Otol 126(2): 136–141
82. Naganawa S, Satake H, Kawamura M, Fukatsu H, Sone M, Nakashima T (2008) Separate visualization of endolymphatic space, perilymphatic space and bone by a single pulse sequence; 3D-inversion recovery imaging utilizing real reconstruction after intratympanic Gd-DTPA administration at 3 Tesla. Eur Radiol 18(5):920–924
83. Attye A, Dumas G, Tropres I, Roustit M, Karkas A, Banciu E, Pietras J, Lamalle L, Schmerber S, Krainik A (2015) Recurrent peripheral vestibulopathy: is MRI useful for the diagnosis of endolymphatic hydrops in clinical practice? Eur Radiol. doi:10.1007/s00330-015-3712-5
84. Hornibrook J, Coates M, Goh T, Bird P (2010) MRI imaging of the inner ear for Meniere's disease. N Z Med J 123(1321):59–63
85. Langhagen T, Schroeder AS, Rettinger N, Borggraefe I, Jahn K (2013) Migraine-related vertigo and somatoform vertigo frequently occur in children and are often associated. Neuropediatrics 44(1):55–58
86. Chen X, Zhang XD, Gu X, Fang ZM, Zhang R (2012) Endolymphatic space imaging in idiopathic sudden sensorineural hearing loss with vertigo. Laryngoscope 122(10):2265–2268
87. Horii A, Osaki Y, Kitahara T, Imai T, Uno A, Nishiike S, Fujita N, Inohara H (2011) Endolymphatic hydrops in Meniere's disease detected by MRI after intratympanic administration of gadolinium: comparison with sudden deafness. Acta Otolaryngol 131(6): 602–609
88. Naganawa S, Kawai H, Sone M, Ikeda M (2015) Ratio of Vestibular Endolymph in Patients with Isolated Lateral Semicircular Canal Dysplasia. Magn Reson Med Sci 14(3):203–210
89. Kasai S, Teranishi M, Katayama N, Sugiura M, Nakata S, Sone M, Naganawa S, Nakashima T (2009) Endolymphatic space imaging in patients with delayed endolymphatic hydrops. Acta Otolaryngol 129(11):1169–1174
90. Nonoyama H, Tanigawa T, Tamaki T, Tanaka H, Yamamuro O, Ueda H (2014) Evidence for bilateral endolymphatic hydrops in ipsilateral delayed endolymphatic hydrops: preliminary results from examination of five cases. Acta Otolaryngol 134(3): 221–226
91. Naganawa S, Kawai H, Sone M, Nakashima T, Ikeda M (2011) Endolympathic hydrops in patients with vestibular schwannoma: visualization by non-contrast-enhanced 3D FLAIR. Neuroradiology 53(12):1009–1015
92. Friberg U, Stahle J, Svedberg A (1984) The natural course of Meniere's disease. Acta Otolaryngol Suppl 406:72–77

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Management of Intractable Ménière's Disease After Intratympanic Injection of Gentamicin

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Objectives/Hypothesis: 1) To evaluate the efficacy of, and problems with, intratympanic gentamicin injection (ITG) in medically intractable definite Ménière's disease (MD) and secondary endolymphatic hydrops (EH); and 2) to review the vestibular status and treatment options of intractable vertigo even after ITG.

Study Design: Retrospective case review and survey.

Methods: 780 patients with definite MD and secondary EH were enrolled. Long-term outcomes and problems of applied treatment options including ITG and exploratory tympanotomy and gentamicin application (ETG) were analyzed.

Results: Of the 780 patients, 95 patients received ITG. Class A and B control of vertigo was achieved in 85 (89.5%) patients; two patients were class C and eight patients were class F (ETG: 6; labyrinthectomy: 1; vestibular neurectomy: 1). Among seven patients who received ETG including 1 patient who skipped ITG due to chronic otitis media, five patients improved to class A, showing a 71.4% success rate; and labyrinthectomies were performed subsequently in the two remaining patients. Vertigo was controlled (class A) in all the patients who received labyrinthectomies (n = 4) or vestibular neurectomy (n = 1). Eight patients (8.4%) experienced more than 10 dB worsening, and two patients (2.1%) progressed to bilateral Ménière's disease.

Conclusion: ITG failed to control vertigo in 10.5% of cases. ETG may be a reasonable option to facilitate the delivery of gentamicin into the inner ear by direct application of gentamicin over the round window and the oval window. Labyrinthectomy and vestibular neurectomy still have roles in the era of ITG.

Key Words: Gentamicin, intratympanic injection, Ménière's disease, vertigo.

Level of Evidence: 4.

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INTRODUCTION

Ménière's disease is a clinically defined disorder, characterized by recurrent episodic vertigo with aural fullness, tinnitus, and sensorineural hearing loss. Medical management such as salt restriction, diuretics, beta histine, and corticosteroids is usually tried as a first step.[1,2] About 60% to 87% of patients with Ménière's disease have been reported to maintain their normal daily activities with such medical management.[3,4] Surgical intervention may be considered for those patients who still have disabling attacks despite medical management.[5] However, no consensus has been reached for the management of Ménière's disease.[6]

Among additional interventions for Ménière's disease intractable to medical treatments, intratympanic injection of gentamicin (ITG) seems to have gained popularity with its convenient application; it is now widely performed for the control of vertigo in most patients, with reported success rates of 83% to 91%.[7–10] However, a certain proportion of patients suffer from several clinical problems such as hearing loss and progression to bilateral disease after ITG.[9,10] Moreover, a significant portion of patients (5%–15%) have been reported to experience recurrent attacks of vertigo even after ITG.[9–12]

There is a need to determine the most effective and safe protocol(s) for these patients. However, most surgeons face difficulties in choosing subsequent procedures because a labyrinthectomy results in complete loss of cochlear function, and vestibular neurectomy may have surgical risks associated with the craniotomy.[13] Crane et al. explored the middle ear space in eight cases who were refractory to ITG. They found some suspect middle ear pathologies and achieved good results by eradicating those problems and direct application of gentamicin during middle ear exploration.[14]

In this study, we reviewed the efficacy and problems of ITG in both definite Ménière's disease (MD) and secondary endolymphatic hydrops (EH). We also reviewed the vestibular status of the intractable patients, even after ITG, and their management options.

MATERIALS AND METHODS

Selection of the Patients

In total, 667 patients were diagnosed with definite MD and 113 patients were diagnosed with secondary EH from March 2003 to April 2012, based on the 1995 guideline of the

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American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS).

Eighty-nine patients of definite MD group and seventeen patients of secondary EH group received additional interventions such as ITG, endolymphatic sac decompression (ELSD), and application of the Meniett device after the failure of medical treatment. They were followed up for at least 2 years (range: 2.1–7.5 years), and their treatment flow and outcomes were analyzed. A total of 21 patients were excluded from analysis due to the inadequate follow up or data collection. This study was approved by the Seoul National University Bundang Hospital Institutional Review Board (B-1310/222-102).

Selection of the Treatment Options

For intractable patients, next treatment options were discussed with patients and considered mainly depending on the patient's hearing status. ELSD was suggested if the patient's pure tone average was better than 40 dB by averaging the 0.5, 1, 2, and 3 kHz; and ITG was recommended if it was not. In some patients, ITG was not feasible due to chronic otitis media, and gentamicin was applied around the round window and oval window after removing of thickened mucosa during a tympanomastoidectomy. ITG was basically considered for the patients whose vertigo was not controlled by medical treatment for more than 3 to 6 months and had worse than 40 dB hearing thresholds. However, ITG was also performed for some patients under serious risk of head trauma due to recurrent Tumarkin crises, although they had better than 40 dB hearing level.

Protocols for the Intratympanic Injection of Gentamicin

Gentamicin was administered as described below. Patients were lying down in supine position with the head elevated up to 30 degrees and turned to the other side at 45 degrees. The ear canal and tympanic membrane were anesthetized, and two holes were made with a 26-G needle at anterosuperior area of tympanic membrane. About 0.3 to 0.5 mL of gentamicin solution (gentamicin sulfate, 40 mg/mL) was administered into the middle ear cavity. Patients were advised to remain in the same position at least 20 minutes and to avoid swallowing or yawning.

Characteristics of dizziness were asked, and an office exam was conducted to evaluate vestibular status at 2 weeks and 4 weeks after injection to determine the efficacy of the previous administration. If typical paralytic nystagmus to the contralateral side (spontaneous nystagmus, post-head shaking nystagmus, vibration-induced nystagmus) or laboratory evidence of attenuation (or ablation) of remaining vestibular function on a caloric test was evident, the injection was thought to be successful and no additional administration was considered. However, if the patients experienced episodic vertigo spells instead of crescendo–decrescendo type persistent dizziness or there was no evidence of attenuation of vestibular function, injections were repeated until signs of ipsilateral vestibular hypofunction were more evident.

Analysis of Changes in Hearing and Vertigo

All hearing and vertigo data were analyzed according to the 1995 AAO–HNS guideline.[15] Vertigo was assessed as the average number of definite spells per month for the 6 month periods prior to ITG and compared with that assessed between 18 to 24 months after ITG. Hearing level was assessed at the same time periods by averaging the 0.5, 1, 2, and 3 kHz pure tone thresholds. We compared changes in hearing threshold and frequency of vertigo after ITG.

Analysis of Problems After ITG

For the patients who were refractory even after ITG, exploratory tympanotomy and gentamicin application (ETG), labyrinthectomy, and vestibular neurectomy were then considered. Among them, ETG was primarily considered the next step to rule out any anatomical problem that might obscure the passage of gentamicin into the inner ear for those whose vestibular function was not ablated sufficiently by ITG. We applied ETG when the patients showed no improvement after three or four attempts of ITG. That was determined on the basis of our findings that most cases with successful improvement of vertigo improved after only two (75%) or three (86%) rounds of ITG and that the chance of failed control of vertigo increased with multiple injections (odds ratio = 11.8; $P = 0.005$, Fischer's exact test). Failure due to insufficient attenuation of vestibular function or recurrent dangerous event, such as Tumarkin crises even after ITG, was also considered. Labyrinthectomy and vestibular neurectomy were considered if symptoms had not improved even after ETG. We analyzed the outcomes of the treatment options used and their problems. Long-term time course of hearing loss were analyzed to clarify the cause of hearing aggravation after ITG. Bilateral progression of MD after ITG and its problems were analyzed.

RESULTS

Patients' Characteristics and Applied Treatment Options

The average age of the total 95 patients was 58 years old (range: 28–75 years old; definite MD group: 57.5 years old, secondary EH group: 60.1 years old); there were 38 male patients (48.7%) in the definite MD group and eight male patients (47.0%) in the secondary EH group. The patients experienced 7.1 vertigo attacks in a month for the definite MD group and 5.4 vertigo attacks in a month for the secondary EH group when averaged for 6 months prior to ITG. Vestibular function on bithermal caloric test before injection was decreased in 14 patients (82.4%) of the secondary EH group and in 53 patients (67.9%) of the definite MD group ($P = 0.38$, Fischer's exact test). Tumarkin attacks were present in five cases (29.4%) of the secondary EH group and in 15 patients (19.2%) of the definite MD group ($P = 0.34$, Fischer's exact test).

Overall Treatment Flow

Of the 667 patients with definite MD, 578 (86.7%) patients showed improvements with lifestyle modification or medical treatment. Additional interventions such as ITG, ELSD, and application of the Meniett device were performed in 89 (13.3%) patients due to intractable vertigo, and ITG (78 patients, 87.6%) occupied the majority among them (Fig. 1). The patients group who received ITG included four patients whose vertigo attack was not controlled, even after ELSD treatment. ELSD achieved 45.5% (5 of 11 patients) of class A and B vertigo control and showed 9.1% (1 of 11 patients) of more than 10 dB hearing loss after surgery. Although treatments

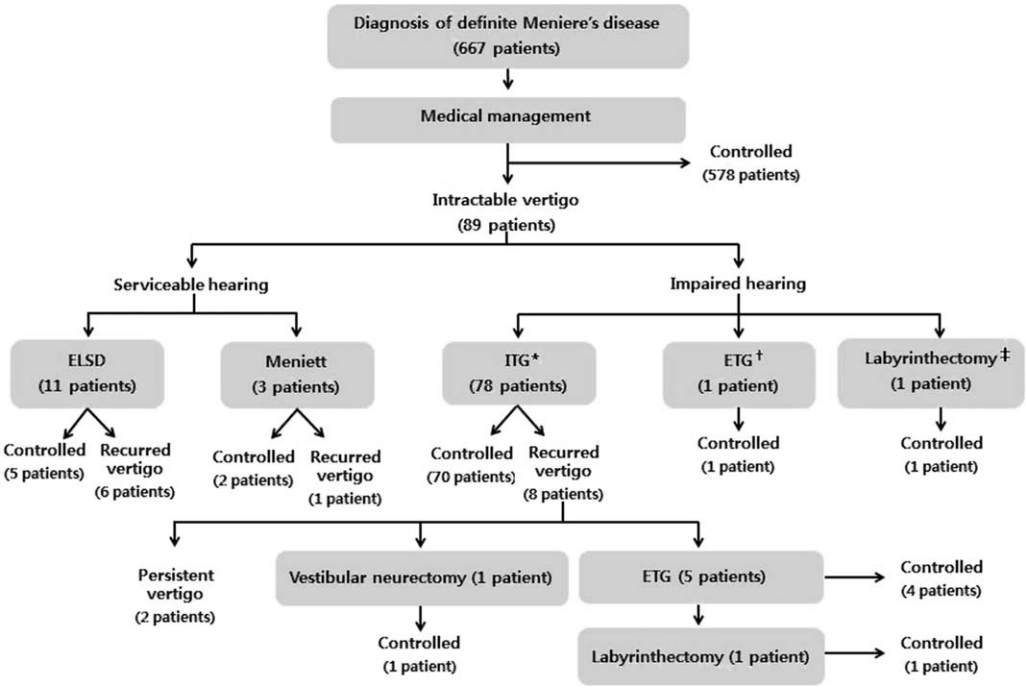

Fig. 1. Treatment of definite Ménière's disease. Among 667 patients with definite Ménière's disease, 89 (13.3%) patients needed additional intervention to control intractable vertigo despite medical treatment. ELSD (11 patients), application of a Meniett device (3 patients), ITG (78 patients), ETG (1 patient), and labyrinthectomy (1 patient) were carried out. Eight patients still experienced vertigo even after ITG. Five patients got ETG; and vertigo was resolved in four patients and persisted in one, who subsequently underwent labyrinthectomy. Vestibular neurectomy was chosen due to recurrent vertigo in a patient in whom vestibular function was sufficiently attenuated after ITG. The two remaining patients were class C.
*Including four patients who suffered from persistent vertigo even after ELSD.
†This patient developed chronic draining ear after application of the Meniett device and then underwent ETG during a tympanomastoidectomy.
‡This patient had severe chronic otitis media with severe hearing loss and underwent a labyrinthectomy during a subtotal petrosectomy. ELSD = endolymphatic sac decompression; ETG = exploratory tympanotomy and gentamicin application; ITG = intratympanic gentamicin injection.

such as ETG, labyrinthectomy, and vestibular neurectomy were initially considered as second-line treatment options for the patients who failed to achieve improvement even after ITG, some cases were carried out just after the failure of medical management for special reasons. A patient developed chronic otitis media with recurrent otorrhea after ventilation tube insertion for the application of the Meniett device and received ETG during the tympanoplasty for chronic otitis media. Another patient with profound mixed hearing loss got labyrinthectomy during a subtotal petrosectomy for chronic suppurative otitis media.

Of 113 patients with secondary EH, 96 patients (85.0%) showed improvements with medical management. Seventeen patients (15.0%) needed additional treatment to control intractable vertigo after medical treatment, and all received ITG (Fig. 2). Details about the applied treatment options are summarized in Table I.

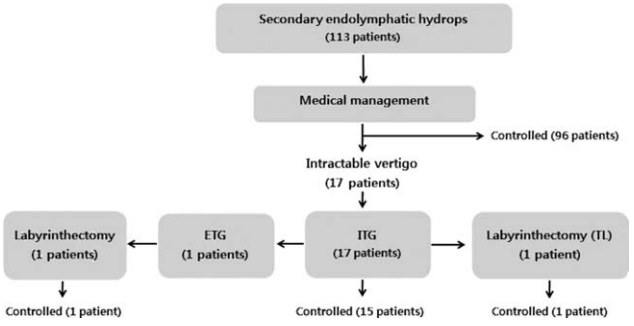

Fig. 2. Treatment flow of secondary endolymphatic hydrops. Among 113 patients, 17 (15.0%) patients needed additional intervention to control intractable vertigo despite medical treatment. ETG was tried in a patient; however, vertigo persisted and labyrinthectomy was carried out subsequently. An incidental intralabyrinthine schwannoma was found during the labyrinthectomy, and the surgery was completed with a translabyrinthine approach (TL) to check for any residual tumor.
ETG = exploratory tympanotomy and gentamicin application; ITG = intratympanic gentamicin injection.

Vertigo Control After ITG and Its Problems

In the 95 patients who received ITG, complete control of vertigo (class A) was achieved in 73 patients (76.8%), and substantial control of vertigo (class B) was achieved in 12 patients (12.6%). Among the 10 patients who suffered from persistent recurrent vertigo, two patients (2.1%) were class C. One patient suffered from persisting vertigo even after four rounds of ITG, and the other patient who received ELSD was not improved

TABLE I.
Additional Interventions Performed to Control Intractable Vertigo.

Treatment	Class*	No.	Comments
ITG (n = 95)	A	73	s/p ELSD (n = 3)
	B	12	
	C	2	s/p ELSD (n = 1)
	F	8	Subsequently ETG (n = 6), labyrinthectomy (n = 1), vestibular neurectomy (n = 1)
ELSD (n = 11)	A	5	
	C	2	
	F	4	Subsequently ITG (n = 4)
Meniette (n = 3)	A	2	
	F	1	Subsequently ETG (n = 1)
ETG (n = 7)	A	5	s/p Meniett, then chronic draining ear (n = 1)
	F	2	Subsequently labyrinthectomy (n = 2)
Labyrinthectomy (n = 4)	A	4	Labyrinthectomy + STP† (n = 1), intralabyrinthine tumor removal‡ (n = 1)
Vestibular neurectomy (n = 1)	A	1	

*Functional classification according to the 1995 American Academy of Otolaryngology–Head and Neck Surgery guideline.
†Surgery to control chronic otitis media.
‡Translabyrinthine approach and tumor removal for incidentally detected intralabyrinthine schwannoma.
ITG = intratympanic gentamicin injection; ELSD = endolymphatic sac decompression; ETG = exploratory tympanotomy and gentamicin application; n = number of patient(s); s/p = status post; STP = subtotal petrosectomy.

even after ITG. The remaining 8 (8.4%) patients were class F (Table I). Six patients received ETG after failure of ITG. Vestibular function on a caloric test was not sufficiently attenuated in four of six patients after ITG (patients 3, 4, 6, and 7 in Table II), whereas it was attenuated substantially but vertigo attacks were not controlled in two patients (patients 2 and 5 in Table II). After ETG, five of seven (71.4%) patients whose caloric function was attenuated substantially achieved class A, and the remaining two patients (patients 6 and 7), whose caloric functions were not sufficiently attenuated even after ETG, needed subsequent labyrinthectomies.

We tried to determine any possible anatomical problems that might obscure the passage of gentamicin. Prominent bony overhang over the round window niche was remarkable in two patients; otherwise, there was no definite suspected barrier such as mucosal thickening, thickening of the round window membrane, or bone chips (Table II). Including one patient administered gentamicin during a tympanomastoidectomy due to chronic otitis media after trial use of the Meniett device, a total of seven patients underwent ETG. Although the bone conduction threshold was aggravated by 12.5 dB in one of the seven (14.3%) patients, the hearing level was already more than 55 dB in each patient who received ETG.

Three patients finally underwent labyrinthectomies after the failure of ITG, including two patients whose vertigo was not controlled by ITG or ETG. The two did improve after the labyrinthectomy, up to class A. An intralabyrinthine schwannoma was found incidentally during the labyrinthectomy (patient 2 in Table III), and tumor removal was completed via translabyrinthine approach.

TABLE II.
Changes in Vestibular Function Before ITG, After ITG, and After ETG.

Pt	CP (%) Before ITG	CP (%) After ITG	CP (%) After ETG	Class*	Dx	Comments
1	21%	–	HIT(+)†	A	MD	s/p Meniett, then chronic draining ear
2	35%	62% (7 inj‡)	56%	A	MD	
3	10%	25% (3 inj‡)	66%	A	MD	Persistent unsteadiness
4	46%	44% (2 inj‡)	97%	A	MD	Prominent bony overhang
5	32%	90% (3 inj‡)	90%	A	MD	
6	15%	28% (3 inj‡)	32%	F	EH	
7	4%	31% (3 inj‡)	29%	F	MD	Prominent bony overhang

*Functional classification according to the 1995 American Academy of Otolaryngology–Head and Neck Surgery guideline.
†Positive head impulse sign indicates attenuation of ipsilateral canal function after ETG.
‡Number of intratympanic injections of gentamicin.
CP = canal paresis bithermal caloric test; Dx = diagnosis; EH = secondary endolymphatic hydrops; ETG = exploratory tympanotomy and gentamicin application; HIT = head impulse test; inj = injection; ITG = intratympanic gentamicin injection; MD = definite Ménière's disease; Pt = patient; s/p = status post.

TABLE III.
Summary of Patients Undergoing Labyrinthectomies and Vestibular Neurectomies.

Pt	CP Before ITG	CP After ITG	CP After ETG	Class*	Dx	Comments
1	75%	–	No ETG	A	MD	Labyrinthectomy + STP†
2	77%	83% (3 inj‡)	No ETG	A	EH	Labyrinthectomy (intralabyrinthine schwannoma)
3	15%	28% (3 inj‡)	32%	A	EH	Labyrinthectomy
4	4%	31% (3 inj‡)	29%	A	MD	Labyrinthectomy
5	44%	89% (4 inj‡)	No ETG	A	MD	Vestibular neurectomy

*Functional classification according to the 1995 American Academy of Otolaryngology–Head and Neck Surgery guideline.
†Surgery to control chronic otitis media.
‡Number of intratympanic injections of gentamicin.
CP = canal paresis on bithermal caloric test; Dx = diagnosis; EH = secondary endolymphatic hydrops; ETG = exploratory tympanotomy and gentamicin application; ITG = intratympanic gentamicin injection; MD = definite Ménière's disease; Pt = patient; STP = subtotal petrosectomy.

Vestibular neurectomy via middle fossa approach was performed in one patient to control intractable vertigo, even after successful ablation of vestibular function on a caloric test (canal paresis: 89%) with five rounds of intratympanic gentamicin injections. The hearing of the 52-year-old woman after ITG was still acceptable (36.25 dB of pure tone average, with 82% for speech discrimination in the audiometry taken on a day prior to the surgery). After surgery, complete control of vertigo (class A) was achieved and hearing threshold was 35 dB after surgery. However, the hearing was progressively worsened to 55 dB after 1 year 6 months postoperatively, which was comparable with the worst hearing (53.75 dB) during 6 months prior to the surgery.

Hearing Outcomes

Overall, there was no significant change in hearing thresholds with the mean pure tone average 59.7 dB prior to ITG and 63.2 dB after ITG ($P = 0.343$, Student's t-test). In total, 80 (84.2%) patients showed less than 10 dB change in hearing after ITG; hearing was improved more than 10 dB even after ITG in six (6.3%) patients; and three of them improved by more than 20 dB. Five of the six patients with hearing improvement achieved successful ablation of vestibular function on bithermal caloric test, and all of them did not show hearing fluctuation thereafter. In contrast, a patient with initially impaired vestibular reflex showed fluctuation of hearing with temporary hearing improvement at the point of assessment according to the 1995 AAO–HNS guideline. Two of the six patients experienced hearing aggravation in the proximity of the ITG, with the worsening of vertigo including the patient with hearing fluctuation. A total of eight (8.4%) patients experienced more than a 10 dB worsening of hearing levels. Four of the eight patients received more than three rounds of ITG; and 2.6 injections were applied, on average, in the eight patients. However, a careful review of the data revealed that most hearing loss took place after one (4 patients) or two (2 patients) injection(s), and only two patients experienced hearing loss after three injections. We compared the results of hearing changes with the success of ablation and the preoperative vestibular status, but neither showed a statistically significant difference ($P = 1.00$ and 0.54, respectively, Fischer's exact test).

Bilateral Progression of Ménière's Disease After ITG

Two patients progressed to bilateral Ménière's disease after ITG. Both of them developed vertigo with aggravation of hearing on the other side. The hearing levels of the injected side were already worse than 60 dB HL prior to ITG and were not aggravated after injection in both patients. Physical examination and the caloric test revealed apparently successful ablation of vestibular function on the injected side. One patient developed contralateral Ménière's disease at 2 years after ITG, and the other patient developed it at 5 years after ITG.

DISCUSSION

Previously, the effectiveness of ITG was commonly highlighted, with little discussion of its limitation.[7–12] The reason for failure is important because there could be some substantial limitation to drug passage through the round window membrane. In previous studies, markedly limited permeability or impermeability was reported in approximately 20% of cases.[16] In another study that directly visualized the passage of gadolinium injected into the tympanic cavity into the inner ear, 13% showed poor drug passage through the round window membrane, with 5% of cases showing no permeability.[17] This is very similar to our failure rate for ITG.

The tympanum was inspected for any possible anatomical barrier around the oval window and/or the round window membrane that might limit the access of gentamicin. However, no obvious barrier such as mucosal folds, mucosal thickening, or bone chips was evident, except a prominent bony overhang over the round window in two patients. Such a prominent bony overhang could be a possible reason for the failure of ITG, according to a previous report,[14] because vestibular function was attenuated substantially and recurrent vertigo attacks were controlled after ETG in a patient. However, the reasons for the failure, especially in the two cases who needed additional labyrinthectomy, remain unclear. The permeability of the round window membrane is determined by several factors, such as the thickness of the membrane, the size of the particles, concentration, liposolubility, and electrical charge.[18] Considering that most of the listed variables were almost identical

throughout the cases, the thickness of the round window membrane may be the most important reason determining permeability. Thus, a thickened or false round window membrane could have obscured drug passage, which may be missed under the operating microscope. Another possible reason is that large endolymphatic hydrops in the vestibule may prevent the drug from moving into the vestibule. That has been shown by direct visualization of the blocked movement of intratympanically administered gadolinium by three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) MRI.[19] This could be supported by the fact that ETG was carried out at the time of a recurrent severe vertigo attack in most cases.

With regard to why ETG improved some cases, although no definite problem was found or corrected in the middle ear space, the increased contact time of gentamicin with the round window membrane should be considered. A previous study revealed that gadolinium contrast medium stayed in middle ear cavity for far less than 1 hour.[19] By applying gentamicin-soaked gelfoam directly on the round window membrane, the contact time could be extended considerably.

ETG seems to be necessary for patients who failed to achieve sufficient attenuation of vestibular function even after three or four rounds of ITG. For intractable cases even with profound ipsilateral canal paresis after ITG/ETG, definitive surgical ablations could be necessary because ITG/ETG could not achieve complete ablation of vestibular function. In addition, ETG or definite ablative procedures could provide additional information about undiscovered or missed disease. One patient experienced recurrent vertigo and a Tumarkin attack even after three rounds of ITG. Unilateral hearing loss had started more than 10 years previously. It was progressive, and the subject has been completely deaf for the past 3 years. Unilateral weakness was already 77% on a bithermal caloric test prior to ITG. Because this patient had undergone brain MRIs twice during the last 2 years before visiting our clinic due to fear of cerebrovascular disorders, which were reviewed, another request for MRI was not ordered, although the previous ones were not thin-sectioned and did not include contrast enhancement. An incidental intralabyrinthine schwannoma was found during the labyrinthectomy. This case teaches the importance of a high index of suspicion for Ménière's syndrome caused by tumors and the futility or even danger of simply repeated injections. Moreover, ETG is helpful for patients who have a history of previous surgery or inflammation in the middle ear cavity. Previous studies have reported bone dust after surgical manipulation of the middle ear and obstructions caused by mucosal adhesion in patients with chronic middle ear inflammation.[14,16]

Intratympanic steroid injection is one of actively performed procedures also in our institute; however, it is usually presumed to restore recent hearing loss for those who were not responded to systemic steroid or in whom systemic steroid is contraindicated, but not for recurrent vertigo. For this reason, we did not seriously consider intratympanic steroid as an option for intractable MD and mainly used it for restoring combined acute hearing loss.

Detailed analysis of the patients with hearing improvement after ITG revealed that two of six patients experienced hearing loss with aggravation of vertigo just prior to ITG because ITG usually conducted when the symptom was aggravated. The fact that all six patients showed typical low-tone hearing loss suggests that these hearing changes could be explained by the resolution and enlargement of hydrops that usually begins at the apical turn of the cochlea.[20,21] These results also suggest that the hearing improvement in some cases might be resulted from transient hearing loss in the proximity of ITG as the enlargement of hydrops rather than a real improvement of hearing after ITG.

Two patients progressed to bilateral Ménière's disease after ITG in our study. Previous studies reported that 5% to 33.3% of unilateral Ménière's disease progresses to bilateral disease,[22–24] and 25% to 30% of bilateral endolymphatic hydrops were found according to a human temporal bone study.[25,26] A more confusing issue is that most cases progress to bilateral disease serially rather than simultaneously and that contralateral disease begins usually at least 2 to 5 years after the first manifestation.[27] Therefore, procedures essentially resulting in the ablation of hearing should be performed carefully, and ETG could be an alternative to them.

For the possibility of carrying out ELSD as a salvage procedure after the failure of ITG, it seems to be reasonable to compare ELSD with ETG. Labyrinthectomy or vestibular neurectomy is far more destructive procedures than ELSD or ETG, which in turn can result in the ablation of a vestibular reflex. Our results showed complete control of vertigo (class A) with ETG in five of seven cases (71.4%). This was superior to that of ELSD (45.5% up to class A), although it was performed for failed cases of ITG. Hearing aggravation after ETG (1/7 patients; 14.3%) was slightly higher than ELSD (1/11 patients; 9.1%); however, the hearing level was not a serious matter because most patients already had more than 55 dB hearing loss.

CONCLUSION

ITG showed favorable vertigo control (89.5%) and hearing preservation rate (91.6%). However, 10 (10.5%) cases still suffered from intractable episodic vertigo, and six of them were revealed to have failed to achieve sufficient attenuation of vestibular function even after multiple ITGs. For those who have failed ITG, ETG can be considered (success rate in this study: 71.4%). Labyrinthectomy or vestibular neurectomy can be chosen for those who failed to achieve vertigo control even after ETG.

BIBLIOGRAPHY

1. Schessel D, Minor LB, Nedzelski J. Meniere's disease and other peripheral vestibular disorders. In: Cummings CW, Haughey BH, Thomas JR, eds. *Cummings Otolaryngology—Head and Neck Surgery (4th ed.)* Chicago IL: Mosby; 2004:3209–3253.
2. Boleas-Aguirre MS, Lin FR, La Santina CC, et al. Longitudinal results with intratympanic dexamethasone in the treatment of Meniere's disease. *Otol Neurotol* 2008;29:33–38.
3. Santos PM, Hall RA, Snyder JM, et al. Diuretic and diet effect on Meniere's disease evaluated by the 1985 Committee on Hearing and Equilibrium guidelines. *Otolaryngol Head Neck Surg* 1993;109:680–689.

4. Claes J, Van de Heyning PH. A review of medical treatment for Meniere's disease. *Acta Otolaryngol* 2000;544:34–39.
5. Konrad HR. Intractable vertigo—when not to operate. *Otolaryngol Head Neck Surg* 1986;95:482–484.
6. Coelho DH, Lalwani AK. Medical management of Meniere's disease. *Laryngoscope* 2008;118:1099–1106.
7. Blakley BW. Update on intratympanic gentamicin for Meniere's disease. *Laryngoscope* 2000;110:236–239.
8. Bodmer D, Morong S, Stewart C, et al. Long term vertigo control in patients after intatympanic gentamicin instillation for Meniere's disease. *Otol Neurotol* 2007;28:1140–1144.
9. Chia SH, Gamst AC, Anderson JP, et al. Intratympanic gentamicin therapy for Meniere's disease: a meta-analysis. *Otol Neurotol* 2004;25:544–552.
10. Cohen-Kerem R, Kislevsky V, Einarson TR, et al. Intratympanic gentamicin for Meniere's disease: a meta-analysis. *Laryngoscope* 2004;114:2085–2091.
11. Perez N, Martin E, Garcia-Taipa R. Intratympanic gentamicin for intractable Meniere's disease. *Laryngoscope* 2003;113:456–464.
12. Kaplan DM, Nedzelski JM, Chen JM, et al. Intratympanic gentamicin for the treatment of unilateral Meniere's disease. *Laryngoscope* 2000;110: 1298–1305.
13. De La Cruz A, Teufert KB, Berliner KI. Transmastoid labyrinthectomy versus translabyrinthine vestibular nerve section: does cutting the vestibular nerve make a difference in outcome? *Otol Neurotol* 2007;28:801–808.
14. Crane BT, Minor LB, Della Santina CC, et al. Middle ear exploration in patients with Meniere's disease who have failed outpatient intratympanic gentamicin therapy. *Otol Neurotol* 2009;30:619–624.
15. Committee on Hearing and Equilibrium. Committee on Hearing and Equilibrium Guidelines for the diagnosis and evaluation of treatment of therapy in Meniere's Disease. *Otolaryngol Head Neck Surg* 1995;113:181–185.
16. Silverstein H, Rowan PT, Olds MJ, et al. Inner ear perfusion and the role of round window patency. *Am J Otol* 1997;18:586–589.
17. Yoshioka M, Naganawa S, Sone M, et al. Individual differences in the permeability of the round window: evaluating the movement of intratympanic gadolinium into the inner ear. *Otol Neurotol* 2009;30:645–648.
18. Goycoolea MV, Lundman L. Round window membrane. Structure function and permeability: a review. *Microsc Res Tech* 1997;36:20–11.
19. Nakashima T, Naganawa S, Sugiura M, et al. Visualization of endolymphatic hydrops in patients with Meniere's disease. *Laryngoscope* 2007; 117:415–420.
20. Thai-Van H, Bounaix MJ, Fraysse B. Meniere's disease: pathophysiology and treatment. *Drugs* 2001;61:1089–1102.
21. Imamura S, Nozawa I, Imamura M. Clinical observations on acute low-tone sensorineural hearing loss. Survey and analysis of 137 patients. *Ann Otol Rhinol Laryngol* 1997;106:746–750.
22. Shojaku H, Watanabe Y, Yagi T, et al. Changes in the characteristics of definite Meniere's disease over time in Japan: a long-term survey by the Peripheral Vestibular Disorder Research Committee of Japan. *Acta Otolaryngol* 2009;129:155–160.
23. Perez R, Chen JM, Nedzelski JM. The status of the contralateral ear in established unilateral Meniere's disease. *Laryngoscope* 2004;114:1373–1376.
24. Navi S, Parnes LS. Bilateral Meniere's disease. *Curr Opin Otolaryngol Head Neck Surg* 2009;17:356–362.
25. Tsuji K, Velazquez-Villaserior L, Rauch SD, et al. Temporal bone studies of the human peripheral vestibular system. Meniere's disease. *Ann Otol Rhinol Laryngol Suppl* 2000;181:26–31.
26. Yazawa Y, Kitahara M. Bilateral endolymphatic hydrops in Meniere's disease: review of temporal bone autopsies. *Ann Otol Rhinol Laryngol* 1990;99:524–528.
27. Enander A, Stahle J. Hearing in Meniere's disease. A study of pure-tone audiograms in 334 patients. *Acta Otolaryngol* 1967;64:543–546.

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Endolymphatic Sac Surgery for Ménière's Disease: A Systematic Review and Meta-analysis

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Objective: To analyze current endolymphatic surgery techniques and quantify their efficacy in controlling vertigo and maintaining hearing in the short and long term.
Data Sources: A comprehensive literature search using the PubMed-NCBI database from 1970 to 2013.
Study Selection: Articles on sac decompression and mastoid shunt (*with* and *without* silastic) were included. Included studies had to report data using the 1985 or 1995 American Academy of Otolaryngology–Head and Neck Foundation (AAO-HNS) guidelines, describe surgical technique in detail, include a minimum of 10 patients, and have minimum 12 months of follow-up.
Data Extraction: Endpoints were vertigo control and hearing preservation using AAO-HNS guidelines. Analysis included short-term (>12 mo) and long-term (>24 mo) follow-up.
Data Synthesis: Data analysis was performed using MedCalc 12.7.0. Each article was weighted according to the number of patients treated. Analysis of pooled proportion was performed, and Freeman–Tukey transformation was used to correct for probable variance. A *t* test (of proportions) was performed to compare differences between groups.
Conclusion: Endolymphatic sac surgery (sac decompression or mastoid shunt) is effective at controlling vertigo in the short term (>1 yr of follow-up) and long term (>24 mo) in at least 75% of patients with Ménière's disease who have failed medical therapy. Sac decompression and mastoid shunting techniques provide similar vertigo control rates. Mastoid shunting, *with* and *without* silastic, also provides similar vertigo control rates. Non-use of silastic, however, seems to maintain stable or improved hearing in more patients compared to silastic sheet placement. The data suggest that, once the sac is opened, placing silastic does not add benefit and may be deleterious.
Key Words: Endolymphatic mastoid shunt—Endolymphatic sac decompression—Endolymphatic sac surgery—Ménière's disease—Meta-analysis—Systematic review.

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First described by French physician Prosper Ménière in 1861, Ménière's disease (MD) is currently defined as recurrent vertigo, low-frequency sensorinueral hearing loss, and tinnitus with or without the sensation of aural fullness (1,2). Its prevalence has been estimated to range from 3.5 to 513 per 100,000, with the most current estimate at approximately 1 per 500, peaking in the fourth to fifth decade of life (3,4); females are more commonly affected than males (3,4). Despite its prevalence, the treatment of MD remains controversial, with multiple medical and surgical options being used. Initial management is typically medical, with dietary modifications, diuretics, and oral steroids. For the 15% to 40% of intractable patients, intratympanic injections of steroids or gentamicin can be considered. Surgical options include endolymphatic sac surgery (ESS), vestibular nerve section, and surgical labyrinthectomy (4–6). Of the surgical options, ESS provides the greatest hearing preservation (7,8).

Endolymphatic sac surgery was first described by Portmann in 1923, as he demonstrated its role in preserving balance in Selacian fish (9,10). Since Portmann's initial description, various sac surgery procedures have been devised (11–15). Many view ESS as an effective, nondestructive operation with initial vertigo control rates between 60% and 90% (11–13,16–22). Others, however, question its short-term and long-term efficacy (23–25). Despite intratympanic injections being performed more frequently than ESS over the last decade, ESS is still the most common operative procedure performed for MD in the United States (7,26).

Although vertigo control guidelines were created in 1972 (27) and revised in 1985 and 1995 (1,2), reporting of ESS outcomes still remains as subjective as the fluctuating disease process itself. In fact, Thorp et al. (28) demonstrated that, during 1989 to 1999, 79% of otolaryngologists

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Supplemental digital content is available in the text.

attempted to use the guidelines but only 50% applied the guidelines correctly. This discrepancy has undoubtedly generated significant perception differences over treatment efficacy. Currently, no objective systematic analysis on ESS exists in the literature. This study was undertaken to systematically analyze current ESS procedures using the American Academy of Otolaryngology–Head and Neck Foundation (AAO-HNS) guidelines to better quantify their efficacy in controlling vertigo and preserving hearing in the short and long term. It should be noted that this study did not compare ESS to the natural history of MD (nonsurgical); rather its focus was to explore possible outcome differences in patients undergoing current ESS techniques.

DESIGN

Systematic review and meta-analysis

METHODS

Literature Search

A comprehensive literature search was conducted using the PubMed-NCBI database. The following searches were conducted:

Inclusion Criteria

1) Endolymphatic surgery was performed for medically intractable MD*
2) Prospective or retrospective studies
3) All current ESS procedures: sac decompression and mastoid shunt
4) Surgical technique described in detail
5) 1985 or 1995 AAO-HNS guidelines utilized [1, 2]
6) If 1972 AAOO guidelines were utilized, data could be extrapolated into the 1985 AAO-HNS guidelines format [27]
7) Minimum of 12 months follow-up
8) Minimum of 10 patients treated
9) Full manuscript could be obtained in English

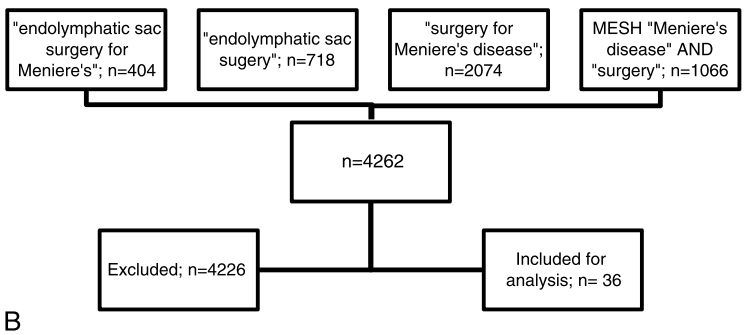
Exclusion criteria

1) Subarachnoid shunt and inner endolymphatic valve procedures**
2) 1985 or 1995 AAO-HNS guidelines not utilized
3) 1972 AAOO guidelines were not amenable to extrapolation
4) Patients had undergone previous surgery for vertigo control
5) Surgical technique not described in detail
6) < 12 months follow-up
7) < 10 patients treated
8) Full manuscript text could not be obtained or was in another language

*MD patients failed prior trials of dietary medication, diuretic therapy, osmotic agents, labyrinthine sedatives (betahistine), pressure devices (Meniett), and oral steroids. Although not always explicitly stated, the vast majority of patients had not received intratympanic steroids or gentamicin injections prior to surgery.

**Subarachnoid shunts and inner endolymphatic valve procedures were not included in analysis comparison as these are no longer commonly performed.

A



B

FIG. 1. *A*, Inclusion and exclusion criteria. *B*, Literature search algorithm.

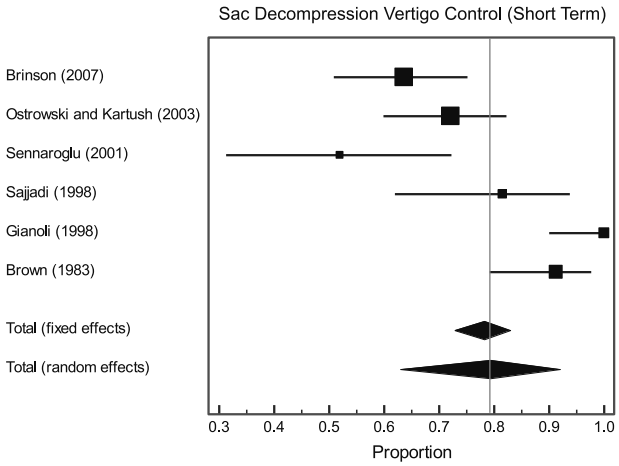


FIG. 2. Vertigo control: Forest plot for endolymphatic sac decompression with Category A/B vertigo control at a minimum of 12 months of follow-up.

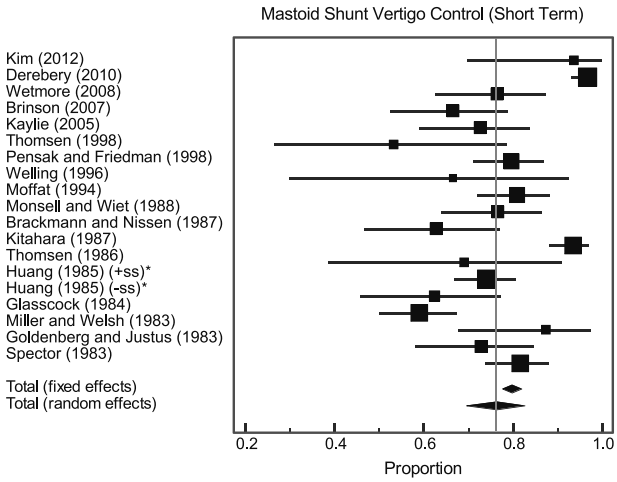


FIG. 4. Vertigo control: Forest plot for mastoid shunt (including both *with* and *without* silastic sheeting) with Category A/B vertigo control at a minimum of 12 months of follow-up. +ss indicates with silastic sheeting; −ss, without silastic sheeting.

1) ''endolymphatic sac surgery for Ménière's disease''; 2) ''endolymphatic sac surgery''; 3) ''surgery for Ménière's disease''; 4) MeSH ''Ménière's disease/surgery.'' This resulted in a total of 4,262 abstracts and manuscripts that were subjected to our inclusion and exclusion criteria (Fig. 1A). Our search is graphically depicted in an algorithmic format (Fig. 1B).

Endpoints

Primary endpoint defined as postoperative vertigo control was evaluated using the AAO-HNS guidelines (1,2). Categories A/B were grouped together and represented either ''complete vertigo control'' or ''substantial vertigo control.'' These categories were combined because Category B is generally viewed as a success as it represents a substantial reduction (99%–60%) in vertiginous attacks. Also, patients with Category B vertigo control typically report great improvement in quality of life and functional level (29).

Secondary endpoint defined as postoperative hearing preservation was evaluated using the AAO-HNS guidelines (1,2). Mean pure-tone audiometry (PTA) threshold changes were calculated and were categorized either as ''improved''/''stable'' (postoperative thresholds within 10 dB of preoperative levels) or ''worsened'' (postoperative levels >10 dB of preoperative levels). Further, weighted mean PTA ΔdB (500, 1,000, and 2,000 Hz) was calculated for each ESS subtype.

Both primary and secondary endpoints were evaluated for short-term and long-term results, defined as more than 12 and more than 24 months of follow-up, respectively.

Data Extraction

Data from studies meeting inclusion and exclusion criteria were extracted and verified by a second author. Information extracted from each study included author, year of publication, number of patients studied, mean length of follow-up, and any reported preoperative and postoperative outcomes.

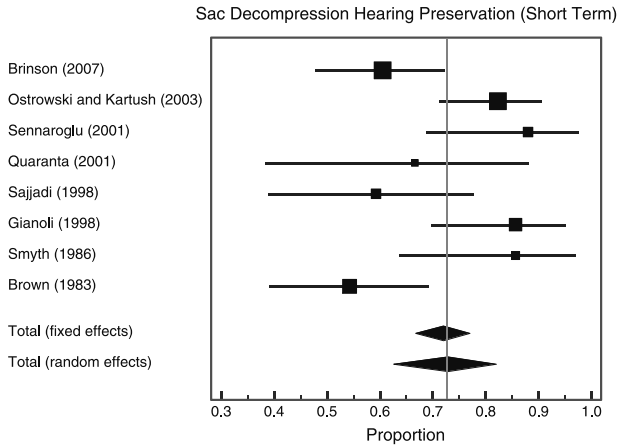


FIG. 3. Hearing outcomes: Forest plot for endolymphatic sac decompression with hearing improved or stable at a minimum of 12 months of follow-up.

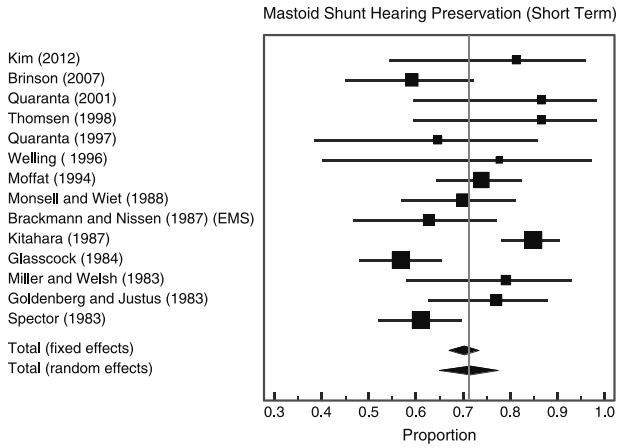


FIG. 5. Hearing outcomes: Forest plot for mastoid shunt (including both *with* and *without* silastic sheeting) with hearing improved or stable at a minimum of 12 months of follow-up.

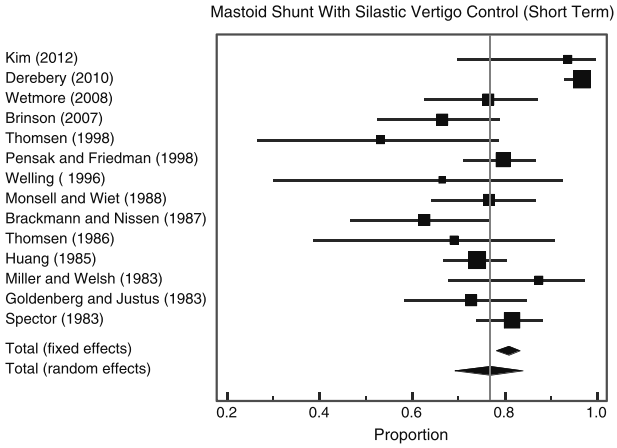


FIG. 6. Vertigo control: Forest plot for mastoid shunt *with* silastic with Category A/B vertigo control at a minimum of 12 months of follow-up.

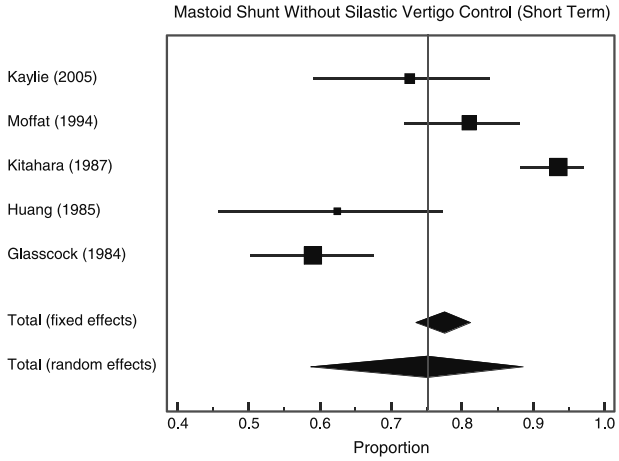


FIG. 8. Vertigo control: Forest plot for mastoid shunt *without* silastic with Category A/B vertigo control at a minimum of 12 months of follow-up.

Endolymphatic sac decompression was defined as complete mastoidectomy with wide exposure of the posterior fossa dura in the area of the endolymphatic sac but no incisions into the sac. *Shunting procedures* included mastoid shunt (opening the sac) with or without silastic. If the author reported a sac decompression procedure but described opening the endolymphatic sac in the surgical technique, the study was included in the mastoid shunting without silastic group.

If the surgical technique was unclear, we emailed the corresponding author to ensure correct categorization of data.

Statistical Analysis

A meta-analysis of proportions was performed using MedCalc 12.7.0. Short-term and long-term endpoints were evaluated for the following treatment groups:

1) Current ESS procedures
   a. sac decompression versus mastoid shunt procedures
2) Current mastoid shunt procedures
   b. mastoid shunt *with* silastic sheeting versus mastoid shunt *without* silastic sheeting

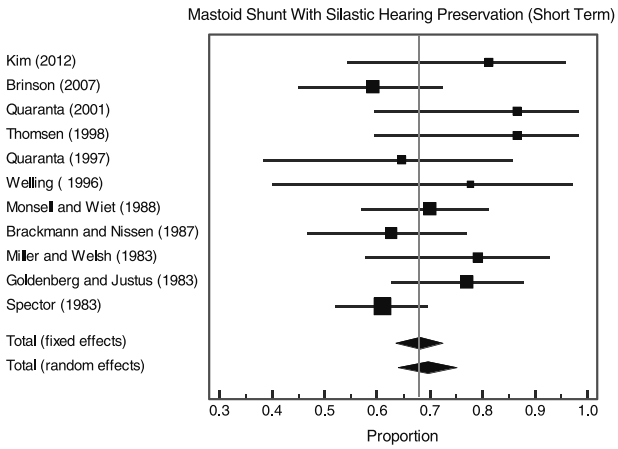


FIG. 7. Hearing outcomes: Forest plot for mastoid shunt *with* silastic with hearing improved or stable at a minimum of 12 months of follow-up.

Each technique was weighted according to the number of patients treated. Analysis of pooled proportions was performed where appropriate. MedCalc used a Freeman–Tukey transformation (30) to calculate the weighted summary proportion under the fixed and random effects model (31). Data were presented as weighted proportions with corresponding 95% confidence intervals (CIs). Both the fixed effects model and the random effects model were used in this study.

In addition, a χ^2 test with Yates correction for continuity was applied with 2-sided (or 2-tailed) p values for the comparison of 2 proportions from independent samples (these proportions being the vertigo control and hearing preservation) expressed as a percentage, as calculated from the aforementioned aggregations.

Complete methods are described in the Supplemental Methods Section, http://links.lww.com/MAO/A220.

RESULTS

The literature search resulted in a total of 4,262 manuscripts/abstracts. Of these, a total of 36 manuscripts

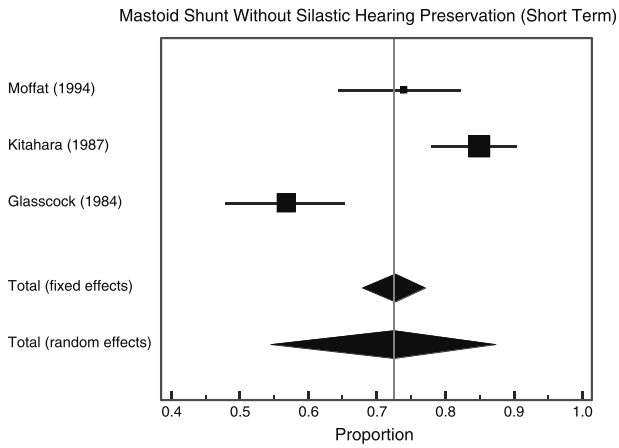


FIG. 9. Hearing outcomes: Forest plot for mastoid shunt *without* silastic with hearing improved or stable at a minimum of 12 months of follow-up.

TABLE 1. *Summary of endolymphatic sac surgery procedures with Category A/B vertigo control in the short term (>12 mo)*

Procedure	Mean weighted follow-up (mo)	Category A/B vertigo control
Sac decompression	26.2	79.3%[a,b]
Mastoid shunt (*with* and *ithout* silastic)	31.0	76.4%[a]
Mastoid *with* silastic	28.3	76.9%[c]
Mastoid *without* silastic	31.1	75.0%[b,c]

[a]Sac decompression versus mastoid shunt (with and without silastic) Category A/B vertigo control; $p = 0.34$.
[b]Sac decompression versus mastoid shunt *without* silastic Category A/B vertigo control; $p = 0.21$.
[c]Mastoid shunt *with* silastic versus Mastoid shunt *without* silastic Category A/B vertigo control; $p = 0.47$.

were included in our statistical analysis (12–14,16–22, 25,32–56).

Short-term Analysis

Endolymphatic Sac Decompression Versus Mastoid Shunt

Endolymphatic Sac Decompression. Vertigo: Six articles, totaling 267 patients, were analyzed to determine the efficacy of endolymphatic sac decompression in controlling vertigo. Mean follow-up was 26.2 months (range, 12–55 mo). Complete or substantial (Category A/B) vertigo control was achieved in 79.3% (95% CI, 62.9%–91.9%) of patients (Fig. 2).

Hearing: Eight articles, totaling 303 patients, were analyzed to determine the efficacy of endolymphatic sac decompression in hearing preservation. Mean follow-up was 25.8 months (range, 12–55 mo). Postoperative hearing was stable or improved in 72.8% (95% CI, 62.5%–81.9%) of patients (Fig. 3). Mean PTA worsened by 1.3 dB (range, −1.4 to 9.6 dB).

Mastoid Shunts (With and Without Silastic). Vertigo: Nineteen articles, totaling 1,384 patients, were analyzed to determine the efficacy of current mastoid shunting procedures in controlling vertigo symptoms. Mean follow-up was 31.0 months (range, 12–72 mo). Complete or substantial (Category A/B) vertigo control was achieved in 76.4% (95% CI, 69.5%–82.7%) of patients (Fig. 4).

Hearing: Fourteen articles, totaling 799 patients, were analyzed to determine the efficacy of current mastoid shunting procedures in hearing preservation. Mean follow-up was 34.8 months (range, 12–132 mo). Postoperative hearing was stable or improved in 71.4% (95% CI, 64.9%–77.5%) of patients (Fig. 5). Mean PTA worsened by 7.2 dB (range, 0.0–13.3 dB).

Mastoid Shunt With Silastic Versus Mastoid Shunt without Silastic

Mastoid With Silastic. Vertigo: Fourteen articles, totaling 917 patients, were analyzed to determine the efficacy of mastoid shunting with silastic sheeting in controlling vertigo. Mean follow-up was 28.3 months (range, 12–51 mo). Complete or substantial (Category A/B) vertigo control was achieved in 76.9% (95% CI, 69.1%–83.9%) of patients (Fig. 6).

Hearing: Eleven articles, totaling 427 patients, were analyzed to determine the efficacy of mastoid shunting with silastic sheeting in hearing preservation. Mean follow-up was 32.5 months (range, 12–132 mo). Postoperative hearing was stable or improved in 68.0% (95% CI, 62.7%–72.1%) of patients (Fig. 7). Mean PTA worsened by 7.2 dB (range, 0.0–13.3 dB).

Mastoid Without Silastic. Vertigo: Five articles, totaling 467 patients, were analyzed to determine the efficacy of mastoid shunting without silastic in controlling vertigo. Mean follow-up was 31.1 months (range, 12–72 mo). Complete or substantial (Category A/B) vertigo control was achieved in 75.0% (95% CI, 58.6%–88.5%) of patients (Fig. 8).

Hearing: Three articles, totaling 372 patients, were analyzed to determine the efficacy of mastoid shunting without silastic in hearing preservation. Mean follow-up was 32.6 months (range, 12–72 mo). Postoperative hearing was unchanged or improved in 72.5% (95% CI, 59.4%–84.9%) of patients (Fig. 9). Mean PTA worsened by 13.3 dB (only value, no range).

TABLE 2. *Summary of endolymphatic sac surgery procedures of hearing preservation in the short term (>12 mo)*

Procedure	Mean weighted follow-up (mo)	Hearing stable/improved (%)	ΔPTA (dB; hearing worsened)
Sac decompression	25.8	72.8%[a,b,c]	1.3
Mastoid shunt (*with* and *without* silastic)	34.8	71.4%[a]	7.2
Mastoid *with* silastic	32.5	68.0%[c,d]	7.2
Mastoid *without* silastic	32.6	72.5%[b,d]	n/a

[a]Sac decompression versus mastoid shunt (with and without silastic) hearing stable/improved; $p = 0.69$.
[b]Sac decompression versus mastoid shunt *without* silastic hearing stable/improved; $p = 0.99$.
[c]Sac decompression versus mastoid shunt *with* silastic hearing stable/improved; $p = 0.18$.
[d]Mastoid shunt *with* silastic versus mastoid shunt *without* silastic hearing stable/improved; $p = 0.004$.
PTA indicates pure-tone audiometry.

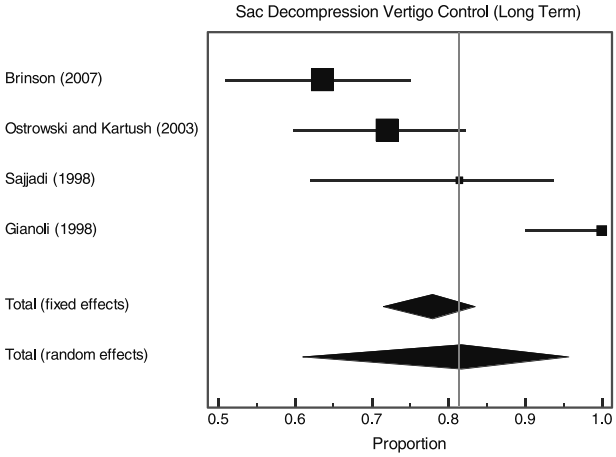


FIG. 10. Vertigo control: Forest plot for endolymphatic sac decompression with Category A/B vertigo control at a minimum of 24 months of follow-up.

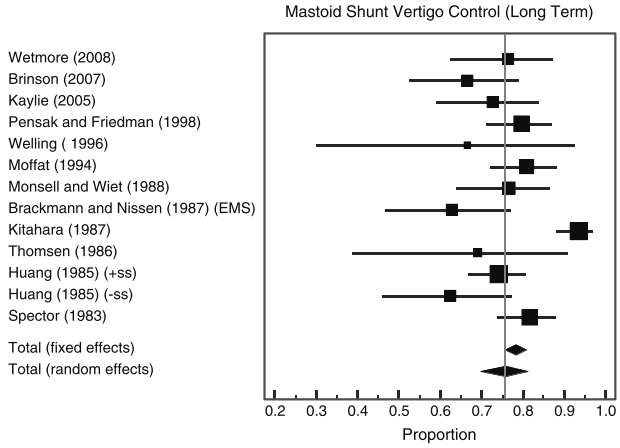


FIG. 12. Vertigo control: Forest plot for mastoid shunt (including both *with* and *without* silastic sheeting) with Category A/B vertigo control at a minimum of 24 months of follow-up. +ss indicates with silastic sheeting; −ss, without silastic sheeting.

A summary of vertigo control and hearing preservation in the short-term (>12 mo) is provided in Tables 1 and 2.

Long-term Analysis

Endolymphatic Sac Decompression Versus Mastoid Shunt

Endolymphatic Sac Decompression. Vertigo: Four articles, totaling 196 patients, were analyzed to determine the efficacy of endolymphatic sac decompression in controlling vertigo. Mean follow-up was 34.8 months (range, 24–55 mo). Complete or substantial (Category A/B) vertigo control was achieved in 81.6% (95% CI, 61.0%–95.7%) of patients (Fig. 10).

Hearing: Five articles, totaling 211 patients, were analyzed to determine the efficacy of endolymphatic sac decompression in hearing preservation. Mean follow-up was 34.0 months (range, 24–132 mo). Postoperative hearing was stable or improved in 71.6% (95% CI, 59.2%–82.5%) of patients (Fig. 11). Mean PTA worsened by 1.4 dB (range, −1.4 to 9.6 dB).

Mastoid Shunts (With and Without Silastic). Vertigo: Thirteen articles, totaling 966 patients, were analyzed to determine the efficacy of current mastoid shunting procedures in controlling vertigo symptoms. Mean follow-up was 40.7 months (range, 24–72 mo). Complete or substantial (Category A/B) vertigo control was achieved in 75.7% (95% CI, 69.8%–81.2%) of patients (Fig. 12).

Hearing: Eight articles, totaling 549 patients, were analyzed to determine the efficacy of current mastoid shunting procedures in hearing preservation. Mean follow-up was 41.5 months (range, 24–132 mo). Postoperative hearing was stable or improved in 69.3% (95% CI, 60.9%–77.2%)

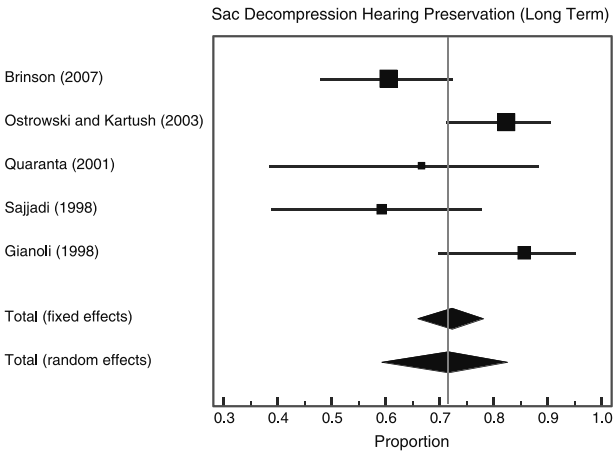


FIG. 11. Hearing outcomes: Forest plot for endolymphatic sac decompression with hearing improved or stable at a minimum of 24 months of follow-up.

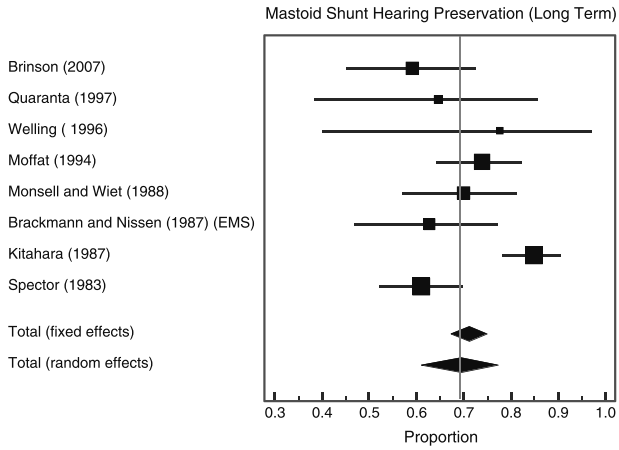


FIG. 13. Hearing outcomes: Forest plot for mastoid shunt (including both *with* and *without* silastic sheeting) with hearing improved or stable at a minimum of 24 months of follow-up.

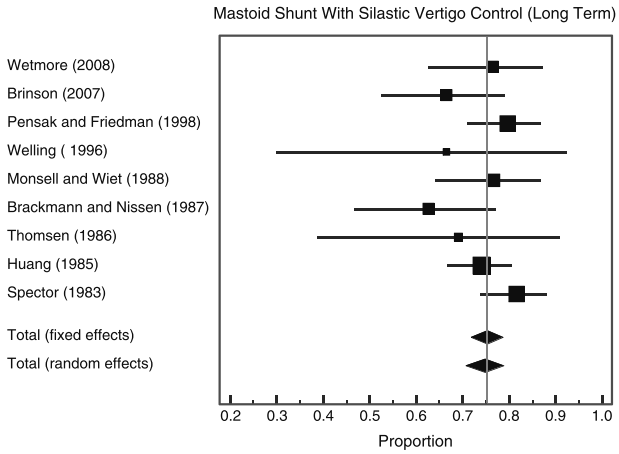


FIG. 14. Vertigo control: Forest plot for mastoid shunt *with* silastic with Category A/B vertigo control at a minimum of 24 months of follow-up.

of patients (Fig. 13). Mean PTA worsened by 6.0 dB (range, 0.0–13.3 dB).

Mastoid Shunt With Silastic Versus Mastoid Shunt without Silastic

Mastoid With Silastic. Vertigo: Nine articles, totaling 631 patients, were analyzed to determine the efficacy of mastoid shunting with silastic in controlling vertigo. Mean follow-up was 40.7 months (range, 24–60 mo). Complete or substantial (Category A/B) vertigo control was achieved in 75.3% (95% CI, 71.8%–78.6%) of patients (Fig. 14).

Hearing: Seven articles, totaling 324 patients, were analyzed to determine the efficacy of mastoid shunting with silastic in hearing preservation. Mean follow-up was 38.8 months (range, 24–132 mo). Postoperative hearing was stable or improved in 64.4% (95% CI, 59.0%–69.5%)

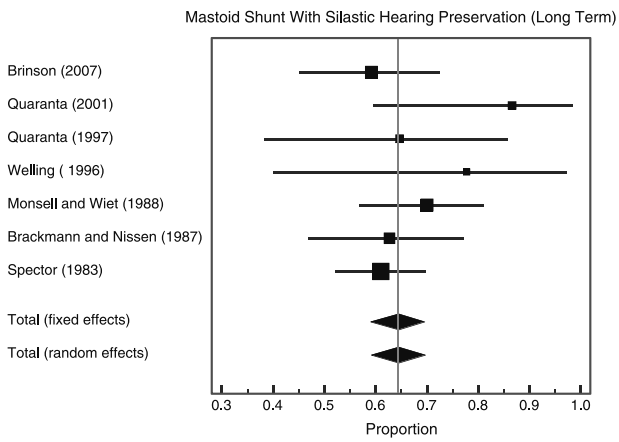


FIG. 15. Hearing outcomes: Forest plot for mastoid shunt *with* silastic with hearing improved or stable at a minimum of 24 months of follow-up.

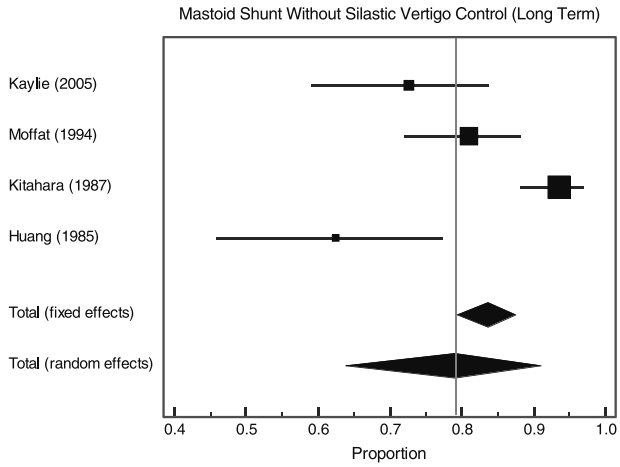


FIG. 16. Vertigo control: Forest plot for mastoid shunt *without* silastic with Category A/B vertigo control at a minimum of 24 months of follow-up.

of patients (Fig. 15). Mean PTA worsened by 6.2 dB (range, 4.0–13.3 dB).

Mastoid Without Silastic. Vertigo: Four articles, totaling 335 patients, were analyzed to determine the efficacy of mastoid shunting without silastic in controlling vertigo. Mean follow-up was 40.8 months (range, 24–72 mo). Complete or substantial (Category A/B) vertigo control was achieved in 79.0% (95% CI, 63.8%–90.9%) of patients (Fig. 16).

Hearing: Two articles, totaling 240 patients, were analyzed to determine the efficacy of mastoid shunting without silastic in hearing preservation. Mean follow-up was 49.8 months (range, 24–72 mo). Postoperative hearing was unchanged or improved in 79.8% (95% CI, 68.1%–89.3%) of patients (Fig. 17). We were unable to calculate mean dB PTA change.

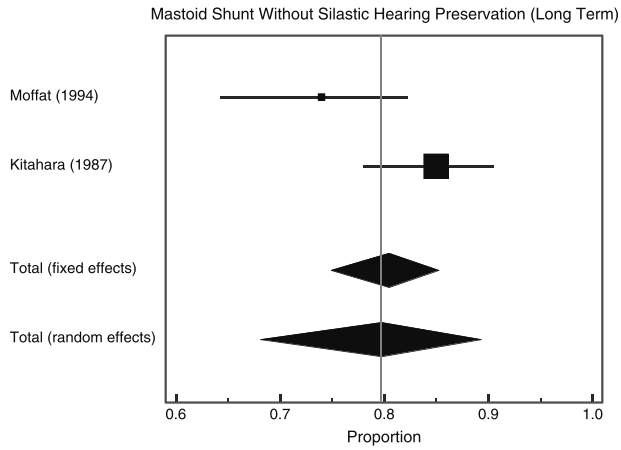


FIG. 17. Hearing outcomes: Forest plot for mastoid shunt *without* silastic with hearing improved or stable at a minimum of 24 months of follow-up.

TABLE 3. *Summary of endolymphatic sac surgery procedures with Category A/B vertigo control in the long term (>24 mo)*

Procedure	Mean weighted follow-up (mo)	Category A/B vertigo control
Sac decompression	34.8	81.6%[a,b]
Mastoid shunt (*with* and *without* silastic)	40.7	75.7%[a]
Mastoid shunt *with* silastic	40.7	75.3%[c]
Mastoid shunt *without* silastic	40.8	79.0%[b,c]

[a]Sac decompression versus mastoid shunt Category A/B vertigo control; $p = 0.09$.
[b]Sac decompression versus mastoid shunt *without* silastic Category A/B vertigo control; $p = 0.54$.
[c]Mastoid shunt *with* silastic versus mastoid shunt *without* silastic Category A/B vertigo control; $p = 0.22$.

A summary of vertigo control and hearing preservation in the long-term (>24 months) is provided in Tables 3 and 4, respectively.

Current ESS Procedures From Studies With Both Short-term and Long-term Follow-ups. Vertigo: Six articles provided continual data for the same patient cohort, allowing both short-term and long-term follow-ups. These articles, totaling 448 patients, were analyzed to determine the efficacy of current ESS techniques (sac decompression and mastoid shunting *with* or *without* silastic) in controlling vertigo. With a mean short-term follow-up of 16.0 months (range, 12–24 mo), complete or substantial (Category A/B) vertigo control occurred in 72.6% (95% CI, 68.3%–76.7%) of patients (Fig. 18). With mean long-term follow-up in the same patient cohort of 79.0 months (range, 48–120 mo), complete or substantial (Category A/B) control was present in 63.4% (95% CI, 51.3%–74.7%) of patients (Fig. 19). A summary of short-term and long-term vertigo control from these articles is provided in Table 5.

Hearing: We did not find any continual articles that provided both short-term and long-term follow-ups.

Complete meta-analysis data are provided in the Supplemental Results Section, http://links.lww.com/MAO/A221.

DISCUSSION

The endolymphatic sac is thought to provide immunologic responses and maintain hydrostatic pressure and endolymph homeostasis for the inner ear (57). Loss of these functions may contribute to the etiopathophysiology of MD (57). Initial studies on the endolymphatic sac of mice demonstrated an inner ear immunologic response to keyhole limpet hemocyanin (58). More recent studies have shown an inner ear proimflammatory expression of cytokine tumor necrosis factor α in response to keyhole limpet hemocyanin in the human endolymphatic sac (59). These studies suggest that the endolymphatic sac performs innate immunologic response (initial antigen presentation) for the inner ear, similar to the mucosa associated lymphatic tissue in the gastrointestinal tract (58–60).

A possible contributor to the etiopathophysiology of MD is the repetitive presentation of viral and bacterial antigens to the endolymphatic sac, generating a proinflammatory response through numerous fenestrated subepithelial blood vessels within the inner ear. Single or multiple inflammatory responses eventually may cause destruction of the endolymphatic sac, obliterating its role in inner ear function (60–62). In addition to innate immunity, others have speculated that endolymphatic sac dysfunction results from a humoral-mediated immunologic response. In this hypothesis, antibodies to the endolymphatic sac and/or immune complex deposition contribute to endolymphatic sac dysfunction (60,63,64). Loss of endolymphatic sac function impairs the ability to maintain hydrostatic pressure and endolymph homeostasis, eventually causing rupture in Reissner membrane triggering episodic vertigo attacks (61).

Recent studies have suggested that stress-related events may impair the endolymphatic sac's ability to maintain homeostasis (65–67). These studies have demonstrated elevated levels of the plasma stress hormone vasopressin along with an elevated level of vasopressin receptor (V2R) mRNA expression in the endolymphatic sac of patients with MD in comparison to their respective control group counterparts (65–67). Others have suggested that dysfunction of $Na^+/K^+/2Cl^-$ cotransporters and aquaporins, similar to those in renal tubules, on the endolymphatic sac membrane may contribute to the inability to maintain hydrostatic pressure and endolymph homeostasis (65,67,68). Regardless of dysfunction mechanism, the

TABLE 4. *Summary of endolymphatic sac surgery procedures of hearing preservation in the long term (>24 mo)*

Procedure	Mean weighted follow-up (mo)	Hearing stable/improved (%)	ΔPTA (dB; hearing worsened)
Sac decompression	34.0	71.6%[a,b]	1.4
Mastoid shunt (*with* and *without* silastic)	41.5	69.3%[a]	6.0
Mastoid shunt *with* silastic	38.8	64.4%[c]	6.2
Mastoid shunt *without* silastic	49.8	79.8%[b,c]	n/a

[a]Sac decompression versus mastoid shunt (with and without silastic) hearing stable/improved; $p = 0.59$.
[b]Sac decompression versus mastoid shunt *without* silastic hearing stable/improved; $p = 0.05$.
[c]Mastoid shunt *with* silastic versus mastoid shunt *without* silastic hearing stable/improved; $p = 0.0001$.
n/a indicates not available; PTA, pure-tone audiometry.

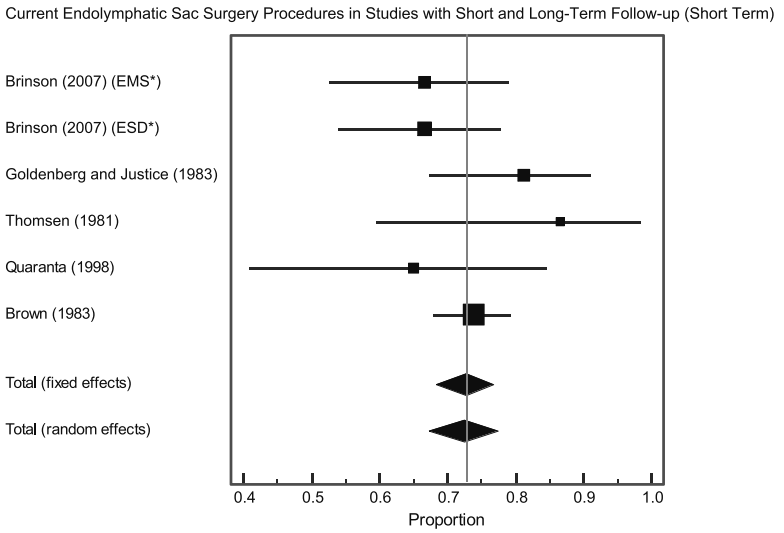


FIG. 18. Vertigo control: Forest plot for current endolymphatic sac procedures (i.e., sac decompression and mastoid shunt *with* and *without silastic* in studies with short-term and long-term follow-up), short-term follow-up Category A/B vertigo control. Mean weighted follow-up was at 16 months. EMS indicates mastoid shunt; ESD, sac decompression.

evidence points toward the endolymphatic sac contributing to the etiopathophysiology of MD.

Short-term Analysis

Decompression

The first successful human endolymphatic sac decompression procedure was performed in France in 1926 (9,10), before Hallpike and Cairns' microscopic studies and description of labyrinthine hydrops (9,69). Since then, decompression has generally been viewed as a safe surgical option because it does not significantly impact hearing (8,49). The theory behind decompression is that removal of mastoid bone provides pressure relief and allows for expansion of the endolymphatic sac, thereby decreasing episodic vertigo attacks (8,70). Despite the safety and low morbidity of sac decompression, its efficacy in controlling vertiginous attacks of MD has been debated with great inconsistency. Some studies endorse 94% to 100% improvement (Category A/B) (13,17–19), while others state 60% to 64% (16,21).

In our analysis, 79.3% of patients undergoing endolymphatic sac decompression achieved complete or substantial (Category A/B) vertigo control with a minimum

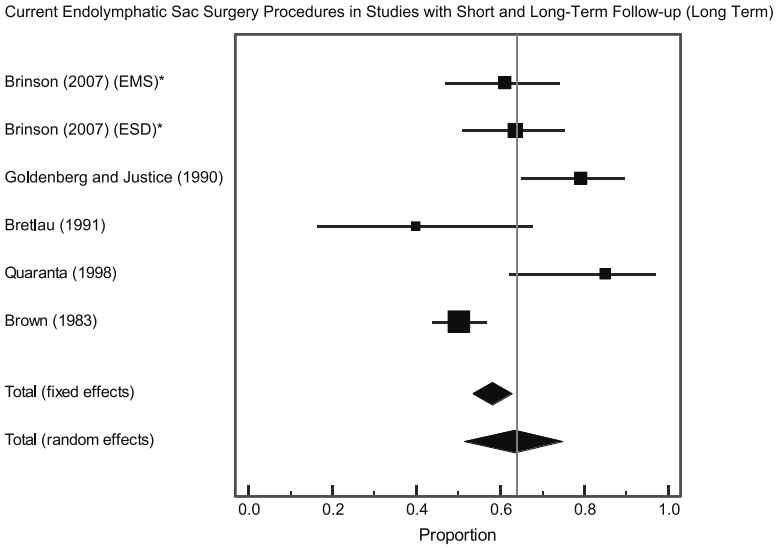


FIG. 19. Vertigo control: Forest plot for current endolymphatic sac procedures (i.e., sac decompression and mastoid shunt *with* and *without silastic*), long-term follow-up Category A/B vertigo control. Mean weighted follow-up was at 79.0 months. EMS indicates mastoid shunt; ESD, sac decompression.

TABLE 5. *Summary of current ESS procedures from 6 studies with both short-term and long-term follow-up*

	Mean weighted short-term follow-up (mo)	Category A/B vertigo control (short term)	Mean weighted long-term follow-up (mo)	Category A/B vertigo control (long term)
Current ESS procedures[a]	16.0	72.6%[b]	79.0	63.4%[b]

[a]Current ESS procedures = sac decompression and mastoid shunts *with* and *without* silastic sheeting.
[b]Short-term versus long-term follow-up Category A/B vertigo control; $p = 0.004$.

of 1 year of follow-up (Fig. 2 and Table 1). Although not statistically significant, there was a trend toward sac decompression providing the greatest hearing preservation compared to all endolymphatic sac surgical procedures. At short-term follow-up, sac decompression resulted in only +1.3 dB PTA change, the smallest threshold increase compared to other endolymphatic sac procedures (Table 2).

Shunting

Endolymphatic sac shunt procedures gained popularity in the 1960s through House's (15) subarachnoid shunting procedure. Over the years, various shunting techniques have emerged, including mastoid shunts, subarachnoid shunts, and endolymphatic duct valve placement (11,12, 15,16,22,24,42,45,55,56,71). Each of these approaches has generated controversy (12,24,72). Thomsen et al. (72) were some of the first to question the efficacy of mastoid shunts in their trial comparing mastoid shunt versus ''sham procedure'' (mastoidectomy). With nearly a decade of follow-up, they concluded that there was no statistical difference between mastoid shunts and placebo sham surgery in controlling vertiginous symptoms. Their study, however, has received much criticism for its potential inaccuracies and study design (73–76).

Since House, many have performed a subarachnoid shunt to treat medically recalcitrant MD, reporting complete or substantial vertigo control (Category A/B) ranging from 66% to 93% (11,13,20,22). Despite the early successes of this technique, it has been rarely performed for the last 25 years. In the 1970s, Arenberg offered another shunting approach, the inner ear endolymphatic valve (55,56,77). A unidirectional valve was placed directly into the endolymphatic duct with the intent to promote endolymph flow from the labyrinth to the sac. The inner ear endolymphatic valve was discontinued because of questionable long-term vertigo control, with failures attributed to fibroproliferative responses, valve migration, and valve plugging (78). Because subarachnoid shunts and inner endolymphatic duct valve placement techniques are rarely performed today, we did not include these shunt procedures in our statistical comparison.

Current mastoid shunt procedures—mastoid shunt with and without silastic—achieved 76.4% complete or substantial (Category A/B) vertigo control at a mean follow-up of approximately 2.5 years (Fig. 4 and Table 1). With similar mean follow-up, 71.4% of patients either improved or maintained initial hearing, with a mean PTA worsening of 7.2 dB (Fig. 5 and Table 2).

When comparing current procedures (sac decompression versus mastoid shunt *with* and *without* silastic), both groups had similar rates of complete or substantial (Category A/B) vertigo control (79.3% versus 76.4%, $p = 0.34$) at a minimum of 1 year of follow-up (Table 1). Although both groups maintained similar rates of stable or improved hearing (72.8% versus 71.4%, $p = 0.69$), the notable difference was in mean change in PTA. Sac decompression resulted in PTA worsening of 1.3 dB, whereas current mastoid shunting techniques resulted in PTA worsening of 7.2 dB (Table 2). The significance of this 6-dB difference could not be statistically calculated because raw data were unavailable. Although the cause of worsened PTAs observed with current shunting procedures in our analysis is unknown, a few speculations may account for this difference. One speculation may be related to the added invasiveness involved with incision of the endolymphatic sac performed in shunting procures. Second, differences in follow-up time may have contributed to this difference because current mastoid shunting techniques and decompression patients were seen at an average of 34.8 and 25.8 months, respectively. One could argue that increased time to follow-up may have resulted in worse hearing PTAs with the progression of MD. In addition, several studies have demonstrated worse hearing outcomes with shunt procedures in comparison to the natural course of MD (44,79). Overall, the 6-dB difference may not be functionally relevant.

Mastoid Shunt With Silastic Versus Mastoid Shunt Without Silastic

Groups undergoing mastoid shunting *with* and *without* silastic demonstrated nearly identical rates of complete or substantial (Category A/B) vertigo control (76.9% versus 75.0%, $p = 0.47$) with a minimum of 1 year of follow-up, comparable to the high efficacy rate seen in sac decompression patients (Figs. 6 and 8). A difference between the 2 groups, however, was noted with hearing outcomes. The mastoid shunting with silastic group achieved 68.0% (mean follow-up, 32.5 mo) stable or improved hearing, whereas the mastoid shunt without silastic group achieved 72.5% (mean follow-up, 32.6 mo) (Figs. 7 and 9 and Table 2), a difference that was statistically significant ($p = 0.004$). Although the etiology of this discrepancy is unknown, some have suggested that the silastic sheeting incites a foreign body reaction affecting inner ear function (78,80,81). The functional significance of this difference is uncertain. Interestingly, mastoid shunt without silastic did not demonstrate a statistical difference in short-term hearing preservation compared to simple sac decompression (72.5% versus 72.8%, $p = 0.99$). Further, although not statistically significant, sac decompression preserved hearing in more patients than mastoid shunt *with* silastic in the short term (72.8% versus 68.0%, $p = 0.18$).

These findings may further implicate silastic as a potential contributor to worse hearing preservation.

Long-term Analysis

The natural progression of MD (continued hearing loss, ''burn-out,'' etc.) complicates analysis of long-term surgical results (4,54,82). Several studies have attempted to compare ESS outcomes to nonsurgical outcomes (natural history) in patients with MD (54,82). In the study by Silverstein et al., complete vertigo control was obtained in 71% and 70% of patients in the group not operated on and the group who underwent subarachnoid shunt surgery, respectively, at 8 years of follow-up. Quaranta et al. performed a similar study that resulted in 74% and 85% vertigo control at 6 years of follow-up in the groups not operated on and the group who underwent mastoid shunt surgery, respectively.

Sac Decompression Versus Mastoid Shunt (With and Without Silastic) in the Long Term

In our analysis, we were unable to compare the natural history of MD to ESS. We did, however, analyze the long-term efficacy of current endolymphatic sac procedures. With approximately 3 years of follow-up, sac decompression achieved 81.6% Category A/B vertigo control compared to 75.7% for current mastoid shunt techniques (Table 3). This difference was not found to be statistically significant ($p = 0.09$). Further, at similar follow-up times, sac decompression and current mastoid shunt techniques achieved relatively similar rates of hearing preservation (71.6% versus 69.3%, $p = 0.59$; Table 4). The mean PTA worsened by 1.4 dB in the sac decompression group and by 6.0 dB in the current mastoid shunt group. The significance of this difference, however, could not be statistically determined because the raw data were unavailable, and, as with the short-term conclusion, may not be clinically relevant.

Mastoid Shunt With Silastic Versus Mastoid Shunt Without Silastic in the Long Term

In the long term, both mastoid shunt *with* and *without* silastic achieved similar rates (75.3% versus 79.0%, $p = 0.22$) of Category A/B vertigo control (Table 3). Long-term hearing preservation differences were consistent with our short-term analysis, as the group *with* silastic sheet placement had worse hearing preservation compared to the group *without* silastic sheet placement (64.4% versus 79.8%, $p = 0.0001$). This difference was noted to be statistically significant, despite nearly an additional year of follow-up for the nonsilastic group (Table 4). Interestingly, mastoid shunt without silastic placement maintained a statistically significant higher rate of hearing preservation in the long term compared to sac decompression (79.8% versus 71.6%, $p = 0.05$). This suggests that opening of the sac (mastoid shunt), but not inserting silastic, does not negatively impact hearing outcomes in the long term and may actually be beneficial.

To further assess long-term efficacy of ESS, we analyzed studies that provided both short-term and long-term follow-up data in the same cohort of patients. Although we were unable to assess differences between ESS subtypes, we were able to analyze all current ESS techniques (sac decompression and mastoid shunts) as a collective group. At approximately 16 months, current ESS procedures demonstrated a high efficacy of vertigo control with 72.6% achieving complete or substantial (Category A/B) vertigo control (Fig. 18 and Table 5). With a mean follow-up of approximately 6.5 years, vertigo control decreased to 63.4%, a statistically significant change ($p = 0.004$; Fig. 19 and Table 5). The decrease in vertigo control may reflect the degree of overall ESS failure in the long term or may simply reflect the progression of disease in this cohort of patients.

CONCLUSIONS

In conclusion, ESS (sac decompression or sac shunting) controls vertigo in the short term (>1 yr of follow-up) in at least 3 of 4 patients with MD who have failed medical therapy, without prior trial of intratympanic steroids or gentamicin. In the long term, vertigo control with the pooled patient data demonstrates a similar 75% Category A/B result. It should be noted, however, that the long-term results are less favorable when the same cohort of patients is followed up over time (73% control at 16 mo follow-up versus 63% at approximately 6.5 yr of follow-up).

There is no statistical difference between sac decompression and mastoid shunting procedures in controlling vertiginous symptoms or preserving hearing in the short-term or long-term follow-up periods. There is also no difference in vertigo control between shunt procedures with and without silastic. There is, however, a statistical difference in hearing preservation, both in the short and long term, between shunting with and without silastic, in favor of no silastic.

This analysis raises the issue of using silastic in ESS. Although vertigo control is similar in the short and long term, silastic sheeting seems to have a small but statistically significant adverse effect on hearing. In our opinion, a fair assessment would be that once the sac is opened, placing silastic does not add benefit and may be deleterious.

REFERENCES

1. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Ménière's disease. American Academy of Otolaryngology–Head and Neck Foundation, Inc. *Otolaryngol Head Neck Surg* 1995;113:181–5.
2. Pearson BW, Brackmann DE. Committee on Hearing and Equilibrium guidelines for reporting treatment results in Ménière's disease. *Otolaryngol Head Neck Surg* 1985;93:579–81.
3. Alexander TH, Harris JP. Current epidemiology of Ménière's syndrome. *Otolaryngol Clin North Am* 2010;43:965–70.
4. Pullens B, Verschuur HP, van Benthem PP. Surgery for Ménière's disease. *Cochrane Database Syst Rev* 2013;2:CD005395.
5. Claes J, Van de Heyning PH. A review of medical treatment for Ménière's disease. *Acta Otolaryngol Suppl* 2000;544:34–9.
6. Santos PM, Hall RA, Snyder JM, Hughes LF, Dobie RA. Diuretic and diet effect on Ménière's disease evaluated by the 1985 Committee on

Hearing and Equilibrium guidelines. *Otolaryngol Head Neck Sug* 1993;109:680–9.
7. Silverstein H, Lewis WB, Jackson LE, Rosenberg SI, Thompson JH, Hoffmann KK. Changing trends in the surgical treatment of Ménière's disease: results of a 10-year survey. *Ear Nose Throat J* 2003;82:185–7, 191–4.
8. Durland WF Jr, Pyle GM, Connor NP. Endolymphatic sac decompression as a treatment for Ménière's disease. *Laryngoscope* 2005;115:1454–7.
9. Lacher G. Current and historical perspectives on endolymphatic sac surgery. *Acta Otolaryngol Suppl* 1997;526:50–3.
10. Portmann G. The saccus endolymphaticus and an operation for draining for the relief of vertigo. *Proc R Soc Med* 1927;20:1862–7.
11. Telischi FF, Luxford WM. Long-term efficacy of endolymphatic sac surgery for vertigo in Ménière's disease. *Otolaryngol Head Neck Surg* 1993;109:83–7.
12. Arenberg IK. Results of endolymphatic sac to mastoid shunt surgery for Ménière's disease, refractory to medical therapy. *Rev Laryngol Otol Rhinol (Bord)* 1987;108:453–8.
13. Brown JS. A ten year statistical follow-up of 245 consecutive cases of endolymphatic shunt and decompression with 328 consecutive cases of labyrinthectomy. *Laryngoscope* 1983;93(11 Pt 1):1419–24.
14. Spector GJ, Smith PG. Endolymphatic sac surgery for Ménière's disease. *Ann Otol Rhinol Laryngol* 1983;92(2 Pt 1):113–8.
15. House WF. Subarachnoid shunt for drainage of endolymphatic hydrops. A preliminary report. *Laryngoscope* 1962;72:713–29.
16. Brinson GM, Chen DA, Arriaga MA. Endolymphatic mastoid shunt versus endolymphatic sac decompression for Ménière's disease. *Otolaryngol Head Neck Surg* 2007;136:415–21.
17. Gianoli GJ, Larouere MJ, Kartush JM, Wayman J. Sac–vein decompression for intractable Ménière's disease: two-year treatment results. *Otolaryngol Head Neck Surg* 1998;118:22–9.
18. Kim SH, Ko SH, Ahn SH, Hong JM, Lee WS. Significance of the development of the inner ear third window effect after endolymphatic sac surgery in Ménière disease patients. *Laryngoscope* 2012; 122:1838–43.
19. Kitahara M, Kitajima K, Yazawa Y, Uchida K. Endolymphatic sac surgery for Ménière's disease: eighteen years' experience with the Kitahara sac operation. *Am J Otol* 1987;8:283–6.
20. Luetje CM. A critical comparison of results of endolymphatic subarachnoid shunt and endolymphatic sac incision operations. *Am J Otol* 1988;9:95–101.
21. Huang TS, Lin CC. Endolymphatic sac surgery for Ménière's disease: a composite study of 339 cases. *Laryngoscope* 1985;95 (9 Pt 1):1082–6.
22. Glasscock ME 3rd, Kveton JF, Christiansen SG. Current status of surgery for Ménière's disease. *Otolaryngol Head Neck Surg* 1984; 92:67–72.
23. Morrison GA, O'Reilly BJ, Chevretton EB, Kenyon GS. Long-term results of revision endolymphatic sac surgery. *J Laryngol Otol* 1990;104:613–6.
24. Jackson CG, Dickins JR, McMenomey SO, et al. Endolymphatic system shunting: a long-term profile of the Denver Inner Ear Shunt. *Am J Otol* 1996;17:85–8.
25. Thomsen J, Bretlau P, Tos M, Johnsen NJ. Endolymphatic sac–mastoid shunt surgery. A nonspecific treatment modality? *Ann Otol Rhinol Laryngol* 1986;95(1 Pt 1):32–5.
26. Ghossaini SN, Wazen JJ. An update on the surgical treatment of Ménière's diseases. *J Am Acad Audiol* 2006;17:38–44.
27. Committee on Hearing and Equilibrium. Report of Subcommittee on Equilibrium and its Measurement. Ménière's disease: criteria for diagnosis and evaluation of therapy for reporting. *Trans Am Acad Ophthalmol Otolaryngol* 1972;76:1462–4.
28. Thorp MA, Shehab ZP, Bance ML, Rutka JA. The AAO-HNS Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Ménière's disease: have they been applied in the published literature of the last decade? *Clin Otolaryngol Allied Sci* 2003;28:173–6.
29. Hu A, Parnes LS. 10-year review of endolymphatic sac surgery for intractable meniere disease. *J Otolaryngol Head Neck Surg* 2010; 39:415–21.
30. Freeman MF, Tukey TJ. Transformations related to the angular and the square root. *Ann Math Stat* 1950;21:607–11.
31. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
32. Derebery MJ, Fisher LM, Berliner K, Chung J, Green K. Outcomes of endolymphatic shunt surgery for Ménière's disease: comparison with intratympanic gentamicin on vertigo control and hearing loss. *Otol Neurotol* 2010;31:649–55.
33. Wetmore SJ. Endolymphatic sac surgery for Ménière's disease: long-term results after primary and revision surgery. *Arch Otolaryngol Head Neck Surg* 2008;134:1144–8.
34. Convert C, Franco-Vidal V, Bebear JP, Darrouzet V. Outcome-based assessment of endolymphatic sac decompression for Ménière's disease using the Ménière's disease outcome questionnaire: a review of 90 patients. *Otol Neurotol* 2006;27:687–96.
35. Kaylie DM, Jackson CG, Gardner EK. Surgical management of Ménière's disease in the era of gentamicin. *Otolaryngol Head Neck Surg* 2005;132:443–50.
36. Ostrowski VB, Kartush JM. Endolymphatic sac–vein decompression for intractable Ménière's disease: long term treatment results. *Otolaryngol Head Neck Surg* 2003;128:550–9.
37. Sennaroglu L, Sennaroglu G, Gursel B, Dini FM. Intratympanic dexamethasone, intratympanic gentamicin, and endolymphatic sac surgery for intractable vertigo in Ménière's disease. *Otolaryngol Head Neck Surg* 2001;125:537–43.
38. Quaranta N, De Thomasis G, Gandolfi A, Piazza F, Zini C, Quaranta A. Long-term audition results in patients with chronic endolymphatic hydrops after selective vestibular neurotomy and endolymphatic sac surgery. *Acta Otorhinolaryngol Ital* 2001;21:131–7.
39. Huang TS. Three new surgeries for treatment of intractable Ménière's disease. *Am J Otol* 1999;20:233–7.
40. Sajjadi H, Paparella MM, Williams T. Endolymphatic sac enhancement surgery in elderly patients with Ménière's disease. *Ear Nose Throat J* 1998;77:975–82.
41. Thomsen J, Bonding P, Becker B, Stage J, Tos M. The non-specific effect of endolymphatic sac surgery in treatment of Ménière's disease: a prospective, randomized controlled study comparing ''classic'' endolymphatic sac surgery with the insertion of a ventilating tube in the tympanic membrane. *Acta Otolaryngol* 1998;118: 769–73.
42. Pensak ML, Friedman RA. The role of endolymphatic mastoid shunt surgery in the managed care era. *Am J Otol* 1998;19:337–40.
43. Quaranta A, Onofri M, Sallustio V, Iurato S. Comparison of long-term hearing results after vestibular neurectomy, endolymphatic mastoid shunt, and medical therapy. *Am J Otol* 1997;18:444–8.
44. Welling DB, Pasha R, Roth LJ, Barin K. The effect of endolymphatic sac excision in Ménière disease. *Am J Otol* 1996;17:278–82.
45. Moffat DA. Endolymphatic sac surgery: analysis of 100 operations. *Clin Otolaryngol Allied Sci* 1994;19:261–6.
46. Monsell EM, Wiet RJ. Endolymphatic sac surgery: methods of study and results. *Am J Otol* 1988;9:396–402.
47. Brackmann DE, Nissen RL. Ménière's disease: results of treatment with the endolymphatic subarachnoid shunt compared with the endolymphatic mastoid shunt. *Am J Otol* 1987;8:275–82.
48. Smyth GD, Kerr AG, Primrose W. Operations on the saccus endolymphaticus and vestibular nerve: have they fulfilled their promise? *Otolaryngol Head Neck Surg* 1986;94:594–600.
49. Miller GW, Welsh RL. Surgical management of vestibular Ménière's disease with endolymphatic mastoid shunt. *Laryngoscope* 1983;93 (11 Pt 1):1430–40.
50. Goldenberg RA, Justus MA. Endolymphatic mastoid shunt for treatment of Ménière's disease: a five year study. *Laryngoscope* 1983;93(11 Pt 1):1425–9.
51. Bretlau P, Thomsen J, Tos M, Johnsen NJ. Placebo effect in surgery for Ménière's disease: nine-year follow-up. *Am J Otol* 1989;10:259–61.
52. Bretlau P, Thomsen J, Tos M, Johnsen NJ. Placebo effect in surgery for Ménière's disease: a three-year follow-up study of patients in a double blind placebo controlled study on endolymphatic sac shunt surgery. *Am J Otol* 1984;5:558–61.
53. Thomsen J, Bretlau P, Tos M, Johnsen NJ. Ménière's disease: endolymphatic sac decompression compared with sham (placebo) decompression. *Ann N Y Acad Sci* 1981;374:820–30.

54. Quaranta A, Marini F, Sallustio V. Long-term outcome of Ménière's disease: endolymphatic mastoid shunt versus natural history. *Audiol Neurootol* 1998;3:54–60.
55. Arenberg IK. Endolymphatic sac valve implant surgery. III. Preliminary results in 61 cases (66 ears). *Laryngoscope* 1979;89 (7 Pt 2):26–39.
56. Arenberg IK, Spector GJ. Endolymphatic sac surgery for hearing conservation in Ménière disease. *Arch Otolaryngol* 1977;103: 268–70.
57. Couloigner V, Teixeira M, Sterkers O, Rask-Andersen H, Ferrary E. [The endolymphatic sac: its roles in the inner ear]. *Med Sci (Paris)* 2004;20:304–10.
58. Tomiyama S, Harris JP. The role of the endolymphatic sac in inner ear immunity. *Acta Otolaryngol* 1987;103:182–8.
59. Satoh H, Firestein GS, Billings PB, Harris JP, Keithley EM. Proinflammatory cytokine expression in the endolymphatic sac during inner ear inflammation. *J Assoc Res Otolaryngol* 2003;4: 139–47.
60. Arnold W, Altermatt HJ. The significance of the human endolymphatic sac and its possible role in Ménière's disease. *Acta Otolaryngol Suppl* 1995;519:36–42.
61. Derebery MJ. Allergic and immunologic aspects of Ménière's disease. *Otolaryngol Head Neck Surg* 1996;114:360–5.
62. Wackym PA, Friberg U, Linthicum FH Jr, et al. Human endolymphatic sac: morphologic evidence of immunologic function. *Ann Otol Rhinol Laryngol* 1987;96(3 Pt 1):276–81.
63. Arnold W, Pfaltz R, Altermatt HJ. Evidence of serum antibodies against inner ear tissues in the blood of patients with certain sensorineural hearing disorders. *Acta Otolaryngol* 1985;99:437–44.
64. Soliman AM. A subpopulation of Ménière's patients produce antibodies that bind to endolymphatic sac antigens. *Am J Otol* 1996;17:76–80.
65. Maekawa C, Kitahara T, Kizawa K, et al. Expression and translocation of aquaporin-2 in the endolymphatic sac in patients with Ménière's disease. *J Neuroendocrinol* 2010;22:1157–64.
66. Kitahara T, Maekawa C, Kizawa K, Horii A, Doi K. Plasma vasopressin and V2 receptor in the endolymphatic sac in patients with delayed endolymphatic hydrops. *Otol Neurotol* 2009;30:812–9.
67. Taguchi D, Takeda T, Kakigi A, Takumida M, Nishioka R, Kitano H. Expressions of aquaporin-2, vasopressin type 2 receptor, transient receptor potential channel vanilloid (TRPV) 1, and TRPV4 in the human endolymphatic sac. *Laryngoscope* 2007;117:695–8.
68. Kakigi A, Nishimura M, Takeda T, Taguchi D, Nishioka R. Expression of aquaporin1, 3, and 4, NKCC1, and NKCC2 in the human endolymphatic sac. *Auris Nasus Larynx* 2009;36:135–9.
69. Hallpike CS, Cairns H. Observations on the pathology of Ménière's syndrome: (section of otology). *Proc R Soc Med* 1938;31:1317–36.
70. Light JP, Silverstein H. Transtympanic perfusion: indications and limitations. *Curr Opin Otolaryngol Head Neck Surg* 2004;12: 378–83.
71. Arenberg IK. Endolymphatic sac valve implant surgery. V. Experiences with reporting results of treatment in Ménière's disease. *Laryngoscope* 1979;89(7 Pt 2):48–53.
72. Thomsen J, Bretlau P, Tos M, Johnsen NJ. Placebo effect in surgery for Ménière's disease. A double-blind, placebo-controlled study on endolymphatic sac shunt surgery. *Arch Otolaryngol* 1981; 107:271–7.
73. Pillsbury HC 3rd, Arenberg IK, Ferraro J, Ackley RS. Endolymphatic sac surgery. The Danish sham surgery study: an alternative analysis. *Otolaryngol Clin North Am* 1983;16:123–7.
74. Smith WC, Pillsbury HC. Surgical treatment of Ménière's disease since Thomsen. *Am J Otol* 1988;9:39–43.
75. Arenberg IK. Placebo effect for Ménière's disease sac shunt surgery disputed. *Arch Otolaryngol* 1981;107:773–4.
76. Welling DB, Nagaraja HN. Endolymphatic mastoid shunt: a reevaluation of efficacy. *Otolaryngol Head Neck Surg* 2000; 122:340–5.
77. Arenberg IK, Newkirk JB, Stahle J. Endolymphatic sac valve implant surgery. II: The unidirectional inner ear valve implant. *Laryngoscope* 1979;89(7 Pt 2):21–5.
78. Arenberg IK, Balkany TJ. Revision endolymphatic sac and duct surgery for recurrent Ménière's disease and hydrops: failure analysis and technical aspects. *Laryngoscope* 1982;92:1279–84.
79. Goin DW, Mischke RE, Esses BA, Young D, Priest EA, Whitmoyer-Goin V. Hearing results from endolymphatic sac surgery. *Am J Otol* 1992;13:393–7.
80. Paparella MM. Endolymphatic sac revision for recurrent intractable Ménière's disease. *Otolaryngol Clin North Am* 2006;39:713–21, vi.
81. Paparella MM. Revision of endolymphatic sac surgery for recurrent Ménière's disease. *Otolaryngol Clin North Am* 2002;35: 607–19, viii.
82. Silverstein H, Smouha E, Jones R. Natural history vs. surgery for Ménière's disease. *Otolaryngol Head Neck Surg* 1989;100:6–16.

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Best Practice

What Is the Best Imaging Modality in Evaluating Patients With Unilateral Pulsatile Tinnitus?

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BACKGROUND

Pulsatile tinnitus (PT) is a relatively rare cause of tinnitus. It makes up about 4% of patients with tinnitus, which in turn affects up to 10% of the population.[1] PT can be described as objective or subjective, as well as venous, arterial, or nonvascular. About 20% of PT patients will have objective tinnitus. Incidence of abnormal, often treatable, structural findings in patients with PT has been noted to be high, ranging from 44% to 91%.[1] PT can be a result of vascular as well as neoplastic causes, and if left undiagnosed, it can lead to significant morbidity and mortality. Overlooking an aneurysm or a tumor maybe catastrophic for the patient; therefore, further investigation is highly recommended. In this Best Practice review, we aim to evaluate the various imaging modalities and determine which may be the best initial test in patients presenting with unilateral PT.

LITERATURE REVIEW

PT is often due to the transmission of vibrations from turbulent blood flow to the cochlea. Objective PT is audible to the examining physician. Vascular abnormalities are the most common radiological findings in these patients. The diagnosis is made through a complete neurotological examination, including otoscopy and auscultation of the external ear canal, the periauricular area, and the neck.[2,3] In the elderly, the most common causes of PT are arteriosclerotic plaques and stenosis of vessels in the head and neck.[4] If the initial evaluation reveals a mass in the middle ear, a CT scan of the temporal bone with contrast is the most helpful initial test. The three most common entities in this situation are high-riding jugular bulb, aberrant internal carotid artery (ICA), or a paraganglioma.[1] Other rare causes include endolymphatic sac tumors, vascular metastasis, extension of intracranial meningioma, and facial nerve hemangiomas.

If the patient has an audible bruit around the periauricular region, a CT angiogram may be the best first test to perform. If that is normal and there is a high index of suspicion, a four-vessel angiogram is appropriate to assess for aneurysm, dissection, or arteriovenous malformations.[4,5]

However, the dilemma occurs when a patient presents with unilateral PT without a middle ear mass or audible bruit. It is important to compartmentalize the evaluation in terms of venous, arterial, and nonvascular PT. Venous PT is determined by the finding that the tinnitus subsides by gentle pressure over the neck vessels on the side of the symptom. In older patients without an audible bruit but with a history of transient ischemic attack, cerebrovascular accident, hypertension, diabetes, hyperlipidemia, or smoking, a suspicion for atherosclerotic carotid artery disease should be maintained.[1,4] These patients are best evaluated by duplex carotid ultrasound and echocardiogram. In obese females with associated headaches, hearing loss, and blurred vision, magnetic resonance imaging/magnetic resonance venogram (MRI/MRV) should be the initial test to evaluate for idiopathic intracranial hypertension (IIH). Radiographic findings of venous sinus stenosis, empty sella, flattening of the posterior globes, and distension of the perioptic arachnoid spaces have been described in such cases.[1] If indicated, a definitive diagnosis of IIH can be made by measuring the opening pressure at lumbar puncture. Other causes of venous PT are atypical formation of the jugular bulb (high-riding bulb; diverticulum) and sigmoid sinus diverticulum or dehiscence (SSDD). In addition, nonvascular causes of PT are superior semicircular canal dehiscence and otosclerosis.[3,4] These entities are best visualized with a CT scan. Therefore, an initial test for most patients with venous PT not suspicious for IIH is with a computed tomography angiogram/computed tomography venogram (CTA/CTV), which will evaluate both the bony structure surrounding the ear as well as the vasculature with less risks than would the definitive four-vessel angiogram.[4]

CTA/CTV appears to be a promising initial imaging in most cases of PT. Narvid et al. evaluated the benefits of CTA/CTV in patient with PT.[5] The authors compared seven patients with angiographic-proven dural

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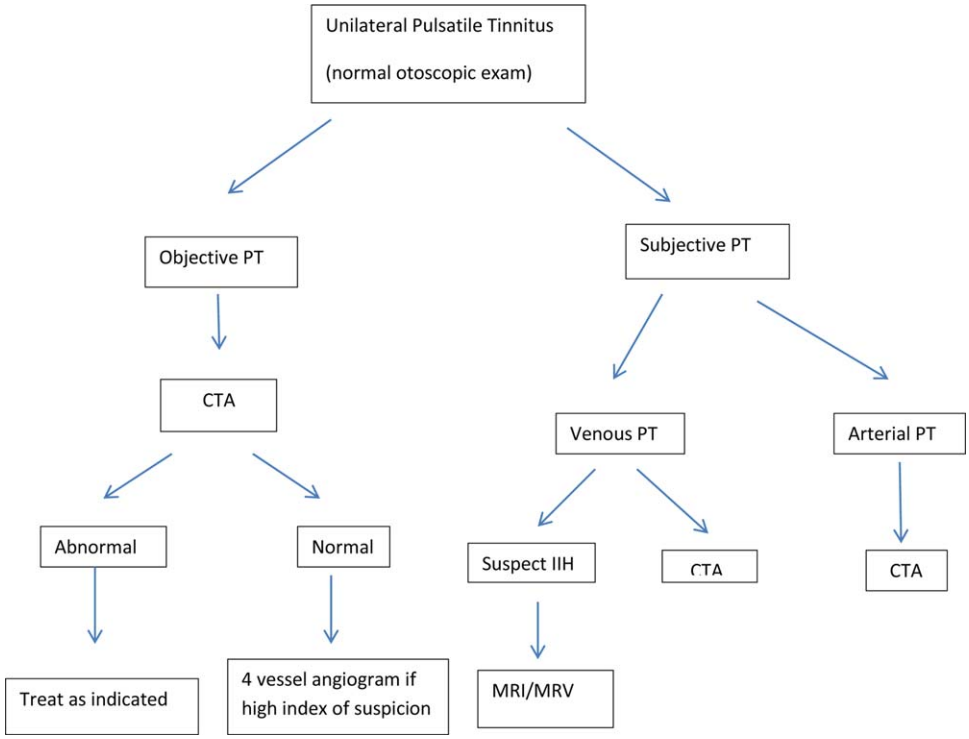

Fig. 1. Diagnostic algorithm for patients with unilateral pulsatile tinnitus. CTA = computed tomography angiogram; IIH = idiopathic intracranial hypertension; MRI = magnetic resonance imaging; MRV = magnetic resonance venogram; PT = pulsatile tinnitus. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

arterio-venous fistula (DAVF) with seven age-matched controls with PT but no DAVF. They proposed that the presence of asymmetrically visible and enlarged arterial feeding vessels, shaggy sinus/tentorium, and asymmetric jugular-venous attenuation had a sensitivity of 86% and a specificity of 100% in identifying DAVF.[5] MRI/MRA evaluation have yielded a wide range of sensitivities for vascular pathology, ranging from 50% to 100%. Shweel et al. report that MRI/MRA scans diagnosed the cause of PT in nine of 27 patients.[2] Two patients were subsequently diagnosed with small ICA aneurysm via angiogram, which was missed in the initial MRI/MRA study. The authors report an overall sensitivity of 80% and a specificity of 88%, with an error rate of 15% in diagnosing the cause of PT.[2] However, it is also important to note that MRI cannot evaluate osseous pathology as well as CT-based imaging.[5] Schoeff et al. also report a 23% incidence of SSDD in patients with PT compared to 1.2% among asymptomatic patients.[3] This is best identified with a CT or CTA.

In evaluating arterial subjective PT, the most widely performed tests are MRI/MRA, CTA, or a four-vessel angiogram. Both MRI/MRA and CTA are useful in evaluating PT; however, MRI/MRA is limited by poor bony resolution, flow, and artifacts related to air–fat interface. It is felt that the initial test in these cases should begin with a CTA. Due to cost and risks of complications, a four-vessel angiogram should not be used in most cases.[4]

BEST PRACTICE

Deciding on the initial radiographic evaluation in patients with unilateral PT can be challenging due to the many causes as well as the questionable results of some of the imaging findings. Recent studies have shown an increase in the cases of SSDD, which is best visualized on a CT scan. In addition, sensitivity and specificity analysis have shown that CTA may be the best initial test in patients with unilateral subjective PT. For patients with objective PT with no middle ear mass, a CTA is the best initial exam. For those others with subjective unilateral PT, it is important to distinguish between venous and arterial PT. For patients with signs and symptoms of IIH, MRI/MRV is the appropriate initial study. And for the remaining cases of venous and arterial PT, consider CTA as the best initial study due to safety and broad effectiveness (Fig. 1).

LEVEL OF EVIDENCE

All five of the articles in this review were level 4 (retrospective studies and nonsystematic reviews). There were no randomized control trials or systematic reviews looking at the role of imaging in evaluation patients with unilateral PT. There is a need for a prospective study comparing the sensitivity and specificity of the various imaging modalities.

BIBLIOGRAPHY

1. Madani G, Connor SEJ. Imaging in pulsatile tinnitus. *Clin Radiol* 2009; 64:319–328.
2. Shweel M, Hamdy B. Diagnostic utility of magnetic resonance imaging and magnetic resonance angiography in the radiological evaluation of pulsatile tinnitus. *Am J Otolaryngol* 2013;34:710–717.
3. Schoeff S, Nicholas B, Mukherjee S, Kesser B. Imaging Prevalence of sigmoid sinus dehiscence among patients with and without pulsatile tinnitus. *Otolaryngol Head Neck Surg* 2014;150:841–846.
4. Sismanis A. Pulsatile tinnitus: contemporary assessment and management. *Curr Opin Otolaryngol Head Neck Surg* 2011;19:348–357.
5. Narvid J, Do H, Blevins N, Fischbein N. CT Angiography as a screening tool for dural arteriovenous fistula in patients with pulsatile tinnitus: feasibility and test characteristics. *AJNR Am J Neuroradiol* 2011;32: 446–453.

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PICTORIAL REVIEW

Imaging in pulsatile tinnitus

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Tinnitus may be continuous or pulsatile. Vascular lesions are the most frequent radiologically demonstrable cause of pulsatile tinnitus. These include congenital vascular anomalies (which may be arterial or venous), vascular tumours, and a variety of acquired vasculopathies. The choice of imaging depends on the clinical findings. If a mass is present at otoscopy, thin-section computed tomography (CT) is indicated. In the otoscopically normal patient, there is a range of possible imaging approaches. However, combined CT angiography and venography is particularly useful.
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Introduction

Tinnitus is the perception of an auditory sensation, most frequently a ringing sound, in the absence of an external stimulus. Tinnitus may be classified as pulsatile (PT) or continuous. PT is usually related to vascular causes and is pulse-synchronous (coinciding with the patient's heartbeat). It may be subjective (heard only by the patient) or objective (also audible to the examiner).

The prevalence of persistent tinnitus (lasting more than 5 min) in the UK adult population is around 10%; half of these patients find the symptom moderately or severely annoying.[1] PT is much less common than non-PT, affecting approximately 4% of patients with tinnitus.[2] PT may not require radiological investigation; cases may be transient, related to drugs, systemic processes (e.g. hypertension, anaemia, pregnancy), or other conditions, such as migraine.

Radiological investigation aims to find treatable causes of tinnitus. In the setting of non-PT, the main entity to exclude is a cerebellopontine cistern mass lesion. In the absence of additional audiological findings, the diagnostic yield of radiological investigation of non-PT is low and thin-section, T2-weighted magnetic resonance imaging (MRI) sequences are generally used for screening.[3] Thus knowledge of the nature of the tinnitus (PT versus non-PT) is essential.

There is a wide variation in the reported incidence of structural abnormalities in patients with PT ranging from 44–91% (Table 1).[4–9] This is likely to reflect variations in the study populations, expertise, and methods of investigation. Paragangliomas, dural arteriovenous fistulae (dAVFs), idiopathic intracranial hypertension (IIH), venous anatomical variations, and atheromatous arterial disease represent the most frequent causes.[4–9] An underlying cause is usually identified in patients with objective tinnitus (Table 1).[4–9]

This review focuses on the radiological imaging of PT. The choice and focus of imaging for PT is guided by the clinical findings. The presence of a visible intratympanic or retrotympanic mass and the suspicion of arterial [reduced by pressure on the ipsilateral internal carotid artery (ICA)] or venous (reduced by pressure on the ipsilateral jugular vein) aetiologies are particularly important.

Radiological investigation

If a mass is seen at otoscopy, then a thin-section computed tomography (CT) of the petrous temporal bones is needed to assess the middle ear.

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Table 1 Reported incidence of structural abnormalities in patients investigated for all causes of pulsatile tinnitus

Author	Waldvogel[4]	Sonmez[5]	Remley[6]	Krishnan[7]	Dietz[8]	Sismanis[9]
Total no. of patients (Percentage with objective tinnitus)	84 (42%)	74 (15%)	100 (25%)	16 (6%)	49 (33%)	145 (8%)
Investigations[a]						
Ultrasound	68	12				Not stated
Computed tomography	26	72	69		10	
Magnetic resonance imaging	33	7	24		49	
Magnetic resonance angiography	7	7			49	
Selective angiography	46	5	68		17	
CTA/V				16		
Cause found	57 (68%)	50 (68%)	80 (80%)	7 (44%)	28 (57%)	132 (91%)
Vascular anomaly						
Aberrant ICA		1 (1%)	8 (8%)			
Dehiscent jugular bulb		3 (4%)	5 (5%)		1 (2%)	
High-riding jugular bulb		21 (28%)	7 (7%)	1 (6%)		
JB/transverse sinus diverticulum		1 (1%)	1 (1%)	1 (6%)	2 (4%)	
Enlarged cortical draining vein			1 (1%)		1 (2%)	
Vascular loop	1 (1%)					1 (1%)
Vascular tortuosity						6 (4%)
Dominant venous system[b]				6 (38%)		
Acquired vasculopathy						
Dural AVF	17 (20%)	2 (3%)	15 (15%)			3(%)
Pial AVF					9 (18%)	
Carotico-cavernous fistula	6 (7%)				1 (2%)	
Atheromatous ICA disease	7 (8%)	16 (22%)	5 (5%)			
Fibromuscular dysplasia	5 (6%)		4 (4%)		2 (4%)	
ICA aneurysm	1 (1%)	3 (4%)	2 (2%)			2 (1%)
ICA dissection			1 (1%)			
Extracranial AVF/M					1 (2%)	1 (1%)
					1 (2%)	
Venous sinus thrombosis	1 (1%)					
Tumour						
Paraganglioma	5 (6%)	2 (3%)	25(25%			17 (12%)
Meningioma	1 (1%)		2 (2%)		5 (10%)	
Other	1 (1%)	1 (1%)	2 (2%)			1 (1%)
Idiopathic intracranial hypertension	4 (5%)				2 (4%)	56[c] (39%)
Venous sinus stenosis	1 (1%)			1 (6%)		
Other						
Otospongiosis						4 (3%)
Myoclonus						1 (1%)
Systemic causes	1 (1%)					10 (8%)
No aetiology found in patients with objective tinnitus (%)	7 (8%)	0	0	Not stated	0	Not stated

CTA/V, computed tomography angiography/venography; ICA, internal carotid artery; AVF, arteriovenous fistulae.
[a] Some patients underwent multiple investigations.
[b] Association with the venous sinus dominance is speculative.
[c] Four other patients had radiographic features of idiopathic intracranial hypertension but declined lumbar puncture.

Various imaging strategies have been proposed for the investigation of PT in the otoscopically normal patient and they continue to evolve. MRI (with gadolinium), MR angiography (MRA), MR venography (MRV), carotid ultrasound, CT with and without contrast medium, and conventional angiography have all been used rather inconsistently in previous patient series. Combined CT angiography and venography (CTA/V) may be performed with 100 ml contrast medium injected at 3—4 ml/s and a fixed delay of 25 s using contemporary multisection CT. This approach shows considerable promise and has the advantage of demonstrating arterial, venous, skull-base, and middle-ear disease entities

with one study.[7] If non-invasive imaging is negative in the setting of arterial tinnitus (particularly if it is objective) then conventional angiography should be considered to exclude a small dAVF. Fig. 1 summarizes the suggested imaging algorithm.

Causes of PT and their radiological manifestations

Table 2 summarizes the causes of PT.

Visible intratympanic or retrotympanic mass

The three entities that may be diagnosed in this setting are arterial anomalies, exposed jugular bulb, or an intratympanic tumour (most frequently paraganglioma). An aberrant ICA is an uncommon anomaly due to failure of formation of the proximal ICA in foetal life. This is replaced by the inferior tympanic artery and enters the skull lateral to the expected position of the vertical portion of the carotid canal (which is absent) (Fig. 2). The artery then passes through an enlarged inferior tympanic canaliculus along the medial aspect of the middle ear where it forms the petrous ICA. An aberrant course of the ICA manifests as a vascular retrotympanic mass and may provoke a biopsy with disastrous consequences.[5,6]

An aberrant ICA may also be associated with the rare finding of a persistent stapedial artery (PSA), which arises from the petrous ICA, enters the hypotympanum, courses through the obturator foramen (between the stapes crura), and enlarges the tympanic segment of the facial nerve.[10] As the PSA replaces the normal middle meningeal artery, the foramen spinosum is absent or hypoplastic.[10]A normally sited ICA, which is dehiscent into the mesotympanum, may also cause PT and present a surgical hazard.

Jugular bulb anomalies may be associated with PT and if the jugular plate is dehiscent, this manifests as a bluish mass at otoscopy.

Paraganglioma or glomus tumour is the most common neoplastic cause of PT.[6] This is a benign, but locally aggressive, tumour which arises from glomus bodies (chemoreceptor cells) at predictable locations along nerves. Glomus jugulare, tympanicum and jugulotympanicum (Fig. 3) are associated with PT. Glomus jugulare arises along the adventitia of the jugular bulb. The cochlear promontory is the most common site of glomus tympanicum.[11] On CT, glomus tumours cause permeative erosion of the skull base and CT is the ideal technique for defining the extent of tumour. Widening of the inferior tympanic canniliculus in glomus jugulare, due to hypertrophy of the artery, is a useful early sign of tumour.[12] The vascular

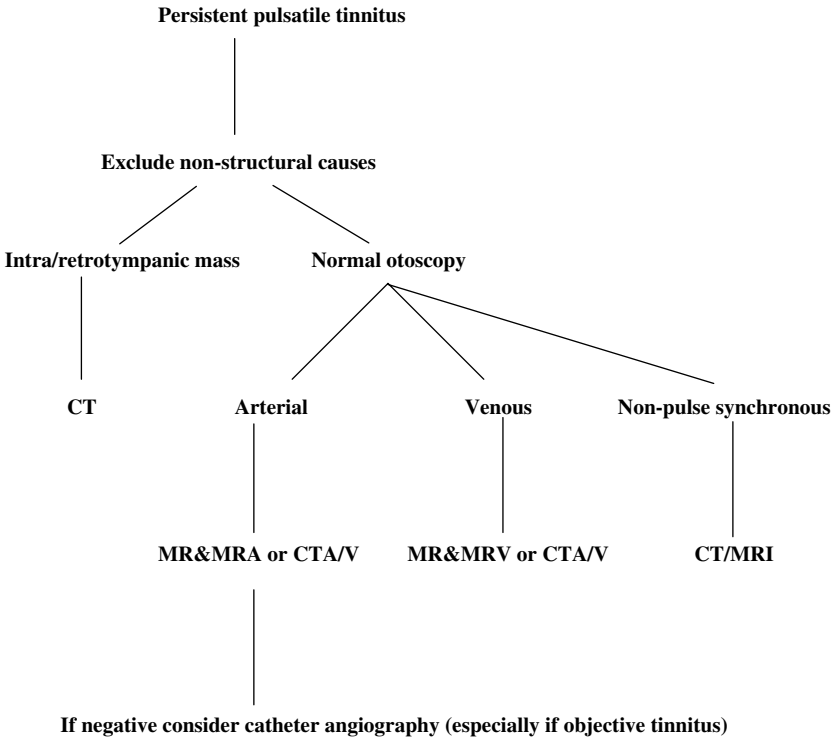

Figure 1 Imaging algorithm for PT.

Table 2 Causes of pulsatile tinnitus

Arterial
Arterial anomalies
Aberrant internal carotid artery[a]
Persistent stapedial artery
Neurovascular contact
Arteriopathy
Atherosclerosis
Fibromuscular dysplasia
Internal carotid artery dissection
Aneurysms
Vascular tumours
Paraganglioma[a]
Endolymphatic sac tumour
Meningioma
Haemangipericytoma
Vascular metastases
Haemangioma
Bone dyplasias
Otospongiosis
Paget's disease
Intrameatal vascular loops
Vascular malformations and fistulae
Venous
Venous anomalies
High-riding or dehiscent jugular bulb[a]
Aberrant sigmoid sinus
Venous sinus thrombosis
Abnormal emissary vains
Benign intracranial hypertension
Non-vascular
Myoclonus (palatal, tensor tympani, stapedius)
Chronic middle-ear disease
Dehiscent semicircular canal

[a] Evident at otoscopy as retro/intratympanic mass.

nature of glomus tumours accounts for the classic ''salt and pepper'' appearance on T2 and contrast-enhanced T1-weighted MRI resulting from multiple flow voids against a T2 hyperintense or enhancing stroma. Hypervascularity is demonstrated at angiography (Fig. 4).

Arterial tinnitus

Arteriopathy

Atherosclerosis is one of the more common causes of PT, accounting for 8—20% of cases (Table 1). In

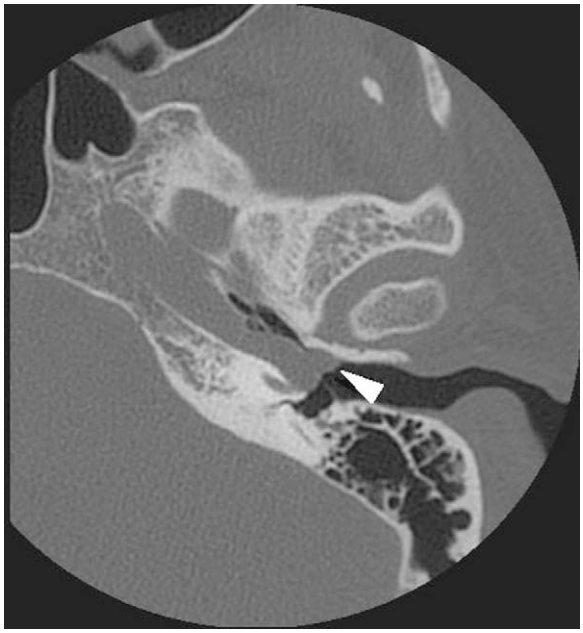

Figure 2 Transverse CT image demonstrates an aberrant left ICA. The focal projection laterally (arrowhead) corresponds to a pseudoaneurysm at the site of previous middle ear exploration.

a study of 100 consecutive patients with cerebrovascular disease, 29% suffered from PT.[13] Those with PT were more likely to have severe (greater than 70%) stenosis, complete occlusion, or ICA disease (Fig. 5).[13] Daneshi et al. [14] investigated

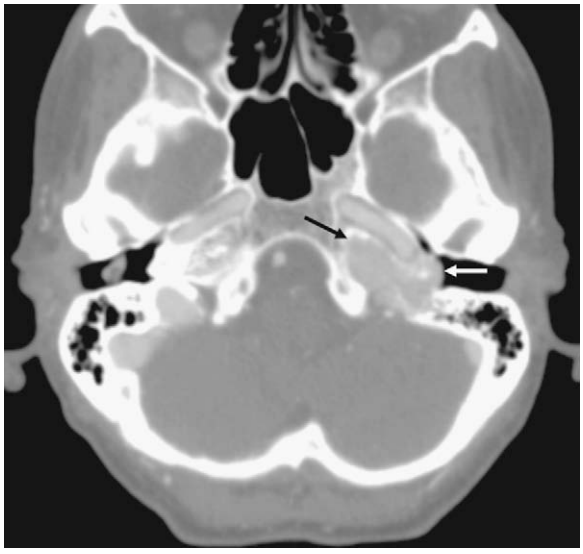

Figure 3 Transverse CTA/V image demonstrating a large glomus jugulotympanicum in a patient who presented with PT (who had previously undergone resection of a large glomus vagale tumour). There is erosion of the left jugular fossa up to the horizontal portion of the carotid canal and of the cochlear promontory. Enhancing tissue fills the jugular foramen extending to the petrous apex (black arrow) and middle ear (white arrow).

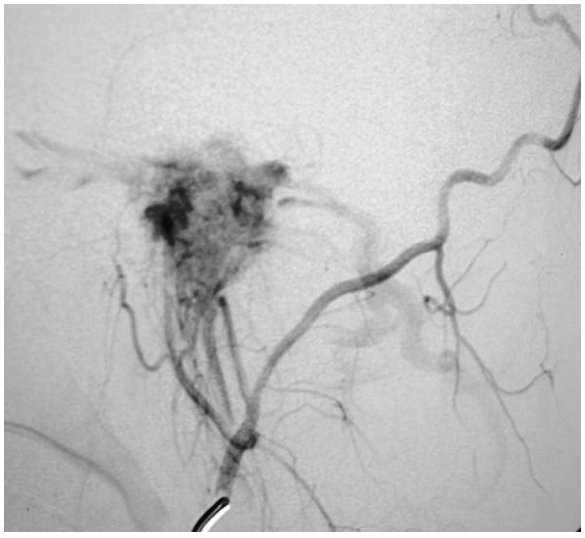

Figure 4 Lateral projection of an external carotid artery angiogram in a patient with glomus jugulare who presented with lower cranial nerve palsies and PT. Angiography shows the neuromeningeal branches of the ascending pharyngeal artery that supply the tumour arise directly from the occipital artery with a rapid intense tumour blush.

a series of 34 patients with PT using colour Doppler ultrasound and found a 12% incidence of carotid atherosclerosis. Duplex ultrasound is the traditional non-invasive method of assessing carotid atherosclerosis, but CT or MR angiography may be effectively combined with skull-base imaging in the setting of PT.

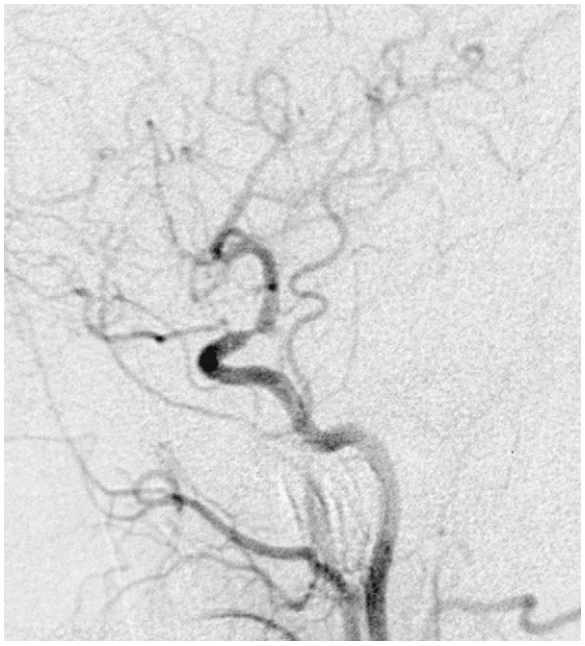

Figure 5 Lateral projection in a woman with intractable and objective PT with ''normal'' MRI/MRA who was advised to undergo conventional angiography to exclude a dAVF. There is a severe stenosis of the supraclinoid carotid artery ipsilateral to the PT.

PT was the presenting symptom in 16 out of 136 consecutive cases of cervicocephalic (14 internal carotid and two vertebral) dissection.[15] On MRI dissection manifests as a crescent of high T1-weighted signal intensity (mural haematoma), which narrows the signal void within the residual lumen (Fig. 6). CTA may demonstrate an intimal flap and a double lumen, which should be viewed on a wide window width.[11]

Fibromuscular dysplasia affects medium-sized vessels and is the second most common cause of extra-cranial carotid artery narrowing.[16] After ischaemia, PT is the most common clinical presentation and is the cause of PT in up to 6% of cases in the reported literature.[4,6] The characteristic string of beads angiographic pattern is the result of focal areas of stenosis and dilatation.

Other vascular neoplasms

Endolymphatic sac tumour is an aggressive vascular tumour that arises from the distal (posterior) end of the endolymphatic sac (Fig. 7). The tumour is rare but strongly associated with Von Hippel—⊜ Lindau syndrome.[17] Clinical presentation includes PT, conductive and sensorineural hearing loss, facial palsy, and vestibular dysfunction.[18] On MRI, areas of T1-weighted hyperintensity reflect blood

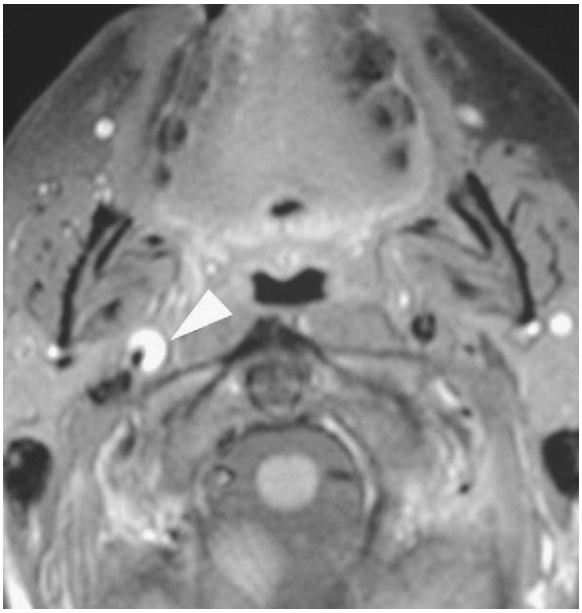

Figure 6 T1-weighted, fat-saturated, transverse MR image in a patient with ICA dissection, demonstrates an eccentric hyperintense rim of intramural haematoma (arrowhead) and narrowing of the vessel lumen.

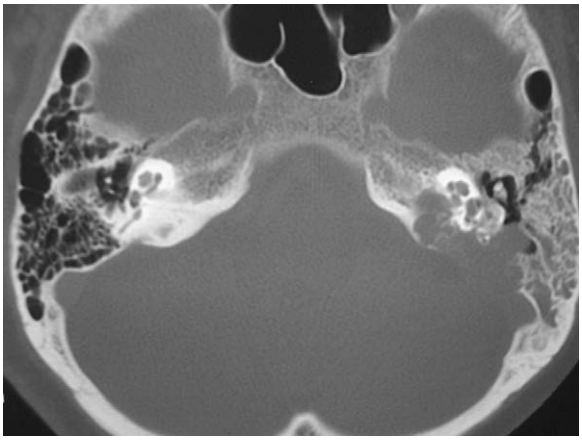

Figure 7 Transverse CT image of a 68-year-old patient with facial nerve paralysis, sensorineural hearing loss, and PT. There is aggressive bony destruction of the posterior left petrous ridge (at the level of the vestibular aqueduct) containing spiculated calcification. The appearance and location are characteristic of an endolymphatic sac tumour, sporadic in this case, which was confirmed histologically.

products, the lesion enhances avidly and may contain flow voids.

Meningiomas may diffusely infiltrate the skull base extending into the middle ear and skull base foramina. There may be a ''permeative sclerotic'' appearance to the bone on CT and there is usually diffuse ''en plaque'' intracranial enhancement (Fig. 8).

Vascular metastases in and around the jugular foramen, from breast, lung, and thyroid primary sites, are a recognized cause of PT. Metastases from the thyroid may contain flow voids mimicking a glomus tumour.[18]

Haemangiopericytoma is a rare vascular tumour associated with PT. Its avid enhancement characteristics are similar to meningioma and these tumours may be indistinguishable on imaging.[19]

Other rare neoplastic causes of PT include ossifying haemangiomas of the facial nerve and cavernous haemangiomas.[11]

Arteriovenous fistulae and malformations

Dural arteriovenous fistulae (dAVFs) account for only 10—15% of all intracranial arteriovenous malformations (AVMs) but they are a much more frequent cause of PT than cerebral or neck AVMs. They are usually acquired and may result from recanalized venous sinus thrombosis. Dural AVFs involving the transverse or sigmoid sinus are most frequently implicated in PT (Fig. 9).[20]

Direct AVFs between the ICA and the cavernous sinus (carotico-cavernous fistulae) may also cause PT, although pulsatile exophthalmos is a more common presentation. Extracranial AVFs, which usually involve branches of the vertebral artery (but may involve the internal or external carotid arteries), may rarely cause PT.[21]

These abnormalities may be detected on CTA/V or post-gadolinium MRI/MRA studies. Findings may be subtle, particularly with indirect dAVFs. Shin et al.[22] retrospectively reviewed 54 patients with PT who were evaluated for transverse sinus dural AVFs. CT

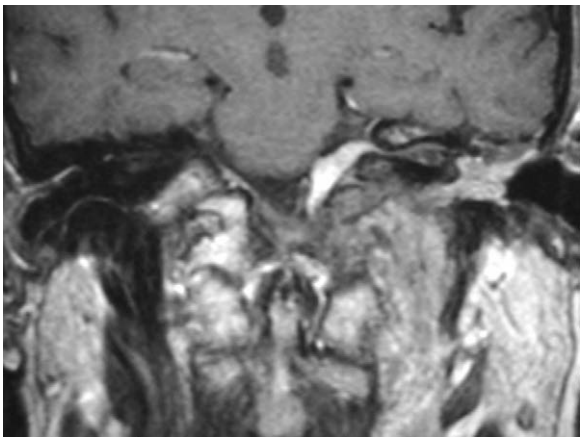

Figure 8 Post-gadolinium, T1-weighted, coronal image demonstrates enhancing meningioma in the inferior left cerebellopontine angle cistern with enhancement extending into the IAM. There is further extension of the meningioma to fill the left middle ear cavity (other images demonstrated this tissue to be continuous with that in the jugular foramen).

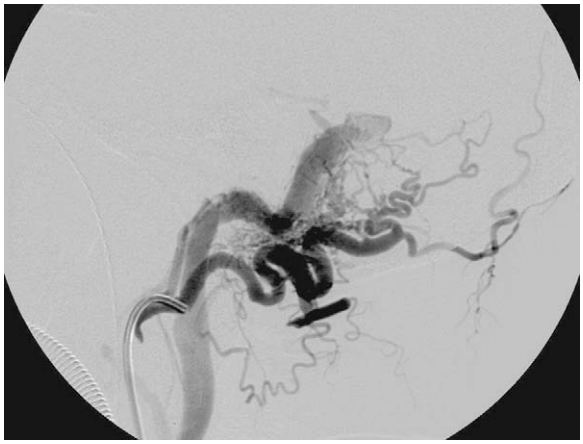

Figure 9 Lateral projection of an occipital artery angiogram in a patient with a palpable thrill which was transmitted to the frame of the bed. There is rapid anterograde drainage of the fistula into the sigmoid sinus. When there is retrograde dural sinus flow and cortical venous drainage, treatment is mandatory to prevent venous hypertension, intracranial haemorrhage, and focal neurological deficits.

studies were poorly sensitive and MRI/A detected only 68% of cases. Although contemporary imaging is likely to be more diagnostically accurate overall, catheter angiography may still be needed for the diagnosis of AVFs.

Intrameatal vascular loops

Based on radiological and surgical data some investigators hypothesize that there is a relationship between vascular loops extending deep into the internal auditory meati and PT (Fig. 10). There are reports relating neurovascular contact with the vestibulocochlear nerve to non-PT and microvascular decompression has abolished tinnitus in some cases.[23,24] Other studies found no significant relationship between intrameatal vascular loops and tinnitus and a similar incidence of vestibulocochlear neurovascular contact in the asymptomatic population.[25,26] More recently, there have been data specifically related to patients with PT. Nowé et al. [27] found a significantly higher number of vascular loops in the IAC (as opposed to within the cerebellopontine angle) on MRI in patients with PT compared with those with continuous tinnitus. It is proposed that turbulent flow within the arterial loop creates sound waves that are conducted within the cerebrospinal fluid and then through the perineural spaces, via the fundus of the IAC to the cochlea (by bone conduction).

Bone dysplasia

Otospongiosis (commonly called otosclerosis) is the replacement of the normally dense middle layer of the bony labyrinth with areas of ''spongy'' haversian bone. Fenestral otospongiosis, which affects the lateral bony labyrinth, is the most common type and most frequently manifests as spongiosis in the area anterior to the oval window (fissula antefenestrum) with or without involvement of the stapes footplate (Fig. 11). The condition is the most common cause of mixed hearing loss in adults and is bilateral in 85% of cases.[21] There is a 65—85% reported prevalence of tinnitus (usually continuous but occasionally pulsatile), which improves in 85% of patients following stapes surgery.[28,29]

Paget's disease may cause demineralization of the temporal bone resulting in hearing loss, vestibular dysfunction, or tinnitus.[21] Continuous

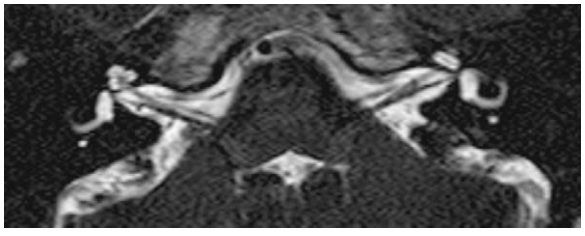

Figure 10 Three-dimensional, T2-weighted, turbo spin-echo, driven equilibrium (TSE DRIVE) transverse image in a patient with continuous left-sided tinnitus. The presence of bilateral deep intrameatal vascular loops (seen to arise from the anterior inferior cerebellar arteries) are most likely incidental.

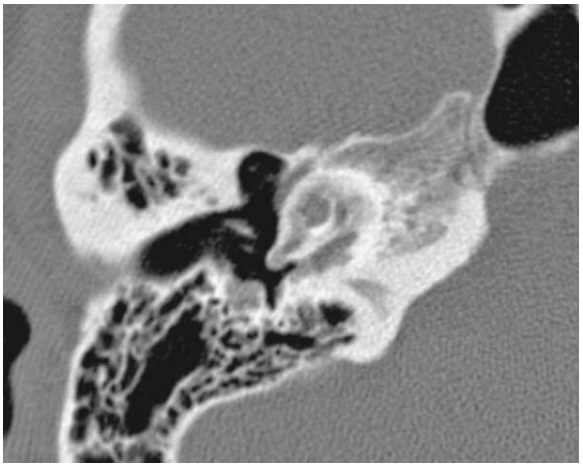

Figure 11 Transverse CT section demonstrates confluent pericochlear radiolucency in a patient with cochlear otospongiosis.

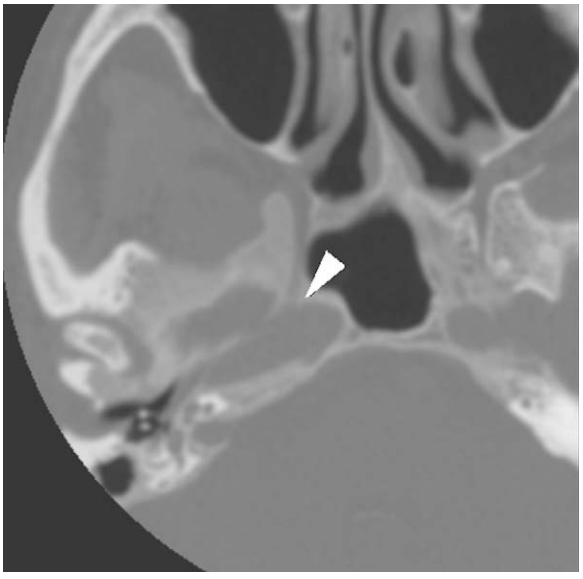

Figure 12 Transverse CT section in a patient with extensive lytic Paget's disease of the skull base and vault with biochemical and isotope bone scintigraphy features of the disease. Note the lucency on the right petrous temporal bone (arrowhead), basisphenoid, and left petrous apex. Bone thickening and heterogeneity is more typical in the later phases.

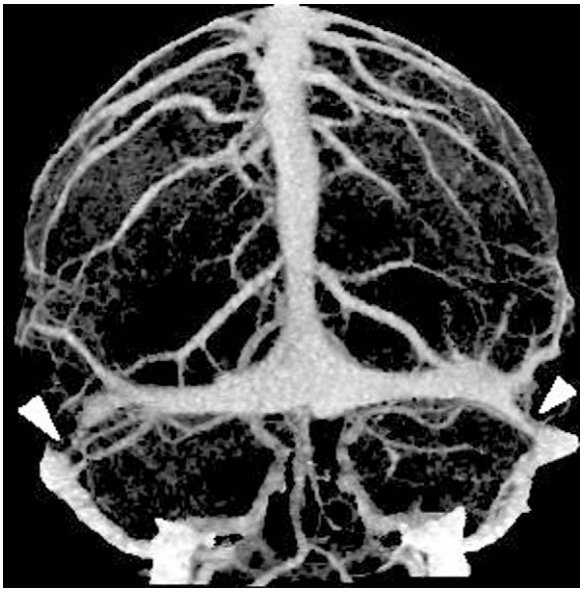

Figure 13 A middle-aged woman was referred with an asymmetric hearing loss, balance disturbance, headache, and right-sided PT. Volume-rendered image from a CT venogram study demonstrates bilateral severe stenoses of the transverse sinuses (arrowheads), typical of that seen in idiopathic intracranial hypertension.

tinnitus is prevalent in Paget's disease (61%) but PT is also recognized.[30] On CT the appearance may mimic a severe case of pericochlear and fenestral otospongiosis but the bony changes usually extend beyond the otic capsule (Fig. 12).

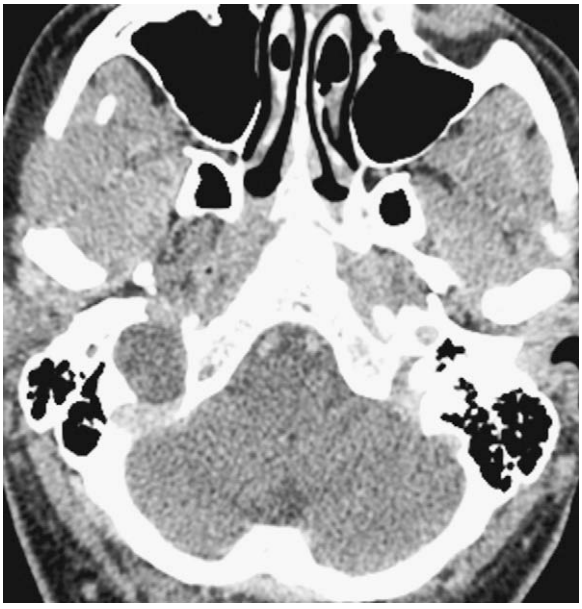

Figure 14 A 36-year-old woman with PT developed raised intracranial pressure for which she was treated by serial lumbar punctures and diuretics. CT showed a low-density mass in the right jugular foramen (which enhanced peripherally and extended subcranially on MRI studies). This was felt to represent a vagal schwannoma resulting in venous outflow obstruction and secondary intracranial hypertension.

Venous tinnitus

Venous tinnitus may be due to IIH or venous anomalies and variations.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is a disease of undefined pathophysiology associated with PT, although it more commonly presents with headache,

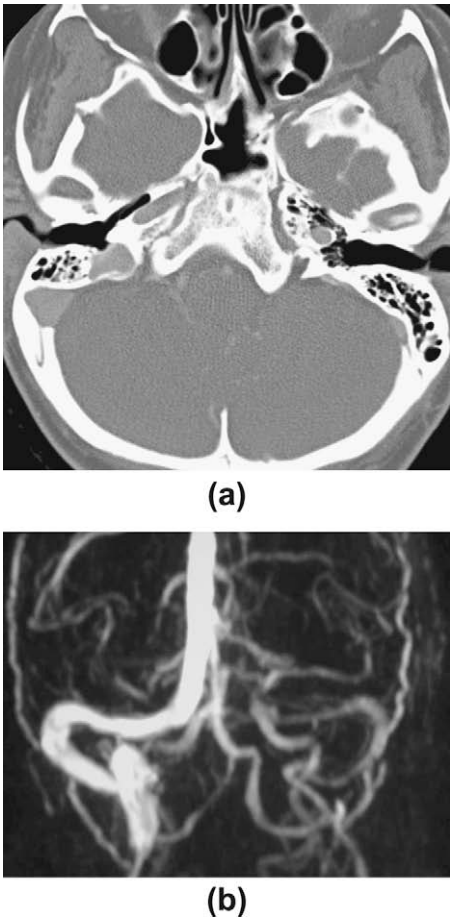

Figure 15 (a) Contrast-enhanced CT study in a patient with venous tinnitus, shows dominant right-sided venous drainage, a laterally deviated right sigmoid sinus, with small sigmoid and jugular diverticulae, and a dehiscent jugular bulb (confirmed on bone windows). (b) A 12-year-old child presented with right-sided hearing loss and PT. A ''blue drum'' was explored and found to represent a middle ear filled by his only jugular bulb. Frontal maximum intensity projection of an MRV study demonstrates markedly right-sided dominant venous drainage with a high-riding jugular bulb.

papilloedema, and visual disturbance.[9] In a series of 145 cases of PT, IIH was the most frequent diagnosis accounting for 56 cases.[9] There is a high prevalence of venous sinus stenoses (with more than 90% of cases having bilateral stenoses on MRV; Fig. 13).[31] Imaging studies are aimed at excluding other causes of intracranial hypertension (Fig. 14) but some associated imaging features, such as an empty sella, flattening of the posterior globes, and distension of the perioptic arachnoid spaces, have been described.[32] Diagnosis is made by measuring the opening pressure at lumbar puncture.

Venous anomalies and variations

Venous variations and anomalies are frequently associated with subjective PT. Some, such as venous sinus dominance and a high-riding jugular bulb (Fig. 15a) (which extends above the inferior border of the round window, occurring in 25% of the population), are far more prevalent than venous tinnitus. This implies that although they may predispose to PT in some cases, the association is frequently speculative. If identified, there should be a continued search for other treatable causes of PT. Other entities related to venous PT include an aberrant anteromedially placed or laterally placed sigmoid sinus (Fig. 15b), venous sinus stenoses, and large emissary or subcranial veins.[7,11,31]

Non-vascular pulsatile tinnitus

Non-vascular causes of PT include muscular tinnitus (palatal and middle ear myoclonus) where rhythmic contractions of the muscle around the skull base result in objective PT. Such non-vascular tinnitus may not be pulse-synchronous. Disease of the middle ear and mastoid, such as cholesterol granuloma (Fig. 16), patulous eustachian tubes, and dehiscent semicircular canals, are also documented causes.[6,33]

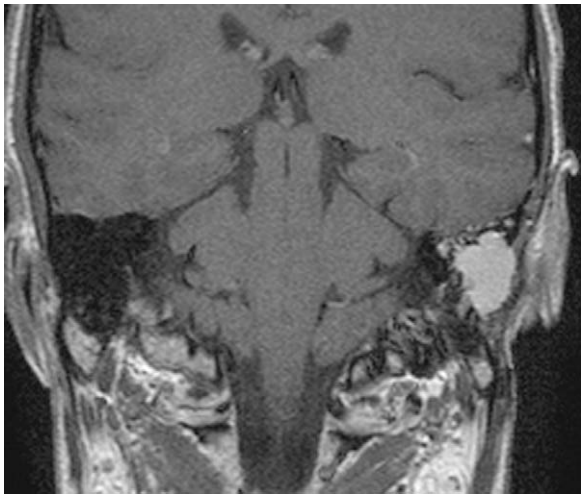

Figure 16 T1-weighted, coronal MR image demonstrates a hyperintense left mastoid cholesterol granuloma.

Conclusion

PT has diverse causes. The aim of radiology is to demonstrate treatable causes. Combined CTA/V has the advantage of demonstrating middle ear, skull base, and vascular diseases in a single examination, and is the ideal first-line radiological studying in patients without an intra/retrotympanic mass. Small arteriovenous fistulae may be occult on cross-sectional imaging and require catheter angiography for diagnosis.

References

1. McFerran DJ, Phillips JS. Tinnitus. *J Laryngol Otol* 2007; **121**:201—8.
2. Stouffer JL, Tyler RS. Characterization of tinnitus by tinnitus patients. *J Speech Hear Disord* 1990;**55**:439—53.
3. Levy RA, Arts HA. Predicting neuroradiologic outcome in patients referred for audiovestibular dysfunction. *AJNR Am J Neuroradiol* 1996;**17**:1717—24.
4. Waldvogel D, Mattle HP, Sturzenegger M, et al. Pulsatile tinnitus—a review of 84 patients. *J Neurol* 1998;**245**: 137—42.
5. Sonmez G, Basekim CC, Ozturk E, et al. Imaging of pulsatile tinnitus: a review of 74 patients. *Clin Imaging* 2007;**31**: 102—8.
6. Remley KB, Coit WE, Harnsberger HR, et al. Pulsatile tinnitus and the vascular tympanic membrane: CT, MR, and angiographic findings. *Radiology* 1990;**174**:383—9.
7. Krishnan A, Mattox DE, Fountain AJ, et al. CT arteriography and venography in pulsatile tinnitus: preliminary results. *AJNR Am J Neuroradiol* 2006;**27**:1635—8.
8. Dietz RR, Davis WL, Harnsberger HR, et al. MR imaging and MR angiography in the evaluation of pulsatile tinnitus. *AJNR Am J Neuroradiol* 1994;**15**:879—89.
9. Sismanis A. Pulsatile tinnitus. A 15-year experience. *Am J Otol* 1998;**19**:472—7.
10. Roll JD, Urban MA, Larson 3rd TC, et al. Bilateral aberrant internal carotid arteries with bilateral persistent stapedial arteries and bilateral duplicated internal carotid arteries. *AJNR Am J Neuroradiol* 2003;**24**:762—5.
11. Branstetter 4th BF, Weissman JL. The radiologic evaluation of tinnitus. *Eur Radiol* 2006;**16**:2792—802.
12. Weissman JL, Hirsch BE. Imaging of tinnitus: a review. *Radiology* 2000;**216**:342—9.
13. Hafeez F, Levine R, Dulli D. Pulsatile tinnitus in cerebrovascular arterial diseases. *J Stroke Cerebrovasc Dis* 1999;**8**: 217—23.
14. Daneshi A, Hadizadeh H, Mahmoudian S, et al. Pulsatile tinnitus and carotid artery atherosclerosis. *Int Tinnitus J* 2004; **10**:161—4.

15. Pelkonen O, Tikkakoski T, Luotonen J, et al. Pulsatile tinnitus as a symptom of cervicocephalic arterial dissection. *J Laryngol Otol* 2004;**118**:193—8.
16. Slovut DP, Olin JW. Fibromuscular dysplasia. *N Engl J Med* 2004;**350**:1862—71.
17. Manski TJ, Heffner DK, Glenn GM, et al. Endolymphatic sac tumors. A source of morbid hearing loss in von hippel—lindau disease. *J Am Med Assoc* 1997;**277**:1461—6.
18. Swartz JD. An approach to the evaluation of the patient with pulsatile tinnitus with emphasis on the anatomy and pathology of the jugular foramen. *Semin Ultrasound CT MR* 2004;**25**:319—31.
19. Akiyama M, Sakai H, Onoue H, et al. Imaging intracranial haemangiopericytomas: study of seven cases. *Neuroradiology* 2004;**46**:194—7.
20. Roy D, Lavigne F, Raymond J. Pulsatile tinnitus and dural arteriovenous fistula of the transverse sinus. *J Otolaryngol* 1993;**22**:409—12.
21. Harnsberger HR, Schwarz JD. Vascular anatomy, anomalies, and diseases emphasizing the clinical—radiological problem of pulsatile tinnitus. In: Swartz JD, Harnsberger HR, editors. *Imaging of the temporal bone*. 3rd ed. New York: Thieme; 1998. p. 240—317.
22. Shin EJ, Lalwani AK, Dowd CF. Role of angiography in the evaluation of patients with pulsatile tinnitus. *Laryngoscope* 2000;**110**:1916—20.
23. Moller MB, Moller AR, Jannetta PJ, et al. Vascular decompression surgery for severe tinnitus: selection criteria and results. *Laryngoscope* 1993;**103**:421—7.
24. Okamura T, Kurokawa Y, Ikeda N, et al. Microvascular decompression for cochlear symptoms. *J Neurosurg* 2000;**93**: 421—6.
25. Makins AE, Nikolopoulos TP, Ludman C, et al. Is there a correlation between vascular loops and unilateral auditory symptoms? *Laryngoscope* 1998;**108**:1739—42.
26. McDermott AL, Dutt SN, Irving RM, et al. Anterior inferior cerebellar artery syndrome: fact or fiction. *Clin Otolaryngol Allied Sci* 2003;**28**:75—80.
27. Nowé V, De Ridder D, Van de Heyning PH, et al. Does the location of a vascular loop in the cerebellopontine angle explain pulsatile and non-pulsatile tinnitus? *Eur Radiol* 2004;**14**:2282—9.
28. Gristwood RE, Venables WN. Otosclerosis and chronic tinnitus. *Ann Otol Rhinol Laryngol* 2003;**112**:398—403.
29. Sparano A, Leonetti JP, Marzo S, et al. Effects of stapedectomy on tinnitus in patients with otosclerosis. *Int Tinnitus J* 2004;**10**:73—7.
30. Mackenzie I, Young C, Fraser WD. Tinnitus and Paget's disease of bone. *J Laryngol Otol* 2006;**120**:899—902.
31. Farb RI, Vanek I, Scott JN, et al. Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. *Neurology* 2003;**60**:1418—24.
32. Suzuki H, Takanashi J, Kobayashi K, et al. MR imaging of idiopathic intracranial hypertension. *AJNR Am J Neuroradiol* 2001;**22**:196—9.
33. Brantberg K, Bergenius J, Mendel L, et al. Symptoms, findings and treatment in patients with dehiscence of the superior semicircular canal. *Acta Otolaryngol* 2001;**121**:68—75.

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Prevalence of Pulsatile Tinnitus Among Patients With Migraine

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Objective: To examine the prevalence of pulsatile tinnitus (PT) among patients with a diagnosis of migraine and to determine if treatment of migraine improves symptoms.
Study Design: Single-institution retrospective patient review.
Setting: Academic tertiary referral center.
Patients: Billing data capturing ICD-9 codes 346.xx and 388.3x was used to identify patients with history of migraine and tinnitus. Patients were excluded if the symptom of PT could be attributed to an alternate diagnosis. Data were extracted from the patients' electronic medical records.
Intervention(s): Therapeutic patients were prescribed a strict migraine diet with or without migraine medication.
Main Outcome Measure(s): Subjective improvement in tinnitus as documented in electronic medical records.
Results: One thousand two hundred four patients were identified with an ICD-9 code for migraine and of those patients, 12% (n = 145) had an ICD-9 code for tinnitus. After ruling out alternative causes, the prevalence of PT among all patients with migraine was 1.9%. Of migrainers with PT who underwent migraine treatment, 11 out of 16 reported resolution or improvement of their PT.
Conclusion: PT can be observed in the context of migraine. Migraine treatment with avoidance of dietary triggers with or without medication can possibly lead to resolution of PT. **Key Words:** Diet—Headache—Migraine—Pulsatile tinnitus.

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Pulsatile tinnitus (PT) is the perception of a pulsing or rhythmic sound. The differential is broad and includes vascular, nonvascular, and serious pathology such as dural arteriovenous fistulas. An aggressive workup should be performed given the risk of missing a serious diagnosis. The dilemma occurs when no middle ear mass or audible bruit is found. Even after extensive imaging, no diagnosis is found in one-third of patients (1). We propose migraine as a possible cause.

Migraine is one of the most common conditions in the United States (2). Approximately one-fifth of the population reports migraine with the highest prevalence among women (3). Abnormal electrical activity and then depression in or around the brain leading to vascular changes is observed during migraine (4). One theory is central neuronal hyperexcitability involving overactivity of excitatory neurotransmitters (5). Nitric oxide affects the trigeminal system leading to increased calcitonin gene-related peptide release and downstream effects of vasodilation and nociceptive transmission (6). Is it possible this vasodilation not only leads to the sensation of a throbbing headache but also the perception of throbbing either by a central process or by vasodilation of vessels around the cochlea leading to PT?

Information regarding migraine and PT is lacking in the literature. The objective of this study was to examine the prevalence of PT among patients with a migraine diagnosis and to determine if migraine treatment improved PT.

METHODS

The study is a single-institution retrospective medical chart review. The author's billing data (May 1, 2004 to December 31, 2014) of patients who received care at the Johns Hopkins Outpatient Center Otolaryngology clinic were eligible for review. This study qualified for institutional review board exemption as approved by The Johns Hopkins Institutional Review Board.

Inclusion criteria included visit diagnoses of ICD-9 346.xx (migraine) and 388.3x (tinnitus). PT was determined if the chart described tinnitus as pulsatile, pulse-like, or if the assessment's final diagnosis was PT. Tinnitus laterality was determined by patient report. Patients were excluded if PT was attributed to an alternate diagnosis noted on imaging or if ocular or cervical vestibular myogenic potentials (o or cVEMPs) suggesting superior canal dehiscence (SCD).

All patients were prescribed a strict migraine diet (see supplemental digital content, http://links.lww.com/MAO/A363) with or without migraine medication. Addition of antimigraine medication was at the clinician's discretion. Treatment adherence and subjective tinnitus improvement was documented in the chart. Presence of headache and comorbidities were determined from patient report and medical record. Presence of sensorineural hearing loss was noted on audiograms.

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The authors disclose no conflicts of interest.

Supplemental digital content is available in the text.

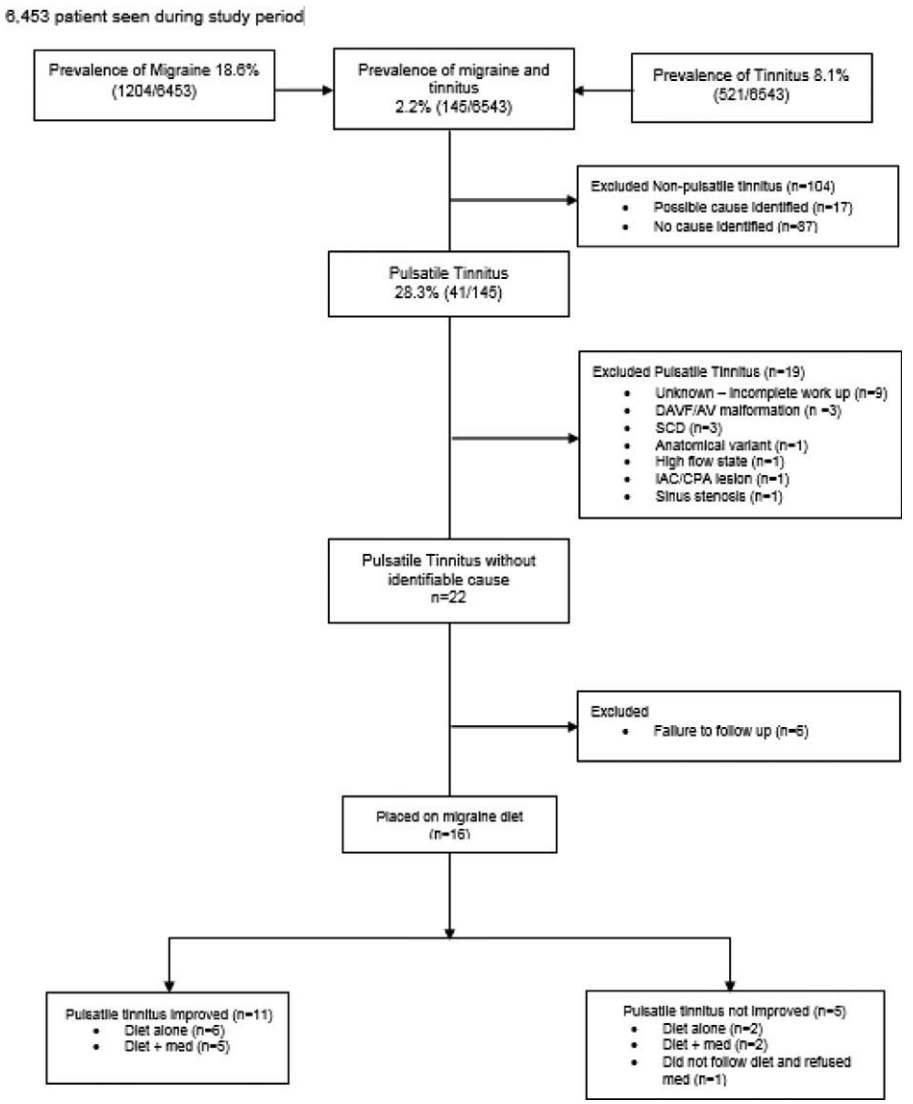

FIG. 1. Flow of patients with prevalence of migraine and tinnitus.

Descriptive statistics, χ^2 test, and two-sided t test with unequal variances were performed. A p value <0.05 was significant.

RESULTS

Six thousand four hundred fifty-three patients were observed during the study time period. The prevalence of migraine, tinnitus, and migraine with tinnitus is reported in the figure. All 521 tinnitus patients were reviewed and 20.9% reported PT with a PT prevalence of 1.7% among all patients. After excluding migraine patients with potential objective tinnitus ($n = 36$), significantly more migrainers reported history of any tinnitus as compared with nonmigrainers (9.3% versus 7.0%, $p = 0.007$). Of those with tinnitus, the percentage reporting PT migrainers as compared with nonmigrainers was the same (20.2% versus 18.1%, $p = 0.62$). The prevalence of PT among all migrainers was 1.9%.

Of the 145 patients with migraine and tinnitus, 129 were excluded (Fig. 1). The remaining 16 were assessed for PT improvement with migraine treatment. Average age was 45.4 years (range, 31.8–55.2), follow-up was 351 days (64–1,366 days). Fourteen out of 16 were white. Seven out of 16 described the PT as episodic whereas 4 reported constant PT. Eleven of the 16 patients reported improvement in PT with migraine treatment. There were no differences in demographics, sensorineural hearing loss, quality, or laterality of tinnitus between those who improved and those who did not.

All patients were recommended the diet. In addition to diet, seven patients were prescribed antimigraine medications. Decision to start a medication, type, and dosing varied by patient history and side effect profile. Table 1

TABLE 1. *Antimigraine medications and doses*

Medication	Dose
Amitriptyline	15 mg q day
Diltiazem	120 mg q day
Nortriptyline	10–30 mg q day
Topiramate	50–150 mg q day
Venlafaxine	75 mg q day

lists medications and dosing. Duration of medication treatment could not be calculated.

Fifteen of the 16 patients reported history of headache and/or vertigo in addition to PT. Specifically looking at treatment among patients with headache, most patients found improvement in headaches as well as PT (Table 2). One patient did not try the diet, did not start a medication, and had no improvement in headache or PT.

DISCUSSION

The PT prevalence among migrainers was 1.9% in a tertiary neurotology practice with 11 out of 16 patients reporting PT improvement with migraine treatment. This is the first study to examine the PT prevalence among migrainers. The pathophysiology for this is not clear. Possibilities include pulsations of the brain, cortical depression, or vascular changes transmitted to the cochlea or perceived by the brain.

This idea is supported given 14 patients experienced headache with their PT and 12 had resolution of one or both symptoms. An interesting example is a patient with known SCD who elected not to undergo repair. He presented with PT, sinus congestion, autophony, and vertigo triggered by straining. oVEMPs and imaging were consistent with SCD. Before undergoing SCD repair, he was treated for migraine and reported resolution of headaches, vertigo, and PT.

Obesity could be a confounding factor. The odds of chronic headaches are 26 to 34% higher among overweight individuals (7). Ohayon (8) found adults with BMIs >27 were more likely to report headaches than adults with BMIs 20 to 25. The relationship between conditions known for PT and obesity is well known. Benign intracranial hypertension (BIH) prevalence is two per 100,000 (9) with a higher incidence among obese individuals. Large population studies show patients with greater than 20% over ideal weight are at risk for BIH (10). Weight loss is one of the initial treatments of BIH. Our patients generally report losing weight while on a migraine diet. It is possible that patients had underlying BIH and loss weight, thus leading to resolution of their PT. This is unlikely as many had negative imaging. Unfortunately, though, we were not able to assess weight loss as these data were missing.

The addition of migraine into a PT differential could potentially alter the work-up. However, the authors do not advocate treating migraine and abandoning diagnostic testing to rule out more serious causes. A complete head and neck examination should be performed including palpation and auscultation of the periauricular region, orbita, neck, and chest. A history and examination that includes: objective tinnitus, PT that can be altered with pressure on the neck, blurred vision, papilledema, syncope with head position or headaches not meeting criteria for migraine cannot be ignored and warrant further work-up.

In our study, 12 out of 14 patients reported headache improvement while on a migraine diet. Numerous studies have supported the theory of food as a migraine trigger and an elimination diet as treatment. Finocchi and Sivori (11) suggest a non-IgE antibody-mediated mechanism in food allergy that may play a role in migraine.

The study is a retrospective review to formulate a hypothesis and determine if this warrants further exploration. Given small numbers, inconsistent data collection, and variability in definitions, minimal statistics were performed. We relied on ICD-9 coding to determine diagnosis of migraine and tinnitus. Failure to assign these as a visit diagnoses means individuals were missed. Second, no consistent definitions were applied although usage of one surgeon's experience minimized variability. Moreover, there is no ICD-9 PT code and a PT categorization required a description in the chart.

The lower prevalence of tinnitus is a reflection of the senior author's practice and referral pattern whereby vertigo is more commonly observed than tinnitus. If the primary chief complaint was not tinnitus, it may not have been listed as a visit diagnosis and therefore, patients with tinnitus were missed. Some of this data was captured on paper questionnaires. However, with a transition to an EMR, the paper records were not available for every patient and the data were incomplete.

TABLE 2. *Symptom improvement among patients with headache*

	Symptom Improved				
Migraine Treatment	Pulsatile Tinnitus Only	Headache Only	Both Better	Neither Better	Total
Diet only	0	2	5	0	8
Diet + medication	0	1	4	1	6
Did not try diet	0	0	0	1	1
All patients	0	3	9	2	14

Two patients excluded as they did not have headache.

We also were unable to control institution of the diet. Patients were given a hand out regarding foods to avoid. Administration and adherence were at the patient's discretion. It is possible those that did not improve did not follow the diet as was the case in one patient. Even if the patients followed the diet, they may not have improved. Finocchi and Sivori (11) report that only 20% of patients in their study had dietary triggers.

A study strength is over 10 years of management with one surgeon providing a consistent treatment approach. It is also an interesting concept to add to the literature, especially in the light of the prevalence of migraine.

A necessary next step is a prospective study. Patients with PT, who have definitive imaging to rule out serious pathology, could be randomized to a migraine diet and followed prospectively to determine resolution of symptoms.

CONCLUSION

PT can be observed in the context of migraine. Treatment of migraine with diet and medication can possibly lead to resolution of PT. However, the true association between migraine and PT needs to be evaluated with prospective well-controlled studies.

REFERENCES

1. Mattox DE, Hudgins P. Algorithm for evaluation of pulsatile tinnitus. *Acta Otolaryngol* 2008;128:427–31.
2. IHS Classification. ICHD-II Migraine. Available at: http://www.ihsclassification.org/en/02_klassifikation/02_teil1/01.00.00_migraine.html. Accessed March 20, 2015.
3. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: Updated statistics from government health surveillance studies. *Headache* 2015;55:21–34.
4. Tfelt-Hansen PC. History of migraine with aura and cortical spreading depression from 1941 and onwards. *Cephalalgia* 2010;30:780–92.
5. Welch KMA, Dandrea G, Tepley N, Barkley G, Ramadan NM. The concept of migraine as a state of central neuronal hyperexcitability. *Neurol Clin* 1990;8:817–28.
6. Messlinger K, Lennerz JK, Eberhardt M, Fischer MJM. CGRP and NO in the trigeminal system: Mechanisms and role in headache generation. *Headache* 2012;52:1411–27.
7. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain* 2003;106:81–9.
8. Ohayon MM. Prevalence and risk factors of morning headaches in the general population. *Arch Intern Med* 2004;164:97–102.
9. Wakerley B, Tan M, Ting E. Idiopathic intracranial hypertension. *Cephalalgia* 2015;35:248–61.
10. Durcan FJ, Corbett JJ, Wall M. The incidence of pseudotumor cerebri. Population studies in Iowa and Louisiana. *Arch Neurol* 1988;45:875–7.
11. Finocchi C, Sivori G. Food as trigger and aggravating factor of migraine. *Neurol Sci* 2012;33:S77–80.

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Malignant Otitis Externa: Evolving Pathogens and Implications for Diagnosis and Treatment

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Abstract

Objective. Malignant otitis externa (MOE) is an invasive infection of the temporal bone that is classically caused by *Pseudomonas aeruginosa*. Increasingly, however, nonpseudomonal cases are being reported. The goal of this study was to evaluate and compare the clinical presentation and outcomes of cases of MOE caused by *Pseudomonas* versus non-*Pseudomonas* organisms.

Study Design. Retrospective case series with chart review.

Setting. Tertiary care institution.

Subjects and Methods. Adult patients with diagnoses of MOE between 1995 and 2012 were identified. Charts were reviewed for history, clinical presentation, laboratory data, treatment, and outcomes.

Results. Twenty patients diagnosed with and treated for MOE at the University of Pittsburgh Medical Center between 1995 and 2012 were identified. Nine patients (45%) had cultures that grew *P aeruginosa*. Three patients (15%) had cultures that grew methicillin-resistant *Staphylococcus aureus* (MRSA). Signs and symptoms at presentation were similar across groups. However, all of the patients with *Pseudomonas* had diabetes, compared with 33% of MRSA-infected patients ($P = .046$) and 55% of all non-*Pseudomonas*-infected patients ($P = .04$). Patients infected with MRSA were treated for an average total of 4.7 more weeks of antibiotic therapy than *Pseudomonas*-infected patients ($P = .10$). Overall, patients with non-*Pseudomonas* infections were treated for a total of 2.4 more weeks than *Pseudomonas*-infected patients ($P = .25$).

Conclusions. A high index of suspicion for nonpseudomonal organisms should be maintained in patients with signs and symptoms of MOE, especially in those without diabetes. MRSA is an increasingly implicated organism in MOE.

Keywords

malignant otitis externa, necrotizing otitis externa, methicillin-resistant *Staphylococcus aureus*, MRSA, *Pseudomonas aeruginosa*, otitis externa

Introduction

Malignant otitis externa (MOE) is a potentially life-threatening osteomyelitis of the temporal bone that can extend to involve the surrounding soft tissues, cranial nerves, and adjacent skull base. Elderly, diabetic, or immunocompromised patients are most frequently afflicted. In 1959, Meltzer and Kelemen[1] first described this infection in a case report of a patient with diabetes with fatal temporal bone osteomyelitis that originated from otitis externa. Cultures from their patient's ear grew *Bacillus pyocyanea*, which is now known as *Pseudomonas aeruginosa*. In 1968, Chandler[2] coined the term ''malignant otitis externa'' to describe this morbid pseudomonal infection. Since then, the presence of *Pseudomonas* in affected ears has been thought to be one of the hallmark features of this disease.[3]

It was not until 1982 that the first case of nonpseudomonal MOE was reported. In that report, Bayardelle et al[4] described a case of MOE due to oxacillin-sensitive *Staphylococcus aureus*. Since then, there have been multiple reports of *S aureus* as the sole offending organism in MOE.[5,6] There have been few reports of methicillin-resistant *S aureus* (MRSA) as the causative pathogen in MOE[7,8]; however, the overall incidence of MRSA skin and soft tissue infections has been rising steadily.[9] Additionally, although earlier reports revealed *P aeruginosa* as the causative organism in most cases of MOE,

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Table 1. Pathogens and Clinical Features.

Clinical Feature	All Patients (n = 20)	*Pseudomonas* (n = 9)	*MRSA* (n = 3)	Other (n = 5)	Negative (n = 3)
Percentage of patients	100	45	15	25	15
Average age (y)	64.9	62.3	63.0	65.0	74.3
Age range (y)	42-100	42-77	44-100	52-79	61-84
Diabetes mellitus	75%	100.0%	33.3%	80.0%	33.3%
Facial nerve palsy	25%	33.3%	0%	20%	33.3%
Bony erosion (on CT scan)	95%	100%	100%	100%	66.7%
Failed local treatment	80%	66.7%	100%	80%	100%
Definitive therapy (wk)	7.8	6.1	8.5	11.8	6.7
Total therapy (wk)	9.2	7.9	12.6	12.0	6.7

Abbreviations: CT, computed tomographic; MRSA, methicillin-resistant *Staphylococcus aureus*.

more recent reports have documented *Pseudomonas* infection less frequently, with *Pseudomonas* cultured in as few as 27% to 54% of cases.[5-7]

Given the increasing frequency of nonpseudomonal MOE, we decided to retrospectively review our clinical experience with MOE and specifically compare clinical presentations, management, and outcomes of this infection between cases caused by *Pseudomonas* and MRSA. We hypothesized that the clinical presentation would be similar, regardless of the causative organism, and that treatment might be prolonged when caused by MRSA or other non-*Pseudomonas* organisms.

Methods

Institutional review board approval was obtained for this retrospective study (University of Pittsburgh institutional review board approval #PRO12010268, principal investigator Andrew A. McCall). The University of Pittsburgh Medical Center Department of Otolaryngology clinical record database was searched for all patients diagnosed with MOE between 1995 and 2012. Diagnosis was confirmed by the documented presence of the all of the obligatory Cohen criteria with 2 modifications.[10] First, it is generally our practice to obtain computed tomographic (CT) scans in lieu of nuclear medicine studies to confirm the presence of MOE.[11] We therefore included patients with documented evidence of bony erosion on CT scans in place of the obligatory Cohen criterion of either positive results on a technetium-99 scan or failure of local therapy. Second, because of the retrospective nature of the study, in some cases, not all of the obligatory clinical criteria were documented for each patient. We accepted patients into the present cohort who were missing documentation of no more than 1 of the clinical signs or symptoms of the obligatory Cohen criteria, as has been done by others.[12] Resolution of infection was based on the absence of clinical signs or symptoms of disease and the absence of radiographic progression of disease after a minimum follow-up period of 1 month after the completion of antibiotic therapy. Microsoft Excel 2011 (Microsoft Corporation, Redmond, Washington) and GraphPad Prism 6 (GraphPad Software, San Diego, California) were used for data management and statistical analysis. Statistical comparisons between groups were performed using Fisher's exact test and Student's *t* test as appropriate, and statistical significance was set at $P < .05$.

Results

Demographics

Twenty patients were identified from the database with supporting documentation that permitted confirmation of the diagnosis of MOE. The mean age at diagnosis was 65 years for all patients, 62 years for *Pseudomonas*-infected patients, and 63 years for MRSA-infected patients. There were 12 men and 8 women (**Table 1**).

Culture Data

Culture and sensitivity data were documented for all 20 patients. The means of obtaining culture data and therapy prior to culture are documented in **Table 2**. There were 9 patients (45%) whose cultures grew *P aeruginosa*. There was no documented ciprofloxacin resistance in any of the *Pseudomonas* specimens; 1 *Pseudomonas* isolate was resistant to levofloxacin. Two patients had cultures that grew methicillin-sensitive *S aureus* in addition to *Pseudomonas*. Three patients (15%) had cultures that grew MRSA in the absence of *Pseudomonas*. One patient infected with MRSA also grew *Klebsiella* and another grew pan-resistant *Acinetobacter* spp. One MRSA isolate was resistant to clindamycin; there was no documented resistance to doxycycline, trimethoprim-sulfamethoxazole, or vancomycin.

In the 5 remaining patients with positive cultures, the following organisms were documented (often in a polymicrobial fashion): *Enterococcus* spp (n = 2), methicillin-sensitive *S aureus* (n = 1), *Candida* spp (n = 1), *Aspergillus* (n = 1), *Staphylococcus lugdunensis* (n = 1), *Lactobacillus* (n = 1), *Peptostreptococcus* (n = 1), and *Alcaligenes faecalis* (n = 1). Three patients had negative cultures.

Cranial Neuropathies

Thirty-three percent of the *Pseudomonas*-infected patients presented with facial nerve palsies, compared with none of

Table 2. Culture Methods and Prior Therapy.

Patient	Therapy Prior to Culture	Culture Method
Pseudomonas		
1	None	Canal swab
2	Oral amoxicillin-clavulanic acid and topical ciprofloxacin-dexamethasone	Canal swab
3	Unknown	Canal swab
4	Unknown	Canal swab
5	Oral ciprofloxacin and topical ciprofloxacin-dexamethasone	Unknown
6	Oral ciprofloxacin and topical ciprofloxacin-dexamethasone	Canal swab
7	Oral antibiotic	Unknown
8	Topical antibiotic	Canal swab (tissue negative)
9	Oral ciprofloxacin and topical ciprofloxacin-dexamethasone	Canal swab
MRSA		
10	Oral trimethoprim-sulfamethoxazole	Canal swab
11	Topical ciprofloxacin-dexamethasone	Canal swab
12	Topical ciprofloxacin-dexamethasone	Canal tissue
Other		
13	Oral amoxicillin-clavulanic acid and topical ciprofloxacin-dexamethasone	Canal swab
14	Oral moxifloxacin and topical ciprofloxacin-dexamethasone	Canal swab
15	Topical ciprofloxacin-dexamethasone	Canal swab and tissue
16	Unknown	Canal swab
17	Oral ciprofloxacin and topical ciprofloxacin-dexamethasone	Canal swab and tissue
Negative		
18	Oral and topical antibiotics	Canal tissue
19	Oral/IV ciprofloxacin and topical ciprofloxacin-dexamethasone	Canal swab
20	Topical antibiotic	Canal swab

Abbreviations: IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

the MRSA-infected patients and 18% of all non-*Pseudomonas*-infected patients. These differences were not statistically significant ($P = .51$ and $P = .62$). No other cranial neuropathies were documented (**Table 1**).

Comorbidities

Fifteen patients (75%) had diabetes mellitus. All 9 patients infected with *Pseudomonas* had diabetes mellitus, compared with 33% of MRSA-infected patients and 55% of all non-*Pseudomonas* infected patients. These differences were statistically significant ($P = .046$ and $P = .04$, respectively). One patient (non-*Pseudomonas*, non-MRSA) had acute myeloid leukemia and received chemotherapy at around the time of his infection; this patient also had diabetes. One patient (non-*Pseudomonas*, non-MRSA) had rheumatoid arthritis and was taking immunosuppressive medications at the onset of infection. Another patient (non-*Pseudomonas*, non-MRSA) had systemic lupus erythematous but was not receiving immunosuppressive therapy. Overall, 63% of the non-*Pseudomonas*-infected patients either had diabetes or were immunosuppressed, compared with 100% of the *Pseudomonas*-infected patients ($P = .09$).

Treatment Summary

At the time of this study, 1 patient had an ongoing infection, 3 patients were lost to follow-up, and 1 patient (MRSA, panresistant *Acinetobacter*) died from a central catheter infection while undergoing ongoing therapy for MOE. The remaining 15 patients (75%) had documented resolution of their infections. Two patients had recurrences of their infections and were treated with a second course of antibiotics. Of the 15 patients with documented resolution of their infections, the mean definitive antibiotic course was 7.8 $\pm$ 3.9 weeks, and the mean total antibiotic course was 9.2 $\pm$ 4.2 weeks. The most frequent treatment duration, including treatment of recurrences, was 6 weeks. Three patients underwent mastoidectomy during their treatment for MOE: 2 mastoidectomies were performed for patients who, while receiving intravenous antibiotic therapy, had sequestered bone in the mastoid seen on CT scans; 1 patient underwent mastoidectomy to evaluate for malignancy, as that patient exhibited radiographic evidence of progressive bony erosion and a soft tissue lesion despite treatment.

One of the *Pseudomonas*-infected patients was lost to follow-up. The remaining 8 had resolution of their infections with an average of 6.1 $\pm$ 2.1 weeks of definitive antibiotic therapy and 7.9 $\pm$ 3.4 total weeks of antibiotic therapy. Five of those 8 patients were treated with oral quinolone antibiotics, 3 in combination with an intravenous anti-*Pseudomonal* cephalosporin. One patient was treated with intravenous moxifloxacin. The 2 patients who were not treated with quinolone antibiotics were treated with an intravenous anti-*Pseudomonal* penicillin. One patient, who did not follow up, underwent a canal wall up mastoidectomy.

Two of 3 MRSA-infected patients had resolution of their infections, averaging 8.5 ± 0.7 weeks of definitive antibiotic therapy and 12.6 ± 0.9 total weeks of antibiotic therapy. One patient infected with MRSA and *Acinetobacter* died from an infected central catheter while undergoing treatment for MOE. Although the treatment duration was longer for MRSA-infected than for *Pseudomonas*-infected patients, these differences in duration were not statistically significant ($P = .18$ for total and $P = .10$ for definitive therapy). None of the MRSA-infected patients underwent surgical intervention beyond debridement of the ear canal. The MRSA-infected patients were treated with intravenous vancomycin.

Overall, the 7 patients with documented resolution of non-*Pseudomonas* infections were treated with antibiotics for an average of 9.3 ± 4.5 weeks of definitive antibiotic therapy and 10.4 ± 4.6 total weeks of antibiotic therapy. These treatment durations were longer (3.2 and 2.5 weeks, respectively) than those for the *Pseudomonas*-infected patients but did not reach significance ($P = .09$ and $P = .25$). Six of these 7 patients (86%) received intravenous therapy with nonquinolone antibiotics.

Discussion

Classically, MOE has been thought to be due exclusively to *Pseudomonas* infection. In fact, Cohen and Friedman[10] suggested the presence of *Pseudomonas* on cultures as an obligatory diagnostic criterion for this disease, though noting that this required further investigation. In 1988, Rubin and Yu[3] performed a literature review of 260 cases of MOE and found that virtually all cases (99.2%) were caused by *Pseudomonas*. With increasing frequency, however, nonpseudomonal cases of MOE are being reported. Fewer than half (45%) of the patients in our study had cultures that grew *Pseudomonas*. Similarly, in 2010, Chen et al[7] and Jacobsen and Antonelli[13] reported relatively low proportions of pseudomonal MOE, with only 26.9% and 34% of their respective patients having *Pseudomonas* isolated in cultures. Commensurate with the decline in *Pseudomonas* isolates has been a rise of other organisms leading to MOE.[5-7,13] The second most common isolate in our series was *S aureus*, with 3 isolates being MRSA (15%). To our knowledge, there are few reports documenting MRSA as a causative organism in cases of MOE.[7,8]

With the evolving microbiology of MOE, it is essential that treatment be tailored to the causative organism(s). Since its introduction in the late 1980s, oral ciprofloxacin has commonly been used as a first-line empiric treatment for MOE.[14] This allowed patients with early-stage disease to be treated empirically in an outpatient setting. Now, however, with the increasing frequency of nonpseudomonal MOE, ciprofloxacin may not always be an effective treatment, as it has poor gram-positive coverage and is ineffective against MRSA.

Additionally, the incidence of ciprofloxacin-resistant *Pseudomonas* has been rising. Although there was 1 instance of levofloxacin resistance and not any documented ciprofloxacin resistance in our *Pseudomonas* isolates, other investigators have reported an increasing incidence ciprofloxacin-resistant *Pseudomonas* as a cause of MOE.[14,15] In 2002, Berenholz et al[15] were the first to report MOE caused by ciprofloxacin-resistant *Pseudomonas*, with 33% of their *Pseudomonas* isolates being resistant to ciprofloxacin.

The clinical features of MOE caused by *Pseudomonas* and MRSA were similar in many respects (average age of onset, signs and symptoms, etc), but some important differences were noted. Diabetes is a commonly noted comorbidity in patients with MOE and, along with immunocompromised state, is thought to be a risk factor for development of the disease.[3] In our series, all of the *Pseudomonas*-infected patients had diabetes, whereas only 1 of the 3 MRSA-infected patients did ($P = .046$). Additionally, only 55% of the patients with non-*Pseudomonas* infections had diabetes, which was also significantly less than in the *Pseudomonas*-infected patients ($P = .04$). These findings illustrate the point that a diagnosis of MOE must be considered in any patient with refractory otitis externa, even in those without diabetes. Furthermore, it suggests that atypical organisms, such as MRSA, should be suspected in patients without diabetes who present with MOE.

There were important limitations of this study worth mentioning. First, the study was retrospective in nature, and data were limited to the available records. Additionally, the patient population was heterogeneous in terms of prior therapy and the manner in which cultures were obtained. It is possible that prior therapy would eradicate organisms that would have otherwise have been detected on culture. This means that potentially pathogenic organisms (in isolation or as a part of a polymicrobial infection) may have been eradicated or rendered undetectable by culture prior to presentation to our offices in some instances. Furthermore, ear-swab culture may not always be reflective of the pathogenic organism infecting the temporal bone in MOE. Although the specific role of culture method has not been investigated in MOE, discordance between swab and bone culture has been shown for diabetic foot osteomyelitis.[16] For this reason, we recommend tissue biopsy in cases in which there is poor or no response to ear-swab culture–directed therapy. Additionally, the choice of antibiotic was based on the preference of the treating neurotologist in conjunction with an infectious disease specialist. Many patients were treated with intravenous antibiotics, while sensitivities suggested that an oral antibiotic could have been used. Because MRSA is a rare organism to cause MOE, there are few data guiding treatment of this offending organism. It is worth noting that 1 of our MRSA-infected patients was being treated with oral trimethoprim-sulfamethoxazole at the time of presentation and culture. Although sensitivities indicated that the organism was susceptible to this antibiotic, the patient's infection was not responsive to this treatment. The infection was resolved with intravenous vancomycin treatment.

In general, treatment durations were planned for 6 weeks and extended as needed on the basis of clinical or radiographic evidence of persistent or progressive disease. It is

worth mentioning that neither technetium nor gallium scans were routinely used for diagnosis or monitoring of disease; thus, it is possible that some patients with clinical and radiographic evidence of resolution may have in fact had ongoing infections. Finally, because many of our patients travel long distances for care at our center, they often elect to follow up with their local otolaryngologists after the completion of treatment and apparent resolution of their infections. This precluded us from following outcomes for the majority of the patients in our study beyond 1 month after the completion of antibiotic therapy.

Conclusions

Our study underscores the increasing frequency of non-*Pseudomonas* causes of MOE and specifically highlights that MRSA is an increasingly important organism leading to MOE. A high index of suspicion for atypical organisms, such as MRSA, should be maintained in patients with signs and symptoms of MOE who do not have diabetes.

Author Contributions

Candace E. Hobson, Data acquisition and analysis, interpretation of data, drafting of manuscript, final approval; **Jennifer D. Moy**, data acquisition, critical revision of manuscript, final approval; **Karin E. Byers**, Study conception and design, critical revision of manuscript, final approval; **Yael Raz**, study conception and design, critical revision of manuscript, final approval; **Barry E. Hirsch**, study conception and design, critical revision of manuscript, final approval; **Andrew A. McCall**, study conception and design, analysis and interpretation of data, drafting and critical revision of manuscript, final approval.

Disclosures

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References

1. Meltzer PE, Keleman G. Pyocyaneous osteomyelitis of the temporal bone, mandible and zygoma. *Laryngoscope*. 1959;69:1300.
2. Chandler JR. Malignant external otitis. *Laryngoscope*. 1968; 78:1257-1294.
3. Rubin J, Yu VL. Malignant external otitis: insights into pathogenesis, clinical manifestations, diagnosis, and therapy. *Am J Med*. 1988;85:391-398.
4. Bayardelle P, Jolivet-Granger M, Larochelle D. Staphylococcal malignant external otitis. *Can Med Assoc J*. 1982;126:155-156.
5. Ali T, Meade K, Anari S, ElBadawey MR, Zammit-Maempel I. Malignant otitis externa: case series. *J Laryngol Otol*. 2010; 124:846-851.
6. Soudry E, Hamzany Y, Preis M, Joshua B, Hadar T, Nageris BI. Malignant external otitis: analysis of severe cases. *Otolaryngol Head Neck Surg*. 2011;144:758-762.
7. Chen CN, Chen YS, Yeh TH, Hsu CJ, Tseng FY. Outcomes of malignant external otitis: survival vs mortality. *Acta Otolaryngol*. 2010;130:89-94.
8. Yu LH, Shu CH, Tu TY, Shiao AS, Lien CF. Malignant otitis externa. *Chin Med J*. 1999;62:362-368.
9. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant S. aureus infections among patients in the emergency department. *N Engl J Med*. 2006;355:666-674.
10. Cohen D, Friedman P. The diagnostic criteria of malignant external otitis. *J Laryngol Otol*. 1987;101:216-221.
11. Mehrotra P, Elbadawey MR, Zammit-Maempel I. Spectrum of radiological appearances of necrotising external otitis: a pictorial review. *J Laryngol Otol*. 2011;125:1109-1115.
12. Joshua BZ, Sulkes J, Raveh E, Bishara J, Nageris BI. Predicting outcome of malignant external otitis. *Otol Neurotol*. 2008;29:339-343.
13. Jacobsen LM, Antonelli PJ. Errors in the diagnosis and management of necrotizing otitis externa. *Otolaryngol Head Neck Surg*. 2010;143:506-509.
14. Bernstein JM, Holland NJ, Porter GC, Maw AR. Resistance of Pseudomonas to ciprofloxacin: implications for the treatment of malignant otitis externa. *J Laryngol Otol*. 2007;121:118-123.
15. Berenholz L, Katzenell U, Harell M. Evolving resistant pseudomonas to ciprofloxacin in malignant otitis externa. *Laryngoscope*. 2002;112:1619-1622.
16. Elamurugan TP, Jagdish S, Kate V, Chandra Parija S. Role of bone biopsy specimen culture in the management of diabetic foot osteomyelitis. *Int J Surg*. 2011;9:214-216.

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Malignant Otitis Externa: An Asian Perspective on Treatment Outcomes and Prognostic Factors

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Abstract

Objective. Malignant otitis externa (MOE) is a severe disease with varying outcomes. Despite advances in antibiotic treatment, a significant proportion still succumbs to this disease. We aimed to analyze the effect of clinical factors on prognosis and to review treatment outcomes in our institution.

Study Design. Case series with retrospective chart review of MOE cases from 2006 to 2011.

Setting. Department of Otolaryngology–Head and Neck Surgery, National University Hospital, Singapore, a tertiary referral center.

Subjects and Methods. Patients with MOE admitted for treatment were studied and divided into 2 outcome groups depending on response to a 6-week course of intravenous antibiotics. Demographic and disease factors were analyzed with regard to outcome.

Results. Nineteen cases were analyzed. Disease resolved in 63.2% after 6 weeks of antibiotics. Mortality was 21.1%. Age, diabetic control, duration of diagnostic delay, cranial nerve involvement, and inflammatory markers were not found to predict prognosis. Erythrocyte sedimentation rate and C-reactive protein levels correlated with disease activity and can be used to monitor progress. Clival involvement was associated with persistent disease ($P = .002$). Only 63.2% of cases had positive cultures. *Pseudomonas aeruginosa* was the main organism, and 33.3% of isolates were multidrug resistant. Outcome was not different in cases where culture-directed therapy was employed vs those where empirical ceftazidime and fluoroquinolone were used ($P = .650$).

Conclusion. Malignant otitis externa remains an insidious disease with significant mortality. Involvement of the clivus portends a poorer prognosis. Combination therapy with intravenous ceftazidime and oral fluoroquinolone remains relevant despite concerns of culture-negative cases and multidrug-resistant *Pseudomonas*.

Keywords

malignant otitis externa, necrotizing otitis externa, skull base osteomyelitis

Malignant otitis externa (MOE) is a severe infection that typically affects the elderly, patients with diabetes, and immunocompromised patients.[1] *Pseudomonas aeruginosa* is the main causative organism.[2] Infection begins in the external auditory canal (EAC), spreading through the fissures of Santorini to surrounding structures.[3] Advances in anti-pseudomonal antibiotics have reduced mortality, which was 50% when MOE was first described.[1] The clinical course is varied and outcome prediction is difficult. Studies have attempted to identify prognostic factors to guide treatment, but a lack of consensus exists.

This series aims to review our experience and to identify prognostic factors that might influence outcome.

Methods

The study was approved by the Ethics Committee at the National University Hospital, Singapore. The database of the Department of Otolaryngology–Head and Neck Surgery was searched for cases of MOE treated at our tertiary center between 2006 and 2011.

All patients with MOE were admitted for intravenous antibiotics. The regimen used consisted of intravenous ceftazidime and oral fluoroquinolone. Oral fluoroquinolone was omitted only in patients who had already been pretreated with long courses of this without improvement. Isolated cases where cultures showed organisms resistant to ceftazidime were given culture-specific antibiotics. Patients who improved were discharged with outpatient antibiotic therapy. Those who did not improve continued inpatient treatment. Disease was deemed to have resolved in patients who were symptom free for more than 2 weeks with

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normalization of inflammatory markers and without relapse within 12 weeks.

Those in whom disease resolved after a 6-week course of intravenous antibiotics were deemed as having a good outcome. Those who had persistent symptoms despite 6 weeks of therapy were considered to have a poor outcome.

The clinical characteristics and laboratory and imaging findings between the 2 groups were compared to identify possible prognostic factors. Data analysis was performed with SPSS 16.0 software (SPSS, Inc, an IBM Company, Chicago, Illinois). Statistically significant differences in categorical variables were cross-tabulated and analyzed with the Fisher exact test. The Mann-Whitney *U* test and *t* test were used to analyze continuous variables as appropriate. *P* values $\leq$.05 were considered statistically significant.

Results

Demographics and Outcome

Twenty-two cases of MOE were identified. Three were excluded from analysis: 2 foreign patients chose to continue treatment in their own country, and 1 died of pneumonia shortly after initiating treatment. The remaining 19 patients consisted of 16 men and 3 women. Mean age was 69.1 years (range, 51-86 years).

Disease resolved in 63.2% (n = 12) after 6 weeks of antibiotics. In 36.8% (n = 7), disease was persistent after 6 weeks, and additional antibiotics were required. Four in this group ultimately died. The overall mortality rate in our series was 21.1% (n = 4). Three patients died from MOE-associated intracranial complications. The remaining patient died from intracranial hemorrhage secondary to ceftazidime-induced thrombocytopenia.

There was a tendency for those 65 years and older to have disease that persisted after 6 weeks of antibiotics (45.0% of those 65 years and older vs 25.0% of those younger than 65 years), but this did not reach statistical significance (*P* = .633).

Comorbidities

All patients were immunocompromised. Diabetes was present in 94.7% (n = 18). The only patient (n = 1) without diabetes was on long-term steroids for rheumatoid arthritis. The macrovascular and microangiopathic effects of diabetes were present in a significant proportion: 63.2% (n = 12) had ischemic heart disease, 15.8% (n = 3) had peripheral vascular disease, and 26.3% (n = 5) had end-stage renal failure. Diabetes severity was assessed based on glycated hemoglobin (HbA1c) levels at diagnosis. Of those with diabetes, 55.6% (n = 10) had HbA1c in excess of 7.0%, reflecting poor glucose control prior to diagnosis of MOE. There was no association between HbA1c levels and outcome (*P* = 1.00).

Clinical Presentation

The most common complaint, present in 73.7% (n = 14), was concomitant otalgia and otorrhea; 10.5% (n = 2) had parotid swelling. Facial nerve palsy was the main symptom in 21.0% (n = 4). The mean duration of symptoms before MOE was diagnosed was 6.79 weeks (range, 1-12 weeks). There was no statistically significant difference in the duration of symptoms prior to diagnosis between the group in which disease resolved after 6 weeks of intravenous treatment and the group in which disease persisted. Mean duration of symptoms was 6.67 weeks in the former group compared with 7.0 weeks in the latter group (*P* = .859). Although patients with cranial nerve involvement tended to have more persistent disease, this did not reach statistical significance (50.0% of patients with cranial nerve palsy had poor outcome vs 33.3% of those without; *P* = .603).

Inflammatory Markers

Inflammatory markers were evaluated at diagnosis and serially as treatment progressed. Total white cell count (TWC; normal range, 3.40-9.60 $\times$ 10^9/L), C-reactive protein (CRP; normal range, 0-10 mg/L), and erythrocyte sedimentation rate (ESR; normal range, 5-15 mm/h) levels were measured. Leukocytosis was less prominent compared with derangements in CRP and ESR levels. At diagnosis, only 26.3% (n = 5) had abnormal TWC levels compared with 72.2% (n = 13) with raised CRP and 84.2% (n = 16) with raised ESR. The mean (SD) values of these inflammatory markers were as follows: TWC, 9.98 (4.12) $\times$ 10^9/L; CRP, 42.56 (51.89) mg/L; and ESR, 66.82 (34.73) mm/h.

Inflammatory marker levels were compared between the 2 outcome groups at the time of diagnosis and at the 2- and 6-week point after initiating antibiotics. The results are presented in **Table 1**. No significant difference in mean CRP and ESR levels was detected between the 2 outcome groups at these 3 intervals. The group in which disease progressed had a statistically significant higher TWC after 6 weeks of antibiotics compared with the group in which disease resolved, but overall, leukocytosis was not prominent and remained at the upper limit of normal. Although the absolute levels of the inflammatory markers appeared to be of limited usefulness in predicting outcome, a more prominent downward trend of levels was seen as treatment progressed in the group in which disease resolved, as compared with the group in which it persisted (**Figure 1**).

Imaging

Computed tomography (CT) was the imaging modality of choice at our institution and was performed in 89.5% (n = 17) at diagnosis. Computed tomography findings were divided into minor and major findings based on a study by Soudry et al[4] that showed a correlation between major CT findings and persistent disease. Minor findings were defined as EAC tissue swelling, EAC bony erosion, and mastoid involvement. Major findings were defined as infratemporal fossa involvement, temporomandibular joint involvement, parapharyngeal involvement, and nasopharyngeal involvement. The CT findings are presented in **Table 2**.

The presence of major findings on initial CT scans was not seen to be predictive of outcome (33.3% in the poor outcome group and 36.4% in the good outcome group had major findings; *P* = 1.00).

Table 1. Inflammatory marker level comparison between disease progression and disease resolution groups.

	Disease Resolved	Disease Progressed	*P* Value
At diagnosis			
TWC, mean, $\times 10^9$/L	8.81	12.02	.118
CRP, mean, mg/L	41.60	34.00	.759
ESR, mean, mm/h	58.11	75.00	.357
2 weeks after antibiotics			
TWC, mean, $\times 10^9$/L	7.68	9.14	.300
CRP, mean, mg/L	13.80	29.57	.209
ESR, mean, mm/h	51.20	58.71	.669
6 weeks after antibiotics			
TWC, mean, $\times 10^9$/L	7.09	10.72	.014
CRP, mean, mg/L	17.89	27.00	.491
ESR, mean, mm/h	49.00	74.67	.120

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TWC, total white cell count.

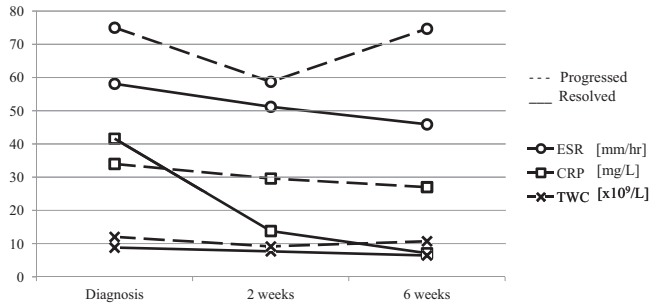

Figure 1. Inflammatory marker trends during a period of antibiotic treatment in the group in which disease resolved compared with the group in which disease progressed. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TWC, total white cell count.

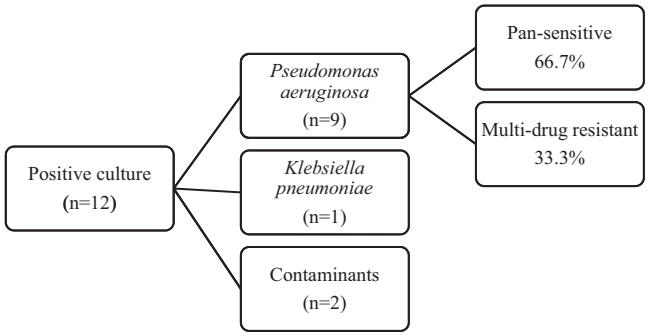

Figure 2. Breakdown of positive ear swab culture results.

Table 2. Frequency of minor and major CT scan findings.

	No. (%)
Minor findings	
EAC tissue swelling	16 (94.1)
EAC bony erosion	15 (88.2)
Mastoid involvement	16 (94.1)
Major findings	
Infratemporal fossa	4 (23.5)
Temporomandibular joint	4 (23.5)
Parapharyngeal involvement	3 (17.6)
Nasopharyngeal involvement	1 (5.9)

Abbreviation: EAC, external auditory canal.

Magnetic resonance imaging (MRI) was used in 52.6% (n = 10) to delineate soft tissue involvement or intracranial extension. Common areas of involvement were the masticator space in 50% (n = 5), condylar bone marrow in 30% (n = 3), parapharyngeal space in 40% (n = 4), nasopharynx in 60% (n = 6), clivus in 50% (n = 5), and dural enhancement in 40% (n = 4).

A subset of our patients had clival involvement, either as contiguous spread or direct involvement. This subset was noted to have poorer prognosis and required lengthier antibiotic therapy. Five patients had clival involvement on CT or MRI. All patients with clival involvement had disease that persisted after 6 weeks of antibiotics compared with 14.3% (n = 2) in those without (*P* = .002). Clival involvement was also strongly associated with mortality and was seen in 75% (n = 3) of mortalities.

Microbiology and Antibiotic Therapy

Ear swabs were routinely performed. Organisms were identified in only 63.2% (n = 12). The results of those with positive cultures are represented in **Figure 2**. *Pseudomonas aeruginosa* was the main organism and was present in 75.0% (n = 9). Multidrug-resistant *Pseudomonas* contributed to 33.3% (n = 3) of *P aeruginosa* isolates. Two patients with positive cultures had light growth of *Staphylococcus epidermidis* that were deemed as contaminants. There was no particular organism that occurred more often in the 3 patients

who died from intracranial complications (1 = *Klebsiella pneumoniae*, 1 = *P aeruginosa*; 1 = negative culture).

Based on culture sensitivity, 52.6% (n = 10) received culture-specific therapy. Those with negative cultures received empirical intravenous ceftazidime and oral fluoroquinolone. The mean (SD) duration of antibiotic therapy was 42.2 (15.3) days. Outpatient therapy was used in 63.2% (n = 12) to reduce inpatient stay, reducing the mean (SD) inpatient antibiotic duration to 24.3 (20.1) days.

There was no statistically significant difference in outcome between those who received culture-specific therapy and those who received ceftazidime and fluoroquinolone empirically (70.0% of the directed therapy group had disease that resolved vs 55.6% in the empirical therapy group; $P = .650$).

Discussion

Malignant otitis externa had associated mortality rates of 50% when it was first characterized in 1968.[1] The development of anti-pseudomonal antibiotics has since reduced mortality significantly. Studies have reviewed factors such as clinical presentation, laboratory and imaging findings, and microbiology in an attempt to identify prognostic factors. However, conclusive prognostic factors have yet to be identified, and there is still no consensus on the optimal choice of antibiotics and duration of therapy.

Demographic Factors

The impact of age on prognosis is disputed. Franco-Vidal et al[5] reviewed 46 patients and found that age did not affect outcome. On the contrary, Soudry et al[4] studied 57 patients, and their results suggested a lower life expectancy for those aged 70 years and older. However, this was also attributed to additional risks contributed by diabetes and other atherosclerosis-related comorbidities frequently present in these patients. Our experience suggests that age is not an accurate prognostic factor.

The link with diabetes is well established,[1,6] with recent studies reporting the prevalence of diabetes in MOE to be between 65% and 95%.[4,5,7] Our results concurred, with 94.7% (n = 18) having diabetes in our study. Diabetes-related microangiopathy is thought to predispose to MOE as the impaired local circulation within the EAC diminishes the ability of immunological cells to respond to invasion by *P aeruginosa.*[8,9] Glycemic control is linked to the severity of microangiopathy in the retina and renal circulations. Hence, we postulated that poorer glycemic control would imply more severe microangiopathy within the EAC, and this could predict severe disease. However, analysis of HbA1c levels failed to show relation to outcome. This concurs with earlier studies that also failed to show any relation between degree of glucose intolerance and outcome.[6,9] A possible explanation could be that as most patients are elderly with longstanding diabetes, microangiopathy within the EAC is already end stage, therefore making little difference in the local immune response.

Presentation

Initial symptoms are indistinguishable from simple otitis externa. It is usually only after multiple failed treatment attempts that MOE is suspected. The mean diagnostic delay was significantly long at 6.79 weeks, similar to the literature, which has been reported to be between 1 and 7 months.[10,11] Similar to other studies,[4,12] our results suggest that a delay in the commencement of intravenous antibiotics does not adversely affect outcome. However, this delay leads to prolonged suffering, and physicians should always maintain a high index of suspicion in susceptible patients.

Soudry et al[4] and Franco-Vidal et al[5] found that those with facial nerve palsy at presentation had a poorer outcome. This trend was noted in our series, but the number of patients with facial nerve involvement was small, and the findings did not reach statistical significance (50.0% poor outcome in the group with cranial nerve involvement vs 33.3% poor outcome in the group without; $P = .603$).

Hematological Parameters

Leukocytosis, a traditional marker of inflammation, was not prominent, and its use in monitoring activity is limited. In contrast, the usefulness of CRP and ESR as markers for activity is apparent, concurring with previous studies.[3,6] Our results showed that the absolute ESR and CRP levels could not be relied upon alone to predict outcome, but the usefulness of these markers became evident when serial readings showed that trends were seen to correlate closely with disease activity. Patients with disease that resolved after 6 weeks of intravenous therapy showed a 21.71% reduction in mean ESR values compared with the group with persistent disease, in which ESR values remained unchanged (**Figure 1**). A similar downward trend was also seen in CRP levels. By trending inflammatory marker levels, clinicians are able to decide more confidently which patients are suitable for antibiotic cessation or outpatient treatment, especially when one does not have ready access to radionuclide scans.

Imaging Findings

Radionuclide bone and white cell–tagged scans have proven valuable in MOE. Bone scans are sensitive because the radionuclide tracer (technetium-99m methylene diphosphonate) accumulates at areas of osteoblastic activity. However, osteoblastic activity persists long after the infective process, hence limiting the usefulness for charting progress or confirming resolution. White cell–tagged scans using gallium citrate (Ga67) have been more useful in monitoring disease as the tracer is incorporated directly into granulocytes at sites of infection. These scans are undoubtedly valuable; however, they may not be available in all institutions dealing with MOE. In our experience, we have used anatomic imaging modalities such as CT and MRI to assess our patients.

Computed tomography is ideal for assessing bony involvement. In theory, the anatomical extent of disease should be useful for prognosis. Peleg et al[13] reported that severe

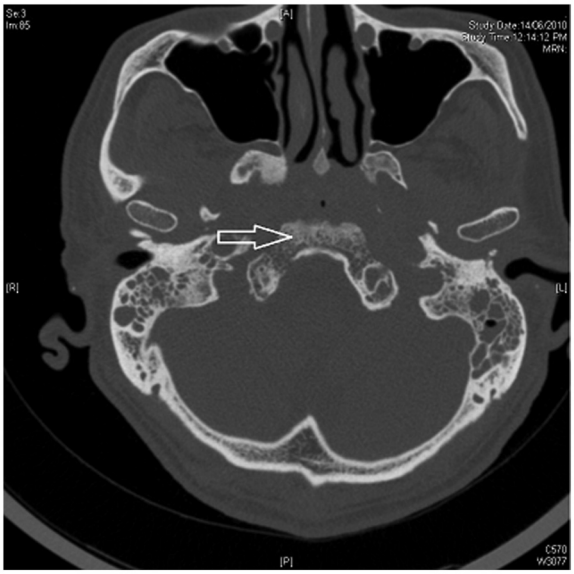

Figure 3. Clival erosion in central skull base osteomyelitis.

disease was likely with involvement of 2 or more of the following areas: temporomandibular joint, temporal bone, and base of skull. The CT findings of our patients were stratified into major and minor findings based on the studies by Peleg et al[13] and Soudry et al.[4] Contrary to the observations by Peleg et al,[13] no correlation was seen between the presence of major area involvement and poor outcome. This lack of correlation was also noted by Sudhoff et al.[14] Bone erosion can only be seen once demineralization has occurred. Demineralization becomes evident after weeks of inflammation,[3] making early disease hard to detect. Moreover, once demineralization has occurred, the bony changes persist even after inflammation has settled.[6] This loose association between bone demineralization and disease activity could account for the lack of reliability of CT scans in predicting outcome. In cases where medial and intracranial extension of disease had to be visualized, we used MRI to better delineate soft tissue involvement.

Direct extension of disease medially from the petrous temporal bone can progress to involve the clivus, a central structure at the anterior-most portion of the basilar occipital bone where it meets the sphenoid bone. We considered patients with clival involvement to have central skull base osteomyelitis (**Figure 3**). Central skull base osteomyelitis can affect the surrounding soft tissues, compromising the lower cranial nerves and brainstem.[15] Extension of disease through the petroclival synchondrosis can result in intracranial involvement with the development of meningitis, abscess, and venous sinus thrombosis.[1] Clival involvement was noted in 5 patients. All these patients had disease that persisted after 6 weeks of antibiotics. In the group without clival involvement, only 14.3% (n = 2) had persistent disease. Clival involvement was also seen in all the mortalities that resulted from intracranial involvement. We suggest that patients with clival erosion should be counseled appropriately on prognosis and have more aggressive treatment.

Antibiotic Treatment

It has become increasingly difficult to isolate causative microorganisms from the EAC for culture-directed therapy because of the use of otic antibiotics at primary care. Only 63.2% (n = 12) of ear swabs were positive. Increasing antibiotic resistance in *P aeruginosa* represents another problem. This organism has properties that make it inherently resistant to many drug classes and able to acquire resistance through mutation.[16,17] Taking into consideration all forms of infections caused by *P aeruginosa* from 33 European countries, the European Antimicrobial Resistance Surveillance System Annual Report for 2006 (http://www.rivm.nl/earss/result/Monitoring_reports/) reported that 18.0% of isolates were multidrug resistant (ie, resistant to 3 or more antibiotics). Specific to *P aeruginosa* in MOE, Berenholz et al[18] raised the concern of ciprofloxacin resistance when they reported that 33.0% of isolates were resistant to ciprofloxacin. This was mirrored in other studies in which the rates of ciprofloxacin resistance have ranged from 31.0% to 37.5%.[18-20] Similarly, 33.3% (n = 3) of *P aeruginosa* isolates in our series were ciprofloxacin resistant. Levenson et al[21] declared that ciprofloxacin monotherapy was the treatment of choice in MOE. However, current resistance rates suggest that monotherapy with ciprofloxacin is imprudent in almost one-third of cases. Antibiotic choices in culture-negative patients therefore represent a therapeutic challenge in view of the high antibiotic resistance rates of *P aeruginosa*. Our results suggest that the empirical use of combination anti-pseudomonal therapy with intravenous ceftazidime and oral ciprofloxacin in culture-negative cases remains relevant despite increasing antibiotic resistance in *P aeruginosa*. This is consistent with reports in the literature.[18,22] Rubin et al[23] proposed the use of combination therapy with oral rifampacin and ciprofloxacin in treating drug-resistant *P aeruginosa*, and they showed that their oral and intravenous regimes were equally efficacious. However, in another study by Korvick et al[24] involving 121 patients with positive blood cultures for *P aeruginosa*, no significant benefit was demonstrated from the addition of rifampacin to existing anti-pseudomonal therapy, suggesting that further clinical studies on the anti-pseudomonal properties of rifampacin are needed. In addition, due to the significant risk of hepatotoxicity and drug interactions related to hepatic cytochrome P450 upregulation, rifampacin was not considered for our regime.

The role of surgery is limited. Only 3 patients in our series underwent surgery, and the indications for surgery were local debridement and to obtain cultures. The usefulness of surgery was limited in these cases as intraoperative cultures did not yield additional information over ear swab specimens, and disease persisted despite debridement.

Conclusion

Definite prognostic factors remain elusive. Our experience has shown that age, severity of diabetes, and duration of symptoms cannot be relied upon to predict prognosis. When radionuclide scans are not readily available, anatomic

assessment of disease involvement by CT and MRI remains valuable. Although the extent of anatomical involvement does not reliably predict outcome, those with clival involvement indicating central skull base osteomyelitis were noted to do much poorer with conventional treatment, and this should be explored in future studies. The choice of antibiotic therapy is difficult in culture-negative cases in view of increasing reports of antibiotic resistance in *P aeruginosa*, but our outcomes with empirical combination therapy using intravenous ceftazidime and oral fluoroquinolone suggests that this regime remains effective.

Author Contributions

Shaun Loh, data collection, entry, analysis and writing of manuscript; **Woei Shyang Loh**, study idea, advice on analysis, review of manuscript.

Disclosures

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References

1. Chandler JR. Malignant external otitis. *Laryngoscope*. 1968; 78:1257-1294.
2. Carfrae MJ, Kesser BW. Malignant otitis externa. *Otolaryngol Clin North Am*. 2008;41:537-549.
3. Rubin Grandis J, Branstetter BF, Yu VL. The changing face of malignant external otitis: clinical, radiological, and anatomic correlations. *Lancet Infect Dis*. 2004;4:34-39.
4. Soudry E, Hamzany Y, Preis M, Joshua B, Hadar T, Nageris BI. Malignant external otitis: analysis of severe cases. *Otolaryngol Head Neck Surg*. 2011;144:758-762.
5. Franco-Vidal V, Blanchet H, Bebear C, Dutrone H, Darrouzet V. Necrotizing external otitis: a report of 46 cases. *Otol Neurotol*. 2007;28:771-773.
6. Rubin J, Yu VL. Malignant external otitis: insights into pathogenesis, clinical manisfestations, diagnosis and therapy. *Am J Med*. 1988;85:391-398.
7. Hariga I, Mardassi A, Younes FB, et al. Necrotizing otitis externa: 19 cases' report. *Eur Arch Otorhinolaryngol*. 2010; 267:1193-1198.
8. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol*. 1999;26:259-265.
9. Chen CN, Chen YS, Yeh TH, Hsu CJ, Tseng FY. Outcomes of malignant external otitis: survival vs mortality. *Acta Otolaryngol*. 2010;130:89-94.
10. Jacobsen LM, Antonelli PJ. Errors in the diagnosis and management of necrotizing otitis externa. *Otolaryngol Head Neck Surg*. 2010;143:506-509.
11. Amorosa L, Modugno GC, Pirodda A. Malignant external otitis: review and personal experience. *Acta Otolaryngol Suppl*. 1996; 521:3-16.
12. Mani N, Sudhoff H, Rajagopal S, Moffat D, Axon PR. Cranial nerve involvement in malignant external otitis: implications for clinical outcome. *Laryngoscope*. 2007;117:907-910.
13. Peleg U, Perez R, Raveh D, Berelowitz D, Cohen D. Stratification for malignant external otitis. *Otolaryngol Head Neck Surg*. 2007;137:301-305.
14. Sudhoff H, Rajagopal S, Mani N, Moumoulidis I, Aron PR, Moffat D. Usefulness of CT scans in malignant external otitis: effective tool for the diagnosis, but of limited value in predicting outcome. *Eur Arch Otorhinolaryngol*. 2008;265:53-56.
15. Sreepada GS, Kwartler JA. Skull base osteomyelitis secondary to malignant otitis externa. *Curr Opin Otolaryngol Head Neck Surg*. 2003;11:316-323.
16. Livermore DM. Multiple mechanisms of antimicrobial resistance in *Pseudomonas aeruginosa*: our worst nightmare? *Clin Infect Dis*. 2002;34(5):634-640.
17. GIamarellou H, Kanellakopoulou L. Current therapies for *Pseudomonas aeruginosa*. *Crit Care Clin*. 2008;24(2):261-278.
18. Berenholz L, Katzenell U, Harell M. Evolving resistant *Pseudomonas* to ciprofloxacin in malignant otitis externa. *Laryngoscope*. 2002;112:1619-1622.
19. Jones ME, Karlowsky JA, Draghi DC, Thornsberry C, Sahm DF, Nathwani D. Antibiotic susceptibility of bacteria most commonly isolated from bone related infections: the role of cephalosporins in antimicrobial therapy. *Int J Antimicrob Agents*. 2004;23:240-246.
20. Jang CH, Park SY. Emergence of ciprofloxacin-resistant *Pseudomonas* in chronic suppurative otitis media. *Clin Otolaryngol*. 2004;29:321-323.
21. Levenson MJ, Parisier SC, Dolitsky J, Bindra G. Ciprofloxacin: drug of choice in the treatment of malignant external otitis (MEO). *Laryngoscope*. 1991;101:821-824.
22. Kimmelman CP, Lucente FE. Use of ceftazidime for malignant external otitis. *Ann Otol Rhinol Laryngol*. 1989;98:721-725.
23. Rubin J, Stoehr G, Yu VL, Muder RR, Matador A, Kamerer DB. Efficacy of oral ciprofloxacin plus rifampin for treatment of malignant external otitis. *Arch Otolaryngol Head Neck Surg*. 1989;115(9):1063-1069.
24. Korvick JA, Peacock JE, Muder RR, Wheeler RR, Yu VL. Addition of rifampin to combination antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: prospective trial using the Zelen protocol. *Antimicrob Agents Chemother*. 1992;36(3): 620-625.

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Fungal Malignant Otitis Externa: Pitfalls, Diagnosis, and Treatment

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Hypothesis: Oral voriconazole is a viable alternative modality treatment to traditionally used intravenous vancomycin in the treatment of malignant otitis externa (MOE).
Background: The incidence of MOE is on the rise, more so in Saudi Arabia where diabetes mellitus is endemic. Although *Pseudomonas aeruginosa* is the most common offending organism, we are observing an increasing number of fungal MOE, in particular, *Aspergillus* species. The clinical findings in these patients can be quite different from those of the classic gram-negative bacteria.
Methods: Chart review of patients with a diagnosis of MOE who underwent oral voriconazole treatment.
Results: Three cases of *Aspergillus* MOE are reported in detail, pointing the pitfalls in clinical findings, diagnosis, and management of this entity.
Conclusion: Oral voriconazole proved to be an excellent alternative modality treatment in this population of patients with MOE. **Key Words:** *Aspergillus*—Malignant otitis externa—Voriconazole.
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The incidence of diagnosed malignant otitis externa (MOE) seems to be on the rise since the first case described by Chandler in 1968, as the index of suspicion for this disease has increased among generalist physicians (1). Of all cases, 90% are attributed to *Pseudomonas aeruginosa*. Other reported offending organisms include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Proteus mirabilis*, *Klebsiella oxytoca*, and fungi species. The most common fungal organism is *Aspergillus fumigatus* (2). The first case of *Aspergillus* MOE was described in 1985 in a 68-year-old man with relapsing acute myelogenous leukemia (3). A recent review of the infectious disease literature found that 24 additional cases had since been reported (4).

The traditional treatment of *Aspergillus* MOE has been intravenous administration of amphotorecin for 4 to 6 weeks. Voriconazole was approved by the U.S. Food and Drug Administration in 2002 for primary treatment of acute, invasive aspergillosis and is an excellent alternative for the treatment of *Aspergillus* MOE because amphotericin has known adverse effects and toxicity in already-vulnerable patients (5).

Diabetes mellitus (DM) is endemic in the authors' country, Saudi Arabia, with a reported incidence of 23.7% (6). Because of this high incidence and the hot and humid weather, we see a significant number of patients with MOE. Most of them have already been treated by a general practitioner with multiple short courses of oral and local antibiotics. In our clinical setting, we are rarely faced with the typical case of MOE, presenting with granulation tissue at the osseocartilagenous junction and multisensitive pseudomonas as the offending organism. The challenges that present to us are the partially treated cases with culture-negative ear culture.

Here we describe 3 cases of *Aspergillus* MOE treated effectively with oral voriconazole after failing previous treatment. Although voriconazole has been available for this purpose for nearly a decade, to our knowledge, there are no publications in the otologic literature advocating voriconazole as an alternative treatment for fungal MOE. Otologists in tertiary referral practices continue to evaluate many cases treated first in general practice or even by other otolaryngologists, whose diagnosis may be made more difficult because of the previous treatment. The presentation and clinical findings in these cases do not always conform to the classic presentation of bacterial MOE.

PATIENT REPORTS

Patient 1

This patient was a 77-year-old man with a history of poorly controlled Type 2 DM. He presented with a 2-month history of right ear pain and discharge. The pain was severe enough to interrupt his sleep. The patient had

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The authors disclose no conflicts of interest.

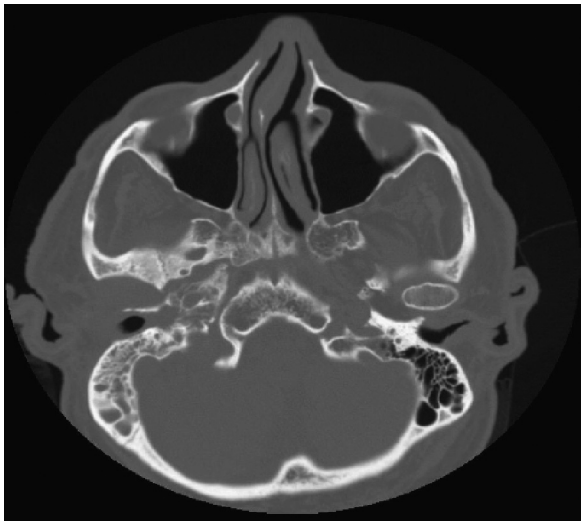

FIG. 1. Axial computed tomographic scan shows soft tissue attenuation of the right mastoid and right middle ear, with suspected mild erosive changes of the anterior wall of the external auditory canal.

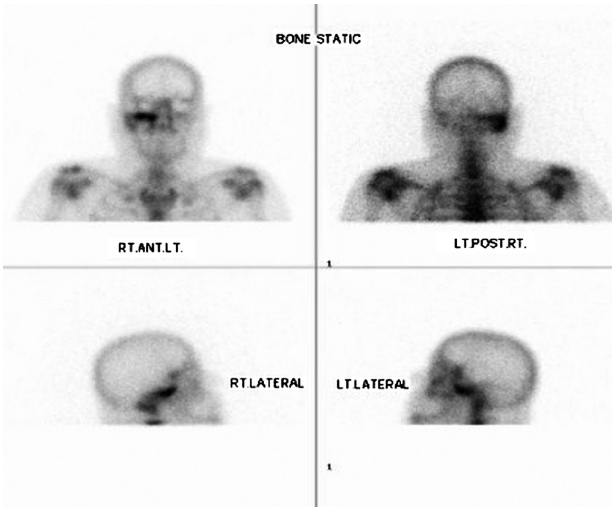

FIG. 3. Technetium scan showing intense uptake within the right cranial base, mainly within the temporal bone and involving the right mastoid and the petrous temporal region.

been treated with multiple courses of oral and local antibiotics, including quinolones.

Examination of the right ear revealed sagging of the superior canal wall and a thickened tympanic membrane with polypoid changes in the mesotympanum. There was mucoid yellowish discharge in the canal as well.

Swab culture from the right ear showed soft tissue attenuation of the right mastoid and right middle ear, with suspected mild erosive changes of the anterior wall of the external auditory canal (Fig. 1). There was mild enhancement of the right side of the nasopharynx and right parapharyngeal space with partial involvement of the masticator space (Fig. 2). There was dense attenuation of the right mastoid and right middle ear, including suspected mild erosive changes of the anterior wall of the external auditory canal (Fig. 2).

Technetium and gallium scans showed intense uptake within the right cranial base, mainly within the temporal bone and involving the right mastoid and the petrous temporal region (Figs. 3 and 4).

The patient began receiving intravenous administration of ciprofloxacin 400 mg every 12 hours and ceftazidime 2 g every 12 hours. However, he did not respond to therapy, and his erythrocyte sedimentation rate rose to 117 mm/h. A right-sided myringotomy with tube placement was performed. The aspirate from the middle ear grew *Aspergillus* species. The patient was then intravenously administered amphotericin B lipid complex 400 mg once daily, but he developed fever, chills, and severe rigors. The medication was changed to intravenous administration of voriconazole 300 mg every 12 hours. One week later, the patient was pain free, and his erythrocyte sedimentation rate (ESR)

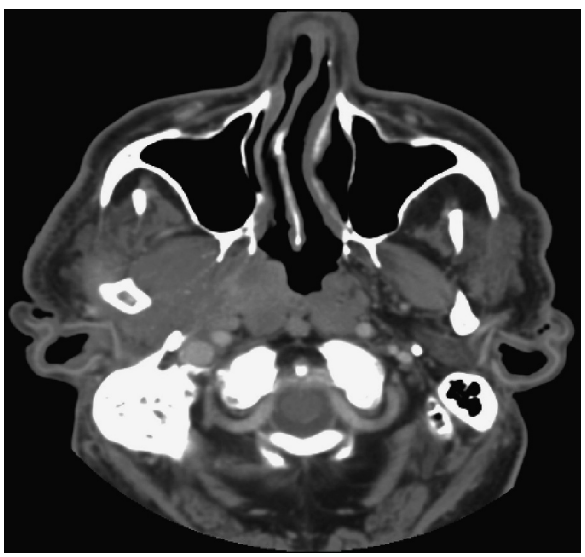

FIG. 2. Axial computed tomographic scan shows mild enhancement of the right side of the nasopharynx and right parapharyngeal space with partial involvement of the masticator space.

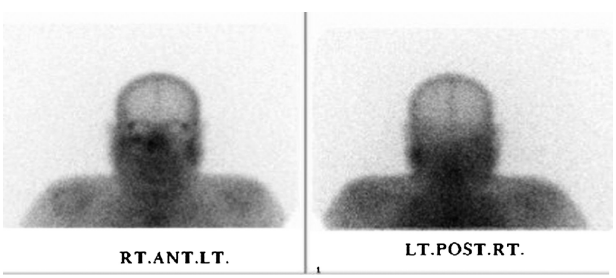

FIG. 4. Gallium scan showing intense uptake within the right cranial base, mainly within the temporal bone and involving the right mastoid and the petrous temporal region.

had decreased to 65 mm/h. The patient was discharged on oral voriconazole 200 mg twice a day for 2 months. While on the medical service, his blood glucose level was also brought under control.

Patient 2

An 85-year-old woman with a history of poorly controlled Type 2 DM and hypertension presented with a 3-month history of right ear pain. She was initially treated with oral and intravenously administered antibiotics, including quinolones, with no improvement. She had a history of penicillin allergy. She was admitted with vomiting and severe headache that prevented sleep.

Examination showed an edematous right ear canal with granulation tissue inferiorly. The canal was filled with squamous debris, and the tympanic membrane could not be visualized. She had an intact facial nerve function.

Erythrocyte sedimentation rate on admission was 93 mm/L, and an ear swab showed *S. epidermidis* and *Candida albicans*. Tissue cultures were negative.

Computed tomographic scan of the temporal bones showed inflammatory changes of the right middle ear and external auditory canal (Fig. 5).

Magnetic resonance image of the brain showed significant soft tissue infiltration and edema involving the infratemporal fossa, masticator, parotid and parapharyngeal spaces, right temporalis muscle and subcutaneous soft tissues. Associated mild dural enhancement of the floor of the right middle cranial fossa (Fig. 6).

Bone and gallium scans showed intense uptake in the right temporal bone involving the petrous apex.

The patient was given intravenously administered aztreonam 2 g every 8 hours for 3 weeks and was then discharged on oral ciprofloxacin 500 mg twice a day. The pain improved and ESR dropped to 83 mm/h. However, she was readmitted 2 weeks later with right facial nerve palsy and recurrent ear pain. Her ESR rose to 105 mm/L.

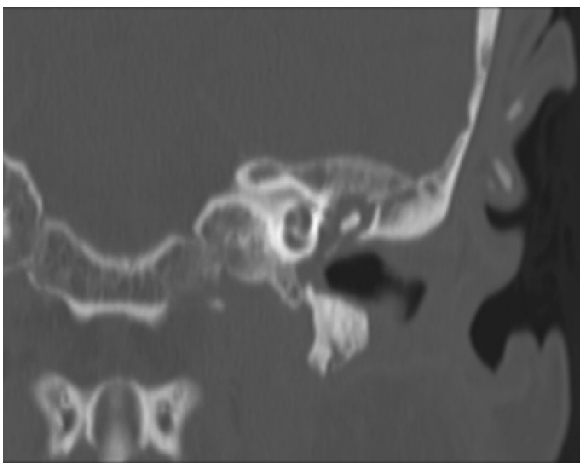

FIG. 5. Coronal computed tomographic scan of the temporal bones shows inflammatory changes of the right middle ear and external auditory canal.

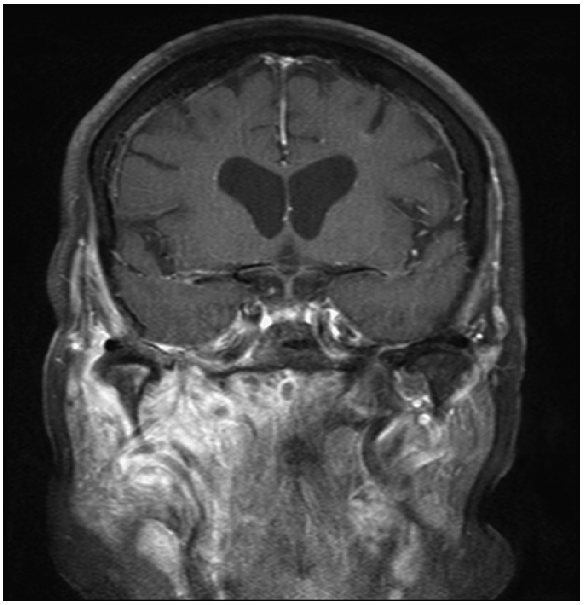

FIG. 6. Coronal magnetic resonance image of the brain shows significant soft tissue infiltration and edema involving the infratemporal fossa, masticator, parotid and parapharyngeal spaces, right temporalis muscle and subcutaneous soft tissues. Associated mild dural enhancement of the floor of the right middle cranial fossa.

The right ear canal was very edematous with squamous debris, and the tympanic membrane could not be observed. The patient underwent debridement of the external ear canal down to the tympanic membrane. There was a mound of granulation tissue in the middle ear but not in the external ear canal. Pathology was negative for malignancy, and tissue cultures were positive for *Aspergillus* species. The patient was, therefore, began receiving intravenously administered amphotericin B lipid 400 mg once-daily complex for 4 weeks, but the medication was discontinued because of renal impairment. Meanwhile, the pain resolved, and ESR dropped to 35 mm/h. Examination showed a normal right ear canal with an intact tympanic membrane. The patient also showed some improvement in function of the lower facial nerve. She was discharged on oral voriconazole 200 mg twice a day for another 2 months. Her blood glucose level had also been brought under control. She remained pain free for another 6 months, when she died as a result of an unrelated cause.

Patient 3

A 70-year-old woman with a history of poorly controlled Type 2 DM and hypertension presented with a 3-month history of left ear pain. She had been treated with oral and local antibiotics with no improvement of symptoms.

Examination showed a dull tympanic membrane, with normal ear canal. The nasopharynx was also normal. An audiogram showed a right, downsloping, moderate sensorineural hearing loss and a left mixed hearing loss with

flat tympanogram. Erythrocyte sedimentation rate was 115 mm/h.

Computed tomographic scan of the temporal bones showed soft tissue fullness of the left pharyngeal mucosal and retropharyngeal spaces and slight soft tissue infiltration of the left parapharyngeal fat plane. There was total opacification of the left mastoid air cells, antrum, and the middle ear cavity. The middle ear ossicles were intact.

Both external auditory canals, the right middle ear cavity and ossicles, and the right inner ear structures were within normal limits.

Magnetic resonance imaging of the neck showed significant soft tissue edema and enhancement at the left infratemporal fossa, with contiguous involvement of the parapharyngeal, retropharyngeal, pharyngeal mucosal, and part of the masticator spaces. Midline extension in the form of clival osteomyelitis was also observed, as was extension into the left temporal fossa as manifested by intracranial dural enhancement via foramen ovale.

Bone and gallium scans showed focal increased activity within the left mastoid bone as well as moderate to intense activity within the base of the left side of the cranium, mainly within the sphenoid bone.

A left-sided myringotomy with tube was performed. The aspirate culture was negative for species, and the patient was treated empirically with intravenously administered ceftazidime 2 g every 12 hours and orally administered ciprofloxacin 750 mg for 2 weeks. Pain improved and ESR decreased to 75 mm/h. The patient was discharged on orally administered ciprofloxacin 750 mg twice a day. One month later, she started complaining of bilateral ear pain. The right tympanic membrane was dull with some air fluid level in the middle ear. On the left side, there was granulation tissue over the tympanic membrane and around the myringotomy tube. This tissue was sent for culture and grew *P. aeruginosa* and *Aspergillus* species. *P. aeruginosa* was sensitive to ciprofloxacin. However, the patient's ESR rose to 88 mm/h, and she was readmitted 6 weeks later. A magnetic resonance image of the temporal bones showed a slightly less pronounced infiltrative process involving the left cranial base. Involvement of the clivus remained about the same. Increased soft tissue and bony inflammatory changes/enhancement were noted within the region of the right cranial base, parapharyngeal and carotid spaces, as well as partial involvement of the right parotid space. Increased inflammatory changes of the mastoid air cells of the right ear were also present.

The patient began receiving intravenously administered ciprofloxacin 400 mg every 12 hours and orally administered voriconazole 200 mg twice a day. Her condition started to improve, with resolving pain and resolution of the granulation tissue. Her ESR dropped to 65 mm/h. She was discharged 3 weeks later on orally administered ciprofloxacin 750 mg twice a day and orally administered voriconazole 200 mg twice a day for another 3 months. Her blood glucose level was under control. Erythrocyte sedimentation rate decreased to 25 mm/h, and the tube on the left was removed, and both tympanic membranes looked normal. One year later, she remains pain free with normal result in the ear examination.

DISCUSSION

Partially treated MOE is particularly challenging because of the culture-negative status. Unfortunately, this is the most common type of patient observed in a tertiary care setting. They are also a high-risk group in terms of complications (7).

By the time of evaluation by the otolaryngologist, the patient has been frustrated by the lack of sleep and severe otalgia, trismus, and headaches. Because of the nonspecific clinical presentation, cases of MOE are frequently missed.

Jacobsen and Antonelli (8) reviewed 51 patients with MOE, with diagnosis delayed for more than 2 months. Fifty-five percent of those patients were observed at the request of other otolaryngologists. In 68%, the referral was for other diagnoses, including chronic suppurative otitis media, cholesteatoma, or otalgia. The one common denominator was pain out of proportion to the clinical findings.

A high index of suspicion is needed in any elderly patient who is diabetic with ear pain out of proportion to the ear findings. The absence of ear canal findings does not preclude the diagnosis of MOE. As a matter of fact, cases of *Aspergillus* MOE are more commonly confined to the middle ear rather than the outer ear. Taking tissues for culture and biopsies from the middle ear, and/or middle ear effusion, is essential to identify the offending organism and to rule out rare cases of malignancy in the middle ear and/or the mastoid. Common ear swabs may only reveal fungal contaminants of the outer ear canal. A highly elevated ESR is quite common and computed tomographic scans or magnetic resonance images delineate the extent of disease, but positive results in bone and gallium scans establish the diagnosis.

Voriconazole is recommended as first-line therapy for invasive aspergillosis (9). An important characteristic of voriconazole is its availability in tissues and bones (10). The activity of this agent has been documented in vitro against *Aspergillus* isolates from the middle ear (11). Although the most commonly used antifungal therapy for aspergillosis infection of the external auditory canal was amphotericin B, the first successful use of voriconazole has been reported in 2 patients with MOE (4). Voriconazole has been used successfully as salvage and primary therapy, either alone or in combination with surgical debridement (8,12,13). Itraconazole also has been used subsequent to amphotericin B in therapy for aspergillous osteomyelitis (14). Voriconazole has the advantage of predictable therapeutic levels after oral administration, in contrast to itraconazole, which yields a lower concentration after oral administration.

A positive culture justifies taking the patient on oral voriconazole for at least 2 months, until results from the patient's examination are completely normal and ESR is back to normal. Some advocate waiting for the results of

the gallium scan to return to normal, but because there can be a lag period between resolution of disease and a normal scan result, we may be overtreating in these cases. A drop in the ESR can be used as a monitor for response to treatment, whereas a negative result in the gallium scan is an indicator to stop treatment altogether.

All 3 patients we report here had already been treated in the community. Patient 3 was particularly interesting, as she was actually referred as a case of glomus jugular tumor. She was found, instead, to have 2 organisms on tissue culture, with *Aspergillus* being one of them. Her disease even progressed to involve the contralateral temporal bone through the clivus. All 3 patients had previously negative swab cultures. They all had findings confined to the middle ear but were complaining of ear pain/trismus/headache out of proportion to their clinical findings.

Various protocols of empiric treatment, which would cover the most likely organisms in culture-negative MOE, have been proposed. Djalilian et al. (15) recommended intravenous administration of ceftazidime or aztreonam for penicillin-allergic patients along with high-dose oral ciprofloxacin and topical aminoglycoside steroid drops. None of these empiric protocols include amphotericin. Owing to its toxic nature, empiric amphotericin treatment for culture-negative MOE is not justified. With the introduction of voriconazole, which has few adverse effects, one might consider adding it as an empiric treatment for culture-negative MOE.

CONCLUSION

The otolaryngologist must have a high index of suspicion for any patient with a background of immunosuppression (diabetes or otherwise) with ear pain out of proportion to the clinical findings, which can sometimes be subtle or confined to the middle ear. It is specific in such cases that fungal MOE should be considered, with tissues and/or middle ear aspirates sent for fungal culture and appropriate treatment started. This can spare the patients grief, frustration, and, sometimes, unnecessary surgery.

Voriconazole has been very effective in treating *Aspergillus* MOE on an outpatient basis. Like quinolones in *Pseudomonas* infection, it dramatically changes the treatment of *Aspergillus* MOE from inpatient to outpatient with much fewer adverse effects and less toxicity.

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REFERENCES

1. Rubin Grandis J, Branstetter BF 4th, Yu VL. The changing face of malignant (necrotising) external otitis: clinical, radiological, and anatomic correlations. *Lancet Infect Dis* 2004;4:34–9.
2. Stodulski D, Kowalska B, Stankiewicz C. Otogenic skull base osteomyelitis caused by invasive fungal infection. Case report and literature review. *Eur Arch Otorhinolaryngol* 2006;263:1070–6.
3. Petrak R, Pottage J, Levin S. Invasive external otitis caused by *Aspergillus fumigates* in an immunocompetent patient. *J Infect Dis* 1985;151:196.
4. Parize P, Chandesris MO, Lanternier F, et al. Antifungal therapy of *Aspergillus* invasive otitis externa: efficacy of voriconazole and review. *Antimicrob Agents Chemother* 2009;53:1048–53.
5. Peman J, Salavert M, Canton E, et al. Voriconazole in the management of nosocomial invasive fungal infections. *Ther Clin Risk Manag* 2006;2:129–58.
6. Al- Nozha MM, Al-Maatouq MA, Al-Mazrou YY, et al. Diabetes mellitus in Saudi Arabia. *Saudi Med J* 2004;25:1603–10.
7. Singh A, Al-Khabori M, Hyder MJ. Skull base osteomyelitis: diagnostic and therapeutic challenges in atypical presentation. *Otolaryngol Head Neck Surg* 2005;133:121–5.
8. Jacobsen LM, Antonelli PJ. Errors in the diagnosis and management of necrotizing otitis externa. *Otolaryngol Head Neck Surg* 2010; 143:506–9.
9. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46:327–60.
10. Denes E, Boumediene A, Durox H, et al. Voriconazole concentrations in synovial fluid and bone tissues. *J Antimicrob Chemother* 2007;59:818–19.
11. Yenişehirli G, Bulut Y, Güven M, Günday E. In vitro activities of fluconazole, itraconazole and voriconazole against otomycotic fungal pathogens. *J Laryngol Otol* 2009;123:978–81.
12. Mouas H, Lutsar I, Dupont B, et al. Voriconazole/Bone Invasive Aspergillosis Study Group. Voriconazole for invasive bone aspergillosis: a worldwide experience of 20 cases. *Clin Infect Dis* 2005; 40:1141–7.
13. Stratov I, Korman TM, Johnson PD. Management of *Aspergillus* osteomyelitis: report of failure of liposomal amphotericin B and response to voriconazole in an immunocompetent host and literature review. *Eur J Clin Microbiol Infect Dis* 2003;22:277–83.
14. Tang TJ, Janssen HL, van der Vlies CH, et al. *Aspergillus* osteomyelitis after liver transplantation: conservative or surgical treatment? *Eur J Gastroenterol Hepatol* 2000;12:123–6.
15. Djalilian HR, Shamloo B, Thakkar KH, Najme-Rahim M. Treatment of culture-negative skull base osteomyelitis. *Otol Neurotol* 2006;27:250–5.

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Cost Analysis and Outcomes of a Second-Look Tympanoplasty-Mastoidectomy Strategy for Cholesteatoma

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Calhoun D. Cunningham III, MD; David M. Kaylie, MD, MS

Objectives/Hypothesis: To analyze cost and compare cholesteatoma recidivism and hearing outcomes with single-stage and second-look operative strategies.

Study Design: Retrospective review and cost analysis.

Methods: Adult and pediatric patients who underwent a tympanoplasty with mastoidectomy for cholesteatoma with a single-stage or second-look operative strategy were identified. Variables included procedure approach, residual or recurrent cholesteatoma, ossicular chain reconstruction frequency, and operative complications. Audiologic outcomes included pre-/postoperative air bone gap (ABG) and word recognition score (WRS). Cost analysis included charges for consultation and follow-up visits, surgical procedures, computed tomography temporal bone scans, and audiology visits.

Results: One hundred and six patients had a tympanoplasty with mastoidectomy for cholesteatoma, with 80 canal wall-up procedures (CWU) as initial approach. Of these, 46 (57.5%) CWU patients had a planned second look. Two (4.3%) CWU patients had recurrent cholesteatoma and 20 (43.4%) had residual identified at second look. Four (11.7%) single-stage CWU strategy patients developed recurrent cholesteatoma. There was no significant difference in pre-/postoperative ABG and WRS between second look and single stage ($P > 0.05$). Compared to second-look patients, single-stage patients had significantly fewer postoperative visits (6.32 vs. 10.4; $P = 0.007$), and significantly lower overall charges for care ($23,529. vs. $41.411; $P < 0.0001$).

Conclusion: The goal of cholesteatoma surgery is to produce a safe ear, and a second-look strategy after CWU has historically been used to evaluate for recurrent or residual disease. The cholesteatoma recurrence rate at a second look after a CWU tympanoplasty-mastoidectomy is low. Costs of operative procedures are a significant proportion of healthcare resource expenditures. Considering the low rate of cholesteatoma recurrence and relatively high cost of care, implementation of a second-look strategy should be individually tailored and not universally performed.

Key Words: Cholesteatoma, second look, tympanoplasty, mastoidectomy.

Level of Evidence: 4.

***Laryngoscope*, 00:000–000, 2016**

INTRODUCTION

Cholesteatoma is a potentially destructive epidermal inclusion cyst of the middle ear. They can be acquired primarily through a retraction pocket in the tympanic membrane, secondarily through a tympanic membrane perforation, or develop as a congenital rest of squamous epithelium behind an intact tympanic membrane. If left untreated, the cholesteatoma can initiate local inflammatory cascades and osteoclast activation, resulting in erosion and destruction of the osseous structures of the middle and inner ear that include the mastoid, ossicles, and semicircular canals. More serious sequelae include erosion of the tegmen, cerebrospinal fluid leak, encephalocele formation, and secondary infection with intracranial extension.

Management of cholesteatoma includes complete surgical removal of all cyst matrix, keratinaceous debris, and squamous epithelium. The surgical approach employed depends upon the extent of the disease. Small, well-contained cysts in the attic can be removed via a transcanal tympanoplasty and atticotomy. In most cases, a tympanoplasty with mastoidectomy is necessary for adequate exposure and removal of all disease. A mastoidectomy can be completed with either a canal wall-down or canal wall-up technique. Reported advantages of the canal wall-down technique include superior exposure of the middle ear and lower disease recurrence rates.[1–3] Advantages of the canal wall-up technique include preserved or improved hearing outcomes, preservation of the natural external ear canal wall, tympanic membrane position, and avoidance of a mastoid cavity.[4,5] However, the canal wall-up technique has a reported higher risk of residual and recurrent cholesteatoma.[6] The incidence of recurrent cholesteatoma at second-look surgery following primary canal wall-up tympanoplasty in contemporary literature

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ranges from 6% to 9%.[7–10] The incidence of residual cholesteatoma is considerably higher and is frequently attributed to insufficient disease resection or inadequate exposure.[11–14] As a result, second-look procedures are often employed to evaluate for residual or recurrent disease and to perform ossiculoplasty, if indicated.

Whereas the canal wall-up tympanoplasty is associated with higher recurrence of cholesteatoma, the routine execution of a second-look procedure is associated with significant cost and risks of a second procedure. There also exists significant difference in opinion regarding the optimal surgical strategy.[15] Costs of a second procedure include cost of the preoperative clinic evaluation, preoperative imaging, procedure, operative time, perioperative staff and perioperative consumables, postoperative prescription medications, and postoperative follow-up clinic visits. Other costs could include patient loss of productivity during the recovery period and the opportunity cost of the surgeon's time. Risks of the procedure include wound infection, hemorrhage, facial nerve paralysis, hearing loss, vestibulopathy, and risks of anesthesia.

To date, no study has investigated outcomes of the second-look procedure from a cost perspective. Our aim is to investigate the outcomes and cost of both single-stage and second-look approaches to cholesteatoma management.

MATERIALS AND METHODS

Patient Population

This study was reviewed and approved by the Duke University Institutional Review Board. We identified 420 adult and pediatric patients who underwent a tympanoplasty-mastoidectomy for cholesteatoma with a single-stage or second-look operative strategy from 2009 to 2014. During initial screening, patients were included if they had a canal wall-up (CWU) or canal wall-down (CWD) primary tympanoplasty-mastoidectomy for cholesteatoma with or without a second-look procedure. Patients were excluded if they had history of a prior tympanoplasty-mastoidectomy, insufficient or incomplete medical records, or procedure for a diagnosis other than cholesteatoma. There are two parameters guiding the decision to perform a second look. One parameter for a planed second look was if the surgeon believed not all cholesteatoma was removed. Another parameter for a second look was if there was evidence of excessive granulation and/or inflammation in the middle ear. In the event of excessive inflammation, our surgeons were concerned that a prosthesis would extrude. In these cases, reconstruction was planned to be completed at a second-look procedure.

Outcomes

Outcome variables tabulated included procedure approach, residual or recurrent cholesteatoma, ossicular chain reconstruction (OCR) frequency, and operative complications. Recurrent cholesteatoma was defined as having found cholesteatoma in a new retraction pocket.[3] Residual cholesteatoma was defined as cholesteatoma found in the middle ear space and secondary to incomplete disease resection.[3] Audiologic outcomes included pre-/postoperative and latest visit air bone gap (ABG) and word recognition scores (WRS). Air conduction and bone conduction thresholds were tabulated at .5, 1, 2, and 3 kHz.

Cost Analysis

The cost data included charges, direct costs, and indirect costs for consultation and follow-up visits, surgical procedures, computed tomography (CT) scans of the temporal bones, and audiology visits. Our financial services office defined charges as the amount billed to the patient or insurance payor for hospital services. Specific cost and charge definitions for each component of care are used internally within our hospital finance department. Total cost includes both direct costs and indirect costs. Direct costs are a product of a variable direct cost and fixed direct cost. These cost types are directly related to patient care, but variable direct costs, such as supplies and direct nursing care, fluctuate with patient volume. Fixed direct costs (e.g., nurse managers, depreciation of medical equipment) do not fluctuate to the same degree. Indirect costs include costs not directly related to patient care but relevant to the upkeep of the hospital and facilities (e.g., administrative salary, utilities, grounds landscaping, building depreciation). When performing the cost analysis comparing patients who have had a second-look procedure versus those who did not, we used charges to set the perspective from that of a patient or insurance payor. We did not account for the probability of complications or the cost of managing these complications in our cost analysis.

Statistics

Statistical analyses were completed using the JMP Pro 11 software suite (Cary, NC). Two-by-two contingency tables were created, and analysis of variance and Fisher's exact tests were performed as appropriate. P values were reported with statistical significance fixed at $P = 0.05$. Statistical analysis was reviewed and approved by a statistician.

RESULTS

We reviewed 420 patients who presented for a tympanoplasty-mastoidectomy at our institution. Of these patients, 314 were excluded and 106 were included in subsequent analyses. Of the included cases, 65 (61.3%) were male and 76 (71.7%) were of adult age, with an average age 36.5 years and range of 2 to 90 years old. The most common initial surgical approach was CWU with 80 (75.5%), followed by 19 (17.9%) CWD, six (5.6%) tympanoplasty only, and one (0.94%) transcanal.

For subsequent analyses, we focused on the 80 patients who underwent a CWU approach. Of these patients, 46 (57.5%) had a planned second-look procedure and 34 (42.5%) did not. When comparing CWU patients who had a planned second look versus no planned second look, there was no significant difference in any demographic variable, including age, % male gender, and ear sidedness.

In CWU patients who had a planned second-look strategy, 22 (47.8%) had cholesteatoma identified at their second-look procedure. At the second-look procedure, two (4.35% of second-look patients; 2.5% of all CWU cases) had recurrent cholesteatoma, and 20 (43.5% of second-look patients; 25% of all CWU cases) had residual cholesteatoma. In CWU patients who had no planned second look, four (7.5%) patients had an unanticipated second-look procedure frequency for clinical findings, suggestive of recurrent disease on a follow-up examination. All four of these patients had recurrent

TABLE I.
Audiometric Outcomes for CWU Patients Who Underwent Either Second Look or No Second-Look Operative Strategy.

	Mean (CI 95%)		
	No Second Look	Second Look	*P* Value*
Preoperative air bone gap	**21.2** (16.8–25.6)	**26.4** (22.8–30.1)	0.07
Preoperative WRS	**85.0** (77.9–92.0)	**92.8** (86.5–99.1)	0.10
Postoperative air bone gap	21.7 (17.1–26.2)	27.0 (23.2–30.8)	0.08
Postoperative WRS	83.2 (75.2–91.3)	91.0 (84.2–97.9)	0.14
Most recent air bone gap	**23.7** (18.3–29.1)	**28.2** (23.7–32.7)	0.21
Most recent WRS	**85.8** (77.1–94.5)	**90.5** (83.7–97.2)	0.40
WRS change preoperative to postoperative	−4.58 (−12.2–3.07)	−1.87 (−8.71–4.98)	0.60
WRS change postoperative latest	−2.48 (−8.87–3.91)	−1.27 (−6.61–4.08)	0.77
WRS change preoperative latest	−2.86 (−10.89–5.17)	−3.16(−9.77–3.45)	0.95

*One-way ANOVA. Two-tailed.
ANOVA = analysis of variance; CI = confidence interval; CWU = canal wall-up procedures; WRS = word recognition score.

cholesteatoma when taken to the operating room, and none had residual cholesteatoma.

There were three (3.8%) CWU patients who had a complication following their first tympanoplasty-mastoidectomy, including postoperative nausea and vomiting requiring admission, a tegmen defect with cerebrospinal fluid leak, and a surgical site infection. For CWU patients undergoing a second-look procedure, two (4.3%) patients experienced a complication including encephalocele and a wound seroma.

For the purposes of assessing the audiology outcomes, CWU patients were grouped into second-look and no second-look cohorts. When examining WRSs and ABGs at pre-, immediate postoperative, and the latest follow-up visits, there were no significant differences observed (Table I) ($P > 0.05$ for all variable pairs). In all CWU patients, no OCR was completed in 42 (52.5%) patients. Seven (8.8%) patients had OCR at a planned single-stage procedure and 31 (38.8%) at a planned second-look procedure. The pre- and posttreatment air conduction pure tone average and WRS results for all CWU patients are reported in supplemental figures (Figs. 1 and 2, respectively).

Charges and costs for the components of care were tabulated (Table II). The most expensive charge component was the surgical procedure, followed by the CT scan of the temporal bones. A cost analysis demonstrated that patients with a second-look strategy had a significantly higher number of postoperative visits compared to patients with no second look (10.4 visits vs. 6.32; $P = 0.0007$) (Table III). There was no significant difference in follow-up period, temporal bone CTs, and audiology clinic visits (each $P > 0.05$). Canal wall-up procedures patients with a second-look management strategy had a significantly higher cost of care versus patients with no second-look strategy (USD mean of $41,411 vs. $23,529; $P < 0.0001$).

DISCUSSION

The primary goal of cholesteatoma surgical management is to produce a safe ear, with a secondary goal to

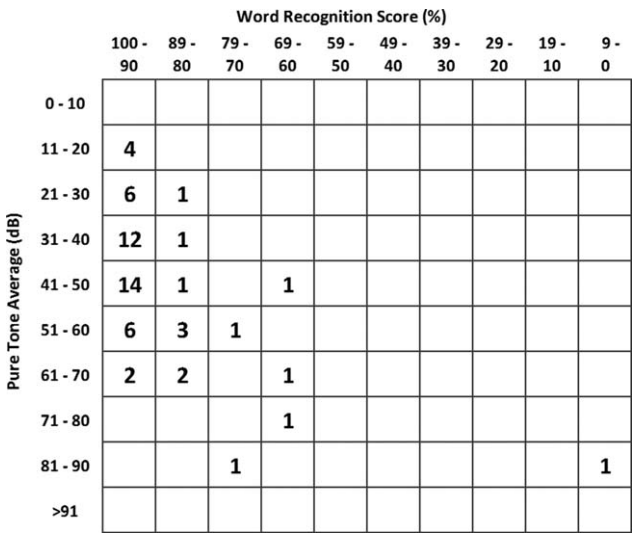

Fig. 1. Pretreatment pure tone average and word recognition score scattergram.

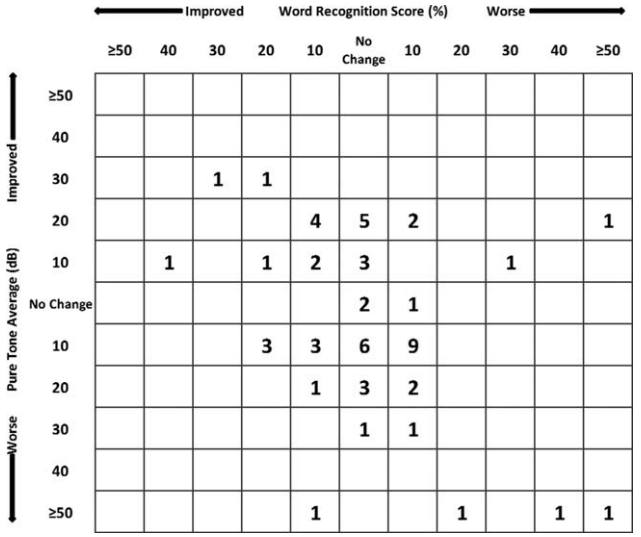

Fig. 2. Posttreatment pure tone average and word recognition score scattergram.

TABLE II.
Charges for Individual Components of Care.

	Mean (CI 95%), in $USD		
	Charges	Direct Cost	Total Cost
Consultation visit	**737.**	158.	270.
	(612.–861.)	(127.–189.5)	(222.5–318.0)
Surgical procedure	**16,032.**	3,196.	4,598.
	(14,707.–17,357.)	(2.899.–3,494.)	(4,672.–4,925.)
Postoperative visit	**244.**	38.	77.
	(175.–313.)	(27.–49.)	(54.–99.)
CT temporal bone	**2,231.**	194.	375.
	(1,987.–2,475.)	(151.–238.)	(319.–432.)
Audiology visit	**833.**	153.	282.
	(743.–923.)	(140.–165.)	(259.–305.)

Each dollar figure rounded to nearest whole dollar.
CI = confidence interval; CT = computed tomography; USD = U.S. dollar.

preserve or improve hearing.[16] Cholesteatoma removal can be a tedious undertaking, and there is a risk of recurrence or residual cholesteatoma left behind, despite best efforts. A second-look operative strategy after CWU tympanoplasty with mastoidectomy has been historically used to evaluate for recurrent or residual disease, as well as opportunity to perform OCR. However, there are significant differences in opinion among otologists regarding the optimal surgical strategy.[15] Compared to previously published studies of CWU and CWD approaches for cholesteatoma and recurrence incidence at second-look, our recurrence rate after CWU.[7–10] In our study, we found that cholesteatoma recurrence rate after primary CWU tympanoplasty-mastoidectomy in all patients is low at 2.5%, and 4.4% in the subgroup of patients who underwent a second-look strategy. In patients with no second look planned, 7.5% of patients required an unanticipated second-look procedure and recurrence was found in all, and none had residual. The patients who we included in our study had no prior otologic surgery. The majority of surgical procedures were performed by fellowship-trained neurotologists and were first attempts at surgical management. The follow-up interval was over 2.5 years for our single-stage cohort and over 3.5 years for our second-look patients.

Considering the low recurrence rate, automatic second-look procedures are not always necessary. In approximately half of our CWU patients, the decision not perform a second look was made due to high certainty that all cholesteatoma was removed at the original surgery. A small group of these CWU patients developed a recurrence, but none had evidence of residual cholesteatoma. We believe our follow-up time was sufficient to allow for recurrence or residual disease to declare itself. The other half of our patients had a planned second look because the surgeon deemed there was a high likelihood of incomplete resection at the original surgery. We found a high residual cholesteatoma rate in these patients. This indicates that performing a second-look is justified when the surgeon is not sure that all of the cholesteatoma was removed at the primary procedure.

We were not surprised that charges for the tympanoplasty with mastoidectomy procedure were the most expensive component of care. In general, operative procedures are among the more costly healthcare interventions owing to the substantial amount of human

TABLE III.
Cost of Care for Patients in Second-Look and No Second-Look Strategy Cohorts.

	No Second Look	Second Look	*P* Value*
Follow-up in days	916.0 (577.6–1254.5)	1312.6 (1018.4–1606.8)	0.08
Consultation clinic visits	1	1	–
Surgical procedures	1	2	–
Postoperative visits	6.32 (4.58–8.06)	10.4 (8.92–11.9)	**0.0007**
CT temporal bone, N	0.88 (0.56–1.2)	1 (0.73–1.27)	0.58
Audiology clinic visits	4.90(4.21–5.59)	3.88 (3.03–4.74)	0.07
Cost of care	**$ 23,529**.	**$41,411.**	**< .0001**
	(22,512.–24,547.)	(40,590.–42,231.)	

Each dollar figure rounded to nearest whole dollar.
*One-way ANOVA. Two-tailed
ANOVA = analysis of variance; CT = computed tomography.

resources and expertise, supplies, and facility requirements required for safe execution. As a result, operative procedures are a significant proportion of the healthcare cost burden. We found that the total charges of a second-look strategy are 76% higher than that of a single-look operative strategy, with arguably no benefit in recurrence rate. Moreover, every surgical procedure carries an inherent risk of a complication. The most important risks of a tympanoplasty-mastoidectomy to consider are facial nerve injury, violation of the bony labyrinth, vascular injury, and dehiscence of the tegmen. These complications beget further procedures and ultimately add costs. In our study, we had a relatively low complication rate; however, after a second procedure, one patient developed an encephalocele and another developed a wound seroma. Although meticulous surgical technique is a cornerstone to optimal outcomes and avoiding complications, surgical complications are best reduced by the reduction of unnecessary procedures.

Hearing preservation is a secondary goal of cholesteatoma removal because the risk of residual cholesteatoma outweighs the benefits of a conservative approach to removing components of the hearing apparatus. A purported benefit of utilizing a second-look strategy as a staged approach is reconstruction of the hearing apparatus, if needed. However, we were unable to find firm evidence substantiating the benefit of this rationale. In our study, we found that there were no significant differences in hearing outcomes between the second-look and single-stage strategies. In our opinion, ossicular chain reconstruction can be performed at the surgery if indicated, and need not be reserved for a separate operative procedure. Other investigators have also reported routinely performing OCR at the primary surgery.[8]

Our study has limitations that need mentioning. This is not a randomized control trial, so we cannot account for all possible confounding variables. We attempted to limit confounding variables and generate clean data by formulating strict inclusion criteria. This strict approach comes at the expense of being left with smaller cohorts of patients. We were also unable to account for the different surgical technique performed by our surgeons. Thus, we cannot explore if specific surgical techniques are responsible for our lower reported recurrent or residual cholesteatoma. We are also unable to characterize the severity of disease preoperatively. The initial burden of cholesteatoma may have an influence on the surgical technique utilized, as well as on recidivism. Lastly, because this is not a formal cost-effectiveness analysis, we are unable to provide a conclusion regarding which strategy is more cost-effective. We hope this study serves as a basis for a formal cost-effectiveness analysis and are in the process of designing such a study.

Considering the high cost of operative procedures and increased scrutiny on cost-effective care, the development of novel methods for evaluating for recurrent and residual cholesteatoma may gain traction. An emerging noninvasive modality for assessing cholesteatoma recidivism is with the use of specialized radiographic techniques. A recent systematic review has demonstrated that magnetic resonance imaging (MRI) with diffusion-weighted imaging may be a more practical method for assessing for cholesteatoma recidivism compared to a second-look procedure.[17,18] High-resolution CT is also being investigated as a potential alternative to a second-look operation; however, with possibly less specificity, sensitivity, and positive predictive value compared to MRI.[19] Middle ear endoscopy has also arisen as a useful tool for reducing cholesteatoma recidivism. A recent investigation has shown that a progressive hybrid transcanal-endoscopic approach yields cholesteatoma residual rates comparable to the CWD.[20] A systematic review has also found that endoscopy has been used as both an adjunct to the microscope or as the sole visualization instrument for improved cholesteatoma localization or for clinic surveillance.[21] Prospective studies with comparisons to traditional microscopy will be needed to substantiate the reported benefits. Moreover, future formal cost-effectiveness analyses of the optimal surgical management of cholesteatoma should include consideration of these adjunctive technologies and techniques.

If the surgeon is confident that no residual cholesteatoma remains, then an automatic second-look strategy is unnecessary and costly. If after an initial procedure the surgeon believes there is residual cholesteatoma despite best efforts, then a second-look strategy is likely worth the cost and risks of an additional procedure. Another reasonable indication for a second-look is if there is evidence of excessive inflammation in the middle ear that may compromise primary ossicular chain reconstruction. Considering the low rate of cholesteatoma recurrence and relatively high cost of care, implementation of a second-look strategy should be individually tailored and not universally performed. If we aim to narrow the scope of the second-look strategy and reap cost-savings in the management of cholesteatoma, further discussion is needed to achieve consensus on an acceptable cholesteatoma recurrence rate that balances safety and cost-effectiveness.

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BIBLIOGRAPHY

1. Smyth GD. Canal wall for cholesteatoma: up or down? Long-term results. *Am J Otol* 1985;6:1–2.
2. Mishiro Y, Sakagami M, Kitahara T, Kondoh K, Okumura S. The investigation of the recurrence rate of cholesteatoma using Kaplan-Meier survival analysis. *Otol Neurotol* 2008;29:803–806.
3. Farrior JB, Farrior JB. Recurrent and residual cholesteatoma. *Am J Otol* 1985;6:13–18.
4. Kinney SE. Intact canal wall tympanoplasty with mastoidectomy for cholesteatoma: long-term follow-up. *Laryngoscope* 1988;98:1190–1194.
5. Wilson KF, London NR, Shelton C. Tympanoplasty with intact canal wall mastoidectomy for cholesteatoma: long-term hearing outcomes. *Laryngoscope* 2013;123:3168–3171.
6. Tomlin J, Chang D, McCutcheon B, Harris J. Surgical technique and recurrence in cholesteatoma: a meta-analysis. *Audiol Neurootol* 2013;18: 135–142.
7. Barakate M, Bottrill I. Combined approach tympanoplasty for cholesteatoma: impact of middle-ear endoscopy. *J Laryngol Otol* 2008; 122:120–124.

8. Stew BT, Fishpool SJ, Clarke JD, Johnson PM. Can early second-look tympanoplasty reduce the rate of conversion to modified radical mastoidectomy? *Acta Otolaryngol* 2013;133:590–593.
9. Syms MJ, Luxford WM. Management of cholesteatoma: status of the canal wall. *Laryngoscope* 2003;113:443–448.
10. Wilson KF, Hoggan RN, Shelton C. Tympanoplasty with intact canal wall mastoidectomy for cholesteatoma: long-term surgical outcomes. *Otolaryngol Head Neck Surg* 2013;149:292–295.
11. Gaillardin L, Lescanne E, Moriniere S, Cottier JP, Robier A. Residual cholesteatoma: prevalence and location. Follow-up strategy in adults. *Eur Ann Otorhinolaryngol Head Neck Dis* 2012;129:136–140.
12. Ho SY, Kveton JF. Efficacy of the 2-staged procedure in the management of cholesteatoma. *Arch Otolaryngol Head Neck Surg* 2003; 129:541–545.
13. Neudert M, Lailach S, Lasurashvili N, Kemper M, Beleites T, Zahnert T. Cholesteatoma recidivism: comparison of three different surgical techniques. *Otol Neurotol* 2014;35:1801–1808.
14. Gyo K, Sasaki Y, Hinohira Y, Yanagihara N. Residue of middle ear cholesteatoma after intact canal wall tympanoplasty: surgical findings at one year. *Ann Otol Rhinol Laryngol* 1996;105:615–619.
15. Sheehy JL, Shelton C. Tympanoplasty: to stage or not to stage. *Otolaryngol Head Neck Surg* 1991;104:399–407.
16. Brown JS. A ten year statistical follow-up of 1142 consecutive cases of cholesteatoma: the closed vs. the open technique. *Laryngoscope* 1982;92: 390–396.
17. Jindal M, Riskalla A, Jiang D, Connor S, O'Connor AF. A systematic review of diffusion-weighted magnetic resonance imaging in the assessment of postoperative cholesteatoma. *Otol Neurotol* 2011;32:1243–1249.
18. Williams MT, Ayache D, Alberti C, et al. Detection of postoperative residual cholesteatoma with delayed contrast-enhanced MR imaging: initial findings. *Eur Radiol* 2003;13:169–174.
19. Songu M, Altay C, Onal K, et al. Correlation of computed tomography, echo-planar diffusion-weighted magnetic resonance imaging and surgical outcomes in middle ear cholesteatoma. *Acta Otolaryngol* 2015;135:776–780.
20. Hanna BM, Kivekas I, Wu YH, et al. Minimally invasive functional approach for cholesteatoma surgery. *Laryngoscope* 2014;124:2386–2392.
21. Kozin ED, Gulati S, Kaplan AB, et al. Systematic review of outcomes following observational and operative endoscopic middle ear surgery. *Laryngoscope* 2015;125:1205–1214.

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Systematic Review

The Disease Recurrence Rate After the Canal Wall Up or Canal Wall Down Technique in Adults

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Objectives/Hypothesis: To review which type of cholesteatoma surgery, canal wall up (CWU) or canal wall down (CWD), provides the lowest risk for residual and/or recurrent disease in adults with primary acquired cholesteatoma.

Data Sources: PubMed, Embase, CINAHL, the Cochrane Library, Scopus and Web of Science.

Study Design: We selected articles comparing CWU with CWD, reporting on disease recidivism (combined residual and recurrent disease) or independent residual or disease recurrence rates. We included studies with a moderate to high relevance.

Results: Our search yielded 2,060 articles. We selected seven studies that carried a moderate risk of bias. Six studies described higher disease recidivism after the CWU procedure [16.7–61.0%] compared to the CWD technique [0–13.2%]. Four studies showed statistical significant difference ($P < .05$). One study showed opposite results: recidivism was found in 7.8% CWU and in 22.1% CWD cases ($P < .001$). Studies showed CWU recidivism more likely to be residual disease, whereas CWD recidivism tended to be recurrent disease.

Conclusion: The majority of included studies showed CWU to result in more disease recidivism compared to the CWD technique in adult patients with a primary acquired cholesteatoma. If recidivism risk is the most important factor to consider a certain surgical technique, we recommend application of the CWD procedure. However, many additional factors in patient care will define the best treatment decision, such as residual hearing and access to health care. Our recommendations are based on Level II evidence, which underlines the need for future high-level evidence studies.

Key Words: Cholesteatoma, recurrence, residual disease, canal wall up, canal wall down, hearing outcome, hearing loss.

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INTRODUCTION

Cholesteatoma is a cystic lesion formed from keratinizing stratified squamous epithelium.[1] The disease entity can be divided into congenital and acquired disease. Acquired cholesteatomas can be divided into primary and secondary cholesteatoma: disease enters the middle ear in primary cholesteatoma either through the weakest location of the tympanic membrane (Shrapnell's membrane) or medially to the posterior–superior quadrant of the tympanic membrane (TM)[2,3]; in secondary cholesteatoma, however, squamous epithelium migrates to the middle ear by an iatrogenic or traumatic TM perforation. Both primary and secondary cholesteatoma therapy consist of surgical removal. Two main surgical techniques are the canal wall down (CWD) and the canal wall up (CWU) procedure. With the CWD procedure, the posterior auditory canal wall is removed, whereas it remains intact during the CWU procedure. The disadvantage of CWD is that an open cavity remains, necessitating hospital follow-up for earwax removal and cleaning, possible cavity infection and/or recurrence checkups and lifestyle adjustments.[4,5] Although CWU avoids these consequences, the intact canal wall might deter intraoperative visualization for complete cholesteatoma removal. This could result in a higher risk of residual disease.[3,4] Furthermore, since the original anatomy is left intact, the recurrent disease risk might be higher. Current literature often fails to make a distinction between residual and recurrent disease.[6,7] Residual cholesteatoma is defined as nonradically removed *epidermoid cells*. Alternatively, a new retraction pocket containing keratin could arise and develop into a secondary episode of cholesteatoma: recurrence.[8] Cholesteatoma behind the epitympanum could be suggestive for recurrent disease.[9] However, cholesteatoma found behind the mesotympanum mainly contains residual

Additional supporting information may be found in the online version of this article.

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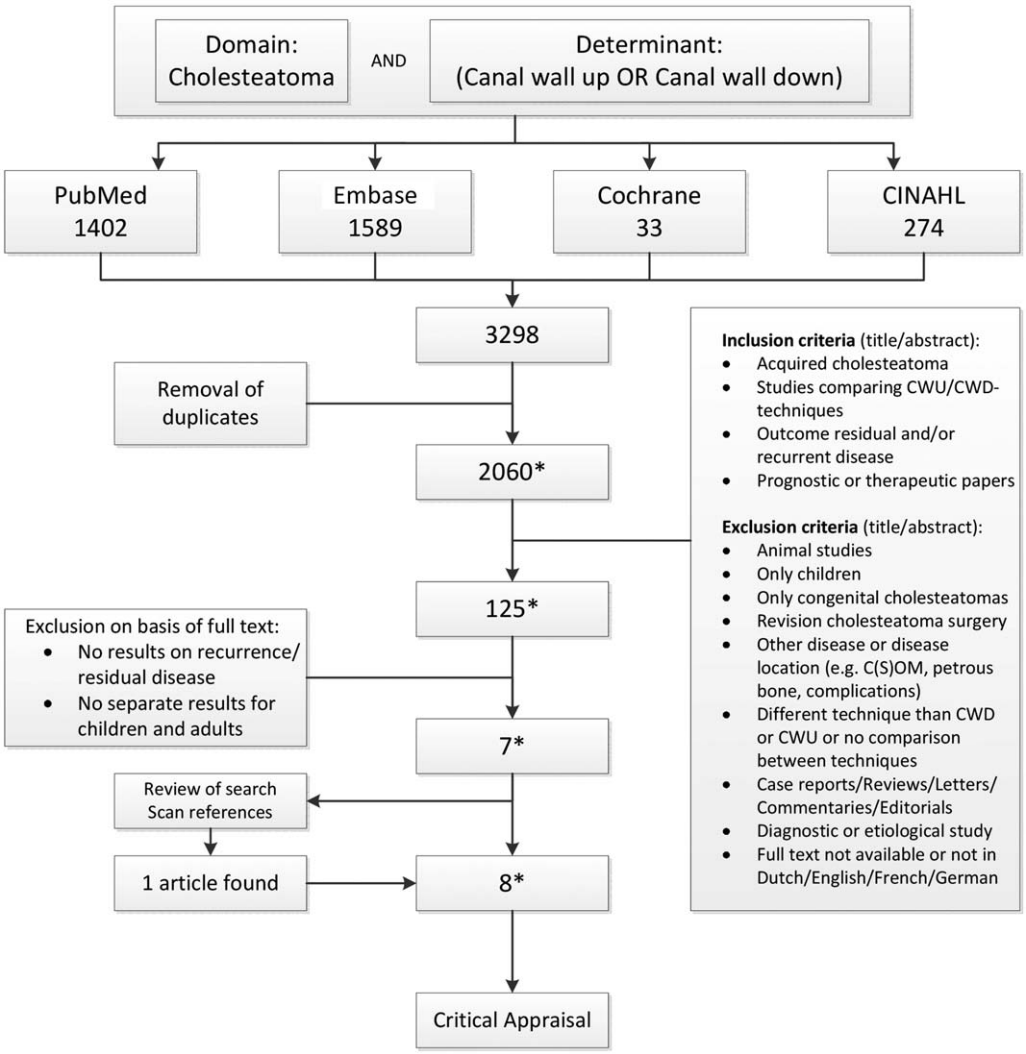

Fig. 1. Flowchart for study selection. Literature search performed on the 10th of December, 2014.
After removal of duplicates, screening on title and abstract using the inclusion and exclusion criteria, screening on full-text and study assessment, 8 articles remained for critical appraisal.
Legend: CINAHL = Cumulative Index to Nursing and Allied Health Literature; C(S)OM = chronic (suppurative) otitis media, CWD = canal wall down, CWU = canal wall up.
*All inclusions and exclusions were made by consensus of at least two authors.

disease.[9] In the current review, we will use recidivism as a complete term for both residual and recurrent disease.[10] We aim to identify which cholesteatoma removal technique, CWU or CWD surgery, results in the lowest rate of cholesteatoma recidivism in adult patients with a primary acquired cholesteatoma. We expect the CWD technique to have a lower cholesteatoma recidivism risk.

MATERIALS AND METHODS

Search Strategy

We conducted a search in the PubMed, Embase, Cochrane and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases on December 10th, 2014. Our search syntax is provided in the Appendix (available online only). Both title/abstract and full-text screening were based on predefined inclusion and exclusion criteria and performed by a combination of at least two authors (combination of K.G.P.K., M.B.J.K., T.H.L.vS., S.J.A.V.) (Fig. 1). Studies that compared residual and recurrent risks of both cholesteatoma removal techniques (CWU and CWD) in adult patients with primary cholesteatoma were selected. We excluded studies applying partly performed CWU techniques.[11] We reviewed references of included articles and used Scopus and Web of Science to apply a cross-reference check.

Quality Assessment

We constructed a critical appraisal tool (CAT) to verify the relevance and validity of included studies (Table I). A minimal of two authors (combination of K.G.P.K., M.B.J.K., S.J.A.V., T.H.L.vS.) appraised included studies. Relevance of determinant (CWU or CWD) was not assessed because all studies with an undefined determinant were excluded at the initial screening (title/abstract and full-text screening). We considered the following factors important during CAT screening: 1) definition of patients' age, 2) reported length of follow-up and 3) distinction between residual and recurrent disease. Firstly, definition of age was important because the incidence of disease recidivism

TABLE I.
Study Assessment of Studies Comparing Recurrence Rates Between the CWU Technique and the CWD Technique.

			Domain				Outcome			Selection Bias		Information bias		Confounding	
Author (publication year)	Design	No.	Age*	Acquired	First	Baseline Charact.	Recurrent/ Residual Disease*	FU Duration*	Rel.	Loss to FU*	Missing Data*	Standardization Determinant	Standardization Outcome	Confounding by Indication*	Val.
Palmgren (1979)[20]	RCS	347	–	?	?	–	±	+	M	+	–	±	±	–	M
Brown (1982)[6]	RCS	1142	–	?	?	±	±	+	M	–	–	+	–	–	L
Roden (1996)[18]	RCS	97	+	?	–	±	+	–	M	–	±	–	±	±	L
Nyrop (1997)[7]	RCS	85	–	+	?	±	±	±	M	±	–	±	+	+	M
Ajalloueyan (2006)[19]	RCS	108	–	?	?	+	±	+	M	–	–	+	–	±	L
Stankovic (2007)[15]	PCS	758	–	?	?	±	+	±	M	+	+	±	–	±	M
Declerck (2010)[4]	RCS	161	+	+	?	±	+	±	H	–	±	–	+	–	L
Charachon (1980)[17]	*RCS*	*211*	–	*?*	*?*	±	–	+	*L*	+	–	±	±	–	*M*

*Priority items.

Legend: charact. = characteristics; CWU = canal wall up; CWD = canal wall down; FU = follow-up; H = high; L = low; M = moderate; No. = number of patients; PCS = prospective cohort study; RCS = retrospective cohort study; Rel. = relevance; Val. = validity.

Domain

Age: + = only adults (≥ 18 years old) included; – = also adolescents (14–17 years old) included. Acquired: + = only acquired cholesteatoma mentioned; – = acquired and congenital; ? = not reported. First: + = primary surgery only; – = reoperations included; ? = not reported. Baseline characteristics: + = complete and equally distributed; ± = incomplete or unequally distributed; – = absent.

Outcome

Recurrent/residual disease: + = reported separately; ± = combined data; – = only data of residual disease. Follow-up duration: + = > 5 years; ± = 2−5 years; – = < 2 years.

Selection Bias

Loss to follow-up: + = ≤ 20%; ± = > 20%; − = not available. Missing data: + = reported and quantified, method of handling described; ± = reported and quantified, method of handling not described; − = not reported.

Information Bias

Standardization determinant: + = according to protocol, well described; ± = according to protocol; – = no protocol. Standardization outcome: + = according to protocol, well described; ± = according to protocol; − = no protocol.

Confounding

Confounding by indication: + = no confounding by indication; ± = confounding present but well documented; − = confounding poorly documented.

Overall Relevance

+ = 1 point; ± = 0.5 point; − or ? = 0 points. For priority items: + = 2 points; ± = 1 point; − or ? = 0 points. L = 0–2.5 points; M = 3–5.5 points; H = ≥ 6 points.

Overall Validity

+ = 1 point; ± = 0.5 point; − or ? = 0 points. For priority items: + = 2 points; ± = 1 point; − or ? = 0 points. L = 0–2.5 points; M = 3–5.5 points; H = ≥ 6 points

is higher in younger (< 9 years) than in older CWU patients.[12] Secondly, the ratio between residual and recurrent disease might depend on follow-up length. Therefore, a 5-year follow-up is essential to evaluate both types of disease recurrence.[7,13,14] Thirdly, distinction within the study between residual and recurrent disease was important because of different key aspects in etiology.[8] The aforementioned items for relevance were appointed priority items (see Table I, marked with *). Priority items for validity were: "loss to follow-up", "missing data", and "confounding by indication". Both a high loss to follow-up percentage and missing data could lead to biased outcomes. In the third place, confounding by indication is important because severe cholesteatoma cases tend to be treated by CWD rather than CWU.[15] Subsequent to scoring each individual CAT item, studies received an overall score for both relevance and validity: low (L) (0–2.5 points), moderate (M) (3–5.5 points) or high (H) (≥ 6 points) (Table I). Articles received 1 point per item when a plus (+) was scored and 0.5 point when a plus/minus (±) was scored; priority items received double points. We selected studies with a moderate to high relevance for inclusion in the current review.

Calculations and Statistics

We performed statistical pooling of data when there was similarity between studies in: patients' age groups, applied outcome measures, type of applied statistical analysis and elected follow-up moments. We used Review Manager (RevMan) 5.3 software to establish analysis (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We preserved meta-analysis results when the I^2 was between 0% and 40%.[16] We extracted original data from included studies to calculate the absolute risk reduction (ARR) and relative risk (RR). We used the Fisher's exact test in SPSS 22 (IBM Corp., Armonk, NY) to calculate *P* values. We considered a value of $P < .05$ significant.

RESULTS

Retrieving Studies

We retrieved a total of 2,060 articles, which were all screened by evaluating the title and abstract. From this process, 125 articles were selected for full-text screening (Fig. 1). We considered seven articles eligible to answer our research question (Fig. 1). Snowballing revealed an eighth article[4], a master's thesis, which was not indexed in selected databases (Fig. 1). Reverse snowballing revealed no additional articles.

Assessing Studies

The overall relevance was moderate in six studies (Table I). One study[4] scored high and one study[17] scored low on relevance. The overall validity of the retrieved studies was graded low to moderate (Table I). Publication years of the articles ranged from 1979 to 2010. Two studies included only adults in their studied cohort.[4,18] In addition, two studies only included acquired cholesteatomas.[4,7] Seven studies did not report whether reoperations were included. Only one study[19] provided well-described baseline characteristics. Three studies defined the difference between residual and recurrent disease[4,15,18] (Table III). The follow-up duration was at least 5 years in four studies.[6,17,19,20] In only three studies, all patients were operated on by the same surgeon.[7,15,18] In four studies[7,15,17,20] the overall validity was moderate; whereas it was low in the remaining studies.[4,6,18,19] Loss to follow-up was 20% or less in three studies[15,17,20] and the method of handling of missing data was reported in only one study.[15] In two studies,[6,19] the operation technique was described in a protocol. In the study of Brown[6], the elected surgical technique for cholesteatoma removal was the intact canal wall tympanoplasty and mastoidectomy, as advocated by House and Sheehy.[21] Only one of our included studies (Ajalloueyan[19]) applied an obliteration technique, published previously by Quaranta et al.[22] In the remaining four studies[7,15,17,20], the operation protocols were not clearly defined. The method of determining whether cholesteatoma recidivism had developed, occurred according to a well-defined protocol in two studies.[6,19] Seven articles were biased by confounding by indication.[4,6,15,17–20] We excluded one of the eight studies[17] with a low relevance: report of adult residual disease only. Conclusions are based on the remaining seven included studies with a moderate to high relevance (Table I). The study reported by Declerck[4] seemed to be the most relevant to answer our research query because adult patients with an acquired cholesteatoma were included. However, the studies of Nyrop[7] and Stankovic[15] scored the highest values on validity in our CAT (Table I). Therefore, results from the latter two studies were suggested to provide the most unbiased insight. There was a high amount of statistical heterogeneity in the reported risk differences ($I^2 = 96\%$). We decided not to include Palmgren's study[20] in the heterogeneity analysis because patient numbers could not be derived from recurrence percentages. In addition, we defined whether heterogeneity was different for residual or recurrence numbers of the six studies: 89% and 92%, respectively. We considered an I^2 below 40% to be acceptable; therefore, we decided not to pool results.

Data Extraction

The extracted data are presented in Tables II and III. The selected studies included 1,268 operated ears for the CWU group and 1,038 ears for the CWD group (Table II). The follow-up ranged between 6 months and 10 years. Two studies[4,18] reported results for patients above 18 years and four studies reported results for patients over 15 years.[6,7,15,19] The remaining study[20] mentioned the mean ages of the youngest 50 patients and the oldest 50 patients (Table II). The data of the study of Declerck[4] are displayed in separate rows because one group was followed until the second-look operation and the second had a longer follow-up (mean follow-up: 2.5 years) (Table II). Six articles[4,6,7,18–20] reported a higher percentage of disease recidivism after the CWU (range 15% to 61%) than after the CWD procedure (0 to 13%) (Table II). Four of these differences were statistically significant (Table II). Contrarily, Stankovic[15] reported disease recidivism of 8% after the CWU and 22% after the CWD technique ($P < .001$). Both the absolute risk reduction (ARR range −14% to 61%) and the

TABLE II.
Results of Studies Comparing Disease Recidivism Rates Between the CWU Technique and the CWD Technique.

		Study Population					Residual/Recurrent Risk			
Article		No. of Ears*	CWU/CWD	Follow-up (mean, yr.)	Age Range (yr.)	CWU No. (%)	CWD No. (%)	Absolute Risk Reduction % (95% CI)	*P* Value	Relative Risk (95 % CI)
Palmgren (1979)[20]		194	50/144	9.4	n/a[†]	n/a (15)	(6%)	9 (n/a)	NS[‡]	2.5 (n/a)
Brown (1982)[6]		1044	628/416	10	15 to 75	214 (34.1)	54 (13)	21 (16 to 26%)	<.001	2.6 (2.0 to 3.4)
Roden (1996)[18]		97	54/43	0.5 to 5	19 to 85	11 (20.4)	2 (4.7)	16 (3 to 28%)	.03	4.4 (1.0 to 18.7)
Nyrop (1997)[7]		58	41/17	10	15 to 77	25 (61.0)	0 (0)	61 (46 to 76%)	<.001	n/a
Ajalloueyan (2006)[19]		108	36/72	10	16 to 81	6 (16.7)	4 (5.6)	11 (−2 to 24%)	.08	3.0 (0.9 to 10.0)
Stankovic (2007)[15]		658	360/298	3	> 16	28 (7.8)	66 (22.1)	−14 (−20 to −9%)	<.001	0.35 (0.23 to 0.53)
Declerck (2010)[4]	2nd look	88	74/14	1 to 1.2	18 to 84	19 (25.7)	0 (0)	26 (16 to 36%)	.03	n/a
	Total	165	117/48	2.5	18 to 84	21(18.9)[§]	0 (0)	19 (12 to 26%)	.001	n/a

*Adult cases only.
[†]No exact age range reported. Mean ages for the youngest 50 and the oldest 50 patients: 21 and 55 years, respectively.
[‡]No exact patient numbers reported.
[§]111 patients had follow-up.
CI = confidence interval; CWD = canal wall down; CWU = canal wall up; No. = number; n/a = not available/applicable; NS = not significant; yr. = year.

TABLE III.
Outcomes of Studies Comparing the CWU Technique and the CWD Technique and Making a Distinction Between Residual and Recurrent Disease Rates.

				CWU Technique No. (%)		CWD Technique No. (%)		Risk Difference (95% CI)		Relative Risk (95% CI)	
Article	No.*	CWU/ CWD	FU (mo.)	Residual	Recurrent	Residual	Recurrent	Residual	Recurrent	Residual	Recurrent
Roden (1996)[18]	97	54/43	6 to 60	11 (20.4%)	0 (0%)	2 (4.7%)	0 (0%)	16% (3 to 28%)	0% (0%)	4.4 (1.0 to 8.7)	n/a
Stankovic (2007)[15]	658	360/298	36	11 (3.1%)	17 (4.7%)	21 (7.0%)	45 (15.1%)	−4% (−7 to 1%)	−10% (−15 to 6%)	0.43 (0.21 to 0.88)	0.31 (0.18 to 0.53)
Declerck (2010)[4] 2nd look	88	74/14	CWU: 12 CWD: 14	13 (17.6%)	6 (8.1%)	0 (0%)	0 (0%)	18% (9 to 26%)	8% (2 to 14%)	n/a	n/a

CI = confidence interval; CWD = canal wall down; CWU = canal wall up; FU = follow-up; mo. = months; No. = Number; n/a = not available/applicable; No.* = number of operated ears.

relative risk (RR range 0.35 to 4.4) varied greatly between studies[4,6,7,15,18] (Table II). This indicates that studies showed different results on which surgical procedure would result in the lowest disease recidivism percentage. Nyrop and Bonding[7] reported the largest absolute risk reduction: 61% (46% to 76%) in favor of the CWD procedure.

We identified three articles that made a distinction between residual and recurrent disease[4,15,18] (Table III). Roden et al.[18] found a significant higher risk of residual disease in the CWU group (20.4% vs. 4.7%, P =.03). Recurrence risks between both techniques were equal (Table III). Similarly, Declerck found more residual disease after the CWU procedure (17.6% vs. 0%).[4] However, also more recurrent disease was found after the CWU procedure (8.1% vs. 0%) (Table III).[4] Stankovic showed opposite results: less residual (3.1% vs. 7.0%) and recurrent disease (4.7% vs. 15.1%) occurred in the CWU group (Table III).[15] We used data from the latter three studies to calculate the risk difference and relative risk for cholesteatoma residual and recurrent disease (Table III). Two studies showed a risk difference in favor of CWD for residual disease: 16% and 18%, respectively.[4,18] In addition, recurrent disease risk difference showed to be in favor of CWD in the studies of Declerck[4] (8%) and Roden et al.[18] (4.4%) (Table III). Contrarily, Stankovic[15] found a risk difference in favor of CWU for both residual (risk reduction −4%; relative risk 0.43) and recurrent disease (risk reduction −10%; relative risk 0.31) (Table III).

DISCUSSION

We reviewed the literature to assess which surgical removal technique for adult acquired cholesteatoma (CWU or CWD) provided the lowest rate of disease recidivism. The number of available studies was substantial. The seven included studies were all of moderate or high relavance. However, the validity of included studies ranged from low to moderate.

The majority of included studies showed that adult cholesteatoma patients suffer from a higher recidivism risk after the CWU procedure as compared to the CWD procedure. Three studies[4,15,18] reported on residual and recurrent disease rates independently. Canal wall up recidivism was more likely to be residual disease, whereas CWD recidivism tended to be recurrent disease. Because CWU is not performed in severe cases in common practice, and the feasibility of performing CWU or CWD is related to the severity of the disease, confounding by indication might have masked even higher disease recidivism percentages.[23] This confounding could explain heterogeneity in our results: Stankovic[15] showed significant results in favor of CWU. In this study, severity of the disease was different between study populations; extensive disease, a small mastoid and a damaged posterior wall were indications for CWD surgery. Only Nyrop and Bonding's study[7] was unaffected by confounding by indication. Authors described CWU and CWD groups to be similar regarding the extent of cholesteatoma disease. The latter results showed higher CWU recidivism rates compared to results from the CWD technique ($P < .0001$). Because Nyrop and Bonding's study[7] provided the most unbiased insight according to our CAT, we recommend that the CWD procedure should be performed in adult patients with acquired cholesteatoma.

Tomlin et al.[5] performed a meta-analysis on the risk of cholesteatoma recidivism after CWU and CWD. Authors reported a lower percentage of residual and recurrent disease after CWD (range 5% to 17%) compared to CWU surgery (range 9% to 70%). The relative risk of recurrent or residual disease was 2.87 (95% confidence interval: 2.45 to 3.37) after CWU compared to CWD. The results of Tomlin et al.[5] are in line with our findings, although the inclusion of Stankovic's article[15] in the current review introduces new uncertainty about the generalizability of reported surgical outcomes. Tomlin et al.[5] included 13 articles, of which three were included in our study.[6,7,18] In contrast to Tomlin et al.,[5] results from our selected studies could not be pooled in meta-analysis, a difference that marks a more heterogeneous and different retrieval of literature. Similar to their included studies,[5] none of our included studies mentioned the use of magnetic resonance imaging (MRI) in detecting cholesteatoma recidivism in CWU patients. This could be explained by recent MRI use in CWU follow-up, whereas the majority of included studies was performed before 2006 and consisted of retrospective case series of earlier performed surgeries. Compared to Tomlin's study, we provide additional insight because we excluded children, and in addition calculated relative risks and absolute risk reductions (both significant in five out of seven selected studies[4,6,7,15,18]).

Risk of Bias

In interpreting the findings, the following considerations need to be taken into account. Firstly, included studies differed in their methods of follow-up. Studies with a shorter duration of follow-up might have been subjected to bias in favor of CWU.[4,7,15,18]

Secondly, in the detection of residual or recurrent cholesteatoma, second-look surgery is a more sensitive method compared to clinical examination in CWU patients.[24] Therefore, results of the study that applied second-look surgery[4] might be influenced by the higher sensitivity of confirmation of disease recidivism. However, diffusion-weighted MRI is expected to replace second-look surgery completely to detect cholesteatoma recidivism in the near future.[5] Diffusion-weighted imaging has shown to have high sensitivity and specificity for detecting cholesteatoma, especially nonecho planar diffusion-weighted MRI.[25] Lastly, surgical experience needs to be taken into consideration, because differences in skills can lead to different outcomes. However, none of our included studies mentioned the experience of the surgeons. Therefore, we cannot exclude the possibility of one surgeon achieving superior results when applying either one of the techniques.

Surgical Considerations

Several factors need to be taken into account when opting for a CWU or CWD operation: hearing outcome,

consequences of an open cavity and cost-effectiveness. Three included articles assessed postoperative hearing outcomes, measured by air bone gap in two studies[4,18] and air conduction in the remaining study.[19] Although no general conclusion on hearing outcomes can be drawn from results of these studies, none of the three studies reported significant differences between techniques.[4,18,19] A quality-of-life study[26] compared interference with social activities between 50 CWU and 50 CWD patients: 16% of the CWU patients and 24% of the CWD patients reported interference with daily activities (not significant).

It is essential to clarify that the operation technique is not the only factor influencing the risk of cholesteatoma recidivism. In addition, this risk is affected by the extent of the disease[27–30] (especially mastoid extension[31]), ossicular chain disruption,[29,30,32–34] cholesteatoma location[27,34,35] and preoperative ear discharge.[27,35] However, it should be emphasized that all studies investigating the aforementioned risk factors included only children[29–33,35] or studied a population consisting of both children and adults.[27,28] Therefore, the question remains whether these results can be extrapolated to an adult cholesteatoma population. Six of the included studies[4,6,7,15,19,20] collected data on the presence of the aforementioned risk factors. However, three studies[6,7,20] did not mention the possible influence of these factors on the cholesteatoma recidivism risk: 1) Palmgren[20] recorded data regarding ear discharge and ossicular chain disruption; 2) Brown[6] collected information about the extent and location of disease; and 3) Nyrop and Bonding[7] recorded the extent and location of cholesteatoma, as well as ossicular chain disruption. The remaining three studies[4,15,19] did mention risk factor influence on disease recidivism. 1) In the study of Declerck,[4] significantly more recidivism occurred in pars tensa cholesteatoma compared to pars flaccida cholesteatoma. 2) Similarly, Stankovic[15] found more cases of disease recidivism in patients with pars tensa cholesteatoma compared to patients with attic or sinus tympani cholesteatoma. 3) Ajalloueyan[19] stated that ear discharge, especially in combination with TM retraction, is a major predisposing factor for recurrence. Therefore, pars tensa cholesteatoma showed to be an important additional recidivism risk factor in two studies[4,15] and ear discharge in one study, especially in combination with TM retraction.[19] Currently, new surgical techniques are being developed to be applied in cholesteatoma surgery, for example, intraoperative otoendoscopy to improve visualization intraoperatively.[36] However, these new developments are not yet applied worldwide; the additional benefits of these newer procedures must be elucidated in the future.

Strengths and Weaknesses

The strength of this study is the extensive literature search, even identifying a nonindexed study. Also, we provide specific patient information on disease recidivism after cholesteatoma surgery by 1) exclusively presenting data concerning adolescents and adults and 2) making a distinction between residual and recurrent disease rates. We constructed our own CAT; however, we believe we performed a thorough relevance and validity assessment that reassures transparent assessment of retrieved studies. A remark needs to be made regarding the limited level of identified evidence. Articles scored low on overall validity (Table I). Loss to follow-up and handling of missing data were often not described and confounding by indication makes it hard to draw accurate conclusions about recidivism risks. This is not necessarily a limitation of our study but rather a limitation of the current available evidence. Although standardized research methods of evidence-based medicine are increasingly being used since 2000,[37] studies published after this year still not all provided high validity in their reported results. Except for one study,[15] all included articles were retrospective case series (Table I). Therefore, we recommend that a randomized controlled trial (RCT) should be performed in which cholesteatoma disease residue and recurrence risks are compared between both surgical procedures at 5-year follow-up. Only cholesteatoma patients who are eligible for undergoing both surgical removal techniques (CWU and CWD) should be included.

CONCLUSION

In conclusion, the majority of included studies showed more cholesteatoma recidivism after the CWU technique than after the CWD technique in adult patients at 5-year follow-up. Studies showed that CWU recidivism was more likely to be residual disease, whereas CWD recidivism tended to be recurrent disease. Besides the elected surgical technique, the risk for cholesteatoma recidivism could be influenced by the extent of the disease, the cholesteatoma location (pars tensa) and presentation of preoperative ear discharge. Therefore, if one or more of these factors are present, a high cholesteatoma recidivism risk could exist, and we recommend that a CWD procedure should be performed. In addition, factors such as residual hearing need to be taken into account when opting for the surgical technique. Our recommendation is based on level II evidence, which underlines the need for an RCT to clarify disease recidivism after cholesteatoma removal by either the CWU or CWD technique.

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BIBLIOGRAPHY

1. Semaan MT, Megerian CA. The pathophysiology of cholesteatoma. *Otolaryngol Clin North Am* 2006;39:1143–1159.
2. Ramakrishnan Y, Kotecha A, Bowdler DA. A review of retraction pockets: past, present and future management. *J Laryngol Otol* 2007;121:521–525.
3. Heyning P Van de, Mulder JS. Aandoeningen van het trommelvlies en het middenoor. In: Huizing EH, Snow GB, Vries Nd, Graamans K, Heyning P Van de, eds. Keel-neus-oorheelkunde en hoofd-halschirurgie. 1st ed. Houten, The Netherlands: Bohn Stafleu van Loghum; 2009:61–78.
4. Declerck T. *Resultaten na cholesteatoomchirurgie: Een retrospectieve analyse*. 2010. Available at: http://lib.ugent.be/fulltxt/RUG01/001/458/841/RUG01-001458841_2011_0001_AC.pdf. Accessed September 3, 2014.

5. Tomlin J, Chang D, McCutcheon B, Harris J. Surgical technique and recurrence in cholesteatoma: a meta-analysis. *Audiol Neurootol* 2013;18: 135–142.
6. Brown JS. A ten year statistical follow-up of 1142 consecutive cases of cholesteatoma: the closed vs. the open technique. *Laryngoscope* 1982;92: 390–396.
7. Nyrop M, Bonding P. Extensive cholesteatoma: Long-term results of three surgical techniques. *J Laryngol Otol* 1997;111:521–526.
8. Kos MI, Castrillon R, Montandon P, Guyot JP. Anatomic and functional long-term results of canal wall-down mastoidectomy. *Ann Otol Rhinol Laryngol* 2004;113:872–876.
9. Jackler RK. The surgical anatomy of cholesteatoma. *Otolaryngol Clin North Am* 1989;22:883–896.
10. Neudert M, Lailach S, Lasurashvili N, Kemper M, Beleites T, Zahnert T. Cholesteatoma recidivism: comparison of three different surgical techniques. *Otol Neurotol* 2014;35:1801–1808.
11. Kuo CL, Liao WH, Shiao AS. A review of current progress in acquired cholesteatoma management. *Eur Arch Otorhinolaryngol.* 2014. Epub ahead of print.
12. Abramson M, Lachenbruch PA, Press BH, McCabe BF. Results of conservative surgery for middle ear cholesteatoma. *Laryngoscope* 1977;87:1281–1287.
13. Yang WY, Watson C. Post-operative follow up of cholesteatoma-how long is adequate? *Clin Otolaryngol* 2012;37:160.
14. Lau T, Tos M. Tensa retraction cholesteatoma: treatment and long-term results. *J Laryngol Otol* 1989;103:149–157.
15. Stankovic M. Follow-up of cholesteatoma surgery: open versus closed tympanoplasty. *ORL J Otorhinolaryngol Relat Spec* 2007;69:299–305.
16. *Cochrane Handbook*. 9.5.2 identifying and measuring heterogeneity. http://handbook.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm. Accessed January 13, 2015.
17. Charachon R, Roux O, Eyraud S. Cholesteatoma of the middle ear. Choice of technique and results in the adult and child. *Ann Otolaryngol Chir Cervicofac* 1980;97:65–78.
18. Roden D, Honrubia VF, Wiet R. Outcome of residual cholesteatoma and hearing in mastoid surgery. *J Otolaryngol* 1996;25:178–181.
19. Ajalloueyan M. Surgery in cholesteatoma: ten years follow-up. *Iran J Med Sci* 2006;31:37–40.
20. Palmgren O. Long-term results of open cavity and tympanomastoid surgery of the chronic ear. *Acta Otolaryngol* 1979;88:343–349.
21. House WF, Sheehy JL. Functional restoration in tympanoplasty. *Arch Otolaryngol* 1963;78:304–309.
22. Quaranta A, Cassano P, Carbonara G. Cholesteatoma surgery: Open vs closed tympanoplasty. *Am J Otol* 1988;9:229–231.
23. Ikeda M, Yoshida S, Ikui A, Shigihara S. Canal wall down tympanoplasty with canal reconstruction for middle-ear cholesteatoma: postoperative hearing, cholesteatoma recurrence, and status of reaeration of reconstructed middle-ear cavity. *J Laryngol Otol* 2003;117: 249–255.
24. Gerlach H. Is the "second look" justified after cholesteatoma surgery according to the closed technique? (our concept of "indicator-pearl"). *Laryngol Rhinol Otol (Stuttg)* 1982;61:294–296.
25. Elefante A, Cavaliere M, Russo C, et al. Diffusion weighted MR imaging of primary and recurrent middle ear cholesteatoma: an assessment by readers with different expertise. *Biomed Res Int* 2015;2015:597896.
26. Quaranta N, Iannuzzi L, Petrone P, D'Elia A, Quaranta A. Quality of life after cholesteatoma surgery: intact-canal wall tympanoplasty versus canal wall-down tympanoplasty with mastoid obliteration. *Ann Otol Rhinol Laryngol* 2014;123:89–93.
27. Vartiainen E. Factors associated with recurrence of cholesteatoma. *J Laryngol Otol* 1995;109:590–592.
28. Lynrah ZA, Bakshi J, Panda NK, Khandelwal NK. Aggressiveness of pediatric cholesteatoma. Do we have an evidence? *Indian J Otolaryngol Head Neck Surg* 2013;65:264–268.
29. Stapleton AL, Egloff AM, Yellon RF. Congenital cholesteatoma: predictors for residual disease and hearing outcomes. *Arch Otolaryngol Head Neck Surg* 2012;138:280–285.
30. Visvanathan V, Kubba H, Morrissey MS. Cholesteatoma surgery in children: 10-year retrospective review. *J Laryngol Otol* 2012;126:450–453.
31. Ahn SH, Oh SH, Chang SO, Kim CS. Prognostic factors of recidivism in pediatric cholesteatoma surgery. *Int J Pediatr Otorhinolaryngol* 2003;67: 1325–1330.
32. Lazard DS, Roger G, Denoyelle F, Chauvin P, Garabedian EN. Congenital cholesteatoma: risk factors for residual disease and retraction pockets—a report on 117 cases. *Laryngoscope* 2007;117:634–637.
33. Stangerup SE, Drozdziewicz D, Tos M. Cholesteatoma in children, predictors and calculation of recurrence rates. *Int J Pediatr Otorhinolaryngol* 1999;49(suppl 1):S69–S73.
34. Roger G, Denoyelle F, Chauvin P, Schlegel-Stuhl N, Garabedian EN. Predictive risk factors of residual cholesteatoma in children: a study of 256 cases. *Am J Otol* 1997;18:550–558.
35. Iino Y, Imamura Y, Kojima C, Takegoshi S, Suzuki JI. Risk factors for recurrent and residual cholesteatoma in children determined by second stage operation. *Int J Pediatr Otorhinolaryngol* 1998;46:57–65.
36. Roux A, Bakhos D, Lescanne E, Cottier JP, Robier A. Canal wall reconstruction in cholesteatoma surgeries: rate of residual. *Eur Arch Otorhinolaryngol* 2014. Epub ahead of print.
37. Muir Gray, JA. Evidence-Based Healthcare and Public Health: How to Make Decisions About Health Services and Public Health. Edinburgh, Scotland; New York, NY: Churchill Livingstone/Elsevier; 2009.

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Non-EPI DW MRI in Planning the Surgical Approach to Primary and Recurrent Cholesteatoma

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Objective: To investigate a correlation between preoperative non-echo planar diffusion-weighted magnetic resonance imaging (non-EPI DW MRI) with surgical findings of localization and extension of cholesteatoma and to develop criteria for surgical planning.
Patients: Preoperative non-EPI DWMRI was available and positive for cholesteatoma in 27 patients with primary and 23 with residual/recurrent lesions.
Interventions: Patients with cholesteatoma limited to the middle ear and its extensions were managed with a transcanal endoscopic approach. Patients with extension of the cholesteatoma posteriorly to the lateral semicircular canal underwent retroauricular mastoidectomy combined with an endoscopic approach.
Main Outcome Measure: Comparison of preoperative radiologic to surgical findings.
Results: DWI showed isolated tympanic and attic extension in 33 cases and attico-antral and mastoid extension in 17 cases. MRI findings correlated with surgical findings in all patients with primary cholesteatoma, 19 of whom were managed with a transcanal endoscopic approach and 8 with endoscope-assisted ear surgery. The transcanal endoscopic approach was applied in 14 of the patients with residual/recurrent cholesteatoma, and the other 9 residual/recurrent lesions were eradicated using endoscope-assisted mastoidectomy. DWI overestimated cholesteatoma sites in 1 patient with residual lesion. The smallest cholesteatoma detected on DWI was a 3-mm lesion in the middle ear over the facial nerve.
Conclusion: Primary and residual/recurrent cholesteatoma was accurately detected on non-EPI DWI with 98% clinical and radiologic concordance. Lesions less than 8 mm confined to the middle ear and its extensions can be eradicated with a minimally invasive endoscopic transcanal technique, whereas endoscope-assisted retroauricular mastoidectomy is preferred for larger lesions. **Key words:** Cholesteatoma—Imaging—Surgery.
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Non-echo planar (non-EPI) diffusion-weighted (DW) magnetic resonance imaging (MRI) has emerged as the optimal imaging technique for diagnosing the presence and extent of cholesteatoma. Recent studies have already shown a high correlation between preoperative non-EPI DWI and findings at surgery, demonstrating that DWMRI can accurately predict the presence of cholesteatoma in both primary and residual cases. The application of non-EPI DWI with a detection limit for a cholesteatoma as low as 2 mm is rapidly becoming a widely accepted practice in the postoperative follow-up of these patients (1–14).

The surgical management of cholesteatoma tends to use the least invasive surgical techniques (15–18). The choice of surgical approach depends on the extension of the disease and on the preoperative otoscopic and radiologic findings. Cholesteatoma is usually endoscopically accessible when the lesion does not involve the mastoid beyond the level of the lateral semicircular canal (15), whereas mastoid obliteration techniques can be used in more extended cases (19). The growing utilization of endoscopic procedures in the eradication of cholesteatoma requires precise preoperative imaging data for assistance in optimal planning of endoscopic ear surgery (EES) or endoscope-assisted ear surgery (EAES).

The objective of the present work was to investigate a correlation between preoperative non-EPI DWI and surgical findings in terms of localization and extension of primary and residual/recurrent cholesteatoma and to develop criteria for surgical technique planning. This is the first study to present the results of endoscopic or endoscope-assisted ear surgeries that were planned according to the preoperative non-EPI DW MRI findings.

METHODS

Only the surgeries performed by the same surgeon (L. M.) were analyzed in the current study. Between July 2008 and June 2013, an endoscopic approach was applied in 185 surgeries, of which, 120 were performed for primary (n = 87) or residual/

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recurrent cholesteatoma (n = 33) that had been operated elsewhere. Preoperative non-EPI DWMRI was available and positive for cholesteatoma in 27 patients with primary disease and in 23 patients with residual/recurrent lesion. Patients who were preoperatively assessed solely by computerized tomography or EPI MRI were excluded to achieve homogeneity of preoperative assessment. The diagnosis of cholesteatoma was verified histologically. MRI studies were carried on 3T scanners using a combination of standard head/IAC protocol, applying both conventional sequences together with non-EPI-based diffusion-weighted images. Our imaging studies included 2 non-EPI techniques, a coronal HASTE DWI (half-Fourier acquisition single-shot turbo spin-echo) or an axial PROPELLER DWI (multishot fast spin-echo periodically rotated overlapping parallel lines with enhanced reconstruction). Both non-EPI sequences are highly sensitive for detection of the keratinized content of cholesteatomas (1–14). MRI studies were analyzed by one of the neuroradiologists (G. G. or A. E.) in cooperation with a surgeon (L. M.). Transcanal endoscopic surgical technique is well described previously and is beyond the scope of the current article (15–18). Surgical findings were compared with preoperative findings on DWI. A lesion found posterior to the posterior limb of the lateral semicircular canal (LSCC) was defined as being within the mastoid (14).

RESULTS

The study cohort was composed of 29 male and 21 female subjects aged 4 to 70 years (mean, 29.2 yr). The non-EPI DW MRI studies revealed isolated tympanic and attic extension in 33 cases and attico-antral and mastoid extension in 17 cases. Patients with cholesteatoma limited to the middle ear and its extensions were managed solely with a transcanal endoscopic approach (Figs. 1–3). Extension posteriorly to the LSCC was the criterion for performing traditional retroauricular mastoidectomy combined with an endoscopic approach (Figs. 4–6).

Nineteen of the 27 patients in the primary cholesteatoma group were managed with transcanal EES, and the remaining 8 underwent EAES (3 canal wall-up [CWU] and 3 canal wall down [CWD] mastoidectomies without mastoid obliteration and 2 CWU mastoidectomies with mastoid obliteration). The MRI findings correlated with the surgical findings in all 27 patients. Up to now, postoperative non-EPI DWMRI was performed in 11 of 19 patients who underwent transcanal EES and in 3 of 8 who underwent EAES. The only one positive to cholesteatoma in the attic MRI was in patient who was treated with transcanal EES. The patient is scheduled for revision surgery.

Exclusive transcanal EES was carried out in 14 patients with residual/recurrent lesion and EAES was performed in the remaining 9 (1 CWU, 2 radical mastoidectomies, and 6 CWD with mastoid obliteration). The MRI of 1 patient showed a few punctate hyperintensities of 2 mm in the middle ear and its extensions; however, only one 4-mm lesion was found over the tympanic portion of the facial nerve during surgery. The other sites that were positive for cholesteatoma on MRI were attributed to the presence of cartilage that was used for reconstruction in the previous surgery. The MRI findings correlated with the surgical findings in 22 (95.6%) of 23 cases in this group. To date, postoperative non-EPI DWMRI was performed in 9 of 14 patients who underwent transcanal EES and in 5 of 9 who underwent EAES and did not detect cholesteatoma in these 14 cases.

Non-EPI DW MRI detected the precise localization and extension of cholesteatoma in 49 (98%) of 50 cases, with overestimation of the number of cholesteatoma sites

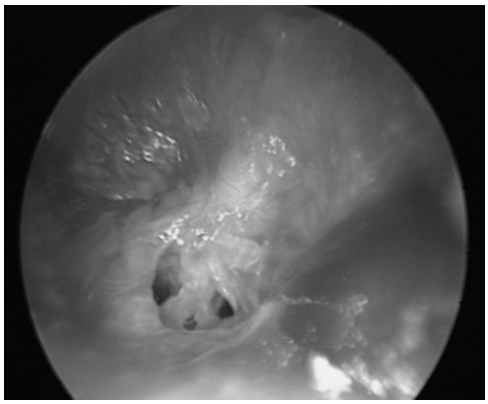

FIG. 1. Endoscopic view of a retraction pocket cholesteatoma in the left ear of 6-year-old patient.

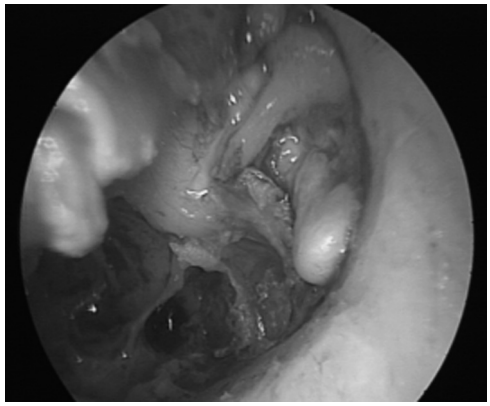

FIG. 2. Endoscopic view of the same ear after an elevation of tympano-meatal flap. Necrosis of the lenticular process of the incus and cholesteatoma in the middle ear and attic can be seen.

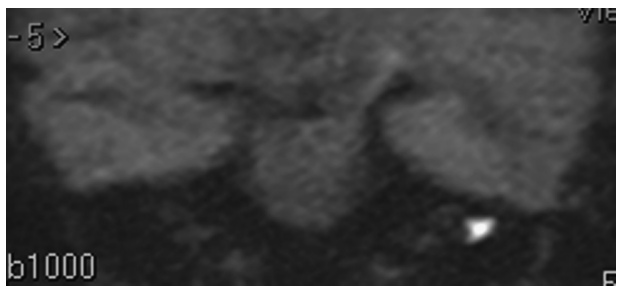

FIG. 3. HASTE coronal images showing a 6-mm hyperintense lesion in the left tympanic cavity.

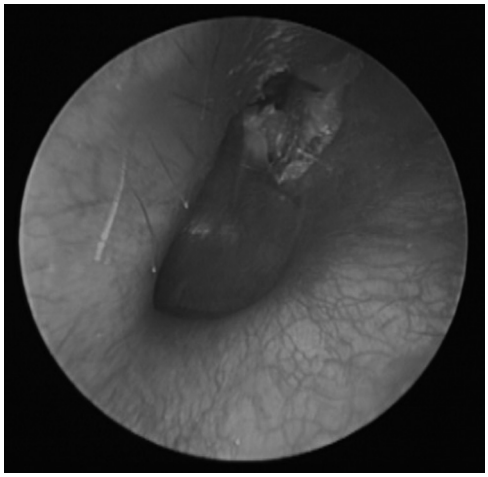

FIG. 4. Endoscopic view of a retraction pocket cholesteatoma in the left ear of a 21-year-old patient with no history of ear infections.

in the middle ear and attic of only 1 patient who had already undergone intervention for cholesteatoma in the past. The smallest lesion that had been detected on MRI and resected with an endoscopic transcanal approach was 3 mm, and it was located in the middle ear over the facial nerve. There was some tendency toward underestimation (1 mm) of the cholesteatoma size in 5 patients with primary lesions, possibly because of the delay between the MRI and surgery (range, 2 wk to 6 mo).

Labyrinthine invasion by the cholesteatoma and tegmen tympani erosion was demonstrated on DWI and found at surgery in 2 cases each. The labyrinthine fistula did not involve the endosteal membrane, and it was located in the lateral semicircular canal in both patients. The matrix was easily removed, and the fistula was occluded by bone wax. A cholesteatoma-induced defect of the bony external auditory canal was detected on DWI and observed intraoperatively in 3 cases.

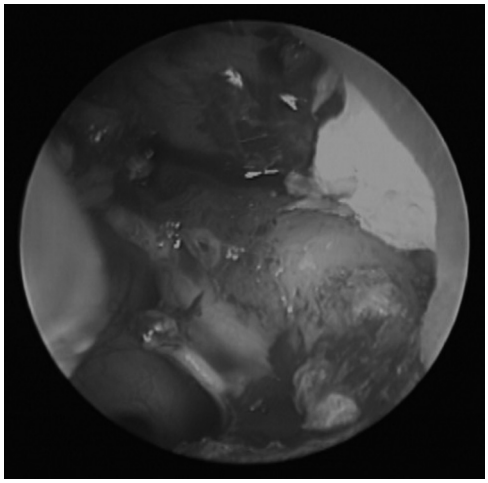

FIG. 5. Endoscopic view of the same ear after partial removal of a cholesteatoma transmeatally. This cholesteatoma extends posteriorly to the lateral semicircular canal.

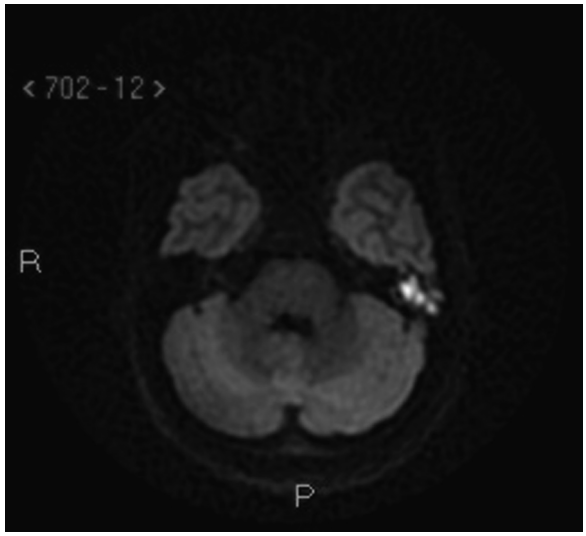

FIG. 6. Non-EPI DW axial images showing a hyperintense lesion involving the left middle ear and mastoid.

Thirty-three cases in which non-EPI DW MRI showed the cholesteatoma as being limited to the middle ear and extensions, measuring less than 8 mm and not extending posteriorly to the LSCC, were managed with EES. The endoscope served as a valuable addition to the microscope for enhanced visualization of the sinus tympani, facial recess, eustachian tube, supratubal recess, and hypotympanum in 17 cases of more extensive cholesteatoma.

DISCUSSION

Assessment of the anatomic extent of a cholesteatoma based of contemporary radiologic imaging is essential for planning the optimal surgical approach. Transcanal EES is difficult 1-hand surgery, technically possible only for highly skilled otosurgeons. The experience in performing traditional mastoidectomy and tympanoplasty using the microscope is obligatory before starting the endoscopic approach for eradication of the cholesteatoma. Some difficulties in manipulation of the instruments in patients with narrow ear canal and young children can be overcome with extensive experience and use of appropriate sets including a 3-mm diameter endoscopes, curved instruments and suction tips.

Our experience shows that lesions less than 8 mm in size and confined to the middle ear or its extensions can be eradicated exclusively by a transcanal endoscopic approach, whereas larger lesions should be managed with EAES. The possibility of a labyrinthine fistula in cases of extension of the cholesteatoma posteriorly to the labyrinth must be taken into consideration.

High-resolution computed tomography (CT) can depict the anatomy of the middle ear and mastoid, predict the involvement of the sinus tympani and facial recess, and

has excellent spatial resolution allowing delineation of small soft-tissue masses against bony structures and air (20). To date, CT of the temporal bones is considered as an initial tool to detect cholesteatoma in many departments worldwide. Thus, part of the patients still arrive for preoperative counseling in our hospital with a CT scans, and the patients with images demonstrating well-aerated mastoid and lesions limited to the middle ear cavity are not required to complete the preoperative investigation with the MRI. However, CT is mostly performed when the ear is inflamed and has poor value in distinguishing a cholesteatoma from the inflammatory tissue, granulations, fibrosis, or mucoid secretions in 20% to 70% of cases showing nonspecific opacification of the middle ear and mastoid (21). This is the main reason that, in most cases, it is impossible to diagnose or exclude the presence of a cholesteatoma or to predict its extension on the basis of CT findings and why there is a little benefit of CT in managing these patients. Advances in MRI techniques changed the protocols for the preoperative evaluation and the postoperative follow-up for cases of cholesteatoma resulted in minimizing radiation exposure, especially in children. In our opinion, preoperative CT scan can be helpful but not replace MRI in complicated cases associated with intracranial extension of cholesteatoma, facial nerve impaired movement, disequilibrium or deafness, to better understanding of the bony invasion by the cholesteatoma.

Non-EPI DW imaging performs reasonably well in predicting the presence and location of postoperative cholesteatoma but may miss small foci of disease and may underestimate the true size of cholesteatoma (14). In our series, the smallest cholesteatoma detected by DWI and whose size and location were confirmed at surgery was a 3-mm lesion confined to the anterior attic. Correlation of preoperative radiologic images with intraoperative clinical findings was good with regard to tympanic and mastoid cholesteatoma but weak in cases of facial canal dehiscence. The latter was found intraoperatively in 15 (30%) of 50 cases. This is of little clinical importance, however, since all endoscopic and endoscope-assisted surgeries are routinely performed under facial nerve monitoring in our department. Notably, cartilage that had been used for previous reconstructions can lead to misdiagnosis because it may appear as increased DW signal intensity resembling cholesteatoma. Nevertheless, non-EPI DWI was found as useful tool in predicting localization of cholesteatoma and estimation of its extension. Moreover, the findings of non-EPI DWI altered patient management, particularly in these who underwent cholesteatoma surgery in the past and in whom an adequate clinical inspection of the middle ear or mastoid cavity was impossible.

Our study has some limitations. One of them stems from the difficulty in estimating the exact size of a lesion in cases of diffuse or open cholesteatoma when dissection, irrigation, and suctioning are applied during the surgery. Our observation of there being some tendency for radiologic assessment to underestimate the true size of lesion, possibly attributable to a delay between imaging and surgery, is in agreement with the findings of Khemani et al. (14). In addition, the slice thickness of the non-EPI DW images usually cannot differentiate between cholesteatoma in the facial recess and cholesteatoma in the sinus tympani (14). However, transcanal introduction of variously angulated endoscopes can be used in the assessment of these middle ear structures, and appropriately curved micro-instruments and suction tips can be used for completion of cholesteatoma eradication from these hidden areas.

In our experience, non-EPI DWI in its current resolution cannot predict the need in CWD procedure because even large cholesteatomas can be eradicated with endoscope-assisted CWU technique, and sometimes, the location of cholesteatoma requires performing CWD and even radical mastoidectomy. MRI can help in choosing between transcanal endoscopic procedure and endoscope-assisted traditional mastoidectomy. However, the final decision on CWU or CWD technique still depends on the intraoperative finding.

CONCLUSION

Primary and residual/recurrent cholesteatomas were accurately detected by increased DW signal intensity on non-EPI DWI with a 98% clinical and radiologic concordance. Cholesteatoma size and location are crucial factors in choosing the appropriate surgical approach. Lesions that are less than 8 mm in size and confined to the middle ear or its extensions can be eradicated with a minimally invasive endoscopic transcanal technique, whereas endoscope-assisted retroauricular mastoidectomy is the preferable procedure for larger lesions. Skilled interpretation of the images is essential to maximize the value of preoperative imaging because motion artifacts, cartilage used for reconstructions in previous intervention, or cerumen in the external auditory canal can mimic a cholesteatoma and compromise optimal planning of a surgical approach.

REFERENCES

1. De Foer B, Vercruysse JP, Pouillon M, Somers T, Casselman JW, Offeciers E. Value of high-resolution computed tomography and magnetic resonance imaging in the detection of residual cholesteatomas in primary bony obliterated mastoids. *Am J Otolaryngol* 2007;284:230–4.
2. De Foer B, Vercruysse JP, Spaepen M, et al. Diffusion-weighted magnetic resonance imaging of the temporal bone. *Neuroradiology* 2010;52:785–807.
3. Dhepnorrarat RC, Wood B, Rajan GP. Postoperative non-echo-planar diffusion-weighted magnetic resonance imaging changes after cholesteatoma surgery: implications for cholesteatoma screening. *Otol Neurotol* 2009;30:54–8.
4. Dremmen MH, Hofman PA, Hof JR, Stokroos RJ, Postma AA. The diagnostic accuracy of non-echo-planar diffusion-weighted imaging in the detection of residual and/or recurrent cholesteatoma of the temporal bone. *AJNR Am J Neuroradiol* 2012;33:439–44.
5. Kasbekar AV, Scoffings DJ, Kenway B, et al. Non echo planar, diffusion-weighted magnetic resonance imaging (periodically rotated overlapping parallel lines with enhanced reconstruction sequence) compared with echo planar imaging for the detection of middle-ear cholesteatoma. *J Laryngol Otol* 2011;125:376–80.

6. Pizzini FB, Barbieri F, Beltramello A, Alessandrini F, Fiorino F. HASTE diffusion-weighted 3-Tesla magnetic resonance imaging in the diagnosis of primary and relapsing cholesteatoma. *Otol Neurotol* 2010;31:596–602.
7. Profant M, Sláviková K, Kabátová Z, Slezák P, Waczulíková I. Predictive validity of MRI in detecting and following cholesteatoma. *Eur Arch Otorhinolaryngol* 2012;269:757–65.
8. Sharifian H, Taheri E, Borghei P, et al. Diagnostic accuracy of non-echo-planar diffusion-weighted MRI versus other MRI sequences in cholesteatoma. *J Med Imaging Radiat Oncol* 2012;56:398–408.
9. Rajan GP, Ambett R, Wun L, et al. Preliminary outcomes of cholesteatoma screening in children using non-echo-planar diffusion-weighted magnetic resonance imaging. *Int J Pediatr Otorhinolaryngol* 2010;74:297–301.
10. Huins CT, Singh A, Lingam RK, Kalan A. Detecting cholesteatoma with non-echo planar (HASTE) diffusion-weighted magnetic resonance imaging. *Otolaryngol Head Neck Surg* 2010;143:141–6.
11. Edfeldt L, Strömbäck K, Danckwardt-Lillieström N, Rask-Andersen H, Abdsaleh S, Wikström J. Non-echo planar diffusion-weighted MRI increases follow-up accuracy after one-step step canal wall-down obliteration surgery for cholesteatoma. *Acta Otolaryngol* 2013;133:574–83.
12. Mateos-Fernández M, Mas-Estellés F, de Paula-Vernetta C, Guzmán-Calvete A, Villanueva-Martí R, Morera-Pérez C. The role of diffusion-weighted magnetic resonance imaging in cholesteatoma diagnosis and follow-up. Study with the diffusion PROPELLER technique. *Acta Otorrinolaringol Esp* 2012;63:436–42. [in English, Spanish]
13. Ilıca AT, Hıdır Y, Bulakbaşı N, et al. HASTE diffusion-weighted MRI for the reliable detection of cholesteatoma. *Diagn Interv Radiol* 2012;18:153–8.
14. Khemani S, Lingam RK, Kalan A, Singh A. The value of non-echo planar HASTE diffusion-weighted MR imaging in the detection, localisation and prediction of extent of postoperative cholesteatoma. *Clin Otolaryngol* 2011;36:306–12.
15. Tarabichi M. Endoscopic middle ear surgery. *Ann Otol Rhinol Laryngol* 1999;108:39–46.
16. Ayache S, Tramier B, Strunski V. Otoendoscopy in cholesteatoma surgery of the middle ear. What benefits can be expected? *Otol Neurotol* 2008;29:1085–90.
17. Migirov L, Shapira Y, Horowitz Z, Wolf M. Exclusive endoscopic ear surgery for acquired cholesteatoma: preliminary results. *Otol Neurotol* 2011;32:433–6.
18. Badr-El-Dine M. Surgery of sinus tympani cholesteatoma. Endoscopic necessity. *Int Adv Otol* 2009;5:158–65.
19. Vercruysse JP, De Foer B, Somers T, Casselman J, Offeciers E. Long-term follow up after bony mastoid and epitympanic obliteration: radiological findings. *J Laryngol Otol* 2010;124:37–43.
20. Marchioni D, Mattioli F, Cobelli M, Todeschini A, Alicandri-Ciufelli M, Presutti L. CT morphological evaluation of anterior epitympanic recess in patients with attic cholesteatoma. *Eur Arch Otorhinolaryngol* 2009;266:1183–9.
21. Alzoubi FQ, Odat HA, Al-Balas HA, Saeed SR. The role of preoperative CT scan in patients with chronic otitis media. *Eur Arch Otorhinolaryngol* 2009;266:807–9.

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OPEN

Clinical Performance of a New Magnetic Bone Conduction Hearing Implant System: Results From a Prospective, Multicenter, Clinical Investigation

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Objective: The aim of the investigation was to prospectively evaluate, in a multicenter setting, the clinical performance of a new magnetic bone conduction hearing implant system.
Methods: The test device was the Cochlear Baha Attract System (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden). Instead of the skin-penetrating abutment of traditional bone conduction hearing implants, the test device uses an implantable and an external magnet to transmit sound from the sound processor (SP) through intact skin to the skull bone. Twenty-seven adult patients with a conductive or mild mixed hearing loss or single-sided sensorineural deafness were included in the clinical investigation across four investigational sites. The patients were followed for 9 months after implantation. The study evaluated efficacy in terms of hearing performance compared with unaided hearing and with hearing with the SP on a softband. Patient benefit, soft tissue status, device retention, and safety parameters were monitored continuously throughout the investigation.
Results: Surgery and healing was uneventful. Statistically significant improvements in audibility and speech understanding in noise and quiet were recorded for the test device compared with preoperative unaided hearing. Speech recognition was similar or better than tests performed with the same SP on a softband. Good soft tissue outcomes were reported, without major pressure-related complications. At the end of the investigation, all patients continued to use and benefit from the device.
Conclusion: The test device provides good hearing performance in patients with a conductive hearing loss or single-sided sensorineural deafness, with good wearing comfort and minimal soft tissue complications. **Key Words:** Bone conduction—Bone conduction hearing implant—Clinical outcome—Hearing performance—Magnetic system—Osseointegration—Bone-anchored hearing aid—Baha.

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Bone conduction hearing implants consist of a sound processor (SP) that transforms sound into vibrations, which are transferred via an osseointegrated implant to the skull bone and onward to the cochlea. Bone conduction hearing implants that rely on direct bone conduction via a skin-penetrating abutment have proven successful for patients with conductive/mixed hearing loss and single-sided sensorineural deafness (SSD) (1). The clinical reality, however, is that a relatively large proportion of potential candidates refuse the treatment, often because of esthetic concerns related to the skin-penetrating abutment (2–5). Other patients may, for medical or other reasons, not be able to perform the daily cleaning that is needed to maintain a reaction-free skin penetration. A non–skin-penetrating solution, with implantable components covered by intact skin, constitutes a viable option for this group of patients.

Non–skin-penetrating bone conduction hearing implants that use a magnetic coupling through the skin have been in clinical use for some time, with varying success (6,7). There are two main challenges associated with this type of device. First, energy loss in the intervening skin layer results in less effective sound transmission compared with direct bone conduction (8–10). However, recent

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advances in digital sound processing and fitting tools (11) make it possible to evaluate and partly compensate for sound attenuation by increasing the amplification in the affected frequencies (12). Second, the magnetic coupling must ensure good retention to enable effective sound transmission while not causing discomfort and/or pressure-related soft tissue complications.

A new magnetic bone conduction hearing implant system has been developed, which uses the same digital SP technology as for direct bone conduction as well as the same osseointegrating implant that has shown reliable stability in previous investigations (13–15). Instead of a skin-penetrating abutment, the new system relies on an implanted and an external magnet to retain the SP. A pad of soft material lines the external magnet and distributes the pressure across the skin surface. Research has shown that the combination of advanced sound processing, stable single-point fixation in the bone, and even contact pressure results in efficient sound transmission (16,17) and minimal skin complications (17).

The aim of the present investigation was to evaluate the clinical performance of the new magnetic bone conduction hearing implant system. The study evaluated efficacy in terms of hearing performance compared with unaided hearing and with hearing with the SP on a softband. Patient benefit, soft tissue status, device retention, and safety parameters were monitored throughout the investigation.

MATERIALS AND METHODS

Investigational Sites and Patient Selection

This prospective, international, multicenter, clinical investigation included four sites: The HEARing Cooperative Research Centre (Melbourne, Australia), The Chinese University of Hong Kong (China), Bnai Zion Hospital (Haifa, Israel), and Clínica Las Condes (Santiago, Chile). The investigation was approved by local ethics committees and performed in accordance with the Declaration of Helsinki and international guidelines for Good Clinical Practice.

Adult patients with a conductive or mild mixed hearing loss in the ear to be implanted (bone conduction thresholds with pure-tone average [PTA] [mean of 500, 1,000, 2,000, and 3,000 Hz] of <30 dB hearing level [HL]) or with SSD (PTA <30 dB HL in contralateral ear) were included. Patient exclusion criteria included uncontrolled diabetes, condition that could jeopardize osseointegration and/or wound healing, too thin soft tissue, insufficient bone quality/quantity, and previous radiation therapy in the implant area.

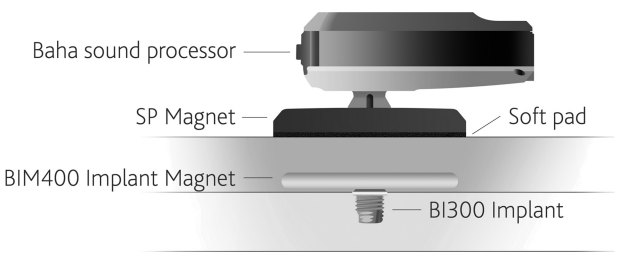

FIG. 1. Cochlear Baha Attract System.

Test Device

The test device was the Cochlear™ Baha® Attract System (Cochlear Bone Anchored Solutions AB, Mölnlycke, Sweden). The system consists of internal (surgically implanted) and external parts (Fig. 1). The internal parts comprise the osseointegrating BI300 Implant, onto which the titanium-encased BIM400 Implant Magnet is fixated. The external parts comprise the SP magnet onto which the SP attaches via a snap coupling. SP magnets with five different strengths—SPM1 (weakest) to SPM5 (strongest)—were available for the investigation to accommodate soft tissue thicknesses of 3 to 6 mm and to provide sufficient retention for different patient lifestyles. The SP magnet is lined with a soft pad made of slow-recovery foam that compresses and adapts to the underlying surface. All patients received the test device unilaterally.

Surgery and Fitting

At the baseline visit before surgery, pure-tone audiograms, including masked/unmasked air- and bone conduction thresholds, were obtained. SP selection was based on patient preference and hearing tests with a Baha Softband. Patients received either the Cochlear Baha BP100 or the BP110 Power Sound Processor. After a home test period of 1 to 2 weeks using the SP on a softband, implant surgery was performed using the procedure recommended by the manufacturer. A C-shaped anterior incision, approximately 1.5 cm lateral to the planned margin of the internal magnet, was used. Periosteum was usually preserved around the osseointegrating implant. Implant stability quotient (ISQ) values (13,18) were obtained using resonance frequency analysis (Osstell ISQ, Osstell, Göteborg, Sweden). A bone-bed indicator was attached to the implant and rotated 360 degrees to ensure clearance over the adjacent bone; if required, periosteum and some bone were removed. The implant magnet was affixed to the implant using 25Ncm tightening torque. Before closure, the soft tissue flap thickness was measured; surgical thinning was advocated if the thickness exceeded 6 mm.

Follow-up Examinations

Follow-up examinations were performed at 2, 4, and 6 weeks and 3 and 9 months after surgery. At 4 weeks, the patients were fitted with the SP magnet and SP. The retention force was measured using a dynamometer (Compact Force Gauge+, Slinfold, United Kingdom) at the time of fitting and at subsequent visits. Average and peak pressure between the magnet and underlying skin were measured using a pressure-sensitive sensor (I-Scan, Tekscan Inc., Boston, MA, U.S.A.).

Free-field hearing tests were performed in a soundproof audiometric chamber for the unaided situation and with the SP on a softband at the preoperative visit and with the test device 4 and 6 weeks and 3 and 9 months after surgery. All tests were performed with the nontest ear blocked by earplugs in case of normal/near-normal hearing in the nontest ear and with the signal processing of the SP set to omnidirectional mode. Pure-tone audiometry was performed according to the ascending Hughson-Westlake method with tones presented through a loudspeaker in the front position (0 degrees azimuth). Speech perception in quiet was evaluated using phonetically balanced words (monosyllabic/spondees) presented from the front. The test was performed at 50, 65, and 80 dB sound pressure level (SPL); scores were recorded as percentage correctly repeated words at each SPL. Adaptive sentence test in noise was conducted to establish the speech-to-noise ratio (SNR), providing 50% level of understanding. In Hong Kong and Santiago, language-specific versions of the Hearing in Noise Test (19)

TABLE 1. *Demographics and baseline characteristics*

Variable	(N = 27)
Sex, n (%)	
Male	12 (44.4)
Female	15 (55.6)
Age, mean (SD) (yr)	47.5 (13.8)
Ethnicity, n (%)	
Asian (East Asia)	9 (33.3)
White (Caucasian)	18 (66.7)
Type of hearing loss, n (%)	
Conductive	17 (63.0)
SSD	10 (37.0)
Bone conduction PTA*, mean (SD) (dB)	
Baha side, patients with conductive loss	21.4 (8.7)
Good ear, patients with SSD	16.6 (6.0)
Smoking status, n (%)	
Nonsmokers	25 (92.6)
Smokers (≤10 cigarettes per day)	2 (7.4)

*Pure-tone average (mean of 500, 1,000, 2,000, and 3,000 Hz).

were used, with speech presented from the front and with noise from the back (Hong Kong) or from 45 degrees (Santiago). Noise was kept constant at 65 dB SPL, and speech was adapted in 2-dB steps. The adaptive Australian Sentence Test in Noise with Bamford-Kowal-Bench-like sentences (20) was used in Melbourne, but with adaptive speech and fixed noise to match the Hearing in Noise Test. In Haifa, the Hebrew version of the Central Institute for the Deaf Everyday Sentence Test (21) was used, with both speech and noise presented from the front (22) according to an adaptive tracking method.

The Abbreviated Profile of Hearing Aid Benefit (APHAB) questionnaire (23) was administered to the patients preoperatively and 3 and 9 months after implantation. The APHAB is a 24-item self-assessment inventory that evaluates the benefit experienced by the patient when using hearing amplification.

The soft tissue at the surgical site was evaluated by the patient and investigator using the Patient and Observer Scar Assessment Scale (POSAS) (24). Patient reports of pain and numbness were collected. Daily usage time and any episodes of insufficient retention were recorded by the patient in a diary. Adverse events were monitored as per Good Clinical Practice.

The investigation was monitored by independent clinical research organizations. Data management was performed by independent data managers (dSharp, Göteborg, Sweden). Statistical analyses were performed by independent biostatisticians (Statistiska Konsultgruppen, Göteborg, Sweden) according to a predefined statistical analysis plan. For paired observations, Fisher's nonparametric permutation test was used. Significance tests were two-tailed and conducted at the 0.05 significance level. All patients who received the test device were included in the analyses.

RESULTS

Patients

Twenty-seven patients received the test device and were included in the investigation: eight patients in Melbourne, eight in Hong Kong, six in Haifa, and five in Santiago. Seventeen patients had a conductive hearing loss, and 10 patients had SSD. Demographics and baseline characteristics and mean baseline audiograms are presented in Table 1 and Figure 2. All patients attended all scheduled study visits.

Surgery and Healing

Surgery was performed under general anesthesia and was uneventful in all patients. Good implant stability was achieved at insertion, with a mean ISQ of 75.7 (SD, 8.8) (mean of highest value out of two perpendicular measurements in each patient). The mean soft tissue thickness was 6.0 mm (SD, 1.1 mm). Flap thinning was performed in three patients. The average surgery time was 45.0 minutes (SD, 14.6 min) from first incision to last suture. The surgical site healed satisfactorily in all patients. No implants or implant magnets were lost, replaced, or removed.

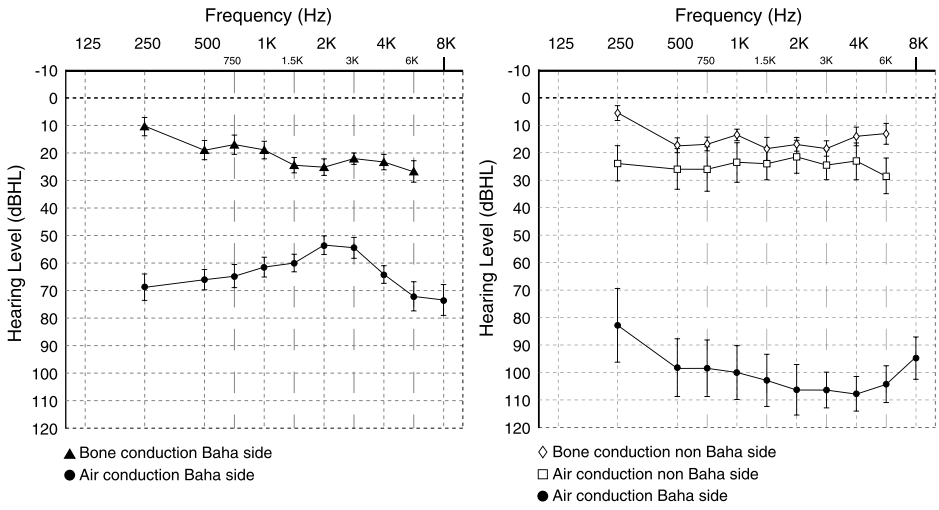

FIG. 2. Mean baseline audiograms. Patients with conductive hearing loss (left, n = 17) and SSD (right, n = 10). Error bars represent standard error of the mean. The slight conductive overlay for subjects with SSD was caused by a coexisting conductive loss contralateral to the deaf ear in three patients. These patients were included in the SSD group because they all selected to wear their SP on the side of the deaf ear.

SP Fitting

Fitting of the SP to the magnetic implant was performed at 4 ± 1 weeks after surgery on all but one patient, for whom fitting was delayed 3 weeks because of trauma to the implant site 10 days after surgery. Six and 21 patients selected the BP100 and BP110 Sound Processor, respectively. Table 2 shows the distribution of SP magnets per visit. After initial magnet selection, 14 patients changed to weaker and two patients to stronger magnets. Four patients changed magnets more than once.

Insufficient magnetic retention was reported for five patients with SPM5, who all had preoperative soft tissue thicknesses exceeding 6 mm; in three of these patients, flap thinning was performed at implant surgery. Sufficient retention force was achieved by removing the soft pad while awaiting availability of a stronger magnet. Three of the patients were able to return to using the soft pad after a period of adaptation of the skin.

Free-field Hearing Tests

Pure-tone audiometry showed a statistically significant improvement in PTA (mean of 500, 1,000, 2,000, and 4,000 Hz) of 18.4 dB HL (SD, 6.9 dB; $p < 0.0001$) with the test device at 9 months compared with unaided hearing. The corresponding improvement for the subgroup of patients with conductive hearing loss and SSD was 17.9 dB HL (SD, 6.6 dB; $p < 0.0001$) and 19.1 dB HL (SD, 7.7 dB; $p = 0.0005$), respectively. No statistically significant difference in PTA compared with softband tests was recorded. Table 3 shows PTA values per visit for all tested conditions.

Statistically significant improvements with the test device compared with unaided hearing were recorded at all frequencies up to and including 6,000 Hz (Fig. 3A). The mean improvement was largest in the frequency range 500 to 3,000 Hz: up to 25.2 dB improvement (SD, 8.4 dB; $p < 0.0001$). Overall similar hearing thresholds were obtained with the SP on a softband, with a slight advantage for the test device between 750 and 1,000 Hz and an advantage for the softband at and above 4,000 Hz.

Speech recognition tests in quiet showed statistically significant improvements at all tested intensity levels with the test device compared with unaided hearing. At 9 months, the mean improvement in percentage correctly repeated words at 50, 65, and 80 dB SPL was 50.0, 46.4, and 24.2 percentage points, respectively. Comparison with softband tests showed no significant differences (Fig. 3B). The percentage improvement for the subgroup of patients with a conductive hearing loss and SSD were similar: 55.6, 45.3, and 23.3 percentage points and 40.1, 48.3, and 25.8 percentage points, respectively, at increasing SPL.

A mean SNR of −4.9 dB (SD, 5.1 dB) was recorded for the test device in adaptive sentence in noise tests at 9 months, providing statistically significant improvements of 15.0 dB (SD, 12.8 dB; $p < 0.0001$) and 3.8 dB (SD, 7.0 dB; $p = 0.0092$) compared with unaided hearing and softband tests, respectively. A slight gradual improvement in SNR from the time of initial fitting to the 3-month follow-up visit was recorded (Fig. 3C). Although there were differences in test language and methodology, the four study sites were all consistent in terms of the improvement compared with both unaided and softband conditions. Similarly, results per type of hearing loss were in line with the global score. The SNR improvement compared with unaided hearing was 17.9 dB (SD, 15.2 dB; $p < 0.0001$) for patients with conductive hearing loss and 10.2 dB (SD, 4.7 dB; $p = 0.002$) for patients with SSD and 3.8 dB (SD, 7.6 dB; $p = 0.05$) and 3.7 dB (SD, 6.1 dB; $p = 0.09$), respectively, compared with softband.

TABLE 2. *Distribution of sound processor magnets by visit, n (%) (N = 27)*

SP magnet	4 wk	6 wk	3 mo	9 mo
SPM 1	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
SPM 2	0 (0.0)	2 (7.4)	3 (11.1)	3 (11.1)
SPM 3	5 (18.5)	4 (14.8)	6 (22.2)	8 (29.6)
SPM 4	5 (18.5)	8 (29.6)	6 (22.2)	4 (14.8)
SPM 5	17 (62.9)	13 (48.1)	12 (44.4)*	11 (40.7)

*A stronger magnet (equivalent to SPM 6) was developed and temporarily used by one subject.

APHAB

Statistically significant improvements with the test device compared with the preoperative unaided situation were obtained for the APHAB subscales Reverberation ($p = 0.016$), Background noise ($p = 0.035$), and the Global score ($p = 0.038$). A nonsignificant improvement and a nonsignificant deterioration were recorded for the subscales Ease of Communication and Aversiveness, respectively (Fig. 3D).

Magnetic Force and Pressure

The mean magnetic retention force across all visits was 0.99 N, with a relatively large variation between patients (SD, 0.23 N); the mean force remained stable across time (Table 3). The mean pressure between the SP magnet and the underlying skin remained relatively constant across time with an average of 0.14 N/cm^2 (SD, 0.04 N/cm^2) across all visits; no single value exceeded 0.4 N/cm^2, which corresponds approximately to the capillary blood pressure. The mean peak pressure across all visits was 0.44 N/cm^2 (SD, 0.27 N/cm^2). For the patients who used the magnet with a soft pad, as indicated, the peak pressure did not exceed the target maximum value of 0.6 N/cm^2 (corresponds approximately to the diastolic blood pressure in children), except at one or two occasions in three patients (only one of the recorded values exceeded 0.8 N/cm^2, which approximates to the diastolic blood pressure in adults). In patients, who used SPM5 without a soft pad, however, significantly higher values were recorded (up to 1.95 N/cm^2).

Daily Use and Retention

The patient-reported average daily use was 7.0 h/d (SD, 3.8 h/d) and ranged between 3.4 and 15.4 h/d. The daily use for the subgroups of patients with conductive

TABLE 3. *Test results by visit (N = 27)*

Pure-tone average by visit, mean (SD) (dB)					
Test condition	Preop	4 wk	6 wk	3 mo	9 mo
Unaided	55.7 (6.9)	-	-	-	-
Softband	36.4 (7.3)	-	-	-	-
Test device	-	38.1 (6.3)	37.2 (6.9)	37.3 (5.4)	37.4 (6.0)
Magnetic retention and pressure by visit, mean (SD)*					
Test type	Preop	4 wk	6 wk	3 mo	9 mo
Retention force (Newton)	-	0.97 (0.30)	1.1 (0.37)	0.98 (0.29)	0.97 (0.28)
Pressure (N/cm^2)	-	0.17 (0.05)	0.14 (0.05)	0.13 (0.04)	0.14 (0.07)
Peak pressure (N/cm^2)	-	0.54 (0.42)	0.46 (0.40)	0.36 (0.21)	0.42 (0.33)
Patient and Observer Scar Assessment Scale (POSAS) by visit, mean (SD) (Observer scale: 1 = normal skin, 10 = worst scar imaginable; Patient scale: 1 = normal skin, 10 = very different)					
Scale and subscales	Preop	4 wk	6 wk	3 mo	9 mo
Observer scale					
Pigmentation	-	2.19 (1.47)	2.15 (1.10)	2.48 (1.85)	1.41 (0.64)
Pliability	-	2.04 (1.40)	1.74 (0.66)	2.22 (1.58)	1.41 (0.89)
Relief	-	2.37 (1.42)	2.30 (1.38)	2.44 (2.22)	1.52 (1.01)
Surface area	-	2.00 (1.44)	1.78 (0.75)	2.04 (1.56)	1.41 (0.89)
Thickness	-	2.38 (1.53)	2.22 (1.25)	2.30 (1.61)	1.67 (1.52)
Vascularity	-	2.11 (1.05)	2.19 (1.18)	2.63 (1.94)	1.81 (1.14)
Overall opinion	-	2.14 (0.96)	2.24 (0.83)	2.38 (1.53)	1.52 (0.93)
Patient scale					
Painful	-	1.74 (1.16)	1.56 (1.12)	1.59 (1.08)	1.37 (0.93)
Itching	-	2.44 (1.37)	2.22 (1.58)	1.63 (1.01)	1.48 (1.05)
Color	-	2.37 (1.62)	1.96 (1.31)	2.08 (1.71)	1.62 (1.20)
Stiffness	-	2.44 (1.76)	2.12 (1.64)	2.29 (1.99)	2.11 (1.60)
Thickness	-	2.96 (2.36)	1.85 (1.17)	2.41 (1.93)	2.00 (1.47)
Irregular	-	2.78 (2.19)	1.70 (1.10)	2.26 (2.26)	1.93 (1.52)
Overall opinion	-	2.26 (1.61)	2.19 (1.64)	2.22 (1.97)	1.81 (1.21)
Numbness and pain scores, by visit. The pain scale rates any presence of pain from 1 = no, not at all to 10 = yes, very much					
Variable	Preop	4 wk	6 wk	3 mo	9 mo
Numbness, n (%)					
No numbness	-	10 (37.0)	15 (55.6)	20 (74.1)	21 (77.8)
Numbness within 2 cm	-	9 (33.3)	9 (33.3)	3 (11.1)	1 (3.7)
Numbness within 2 cm and beyond	-	8 (29.6)	3 (11.1)	4 (14.8)	5 (18.5)
Pain, mean score (SD)					
Neuropathic pain	-	1.41 (0.93)	1.19 (0.48)	1.56 (1.05)	1.19 (0.79)
Pain from the scar	-	1.11 (0.32)	1.26 (0.81)	1.74 (1.79)	1.15 (0.77)

*In case of sound processor magnet change, the measurements were performed with the new magnet.

hearing loss and SSD was 7.6 (SD, 4.0 h/d) and 6.0 h/d (SD, 3.3 h/d), respectively. Incidences of insufficient retention were rare and reported to occur on average less than once every third day during normal daily activities.

Soft Tissue Status, Numbness, and Pain

Overall low and decreasing POSAS scores were recorded, indicating satisfactory soft tissue status. At the last visit, the mean overall opinion of the skin was rated as 1.52 (SD, 0.93) by the investigators and 1.81 (SD, 1.21) by the patients on a scale from 1 to 10, with low values indicating good outcomes. The proportion of patients experiencing numbness was highest at the time of initial fitting (62.9%) and decreased gradually thereafter (22.2% at the last visit). Overall mean pain scores were low, indicating no or limited pain in the majority of patients. See Table 3.

Adverse Events

No cases of pressure-related skin necrosis or significant soft tissue reactions were reported. Four cases of mild erythema were reported. Three events resolved without medical treatment; in one patient, this was achieved by changing to a weaker magnet. The last case was reported as initiated at the time of the last visit and, hence, was ongoing at study end. Four cases of pain at the implant site were reported, two of which resolved within 1 week without treatment. Two patients reported mild/moderate pain after continuous use of the device. One patient reported discomfort in the magnet area, which resolved without medical treatment. No other device-related local adverse events were reported. All patients continue to use and benefit from the device.

DISCUSSION

The investigation evaluated the clinical performance of a novel magnetic bone conduction hearing implant in 27 adult patients with conductive or mild mixed hearing loss or SSD. The study showed statistically significant improvements in hearing performance compared with unaided

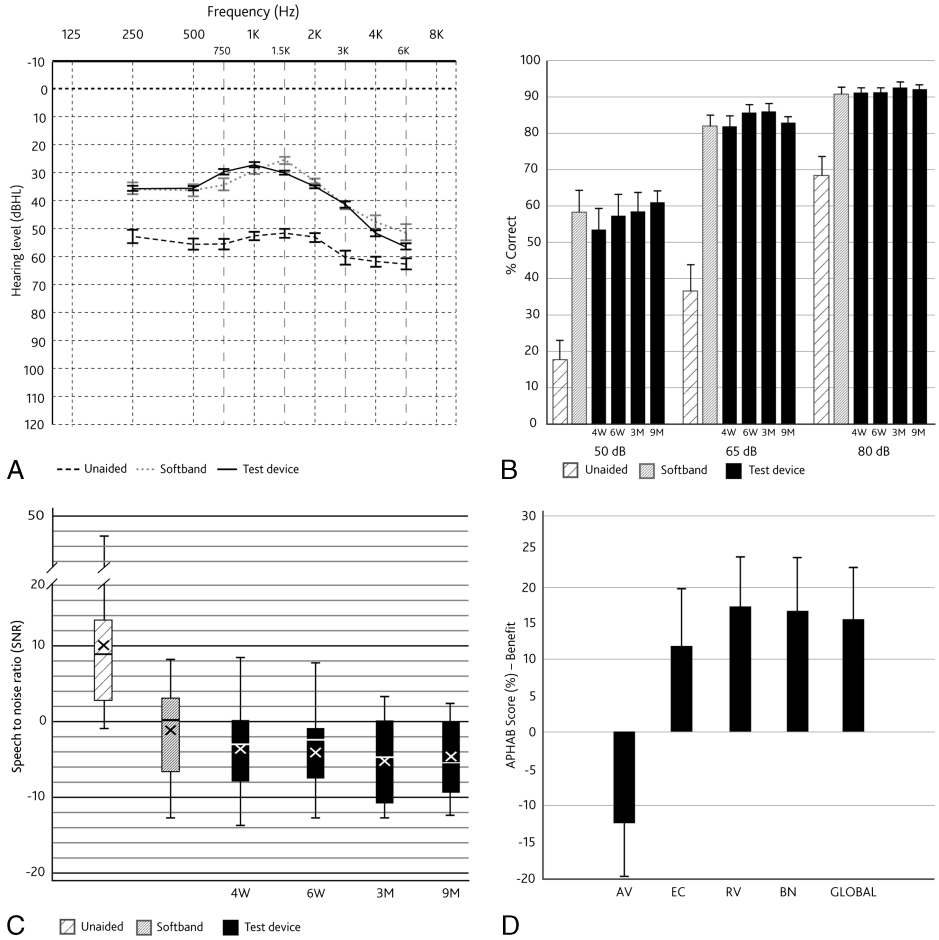

FIG. 3. A, Pure-tone thresholds per frequency for the unaided situation (preop), softband (preop), and test device (9 mo) in decibels. Error bars represent standard error of the mean. N = 27. B, Speech perception in quiet for the unaided situation (preop), softband (preop), and test device (4 wk, 6 wk, 3 mo, 9 mo). Percent correctly repeated words at 50, 65, and 80 dB SPL. Error bars represent standard error of the mean. N = 27. C, Speech-to-noise ratio allowing 50% speech recognition for the unaided situation (preop), softband (preop), and test device (4 wk, 6 wk, 3 mo, 9 mo). N = 27. D, APHAB scores, change between unaided (preop) and test device (Visit 7). Positive values represent benefits for the test device. AV indicates aversiveness; EC, ease of communication; RV, reverberation; BN, background noise; GLOBAL, global score. Error bars represent standard error of the mean. N = 27.

hearing and similar or improved outcomes compared with tests performed with the SP on a softband. No major pressure-related soft tissue complications were reported and no implants were lost or removed, suggesting that the device is efficacious and safe for the tested indication.

Magnetic bone conduction hearing implants have the advantage over skin-penetrating systems of providing improved cosmetics and eliminating the daily cleaning of the site (25). With modern SP technology, it is possible to obtain good sound transmission despite the soft tissue attenuation that is inherent to magnetic bone conduction hearing implants. Although the system must provide reliable retention of the SP to ensure good clinical outcomes, it should not cause irritation of the skin or discomfort. Threshold audiometry showed that the test device provides significant functional gain at all frequencies. The improvement is largest in the important speech frequency range up to and including 3,000 Hz. Above 3,000 Hz, the performance drops gradually as expected because of the soft tissue attenuation, which is known to mainly affect the high frequencies (26,27). It is anticipated that aided high-frequency thresholds could be improved further (particularly by prescribing more amplification in the high frequencies) by less conservative SP settings than were used in the present investigation. It would be expected, however, that some attenuation of sound through soft tissue will remain. In the sentence tests in noise, which represents the most difficult listening situation, significant improvement in SNR was recorded compared with unaided hearing and compared with softband tests. Speech recognition in quiet was significantly better than for the unaided situation and similar to softband. Although not statistically verified, a gradual improvement in speech understanding was noted up to the 3-month visit, followed by relatively stable levels. A possible improvement in hearing performance may be explained by adaptation as patients get used to the sound; it may also be an effect of fine-tuning of the SP by the audiologist. The fact that overall comparable outcomes were obtained with

the SP on a softband as with the test device suggests that preoperative softband tests are a good predictor of the patient's postoperative hearing performance; the importance of preoperative testing to achieve successful clinical outcomes has been reported by several authors (5,28,29).

APHAB scores showed that the test device provides good subjective benefit in terms of the patient's listening experience compared with the unaided situation. Improvements were obtained for the subscales related to reverberation, background noise, and ease of communication. A nonsignificant deterioration was observed for the subscale aversiveness, which quantifies negative reactions to environmental sounds; slightly worse aversiveness scores are a known effect with hearing devices (30,31) and have been attributed to unwanted sound also being amplified (30).

Soft tissue complications were minimal, as reflected by good POSAS scores and only four reports of mild skin irritation. The result suggests that the test device is associated with significantly less adverse soft tissue reactions than implants involving a skin-penetrating abutment (32). Favorable pain and numbness scores together with a high mean daily use (7 h/d) suggest good wearing comfort. Some patients reported average daily use exceeding 15 h/d; however, other patients were only part-time users while still reporting good benefit from the device. The relatively lower usage time in some patients may be reflective of the non–skin-penetrating nature and flexibility of the device, which allows patients to easily attach the SP to the invisible implant site when exposed to challenging listening situations. The ease of use of the device may provide significant advantages for patients with disabilities and/or reduced dexterity.

As with any surgical procedure involving incising soft tissue, a certain degree of transient (or in some cases permanent) numbness can be expected. In the present investigation, gradually reducing numbness was reported. Possibly the degree of paresthesia could be further reduced by placing the incision superior rather than anterior to the planned magnet position.

Assessment of the magnetic retention showed that the patients on average chose a retention force of around 1 Newton. However, the variability between patients was relatively large and most likely relates to different comfort levels and lifestyles of individual patients. For the same reasons and because of different soft tissue thicknesses, the patients chose SP magnets of varying strength. More than half of the patients required a change of SP magnet at some point during the investigation. The majority of these patients changed to a weaker magnet, which suggests that the tissue gradually compresses under the load of the magnet during the initial period after fitting. Similar observations have been reported for other implants incorporating a magnetic coupling (33,34).

The reported rate of insufficient retention was low. A few patients experienced retention difficulties with the strongest available SP magnet (SPM5); sufficient retention was obtained by removing the soft pad to increase the magnetic force. Removing the soft pad may cause areas of higher peak pressure to appear on the skin, as demonstrated by pressure measurements performed in this investigation. To maintain a healthy implant site, peak pressure areas should be avoided because the blood supply in the soft tissue may be affected. Areas of high peak pressure were not seen in the presence of the soft pad, demonstrating its ability to distribute the pressure evenly. All patients with retention difficulties had preoperative soft tissue thicknesses greater than 6 mm, highlighting the importance of flap thinning if the thickness exceeds this value. The need for extra magnet strength also in patients who had flap thinning at surgery suggests the presence of transient postoperative swelling/edema in these patients. Although the majority of patients were successfully fitted with the available range of magnets, additional strength may be required in specific situations as a temporary or permanent solution; hence, the manufacturer has developed a stronger magnet (SPM6) to meet this need.

CONCLUSION

The magnetic bone conduction hearing implant evaluated in the present investigation was shown to be safe and effective because it provides good hearing performance in patients with conductive and mild mixed hearing loss or SSD, with good wearing comfort and minimal soft tissue complications. Future investigations may be considered to address the question of maximum audiometric fitting range for these systems. Magnetic systems constitute a viable alternative for patients who cannot or will not use an implant system that involves skin penetration. Although the investigation was limited to adult patients, it is expected that the device is equally suited for pediatric patients who are candidates for bone conduction surgery.

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REFERENCES

1. Snik AF, Mylanus EA, Proops DW, et al. Consensus statements on the BAHA system: where do we stand at present? *Ann Otol Rhinol Laryngol Suppl* 2005;195:2–12.
2. Desmet J, Bouzegta R, Hofkens A, et al. Clinical need for a BAHA trial in patients with single-sided sensorineural deafness. Analysis of a BAHA database of 196 patients. *Eur Arch Otorhinolaryngol* 2012;269:799–805.
3. Burkey JM, Berenholz LP, Lippy WH. Latent demand for the bone-anchored hearing aid: the Lippy Group experience. *Otol Neurotol* 2006;27:648–52.
4. Andersen HT, Schrøder SA, Bonding P. Unilateral deafness after acoustic neuroma surgery: subjective hearing handicap and the

effect of the bone-anchored hearing aid. *Otol Neurotol* 2006;27: 809–14.
5. Faber HT, Kievit H, de Wolf MJ, Cremers CW, Snik AF, Hol MK. Analysis of factors predicting the success of the bone conduction device headband trial in patients with single-sided deafness. *Arch Otolaryngol Head Neck Surg* 2012;138:1129–35.
6. Gates GA, Hough JV, Gatti WM, Bradley WH. The safety and effectiveness of an implanted electromagnetic hearing device. *Arch Otolaryngol Head Neck Surg* 1989;115:924–30.
7. Siegert R, Kanderske J. A new semi-implantable transcutaneous bone conduction device: clinical, surgical, and audiologic outcomes in patients with congenital ear canal atresia. *Otol Neurotol* 2013; 34:927–34.
8. Håkansson B, Tjellström A, Rosenhall U. Hearing thresholds with direct bone conduction versus conventional bone conduction. *Scand Audiol* 1984;13:3–13.
9. Håkansson B, Tjellström A, Rosenhall U. Acceleration levels at hearing threshold with direct bone conduction versus conventional bone conduction. *Acta Otolaryngol* 1985;100:240–52.
10. Snik AF, Bosman AJ, Mylanus EA, Cremers CW. Candidacy for the bone-anchored hearing aid. *Audiol Neurootol* 2004;9:190–6.
11. Flynn MC, Hillbratt M. Improving the accuracy of BAHA fittings through measures of direct bone conduction. *Clin Exp Otorhinolaryngol* 2012;5:S43–7.
12. Flynn MC, Hedin A, Halvarsson G, Good T, Sadeghi A. Hearing performance benefits of a programmable power BAHA sound processor with a directional microphone for patients with a mixed hearing loss. *Clin Exp Otorhinolaryngol* 2012;5:S76–81.
13. Dun CA, de Wolf MJ, Hol MK, et al. Stability, survival, and tolerability of a novel BAHA implant system: six-month data from a multicenter clinical investigation. *Otol Neurotol* 2011;32:1001–7.
14. McLarnon CM, Johnson I, Davison T, et al. Evidence for early loading of osseointegrated implants for bone conduction at 4 weeks. *Otol Neurotol* 2012;33:1578–82.
15. Faber HT, Dun CA, Nelissen RC, Mylanus EA, Cremers CW, Hol MK. Bone-anchored hearing implant loading at 3 weeks: stability and tolerability after 6 months. *Otol Neurotol* 2013;34:104–10.
16. Kurz A, Flynn M, Caversaccio M, Kompis M. Speech understanding with a new implant technology: a comparative study with a new nonskin penetrating BAHA system. *BioMed Int* 2014;2014:416205.
17. Işeri M, Orhan KS, Kara A, et al. A new transcutaneous bone anchored hearing device—the BAHA Attract System: the first experience in Turkey. *Kulak Burun Bogaz Ihtis Derg* 2014;24:59–64.
18. Sennerby L, Meredith N. Implant stability measurements using resonance frequency analysis: biological and biomechanical aspects and clinical implications. *Periodontol 2000* 2008;47:51–66.
19. Nilsson M, Soli SD, Sullivan JA. Development of the hearing in noise test for the measurement of speech reception thresholds in quiet and in noise. *J Acoust Soc Am* 1994;95:1085–99.
20. Dawson PW, Hersbach AA, Swanson BA. An adaptive Australian Sentence Test in Noise (AuSTIN). *Ear Hear* 2013;34:592–600.
21. Davis H, Silverman SR. *Hearing and deafness*. New York, NY: Holt Rinehart & Winston, 1970.
22. Boyle PJ, Nunn TB, O'Connor AF, Moore BC. STARR: a speech test for evaluation of the effectiveness of auditory prostheses under realistic conditions. *Ear Hear* 2013;34:203–12.
23. Cox RM, Alexander GC. The Abbreviated Profile of Hearing Aid Benefit. *Ear Hear* 1995;16:176–86.
24. Draaijers LJ, Tempelman FR, Botman YA, et al. The patient and observer scar assessment scale: a reliable and feasible tool for scar evaluation. *Plast Reconstr Surg* 2004;113:1960–5.
25. Tjellström A, Håkansson B. The bone-anchored hearing aid. Design principles, indications, and long-term clinical results. *Otolaryngol Clin North Am* 1995;28:53–72.
26. Verstraeten N, Zarowski AJ, Somers T, Riff D, Offeciers EF. Comparison of the audiologic results obtained with the bone-anchored hearing aid attached to the headband, the testband, and to the ''snap'' abutment. *Otol Neurotol* 2009;30:70–5.
27. Tjellström A, Håkansson B, Granström G. Bone-anchored hearing aids: current status in adults and children. *Otolaryngol Clin North Am* 2001;34:337–64.
28. Pennings RJ, Gulliver M, Morris DP. The importance of an extended preoperative trial of BAHA in unilateral sensorineural hearing loss: a prospective cohort study. *Clin Otolaryngol* 2011;36:442–9.
29. Zarowski AJ, Verstraeten N, Somers T, Riff D, Offeciers EF. Headbands, testbands and softbands in preoperative testing and application of bone-anchored devices in adults and children. *Adv Otorhinolaryngol* 2011;71:124–31.
30. Pfiffner F, Caversaccio MD, Kompis M. Comparisons of sound processors based on osseointegrated implants in patients with conductive or mixed hearing loss. *Otol Neurotol* 2011;32:728–35.
31. Boleas-Aguirre MS, Bulnes Plano MD, de Erenchun Lasa IR, Ibáñez Beroiz B. Audiological and subjective benefit results in bone-anchored hearing device users. *Otol Neurotol* 2012;33:494–503.
32. Wazen JJ, Young DL, Farrugia MC, et al. Successes and complications of the BAHA system. *Otol Neurotol* 2008;29:1115–9.
33. James AL, Daniel SJ, Richmond L, Papsin BC. Skin breakdown over cochlear implants: prevention of a magnet site complication. *J Otolaryngol* 2004;33:151–4.
34. Hough J, Himelick T, Johnson B. Implantable bone conduction hearing device: Audiant bone conductor. Update on our experiences. *Ann Otol Rhinol Laryngol* 1986;95:498–504.

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United States Multicenter Clinical Trial of the Cochlear Nucleus Hybrid Implant System

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Objectives/Hypothesis: To evaluate the safety and efficacy of acoustic and electric sound processing for individuals with significant residual low-frequency hearing and severe-to-profound high-frequency sensorineural hearing loss.

Study Design: Prospective, single-arm repeated measures, single-subject design.

Methods: Fifty individuals, $\geq$ 18 years old, with low-frequency hearing and severe high-frequency loss were implanted with the Cochlear Nucleus Hybrid L24 implant at 10 investigational sites. Preoperatively, subjects demonstrated consonant-nucleus-consonant word scores of 10% through 60% in the ear to be implanted. Subjects were assessed prospectively, preoperatively, and postoperatively on coprimary endpoints of consonant-nucleus-consonant words, AzBio sentences in noise, and self-assessment measures.

Results: Significant mean improvements were observed for coprimary endpoints: consonant-nucleus-consonant words (35.8 percentage points) and AzBio sentences in noise (32.0 percentage points), both at $P < 0.001$. Ninety-six percent of subjects performed equal or better on speech in quiet and 90% in noise. Eighty-two percent of subjects showed improved performance on speech in quiet and 74% in noise. Self-assessments were positive, corroborating speech perception results.

Conclusion: The Nucleus Hybrid System provides significant improvements in speech intelligibility in quiet and noise for individuals with severe high-frequency loss and some low-frequency hearing. This device expands indications to hearing-impaired individuals who perform poorly with amplification due to bilateral high-frequency hearing loss and who previously were not implant candidates.

Key Words: Cochlear implant, hybrid cochlear implant, hearing preservation, electric-acoustic stimulation, hearing in noise, bimodal stimulation.

Level of Evidence: 2b.

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INTRODUCTION

Hearing loss is a significant public health concern given the deleterious effects that untreated hearing impairment may have on overall physical and cognitive well-being.[1,2] The Hearing Health Foundation reports that nearly 50 million Americans have hearing loss.[3] Sensorineural hearing losses generally have a high-frequency component. This frequency region is essential for good speech understanding in complex listening environments, particularly in noise.[4,5] Individuals with substantial, bilateral high-frequency hearing loss experience hearing difficulties in most aspects of life: at home, on the phone, at work, and in social situations. They can be highly frustrated because existing hearing aid technology cannot overcome the problems of reduced word understanding in quiet and noise.[6–8] Due to their communication problems, they may become isolated, withdrawing from family, colleagues, and friends. With severe hearing loss, areas of minimal or nonfunctioning hair cells or auditory neurons are often present, resulting in cochlear *dead regions* where vibrations of the basilar membrane are not detected via inner hair cells or neurons in that region. Frequencies falling in a dead region are detected via apical or basal spread of vibrations to other cochlear places. Therefore, hearing loss at a given frequency may be greater than indicated by the audiometric threshold.[9] Typically, acoustic amplification of dead regions does not improve speech understanding and may worsen it.[10,11] Individuals with this hearing loss profile may be candidates for electric plus acoustic stimulation in the same ear.

Treatment options for individuals with bilateral, severe ski-slope hearing loss have been limited to state-of-the art amplification, including frequency lowering,[12] in an effort to improve speech intelligibility. These attempts often end with the rejection of hearing aids due to the lack of benefit, leaving the individual with no other alternatives. Studies have shown that an implant with a shorter electrode

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array provides beneficial electric stimulation for high frequencies while preserving acoustic low-frequency hearing, resulting in improved speech understanding.[13,14] Recently, Lenarz et al. described results from a European multicenter study using the Cochlear Ltd., Sydney, Australia, Nucleus Hybrid L24 implant.[15] We report results of the clinical trial leading to U.S. Food and Drug Administration approval of the first-of-its-kind combined electric and acoustic (hybrid) implant system to address the substantial hearing difficulties of individuals not benefitting from amplification and not eligible for a standard cochlear implant (CI).

MATERIALS AND METHODS

This was a prospective, single-arm, multicenter trial to determine the safety and effectiveness of the hybrid system. Subjects were implanted at 10 clinical sites in the United States and served as their own controls in all test conditions. The protocol was approved by the US Food and Drug Administration and relevant institutional review boards, and all participants gave written informed consent.

Fifty individuals aged 18 years or older were enrolled and implanted. The ear selected for implantation had severe ($\geq$ 75 dB HL averaged over 2000, 3000, 4000 Hz) high-frequency sensorineural hearing loss and relatively good low-frequency hearing ($\leq$ 60 dB HL at 125, 250, and 500 Hz). In addition, an aided consonant-nucleus-consonant (CNC) monosyllabic word score of 10% through 60% using an appropriately fit hearing aid was required. Aided word recognition in the contralateral ear was required to be similar or better than the ear to be treated, but not better than 80%. Those with durations of severe or profound hearing loss greater than 30 years and/or onset of hearing loss less than 2 years were excluded.

The protocol included acoustic thresholds measured for each ear preoperatively and postoperatively, at device activation, and 3, 6, and 12 months postactivation. Speech perception was assessed preoperatively using an appropriately fit hearing aid. Postoperatively, the implanted ear was tested at the same postoperative intervals noted above. All signals were presented from a calibrated loudspeaker in front of the subject. Consonant-nucleus-consonant words were presented at 60 dBA; AzBio sentences in noise were presented at 60 dBA in 10-talker babble noise at +5 dB signal-to-noise ratio. To evaluate effectiveness of the hybrid system as used routinely, speech perception outcomes were analyzed in the everyday listening condition, which is listening through the hybrid system in combination with acoustic hearing in the opposite, unimplanted ear.

To gain insight into how hearing impacts quality of life, the validated Speech, Spatial, and Qualities of Hearing Questionnaire (SSQ)[16] was administered as a self-assessment of hearing within three domains: hearing speech in various environments, spatial hearing, and sound qualities. A score of zero corresponded to minimal ability and 10 to complete ability. A device use questionnaire was administered that addressed overall satisfaction with the hybrid system relative to hearing aids.

Surgery for the Hybrid L24 implant (Cochlear) is a modification of that for standard CIs, similar to the description by Gantz et al.[13]; details are provided in the Nucleus Hybrid L24 Implant Surgeon's Guide (Cochlear).[17] After the postauricular incision, the surgeon creates a well bed on the skull posterior to the mastoid and opens the facial recess (posterior tympanotomy) widely to provide good visibility of the round window niche in the middle ear. Although the hybrid implant electrode may be inserted through the round window or cochleostomy, in this trial all electrodes were inserted through a small cochleostomy created just inferior to the round window. After performing the cochleostomy, the surgeon opens the endosteum of the cochlea with a pick just prior to inserting the electrode array. Suctioning of intracochlear fluid is avoided. The array is slowly inserted 16 mm into the scala tympani instead of the 19 to 24 mm that are more typical for standard CIs.

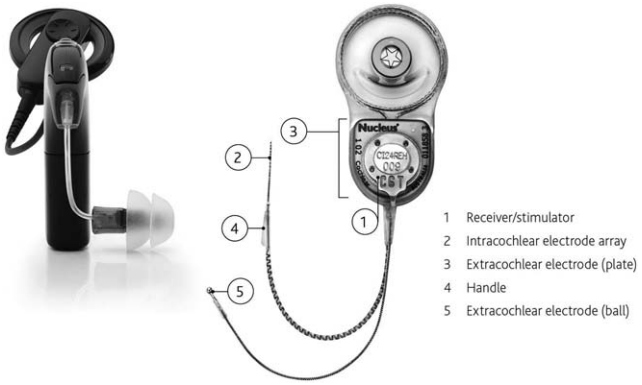

Fig. 1. Image of implanted receiver stimulator and the processor for the Nucleus Hybrid Implant System.

Figure 1 illustrates the Hybrid L24 (Cochlear) implant and processor. The 16-mm straight electrode is very thin and has 22 half-band modiolar-facing electrode contacts to stimulate the basal region of the cochlea, with the intent to maintain apical cochlear structures responsible for low-frequency hearing. The system includes an external processor that integrates electric and acoustic sound processing.

Objectives and Statistical Analyses

Coprimary efficacy hypotheses were that outcomes on CNC words (100 recorded words administered)[18] and AzBio sentences in noise (40 recorded sentences administered)[19] presented through the Hybrid Implant System (Cochlear) would be significantly better at 6 months postimplantation than preoperative performance using a hearing aid. The sample size of 50 subjects exceeded the minimum requirement for 90% statistical power, ensuring adequate power.

Mean differences for subjects on the CNC word and AzBio sentence recognition scores preoperatively and at the 6-month endpoint were analyzed using paired t tests. If there was evidence that assumptions did not hold, a Wilcoxon signed rank test was used. Missing 6-month data were imputed using the last observation carried forward.

Secondary efficacy objectives compared individual preoperative performance with a hearing aid to performance at the 6-month endpoint on CNC words and phonemes and AzBio sentences. Although no formal hypothesis test was conducted for these endpoints, success would be achieved if over 75% of subjects showed equal or better performance from preoperative to postoperative scores using the binomial model.[20]

The primary safety objective was to describe the safety of implantation with the hybrid system. The primary safety endpoint was defined as any surgical and/or device-related event, reported as the number and proportion of individuals experiencing an adverse event.

RESULTS

Demographics

Table I presents demographics for the 50 subjects. Mean age was 64.1 years (standard deviation [SD] = 14.7 years), ranging from 23 to 86.2 years at implantation.

TABLE I.
Demographics and Baseline Clinical Summary.

	Mean ± SD N (min, max)
Age at Implantation in Years	64.1 ± 14.7 50 (23.0 −86.2)
Duration of Overall Hearing Loss in Years	28.1 ± 14.9 50 (3.4 −73.9)
Duration of High Frequency Hearing Loss in Years	13.1 ± 7.2 50 (1.6 −30.1*)
Gender:	N/total (%)
Male	25/50 (50.0%)
Female	25/50 (50.0%)
Preoperative Degree of LF PTA (Implanted Ear):	N/total (%)
Normal (0–25 dB HL)	1/50 (2.0%)
Mild (26 - 40 dB HL)	13/50 (26.0%)
Moderate (41–55 dB HL)	26/50 (52.0%)
Moderate-Severe (56 - 70 dB HL)	10/50 (20.0%)
Preoperative Hearing Aid Use:	N/total (%)
Bilateral Hearing Aids	38/50 (76%)
Unilateral Hearing Aid	9/50 (18%)
No Hearing Aids	3/50 (6%)

HL = hearing loss; LF = low frequency; PTA = pure tone average; SD = standard deviation.

There was a 50/50 split for gender, and 52% of right ears were implanted. Mean duration of overall hearing loss was 28.1 years, and mean duration of severe-to-profound high-frequency loss was 13.1 years. Hearing loss etiologies were: unknown (50%), noise exposure (22%), and familial (20%). Individual cases (8%) were related to ototoxic drugs, autoimmune ear disease, high fever/infection, and noise exposure/viral.

Primary Speech Perception Outcomes

Table II provides a summary of primary outcomes (CNC words and AzBio sentences in noise for the implanted ear). When testing the implanted ear, the contralateral ear was plugged to mitigate its contribution to the speech scores. For CNCs, subjects experienced a significant ($P < 0.001$) improvement of 35.8 (SD = 27.7) percentage points with the hybrid device over a hearing aid preoperatively. Similarly, for AzBio sentences, they experienced a significant ($P < 0.001$) improvement of 32.0 (SD = 29.4) percentage points. One subject missed 6-month assessments, and data were imputed based on the 3-month evaluation. Primary outcome results were consistent under a variety of methods for handling missing data.

Table III presents secondary objective outcomes based on binomial comparisons of preoperative to postoperative changes for CNC words and AzBio sentences for the implanted ear at the 6-month endpoint. The secondary endpoint objectives were met: over 75% of the subjects demonstrated equal or improved performance on CNC words, phonemes, and AzBio sentences with the hybrid implant relative to performance with a hearing aid. Specifically, 96% and 92% of subjects performed equal or better on CNC words and phonemes, respectively, and 90% on AzBio sentences. Furthermore, 82% and 86% showed improved performance on CNC words and phonemes, respectively, and 74% improved on sentences. Results were similar at other study time points (3 and 12 months).

Subgroup Results

The consistency of the primary endpoints for the treated ear was examined across subject subgroups defined by baseline characteristics: gender, age, duration of hearing loss, duration of severe-to-profound high-frequency hearing loss, etiology, and baseline speech perception scores. Results indicated that baseline characteristics gender, age, and duration of hearing loss were the main factors in terms of speech perception outcomes. This was not the case for duration of severe-to-profound high-frequency hearing loss, etiology, and baseline speech scores. Mean benefit scores (i.e., improvement) for females were significantly greater than males for CNC words (females: 48.8%; males: 25.7%) and AzBio tests (females: 42.6%; males: 23.5%) ($P = 0.002$ and 0.02, respectively.) Subjects under the median implantation age of 68 years showed significantly greater benefit for CNCs (< 68 years: 46.6%; > 68 years: 27.8%) ($P = 0.01$) but not AzBio sentences (< 68 years: 41.0%; > 68 years: 25.0%) ($P = 0.05$), although the trend favored younger subjects. The mean benefit for subjects below the median hearing loss duration of 23.5 years was significantly better ($P = 0.01$) than for hearing loss durations above 23.5 years for CNCs (< 23.5 years: 46.2%; > 23.5 years: 27.5%) but not AzBio sentences (< 23.5 years: 40.7%; > 23.5 years: 24.7%) ($P = 0.05$), although the trend favored shorter durations.

TABLE II.
Summary of Co-Primary Efficacy Endpoints.

(N=50)†	Acoustic Alone Preoperative Mean ± S.D.	Hybrid Mode 6 Months Postactivation Mean ± S.D.	Percentage Point Change Mean ± S.D. (95% C.I)
Word scores*	28.4% ± 14.7%	64.2% ± 26.6%	35.8 ± 27.7 (27.9, 43.7)
AzBio scores*	16.3% ± 14.4%	48.3% ± 31.3%	32.0 ± 29.4 (23.7, 40.4)

*Word scores: $p < 0.001$; AzBio scores: $p < 0.001$
†One subject missed 6-month assessments and data were imputed based on the 3-month evaluation.
S.D. = standard deviation.

TABLE III.
Summary of Secondary Objectives for CNC Words and AzBio Sentences in Noise.

	CNC Words	CNC Phonemes	AzBio in Noise
Proportion of subjects with postoperative score equal to or better than preoperative score:	96%	92%	90%
Proportion of subjects with postoperative score better than preoperative score:	82%	86%	74%

CNC = consonant-nucleus-consonant.

Bilateral Outcomes

Mean differences for CNC words and AzBio sentences in noise at 6-months postactivation, using the implant and contralateral hearing aid, were preoperatively compared to bilateral amplification. For CNCs, subjects (N = 49) showed significant ($P < 0.001$) improvement of 34.7 percentage points (SD = 17.4) compared to bilateral amplification. For AzBio sentences, subjects (N = 49) showed significant ($P < 0.001$) improvement of 33.0 percentage points (SD = 23.5) compared to bilateral amplification. No subject showed a significant decrement preoperatively to postoperatively on either measure. At the 6-month endpoint, all subjects performed equal or better than preoperatively with bilateral amplification with hearing aids.

Patient Self-Assessments

Forty-eight subjects completed the SSQ preoperatively using hearing aids and after 6 months using the hybrid system in the everyday listening condition. For the Speech Hearing Scale, subjects improved significantly ($P < 0.001$), showing a mean change score of 2.2 (SD = 1.8). On the Spatial Hearing Scale, there was a significant ($P < 0.003$) mean change score of .9 (SD = 2.0); on the Sound Quality Scale, subjects experienced significantly ($P < 0.001$) improved mean change of 1.3 (SD = 2.0).

Of the 48 subjects who completed the device use survey, four (8%) were "satisfied"/"very satisfied" with preoperative hearing aids, whereas 38 (79%) were "satisfied"/"very satisfied" with the hybrid device.

Adverse Events

Sixty-five adverse events involving 34 of 50 subjects were reported (Table IV). The type and frequency of events were consistent with those reported in cochlear implantation (e.g., electrode open or short circuits, postoperative dizziness, changes in tinnitus) or other mastoid operations; no unanticipated adverse events were reported. Fifty events were medical/surgical in nature and included instances of increased tinnitus, vertigo, and other symptoms associated with a mastoidectomy with facial recess approach used in cochlear implantation. It should be noted that the nine adverse events reporting of dizziness, imbalance, and vertigo were likely reported by a few patients and not nine separate patients; one could have symptoms of dizziness,

TABLE IV.
Number and Percentage of Adverse Events Observed for Hybrid L24 Subjects.

Event	Number of Events	Percentage of Events	Number of Subjects with Event	Percentage of Subjects
Profound/total loss	22	33.8%	22	44.0%
Open/short-circuited electrodes	11	16.9%	11	22.0%
Increased tinnitus	6	9.2%	6	12.0%
Tinnitus not present preoperatively	6	9.2%	6	12.0%
Dizziness	3	4.6%	3	6.0%
Dizziness with change in hearing	2	3.1%	2	4.0%
Increased tinnitus with change in hearing	2	3.1%	2	4.0%
Skin irritation due to externals	2	3.1%	2	4.0%
Sound quality issue	2	3.1%	2	4.0%
Decrease in performance	1	1.5%	1	2.0%
Imbalance	1	1.5%	1	2.0%
Imbalance with change in hearing	1	1.5%	1	2.0%
Increased impedances with change in hearing	1	1.5%	1	2.0%
Local stitch infection	1	1.5%	1	2.0%
Overstimulation	1	1.5%	1	2.0%
Pain in implant ear	1	1.5%	1	2.0%
Vertiginous symptoms with change in hearing	1	1.5%	1	2.0%
Vertigo	1	1.5%	1	2.0%
Total	65			

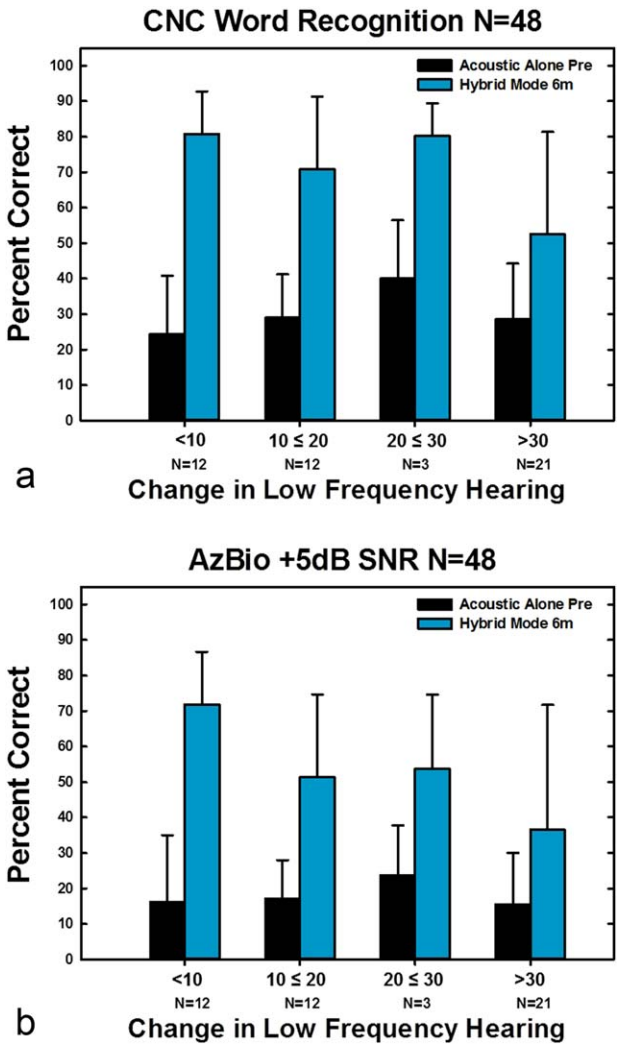

Fig. 2. (a) CNC word scores for subjects with < 10, 10–20, 20–30, and > 30 dB of hearing loss at 6 months post-cochelar implant activation. The number of subjects in each category of hearing loss is shown. (b) AzBio +5 dB signal-to-noise ratio scores for subjects with < 10, 10–20, 20–30, and > 30 dB of hearing loss at 6 months post-cochlear implant activation. The number of subjects in each category of hearing loss is shown.
Abbreviations: CNC = consonant-nucleus-consonant; SNR = signal-to-noise ratio. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

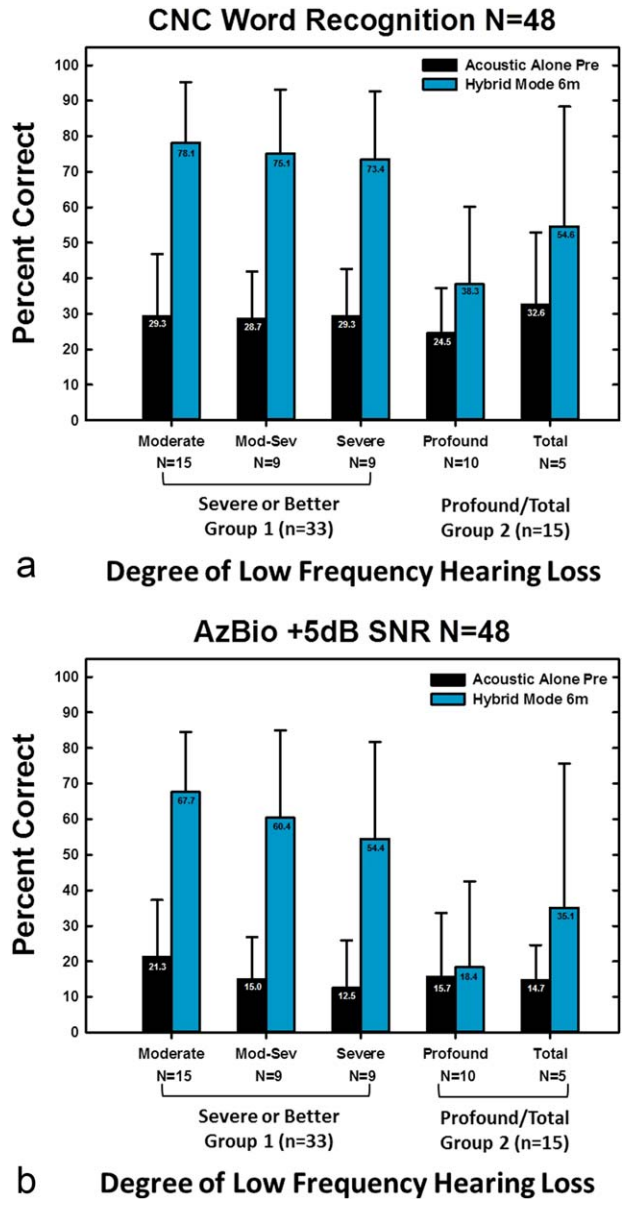

Fig. 3. (a) The CNC word scores for subjects in each category of low-frequency hearing loss. The number of subjects in each category of low-frequency hearing loss is shown. (b) The AzBio +5 dB signal to noise ratio scores for subjects in each category of low-frequency hearing loss. The number of subjects in each category of low-frequency hearing loss is shown.
Abbreviations: CNC=consonant-nucleus-consonant; SNR = signal-to-noise ratio. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

imbalance, and vertigo. This trial specified implanting subjects with functional low-frequency acoustic hearing. Unlike prior CI trials, this was the first to quantify changes in residual hearing; any changes in preoperative to postoperative hearing sensitivity were measured throughout the study period. Changes resulting in profound (> 90 dB HL) hearing loss were reported as anticipated adverse events. At 6-months postactivation, 66% of subjects (33 of 50) retained functional acoustic sensitivity determined by a 5-frequency pure tone average (125, 250, 500, 750, 1000 Hz) of a severe degree or better (≤ 90 dB HL). The degree of hearing loss and the number of subjects in each hearing loss category and their postintervention outcomes are depicted in Figure 2a and b. In addition, the amount of residual hearing and the number of subjects in each category and their postintervention outcomes are depicted in Figure 3a and 3b. Subjects with aidable, residual hearing performed better that those without aidable, residual hearing. However, even if subjects had no residual, aidable hearing, they performed better in the CI electric-only condition than preoperatively with hearing aids. Regarding 17 subjects who did not maintain functional acoustic hearing, five chose to have the hybrid implant explanted and replaced with a standard CI. These revision surgeries were successful, with full insertions achieved in all cases.

Improved speech perception of varying degrees was observed compared to that obtained preoperatively with a hearing aid and at the most recent hybrid evaluation prior to revision surgery. Based on self-assessments, these subjects were satisfied with their outcomes.

There were 15 device-related events. Apart from cases of profound hearing loss, all but two events (one sound quality issue and one decreased performance) were resolved as of database closure.

Association of baseline characteristics with adverse events, including profound hearing loss, was examined by univariate Cox proportional hazards regression models. Baseline characteristics evaluated included age at implantation, hearing loss duration, severe-to-profound hearing loss duration, etiology, and preoperative speech perception. None were found to be significantly associated with either outcome of an adverse event or profound hearing loss.

DISCUSSION

Results from this study support the conclusion that the Nucleus Hybrid System (Cochlear) delivers significantly improved speech understanding in quiet and noise compared to a hearing aid for individuals with bilateral, severe high-frequency hearing loss. Ninety percent of subjects achieved the same or better performance on both speech perception measures when listening with the hybrid system. When using both ears, all subjects performed equal or better than preoperatively on both measures. The SSQ self-assessment supported speech intelligibility results, with significant improvement on all scales and with greatest improvement on the Hearing Speech Scale. On overall listening satisfaction, the number of individuals satisfied increased from 8% preoperatively with amplification to 79% with the hybrid system.

This system delivers important high-frequency information through electrical stimulation and the opportunity to combine it with beneficial low-frequency residual hearing in one or both ears. Outcomes for five subjects undergoing revision surgery suggest that a standard CI remains a viable treatment when hybrid implantation does not meet expectations.

Current hearing aid technology often cannot provide audible, clear high-frequency sound for individuals with this type of hearing loss. Individuals with substantial high-frequency losses frequently have nonfunctional inner and outer hair cells; therefore, amplification cannot be effective. Individuals with precipitously sloping losses predictably are frustrated due to significant communication struggles; they regularly reject amplification, leaving them with no alternative treatments prior to availability of the hybrid system.

Limitations to the study include the nonrandomized design, limited sample size, and duration of follow-up. Using subjects as their own control enables clinically meaningful comparisons that account for patient heterogeneity, and use of standardized objective measures of hearing helps ensure validity. The effect and sample size were large enough to produce statistically significant improvements after 6 months follow-up; additional longer term follow-up for safety and study of the device in larger and diverse subgroups is important.

CONCLUSION

The hybrid system successfully provides high-frequency sensitivity essential for good speech understanding. Typically, this is not accessible through amplification for individuals with bilateral severe high-frequency hearing loss and beneficial, aidable low-frequency hearing. This system is a new and effective treatment that provides clinically significant improvements in speech understanding through integrated electric and acoustic stimulation in the implanted ear, with additional benefit when listening using both ears—thus fulfilling a need in individuals who to date have had no other treatment options.

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BIBLIOGRAPHY

1. Bainbridge KE, Wallhagen MI. Hearing loss in an aging American population: extent, impact, and management. *Annu Rev Public Health* 2014;35: 139–152.
2. Lin FR, Yaffe K, Xia J, et al. Hearing loss and cognitive decline in older adults. *JAMA Intern Med* 2013;173: 293–299.
3. Hearing Health Foundation. Hearing loss & tinnitus statistics. Available at: http://hearinghealthfoundation.org/statistics?gclid=CLb8wcXlp8ACFScV7Aod0HAAFg. Accessed August 22,2014.
4. Hornsby BW, Ricketts TA. The effects of hearing loss on the contribution of high- and low-frequency speech information to speech understanding. *J Acoust Soc Am* 2003;113:1706–1717.
5. Amos NE, Humes LE. Contribution of high frequencies to speech recognition in quiet and noise in listeners with varying degrees of high-frequency sensorineural hearing loss. *J Speech Lang Hear Res* 2007;50: 819–834.
6. Turner CW. Hearing loss and the limits of amplification. *Audiol Neurotol* 2006;11(suppl 1):2–5.
7. Hornsby BW, Ricketts TA. The effects of hearing loss on the contribution of high- and low-frequency speech information to speech understanding. *II. Sloping hearing loss. J Acoust Soc Am* 2006;119:1752–1763.
8. Hornsby BW, Johnson EE, Picou E. Effects of degree and configuration of hearing loss on the contribution of high- and low-frequency speech information to bilateral speech understanding. *Ear Hear* 2011;32:543–555.
9. Moore BC, Alcantara JI. The use of psychophysical tuning curves to explore dead regions in the cochlea. *Ear Hear* 2001;22:268–278.
10. Moore BC. Dead regions in the cochlea: conceptual foundations, diagnosis, and clinical applications. *Ear Hear* 2004;25:98–116.

11. Zhang T, Dorman MF, Gifford RH, Moore BCJ. Cochlear dead regions constrain the benefit of combining acoustic stimulation with electric stimulation. *Ear Hear* 2014;35:410–417.
12. Gifford RH, Dorman MF, Spahr AJ, McKarns SA. Effect of digital frequency compression (DFC) on speech recognition in candidates for combined electric and acoustic stimulation (EAS). *J Speech Lang Hear Res* 2007;50:1194–1202.
13. Gantz BJ, Turner C, Gfeller KE, Lowder MW. Preservation of hearing in cochlear implant surgery: advantages of combined electrical and acoustical speech processing. *Laryngoscope* 2005;115:796–802.
14. Kiefer J, Pok M, Adunka O, et al. Combined electric and acoustic stimulation of the auditory system: results of a clinical study. *Audiol Neurotol* 2005;10;134–144.
15. Lenarz T, James C, Cuda D, et al. European multi-centre study of the Nucleus Hybrid L24 cochlear implant. *Int J Audiol* 2013;52: 838–848.
16. Gatehouse S, Noble W. The speech spatial and qualities of hearing scale (SSQ). *Int J Audiol* 2004;43:85–99.
17. Cochlear Nucleus Hybrid L24 Implant Surgeon's Guide. *CI24REH*. Sydney, Australia: Cochlear Limited; 2014.
18. Peterson GE, Lehiste I. Revised CNC lists for auditory tests. *J Speech Hear Disord* 1962;27:62–70.
19. Spahr AJ, Dorman MF, Litvak LM, et al. Development and validation of the AzBio sentence lists. *Ear Hear* 2012;33:112–117.
20. Thornton AR, Raffin MJ. Speech-discrimination scores modeled as a binomial variable. *J Speech Hear Res* 1978;21:507–518.

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Does Coupling and Positioning in Vibroplasty Matter? A Prospective Cohort Study

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Objective: Vibroplasty has offered a new modality of hearing rehabilitation in patients with mixed, conductive, and sensorineural hearing loss who cannot wear hearing aids. Potentially, the positioning of the floating mass transducer (FMT) in vibroplasty surgery has a critical effect on hearing outputs. In this study, the impact on hearing outputs and coupling efficiency are evaluated by comparing various vibroplasty applications in the middle ear. No other study to date has examined the coupling efficiency of round window (RW) versus an ossicular vibroplasty application.
Study Design: Prospective cohort study of patients with underlying ear pathologies who were not able to wear hearing aids.
Methods: This is an ongoing prospective study of 16 patients. All patients had a standard audiological test battery. Direct drive transfer function analysis results were correlated with bone conduction thresholds to assess the efficiency of the FMT coupling. Speech perception in quiet and quality of life measure questionnaires were used to assess outcomes. Nine patients had round window vibroplasty, six patients had stapes vibroplasty, and one patient had traditional incus vibroplasty.
Results: Patients with a soft tissue coupler between the FMT and the RW had significantly reduced coupling efficiency. Patients who had direct RW contact had significantly improved coupling efficiency. Patients who underwent stapes or incus vibroplasty had the greatest coupling efficiency.
Conclusion: This study demonstrates that attachment to the stapes or incus provides the best coupling when compared to round window vibroplasty. When applicable, stapes or incus coupling should be the first choice when implementing vibroplasty. **Key Words:** Coupling efficiency—Floating mass transducer—Middle ear—Middle ear implants—Vibrant Soundbridge—Vibroplasty.

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For patients with hearing loss, conventional hearing amplification is sometimes not an option because of medical contraindications or amplification limitations. Medical contraindications include conditions that affect the wearing of hearing aids or molds within the ear canal such as chronic otitis externa, aural atresia, or patients who have had multiple ear surgeries for chronic ear disease. A hearing aid is often unable to provide sufficient amplification in cases of significant mixed hearing loss.

The use of middle ear implants such as the Vibrant Soundbridge (VSB), with its floating mass transducer (FMT), provides a possible solution to the limitations of conventional hearing aids.

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Supplemental digital content is available in the text.

The FMT can be placed on different elements of the middle ear (termed vibroplasty) such as the incus and stapes or on the round window (RW).

Transmission of sound through the skin and skull (percutaneous coupling) through a device such as the Baha (bone-anchored hearing aid) can provide good results for those with conductive hearing loss, mild mixed hearing losses (1), and cases of atresia (2). At the commencement of this study, the Baha 3 Power BP110 (Cochlear Ltd, Australia) head-level processor had sufficient gain for cochlear losses of up to and including 55 dB HL whereas the VSB (Vibrant Soundbridge; Med-EL, Innsbruck) is reported to provide gain for cochlear losses of up to 65 dB at 2 to 4 kHz. Furthermore, infection rates with the percutaneous devices can range from 6.7 (3) to 38% of patients experiencing severe skin reactions (4). The VSB can provide ear-specific information which could be an asset with asymmetrical cochlear hearing loss.

The round window vibroplasty has been used since 2005 (5) for mixed and conductive losses. However, the optimal positioning and coupling of the FMT in vibroplasty is an

ongoing debate among the experts. Different variables such as the type of vibroplasty, the level of FMT-RW contact, and the use of soft tissue or titanium couplers all affect the efficiency and outcomes. It is unclear whether better results are achieved by placing the FMT in direct contact with the RW membrane or using an interposed material such as fascia or Tutoplast. It is also unknown whether stapes or incus vibroplasty is comparable to RW vibroplasty with regard to coupling and outcomes especially in cases such as atresia or chronic ear disease where frequently both vibroplasty options can be implemented. This study aims to provide more insight into these aspects.

RW vibroplasty poses surgical challenges that are associated with the anatomy of the round window. There is a clear mismatch between the size of the round window membrane (RWM) with a mean diameter of 0.92 mm (6) and the size of the FMT with a diameter of 1.8 mm and a length of 2.3 mm. Furthermore, the shape of the RW niche and the actual location of the RW membrane present additional challenges. Frequently, the RW niche is funnel-shaped with the RW membrane sitting at the deep narrow end away from the rim of the niche, thus making direct placement impossible, even with the available couplers. Pennings et al. (7) noted that the size of the RW niche and the angle and exposure of the RW membrane were highly variable in 10 cadaveric temporal bones. In addition, many patients who would benefit from the RW application of the VSB have already undergone multiple middle ear surgeries making placement of the FMT challenging due to fibrosis of the middle ear or fibrous obliteration of the RW niche. Rajan et al. (8) demonstrated that whereas the FMT needed to be in contact with the RW to attain good coupling efficiency, the degree of contact required was not a factor in patient outcomes. Therefore, even in cases of partial contact, good hearing outcomes were attained for these subjects. This would potentially be in contrast to patients with a mixed hearing loss who rely on best possible coupling to maximize the amplifying gain and minimize loss of sound transfer energy caused by inefficient FMT coupling.

The role of couplers or soft tissue interposition is controversial. The literature is divided into cadaveric and in vivo patient studies. The latter is more pertinent for making clinical decisions given we are dealing with ''living tissue'' in which there are healing processes and scar tissue formation.

There are human temporal bone studies that demonstrate the improved coupling efficiency of the use of interposed fascia between the FMT and the RWM (7,9–11), and in addition, some clinicians recommend the additional use of a cartilage or soft tissue cap behind the FMT to create some pretension on the FMT which improves the coupling to the RW membrane (7,9,10).

Colletti et al. (12) recommend the use of interposed fascia with ECoG (electrocochleography) measurements guiding optimal placement of the FMT intraoperatively. Conversely, Skarzynski et al. (13) report better coupling with direct FMT to RW contact. Mandala et al. (14) examined positioning of the FMT in 14 children with congenital aural atresia and conductive or mixed hearing loss, and their results found that fascia overlying the FMT and cartilage packing gave the best ECoG recordings.

Rajan et al. (8) investigated the coupling efficiency in seven patients with mixed HL and one with conductive hearing loss. It was demonstrated that all patients had a significant improvement on speech in quiet and in noise scores postoperatively compared with preoperative outcomes. It was also found that coupling efficiency was higher with partial or complete direct contact of the FMT with the RWM and reduced when soft tissue coupling was used. This was one of the first studies that used objective coupling efficiency measurements to demonstrate whether partial or full contact with the RW is essential and whether use of interposed fascia gave better coupling in the RW-FMT application.

This study expands the work of Rajan et al. (8) by examining the coupling efficiency when the FMT has been in contact with the RW either directly or with fascial underlay or crimped to the stapes or the incus.

MATERIALS AND METHODS

Patients

Ethics approval was obtained for this prospective study from the local ethics committee and was in accordance with the Helsinki Declaration. Sixteen patients (nine female, seven male) are involved to date. The average age at implantation was 56.3 years (range 19–78). Nine patients presented with a conductive hearing loss, six had a mixed hearing loss, and one patient a sensorineural hearing loss. All subjects could not benefit from conventional hearing aids because of chronic otitis externa (Subjects 9, 12), chronic suppurative otitis media (Subjects 1, 3, 4, 5, 6, 7, 8, 10, 11, 13, 14, 16), severe to profound mixed hearing loss (Subject 2), and a non-healing external auditory canal resulting from carcinoma removal (Subject 15). The cochlear (bone conduction hearing threshold) of all patients met the manufacturer's specifications and all patients had speech perception results above 50% in the ear considered for implantation. All patients, except Subject 15 who had an open wound in the external auditory canal, trialed a behind-the-ear hearing aid before consideration for the VSB. All surgeries were conducted by an experienced middle ear and implantable device surgeon. See Table 1 for patient demographics and the surgical procedure employed.

The mean hearing loss in the implanted ear using the four-frequency average of air conduction thresholds was 60.4 dB HL (SD = 24.3 dB) and the mean bone conduction threshold was 25.9 dB HL (SD = 10.1 dB). In the non-implanted ear, the mean air conduction four-frequency average was 40.7 dB HL (SD = 25.5 dB) and the bone conduction average was 23.0 dB HL (SD = 10.1 dB).

Materials

All patients received the Vibrant Soundbridge (Vibrant Med-EL, Innsbruck, Austria). Eight patients wore the 404 Audio processor and eight patients wore the Amadé processor. Patients with bone conduction thresholds less than or equal to 25 dB in one frequency were fitted with the Amadé Lo external processor and patients with worse bone conduction thresholds were fitted with the Amadé Hi processor.

TABLE 1. *Subject characteristics, implanted ear pathology, surgical history pre-VSB surgery, and VSB surgical technique employed; 1) fascial recess approach to round window (Fascial Rec) and 2) round window placement in modified radical cavities (RW in MRC); age (yr), four-frequency average (4FAHL) of implanted ear; bone and air conduction*

Subject No.	Pathology	No. of Surgeries pre-VSB	VSB Surgical Technique	FMT Coupling	Age, yr	Bone Conduction 4FAHL	Air Conduction 4FAHL
1	CSOM	4	RW in MRC	Direct Partial	61	10	41
2	Otosclerosis	1	Fascial Rec	Fascia	53	38	101
3	CSOM	4	RW in MRC	Direct Partial	57	29	68
4	CSOM	2	RW in MRC	Fascia	28	23	70
5	CSOM + otosclerosis	4	RW in MRC	Direct Complete	47	20	51
6	CSOM	2	RW in MRC	Fascia	73	21	78
7	CSOM	2	RW in MRC	Direct Partial	53	18	58
8	CSOM	3	RW in MRC	Fascia	79	40	91
9	Otitis externa	1	Post crus of stapes	Stapes	60	16.3	22
10	CSOM	1	Post crus of stapes	Stapes	19	33	85
11	CSOM and congenital abnormality	0	Post crus of stapes	Stapes	31	28.8	37.5
12	Otitis externa	1	Long process of incus	Incus	60	15	27.5
13	CSOM	1	Post crus of stapes	Stapes	74	21.3	80
14	CSOM	2	Post crus of stapes	Stapes	64	20	26
15	External auditory meatus—non-healing post-carcinoma removal	2	Post crus of stapes	Stapes	78	45	60
16	CSOM	1	RW in MRC	Partial	63	36.3	70

CSOM indicates chronic suppurative otitis media.

Methods

Coupling Method

Coupling method was defined for each patient according to whether they had an intact ossicular chain or an ossicular chain remnant in which case the stapes or incus was used as an attachment point. If the round window vibroplasty was employed, then there was either (1) fascia interposed and fascial covering FMT or (2) direct coupling with no fascia interposed but fascial covering. In cases of direct coupling, FMT contact was further delineated by either complete or partial contact. See Figure 1.

Four subjects had fascia interposed between the FMT and RW as per the method of Colletti et al. (5). These patients had a size mismatch between the RWM and the FMT, and a ''coupler'' in the form of soft tissue was required to establish a connection between the transducer and the membrane. For patients where

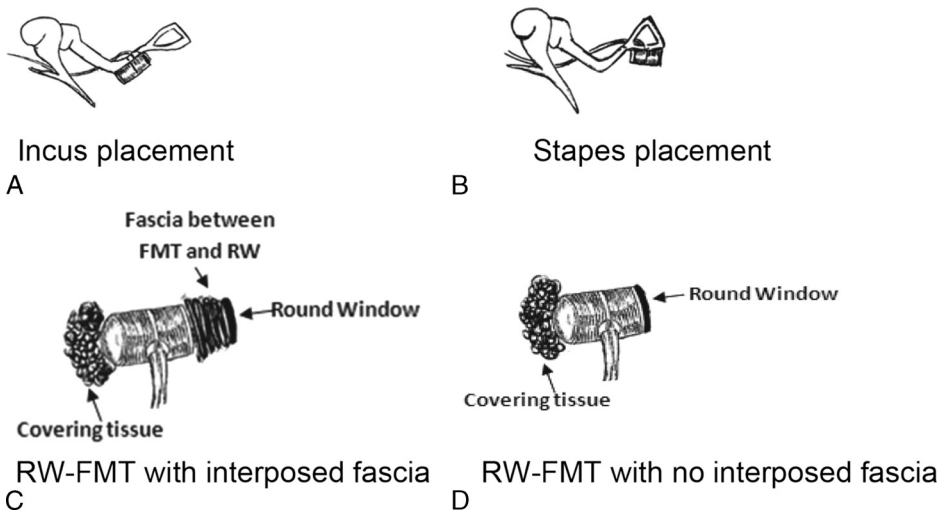

FIG. 1. Diagrammatic representation of FMT positioning. *A*, incus placement. *B*, stapes placement—posterior crus. *C*, RW-FMT with interposed fascia. *D*, RW-FMT with no interposed fascia.

direct contact between the FMT and RWM could be attained, the ''direct coupling with no fascia interposed'' technique as per Rajan et al. (8) was utilized.

Vibroplasty Coupling Measurements

The measurement of the vibroplasty thresholds is similar to pure-tone audiometry with the stimulus being presented via the FMT. All vibroplasty measurements were implemented using a spare clinic Amadé low processor and the ''vibrogram'' function available in the manufacturer's software. The vibrogram is a pure-tone audiogram measured through the VSB processor and implant. Behavioral vibroplasty thresholds are determined by applying the modified Hughson-Westlake method (15). It is now common procedure and recommended by the manufacturers to use the thresholds attained via the vibrogram, to set the processor's initial fitting levels.

Results are reported on a decibel scale, which is normalized to the maximum transducer excitation voltage of the FMT (dB re. 4.47 μV). To find a relationship between vibroplasty thresholds and traditional bone conduction thresholds, the vibroplasty thresholds are entered into a scatter plot versus corresponding bone conduction thresholds. In addition, a linear trend is calculated for each test frequency. The orthogonal distance between the trend line and data points of one individual subject, measured in decibels and averaged across all test frequencies, is used to calculate the relative coupling efficiency. The underlying assumption is that data points below the regression line are indicative for ''good'' coupling, which means ''better than the average within the study''. Please see Supplementary Digital Content 1 (http://links.lww.com/MAO/A316) for an example of how coupling efficiency is calculated.

Audiologic Testing—Speech in Quiet

Standard audiologic measures included air and bone conduction testing, and monosyllabic speech perception testing using AB (Arthur Bootroyd) Words (16). These were conducted preoperatively and at 1, 3, 6, and 12 months postoperatively and annually thereafter.

The free field speech testing in quiet consisted of recorded Consonant Nucleus Consonant (17) (CNC) monosyllabic words presented at 65 dB SPL through a speaker located 1 m directly in front of the patient in the following conditions:

1. implanted ear unaided, and
2. implanted ear wearing the VSB.

The contralateral ear was effectively masked.

Quality of Life Measure

The Tinnitus Reaction Questionnaire (TRQ; 19) was used to assess the impact of tinnitus on well-being, emotions, and lifestyle. The TRQ was completed before and 3, 6, and 12 months post-surgery after to compare the postoperative outcomes. A maximum score of 104 and a minimum score of 0 can be attained on the TRQ. A score of 17 and above denotes clinically significant tinnitus disturbance.

Surgical Technique

A diagrammatic representation of the FMT positions employed can be seen in Figure 1. When coupling the FMT to the stapes or incus, it was critical to confirm transmission through the chain or remnant via the presence of the round window reflex. This involved palpation of the stapes which induces a movement of the RWM. The FMT is then crimped onto the long process of the incus or the posterior crus of the stapes superstructure. When the FMT is placed against the round window, the FMT titanium attachment clip is removed. The FMT conductor link cable is then preshaped to allow placement of the FMT against the RWM. This is after reduction of the superior and anterior lip of the round window niche to facilitate the FMT contact with the RWM. In cases of a funnel-shaped or a deep, narrow round window niche, only a limited degree of lip reduction is possible as the risk of an injury to the cochlear endosteum or RWM is high.

Statistical Analysis

A Mann-Whitney *U* test was used to compare coupling efficiency of the FMT in various placements: (a) fascia between FMT and RW, (b) direct FMT contact, (c) FMT crimped to incus (long process), and (d) FMT crimped to stapes (on the posterior crus). The Wilcoxon signed-rank test was used to determine if there was a significant change in results of speech recognition in quiet.

To detect differences between the preoperative TRQ test results, a difference of 40% was deemed to be significant as per the recommended analysis (18). A nonparametric Wilcoxon signed-rank test was also applied.

RESULTS

Surgical Outcomes

Of the 16 patients, three required FMT re-positioning within the first 6 months after implantation as per the results

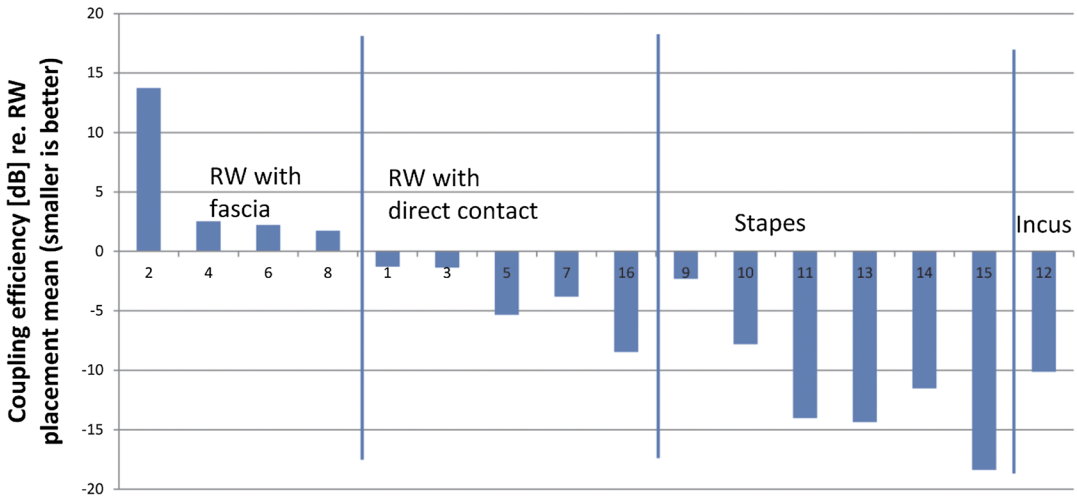

FIG. 2. Summary of coupling efficiency for individual patients. The smaller value is consistent with better coupling efficiency.

of Rajan et al. (8). No subjects undergoing incus or stapes vibroplasty experienced any postoperative complications.

Coupling Measurements

The relation of vibroplasty thresholds and bone conduction thresholds is shown in Figure 2.

Patients with a soft tissue coupler between the FMT and the RW had significantly reduced coupling efficiency as analyzed by a Mann-Whitney *U* test ($p < 0.05$) when compared to all other coupling configurations. When the round window direct placement group's coupling efficiency was compared to that of the round window fascia group, the difference was significant ($p < 0.05$). When the average of the combined RW application groups (both direct contact subjects and fascia interposed subjects) was compared to the stapes vibroplasty, the coupling for the stapes vibroplasty was significantly better ($p < 0.05$). There was also a difference, though not significant ($p = 0.08$), between the round window direct and the stapes vibroplasty groups with the stapes group demonstrating the trend for

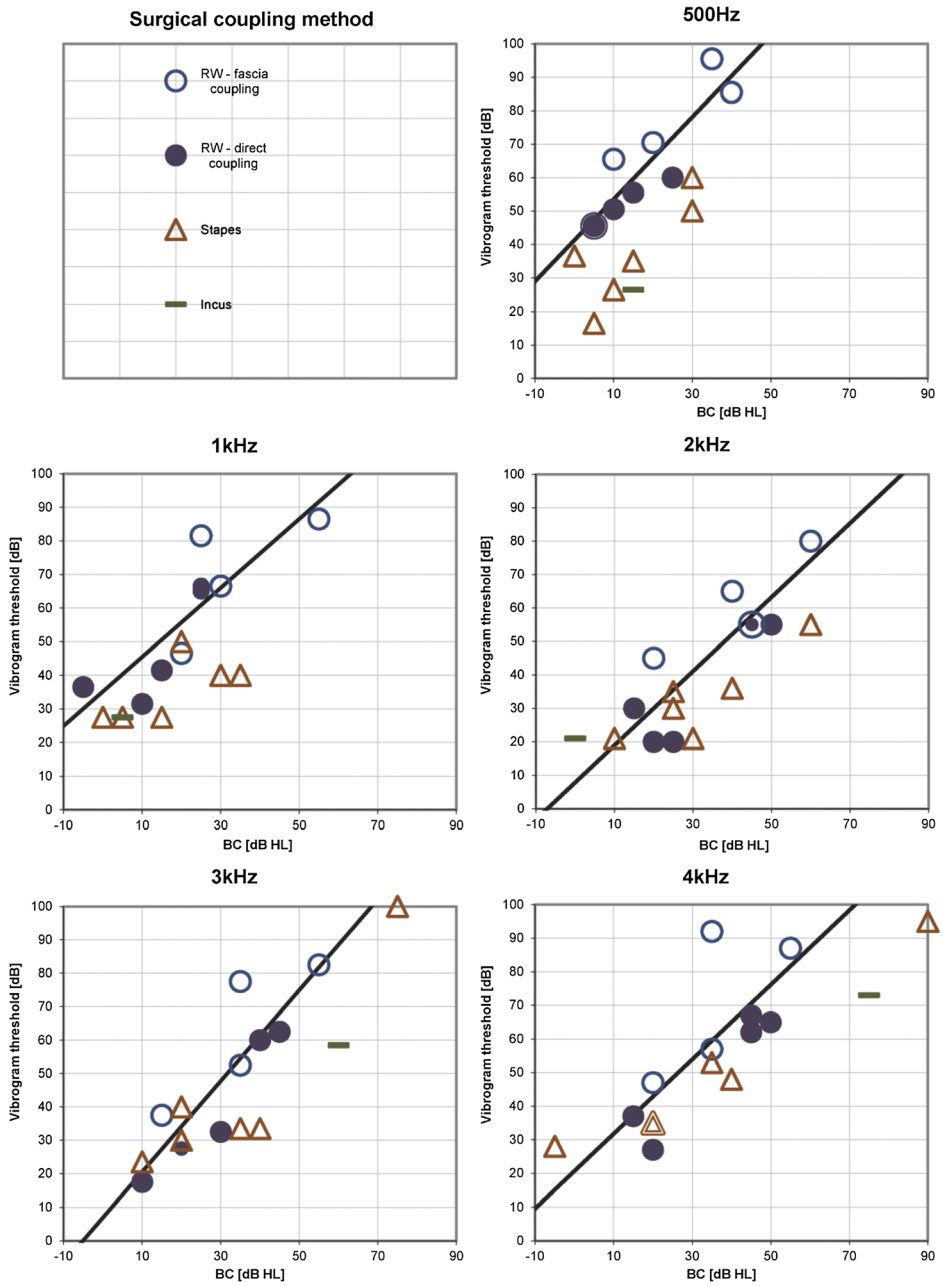

FIG. 3. Vibroplasty of the 16 patients across the different frequencies. Patients with stapes and incus coupling as well as those with direct coupling have below average functions reflecting better coupling efficiency. The underlying assumption is that data points below the regression line are indicative of "good" coupling.

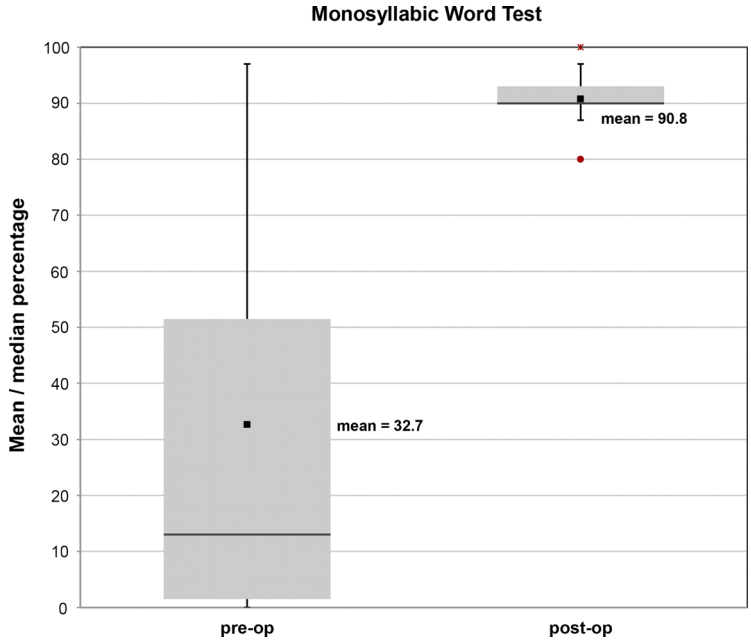

FIG. 4. Speech perception scores. Monosyllabic word test—preoperative versus postoperative percent correct. Note: Mean values are depicted as *black quadrants*; median values as *horizontal lines*. *Circles* and *asterisks* represent outliers.

better coupling efficiency. Please see Supplementary Digital Content 2 (http://links.lww.com/MAO/A317) for full statistical test results.

Figure 3 shows the relative coupling efficiency across frequencies. It was found that the fascia coupling group had a lower coupling efficiency across the frequencies as reflected in their thresholds being to the left of the ''best fit'' line.

Audiologic Testing—Speech in Quiet Outcomes

The improvement in monosyllable speech perception from preoperative to postoperative testing was significant ($p < 0.001$). An average unaided score of 32.7% (SD 35.35%) was attained, compared to 90.8% (SD 5.53%) with the VSB. See Figure 4.

Tinnitus Outcomes

Tinnitus levels decreased for the three subjects (Subjects 2, 4, and 11) experiencing tinnitus pre-surgery. Subjects 4 and 11, with VSB use, experienced a decrease of their tinnitus perception to a nonsignificant level according to the clinical criteria (TRQ ≤17; Wilson et al. [18]) and their percentage score had diminished by more than 40%. See Figure 5 which demonstrates the pre- versus post-VSB tinnitus perception results. The difference in TRQ scoring between pre- and postoperative testing was significant ($p < 0.05$).

DISCUSSION

This study hypothesized that coupling the FMT to the ossicles would provide at least equivalent coupling

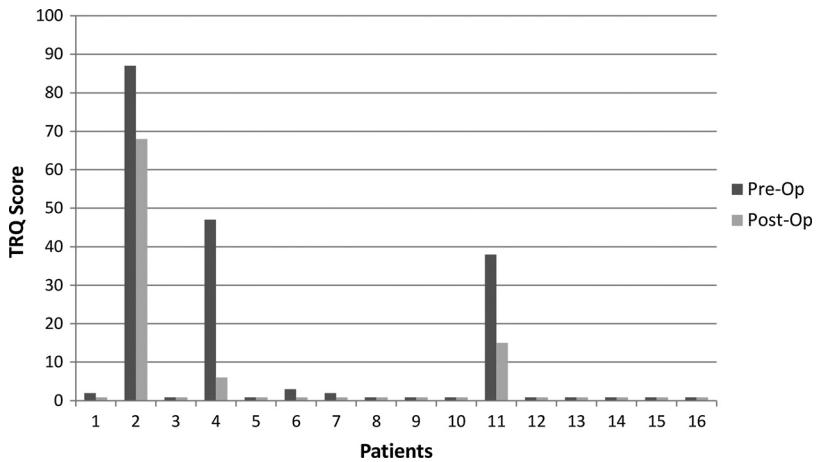

FIG. 5. Tinnitus perception scores as measured by the TRQ (Tinnitus Reaction Questionnaire).

efficiency when compared to round window coupling. It was also hypothesized that regardless of the coupling technique, patients would attain benefits in regards to speech perception and quality of life outcomes.

Initial results in our cohort confirmed that ossicular coupling provides better coupling efficiency than the round window application. In particular, stapes coupling provides the most efficient coupling and the least efficient coupling was when utilizing round window vibroplasty with interposed fascia between the FMT and round window. This finding held true across the frequencies tested. Therefore, based on our clinical in vivo data, coupling the FMT to the ossicular chain or remnants of the chain wherever possible is the preferred option for sensorineural, mixed, or conductive hearing losses.

As well as providing improved coupling efficiency, an ossicular attachment point is less surgically challenging. No drilling of the RW niche is required when using the ossicular chain as an attachment point, thus reducing the risk of iatrogenic sensorineural hearing loss. It also removes the surgical complexity associated with the high degree of variability evidenced in RW anatomy across individual patients. From the patients' perspective, coupling to the ossicular chain allows immediate postoperative VSB activation.

The ossicular chain attachment also reduces the risk of the FMT migration encountered in RW vibroplasty. None of the subjects in this study with stapes or incus placement experienced FMT migration. This is in line with other published data with only one reported FMT displacement in the classic incus application in a patient who underwent magnetic resonance imaging and required revision surgery to re-attach the FMT to the incus (19). In contrast, revision surgery has been required because of FMT displacement in RW vibroplasty. Marino et al. (20) noted 4 of 18 subjects, Skarzynski et al. (13) report 2 of 21 subjects, and Baumgartner et al. (21) report 1 of 12 patients.

Patients who typically require an implantable hearing solution such as the VSB have an underlying chronic middle ear pathology which could potentially persist after device implantation (22). With a more ''secure'' attachment point such as the stapes or incus, the risk of a recurring active middle ear condition affecting FMT placement is perhaps reduced compared to a RW placement. It is important, however, to determine that there is a viable ossicular attachment point and that the round window reflex is present before using the stapes as the preferred attachment point. These surgical prerequisites are also reported in other studies (23–25).

The other question was whether in round window vibroplasty the use or non-use of interposed tissue would affect coupling efficiency. Our ongoing results indicate that coupling efficiency was better without interposed tissue. These results are in contrast to recommended surgical protocols which promote the use of interposed fascia or Tutoplast (7,9,10,12,21,26). However, many of the studies supporting the use of interposed tissue are using results from cadavers with results not able to be applied in ''real life'' patients. The tissues in cadavers also demonstrate an altered compliance and elasticity when compared to the tissue behavior in vivo. Extensive drilling of the round window niche to optimize FMT positioning is far less risky in a cadaver where there is no risk of causing additional hearing loss.

The possibility of scar tissue formation or atrophy in the interposed fascia and a reduction in long-term coupling efficiency has been proposed (7). It has also been proposed that interposed fascia is resorbed after a period of time thereby reducing coupling and that perichondrium is superior for interposition as it is more robust and consistent (27). However, it is uncertain how and to what extent the perichondrium becomes resorbed over time.

The size mismatch between the FMT and RW and the variation of the RW niche remain an ongoing challenge rendering direct contact impossible in some cases. Therefore, in these cases, a soft tissue coupler or commercially available clip coupler is necessary to establish an RWM-coupler interface. Though the coupling efficiency is not as effective with a soft tissue coupler, the FMT properties and programming of the external processor can compensate for any coupling inefficiencies, especially in patients with a conductive hearing loss. It is important, however, to consider that patients with significant mixed hearing losses require significant gain which can be only achieved through optimal coupling.

All subjects in this study attained significant hearing benefits post-VSB surgery regardless of the coupling technique employed. These benefits encompassed improved speech perception at normal conversational levels and decreased tinnitus perception in those experiencing tinnitus preoperatively.

The authors recognize that one of the limitations of this study is that the small sample size with outliers having the potential to skew results. Further investigations are being undertaken to determine if results of a larger group of patients are consistent with our initial findings.

CONCLUSION

We were able to demonstrate that vibroplasty modalities using the ossicular chain elements such as the stapes or incus provide best FMT coupling outcomes. In cases where no ossicular chain is present, direct placement of the FMT on the RW membrane, whether it be complete or partial, is the next best option. In cases where the RW anatomy negates direct RW membrane placement, a mechanical interface such as a soft tissue coupler or a clip coupler is crucial for FMT functioning and subsequent good hearing outcomes.

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REFERENCES

1. Snik AF, Mylanus EA, Cremers CW. The bone-anchored hearing aid: a solution for previously unresolved otologic problems. *Otolaryngol Clin North Am* 2001;34:365–72.
2. Yellon RF. Atresiaplasty versus BAHA for congenital aural atresia. *Laryngoscope* 2011;121.

3. Hakansson B, Liden G, Tjellstrom A, et al. Ten years experience with the Swedish bone-anchored hearing system. *Ann Otol Rhinol Laryngol* 1990;151:1–16.
4. Gluth M, Eager K, Eikelboom R, Atlas M. Long-term benefit, perception, complications, and device malfunction rate of bone-anchored hearing-aid implantation for profound unilateral sensorineural hearing loss. *Otol Neurotol* 2010;21:1427–34.
5. Colletti V, Soli SD, Carner M, Colletti L. Treatment of mixed hearing losses via implantation of a vibratory transducer on the round window. *Int J Audiol* 2006;45:600–8.
6. Roland PS, Wright C, Isaacson B. Cochlear implant electrode insertion: the round window revisited. *Laryngoscope* 2007;117: 1397–402.
7. Pennings RJE, Ho A, Brown J, van Wijhe RG, Bance M. Analysis of Vibrant Soundbridge placement against the round window membrane in a human cadaveric temporal bone model. *Otol Neurotol* 2010;31:998–1003.
8. Rajan GP, Lampacher P, Ambett R, et al. Impact of floating mass transducer coupling and positioning in round window vibroplasty. *Otol Neurotol* 2011;32:271–7.
9. Nakajima HH, Dong W, Olson ES, Rosowski JJ, Raviccz ME, Merchant SN. Evaluation of round window stimulation using the FMT by intracochlear sound pressure measurements in human temporal bones. *Otol Neurotol* 2010;31:506–11.
10. Arnold A, Kompis M, Candreia C, et al. The floating mass transducer at the round window: direct transmission or bone conduction? *Hear Res* 2010;263:120–7.
11. Koka K, Holland NJ, Lupo JE, Jenkins HA, Tollin DJ. Electrocochleographic and mechanic assessment of round window stimulation with an active middle ear prosthesis. *Hear Res* 2009; 263:128–37.
12. Colletti V, Mandala' M, Colletti L. Electrocochleography in round window Vibrant Soundbridge implantation. *Otolaryngol Head Neck Surg* 2012;146:633–40.
13. Skarzynski H, Olszewski L, Skarzynski PH, et al. Direct round window stimulation with the Med-EL Vibrant Soundbridge: 5 years of experience using a technique without interposed fascia. *Eur Arch Otorhinolaryngol* 2014;271:477–82.
14. Mandala' M, Colletti L, Colletti C. Treatment of the atretic ear with round window vibrant soundbridge implantation in infants and children: electrocochleography and audiologic outcomes. *Otol Neurotol* 2011;32:1250–55.
15. British Society of Audiology. Recommended procedures for pure tone audiometry using a manually operated instrument. *Br J Audiol* 1981;15:213–16.
16. Bootroyd A. Developments in speech audiometry. *Br J Audiol* 1968;2:3–10.
17. Peterson G, Lehiste I. Revised CNC list for auditory tests. *J Speech Hear Disord* 1962;27:62–70.
18. Wilson PH, Henry J, Bowen M, Haralambous G. Tinnitus Reaction Questionnaire: psychometric properties of a measure of distress associated with tinnitus. *J Speech Hear Res* 1991;34:197–201.
19. Schmuziger N, Schimmann F, àWengen D, Patscheke J, Probst R. Long-term assessment after implantation of the Vibrant Soundbridge device. *Otol Neurotol* 2006;27:183–8.
20. Marino R, Linton N, Eikelboom RH, et al. A comparative study of hearing aids and round window application of the vibrant sound bridge (VSB) for patients with mixed or conductive hearing loss. *Int J Audiol* 2013;52:209–18.
21. Baumgartner WD, Boheim K, Hagen R, et al. The vibrant soundbridge for conductive and mixed hearing losses; European multicenter study results. *Adv Otorhinolaryngol* 2010;69:38–50.
22. Boheim K, Mylynski R, Lenarz T, et al. Round window vibroplasty: long-term results. *Acta Otolaryngol* 2012;132:1042–8.
23. Tsang WSS, Yu JKY, Wong TKC, Tong MCF. Vibrant Soundbridge system: application of the stapes coupling technique. *J Laryngol Otol* 2012;7:1–5.
24. Tsang WSS, Yu JKY, Wong TKC, Tong MC. Vibrant Soundbridge system: application of the stapes coupling technique. *J Laryngol Otol* 2013;127:58–62.
25. Lesinskas E, Stankeviciute V, Petrulionis M. Application of the Vibrant Soundbridge middle-ear implant for aural atresia in patients with Treacher Collins syndrome. *J Laryngol Otol* 2012;126: 1216–23.
26. Edfeldt L, Rask-Andersen H. Round window vibroplasty in chronic ear surgery: comparison with conventional hearing rehabilitation. *Acta Otolaryngol* 2013;133(8):814–25.
27. Schwabe B. Different coupling techniques for the Vibrant Soundbridge. Asia Pacific Vibrant Soundbridge & Bonebridge Symposium 2014. Hong Kong, 2014; 13–16 March.

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A Systematic Review of the Diagnostic Value of CT Imaging in Diagnosing Otosclerosis

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Objective: To evaluate the diagnostic value of computed tomography (CT) in detecting otosclerosis in patients with conductive hearing loss and a clinical suspicion of otosclerosis.
Data Sources: PubMed, Embase, and the Cochrane Library.
Study Selection: A systematic search was conducted. Studies reporting original study data were included.
Data Extraction: Relevance and risk of bias of the selected articles were assessed. Studies with low relevance, high risk of bias, or both were excluded. Prevalences, sensitivities, specificities, and post-test probabilities were extracted from the included articles.
Data Synthesis: Seven studies characterized by a moderate to high relevance and moderate to low risk of bias were included for data extraction. The prevalence of otosclerosis was high (up to 100%) in the majority of the included studies. In those studies with a high prevalence of disease, both positive and negative post-test probabilities were (relatively) high: 99% and between 51% and 67% respectively. In one study with a low prevalence of disease (9%), both positive and negative post-test probabilities were low (23% and 3% respectively). Overall, reported sensitivities ranged between 60% and 95%.
Conclusion: Preoperative CT has little to add in establishing otosclerosis and may not be necessary to confirm the diagnosis. We would recommend reserving CT for those patients with suspected additional abnormalities, for specific preoperative planning, or out of legal necessity. **Key Words:** Conductive hearing loss—CT imaging—Diagnostic—HRCT—Otosclerosis—Radiology—Systematic review.

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Otosclerosis is characterized by an abnormal bone metabolism in the otic capsule (1). It mostly affects the stapes footplate and results in progressive hearing loss. History taking, physical examination, tuning fork testing, stapedius reflex testing, and pure-tone audiometry all contribute to the diagnosis of otosclerosis. A definitive and reliable diagnosis can only be made during middle-ear inspection. Middle-ear inspection allows for simultaneous restoration of hearing.

Computed tomography (CT) is the imaging modality of choice when imaging is performed (2,3). CT may be used in the diagnostic evaluation of otosclerosis, in the assessment of disease extent including cochlear involvement, and in planning specific surgical treatment. Otosclerosis is characterized by lucent or hypodense foci within the otic capsule on CT. Other CT findings include a thickened footplate, narrowed oval or round window niche, and the double ring sign (4). Several authors have suggested CT findings might serve as prognostic factors regarding surgical success (4–6). Findings such as extensive otosclerotic foci, cochlear involvement, and round window obliteration are associated with a poor prognosis and may influence treatment choice (7). Detection of concomitant anomalies such as large vestibular aqueduct, dehiscent facial canal, and superior semicircular canal dehiscence on CT further impact (surgical) planning (2).

The aim of this review was to determine the diagnostic value of CT in otosclerosis in adult patients with conductive hearing loss and a clinical suspicion of otosclerosis.

METHODS

Search and Selection

A systematic literature search in PubMed, Embase, and the Cochrane Library was conducted with the assistance of a clinical librarian (date of search: September 10, 2014). Relevant synonyms for the search terms ''computed tomography'' and ''otosclerosis'' were used (see Table 1 for the full search strategy). Duplicates were removed. Title and abstract screening was performed independently by two authors per article (I.W., A.v.W., S.H.B., C.F.D, S.A.K., and M.R.) according to predetermined inclusion and exclusion criteria (see Fig. 1 for

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The authors disclose no conflicts of interest.

TABLE 1. *Search strategy (date of last search: September 10, 2014)*

Database	Search Strategy	Hits
PubMed	((computertomography[tiab] OR tomography[tiab] OR CAT[tiab] OR CT[tiab] OR HRCT[tiab] OR CTscan[tiab] OR scan[tiab] OR imaging[tiab] OR radiologic[tiab] OR radiology[tiab]) AND (otoscler*[tiab] OR otospong*[tiab] OR stapes[tiab] OR stirrup[tiab] OR stapedial[tiab] OR ossicular[tiab] OR footplate[tiab] OR stapedot*[tiab] OR stapedec*[tiab] OR (middle AND ear AND inspection[tiab]))) OR ((tomography[MeSH Terms] OR scan[MeSH Terms]) AND (otoscler*[MeSH Terms] OR stapes[MeSH Terms]))	1111
Embase	((computertomography:ab,ti OR tomography:ab,ti OR cat:ab,ti OR ct:ab,ti OR hrct:ab,ti OR ctscan:ab,ti OR scan:ab,ti OR imaging:ab,ti OR radiologic:ab,ti OR radiology:ab,ti) AND (otoscler*:ab,ti OR otospong*:ab,ti OR stapes:ab,ti OR stirrup:ab,ti OR stapedial:ab,ti OR ossicular:ab,ti OR footplate:ab,ti OR stapedot*:ab,ti OR stapedec*:ab,ti OR (middle:ab,ti AND ear:ab,ti AND inspection:ab,ti)) OR ((otosclerosis/exp OR stapes/exp) AND tomography/exp)) AND [embase]/lim	1098
The Cochrane Library	(((computertomography OR tomography OR CAT OR CT OR HRCT OR CTscan OR scan OR imaging OR radiologic OR radiology):ti,ab) AND ((otoscler* OR otospong* OR stapes OR stirrup OR stapedial OR ossicular OR footplate OR stapedot* OR stapedec* OR 'middle ear inspection'):ti,ab)) OR (((otoscler* OR stapes):kw) AND ((tomography OR scan):kw))	8

the criteria). Studies reporting original data on the diagnostic value of CT for the detection of otosclerosis in adult patients with a clinical suspicion of otosclerosis were included. Systematic reviews, opinion papers, non-human studies, and case reports with less than 10 cases were excluded. Studies that predominantly included pediatric patients were excluded. Articles written in languages other than English, Dutch, German, French, or Portuguese were excluded, as well as articles published before the year 2000. Subsequently, the full texts of eligible articles were independently screened by two reviewers per selected article (I.W., A.v.W., S.H.B., C.F.D, S.A.K., and M.R.). Additionally, PubMed and Web of Science were searched for related articles, and reference lists of the selected articles and systematic reviews on the topic were hand-searched for titles not identified by our initial search. Discordances regarding inclusion were solved by consensus discussion.

Study Assessment

The remaining articles were independently assessed for their relevance and risk of bias by two reviewers (I.W. and A.v.W.) using predefined criteria (see Table 2 for assessment criteria). A similar version of this system was previously used in other diagnostic systematic reviews (8–10). The criteria were classified as ''satisfactory'' (●), or ''unsatisfactory or unclear'' (○). Relevance was scored to ensure that studies reported applicable outcomes for a well-defined patient group (diagnostic values of CT for patients with otosclerosis). Studies were classified as having low relevance if two or more criteria were rated unsatisfactory. Studies were classified as having moderate relevance if two criteria were rated satisfactory. The remaining studies were classified as having high relevance.

Risk of bias was assessed by using predetermined criteria based on the Cochrane Collaboration's tool for assessing risk of bias (11). Assessment of risk of bias involved the evaluation of six criteria. Studies were classified as having low risk of bias if five or more criteria were rated satisfactory and moderate risk of bias if at least three criteria were rated satisfactory. The remaining studies were classified as having a high risk of bias. Articles that were rated moderate or high for relevance and carried a low or moderate risk of bias were selected for further review. Initial discordances between reviewers (I.W. and A.v.W.) were again resolved by consensus discussion.

Data Extraction

Two authors (I.W. and A.v.W.) independently extracted descriptive data regarding the study population, the index test (CT), and the reference test (middle ear inspection and/or histopathology) from the included studies. The true positive, false positive, true negative, and false negative test results were extracted to calculate the prevalence, sensitivity, specificity, and post-test probabilities. The positive post-test probability represents the probability of the presence of otosclerosis in case of a positive CT. The negative post-test probability represents the probability of the presence of otosclerosis in case of a negative or normal CT. Positive and negative post-test probabilities were calculated using likelihood ratios (LRs) (12). Positive and negative LRs were calculated and subsequently used to calculate the post-test odds of otosclerosis. The odds were then translated to probabilities (12). Corresponding 95% confidence intervals (95% CIs) were calculated according to standard normal distribution (1.96 × standard error). The method described by Monsour et al. (13) was used to calculate 95% CIs for post-test probabilities.

RESULTS

Search and Selection

The search yielded 1,575 unique articles. After screening these articles on title and abstract and subsequently full text, 1,558 articles were excluded on the basis of the predefined inclusion and exclusion criteria (see Fig. 1 for the criteria). Of the 17 articles (2,3,6,14–27) that were considered eligible after full-text screening, another two were excluded on the basis of language (Japanese and Spanish) (14,15). The article by Marx et al. (16), and Lagleyre et al. (17) described the same study population, as well as the articles written by de Oliveira Vicente et al. in 2004 and 2006 (24,25). Reference checking did not result in any additional articles. Thus, in total 15 articles describing 13 studies were selected for study assessment (2,3,6,16–27).

Study Assessment

As shown in Table 2, two studies, described in three articles, were considered highly relevant (16–18). In the other 11 studies, patients with surgically confirmed otosclerosis were included in the study population instead of patients at risk of otosclerosis (2,3,6,19–27). The risk of

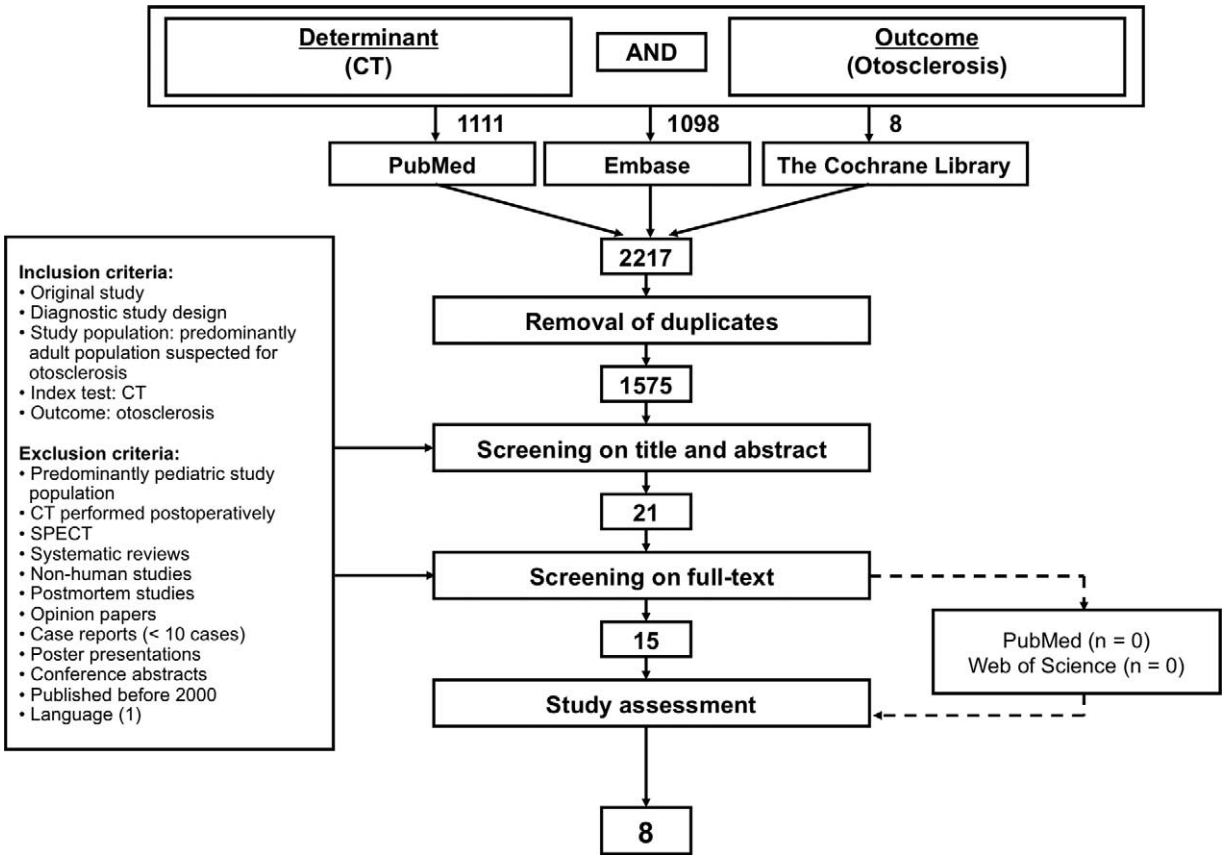

FIG. 1. Flowchart.

bias was low in two studies (2,3), moderate in five studies (6,16–20), and high in the remaining six studies (21–27). In the majority of the included studies, it was not clear whether a consecutive series of patients was included (6,18,20–27). In two studies only those patients with available histopathologic results were included (2,3). Standardization of the index test (CT) was either not achieved or not adequately described in six studies (16,17,21,23–27). Slice thickness varied between 0.6 and 1 mm in the study performed by Marx et al./Lagleyre et al. (16,17) and between 1 and 2 mm in the study performed by de Oliveira Vicente (24,25). Two different types of scanners were used in the study by Mori et al. (23). In the study performed by Berretini et al. (26) some CT scans were assessed on a computer-dedicated workstation, whereas others were manually read from a printed version of the CT scan. The diagnostic criteria and number of assessors were not mentioned in the study performed by Bozorg Grayeli et al. (21). CT settings were not mentioned in the study performed by Shin et al. (27). Standardization of the reference test (middle ear surgery) was either not achieved or not adequately described in nine studies (6,19–27). In two studies (6,23), middle ear surgery was not performed in all of the included patients, but all patients were included in the analyses nonetheless. In nine studies (6,19–27), the criteria used for diagnosing otosclerosis intraoperatively were not mentioned. A substantial amount of outcome data, 37%, 38%, and 52% respectively, were missing in three studies (22,26,27). A complete case analysis was performed in all of these studies. Seven studies characterized by a moderate-to-high relevance and moderate-to-low risk of bias were included for data extraction (2,3,6,16–20).

Data Extraction

The study characteristics are presented in Table 3. There are major dissimilarities between studies regarding the study population, index test, and reference test. As mentioned previously, only two studies included patients with a clinical suspicion of otosclerosis based on the presence of conductive hearing loss, a normal tympanic membrane, and absent stapedial reflexes (16–18). In the other studies patients with an indication for middle ear surgery or patients with confirmed otosclerosis were included (2,3,6,19,20). High-resolution, cone beam, multislice, and helical CTs were evaluated in the included studies. In five studies (6,16–20) middle ear surgery was used as the reference test whereas in two studies (2,3) histopathology was used. We decided to refrain from pooling the data because of these dissimilarities. Prevalences, sensitivities, specificities, and post-test probabilities are presented in Table 4.

TABLE 2. *Study assessment*

		Relevance				Risk of Bias						
Study (year)	No. of Patients (No. of Ears)	Study Population	Index Test	Outcome	Overall Relevance	Selection	Blinding of (IT)	Blinding of (RT)	Standardization (IT)	Standardization (RT)	Missing Data	Overall Risk of Bias
Marx (2011) (16), Lagleyre (2009) (17)	200 (209)	●	●	●	H	●	○	●	○	●	●	M
Shin (2001a) (18)	NR (474)	●	●	●	H	○	○	●	●	●	●	M
Karosi (2012) (3)	57 (57)	○	●	●	M	○	●	●	●	●	●	L
Liktor (2014) (2)	32 (32)	○	●	●	M	○	●	●	●	●	●	L
Trojanowska (2007) (19)	90 (180)	○	●	●	M	●	○	●	●	○	●	M
Kiyomizu (2004) (6)	44 (82)	○	●	●	M	○	○	●	●	○	●	M
Tringali (2007) (20)	NR (119)	○	●	●	M	○	○	●	●	○	●	M
Bozorg Grayeli (2004) (21)	10 (10)	○	●	●	M	○	○	●	○	○	●	H
Lee (2009) (22)	22 (24)	○	●	●	M	○	○	●	●	○	○	H
Mori (2013) (23)	17 (27)	○	●	●	M	○	○	●	○	○	●	H
de Oliveira Vicente (2004) (24), de Oliveira Vicente (2006) (25)	54 (108)	○	●	●	M	○	○	●	○	○	●	H
Berretini (2010) (26)	45 (90)	○	●	●	M	○	○	●	○	○	○	H
Shin (2001b) (27)	NR (211)	○	●	●	M	○	○	●	○	○	○	H

● indicates satisfactory; ○, not satisfactory or unclear; H, high; L, low; M, moderate; NR, not reported.

Relevance. Study population: adult patients suspected of otosclerosis. Index test: CT. Outcome: otosclerosis established during middle ear surgery.

Risk of bias. Selection: consecutive or random sample of patients selected without exclusion based on incompleteness of data. Blinding of index test (IT): outcome assessor blinded for CT results. Blinding of reference test (RT): radiologist blinded for surgery outcome. Standardization of index test (IT): uniform protocol for performing and assessing CT. Standardization of reference test (RT): uniform protocol for or uniform manner of establishing otosclerosis during middle ear surgery or histopathology. Missing data: $\leq$ 20% missing data.

TABLE 3. *Study characteristics*

Study (Year)	Study Population	Type of CT	CT Slice Thickness	Diagnostic Criteria CT	Diagnostic Criteria Surgery and/or Histopathology
Shin (2001a) (18)	Conductive hearing loss with a normal tympanic membrane	HRCT	1 mm	Otospongiotic foci surrounding the otic capsule and/or footplate thickening	Intraoperatively established presence of fixation or macropscopic otosclerotic foci, and absence of minor malformations
Kiyomizu (2004) (6)	Otosclerosis surgically confirmed in at least one ear	NA	1 mm	Focus of demineralization or thick anterior and posterior calcified plaques	Intraoperatively established in at least one ear
Trojanowska (2007) (19)	Indication for middle ear surgery	Multislice CT	0.6 mm	Hypodense foci around otic capsule	Intraoperatively established, not further specified
Tringali (2007) (20)	Intraoperatively confirmed otosclerosis	Helical CT	0.6 mm	Focus of demineralization	Intraoperatively established, not further specified
Marx (2011) (16), Lagleyre (2009) (17)	Conductive hearing loss with a normal tympanic membrane and absent or biphasic stapedial reflex in at least one ear	HRCT	0.6 mm to 1 mm	Hypodense foci around otic capsule	Intraoperatively established macroscopic otosclerotic foci
Karosi (2012) (3)	Intraoperatively confirmed otosclerosis and stapes completely removed for histopathology	HRCT	0.6 mm	Hypodense foci around otic capsule and/or footplate thickening	Pseudovascular spaces filled with osteoclasts (active otosclerosis) or obliterated vascular spaces and resorption of lacunae with decreased numbers of osteoclasts (inactive otosclerosis) histopathologically
Liktor (2014) (2)	Intraoperatively confirmed otosclerosis and stapes completely removed for histopathology	Cone beam CT	0.4 mm	Hypodense foci around otic capsule	Pseudovascular spaces filled with osteoclasts (active otosclerosis) or obliterated vascular spaces and resorption of lacunae with decreased numbers of osteoclasts (inactive otosclerosis) histopathologically

HRCT indicates high-resolution computed tomography; NA, not available.

Prevalence of Otosclerosis

In three studies, the prevalence of otosclerosis was 100% and as a result only sensitivities could be calculated for these studies (2,6,20). Prevalences were high in the studies performed by Marx et al./Lagleyre et al. (16,17), Shin et al. (18), and Karosi et al. (3). In two of these studies patients with a clinical suspicion of otosclerosis were included (16–18). In one study patients with surgically confirmed otosclerosis were included. Since the outcome measure in this study was histopathology instead of middle ear surgery, the prevalence of (histopathologically confirmed) otosclerosis was not

TABLE 4. *Results*

Study (Year)	Reference Test	Prevalence[a]	Sensitivity[a]	Specificity[a]	Positive Post-test Probability[a]	Negative Post-test Probability[a]
Shin (2001a) (18)	Middle ear surgery	92 (89–94)	91 (88–94)	100 (89–100)	NA	51 (NA)
Kiyomizu (2004) (6)	Middle ear surgery	100 (95–100)	61 (50–71)	NA	NA	NA
Trojanowska (2007) (19)	Middle ear surgery	9 (6–14)	75 (50–90)	75 (68–81)	23 (13–36)	3 (2–6)
Tringali (2007) (20)	Middle ear surgery	100 (96–100)	82 (74–88)	NA	NA	NA
Marx (2011) (16), Lagleyre (2009) (17)	Middle ear surgery	97 (94–99)	95 (91–97)	83 (42–98)	99 (96–100)	67 (22–93)
Karosi (2012) (3)	Histopathology	74 (61–83)	60 (45–73)	100 (76–100)	NA	53 (NA)
Liktor (2014) (2)	Histopathology	100 (87–100)	66 (48–80)	NA	NA	NA

NA indicates not available.
[a]% (95% confidence interval).

100%, but 74% (3). In one study, which included various patients with an indication for middle ear surgery, the prevalence was very low (19).

Diagnostic Test Measures

The sensitivity ranged between 60 and 95% in seven studies (2,3,6,16–20). The two studies (2,3) that compared CT to histopathology found lower sensitivities of 60 and 66% than the studies comparing CT to middle ear surgery (6,16–20). Specificity was 100% in two studies (3,18). In another two studies specificity was lower: 83% and 75% (16,17,19). Specificity could be calculated for one of the studies that compared CT to histopathology and was not different from the specificities found in the studies that compared CT to middle-ear surgery (100% (3) compared with 75 to 100% [16–19]).

Post-test Probability of Otosclerosis

In patients with a clinical suspicion of otosclerosis, the positive post-test probability of otosclerosis with an abnormal CT was 99% (16,17). The positive post-test probability was much lower in a study population of patients with an indication for middle-ear surgery (23%) (19). The negative post-test probabilities were reported in three studies: 51%, 53%, and 67% (3,16–18). In patients with an indication for middle-ear surgery, the negative post-test probability of otosclerosis with a normal CT was only 3% (19).

DISCUSSION

Summary of Main Results

The pretest probability or prevalence of otosclerosis was very high in the majority of the included studies (2,3,6,16–18,20). In those studies with a high prevalence of disease (74–97%), both positive and negative post-test probabilities were (relatively) high (3,16–18). Positive post-test probability was 99% in one of these studies (16,17) and negative post-test probabilities ranged between 51% and 67% (3,16–18). In one study (19) with a low prevalence of disease (9%), both positive and negative post-test probabilities were much lower compared with studies with a high prevalence of disease (23% and 3%, respectively). Overall, reported sensitivities ranged between 60% and 95% (2,3,6,16–20). The sensitivity and specificity for operatively confirmed otosclerosis were 61 to 95% (6,16–20) and 75 to 100% (16–19), respectively. The sensitivity and specificity for histopathologically confirmed otosclerosis were 60 to 66% (2,3) and 100% (3), respectively.

The diagnostic measures and post-test probabilities were generally higher in newer studies. The advancements in scanners and techniques may have attributed to higher detection rates in newer studies. Prevalence influences post-test probabilities; post-test probabilities are generally higher in studies with a high prevalence of disease and lower in studies with a low prevalence of disease. Indeed, the studies with a high prevalence of otosclerosis reported higher post-test probabilities than those studies with a low prevalence of otosclerosis. Prevalence of disease in these studies may have been influenced by the choice of inclusion and exclusion criteria (suspected otosclerosis based on clinical history and physical examination versus intraoperatively confirmed otosclerosis) and the choice of reference test (middle-ear surgery versus histopathology).

Previous studies and reviews highlight the importance of CT in the diagnostic evaluation of otosclerosis (2,3,28). However, the prevalence of otosclerosis in patients with a clinical suspicion of otosclerosis and/or an indication for surgery is generally high. As a result, preoperative CT has little to add in establishing otosclerosis and may not be necessary to confirm the diagnosis. Although its role in diagnosing otosclerosis is limited, CT imaging may still be useful in establishing the extent of disease and cochlear involvement, and in detecting concomitant abnormalities.

CT scans were qualitatively analyzed in the included studies. Otosclerosis is usually confirmed on CT on the basis of visual confirmation of double ring signs, hypodensities around the otic capsule, and/or thickening of the footplate. Several authors adopted a more quantitative approach and measured bone densities in the area immediately anterior to the oval window: the fissula ante fenestram (20,21,29,30). These studies did find statistically significant differences in Hounsfield units measured over the fissula ante fenestram region between patients with otosclerosis and control patients, but not in several other regions surrounding the otic capsule. Tringali et al. (20) performed analyses in a subgroup of patients with otosclerosis and normal-appearing CT scan and found no significant differences for densitometric measurements in this subgroup compared with control subjects without otologic disease and control patients with cholesteatoma. Unfortunately, none of these studies defined a cut-off value that can be used to create two-by-two contingency tables and calculate diagnostic test measures.

Quality of Evidence

The majority of the included studies were characterized by a moderate relevance and moderate risk of bias. Most studies only included patients with surgically confirmed otosclerosis. As a result, prevalence of otosclerosis is 100% in these studies and only sensitivities can be calculated. Second, only studies using surgery or histology as a reference test were included, since this is the only adequate reference test for confirming otosclerosis. This implies that all included patients had an indication for surgery. This causes a substantial risk of selection bias, because the study populations probably will not include patients with very mild disease or patients with a severe sensorineural component. Therefore, these results will not translate into the general group of patients with otosclerosis.

Potential Biases in Review

To our knowledge, this is the first review to not only systematically evaluate, but also critically appraise the

available evidence on this topic. The search strategy was transparent and thorough. The screening of eligible articles, as well as the critical appraisal of selected studies, was performed by at least two independent authors, thereby limiting erroneous subjective decisions as much as possible. The critical appraisal ensures the transparent evaluation of strengths and limitations of the included studies. The evaluation of both relevance and validity is based on clear, predetermined criteria and aids the reader in interpreting the evidence.

There is one limitation that could have potentially biased the results presented in this review. Two studies were excluded on the basis of language (Japanese and Spanish) (14,15). None of the authors are fluent in these two languages and therefore we decided not to include these studies. There is a possibility that these articles were relevant to our review.

CONCLUSION

The prevalence of otosclerosis in patients with a clinical suspicion of otosclerosis and/or an indication for surgery is generally high. As a result, preoperative CT has little to add in establishing otosclerosis and may not be necessary to confirm the diagnosis. Furthermore, a normal CT does not fully exclude otosclerosis. We would recommend reserving CT for those patients with suspected additional abnormalities, for specific preoperative planning, or out of legal necessity, but not for diagnosing otosclerosis.

REFERENCES

1. Menger DJ, Tange RA. The aetiology of otosclerosis: A review of the literature. *Clin Otolaryngol Allied Sci* 2003;28:112–20.
2. Liktor B, Révész P, Csomor P, et al. Diagnostic value of cone-beam CT in histologically confirmed otosclerosis. *Eur Arch Otorhinolaryngol* 2014;271:2131–8.
3. Karosi T, Csomor P, Sziklai I. The value of HRCT in stapes fixations corresponding to hearing thresholds and histologic findings. *Otol Neurotol* 2012;33:1300–7.
4. Sakai O, Curtin HD, Fujita A, et al. Otosclerosis: Computed tomography and magnetic resonance findings. *Am J Otolaryngol* 2000;21:116–8.
5. Wycherly BJ, Berkowitz F, Noone AM, et al. Computed tomography and otosclerosis: A practical method to correlate the sites affected to hearing loss. *Ann Otol Rhinol Laryngol* 2010; 119:789–94.
6. Kiyomizu K, Tono T, Yang D, et al. Correlation of CT analysis and audiometry in Japanese otosclerosis. *Auris Nasus Larynx* 2004;31:125–9.
7. Merkus P, van Loon MC, Smit CF, et al. Decision making in advanced otosclerosis: An evidence-based strategy. *Laryngoscope* 2011;121:1935–41.
8. Wegner I, Bittermann AJN, Hentschel MA, et al. Pure-tone audiometry in otosclerosis: Insufficient evidence for the diagnostic value of the Carhart notch. *Otolaryngol Head Neck Surg* 2013;149:528–32.
9. Dorresteijn PM, Ipenburg NA, Murphy KJ, et al. Rapid systematic review of normal audiometry results as a predictor for benign paroxysmal positional vertigo. *Otolaryngol Head Neck Surg* 2014;150:919–24.
10. Adolphs APJ, Boersma NA, van Diemel BDM, et al. A systematic review of CT-detection of cartilage invasion in laryngeal carcinoma. *Laryngoscope* 2015;125:1650–5.
11. Diagnostic Critical Appraisal Sheet. Oxford Centre for Evidence Based Medicine. http://www.cebm.net/?o=1040. March 1, 2014.
12. Shin JJ, Stinnett S, Page J, et al. Evidence-based medicine in otolaryngology, Part 3: Everyday probabilities: Diagnostic tests with binary results. *Otolaryngol Head Neck Surg* 2012;147:185–92.
13. Monsour MJ, Evans AT, Kupper LL. Confidence intervals for post-test probability. *Stat Med* 1991;10:443–56.
14. Yang D, Kodama T, Tono T, et al. High-resolution CT of otosclerosis. *Nihon Igaku Hoshasen Gakkai Zasshi* 1997;57:864–70.
15. Montaño Velázquez BB1, Bello Mora A, Zepeda López EG, et al. Evidence of otospongiosis obtained by computerized tomography. Does it compromise the post-stapedectomy auditory gain? *Acta Otorrinolaringol Esp* 2002;53:387–90.
16. Marx M, Lagleyre S, Escude B, et al. Correlations between CT scan findings and hearing thresholds in otosclerosis. *Acta Otolaryngol* 2011;131:351–7.
17. Lagleyre S, Sorrentino T, Calmels MN, et al. Reliability of high-resolution CT scan in diagnosis of otosclerosis. *Otol Neurol* 2009;30:1152–9.
18. Shin YJ, Deguine O, Cognard C, et al. Reliability of CT-Scan in the diagnosis of cases of conductive hearing loss with normal tympanic membrane. *Rev Laryngol Otol Rhinol* 2001;122:81–4.
19. Trojanowska A, Trojanowski P, Olszanski W, et al. How to reliably evaluate middle ear diseases? Comparison of different methods of post-processing based on multislice computed tomography examination. *Acta Otolaryngol* 2007;127:258–64.
20. Tringali S, Pouget JF, Bertholon P, et al. Value of temporal bone density measurements in otosclerosis patients with normal-appearing computed tomographic scan. *Ann Otol Rhinol Laryngol* 2007;116:195–8.
21. Bozorg Grayeli A, Yrieix CS, Imauchi Y, et al. Temporal bone density measurements using CT in otosclerosis. *Acta Otolaryngol* 2004;124:1136–40.
22. Lee TL, Wang MC, Lirng JF, et al. High resolution computed tomography in the diagnosis of otosclerosis in Taiwan. *J Chin Med Assoc* 2009;72:527–32.
23. Mori N, Toyama Y, Kimura N, et al. Detection of small fenestral otosclerotic lesions by high-resolution computed tomography using multiplanar reconstruction. *Auris Nasus Larynx* 2013;40: 36–40.
24. de Oliveira Vicente A, de Oliveira Penido N, Yamashita HK, et al. Computed tomography in the diagnosis of fenestral otosclerosis. *Rev Bras Otorrinolaringol* 2004;70:66–73.
25. de Oliveira Vicente A, Yamashita HK, Albernaz PLM, et al. Computed tomography in the diagnosis of otosclerosis. *Otolaryngol Head Neck Surg* 2006;134:685–92.
26. Berretini S, Ravecca F, Volterrani D, et al. Imaging evaluation in otosclerosis: Single photon emission computed tomography and computed tomography. *Ann Otol Rhinol Laryngol* 2010;119:215–24.
27. Shin YJ, Calvas P, Deguine O, et al. Correlations between computed tomography findings and family history in otosclerotic patients. *Otol Neurol* 2001;22:461–4.
28. Virk JS, Singh A, Lingam RK. The role of imaging in the diagnosis and management of otosclerosis. *Otol Neurotol* 2013;34: e55–e60.
29. Kutlar G, Koyuncu M, Elmali M, et al. Are computed tomography and densitometric measurements useful in otosclerosis with mixed hearing loss? A retrospective clinical study. *Eur Arch Otorhinolaryngol* 2014;271:2421–5.
30. Kawase S, Naganawa S, Sone M, et al. Relationship between CT densitometry with a slice thickness of 0.5 mm and audiometry in otosclerosis. *Eur Radiol* 2006;16:1367–73.

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A Comparison Between Wireless CROS and Bone-anchored Hearing Devices for Single-sided Deafness: A Pilot Study

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Introduction: This study compared wireless Contralateral Routing of Signals (CROS) hearing aid and bone-anchored hearing device (BAHD) in patients with single-sided deafness.
Methods: Eight adults with single-sided deafness previously implanted with a BAHD were given a 2-week trial with a CROS hearing aid and tested in unaided and aided conditions. Both devices were compared on head shadow effect reduction, speech perception measures in quiet and in noise, self-assessment questionnaires, and daily diaries.
Results: Both the CROS and BAHD significantly reduced the head shadow effect. QuickSIN scores were significantly better with noise presented to the poorer ear, as compared to the better ear, for the unaided condition, the BAHD, and the CROS. Scores showed no significant differences between the CROS and BAHD with noise presented to the better ear, but scores with the CROS were significantly poorer than in the unaided condition with noise presented to the poorer ear. There were no significant differences between BAHD and CROS for the ratings on the Bern Benefit in Single-Sided Deafness and Speech Spatial Qualities questionnaires. Both devices were worn an average of 10 hours per day. Four participants preferred the CROS for sound quality; three preferred the BAHD for comfort.
Conclusion: Comparisons of CROS and BAHD need to be re-evaluated as both technologies have evolved. In our pilot study, both devices seem comparable, with the CROS avoiding the risks of surgery, and we recommend a trial of CROS in our center for first line treatment of single-sided deafness.
Key Words: BAHD—Bone-anchored hearing device—Contralateral routing of signals—CROS—Single-sided deafness—Unilateral hearing loss.
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Unilateral sensorineural hearing loss or single-sided deafness (SSD) results in several communication difficulties particularly in noisy situations (1). These difficulties stem from the loss of binaural hearing and the head shadow effect, in which the good ear is shielded from sounds from the side of the poorer ear (2).

Currently, there are two main intervention methods (SSD aids) used worldwide to help alleviate the head shadow effect: the Contralateral Routing of Signals (CROS) hearing aid and the bone-anchored hearing device (BAHD), which routes sound to the better ear by transcranial bone conduction from a microphone/processor attached to an osseointegrated implant in the skull on the poor hearing ear side. Neither restores hearing to the affected ear, but rather alleviates the head shadow effect. Other, newer interventions for SSD include cochlear implantation (3,4) and the SoundBite (5). These devices will not be discussed in this article.

For several decades, the CROS was the traditional intervention approach, with older CROS models consisting of an analog hearing aid on each ear connected together by a wire along the neck of the patient (6,7). Newer CROS models are wireless and new CROS and BAHD models include more sophisticated digital noise reduction and adaptive directional microphones (8,9). Previous studies have compared older models of CROS to older models of BAHD, but both technologies have improved substantially, especially the CROS.

It is well established that the CROS and BAHD do not improve sound localization abilities for people with SSD (10–18). However, the benefits of the devices for the improvement of communication are not as well understood, as indicated by conflicting results in the literature.

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For example, a recent systematic review by Peters et al. concluded that neither the CROS nor BAHD offered much benefit for speech perception in noise (18), whereas a review by Baguley et al. suggested some benefits for both devices but more so for the BAHD (10). Improvements in sentence perception in noise, when noise is delivered to the better ear, have been documented for the CROS (19) and for the BAHD (20,21). Similarly, improvements have been reported for the BAHD when noise is delivered to the front (12,13). Both devices have been shown to impair speech perception when noise is on the side of the poorer ear (12,13,19,22); in this condition, the CROS or BAHD transmits the noise from the poorer to the better ear and thus interferes with the speech signal. Moreover, subjective benefits have been reported for the BAHD and CROS, as measured by standardized self-assessment questionnaires such as the Abbreviated Profile of Hearing Aid Benefit (12,16,19,21).

A few researchers have examined the performance of the BAHD and CROS within the same study, thus allowing direct comparison between the two devices in the same sample of participants (10–12,14,15,17,18,23,24). Generally, the results of these studies have favored the BAHD over the CROS based on subjective preference and outcome measures using self-assessment questionnaires and on speech perception in noise. However, there are a number of methodological issues present in most of these studies (10,23). Firstly, in most studies, the CROS was always fitted before the BAHD, so there was no randomization, and in some studies only CROS failures were implanted with BAHD. Only Arndt et al. (3) and Hol et al. (14) attempted randomization, but they compared the CROS to a BAHD on a headband (i.e., non-implanted), which attenuates the high frequencies (25) and can be uncomfortable.

The goal of the current study is to address the need for research comparing recent models of wireless CROS hearing aids, with technologies such as digital noise reduction and directional microphones, to BAHD with similar technologies. To allow randomization while not using a BAHD headband, this study used existing implanted BAHD users, assigned to either their BAHD or a CROS in random order for a 2-week period, and measured auditory and subjective measures of perceived benefit.

MATERIALS AND METHODS

Participants

Of nine adult SSD BAHD users recruited, one dropped out, leaving eight participants (one male, seven female, age range 44–66 yr, average 54 yr) each with BAHD experience of 0.5 to 2.5 years. The BAHD were programmed using BC direct and fine-tuned according to the patients' comments when necessary; the devices were verified using aided soundfield thresholds. Adaptive directional microphone and noise reduction algorithm were active. None of the participants had tried CROS hearing aids before BAHD implantation. Participants' characteristics are displayed in Table 1.

Procedure

Participants' performance was compared between their own BAHD and the wireless Unitron Tandem 4 CROS hearing aid, using a within-subject repeated measures design. Data were collected over three one-and-a-half-hour visits spread 2 weeks apart. Audiometric tests were administered in a double-walled sound booth, using a Grason-Stadler GSI-61 audiometer calibrated according to ANSI S3.6 2010 standards, with the participants sitting 1 m away from the loudspeakers.

Unaided Measures

Firstly, the hearing loss was measured for both air and bone conduction using insert earphones. Soundfield thresholds were then obtained with warble tones presented at 90 degrees azimuth to the better ear and at 90 degrees azimuth to the poorer ear, the difference being calculated as the head shadow.

Next, unaided monosyllabic word recognition and the QuickSIN test were administered. The order of word recognition and QuickSIN testing was counterbalanced across participants. Word recognition was tested with the recorded version of the CID W-22 (Auditec of St. Louis), with a different list of 25 monosyllabic words presented at 50 dB HL in three randomized listening conditions: (a) with no noise (quiet) with words presented at 90 degrees azimuth to the poorer ear; (b) with words presented from the front (0 degree azimuth), and multitalker noise (at 45 dB HL) presented at 90 degrees azimuth to the poorer ear (S0Npe); and (c) with words presented from the front and multitalker noise (at 45 dB HL) at 90 degrees azimuth to the better ear (S0Nbe).

The QuickSIN test (Etymotic Research) consists of recorded lists of six short sentences spoken by a female speaker in multitalker background noise. The multitalker noise gradually increases with each sentence presentation such that the signal-to-noise ratio decreases from 25 to 0 dB, in 5-dB steps, over the six sentences. The test measures the signal-to-noise ratio loss (SNR) with a smaller score indicating better performance. The

TABLE 1. *Participants' age, pure tone hearing threshold average, model of BAHD implanted, and length of implantation at enrollment in the study*

ID	Age	PTA (dB HL) Better Ear	PTA (dB HL) Poorer Ear	BAHD Model	Length of Implantation	Implanted Ear
1	49	6	98	Cochlear BP100	1 yr	Right
2	56	10	NR	Cochlear BP100	2.5 yr	Left
3	44	2	NR	Oticon Medical Ponto Pro	1 yr	Left
4	66	12	93	Oticon Medical Ponto Pro	<1 yr	Left
5	46	11	NR	Oticon Medical Ponto Pro	1 yr	Right
6	65	14	NR	Oticon Medical Ponto Pro	<1 yr	Left
7	57	15	NR	Cochlear BP100	2.5 yr	Left
8	54	11	56	Cochlear BP100	2.5 yr	Left

PTA indicates pure tone average unaided thresholds for 500, 1,000, 2,000, 3,000, and 4,000 Hz; NR, no response.

QuickSIN was administered at 50 dB HL in soundfield. Again, two listening conditions were assessed and counterbalanced across participants: the S0Npe (sentences at 0 degree azimuth, noise at 90 degrees azimuth to poor ear) and the S0Nbe (sentences at 0 degree azimuth, noise at 90 degrees azimuth to the better ear) condition. For each condition, two different lists were presented and the scores averaged.

CROS Hearing Aid Fitting

Participants were randomly assigned to be fitted with the CROS hearing aid either at the end of the first visit or at the end of the second visit. They were given a 2-week trial with the CROS and asked to refrain from wearing their BAHD during that time. At the end of the first visit, four participants were fitted with the CROS hearing aid and were subsequently tested with this device on their second visit, at which time they were instructed to use the BAHD for the next 2 weeks. This protocol was reversed in the other four participants, with testing after each device experience.

CROS hearing aids were fitted with a retainer earhook on the poorer ear and a slim tube with an open dome on the better ear. The hearing aid's response was verified with real-ear measures (Audioscan Verifit) using Dillon's (26) recommended approach for probe microphone verification of CROS hearing aids. During real-ear verification, the hearing aid's response was fine-tuned as needed. Adaptive directional microphone and noise reduction algorithm were active.

Aided Measures With CROS and BAHD

Participants were tested with either the CROS or BAHD, depending on which device they had been instructed to use during the previous 2 weeks. Similar to the baseline measures, aided soundfield thresholds were obtained with warble tones delivered at 90 degrees azimuth to the better ear in one condition and at 90 degrees azimuth to the poorer ear in the other condition. Aided word recognition testing and aided QuickSIN were administered using the same protocol as for unaided measures. Moreover, two self-assessment questionnaires, the Bern Benefit in Single-Sided Deafness Questionnaire (BBSS) and the Speech Spatial Qualities Questionnaire (SSQ), were given to assess the self-perceived benefits provided by the device that was worn the previous 2 weeks. The BBSS (27) is a 10-item questionnaire where participants rate the benefit derived from their device in different situations, with ratings that range from −5 (''Much Easier Without the Aid'') to +5 (''Much Easier With the Aid''). The SSQ (28) requires participants to rate their perceived hearing ability for 49 scenarios using a 10-point scale, ranging from ''Not at all'' to ''Perfectly.''

Participants were asked to fill out a diary during the 2-week period for the CROS and for the BAHD; they were instructed to indicate the date the device was worn, hours of device use per day, and specific situations in which the device was worn. Finally, at the end of the study, the researcher verbally asked participants whether the CROS or BAHD was preferred and questioned them on the specific reasons for their choice.

Statistical Analyses

Statistical analyses were conducted in R (29). An alpha of 0.05 was assumed for all analyses. Shapiro-Wilks tests were used to assess normality and Mauchly's test was used to assess sphericity in all repeated measures analyses. No violations of sphericity were detected. Repeated measures ANOVAs were used to compare conditions for normally distributed data, otherwise statistical analysis was performed using Friedman's non-parametric test. All reported p values for parametric post hoc measures were adjusted using Bonferroni corrections. Confidence intervals (CI) were adjusted for within-subjects testing using the Cousineau-Morey method with Baguley's corrections (30).

RESULTS

Head Shadow

Figure 1 shows mean head-shadow values (i.e., threshold increases for sounds presented to the poorer ear) at each frequency in all three conditions, with error bars showing 95% confidence intervals. Significant deviations from normality were detected for the unaided condition (W = 0.912, p = 0.013) and the CROS condition (W = 0.896, p = 0.005), so a Friedman's nonparametric ANOVA was used to test for within-subject device-dependent differences in head shadow across all frequencies. There was a significant main effect of device ($\chi^2(2)$ = 21.769, p = 0.00002). Post hoc analyses conducted using the Friedman post hoc analysis (31) showed significant reductions in head shadow for both the BAHD (mean reduction of 25 dB) and the CROS (mean reduction of 32 dB), relative to the unaided condition. The 7-dB advantage for the CROS over the BAHD did not exceed the critical difference (19.15 dB) required for significance.

Word Recognition Scores

The mean word recognition percentages for each device condition are displayed in Figure 2. Error bars show 95% confidence intervals. Note that the scores for the quiet condition are close to 100%, suggesting a ceiling effect. This observation was indeed the case, as 10 of the scores (42%) were perfect. The quiet condition was therefore excluded from further statistical analysis. Data in the remaining conditions were normally distributed and were analyzed with a repeated measures ANOVA. The ear to which the noise was presented (better or poorer) had a significant effect on word recognition scores ($F(1,7)$ = 32.82, p = 0.0007, η^2 = 0.329), but there was no significant main effect of device ($p > 0.05$). The interaction of

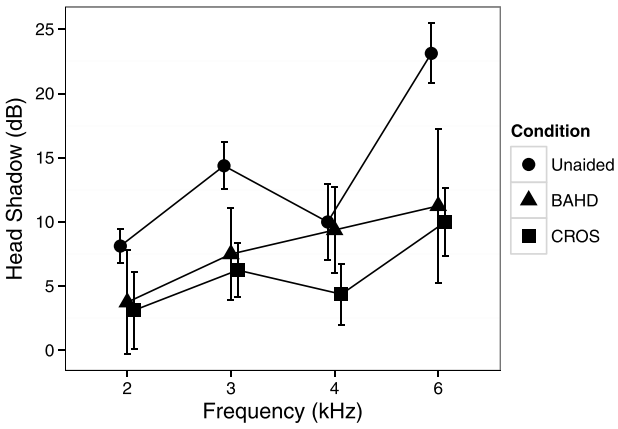

FIG. 1. Mean head shadow in the three device conditions. *Error bars* denote 95% confidence intervals.

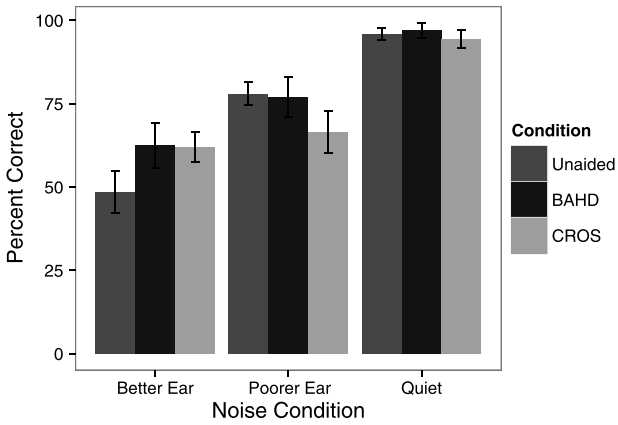

FIG. 2. Mean word recognition scores for each device condition with noise presented to the better ear (S0Nbe), noise presented the poorer ear (S0Npe), and in quiet (Spe). *Error bars* denote 95% confidence intervals.

noise presentation ear and device condition was also significant ($F(2,14) = 6.192$, $p = 0.01$, $\eta^2 = 0.165$). Post hoc pairwise *t* tests showed that scores were significantly lower when noise was presented to the better ear than when noise was presented to the poorer ear, but only in the unaided condition ($t(7) = 8.33$, $p = 0.001$); the differences related to ear of noise presentation for the BAHD and CROS devices were not significant. Figure 2 shows that scores were slightly higher for both devices relative to the unaided condition with noise presented to the better ear (S0Nbe), and slightly lower with noise presented to the poorer ear (S0Npe), although these differences were also not found to be significant.

QuickSIN Scores

Figure 3 shows mean QuickSIN scores for all three device conditions with babble noise presented to the poorer and better ear, with error bars showing 95% confidence intervals. A slight departure from normality was detected in the unaided condition with noise to the poorer ear ($W = 0.796$, $p = 0.026$), but there was no significant skew or kurtosis in any condition, and so data were analyzed with a repeated measures ANOVA. A significant main effect of noise presentation ear was found ($F(1,7) = 54.8$, $p = 0.0001$, $\eta^2 = 0.496$), indicating that scores were better when noise was presented to the poorer ear. The interaction between noise presentation ear and device condition was also significant ($F(2,14) = 15.5$, $p = 0.0002$, $\eta^2 = 0.218$). Post hoc pairwise *t* tests with Bonferroni corrections showed that scores were significantly better with noise presented to the poorer ear for the unaided condition ($t(7) = 7.1$, $p = 0.003$). There were no significant differences between device conditions with noise presented to the better ear, but scores with the CROS device were significantly poorer than in the unaided condition with noise presented to the poorer ear ($t(7) = 8.96$, $p = 0.0007$).

Self-Assessment Questionnaires

The BBSS and SSQ questionnaires were scored using the standard test procedures. As in Kompis et al. (27), individual totals for the BBSS were obtained by adding the ratings for each listening scenario. The average total score was 26.2 (range = 12.5–39) for the BAHD and 25.4 (range = 11–40) for the CROS. This finding corresponds to grand mean ratings of 2.6 for the BAHD and 2.5 for the CROS. Figure 4 displays mean BBSS ratings for all listeners and both devices using an equal-area violin plot, truncated at minimum and maximum values. These data were not distributed normally in 6 of the 20 subconditions, so a Friedman's nonparametric ANOVA was used for subsequent analysis. No significant differences were found between ratings for the BAHD and CROS, but ratings varied significantly across test items ($\chi^2(9) = 35.4$, $p = 0.00005$). Friedman's post hoc measures indicated that ratings for conversation in quiet were significantly higher

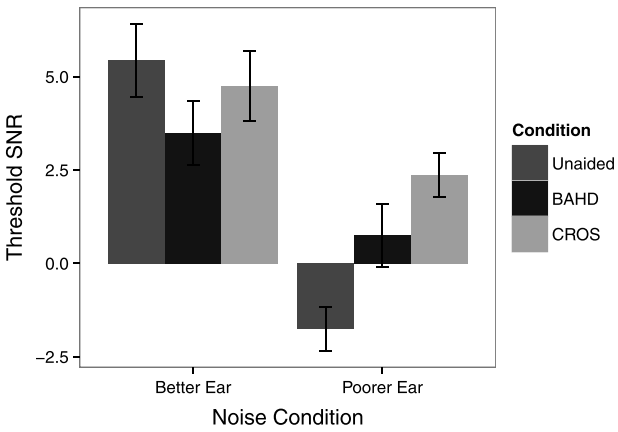

FIG. 3. Mean speech-to-noise ratio thresholds for the QuickSIN test in the S0Nbe and S0Npe conditions. Lower values correspond to better performance. *Error bars* denote 95% confidence intervals.

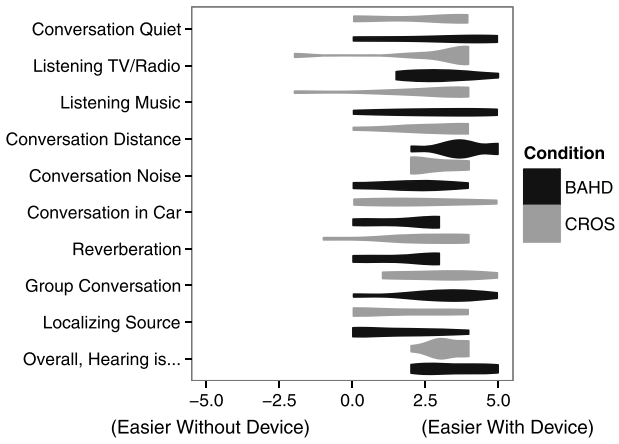

FIG. 4. Equal-area violin plot of BBSS ratings for all listeners and both devices, truncated at maximum and minimum values. Values of −5 correspond to "Much easier without the device," and values of +5 correspond to "Much easier with the device."

than for listening to the television or radio, and these ratings were higher than listening in reverberation.

Mean SSQ scores for each subscale and each device are displayed in Figure 5. Error bars show 95% confidence intervals. As SSQ data for each scale in each device condition were normally distributed, data were analyzed using a repeated measures ANOVA. A significant main effect of subscale was found ($F(2,14) = 15.6$, $p = 0.0003$, $\eta^2 = 0.352$), but there were no significant main effects or interactions related to device. Scores for the Spatial subscale for the BAHD were significantly lower than for the Qualities subscale for both the BAHD ($t(7) = 5.61$, $p = 0.01$) and the CROS ($t(7) = 5.23$, $p = 0.02$).

Device Usage

Data obtained from the BAHD and CROS diaries were used to analyze device usage. Depending on the time that elapsed between visits, some participants wore their hearing device a few days more or less than the 2-week trial period, but the average wearing time for each device was very similar. Paired *t* tests confirmed that there were no differences in the number of days that each device was worn or the number of hours that each device was worn per day. The BAHD was worn for an average of 13.9 days (SD = 2.1) and an average of 10 hours and 6 minutes each day (SD = 2 hr and 38 min). The CROS was worn for an average of 12.9 days (SD = 2.0) and an average of 10 hours and 0 minutes each day (SD = 3 hr and 15 min). One participant reported wearing both the BAHD and the CROS over the same four days.

Participants were also asked to tally the situations in which they used the BAHD or CROS daily. Figure 6 shows the mean number of times that participants reported using each device in each of various conditions. Error bars show 95% confidence intervals. A Friedman's ANOVA found no significant differences in reported usage across conditions between the BAHD and CROS, but there were significant differences between conditions: the devices were worn significantly more often in the home (one-on-one), in the car, and when walking than when doing other activities outdoors.

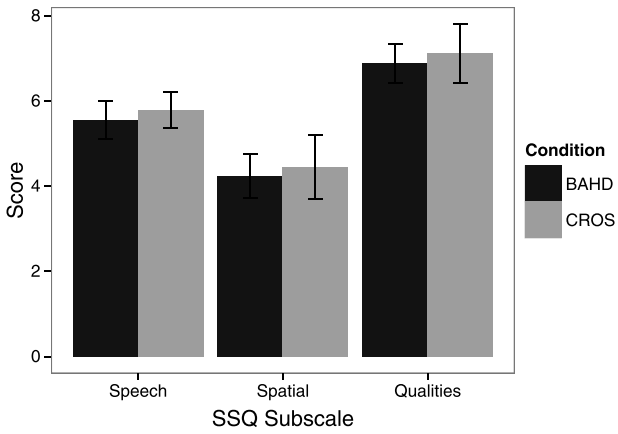

FIG. 5. Mean ratings for each device on the three subscales of the SSQ. Scores correspond to perceived hearing ability on a 10-point scale. *Error bars* denote 95% confidence intervals.

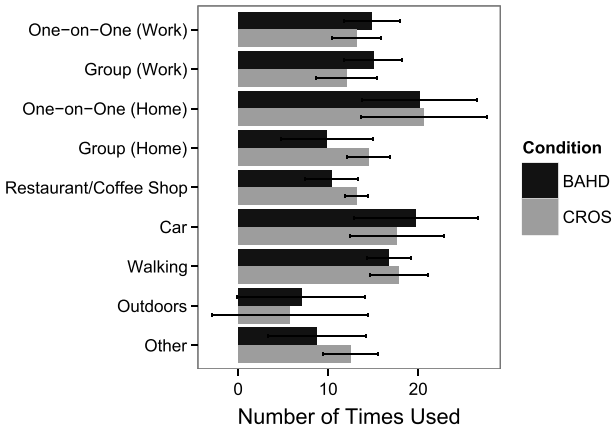

FIG. 6. The mean number of times that each device was reported to be used in the various settings. *Error bars* denote 95% confidence intervals.

Device Preference

When questioned about their preferred hearing device overall, four out of eight participants preferred the CROS to the BAHD, citing sound quality as the main reason for their choice. Three participants preferred the BAHD to the CROS, reporting that they did not like having to wear two hearing aids and struggled with retention of the CROS domes; however, two of them still preferred the sound quality of the CROS. One participant expressed no overall preference but preferred the BAHD for comfort and the CROS for sound quality. These choices varied for both BAHD models used in the experiment. For the four Cochlear BP100 users, two preferred their device to the CROS, one preferred the CROS, and one remained undecided. For the four Oticon Medical Ponto Pro users, one preferred their device to the CROS and three preferred the CROS.

DISCUSSION

Patients and care providers choose a rehabilitative option for SSD based on many complex factors. Some of these factors are aesthetics, comfort, bias and commitment of the healthcare provider, true long-term cost to the patient, restrictions that the technology places on the patient or future medical imaging, medical condition, and the ability to preview technology (e.g., with a headband). Only some of the factors affecting choice are related to the auditory experience, such as sound quality, processor noise, bandwidth, and feedback. Although the questionnaires used here—the SSQ and BBSS—are particularly designed to probe the functional limitations of SSD, it is likely that global non-auditory factors will influence like or dislike of a device and so affect scores even within these instruments.

Older published studies comparing CROS and BAHD (11,12,15,24) (including a systematic review of these studies [10]) have generally concluded that BAHD were preferred for SSD, particularly because of subjective scores rather than objective improvements in speech in noise performance. Two newer studies (3,13) used a BAHD on a headband rather than a percutaneously implanted device and found better speech-in-noise results with noise directed to the better ear with the CROS rather than the BAHD. Because the skin can attenuate the signal in the high frequencies substantially (32), the headband is not a fair comparison of device function in actual usage. All these studies used wired CROS aids. Patients have expressed dissatisfaction with the older wired CROS devices, citing poor cosmetics, discomfort with occlusion of the better ear, poor sound quality and distortion, social stigma, ineffective reduction of high ambient noise, electromagnetic interference by other devices, and interference with sounds heard in the better ear as reasons for being dissatisfied with the CROS (2,23,24,33).

Since these studies, evolution in both technologies (CROS and BAHD) has occurred, particularly in the CROS wearing experience. Modern CROS aids avoid a physically wired connection passing behind the head, are smaller, and do not occlude the functioning ear as much as older devices. However, both devices have changed in ways that should improve the sound quality, such as the sophistication of their signal processing of noise and speech and adaptive directionality of the microphones. Hence, the relative rankings of these devices may well differ from previous studies. Contralateral routing of sound, whether by CROS or BAHD, can be both deleterious and helpful in the hearing experience. When speech is directed to the poorer ear, with noise at the better ear (e.g., SpeN0), then routing speech to the better ear should increase performance (12,24). However, in the S0Nbe condition, contralateral routing actually should decrease performance (12,24). In everyday life, the overall benefit will depend on the relative abundance of these conditions, which may vary from person to person. Across devices, the ability of the processor to distinguish noise from speech and to suppress it, as well as the adaptive directionality of the microphone system, will determine how deleterious the S0Npe situation will be.

It is important to note that the degree of head shadow alleviation is programmable in the CROS device, whereas it is much more limited by the physics of head impedance for bone conduction in the BAHD, particularly in the high frequencies (34).

Our results overall show the trends that we would expect, i.e., an increase in word recognition with SSD aids compared to the unaided state in the SpeN0 condition and a decrease in the S0Npe condition (Fig. 2), an effect also seen with the QuickSin (Fig. 3). With our relatively low numbers, neither the benefit or decrement is significantly different from unaided in Figure 2.

Figure 3 again shows the difference between the condition in which the SSD aid is useful (noise to better ear) and harmful (noise to poor ear). Our results confirmed, as expected, that performance is better (lower SNR) in all device conditions with noise to the poorer ear, i.e., in the condition in which the noise is attenuated by the head shadow before it reaches the better ear to mask speech. The addition of an SSD aid should lower the SNR with noise to the better ear, as it would route more of the speech signal to the better ear. We were not able to show a significant improvement with either SSD aid in this condition, but importantly, nor was there a significant difference between devices, unlike older studies (11,12,15,24).

Subjective results for both questionnaires, which are focused on the particular handicaps of SSD, seem to be similar for both CROS and BAHD (Figs. 4 and 5) as well as conditions and duration of use. This finding is in contrast to older studies, which admittedly used a different questionnaire, the APHAB, but often favored the BAHD (10,18). Perhaps the most telling aspect of the results is that out of the eight participants, four expressed a preference for the CROS device, despite at least 6 months of experience with a BAHD. This finding was not dependent on the device as two of four Cochlear BP100 users preferred the BAHD, with one undecided, and with the Oticon Medical Ponto Pro, three of four users preferred the CROS. The main reasons for preferring the CROS was the sound quality, and reasons for preferring the BAHD were comfort; those participants who preferred the BAHD also expressed difficulty with retention of the dome tips with the CROS and the annoyance of wearing two aids. It should be noted that for the CROS device, disposable dome tips were used. Custom-fitted ear tips may have further improved comfort for the CROS.

This study is the first study to compare BAHD on a percutaneous implant with newer models of CROS devices and to randomize the exposure. Although previous studies have randomized exposure (e.g., Hol et al. [14]), the BAHD was on a headband. The main limitation of this study is the small number of participants. Although the number of participants is comparable to some previous studies (3,14,17), clearly this work should be considered a pilot study to explore if one device provides greater benefit than the other in objective or subjective testing. Differences between the devices, if they exist in objective or subjective measurements, are likely to be relatively small if this study can be considered a point estimate.

Obviously, future work will need to include a larger number of participants to determine if differences between devices emerge. Other factors to explore include whether the Unitron CROS aid used in this study is representative of all modern wireless CROS aids from other manufacturers, such as Phonak. It is not known whether there are differences among different CROS hearing aid models and different BAHD models. We did not have a large enough sample to compare Oticon Medical and Cochlear Corporation BAHD products. Moreover, the CROS device experience may have been enhanced by giving participants more than a 2-week trial and with custom tips rather than domes; these issues should be considered in future research.

CONCLUSION

Our pilot study suggests that both the modern CROS and BAHD seem to perform roughly equivalently in alleviating the auditory and subjective handicap associated with SSD. Previous recommendations from older studies that used older CROS and BAHD devices that seem to favor the BAHD need to be re-evaluated. In our own center, with no obvious advantage of the BAHD, and the risks and cost of surgery, we now recommend a trial of CROS hearing aids as first-line SSD treatment option.

REFERENCES

1. Wie OB, Pripp AH, Tvete O. Unilateral deafness in adults: effects on communication and social interaction. *Ann Otol Rhinol Laryngol* 2010;119:772–81.
2. Taylor B. Contralateral routing of the signal amplification strategies. *Semin Hear* 2010;31:378–92.
3. Arndt S, Aschendorff A, Laszig R, et al. Comparison of pseudobinaural hearing to real binaural hearing rehabilitation after cochlear implantation in patients with unilateral deafness and tinnitus. *Otol Neurotol* 2011;32:39–47.
4. Vermeire K, Van de Heyning P. Binaural hearing after cochlear implantation in subjects with unilateral sensorineural deafness and tinnitus. *Audiol Neurotol* 2009;14:163–71.
5. Moore BC, Popelka GR. Preliminary comparison of bone-anchored hearing instruments and a dental device as treatments for unilateral hearing loss. *Int J Audiol* 2013;52:678–86.
6. Gelfand SA. Usage of CROS hearing aids by unilaterally deaf patients. *Arch Otolaryngol* 1979;105:328–32.
7. Harford E, Barry J. A rehabilitative approach to the problem of unilateral hearing impairment: the contralateral routing of signals CROS. *J Speech Hear Dis* 1965;30:121–38.
8. Oeding K, Valente M. Sentence recognition in noise and perceived benefit of noise reduction on the receiver and transmitter sides of a BICROS hearing aid. *J Am Acad Audiol* 2013;24:980–91.
9. Oeding K, Valente M. The effectiveness of the directional microphone in the Oticon Medical Ponto Pro in participants with unilateral sensorineural hearing loss. *J Am Acad Audiol* 2013;24:701–13.
10. Baguley DM, Bird J, Humphriss RL, Prevost AT. The evidence base for the application of contralateral bone anchored hearing aids in acquired unilateral sensorineural hearing loss in adults. *Clin Otolaryngol* 2006;31:6–14.
11. Bosman AJ, Hol MK, Snik AF, Mylanus EA, Cremers CW. Bone-anchored hearing aids in unilateral inner ear deafness. *Acta Otolaryngol* 2003;123:258–60.
12. Hol MK, Bosman AJ, Snik AF, Mylanus EA, Cremers CW. Bone-anchored hearing aids in unilateral inner ear deafness: an evaluation of audiometric and patient outcome measurements. *Otol Neurotol* 2005;26:999–1006.
13. Hol MK, Kunst SJ, Snik AF, Bosman AJ, Mylanus EA, Cremers CW. Bone-anchored hearing aids in patients with acquired and congenital unilateral inner ear deafness (Baha CROS): clinical evaluation of 56 cases. *Ann Otol Rhinol Laryngol* 2010;119:447–54.
14. Hol MK, Kunst SJ, Snik AF, Cremers CW. Pilot study on the effectiveness of the conventional CROS, the transcranial CROS and the BAHA transcranial CROS in adults with unilateral inner ear deafness. *Eur Arch Otorhinolaryngol* 2010;267:889–96.
15. Lin LM, Bowditch S, Anderson MJ, May B, Cox KM, Niparko JK. Amplification in the rehabilitation of unilateral deafness: speech in noise and directional hearing effects with bone-anchored hearing and contralateral routing of signal amplification. *Otol Neurotol* 2006;27:172–82.
16. Newman CW, Sandridge SA, Wodzisz LM. Longitudinal benefit from and satisfaction with the Baha system for patients with acquired unilateral sensorineural hearing loss. *Otol Neurotol* 2008; 29:1123–31.
17. Niparko JK, Cox KM, Lustig LR. Comparison of the bone anchored hearing aid implantable hearing device with contralateral routing of offside signal amplification in the rehabilitation of unilateral deafness. *Otol Neurotol* 2003;24:73–8.
18. Peters JP, Smit AL, Stegeman I, Grolman W. Review: Bone conduction devices and contralateral routing of sound systems in single-sided deafness. *Laryngoscope* 2015;125:218–26.
19. Ryu NG, Moon IJ, Byun H, et al. Clinical effectiveness of wireless CROS (contralateral routing of offside signals) hearing aids. *Eur Arch Otorhinolaryngol* 2014. doi: 10.1007/s00405-014-3133-0.
20. Zeitler DM, Snapp HA, Telischi FF, Angeli SI. Bone-anchored implantation for single-sided deafness in patients with less than profound hearing loss. *Otolaryngol Head Neck Surg* 2012;147: 105–11.
21. Yuen HW, Bodmer D, Smilsky K, Nedzelski JM, Chen JM. Management of single-sided deafness with the bone-anchored hearing aid. *Otolaryngol Head Neck Surg* 2009;141:16–23.
22. van Wieringen A, De Voecht K, Bosman AJ, Wouters J. Functional benefit of the bone-anchored hearing aid with different auditory profiles: objective and subjective measures. *Clin Otolaryngol* 2011; 36:114–20.
23. Bishop CE, Eby TL. The current status of audiologic rehabilitation for profound unilateral sensorineural hearing loss. *Laryngoscope* 2010;120:552–6.
24. Wazen JJ, Spitzer JB, Ghossaini SN, et al. Transcranial contralateral cochlear stimulation in unilateral deafness. *Otolaryngol Head Neck Surg* 2003;129:248–54.
25. Stenfelt SP, Hakansson BE. Sensitivity to bone-conducted sound: excitation of the mastoid vs the teeth. *Scand Audiol* 1999;28:190–8.
26. Dillon H. CROS, bone conduction and implanted hearing aids. In: Dillon H, ed. *Hearing Aids*, 2nd ed. New York, NY: Thieme, 2012.
27. Kompis M, Pfiffner F, Krebs M, Caversaccio MD. Factors influencing the decision for Baha in unilateral deafness: the Bern benefit in single-sided deafness questionnaire. *Adv Otorhinolaryngol* 2011;71:103–11.
28. Gatehouse S, Noble W. The Speech, Spatial and Qualities of Hearing Scale (SSQ). *Int J Audiol* 2004;43:85–99.
29. *R: A Language and Environment for Statistical Computing [computer program]*. Vienna, Austria: R Foundation for Statistical Computing, 2010.
30. Baguley T. Calculating and graphing within-subject confidence intervals for ANOVA. *Behav Res* 2012;44:158–75.
31. Siegel S, Castellan N. *Nonparametric Statistics*. New York, NY: MacGraw Hill, 1988.
32. Verstraeten N, Zarowski AJ, Somers T, Riff D, Offeciers EF. Comparison of the audiologic results obtained with the bone-anchored hearing aid attached to the headband, the testband, and to the snap abutment. *Otol Neurotol* 2008;30:70–5.
33. Hill SL III, Marcus A, Digges ENB, Gillman N, Silverstein H. Assessment of patient satisfaction with various configurations of digital CROS and BiCROS hearing aids. *Ear Nose Throat J* 2006; 85:427–30.
34. Stenfelt S. Transcranial attenuation of bone-conducted sound when stimulation is at the mastoid and at the bone conduction hearing aid position. *Otol Neurotol* 2012;33:105–14.

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Cochlear Implantation for Single-Sided Deafness: A Multicenter Study

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Objectives/Hypothesis: To report the preliminary outcomes of patients with single-sided deafness and asymmetric hearing loss undergoing cochlear implantation at two centers.

Study Design: Retrospective review and prospective data collection.

Methods: Patients with single-sided deafness who underwent cochlear implantation at two centers were included. Pre- and postoperative measures included monosyllabic word and sentence recognition in quiet for the ear implanted, and sentence recognition in noise in the best-aided bilateral condition.

Results: Average monosyllabic word recognition scores in quiet improved significantly from 11.3% (standard deviation [SD] 15.6%) preoperatively to 48.7% (SD 24.2%) at the 3-month postactivation interval, although they did not increase significantly between the 3-month and 6-month intervals. Sentence recognition scores in quiet increased significantly from 18.4% (SD 28.5%) preoperatively to 65.9% (SD 17.9%) at the 3-month postactivation interval, but not between the 3-month and 6-month intervals. Sentence recognition in noise in the best-aided bilateral condition increased from 59% (SD 16.3%) preoperatively to 72% (SD 16.0%) at 6-months postactivation, though the difference was not statistically significant. Thirteen of the participants reported tinnitus prior to surgery. Of those, 12 reported that tinnitus was improved after implantation, and one reported that tinnitus was unchanged.

Conclusion: Preliminary results suggest that speech recognition in a singly deafened ear is significantly improved after cochlear implantation, although speech recognition in noise measured in the bilateral condition remains the same at 6-months postactivation.

Key Words: Cochlear implant, single-sided deafness, signal-to-noise ratio, tinnitus, speech understanding in noise, sudden sensorineural hearing loss.

Level of Evidence: 4.

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INTRODUCTION

Single-sided deafness (SSD) is characterized by unilateral hearing loss in the presence of normal or near-normal hearing in the opposite ear. Previous research demonstrates that SSD affects some 18.1 million people in the United States and significantly impacts quality of life, resulting in increased stress and a feeling of exclusion in social settings.[1–3] Those affected by SSD have decreased hearing sensitivity, degraded speech recognition, and usually some degree of tinnitus. In fact, more than 90% of adults who experience unilateral sudden sensorineural hearing loss (SSNHL) also report ringing in their ears.[4] Perhaps most disturbing among patients with SSD is the loss of binaural function affecting sound localization and speech understanding in complex listening environments.

Binaural hearing is the result of 1) binaural squelch: the ability of the brain to separate speech from noise, 2) binaural summation: redundancy of auditory input, and 3) the head shadow effect: the decrease in loudness as sound moves from one side of the head to the other.[5,6] Current treatment options for SSD consist of routing the signal from the impaired ear to the normal hearing contralateral side using contralateral routing of signal (CROS) aids/BiCROS aids or an auditory osseointegrated implant system. Previous research has demonstrated that both are effective to overcome head shadow effect and detect sounds from the affected side, although they do not restore binaural hearing because the brain only receives input from one side.[7–9] In fact, research in this area demonstrates that rerouting the signal to the normal hearing side provides little improvement in sound localization and modest improvement for understanding speech in noisy conditions.[7–9]

Cochlear implants (CI) have been suggested as an alternative treatment option for individuals with SSD.

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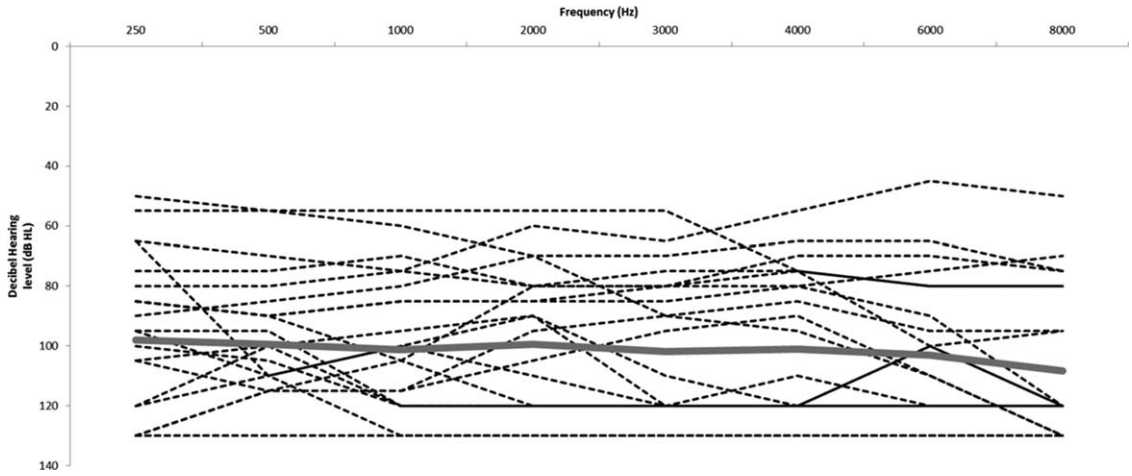

Fig. 1. Preoperative air conduction hearing thresholds for the implanted ear.

The emerging research is positive and suggests that CIs offer partial hearing restoration for the implanted ear, although outcomes related to binaural hearing are mixed. Speech recognition in the ear implanted, when measured in quiet, has been shown to improve significantly following implantation.[10,11] Speech recognition in noise, however, is highly variable and test parameters vary considerably among investigators, making direct comparison difficult. For example, Vermiere, Tavora-Viera, and Stelzig each presented speech and noise from a front center speaker (S0N0) and used an adaptive procedure to find the signal-to-noise ratio (SNR) needed for 50% correct, although speech materials varied among them.[10,12,13] Vermiere et al. found a statistically significant decrease in the SNR needed for sentence understanding, and the other two did not.[10] Later, a meta-analysis pooling all three studies demonstrated a mean decrease in SNR necessary for 50% correct.[14] In other research, Stelzig et al. and Arndt et al. each presented speech and noise at 65-dB sound pressure level (SPL) from S0N0 and found no difference in sentence recognition following cochlear implantation.[13,15] Zeitler et al. showed subjects undergoing CI for SSD demonstrated significant improvement in sentence scores in complex noise environments in the binaural condition, with the greatest improvements when speech is presented to the implanted ear. These same subjects also showed significant improvements in sound source localization, with some subjects localizing sound at or near the accuracy of normal hearing listeners.[16] Other studies have also reported significant improvement for localization among patients with SSD, decreased tinnitus, and improved self-perceived benefit on the Speech Spatial and Qualities of Hearing questionnaire.[17]

Reports of tinnitus suppression after implantation have been reported by several investigators.[15,18] In one study, Arts et al. examined the impact of implantation on tinnitus among patients with SSD by pooling data from several reports.[18] The data were treated as a multicenter study and subjected to matched *t* tests. Results demonstrated improved tinnitus between preoperative and 1-, 3-, 6-, and 24- month postoperative test intervals.

The purpose of this study was to complete a preliminary evaluation of speech recognition in quiet and in noise among a group of adults and children with SSD. Data was compiled from two separate centers.

MATERIALS AND METHODS

The current study was a multisite, single-arm repeated measures research design. Each participating center obtained institutional review board approval from their respective center.

Participants

The participants in this study had mild to severe sensorineural hearing loss with $\leq$ 40% consonant-nucleus-consonant (CNC) word recognition on the affected side. A pure tone average of 30 dB HL or better and a mean word recognition score of 99.3% (standard deviation [SD] 2.8%) were present on the contralateral side. Thus, all patients had truly normal hearing in the nonimplanted ear. The preoperative air conduction hearing thresholds for the ear implanted can be found in Figure 1.

The total sample was comprised of 23 individuals (17 adults, 6 children). The adults ranged in age from 31 to 62 years, and the children ranged in age from 5 to 15 years. Duration of hearing loss was defined as the time between onset of hearing loss and time of implantation. Duration of hearing loss ranged from 0.5 to 9.5 years with an average of 4.0 years. In all, there were 10 left ears and 13 right ears implanted. Demographic information for all participants can be found in Table I.

Materials

Speech understanding was assessed using the CNC word test and the AzBio sentence test.[19,20] The CNC word test is comprised of 10 lists, each containing 50 monosyllabic words produced by a single male talker. The AzBio Sentence Test is comprised of 15 lists of 20 sentences, each produced by two male and two female talkers and scored for each word repeated correctly.

Procedures

Prior to preoperative aided testing, participants' hearing aids were set to National Acoustic Laboratories (prescriptive targets).[21] Participants who did not use hearing aids on a full-time basis were required to complete a 30-day trial before CI candidacy determination.

TABLE I.
Participant Demographics.

Participant	Age at Implantation (yrs)	Etiology of Deafness	Duration of Deafness (yrs)	AOI Conversion	Device
1	5.8	Congenital	5.8		Med-El Synchrony Flex28
2	37.5	SSNHL	1.5		Med-El Concert Flex28
3	50.0	SSNHL	6.0		Med-El Concert Flex28
4	8.9	Congenital	8.9		Med-El Concert Flex28
5	9.5	Congenital	9.5	1	Med-El Concert Flex28
6	10.0	Progressive	4.0	1	Med-El Concert Standard
7	48.2	SSNHL	2.5		Med-El Concert Flex28
8	39.2	MD	3.0		AB HiFocus Mid-Scala
9	62.9	Iatrogenic p NSGY	0.5		Med-El Concert Flex28
10	31.9	SSNHL	1.5		Med-El Concert Flex28
11	52.0	SSNHL	1.0		Med-El Concert Flex28
12	39.3	SSNHL	11.0		Med-El Concert Flex28
13	38.6	SSNHL	1.0		Med-El Concert Flex24
14	49.5	Ear Sx	2.0		Cochlear Nucleus 422
15	47.3	Acoustic neuroma	0.9		Med-El Concert Flex28
16	35.0	Meningitis	0.8		Cochlear Nucleus 422
17	55.0	SSNHL	1.9		Cochlear Nucleus 422
18	55.1	SSNHL	1.0		Med-El Concert Flex24
19	15.0	SSNHL	1.0		Med-El Concert Flex28
20	11.4	Ear Sx	3.0	1	Cochlear CI24 RE(CA)
21	40.8	SSNHL	2.0		AB HiFocus Mid-Scala
22	50.0	Labyrinthitis	5.0		Cochlear Nucleus 422
23	60.9	SSNHL	2.0		Cochlear Nucleus 422

SSNHL = sudden sensorineural hearing loss; MD = Meniere's Disease; Sx = surgery; p NSGY = after neurosurgical procedure; AOI = auditory osseointegrated implant; AB = Advanced Bionics Cochlear Corporation (NSW, Australia), Advanced Bionics (Valencia, CA, USA), Med-El (Innsbruck, Austria).

Testing was completed in quiet in a sound field using recorded stimuli at a calibrated presentation level of 60 dB SPL (A-weighted [SPL(A)]). The contralateral ear was either masked (center 1) or plugged and muffed (center 2). Speech in noise was measured with the impaired ear-aided and the contralateral ear unoccluded in a +5 dB SNR with speech at 65 dB SPL(A). Speech and noise both originated from a single speaker at 0-degree azimuth.

Postoperatively, speech understanding in quiet was measured using a direct audio input (DAI) cable (center 1), or as described above with the contralateral ear plugged and muffed (center 2). Patients tested using DAI were asked to set the volume at a comfortable loudness level prior to starting the test. Speech understanding in noise was tested in the aided bilateral condition with the CI in place. All testing was completed using an omnidirectional program with user settings. Each participant was administered one list per condition at each time interval. Responses were recorded and scored by the experimenter. All speech perception scores were calculated as percent correct. Due to the combination of retrospective and prospective data, not all participants completed testing at each time interval. Statistical analyses were completed using IBM SPSS Statistical Package 21.0.0 (IBM Corp., Armonk, NY). An alpha level of 0.05 was used to determine statistical significance.

RESULTS

Consonant-Nucleus-Consonant Word Understanding in Quiet

Performance on CNC word test was completed on 20 participants preoperatively and 13 participants at 3- and 6-month postactivation intervals. Individual patient scores for each time interval can be found in Figure 2. Pediatric patients are represented with open symbols. Mean CNC word scores were 11.3% (SD 15.6%) preoperatively, 48.7% (SD 24.2%) at the 3-month postactivation interval, and 44.7% (SD 20.0%) at 6-month postactivation interval. The data were analyzed using a repeated measures analysis of variance (RM-ANOVA) using CNC word score in percent correct as the dependent variable, and test interval (preoperative, 3-month, and 6-month

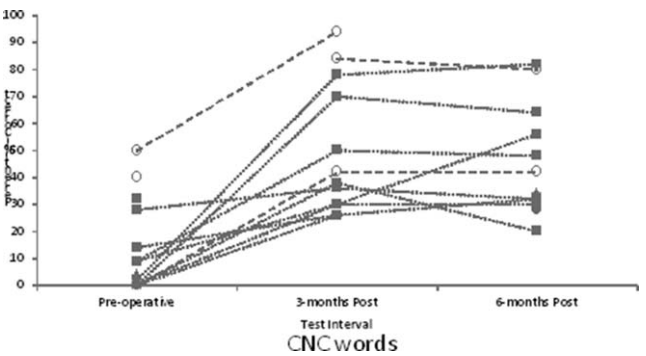

Fig. 2. Individual patient scores for CNC words in quiet for the preoperative, 3-month, and 6-month postactivation test intervals. Pediatric patients are represented with open symbols. CNC = consonant-nucleus-consonant.

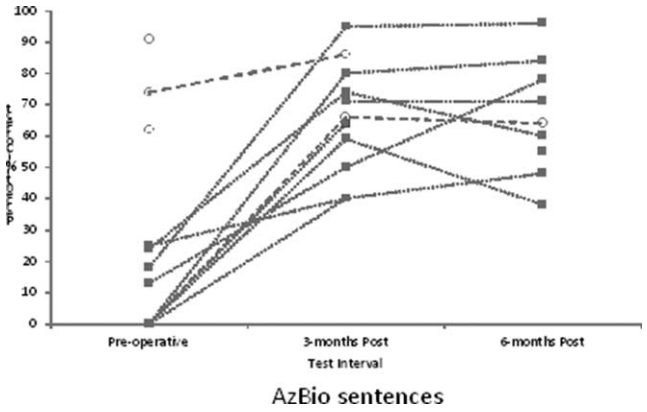

Fig. 3. Individual patient scores for AzBio sentences in quiet for the preoperative, 3-month, and 6-month postactivation test intervals. Pediatric patients are represented with open symbols.

postactivation) as a within-subjects variable. Results showed a significant main effect of test interval, F (2, 20) = 24.1, $P < 0.001$. The main effect of test interval was followed up with post-hoc pairwise comparisons using Bonferonni corrections, which showed significant improvement in CNC word recognition for the ear implanted between the preoperative and 3-month postactivation intervals, $P = 0.001$, but not between the 3-month and 6-month postactivation intervals, $P = 0.45$.

AzBio Sentence Understanding in Quiet

Average AzBio sentence recognition scores in quiet were present for 18 participants preoperatively, 11 participants at 3-months postactivation, and nine participants at 6-months postactivation. Individual patient scores at the three test intervals can be found in Figure 3. Pediatric patients are represented with open symbols. Mean AzBio sentence scores were 18.4% (SD 28.5%) preoperatively, 65.9% (SD 17.9%) at the 3-month postactivation interval, and 66.0% (SD 18.2%) at the 6-month postactivation interval. The data were analyzed using RM-ANOVA with test interval and listening condition as within-subject factors. The results demonstrated a significant main effect of test interval $F(2,12) = 53.26$, $P < 0.001$. The main effect of test interval was followed up with pairwise comparisons with Bonferonni corrections, which showed significant improvement for the unilateral condition between preoperative and 3-month postactivation intervals, $P < .001$, but not between the 3-month and 6-month postactivation test intervals, $P = .89$.

AzBio Sentence Understanding in +5 dB Signal-to-Noise Ratio

Average AzBio sentence recognition scores in +5 dB SNR quiet were present for 10 individuals preoperatively, two individuals at 3-months postactivation, and eight people at 6-months postactivation. Due to the exceptionally low number of scores at 3-months postactivation, statistical analysis was completed using only the preoperative and 6-month postactivation scores. The individual patient scores for the preoperative and 6-month postactivation test intervals can be found in Figure 4. Pediatric patients are represented with open symbols; mean percent correct scores were 59% (SD 16.3%) preoperatively and 72% (SD 16.0%) at 6-months postactivation. Scores were analyzed using a Student t test and showed no significant difference between the preoperative and 6-month test interval $t(8) = 1.71$, $P = 0.12$.

Tinnitus Suppression

The subjective presence of tinnitus was recorded pre- and postoperatively. Among the 23 participants, 13 described having tinnitus before surgery. Of them, 12 (92%) participants reported that their tinnitus was improved after surgery. One person reported no change in tinnitus after surgery.

DISCUSSION

Single-sided deafness impairs auditory function of one ear and leads to deficits for speech in noise understanding and localization. Current treatment options have been limited to devices that route the signal from the affected side to the side with normal hearing but do not restore binaural hearing. Cochlear implantation has been offered as an alternative treatment option and one that can restore true binaural hearing. The emerging literature is encouraging, although comprised of reports with small sample sizes, variable follow-up, heterogeneous populations, differing test parameters, and variable outcomes. The purpose of this study was to evaluate speech recognition performance in a group of adults and children with SSD through a multicenter design.

Results of the current study clearly demonstrate that CI can provide partial hearing restoration and can significantly improve both word and sentence scores in the ear implanted when measured in quiet. This finding is in agreement with previous reports.[10,11,22] The degree of improvement, however, is less than the improvement

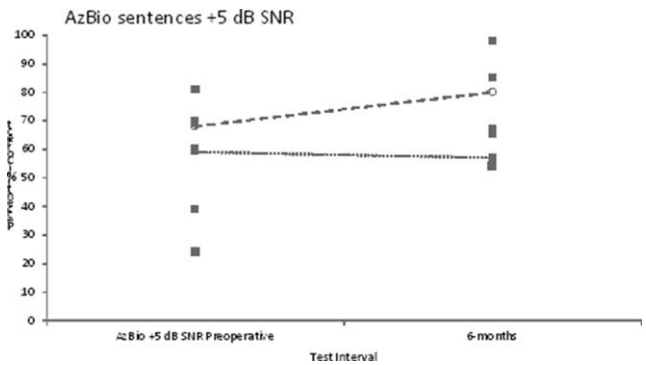

Fig. 4. Individual patient scores for AzBio sentences in +5 dB signal-to-noise ratio at the preoperative and 6-month postactivation test intervals. Pediatric patients are represented with open symbols.

observed in adults and children with bilateral hearing loss. Specifically, the current study found that CNC word recognition was, on average, 44% at 6-months postactivation, whereas studies using adults with bilateral hearing loss, also with 6 months of use, have an average CNC word score of 61%.[23] The primary explanation for this finding is that patients with normal hearing in one ear continue to rely heavily on their good ear because of the natural sound quality, which may reduce the rate of improvement and maximum rehabilitation potential of the deaf ear.

In contrast to speech recognition in quiet, the current study found that speech recognition in noise was not significantly improved after CI, although the scores at 6-months postactivation were higher than those obtained before surgery. As noted earlier, several previous investigators have reported similar findings. However, one recent study by Mertens et al. suggests that speech-in-noise improvement may not emerge until after several years of implant use.[24] In that study, 12 adults with SSD and CI were followed through 36 months of implant use. Speech-in-noise performance was measured with CI_{on} and CI_{off} using various testing parameters, including presentation of both speech and noise from the front, as well as spatially separated signals (S_0N_0, S_0N_{CI}, $S_{CI}N_0$). Results demonstrated improved speech in noise for S_0N_{CI} after 12 months of implant use, whereas improved performance for S_0N_0 was not observed until 36 months of implant use.

Tinnitus suppression continues to be an indirect benefit of implantation among patients with SSD. As seen in the current study, the majority of patients who had tinnitus prior to surgery had a reduction in self-reported tinnitus severity following implantation with the device on, and in many cases also with the device off. The exact underlying reason of tinnitus suppression is not known, although there is speculation that the implant increases afferent stimulation, which offsets one possible underlying cause.[18]

There are several limitations associated with the current study. First, the relatively small sample size makes statistical comparisons less robust and limits generalizability of the data. Larger sample sizes are needed to understand the variability in performance within this population. Another limitation is that data was collected retrospectively from two separate centers, each with unique test protocols. For example, center 2 measured speech recognition in the implanted ear with the contralateral ear plugged and muffed, whereas center 1 used masking on the contralateral side. It is unknown if these two methods are equivalent. Another limitation of this study is the condition of the participants' sound processors. Each participant was tested using the sound processor and program that they use in everyday life. There was no control regarding the volume setting, the presence of noise suppression circuits, or input mixing ratios. It is possible that some participants have much higher volume settings than others.

Demographic factors also limit the current study. For example, the group studied here was comprised of children and adults with various etiologies and durations of deafness. Although the majority (12 of 23 or 52%) had SSNHL, other causes of hearing loss were also represented. The numbers, however, are not large enough to analyze outcomes by etiology. In addition, longer durations of deafness were observed in many of these cases. We know from previous work that duration of deafness negatively impacts CI performance and may have played a role in our patients being implanted after longer periods of nonusable hearing.[23] Our mean duration of deafness (4.0 years) is skewed by three of six of the children in whom congenital hearing loss and long delays to implantation occurred. Future studies with higher numbers of patients in this category will be needed to determine if significant differences in performance occur.

CONCLUSION

Rehabilitation of SSD with CI significantly improves speech understanding in the deafened ear and reduces or eliminates tinnitus in most subjects. Speech understanding in noise remains unchanged between the 3-months and 6-months postactivation test intervals. It is possible that performance on speech in noise will continue to improve that and benefits will be realized with longer-term implant experience.

BIBLIOGRAPHY

1. Hanson H. Unilateral deafness a, social, psychological, and existential aspects [Thesis]. Stockholm, Sweden: University of Stolkholm; 1993.
2. Lin FR, Niparko JK, Ferrucci L. Hearing loss prevalence in the United States. *Arch Intern Med* 2011;171:1851–1852.
3. Wie OB, Pripp AH, Tvete O. Unilateral deafness in adults: effects on communication and social interaction. *Ann Otol Rhinol Laryngol* 2010;119: 772–781.
4. Fetterman BL, Saunders JE, Luxford WM. Prognosis and treatment of sudden sensorineural hearing loss. *Am J Otol* 1996;17:529–536.
5. Akeroyd MA. The psychoacoustics of binaural hearing. *Int J Audiol* 2006; 45(suppl 1):S25–S33.
6. Middlebrooks JC, Green DM. Sound localization by human listeners. *Annu Rev Psychol* 1991;42:135–159.
7. Bishop CE, Eby TL. The current status of audiologic rehabilitation for profound unilateral sensorineural hearing loss. *Laryngoscope* 2010;120: 552–556.
8. Desmet JB, Wouters K, De Bodt M, et al. Comparison of 2 implantable bone conduction devices in patients with single-sided deafness using a daily alternating method. *Otol Neurotol* 2012;33:1018–1026.
9. Saroul N, Akkari M, Pavier Y, et al. Long-term benefit and sound localization in patients with single-sided deafness rehabilitated with an osseointegrated bone-conduction device. *Otol Neurotol* 2013;34:111–114.
10. Vermeire K, Van de Heyning P. Binaural hearing after cochlear implantation in subjects with unilateral sensorineural deafness and tinnitus. *Audiol Neurootol* 2009;14:163–71.
11. Firszt JB, Holden LK, Reeder RM, et al. Auditory abilities after cochlear implantation in adults with unilateral deafness: a pilot study. *Otol Neurotol* 2012;33:1339–1346.
12. Tavora-Vieira D, Marino R, Krishnaswamy J, et al. Cochlear implantation for unilateral deafness with and without tinnitus: a case series. *Laryngoscope* 2013;123:1251–1255.
13. Stelzig Y, Jacob R, Mueller J. Preliminary speech recognition results after cochlear implantation in patients with unilateral hearing loss: a case series. *J Med Case Rep* 2011;5:343.
14. Blasco MA, Redleaf MI. Cochlear implantation in unilateral sudden deafness improves tinnitus and speech comprehension: meta-analysis and systematic review. *Otol Neurotol* 2014;35:1426–1432.
15. Arndt S, Aschendorff A, Laszig R, et al. Comparison of pseudobinaural hearing to real binaural hearing rehabilitation after cochlear implantation in patients with unilateral deafness and tinnitus. *Otol Neurotol* 2011;32:39–47.
16. Zeitler DM, Dorman MF, Natale SJ, et al. Sound source localization and speech understanding in complex listening environments by single-sided deaf listeners after cochlear implantation. *Otol Neurotol* 2015;36:1467–1471.
17. Gatehouse S, Noble W. The Speech, Spatial and Qualities of Hearing Scale (SSQ). *Int J Audiol* 2004;43:85–99.

18. Arts RA, George EL, Stokroos RJ et al. Review: cochlear implants as a treatment of tinnitus in single-sided deafness. *Curr Opin Otolaryngol Head Neck Surg* 2012;20:398–403.
19. Peterson GE, Lehiste I. Revised CNC lists for auditory tests. *J Speech Hear Disord* 1962;27:62–70.
20. Spahr AJ, Dorman MF. Effects of minimum stimulation settings for the Med El Tempo+ speech processor on speech understanding. *Ear Hear* 2005;26:2S–6S.
21. Byrne D, Parkinson A, Newall P. Hearing aid gain and frequency response requirements for the severely/profoundly hearing impaired. *Ear Hear* 1990;11:40–49.
22. Hansen MR, Gantz BJ, Dunn C. Outcomes after cochlear implantation for patients with single-sided deafness, including those with recalcitrant Meniere's disease. *Otol Neurotol* 2013;34:1681–1687.
23. Holden LK, Finley CC, Firszt JB, et al. Factors affecting open-set word recognition in adults with cochlear implants. *Ear Hear* 2013;34: 342–360.
24. Mertens G, Kleine Punte A, De Bodt M, et al. Binaural auditory outcomes in patients with postlingual profound unilateral hearing loss: 3 years after cochlear implantation. *Audiol Neurootol* 2015;20(suppl 1): 67–72.

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Sound Source Localization and Speech Understanding in Complex Listening Environments by Single-sided Deaf Listeners After Cochlear Implantation

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Objective: To assess improvements in sound source localization and speech understanding in complex listening environments after unilateral cochlear implantation for single-sided deafness (SSD).
Study Design: Nonrandomized, open, prospective case series.
Setting: Tertiary referral center.
Patients: Nine subjects with a unilateral cochlear implant (CI) for SSD (SSD-CI) were tested. Reference groups for the task of sound source localization included young (n = 45) and older (n = 12) normal-hearing (NH) subjects and 27 bilateral CI (BCI) subjects.
Intervention: Unilateral cochlear implantation.
Main Outcome Measures: Sound source localization was tested with 13 loudspeakers in a 180 arc in front of the subject. Speech understanding was tested with the subject seated in an 8-loudspeaker sound system arrayed in a 360-degree pattern. Directionally appropriate noise, originally recorded in a restaurant, was played from each loudspeaker. Speech understanding in noise was tested using the Azbio sentence test and sound source localization quantified using root mean square error.
Results: All CI subjects showed poorer-than-normal sound source localization. SSD-CI subjects showed a bimodal distribution of scores: six subjects had scores near the mean of those obtained by BCI subjects, whereas three had scores just outside the 95th percentile of NH listeners. Speech understanding improved significantly in the restaurant environment when the signal was presented to the side of the CI.
Conclusion: Cochlear implantation for SSD can offer improved speech understanding in complex listening environments and improved sound source localization in both children and adults. On tasks of sound source localization, SSD-CI patients typically perform as well as BCI patients and, in some cases, achieve scores at the upper boundary of normal performance. **Key Words:** Cochlear implant—Hearing in noise—Single-sided deafness—Sound localization—Speech perception.
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In one of the newest applications of cochlear implants (CIs), patients with single-sided deafness (SSD), that is, individuals with one normal-hearing (NH) ear and one deafened ear, have been fit with a CI (SSD-CI). After implantation, SSD-CI patients experience a reduction in tinnitus strength, a large improvement in sound source localization, and, in some test environments, an improvement in speech understanding (1–6). These improvements, in combination with a greatly expanded sense of auditory space, underlie an improved health-related quality of life (1,7,8).

In a previous article, we described the results of an experiment using a small sample (n = 4) in which we probed the information that underlies sound source localization by SSD-CI patients (9). Using high- and low-pass noise bands to restrict the patients' access to interaural level difference (ILD) cues and to interaural time difference (ITD) cues, we inferred that sound source localization in SSD-CI patients is based primarily on ILD cues. This is a reasonable outcome given that fine temporal information is not well transmitted by CIs (10).

We also reported that the sound source localization performance of SSD-CI patients, although poorer than normal, was superior to that of bimodal CI patients, that is, patients with a CI in one ear and a traditional hearing aid in the contralateral ear with low-frequency (<500 Hz) residual hearing. We rationalized this outcome by noting that bimodal patients have relatively good access to

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timing information from the ear with low-frequency acoustic hearing and have relatively good access to signal level information from the ear fit with a CI. Neither timing nor level information is well represented at both ears. For that reason, sound source localization is very poor.

CI signal processing severely compresses signal level information because of the automatic gain control function at the front end of the signal processing chain and the logarithmic compression of acoustic signals into the electric dynamic range at the back end (10). For bilateral CI (BCI) patients, this signal level compression should be reasonably symmetric between ears given similar settings of the independent signal processors for each ear. However, for SSD-CI patients, the NH ear will experience relatively large signal levels whereas the CI ear will experience much reduced signal levels. The magnitude of the difference is shown in the following example (taken from Dorman et al. [9]): for NH listeners, the ILD at 3 kHz for a sound source at 45 degrees azimuth is approximately 10 dB; at 15 degrees azimuth, the ILD is approximately 3 dB. After CI signal processing, at 45 degrees azimuth, the ILD is 1.6 dB and, at 15 degrees, it is 0.4 dB (9,11). Thus, SSD-CI patients should experience a distorted representation of signal level as a function of signal azimuth when listening with one NH ear and one deaf ear fitted with a CI. Based on the peripheral representation of signal amplitude, we should expect different levels of sound source localization for BCI and SSD-CI patients.

As noted above, SSD-CI patients have been found to have improved speech understanding but the magnitude of the improvement is critically contingent on the test environment. For example, Arndt et al. (1) reported no benefit in speech understanding in the NH ear plus CI condition versus the NH ear–alone condition when both the signal and the noise were presented from a single speaker at 0 degree azimuth, that is, in a standard audiometric test environment. However, when the signal was at 45 degrees azimuth on the side of the CI and the noise was at 45 degrees azimuth on the side of the NH ear, then a large improvement (~28 percentage points) was observed in the NH ear plus CI condition versus the NH ear–alone condition.

In this article, we compare the sound source localization performance of SSD-CI patients with that of BCI patients. The relative performance of the SSD-CI and BCI patients is of interest because both groups rely on ILDs for sound source localization. However, in contradistinction to the BCI group that receives reasonably symmetric signal levels at the two ears, the SSD-CI group does not. Furthermore, we expand the environments in which SSD-CI patients have been tested and asked whether the benefit to speech understanding extends to a situation in which directionally appropriate restaurant noise is presented from an array of eight loudspeakers surrounding the listener. In our simulated restaurant test environment, the target sentences were presented on the side of the CI in two conditions, NH ear only and NH ear plus CI.

METHODS

Forty-five young NH listeners, 12 older NH listeners, 27 BCI patients, and nine SSD-CI patients who underwent unilateral CI for SSD from 2011 to 2014 served as subjects. The young NH listeners ranged in age from 21 to 40 years and were recruited from the undergraduate and graduate student populations at Arizona State University. All had pure-tone thresholds of 20 dB or less at octave frequencies from 0.125 to 4 kHz (12). The older NH listeners ranged in age from 51 to 70 years. All but one had pure-tone thresholds of 20 dB or less through 2 kHz. One had a 30-dB threshold at 2 kHz. The BCI sample consisted of 16 subjects fit with Med-El implants (as described in Dorman et al. [11]), and 11 subjects fit with Cochlear Corporation devices. These patients ranged in age from 32 to 79 years. For the SSD-CI population, all subjects had a pure-tone average (0.5, 1, 2, and 4 kHz) in the normal range in the contralateral NH ear, but one of the nine subjects (S5) had a mild-to-moderate neurosensory loss at 4, 6, and 8 kHz. The patients ranged in age from 12 to 63 years. All subjects received full consent of the study procedures. This project was reviewed and approved by the Arizona State University's Institutional Review Board.

Surgery was carried out in all cases using a standard transmastoid facial recess approach. All electrode arrays were implanted through either a round window or a cochleostomy approach depending on the intraoperative anatomy encountered.

Sound Source Localization Testing

Test Signal

The stimulus was a wideband noise signal band-pass filtered between 125 and 6,000 Hz. The filter roll-offs were 48 dB per octave. The overall signal level was 65 dBA.

Test Environment

As described in previous publications (11,12), the stimuli were presented from 11 of 13 loudspeakers arrayed within an arc of 180 degrees on the frontal plane. The speakers were 15 degrees apart. An additional speaker was appended to each end of the 11-loudspeaker array but was not used for signal delivery. The room was lined with acoustic foam. Subjects sat in a chair at a distance of 1.67 m from the loudspeakers. Loudspeakers were located at the height of the listeners' pinna.

Test Conditions

Stimulus presentation was controlled by Matlab. Each stimulus was presented four times from each loudspeaker. The presentation level was 65 dBA with a 2-dB rove in level. Level roving was used to reduce any cues that might be provided by the acoustic characteristics of the loudspeakers. Subjects were instructed to look at the midline (center loudspeaker) until a stimulus was presented. They entered the number of the loudspeaker (1–13) on a keypad.

Speech Understanding in Noise Testing

Speech understanding was tested in the R-Space test environment (13). The listener was seated in the middle of an 8-loudspeaker sound system arrayed in a 360-degree pattern around the listener. Directionally appropriate noise, originally recorded in a restaurant, was played from each loudspeaker. The test stimuli were sentences from the AzBio test corpus (14). The sentences were always played from the loudspeaker at 0 degree azimuth to the CI, that is, from the

TABLE 1. *Biographical data for SSD-CI patients*

Subject	Age (yr)	Age at Profound HL (yr)	Etiology	Time Since Activation (mo)	Implant	Electrode	Speech: CI Only	Localization CI + NH ear (RMS error)
S1	39	34	MD	2	Advanced Bionics	Mid-scala	77%	38 degrees
S2	38	36	ISSNHL	9	Med-El	Flex 28	96%	37 degrees
S3	48	42	ISSNHL	3	Med-El	Flex 28	76%	39 degrees
S4	49	48	ISSNHL	16	Med-El	Standard	60%	11 degrees
S5	63	63	Iatrogenic[a]	4	Med-El	Flex 28	53%	40 degrees
S6	12	5	Idiopathic progressive	33	Med-El	Standard	95%	14 degrees
S7	39	37	ISSNHL	6	Med-El	Flex 24	DNT	33 degrees
S8	50	45	ISSNHL	2.5	Med-El	Flex 28	67%	41 degrees
S9	49	43	ISSNHL	2	Med-El	Flex 28	DNT	16 degrees

CI indicates cochlear implant; HL, hearing loss; Speech: CI Only, AzBio sentences in quiet; MD, Ménière's disease; ISSNHL, idiopathic sudden sensorineural hearing loss; NH, normal hearing; RMS, root mean square.

[a]Hearing loss occurred during microvascular decompression for trigeminal neuralgia.

loudspeaker closest to the CI. There were two test conditions. In one, the CI was not activated. In this condition, the sentences were at 180 degrees to the NH ear. In this condition, for each patient, the signal-to-noise ratio (with the signal level fixed at 60 dB SPL) was adjusted to produce performance between 20% and 60% correct. This signal-to-noise ratio was then used for the second condition in which the CI was activated (in addition to the NH ear). Two lists of 20 sentences were used in each condition. Performance was scored in terms of percent words correct. Six of the nine listeners tested in the localization experiment were tested in this experiment.

RESULTS

Demographic data for the nine SSD-CI listeners are shown in Table 1. The mean age of the SSD-CI patients was 43 years (range, 12–63 yr). Four of the included subjects were female. The patients had 1 to 6 years of severe-to-profound hearing loss before receiving the CI. The mean duration of CI experience at the time of testing was 8.6 months (range, 2–33 mo). Eight patients received a Med-El Cochlear Implant System (Innsbruck, Austria), and one received an Advanced Bionics Cochlear Implant System (Valencia, CA, U.S.A.). All patients had a full insertion of the electrode array, and there were no surgical complications.

Localization accuracy was calculated in terms of root mean square (RMS) error using the D statistic of Rakerd and Hartmann (15). Chance performance, calculated using a Monte Carlo method, was 73.5 degrees (SD, 3.2). Localization accuracy for all listeners is summarized in Figure 1.

RMS error for the young NH group was 6.0 degrees (SD, 2.7); for the older NH group, 6.5 degrees (SD, 1.0); for the BCI group, 29.0 degrees (SD, 15); and for the SSD-CI group, 30.0 degrees (SD, 12). The distribution of scores for the SSD-CI patients was clearly bimodal with a cluster of six scores between 33 and 40 degrees RMS error and another cluster of three scores between 11 and 16 degrees RMS error. There was no correlation between any of the studied demographic variables and performance on the localization testing. There was also no difference in RMS error based on the time between implantation and testing.

The results for speech understanding in noise in the combined NH ear plus CI condition are summarized in Figure 2. All listeners showed a significant benefit in speech understanding, that is, for each patient, scores in the combined condition were higher than the 95% critical difference scores for the AzBio sentences (14) in the NH ear–alone condition.

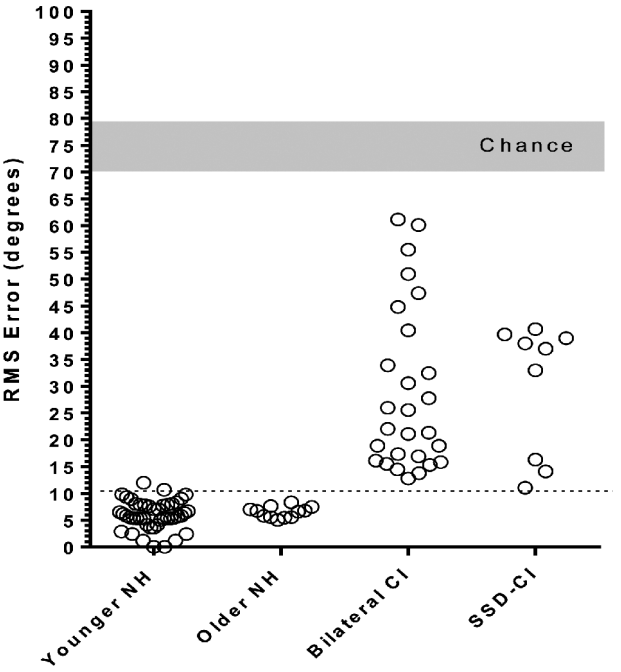

FIG. 1. RMS error for sound source localization to a wideband noise stimulus for young NH listeners, older NH listeners, patients fit with BCIs, and SSD patients fit with a CI. Each *open circle* indicates the performance of one listener. The *light gray area* indicates chance performance. The *dotted line* indicates the 95th percentile for scores from the young NH sample.

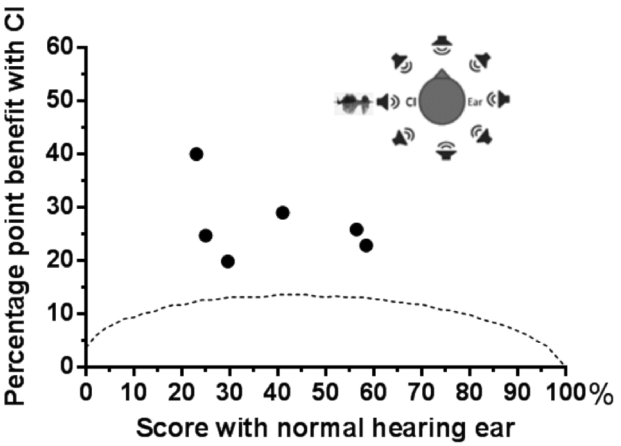

FIG. 2. Percentage point change in performance in the NH ear plus CI condition as a function of the score (percent correct) for the NH ear alone. Each *filled circle* shows the performance of one SSD-CI patient. The *dotted line* indicates the 95% critical difference scores for the test material. The listening environment is illustrated at *top right*. Noise was presented from all loudspeakers, and speech was presented to the side of the CI.

DISCUSSION

In the Introduction, we pointed out that the peripheral representation of ILDs should be very different for NH listeners, BCI patients, and SSD-CI patients. For any patient with a CI, signal levels at the ear with the CI will be compressed because of CI signal processing. We suppose that, for BCI patients, the compression will be relatively symmetric—at least to the degree that the two independent signal processors are set in similar fashion. This symmetry should be lost for SSD-CI patients for whom only one ear receives a compressed signal. As a consequence, we speculated that sound source localization based on ILD cues would likely be poorer for SSD-CI patients than for BCI patients.

Localization by NH Listeners and BCI Patients

The RMS error for the NH listeners as a whole in this study was 6.1 degrees, with an SD of 2.5 degrees. Grantham et al. (16) reported a mean error score for NH listeners of 6.7 degrees with an SD of 1.1 degrees. The mean error score for our sample of BCI patients was 29 degrees with an SD of 15 degrees. Grantham et al. (16) reported a mean score of 31 degrees with an SD of 10 degrees. The similarity of our data to that of Grantham et al. (16) suggests that our data for NH listeners and BCI patients are a reasonable reference for the sound source localization abilities of SSD-CI patients.

Localization accuracy was highly variable across the sample of BCI patients. One account of the variability of scores revolves around deviations from bilateral matching in electrode location (17) and a host of signal processor settings, for example, i) automatic gain control settings, ii) frequency allocation tables, iii) electrode pitch, iv) numbers of activated electrodes, v) electrode dynamic ranges, vi) output compression settings, and vii) processor volumes (11,18). It may be the case that the patients with the better localization scores are the ones for whom electrode locations across ears are well matched and the effective signal compression of the two processors is well matched.

Localization by SSD-CI Patients

The error scores for the SSD-CI patients were clearly bimodal. Six patients had scores that were toward the upper end of the distribution for BCI patients, and three had error scores that were similar to the best scores from patients in the BCI group and at the 95% confidence interval of the NH listeners. Given the different signal levels between ears for the SSD-CI group, the relatively poor scores for six of the patients is not unexpected.

On the other hand, the outcome of three scores equal to that obtained by the best BCI patients and just above the upper end of the distribution of scores for NH listeners is surprising—the more so because of the short interval between device turn-on and testing for two of the three patients. One of these patients was tested at 2 months and obtained an error score of 16 degrees. As we noted in Dorman et al. (9), the patient with 11 degrees of error when tested in our laboratory at 16 months after device turn-on had been tested at another laboratory at 1 month after CI hookup and obtained an RMS error score of 13 degrees. Thus, one of the critical problems confronting SSD-CI patients in sound source localization, a large asymmetry in signal level at the two ears, can be at least partially resolved by central processing mechanisms very soon after device turn-on. Tavora-Vieira et al. (6), using a virtual loudspeaker array and a high-frequency narrowband stimulus, also report a small number of SSD-CI patients with error scores that are at the upper edge of error scores for NH listeners. The listeners in that study, however, had more experience with their CIs than the patients in our study.

Speech Understanding by SSD-CI Patients

As we noted in the Introduction, one of our aims was to assess the value of a CI for SSD patients when the listening environment simulated a ''real-world'' situation, that is, listening in a restaurant when the talker was on the side of the CI. In this environment, each patient exhibited a large and significant improvement in speech understanding. This outcome documents a real-world environment in which a CI significantly aids a listener who has NH in one ear. Although we did not evaluate alternatives to a CI in our listening environment, for example, a CROS hearing aid or a BAHA device, others have shown much better performance with a CI than with a CROS aid or a BAHA in similar environments (1).

CONCLUSION

The provision of a CI to the deaf ear of SSD patients allows for significant improvements in sound source localization and speech understanding in complex listening

environments. However, there is a significant amount of variance between patients regarding their performance on these tasks, and the variance does not seem to be predicated on any of the studied demographic variables or length of CI usage. Future studies should further attempt to account for this observed variance among individuals undergoing CI for SSD as well as to optimize CI signal processing to improve performance on these tasks.

REFERENCES

1. Arndt S, Aschendorff A, Laszig R, et al. Comparison of pseudobinaural hearing to real binaural hearing rehabilitation after cochlear implantation in patients with unilateral deafness and tinnitus. *Otol Neurotol* 2010;32:39–47.
2. Firszt JB, Holden LK, Reeder RM, Waltzman SB, Arndt S. Auditory abilities after cochlear implantation in adults with unilateral deafness: a pilot study. *Otol Neurotol* 2012;33:1339–46.
3. Hassepass F, Aschendorff A, Wesarg T, et al. Unilateral deafness in children: audiologic and subjective assessment of hearing ability after cochlear implantation. *Otol Neurotol* 2013;34:53–60.
4. Jacob R, Stelzig Y. The Koblenz experience in treating single-sided deafness with cochlear implants. *Audiol Neurotol* 2011;16 (Suppl 1):6–8.
5. Nawaz S, McNeill C, Greenberg SL. Improving sound localization after cochlear implantation and auditory training for the management of single-sided deafness. *Otol Neurotol* 2014;35:271–6.
6. Tavora-Vieira D, Marino R, Acharya A, Rajan GP. The impact of cochlear implantation on speech understanding, subjective hearing performance and tinnitus perception in patients with unilateral severe to profound hearing loss. *Otol Neurotol* 2015;36:430–436.
7. Tavora-Vieira D, Marino R, Krishnaswamy J, Kuthbutheen J, Rajan GP. Cochlear implantation for unilateral deafness with and without tinnitus: a case series. *Laryngoscope* 2013;123:1251–5.
8. Vermeire K, Van de Heyning P. Binaural hearing after cochlear implantation in subjects with unilateral sensorineural deafness and tinnitus. *Audiol Neurotol* 2009;14:163–71.
9. Dorman MF, Zeitler D, Cook SJ, et al. Interaural level difference cues determine sound source localization by single-sided deaf patients fit with a cochlear implant. *Audiol Neurootol* 2015;20: 183–8.
10. Wilson B, Dorman MF. The design of cochlear implants. In: Niparko J, editor. *Cochlear Implants, Principals and Practices*. Philadelphia, PA: Lippincott; 2009. pp. 95–136.
11. Dorman MF, Loiselle L, Yost WA, et al. Interaural level differences and sound source localization for bilateral cochlear implant patients. *Ear Hear* 2014;35:633–40.
12. Yost W, Loiselle L, Dorman M, Burns J, Brown CA. Sound source localization of filtered noises by listeners with normal hearing: a statistical analysis. *J Acoust Soc Am* 2013;133:2876–82.
13. Compton-Conley CL, Neuman AC, Killion MC, Levitt H. Performance of directional microphones for hearing aids: real-world versus simulation. *J Am Acad Audiol* 2004;15:440–55.
14. Spahr AJ, Dorman MF, Litvak LF, et al. Development and validation of the AzBio sentence lists. *Ear Hear* 2012;33:112–7.
15. Rakerd B, Hartmann WM. Localization of sound in rooms, III: onset and duration effects. *J Acoust Soc Am* 1986;80:1695–706.
16. Grantham W, Ashmead D, Ricketts T, Labadie R, Haynes D. Horizontal-plane localization of noise and speech signals by postlingually deafened adults fitted with bilateral cochlear implants. *Ear Hear* 2007;28:524–41.
17. Kan A, Litovsky RY, Goupell MJ. Effects of interaural pitch matching and auditory image centering on binaural sensitivity in cochlear implant users. *Ear Hear* 2015;36:e62–8.
18. van Hoesel RJM, Ramsden R, Odriscoll M. Sound-direction identification, interaural time delay discrimination, and speech intelligibility advantages in noise for a bilateral cochlear implant user. *Ear Hear* 2002;23:137–49.

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Stereotactic Radiosurgery for Facial Nerve Schwannomas: Meta-analysis and Clinical Review

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Objective: Although several small individual series on stereotactic radiosurgery (SRS) for facial nerve schwannomas (FNSs) have been published, we aim to systematically aggregate data from the literature as well as from our institution to better understand the safety and efficacy of SRS for FNS.
Data Sources: PubMed English language search for keywords ''facial nerve schwannoma'' AND ''radiation therapy'' published from January 1995 to 2014. Data from our institution were also included in the analysis.
Study Selection: Minimum study inclusion criteria included tumor treatment outcomes yielding 10 studies in the literature. In addition, our institution's data on six patients were included.
Data Extraction: Data included radiation treatment type, radiation dose, tumor size, tumor control, tumor control definition, FN function, hearing outcome, and duration of follow-up.
Data Synthesis: In total, there were 45 patients with at least 2-year follow-up. Forty-two patients (93.3%) had tumor control. Of those patients with described growth/shrinkage definitions, 50.0% had no growth, 43.3% had shrinkage, and 6.7% had growth. Of those articles that included FN functional outcomes, 26 patients (66.6%) had stable FN function, 8 (20.5%) had improved function, and 5 (12.8%) had worsened FN function after treatment. In total, there were 30 patients whose hearing outcomes were discussed in the literature. Of those with serviceable hearing before SRS (n = 14), nine (64.3%) had stable hearing and five (36.7%) had worsened function after SRS. The mean posttreatment follow-up period was 42.1 months.
Conclusion: SRS seems to be effective at either stabilizing or shrinking FNS. However, significant morbidities of FN paralysis hearing loss do exist. **Key Words:** Cyberknife—Facial nerve neuroma—Facial nerve schwannoma—Fractionated radiation—Gamma knife—Radiation therapy—Stereotactic radiosurgery.
Otol Neurotol **36:**393–398, 2015.

Although they represent the most common primary tumor of the facial nerve (FN), FN schwannomas (FNSs) are rare. Like acoustic neuromas, FNSs are benign tumors made of Schwann cells that are slow growing and may be present for years before symptoms arise (1). The decision of when and how to intervene has attempted to be established (2), but there is no clear consensus.

FNSs pose a significant dilemma to the treating physician. First, they can arise anywhere along the FN (3,4) and may be mistaken for acoustic neuromas when isolated to the cerebellopontine angle (CPA) and internal auditory canal (IAC) (4,5). Second, given that FN fascicles have been shown to run through the schwannoma (6), operative intervention is limited to FN decompression or debulking versus resecting the involved FN segment with direct anastomosis or graft when necessary. Third, data on stereotactic radiosurgery (SRS) are limited to small single-institution case series that often provide inconsistent information with regard to FN and hearing outcomes.

If SRSs were able to stop or reverse the growth of FNS, it may be a reasonable initial treatment option if FN function and hearing did not appreciably suffer. Similarly, SRS may also be used as adjuvant therapy in patients whose FNSs continue to grow after undergoing FN decompression. Unfortunately, SRS data on FNS have yet to clarify these questions. Our study attempts to systematically pool the literature on this topic in the hope of better understanding the control rates and side effect profile of SRS for FNS.

METHODS

Data Sources/Study Selection

PubMed English language search was conducted for articles on radiation treatment of FNS published from January 1995 to August 2014. This time frame was used because SRS practices during this period reflect modern dosing strategies. Key word

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search terms used included ''facial nerve schwannoma,'' ''facial nerve neuroma,'' ''radiotherapy,'' ''stereotactic radiosurgery,'' ''stereotactic radiotherapy,'' ''radiosurgery,'' ''radiation therapy,'' ''gamma knife,'' and ''Cyberknife.'' In total, 13 articles were identified that discussed SRS for FNSs. In lieu of repeating the data from our institutions prior manuscript, we updated our experience with longer follow-up. Institutional review board approval was obtained from our institution.

Inclusion criteria for article selection included English language, treatment of FNS with SRS, follow-up period clearly identified. Two articles (2,10) were removed that described treatment of nonvestibular schwannomas with SRS but did not differentiate outcomes between FNS and other schwannomas (7,8). One article was included without individual patient follow-up periods identified (9). However, the overall follow-up period was similar to the other included studies and thus was kept for analysis. In total, 10 articles were evaluated in addition to our institution data, yielding 53 patients.

Hearing data were analyzed only when objective measures were used. Studies that used terms such as ''hearing was stable'' were not included when the hearing data were not clearly defined. In our analysis, hearing data were reported using the American Academy of Otolaryngology (AAO) acoustic neuroma hearing guidelines (10). FN data were included when the pre-SRS and post-SRS functional status was reported using the House-Brackmann (HB) Scale (11).

We defined tumor control as either no change or a decrease in tumor size. Decrease in tumor size was reported as a separate category when studies clearly stated their definition. To make the reporting more uniform, we defined the decrease in tumor size as either 2 mm in linear direction or 20% volume loss in accordance with RECIST criteria 1.1 (12). Although it was not distinctly stated in all of the articles reviewed, all Neurofibromatosis II patients were removed from analysis when possible.

RESULTS

Published Data

Our institution's previous article on this topic was excluded because we have included updated data for these patients in this article. This left nine articles that met our criteria for inclusion for evaluation. When presenting tumor size, three (33.3%) studies used largest tumor dimension, five (55.6%) used either three dimensions or tumor volume, and one (11.1%) did not report tumor size. Three (33.3%) articles did not report post-SRS hearing data in all patients. All studies discussed FN outcomes; however, two (22.2%) used subjective ''improvement'' or ''worsened'' statements rather than the HB score and were not included for FN outcome analysis. The mean follow-up was 42.1 months (range, 12–120 mo). All cases in the literature were determined to be FNS by either involvement of FN segments other than CPA/IAC on magnetic resonance imaging (MRI) or based on intraoperative findings when tumor was initially thought to be an acoustic neuroma.

Treatment Data

Including our institution's experience, a total of 53 patients were identified who received SRS for FNS. In looking at the treatment modalities, 45 (84.9%) patients were treated with gamma knife (GK), 4 (7.5%) with LINAC, and 4 (7.5%) with fractionated SRS. Mean margin radiation doses to the 50% isodose line based on treatment modality were the following: GK, 12.5 Gy (range, 10–16 Gy); LINAC, 36.3 Gy (range, 12–54 Gy); and all fractionated SRS patients received 50.0 Gy administered in 25 fractions (2 Gy per fraction 4 d/wk). There were variable treatment methods used with LINAC. One patient received one single dose at 12 Gy (13). The other three received fractionated therapy: 2 Gy per fraction 5 days per week for 50 Gy (14), 1.8 Gy per fraction 5 days per week for 54 Gy (15), and 0.5 Gy 5 days per week for 25 Gy (13). There were minimal data available with regard to cochlear dose.

Tumor Control

Only patients with 2 years or longer follow-up were included in the tumor control analysis (n = 45). When defined as no tumor growth or decreased tumor size, 42(93.3%) patients had tumor control with SRS and 3(6.7%) did not (Table 1). According to the guidelines in the Methods section, 30 patients were evaluated for growth or reduction in tumor size. Of these, 15 (50.0%) showed no growth, 2 (6.7%) showed growth, and 13 (43.3%) were reduced in size after

TABLE 1. *Data extracted from the literature for patients with a minimum of 2-year follow-up*

Study	n	SRS type	Hearing data in patients with pretreatment serviceable hearing (n = 18)		Facial nerve			Tumor control		Follow-up
			Unchanged	Hearing worsened	Unchanged	Improved	Worsened	Yes	No	
Current	7	GK	1 (50.0%)	1 (50.0%)[a]	6 (85.7%)	0 (0%)	1 (14.3%)	6 (85.7%)	1 (14.3%)	57.1
Ingrosso et al. (14)	1	LINAC	n/a	n/a	1 (100%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	30.2
Kida et al. (16)	14	GK	5 (100%)	0 (0%)	5 (55.5%)	4 (44.4%)	0 (0.0%)	9 (100%)	0 (0%)	31.4
Litre et al (17)	11	GK	2 (66.6%)[a]	1 (33.3%)[a]	n/a	n/a	n/a	8 (88.9%)	1 (11.1%)	39.5
McCelland et al. (15)	1	LINAC	n/a	n/a	0 (0%)	0 (0%)	1 (100%)	1 (100%)	0 (0%)	48.0
Hillman et al. (13)	2	LINAC	0 (0%)	2 (100%)	1 (50%)	1 (50%)	0 (0%)	2 (100%)	0 (0%)	30.0
Madhok et al. (18)	6	GK	n/a	n/a	4 (80.0%)	1 (20.0%)	0 (0%)	5 (100%)	0 (0%)	46.7
Nishioka et al. (19)	4	F-SRS	n/a	n/a	n/a	n/a	n/a	4 (100%)	0 (0%)	67.3
McRackan et al. (4)	1	GK	n/a	n/a	1 (100%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	62.0
Jacob et al. (9)	6	GK	1 (50.0%)[a]	1 (50.0%)[a]	4 (66.6%)	0 (0%)	2 (33.3%)	5 (83.3%)	1 (16.7%)	48.0
Total	45		9 (64.3 %)	5 (36.7%)	22 (68.8%)	6 (18.8%)	4 (12.5%)	42 (93.3%)	3 (6.7%)	47.6

[a]Studies where the topic of interest was reported for only a portion of the cohort.
F-SRS indicates fractionation SRS; n/a, data not available.

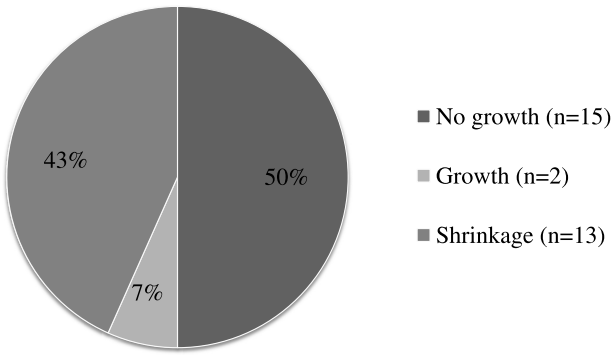

FIG. 1. In total, there were 30 patients with available and well-defined data on tumor growth with at least 2-year follow-up.

SRS (Fig. 1). All patients in our institution's cohort had proven growth of their FNS on repeat MRIs before SRS. Only two other patients in one study (13) explicitly stated that patients had growing FNS before SRS.

Statistical analysis was not performed because of the small number of failures. Although the majority of patients received gamma knife as the primary treatment modality, all failures were also within this group. Mean marginal dose data were available for two treatment failure patients who received 10 Gy and 12.5 Gy, respectively. It is important to note that one other patient received 10 Gy and had evidence of tumor shrinkage, and seven other patients received 12.5 Gy. Of these, four (57.1%) had no tumor growth and three (43.9%) had tumor shrinkage.

Facial Nerve Function

Thirty-nine patients in the literature had preoperative and postoperative data with regard to FN function. The majority (26 patients, 66.7%) showed no change in HB score. Five patients (12.8%) developed worsened FN function, whereas eight (20.5%) reported improved FN function. Table 1 displays FN outcomes in those patients with at least 2-year follow-up.

In looking at those whose FN function worsened, two (40.0%) were pre-SRS HB grade I and three (60.0%) were HB grade II. Unfortunately, data on tumor location were only available for three patients. Notably, however, all three had tumor medial to the geniculate ganglia (GG) involving the IAC. With regard to treatment modality, five (80.0%) received GK (mean margin dose, 12.8 Gy) and one (20.0%) received LINAC (54 Gy). Again, given the small number, it is impossible to make any statistically relevant correlations.

Interestingly, there were two patients in the literature whose FN function improved by two HB grades (one patient IV to II; another, VI to III). Six others improved by one HB grade. Tumor location data were available for seven of these patients. Of these, five (71.4%) patients had tumor involving the GG. No patient in this group had tumor lateral to the GG. Figure 2 displays FN outcomes with regard to initial HB grade.

Hearing Outcomes

Twenty-six patients had available complete pre- and post-SRS hearing data with at least 2-year follow-up. No patient had improved hearing after SRS. Fourteen patients had serviceable hearing (AAO–Head and Neck Surgery [HNS] class A/B) before SRS. Of these, nine (64.3%) showed no change in hearing class and five (36.7%) had worsened hearing—three (21.4%) from class A to B and

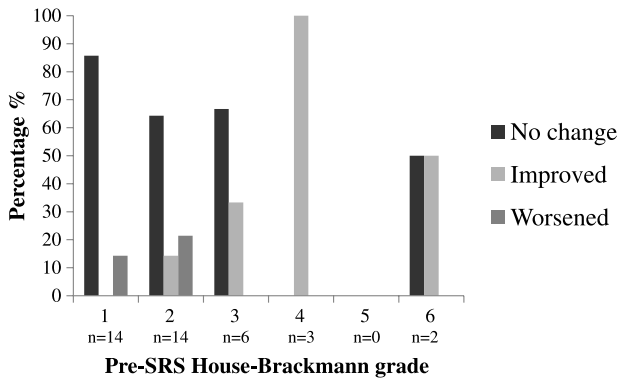

FIG. 2. Change in FN function related to pre-SRS HB grade. Number of patients in each pre-SRS class is listed along the *x* axis.

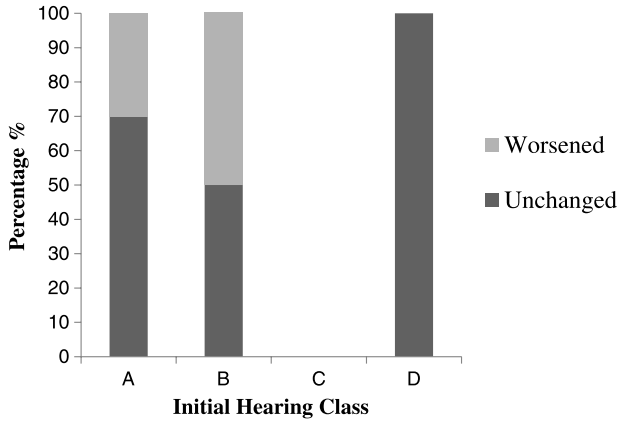

FIG. 3. Hearing change after SRS based on initial hearing class in patients with at least 2-year follow-up. Worsened hearing was defined by a change in AAO-HNS hearing class.

two (14.2%) from class B to D. Figure 3 displays hearing outcomes based on pre-SRS hearing class in those with at least 2-year follow-up.

Longer-Term Outcomes

In a separate analysis, 24 patients had follow-up for 36 months or longer after SRS. The mean follow-up time for this cohort was 60.2 months (range, 36–120 mo). The tumor control rate was 91.7%. With regard to FN function, 80.0% were unchanged at last follow-up, 13.3% worsened, and 6.7% improved. Hearing outcomes were unchanged in 72.7% and worsened in 27.3%. Table 2 displayed outcome results based on duration of follow-up.

DISCUSSION

Given that FNS represent 0.15% to 0.8% of all intracranial tumors (20), it is understandable that very few institutions have large treatment series especially with regard to SRS. In the above meta-analysis, we have combined data from multiple published studies to present a better understanding of the results and complication rates from SRS for FNS.

Treatment of FNSs is difficult because surgical options are limited. In looking at treatment trends across time, there is a clear modern trend toward a more conservative treatment approach (2,4). Patients are typically observed with serial imaging until they become symptomatic (typically FN paralysis). When observed, FN paralysis has been reported to occur in 38% of patients (21).

When symptoms occur, patients are left with several options. With regard to surgery, options are limited to FN decompression or debulking versus resection and FN graft. Total resection with graft is typically only performed when patients are HB grade III or worse because a grade III function is the best possible outcome of FN grafting. Subtotal resections have been described with variable outcomes (22,23). Recently, Mowry et al. (24) reported on 11 patients with preoperative HB grades I to II who underwent debulking with FNS isolated to the IAC/CPA. Using intraoperative FN stimulation as a guide, they were able to remove more than 80% of tumor in 90% of patients. Three patients (27.3%) developed poor FN function (HB grade >2), whereas eight (72.7%) maintained good function with long-term follow-up. These outcomes are most likely caused by histologic evidence of nerve fascicles running in FNS to a variable degree (6). Given this information, it is our institution's practice not to perform subtotal resections.

Limited surgical options create an opportunity for SRS as a treatment modality for FNS. Overall, 93.3% of patients undergoing SRS for FNS had tumor control (defined as either no growth or decreased tumor size). In those studies where tumor shrinkage was clearly defined, 43.3% of patients showed a decrease in size. Like vestibular schwannoma data, most studies included in this analysis did not directly discuss the FNS pretreatment growth pattern before SRS. This greatly hinders our ability to determine whether SRS can stop or reverse tumor growth. We recommend that future studies explicitly state this information to better understand the effect of SRS on FNS.

Given that FN paralysis is the most common presenting symptom in FNS patients (9), we were surprised to find that eight patients (21.1%) had improved FN function after SRS. It is difficult to make physiologic sense of this occurrence. Although the easiest explanation would be decreased tumor size and thus decreased pressure on the FN that would allow increased axonal flow, only one of these patients had radiologic evidence of tumor shrinkage.

TABLE 2. *Rates are displayed as percentages of available data because hearing and FN function data were not available on all patients*

Duration of follow-up	n	Worsened hearing (%)	Worsened FN function (%)	Tumor control rate (%)
>1 yr	53	16.7	12.8	94.3
>2 yr	36	22.2	8.7	94.4
>3 yr	24	27.3	13.3	91.7

The possibility exists, however, that a decrease in tumor size may escape the detection ability of MRI.

There were also five patients (13.2%) who developed worsened FN function after SRS. Given that the SRS dose is given in the area, and directly to the FN, reason would suggest that this would be a more likely occurrence than FN improvement. Although this rate is lower than FN improvement, this risk should be discussed with patients before performing SRS.

There were minimal data available with regard to tumor location. FNSs may arise at different locations within the parotid, temporal bone, and CPA. These tumors are known to affect different portions of the FN or may involve multiple segments of the FN in the parotid, temporal bone, and CPA. Tumors traveling very close to the cochlea or adjacent to the cochlear nerve in the IAC may be at higher risk for associated hearing loss. There also may be factors related to location of which we are unaware that may lead to higher or lower SRS success rates. We suspect that the majority of cases treated with SRS involved the GG/middle fossa, the labyrinthine segment, IAC, or CPA. We could not find reports that included treatment of FNS that arose within the parotid or temporal bone. Unfortunately, the location data were not readily reported and could not be included for evaluation.

Outcome comparison with surgical treatment is difficult to perform for multiple reasons. First, several patients in the literature received a primary surgical decompression before SRS. This was done either purposefully or after the tumor was discovered to be of FN origin during the operation. Analysis of this cohort is impossible because these individual patients are not clearly identified in the literature. Second, when patients do ultimately undergo surgery, it is only after they have had significant deterioration of FN function. These patients often undergo FNS resection with FN graft, which yields repaired FN recovery scale class C at best (25). Conversely, published data on FN decompression for FNS show similar FN outcomes compared with those undergoing SRS (both >95% HB grade III) (2,4). Again, these values include patients who have had surgery before SRS, so direct comparison is imperfect.

As with any meta-analysis, the conclusions are only as good as the data available. There is a wide range of follow-up duration for patients undergoing SRS for FNS. We have attempted to display results based on follow-up period, but many studies did not have long-term follow-up. This is certainly needed to fully understand the results of SRS for FNS with regard to tumor control, FN function, and hearing. Specifically, with hearing outcomes, there was a trend toward worsening hearing results in patients with longer than 3-year follow-up compared with those with longer than 12 months (27.3% worsened hearing compared with 17.2%, respectively). Given that hearing at last follow-up is the only data reported, it is impossible to know whether this increased rate of hearing loss is a delayed result from SRS or function of lack of data. Delayed hearing loss from SRS has been reported in the literature (26), so this is certainly in the realm of possibility. Clearly, long follow-up periods are required to better understand the effect of SRS on FNS with respect to hearing, FN function, and tumor control rates.

We tried to be stringent with the data included in our analysis by excluding patients who did not have standardized outcome measurements reported (AAO-HNS hearing class, HB grade, definitions of tumor growth/regression). This unfortunately eliminated multiple patients from inclusion in the subgroup outcome measures reported in this study. We recommend that these reporting measures be used in the future for standardization of results.

We noticed three other notable faults in the literature on this topic. First, three studies did not report hearing outcome data. This is a major weakness of these studies because both the cochlear nerve and the cochlea are adjacent and often intimately involved with these lesions. It is important that we understand the effects of SRS on hearing for these tumors to compare with surgical options. Second, there is lack of uniformity in reporting tumor size and location. This factor may likely play a role in SRS outcomes, but the variability in literature precludes any evaluation. Third, the reasons for choosing SRS over surgical therapy were not clear in the literature. Stereotactic radiation may have been chosen because of advanced patient age or medical comorbidities. The lack of this information makes application of these data to the general population difficult.

CONCLUSION

Using standard definitions of tumor control, it seems that SRS is an effective therapy for FNS in the short-term. Reports of improved FN function are intriguing, but more data and longer follow-up are needed to determine conclusive results.The above meta-analysis provides information regarding the effect of SRS on FNS growth, hearing outcome, and FN function that can be used to counsel patients before choosing treatment options.

REFERENCES

1. Lipkin AF, Coker NJ, Jenkins HA, Alford BR. Intracranial and intratemporal facial neuroma. *Otolaryngol Head Neck Surg* 1987;96:71–9.
2. Wilkinson EP, Hoa M, Slattery WH III, et al. Evolution in the management of facial nerve schwannoma. *Laryngoscope* 2011; 121:2065–74.
3. Pulec JL. Symposium on ear surgery: facial nerve neuroma. *Laryngoscope* 1972;82:1160–76.
4. McRackan TR, Rivas A, Wanna GB, et al. Facial nerve outcome in facial nerve schwannomas. *Otol Neurotol* 2011;33:78–82.
5. Barrs DM, Brackmann DE, Hitselberger WE. Facial nerve anastamosis in the cerebellopontine angle: a review of 24 cases. *Am J Otol* 1984; 5:269–72.
6. Hajjaj M, Linthicum FH Jr. Facial nerve schwannoma: nerve fibre dissemination. *J Laryngol Otol* 1996;110:632–3.
7. Mabanta SR, Buatti JM, Friedman WA, et al. Linear accelerator radiosurgery for nonacoustic schwannomas. *Int J Radiat Oncol Biol Phys* 1999;43:545–8.
8. Zabel A, Debus J, Thilmann C, et al. Management of benign cranial non-acoustic schwannomas by fractionated stereotactic radiotherapy. *Int J Cancer* 2001;96:356–62.
9. Jacob JT, Driscoll CL, Link MJ. Facial nerve schwannomas of the cerebellopontine angle: the Mayo Clinic experience. *J Neuro Surg Part B* 2012;73:230–5.

10. Committee on hearing and equilibrium guidelines for the evaluation of hearing preservation in acoustic neuroma (vestibular schwannoma). American Academy of Otolaryngology–Head and Neck Surgery Foundation, Inc. *Otolaryngol Head Neck Surg* 1995;113:179–80.
11. House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Head Neck Surg* 1985;93:146–7.
12. Eisenhaue EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
13. Hillman TA, Chen DA, Fuhrer R. An alternative treatment for facial nerve tumors: short-term results of radiotherapy. *Ear Nose Throat J* 2008;87:574–7.
14. Ingrosso A, Ponti E, di Cristino D, et al. Intraparotid facial nerve schwannoma with intratemporal extension: a case report. Is there a role for stereotactic radiotherapy? *Am J Otol* 2013;34:258–61.
15. McClelland S III, Dusenbery KE, Higgins PD, et al. Treatment of a facial nerve neuroma with fractionated stereotactic radiotherapy. *Stereotact Funct Neurosurg* 2007;85:299–302.
16. Kida Y, Yoshimoto M, Hasegawa T. Radiosurgery for facial schwannoma. *J Neurosurg* 2007;106:24–9.
17. Litre CF, Gourg GP, Tamura M, et al. Gamma knife surgery for facial nerve schwannomas. *Neurosurgery* 2007;60:853–9.
18. Madhok R, Kondziolka D, Flickinger JC, et al. Gamma knife radiosurgery for facial schwannomas. *Neurosurgery* 2009;64:1102–5.
19. Nishioka K, Abo D, Aoyama H, et al. Stereotactic radiotherapy for intracranial nonacoustic schwannomas including facial nerve schwannoma. *Int J Radiat Oncol Biol Phys* 2009;75:1415–9.
20. Saito H, Baxter A. Undiagnosed intratemporal facial nerve neurilemmomas. *Arch Otolaryngol* 1972;95:415–9.
21. Perez R, Chen JM, Nedzelski JM. Intratemporal facial nerve schwannoma: a management dilemma. *Otol Neurotol* 2005;26: 121–6.
22. McMenomey SO, Glasscock ME III, Minor LB, Jackson CG, Strasnick B. Facial nerve neuromas presenting as acoustic tumors. *Am J Otol* 1994;15:307–12.
23. Nadeau DP, Sataloff RT. Fascicle preservation surgery for facial nerve neuromas involving the posterior cranial fossa. *Otol Neurotol* 2003;24:317–25.
24. Mowry S, Hansen M, Gantz B. Surgical management of internal auditory canal and cerebellopontine angle facial nerve schwannoma. *Otol Neurotol* 2012;33:1071–6.
25. Gidley PW, Gantz BJ, Rubinstein JT. Facial nerve grafts: from cerebellopontine angle and beyond. *Am J Otol* 1999;20:781–8.
26. Carlson ML, Jacob JT, Pollock BE, et al. Long-term hearing outcomes following stereotactic radiosurgery for vestibular schwannoma: patterns of hearing loss and variables influencing audiometric decline. *J Neurosurg* 2013;118:579–87.

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Contemporary Management of Jugular Paragangliomas

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KEYWORDS

• Jugular paraganglioma • Cranial nerves • Glomus tumor • Jugular foramen • Carotid artery

KEY POINTS

- Jugular paragangliomas are the most common tumors of the jugular foramen.
- The management of jugular paragangliomas is challenging because of their close proximity to cranial nerves (CN) and the internal carotid artery.
- Surgery, radiation, and observation are all viable management options and should be individualized to the patient.
- At the authors' center, there has been a paradigm shift toward conservatism in selected cases in order to minimize morbidity.

INTRODUCTION

Jugular paragangliomas (JPs) are the most common primary neoplasms of the jugular foramen, arising from the paraganglion cells within the adventitia of the jugular bulb. They are slow-growing, highly vascularized tumors that are usually diagnosed during the fourth to fifth decades of life, affecting women 3 times more frequently than men. Although considered histologically benign, the management of jugular paragangliomas is challenging because of their infiltrative nature and close proximity to the facial nerve and lower cranial nerves (CN), carotid canal, posterior fossa meninges, and otic capsule.[1–4] Historically, gross total microsurgical resection was considered the

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Abbreviations

CN Cranial nerves
GJT Glomus jugulare tumor
JP Jugular paragangliomas

treatment of choice, offering complete eradication of disease; however, this strategy may cause significant morbidity, even in the hands of experienced surgeons.[5]

In an effort to explore less invasive treatment methods, stereotactic radiosurgery began gaining popularity in the early 1990s, and today has become the primary treatment modality of choice for many centers. The primary benefit of radiation therapy is a lower risk of up-front cranial neuropathy compared with gross total resection; however, tumor control and length of follow-up in these studies are variable.[6,7]

More recently, observation has been considered for select patients such as those with small tumors and few attributable symptoms, those with multicentric disease and contralateral lower cranial neuropathy, or elderly and infirm patients without brainstem compression. The data concerning observation for JP are scarce, and few centers have looked into the clinical course of untreated JP.[8,9] Such data are needed in order to compare against outcomes with radiation therapy. For example, if it was demonstrated that a large number of tumors do not grow for extended periods of observation, it could be argued that radiation therapy should be reserved until there is definitive evidence of growth.

The Otology Group of Vanderbilt has over 40 years of experience with JP. In the authors' practice, most tumors are managed with microsurgery; however, over the last decade, the authors' group has adopted a less aggressive approach in select patients in order to minimize cranial nerve morbidity. In this article, the authors report their experience managing JP, highlighting the paradigm shift in treatment at the authors' center.

DISEASE PRESENTATION

Pulsatile tinnitus is the most common presenting symptom in patients with JP, followed by hearing decline.[10] Hearing loss is usually conductive in nature but can be sensorineural or mixed.[11] Lower cranial neuropathies resulting in dysphagia, hoarseness, shoulder weakness, and tongue hemiparesis are less common and are usually seen with larger tumors that extend through the medial wall of the jugular bulb. Headache and vomiting are usually late signs associated with increased intracranial pressure caused by brainstem compression and fourth ventricle effacement.[12]

A pulsatile red middle ear mass behind an intact tympanic membrane is the most common finding on physical examination (**Fig. 1**). By definition, a glomus jugulare extends from the jugular bulb and hypotympanum into the middle ear space. Therefore, the middle ear component only represents the tip of the iceberg. Although not universally present, increased canal and tympanic membrane vascularity surrounding the inferiorly based middle red ear mass may result in the characteristic, rising sun appearance. Less commonly, the tympanic portion of the tumor may erupt into the ear canal, resulting in bloody otorrhea.

In contrast to visceral paragangliomas, head and neck paragangliomas are rarely (<4%) secretory.[13] Patients reporting a history of palpitations, sweats, flushing, syncope, hypertension, and headaches should be screened for serum and urine catecholamine levels. If elevated catecholamine levels are found, the patient should undergo further imaging to rule out pheochromocytoma or multicentric paraganglioma disease.

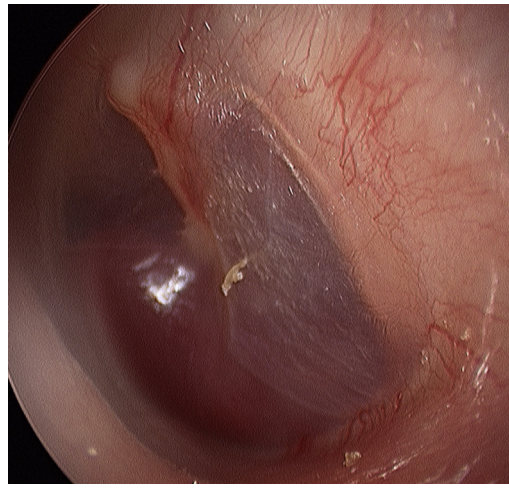

Fig. 1. Otoscopic examination demonstrating a red mass behind an intact tympanic membrane.

IMAGING

A careful review of fine-cut temporal bone computed tomography (CT) and MRI with gadolinium is critical to differentiating jugular foramen tumors. The most common lesions to involve the jugular foramen are JP, meningiomas (**Fig. 2**), and lower cranial nerve schwannomas (**Fig. 3**). Metastatic disease and endolymphatic sac tumors may also secondarily involve this region (**Fig. 4**). On CT and MRI, JPs demonstrate a diffusely infiltrative pattern of disease resulting in bony destruction and early erosion of the jugulo–carotid spine (**Fig. 5**). Vascular flow voids within the tumor result in a characteristic salt-and-pepper appearance on T1 and T2 weighted MRI, and the tumor avidly enhances with contrast administration (**Fig. 6**). Although not completely reliable, most JPs demonstrate middle ear extension, while meningiomas and schwannomas rarely do so. In contrast, meningiomas commonly demonstrate dural tails with en plaque growth and are often associated with underlying hyperostosis. Finally, schwannomas often "dumbbell" between the neck and posterior fossa, with a bottle neck at the jugular foramen. CT generally reveals a widened sharply demarcated jugular foramen without bony destruction.[14,15]

TUMOR CLASSIFICATION

Multiple proposed classifications have been used, and none has gained universal acceptance. Tumor classifications described by Fisch and Glasscock and Jackson are the most commonly used.[16–18]

GENETIC SCREENING

Familial head and neck paragangliomas are associated with germline mutations in genes encoding subunits of succinate dehydrogenase (SDH), which plays a role in the Krebs cycle. Though genetic evaluation of patients with head and neck paragangliomas is emerging as an important topic in the diagnosis and management of these tumors, the most cost-effective way of screening at-risk patients is not yet clear. Because 30% of sporadic head and neck paragangliomas are caused by germline

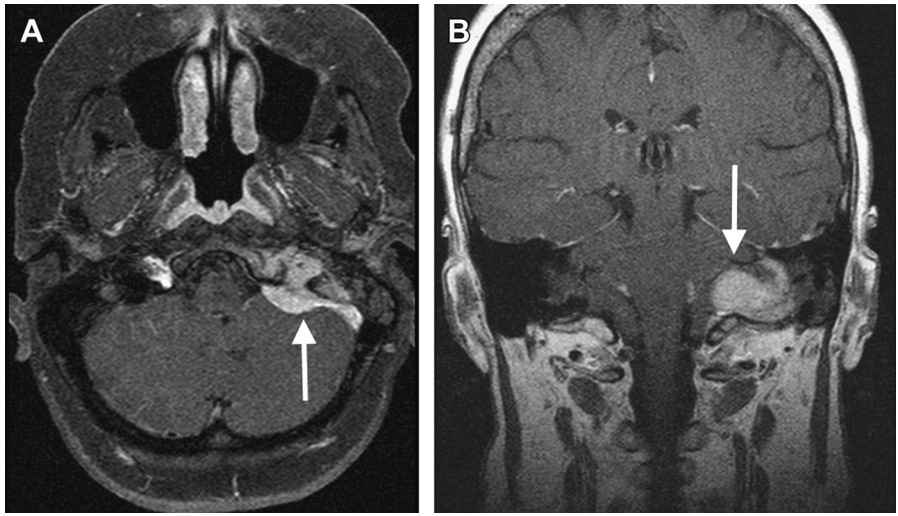

Fig. 2. (*A*) Axial cut of a T1 MRI with contrast showing a left jugular foramen meningioma. The tumor is designated by the white arrow. (*B*) Coronal cut of a T1 MRI with contrast showing a left jugular foramen meningioma. The tumor is designated by the white arrow.

mutation, Bodeker and colleagues recommend molecular genetic screening for SDHB, SDHC, and SDHD in all head and neck paragangliomas.[19,20] The authors' practice has been to offer patients genetic counseling and to collect and bank deidentified blood and tumor DNA from patients with JP undergoing surgery for future studies.

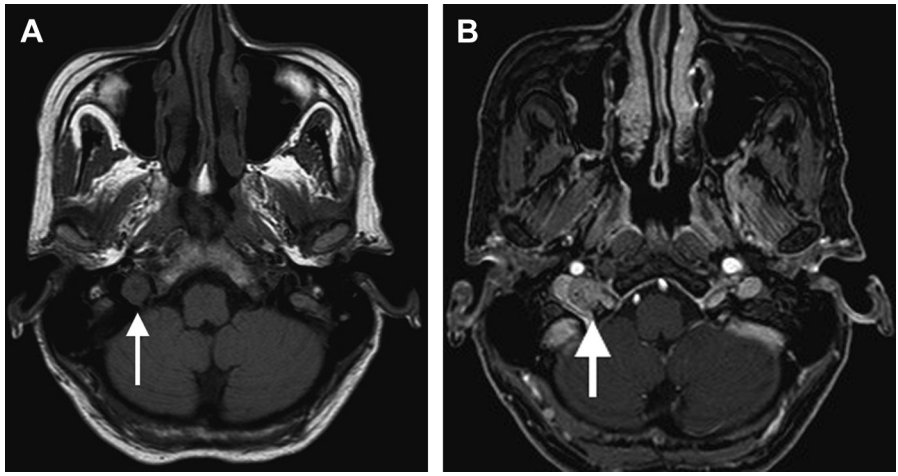

Fig. 3. (*A*) Axial cut of a T1 MRI without contrast showing a right jugular foramen schwannoma. The tumor is designated by the white arrow. (*B*) Axial cut of a T1 MRI with contrast showing enhancement of a right jugular foramen schwannoma. The tumor is designated by the white arrow.

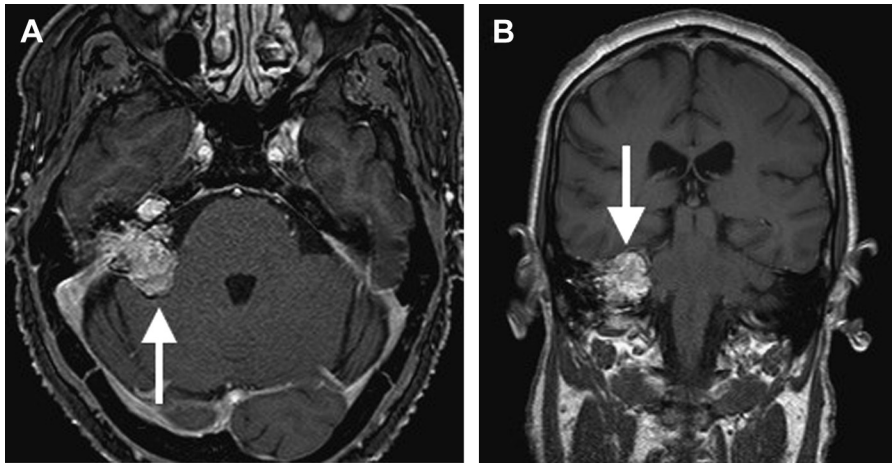

Fig. 4. (*A*) Axial cut T1 MRI with contrast showing a left endolymphatic sac tumor. The tumor is designated by the white arrow. (*B*) Coronal cut T1 MRI with contrast showing a left endolymphatic sac tumor. The tumor is designated by the white arrow.

MANAGEMENT

Embolization

Techniques of preoperative, transfermoral angiography with superselective embolization of feeding vessels have improved dramatically. Preoperative embolization may result in less intraoperative blood loss, thereby improving visualization, reducing morbidity, and increasing the probability of complete resection. Preoperative embolization is generally performed 24 to 72 hours before surgery. The authors' center most commonly uses Onyx (Covidien, Ireland), a nonadhesive liquid embolic agent. The authors' experience, thus far, is encouraging that the degree of embolization achievable with Onyx may decrease the need for intraoperative blood transfusion relative to other

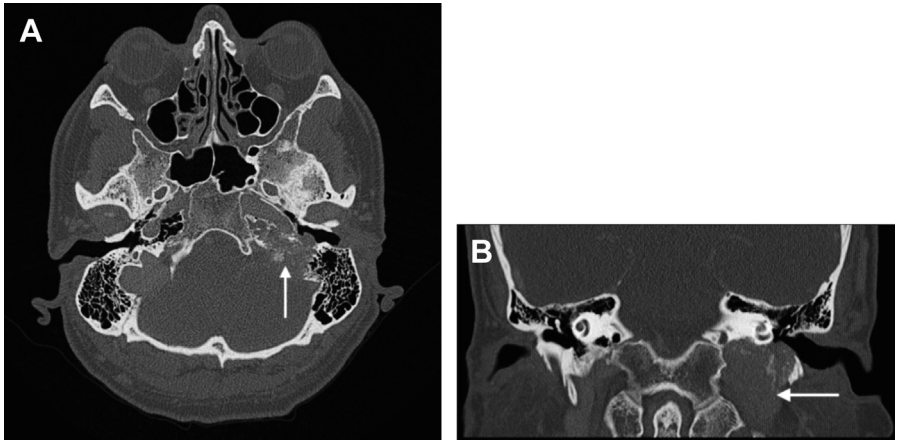

Fig. 5. High-resolution CT demonstrating the expected growth pattern of a GJT relative to the bone of the lateral skull base. The white arrow designates an area of tumor-associated bony destruction. (*A*) is an axial cut; (*B*) is a coronal cut.

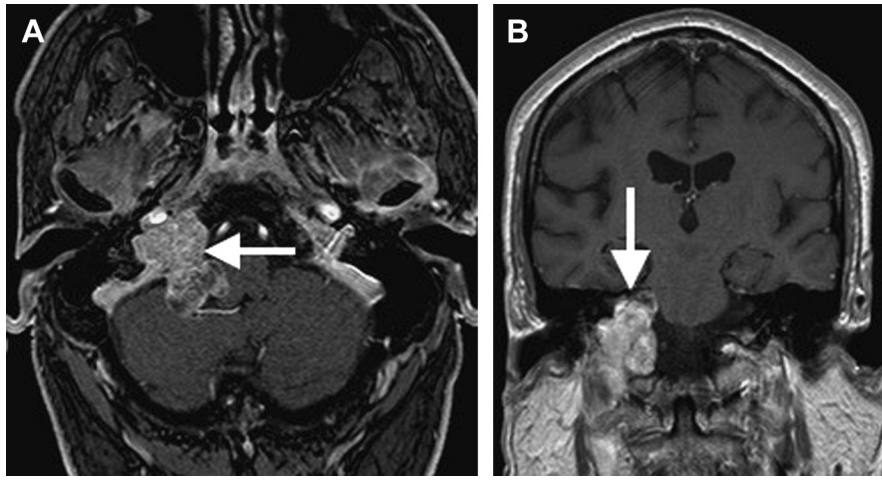

Fig. 6. Glomus jugulare as seen on a contrast-enhanced MRI scan. The arrow designates the tumor with a characteristic salt-and-pepper appearance. (*A*) is an axial cut; (*B*) is a coronal cut.

available substrates (**Fig. 7**). However, it is important to note that cranial nerve palsy can occur after embolization utilizing liquid and small particle agents such as Onyx.[19] Thus, preoperative patient counseling regarding the potential risks and benefits of embolization is warranted. Furthermore, a careful preoperative cranial nerve examination after embolization and immediately before surgery should be performed.

Surgery

Historically, microsurgery with gross total resection was considered the treatment strategy of choice for JP. Although gross total resection is possible in the majority of cases, it may result in debilitating cranial neuropathy and less commonly, vascular injury. In a study done by Sanna and colleagues,[21] 53 patients with Fisch class C or D JP were treated surgically. Gross total resection was achieved in 83% of cases, with a 10% tumor recurrence rate. The presence of new cranial neuropathy varied depending on the presence of intracranial extension, but was as high as 39%. Recently, the same group retrospectively reviewed 122 class C or D tumors. Gross tumor control was achieved in 86% of JPs, though 54% of the patients developed a postoperative lower cranial nerve injury. Cranial nerve IX was most commonly affected at last follow-up.[22] In another study including 119 patients, nearly 75% of patients had tumor control with surgical management, and new cranial neuropathies were noted in approximately 50% of patients after surgery.[23] Lastly, Fayad and colleagues,[3] examined the House Ear Clinic experience with glomus jugulare tumors (GJT), reporting total tumor removal in 81% of surgical cases. In this series, the incidence of postoperative cranial neuropathy varied according to tumor size. For patients with Fisch classification C4 and lower, the incidence of new cranial nerve injury varied from 8.7% to 13%, whereas for patients with classification of C4 and higher, the deficit ranged from 63.6% to 81.8%. Overall, 26.5% of patients in this series developed tumor recurrence at an average of 26 months.

In an effort to minimize morbidity and improve symptoms associated with disease, subtotal resection has been used with increasing frequency by many centers. Subtotal resection may be particularly relevant to older or infirm patients with advanced disease

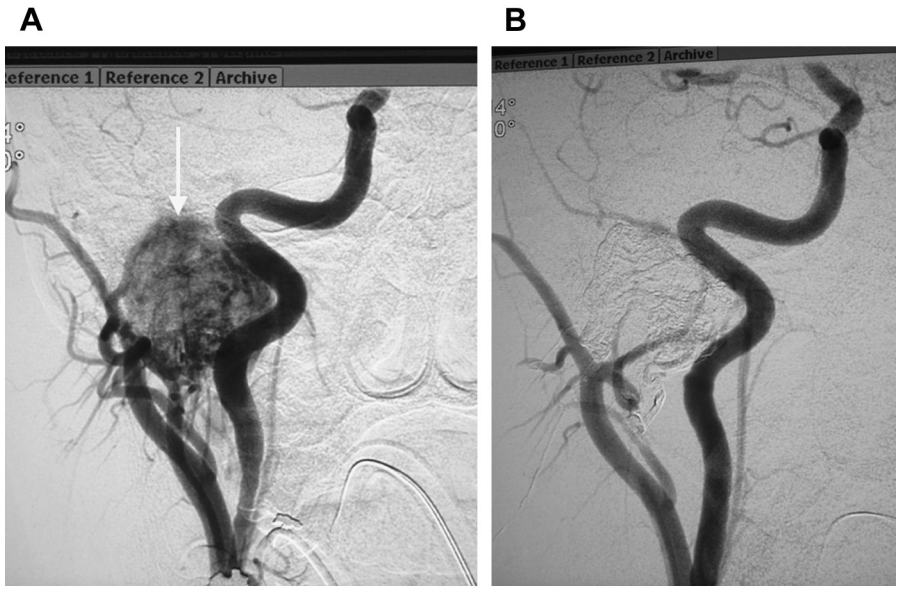

Fig. 7. Pre- and postembolization angiography of a GJT. (*A*) Pre-embolization image in which an arrow designates the highly vascularized tumor. (*B*) Postembolization image in which the major vascular pedicles for the tumor have been obliterated.

or younger patients with large tumors and intact CN who are troubled by aural symptoms such as pulsatile tinnitus, conductive hearing loss, and fullness. In a previous report, Cosetti and colleagues[9] reviewed the role of conservative management of JP and glomus tympanicum in patients over the age of 60 years. In a small sample, they found that 1 of 3 patients experienced tumor growth following subtotal resection nearly 6 years after treatment. In a study of patients over the age of 60 with advanced tumors, Willen and colleagues[24] identified no significant treatment failures at 19 months of mean follow-up with planned subtotal resection and adjuvant radiotherapy. Unfortunately, the published follow-up for these reports is generally short and limited by a relatively small number of cases. However, at this time, the authors' treatment algorithm has evolved to include subtotal resection. Akin to other benign skull base tumors, the authors believe that tumor recurrence is likely related to extent of resection. That is, the more tumor that is removed, the less likely the residual tumor is to grow.

Radiation

Because of the complexity of JP surgery, particularly regarding the close proximity of a vascular tumor to the facial nerve, the lower CN, and the carotid artery, nonsurgical management options such have radiation have emerged. Initially, fractionated external beam radiation was introduced for primary and salvage therapy. Control rates between 86% and 100% were described in early studies, which helped to establish the legitimacy of radiotherapy in the management algorithm for JP.[25–27] Over time, the use of therapeutic radiation evolved to employ stereotactic techniques that offer comparable tumor doses with less radiation injury to surrounding tissue.

Radiosurgery is now a well-accepted treatment modality for GJT. The treatment-specific tumor control and adverse effect profile has been shown to be least

comparable to what can be achieved surgically. In a recent multicenter study of 132 patients, 18% with Jackson-Glasscock grade 4 tumors, Gamma Knife achieved tumor control in 93% of cases.[28] A meta-analysis evaluating 869 patients with glomus jugulare also lent credence to the utility of radiosurgery for JP.[29] Patients were divided in 4 groups: gross total resection, subtotal resection, subtotal resection followed by radiosurgery, and radiosurgery alone. Although differences in tumor size between the groups were not controlled, the authors found that the radiosurgery alone group had the best rates of tumor control and that gross total resection did not appear to offer significantly improved tumor control versus subtotal resection or subtotal resection followed by radiosurgery. Also noteworthy was the finding that patients who underwent gross total resection had significantly worse post-treatment cranial neuropathies when compared with patients undergoing radiosurgery. Although the optimal radiation regimen for JP tumors is not yet standardized,[30] the use of radiotherapy appears to be a valuable addition to the available therapeutic options.

Observation

The natural history of JP tumors is not well established, but evaluations of the wait-and-scan observation strategy have revealed that intervention may not always be necessary. In 1992, Van der Mey and colleagues[31] were among the first groups to provide evidence to this effect. In a subsequent report on 11 patients from the same center, it was revealed that 55% of tumors demonstrated radiologic progression, with a median growth rate of 0.8 mm per year.[8] A complicating factor in these series is the possibility that some of the observed tumors were glomus tympanicum rather than jugulare. However, other reports specific to glomus jugulare have since validated these findings. Recently, Prasad and colleagues[32] analyzed the outcomes of 23 Fisch type C and D tumors that were observed for a minimum of 3 years. They demonstrated that 65% of tumors remained stable or even regressed in size over a median follow-up of 61 months. To date this remains one of the largest series on the natural history of JP. The relative paucity of data on tumor observation can be attributed to the rarity of the tumor and historical trends toward intervention after diagnosis. However, although many tumors will potentially grow if left untreated,[7] the slow rate of growth for most tumors and potential complications of intervention make a wait-and-scan policy a worthy consideration after diagnosis.

THE OTOLOGY GROUP OF VANDERBILT EXPERIENCE

The Otology Group of Vanderbilt has been fortunate to be a tertiary referral center for JP tumors over the course of its existence. During this time, the management algorithm for these tumors has evolved to include tumor observation and planned subtotal resection, as well as gross total resection and radiation. A compilation of the authors' experience is described.

Surgery

Gross total resection

The Otology Group of Vanderbilt reported previously on 202 jugular paragangliomas treated over a period of 35 years. Total resection was achieved in 90% of cases, with a tumor recurrence rate of 6%. Preoperative cranial neuropathies were seen in 47% of cases, most commonly IX, X, and XII. New postoperative cranial nerve injuries were seen in 60% of patients, most commonly IX followed by XI, X, and XII. Nearly 12% (11.8%) of patients experienced disease recurrence requiring revision surgery. Total resection was possible in 93% of the cases involving recurrence, and 95% of

these patients experienced new postoperative cranial nerve deficits. Similar to what was seen in patients undergoing primary surgery, cranial nerve IX (77%) was the most commonly injured nerve.[5]

Subtotal resection

Subtotal resection of JP has become a mainstay of tumor management in the authors' practice. This technique has previously been described as applicable to select patients. Jackson and colleagues[33] published their experience using subtotal resection for attempted hearing preservation and noted that success in this regard was inversely related to tumor size. Over time, the authors' utilization of planned, subtotal resection has increased, particularly in younger patients with advanced tumors (Glasscock-Jackson grade 3–4) and functional lower CN. Reviewing the authors' experience from 1999 to 2013, 12 patients were identified from this demographic who underwent a planned subtotal resection. Although varying degrees of resection were identified on postoperative radiographic evaluation, no patient developed a permanent, postoperative cranial neuropathy, and no patient with a residual disease burden of less than 20% of the original tumor size experienced postoperative tumor growth at a mean of approximately 45 months of follow-up.[34] Although these results have helped to validate the authors' continued use of this strategy, the small size of the patient population and the relatively short time of follow-up prohibit a definitive conclusion that this technique is preferred in all cases. However, the authors believe that the general concept of cranial nerve- and carotid artery-sparing surgery is valid and should be considered in future clinical and research efforts.

Observation

As previously mentioned, the role of tumor observation remains unclear at this time. The authors recently reviewed their experience with tumor observation, focusing on patients with primary GJT and greater than 2 years of documented follow-up. Fifteen patients (80% female, mean age 64.2 years) with 16 tumors were evaluated. Patients were selected for tumor observation due to advanced age (73%) and patient preference (73%). Approximately 40% of tumors demonstrated growth at an average of 0.9 mm per year. However, no significant change in cranial nerve function was seen for most patients through nearly 7 years of follow-up. No deaths were attributable to tumor progression.[35] This experience has led the authors to consider observation with a wait-and-scan policy for patients who do not have brainstem compression or concern for malignancy.

Radiation

Over the last 10 years, 18 patients were treated with linear accelerator-based stereotactic radiotherapy for glomus jugulare at the authors' institution. Over 64% (64.3%) of patients underwent fractionated therapy, and the median follow-up was 28.8 months (range 18.6–56.1 months). Consistent with previous reports, fewer than 10% of patients had experienced disease progression at their last recorded MRI. Although the authors' experience is limited by a smaller patient sample size and relatively short follow-up, stereotactic radiotherapy currently remains an important part of the treatment algorithm.

SUMMARY

JPs continue to represent a management challenge. Surgical resection is complicated by the vascular nature of the tumor and its location relative to the lower CN, the facial nerve, and the carotid artery. Radiation has gained momentum as a viable strategy for

tumor control, but this modality is not without adverse effects, and the natural history of many tumors may involve a lack of significant growth and symptom progression. Cranial nerve- and carotid-sparing subtotal resection may prove to be a valuable strategy in experienced hands, as may hybrid techniques that incorporate initial observation, subtotal resection, and adjuvant radiation. The role of genomic sequencing, both patient- and tumor-based, may also become a significant adjunct to tumor therapy, as this technology becomes readily available and cost-effective.

REFERENCES

1. Gulya A. The glomus tumor and its biology. Laryngoscope 1993;103(11 Suppl 60):7–15.
2. Jackson C. Glomus tympanicum and glomus jugulare tumors. Otolaryngol Clin North Am 2001;34(5):941–70.
3. Fayad JN, Bahar K, Brackmann DE. Jugular foramen tumors: clinical characteristics and treatment outcomes. Otol Neurotol 2010;31(2):299–305.
4. Jackson C. Basic surgical principles of neurotologic skull base surgery. Laryngoscope 1993;103(Suppl 60):29–44.
5. Kaylie D, O'Malley M, Auline J, et al. Neurotologic surgery for glomus tumors. Otolaryngol Clin North Am 2007;40:625–49.
6. Foote R, Pollack B, Gorman D, et al. Glomus jugulare tumor: tumor control and complications after stereotactic radiosurgery. Head Neck 2002;24(4):332–9.
7. Pollock B. Stereotactic radiosurgery in patients with glomus jugulare tumors. Neurosurg Focus 2004;17(2):E10.
8. Jansen JC, van den Berg R, Kuiper A, et al. Estimation of growth rate in patients with head and neck paragangliomas influences the treatment proposal. Cancer 2000;88:2811–6.
9. Cosetti M, Linstrom C, Alexiades G, et al. Glomus tumors in patients of advanced age: a conservative approach. Laryngoscope 2008;118:270–4.
10. Jackson C, Kaylie D, Coppit G, et al. Glomus jugulare tumors with intracranial extension. Neurosurg Focus 2004;17(2):E7.
11. Woods C, Strasnick B, Jackson C. Surgery for glomus tumors: the otology group experience. Laryngoscope 1993;103(11 Suppl 60):65–72.
12. Jackson C. Diagnosis for treatment planning and treatment options. Laryngoscope 1993;103(Suppl 60):17–22.
13. Erickson D, Kudva Y, Ebersold M, et al. Benign paragangliomas: clinical presentation and treatment outcomes in 236 patients. J Clin Endocrinol Metab 2001; 86(11):5210–6.
14. Eldevik O, Gabrielsen T, Jacobsen E. Imaging findings in schwannomas of the jugular foramen. AJNR Am J Neuroradiol 2000;21:1139–44.
15. Olsen W, Dillon W, Kelly W. MR imaging of paragangliomas. Am J Roentgenol 1987;148:201–4.
16. Fisch U. Infratemporal fossa approach for extensive tumors of the temporal bone and base of the skull. In: Silverstein H, Norrel H, editors. Neurological surgery of the ear, vol. 2. Birmingham (England): Aesculapius; 1977. p. 34–53.
17. Glasscock ME III, Jackson C, Harris P. Glomus tumors: diagnosis, classification, and management of large lesions. Arch Otolaryngol 1982;108:409–15.
18. Oldring D, Fisch U. Glomus tumors of the temporal region. Arch Otolaryngol 1981;107:209.
19. Boedeker CC, Neumann H, Offergeld C, et al. Clinical features of paraganglioma syndromes. Skull Base 2009;19(1):17–25.

20. Gaynor BG, Elhammady MS, Jethanamest D, et al. Incidence of cranial nerve palsy after preoperative embolization of glomus jugulare tumors using Onyx. J Neurosurg 2014;120(2):377–81.
21. Sanna M, Jain Y, De Donato G, et al. Management of jugular paragangliomas: the gruppo otologico experience. Otol Neurotol 2004;25:797–804.
22. Bacciu A, Medina M, Ait Mimoune H, et al. Lower cranial nerves function after surgical treatment of Fisch Class C and D tympanojugular paragangliomas. Eur Arch Otorhinolaryngol 2015 Feb;272(2):311–9.
23. Moe KS, Li D, Linder TE, et al. An update on the surgical treatment of temporal bone paraganglioma. Skull Base 1999;9:185–94.
24. Willen SN, Einstein DB, Maciunas RJ, et al. Treatment of glomus jugulare tumors in patients with advanced age: planned limited surgical resection followed by staged gamma knife radiosurgery: a preliminary report. Otol Neurotol 2005;26: 1229–34.
25. Cole JM, Beiler D. Long term results of treatment for glomus jugulare and glomus vagale tumors with radiotherapy. Laryngoscope 1994;104:1461–5.
26. Larner JM, Hahn SS, Spaulding CA, et al. Glomus Jugulare tumors. Long-term control by radiation therapy. Cancer 1992;69:1813–7.
27. Carasco V, Rosenman J. Radiation therapy of glomus jugulare tumors. Laryngoscope 1993;103:23–7.
28. Sheehan JP, Tanaka S, Link M, et al. Gamma Knife surgery for the management of glomus tumors: a multicenter study. J Neurosurg 2012;117:246–54.
29. Ivan ME, Sughrue ME, Clark AJ, et al. A meta-analysis of tumor control creates and treatment-related morbitiy for patients with glomus jugulare tumors. J Neurosurg 2011;114:1299–305.
30. Chen PG, Nyugen JH, Payne SC, et al. Treatment of glomus jugulare tumors with Gamma Knife radiosurgery. Laryngoscope 2010;120:1856–62.
31. Van der Mey AG, Frijns JH, Cornelisse CT, et al. Does intervention improve the natural course of glomus tumors? A series of 108 patietns seen in a 32-year period. Ann Otol Rhinol Laryngol 1992;101(8):635–42.
32. Prasad SC, Mimoune HA, D'Orazio F, et al. The role of wait-and-scan and the efficacy of radiotherapy in the treatment of temporal bone paragangliomas. Otol Neurotol 2014;35(5):922–31.
33. Jackson CG, Haynes DS, Walker PA, et al. Hearing conservation in surgery for glomus jugulare tumors. Am J Otol 1996;17(3):425–37.
34. Wanna GB, Sweeney AD, Carlson ML, et al. Subtotal resection for management of large jugular paragangliomas with functional lower cranial nerves. Otolaryngol Head Neck Surg 2014;151(6):991–5.
35. Carlson ML, Sweeney AD, Wanna GB, et al. Natural history of glomus jugulare: a review of 16 tumors managed with primary observation. Otolaryngol Head Neck Surg 2015;152:98–105.

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Surgical Salvage of Recurrent Vestibular Schwannoma Following Prior Stereotactic Radiosurgery

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Objectives/Hypothesis: To evaluate outcomes of salvage surgery for vestibular schwannoma (VS) that failed primary stereotactic radiosurgery (SRS).

Methods: Case-control study of 37 patients who underwent surgical resection of sporadic VS following prior SRS at two tertiary academic referral centers between 2003 and 2015. A cohort of nonirradiated control subjects, matched according to tumor size, age, and treatment center, were used as comparison.

Results: Thirty-seven patients were included. The median time from radiation to surgical salvage was 36 months (range 9.6–153 months). Following tumor progression after SRS, 18 (49%) patients underwent gross total resection, 10 (27%) underwent near-total resection, and nine (24%) underwent subtotal resection. Postoperative complications following salvage surgery included one (3%) case of stroke, four (11%) cases of cerebrospinal fluid leak, and two (5%) cases of meningitis. Twenty-seven (73%) patients had good postoperative facial nerve outcome (House-Brackmann Score I–II) at long-term follow-up. There were no cases of tumor recurrence or regrowth after a median length of 26 months following microsurgical salvage (range 3–114 months). The rate of satisfactory postoperative facial nerve function was not different between study and control subjects (73% vs. 76%; $P = 0.8$); however, less-than-complete resection was utilized more frequently among previously radiated patients ($P = 0.01$).

Conclusion: Microsurgical salvage of VS following primary radiation therapy is challenging. Less-than-complete resection is required in a greater percentage of patients to preserve facial nerve integrity and prevent neurological complications. Long-term follow-up is needed to determine the risk of delayed progression following incomplete tumor removal.

Key Words: Vestibular schwannoma, acoustic neuroma, recurrence, radiosurgery, gamma knife, microsurgery.

Level of Evidence: Level 3.

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INTRODUCTION

The primary goals of vestibular schwannoma (VS) management include long-term tumor control, preservation of hearing and facial nerve function, and maintenance of quality of life.[1] Currently, there are three primary management strategies for small- to medium-sized VSs, including microsurgery, radiation, and observation.[2] Over the past decade, there has been a trend in the United States toward less frequent use of microsurgery, increasing primary observation, and the use of radiation remaining fairly steady.[3] Options for radiation therapy include stereotactic radiosurgery delivered in one to five fractions (stereotactic radiotherapy [SRS]), fractionated SRS (> 5 fractions), and proton beam therapy. Currently, single fraction SRS is by far the most common radiation modality used for VS in the United States.[4] Stereotactic radiotherapy carries minimal risk of perioperative morbidity or mortality, and the period of convalesce is negligible, making it an attractive treatment choice for many patients.

More than 77,000 VSs have been treated with Gamma Knife (Elekta Instruments AB, Stockholm, Sweden) radiosurgery alone as of 2013.[5] The reported rate of radiation failure, with progressive tumor growth, is less than 10%.[4] Subsequent treatment and outcomes of VS that fail primary radiation therapy are less well documented. With a growing number of patients receiving low-dose radiosurgery, the ability to manage postradiation tumor progression will become increasingly relevant. Microsurgical resection is a common salvage therapy in this setting because repeat radiation therapy is thought by many to carry increased adverse risk and a higher rate of secondary failure, with limited data available to support this alternate treatment paradigm.

Most authors agree that operating on previously radiated VS is more difficult compared to primary treatment.[6–9] Recognizing the greater risks of VS surgery after radiation, it was recently emphasized that subtotal resection should be considered in cases for which an unfavorable dissection plane exists between the tumor and facial nerve in order to preserve facial nerve

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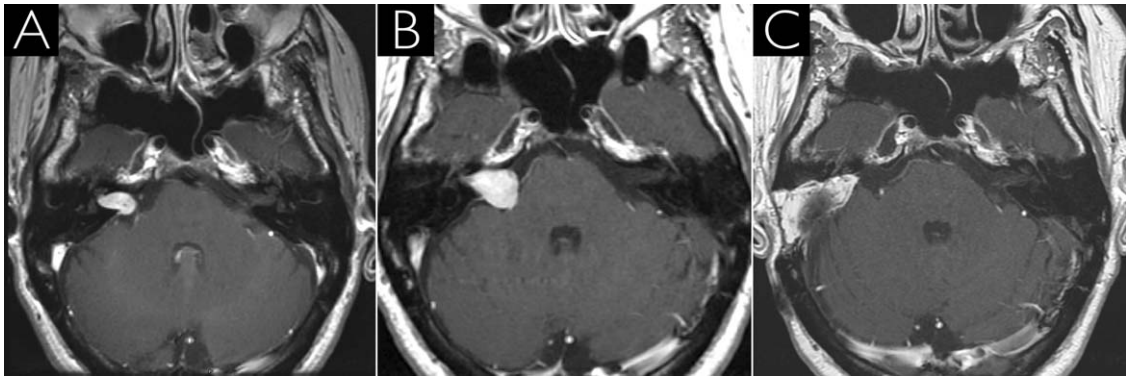

Fig. 1. Serial axial T1-weighted MRI with gadolinium (A) demonstrating a right-sided vestibular schwannoma with 0.5 cm of cisternal extension that was treated with primary stereotactic radiosurgery. (B) Following radiation, the tumor demonstrated progressive growth to a size of 1.2 cm over the course of 3.4 years. (C) The patient subsequently underwent translabyrinthine craniotomy with gross total resection and has no evidence of residual progressive disease with over 2 years of follow-up.

integrity.[6] It has even been argued that primary microsurgery with gross total resection (GTR) is the preferred treatment altogether for VS to avoid the challenges and potential morbidity of surgery following radiation.[8] In this study, we report our experience treating a series of patients with VSs that failed primary SRS and underwent microsurgery for salvage.

MATERIALS AND METHODS

Study Design

Prospectively maintained VS clinical databases at two separate institutions were queried, and all patients who underwent salvage surgery between 2003 and 2015 for recurrent sporadic VS after primary radiation failure were identified. Patients with neurofibromatosis type 2 (NF2) were excluded. Matched controls were identified from the same clinical databases, including subjects who underwent primary microsurgery for treatment of sporadic VS. Match criteria included patient age (within 5 years), tumor size (within 5 mm), and treatment center. Demographic, baseline clinical, and treatment outcome data were collected.

Tumor size and hearing class were reported according to the American Academy of Otolaryngology–Head and Neck Surgery guidelines for VS outcomes.[10] Facial nerve function was scored according to the House-Brackmann (HB) grading scale.[11] Cystic VS was defined as a tumor with a predominant cystic appearance. Growth was defined as greater than 2-mm increase in linear dimension on serial imaging. Great care was taken to avoid misinterpreting postradiation tumor swelling, typically seen on the initial 6-month follow-up magnetic resonance imaging (MRI) scan, as tumor growth.[12] Serial post-SRS imaging was available in 36 of 38 (95%) cases, whereas two patients had only one post-SRS scan prior to salvage surgery. The authors define GTR when all microscopic disease has been removed; near total resection (NTR) is specified when less a $5 \times 5 \times 2$-mm pad of adherent tumor is intentionally left on the facial nerve, brainstem, or vasculature to preserve neurological integrity; and subtotal removal is specified when anything less than near total resection is performed.[13] Following SRS, serial MRI scans are generally obtained every 6 months for the first year, then annually for the next 2 years and biennially thereafter. Following microsurgical resection of VS, postoperative clinical and radiographic (MRI) follow-up was performed at 3 months and at a minimum of every 2 years thereafter. More frequent follow-up was performed when clinically indicated if less than GTR was performed.

Primary outcome measures included facial nerve function and tumor control following salvage surgery. Descriptive statistics were used to describe demographic and clinical data. Wilcoxon rank-sum and Fisher's exact tests were used to compare continuous and categorical variables as appropriate. Logistic regression modeling was performed to identify independent variables associated with good (HB grade I–II) postoperative facial nerve outcome after adjusting for age, tumor size, extent of resection, and duration of follow-up. Research approval was obtained from the institutional review board (IRB 13-009442) and the regional ethical committee (NSD 13199) at each participating institution, respectively, prior to study commencement. Data were analyzed using JMP 10 Statistical Discovery Software (S.A.S. Institute Inc., Cary, NC). P values < 0.05 were considered statistically significant.

RESULTS

Primary Radiation Therapy

Thirty-seven patients underwent salvage surgery for radiation treatment failure between 2003 and 2015 (Fig 1). Indications for initial tumor radiation included documented tumor growth (35, 95%) or patient preference (2, 5%). Fifty-one percent of patients were female, and the median age at time of primary SRS was 57 years (range 30–80 years). At the time of primary presentation, all patients had normal facial nerve function, and pretreatment hearing class was documented in 35 cases: 15 (43%) were class A; two (6%) were class B; two (6%) were class C; and 16 (46%) were class D. Other primary presenting symptoms included imbalance (6, 16%) and trigeminal neuropathy (3, 8%). The median tumor size was 1.5 cm (range 0.5–2.9 cm) and 24 (65%) were right-sided. Four (11%) VSs were confined to the internal auditory canal, two (5%) were cystic, and none presented with brainstem edema. The original tumor size was unknown or missing from the medical record for three patients who initially received radiation treatment elsewhere.

Table I summarizes treatment characteristics of the 37 subjects who received primary radiation therapy. Thirty-three patients (89%) from this group were treated at the authors' institutions, whereas four were referred from outside centers after diagnosis of tumor growth following prior radiation. Following radiation, three (8%)

TABLE I.
Description of Primary Radiation Therapy.

Radiation Modality	Parameters Median (Range)	Complications
Gamma Knife Radiosurgery* (n = 35)	Marginal dose 12 Gy (12–14 Gy)	2 late onset facial weakness
	Maximal dose 26 Gy (24–40 Gy)	17 loss of useful hearing (class D)
	Number of isocenters 8 (4–60)	3 hydrocephalus
	Volume treated 3.4 cm^3 (0.34–17 cm^3)	
Fractionated stereotactic radiosurgery (n = 2)	CyberKnife 18 Gy, 3 fractions (n = 1)	0
	20 Gy, 4 fractions (n = 1)	

*Elekta Instruments AB, Stockholm, Sweden.
Gy = gray.

patients developed hydrocephalus. Of these, two (5%) patients were treated with placement of a ventriculoperitoneal shunt. Two patients had delayed onset facial paresis greater than 4 months following SRS, with HB scores of II and III, respectively. Of the 17 patients who had serviceable hearing (class A and B) prior to treatment, 15 lost useful hearing, and only one retained class A hearing after SRS at a median follow-up of 40 months after treatment.

Characteristics of Recurrent Vestibular Schwannoma

Primary treatment failure was defined as tumor growth after initial treatment with or without new symptoms (37, 97%), or development of refractory symptoms related to mass effect necessitating intervention (1, 3%). Thirty-six of 38 (95%) subjects had two or more post-SRS imaging studies available for review, and the median number of MRI studies per case was four (range 1–9). Two patients had only one MRI scan following primary SRS. In both cases, the degree of tumor growth led to a decision to treat with salvage surgery rather than continue observation. One of these subjects had a tumor that doubled in greatest linear dimension (0.6–1.2 cm) over 2 years. The second subject had 0.8 cm of tumor growth over a 2.8-year interval. Only one patient had salvage surgery for a nongrowing tumor. This patient

TABLE II.
Comparison of Preoperative Baseline Patient Features: Cohort Composed of Previously Irradiated VS and Control Subjects Composed of Previously Untreated VS.

Feature	Study Cohort (n = 37)	Matched Controls (n = 37)	*P* Value
Female gender (n, %)	19 (51%)	21 (57%)	0.8
Age (yrs) Median (range)	61 (31–84)	60 (31–72)	0.7
HB Score (n, %)	I (35, 95%)	I (37, 100%)	0.3
	II (1, 3%)		
	III(1, 3%)		
Hearing class (n, %)	A (1, 3%)	A 7 (19%)	0.001*
	B (0, 0%)	B 8 (22%)	
	C (1, 3%)	C 2 (5%)	
	D (33, 89%)	D 19 (51%)	
Tumor size (cm) Median (range)	2.0 (0.56–4.12)	1.9 (0.5–4.5)	0.4
Tumor laterality, right-sided (n, %)	24 (65%)	27 (73%)	0.6
Intracanalicular (n, %)	0	1 (3%)	1.0
Cystic (n, %)	7 (19%)	9 (24%)	0.8
Brainstem edema (n, %)	2 (5%)	2 (5%)	1.0
Brainstem compression (n, %)	14 (38%)	18 (49%)	0.5
Hydrocephalus (n, %)	1 (3%)	2 (5%)	1.0
Trigeminal dysfunction (n, %)	6 (16%)	9 (24%)	0.6
Intermittent facial spasm (n, %)	3 (8%)	0	0.2
Imbalance (n, %)	10 (27%)	13 (35%)	0.6
Headache (n, %)	1 (3%)	0	1.0

RT, radiation therapy; HB Score = House-Brackmann Score.

TABLE III.
Surgical Approach, Extent of Resection, and Complications Following Salvage Surgery of Previously Irradiated VS Compared to Matched Controls.

Feature	Primary RT n (%)	Matched Control n (%)	*P* Value
Surgical Approach			
Retrosigmoid	23 (62%)	30 (81%)	0.1
Translabyrinthine	14 (38%)	7 (19%)	
Extent of Resection			
Gross total	18 (49%)	30 (81%)	0.01*
Near total	10 (27%)	4 (11%)	
Subtotal	9 (24%)	3 (8%)	
Complications			
Stroke	1 (3%)	0	1.0
Hydrocephalus	0	1 (3%)	1.0
CSF leak	4 (11%)	4 (11%)	1.0
Meningitis	2 (5%)	0	0.5

CSF = cerebrospinal fluid. RT = radiation therapy; VS = vestibular schwannoma.

underwent surgery 26 months after radiosurgery for treatment of medically intractable trigeminal neuralgia.

The median time interval between primary treatment and salvage surgery was 36 months (range 9.6–153 months). The median tumor size at time of salvage surgery was 2.0 cm (range 0.6–4.1 cm), and the median amount of posttreatment tumor growth was 0.7 cm (range 0.3–1.8 cm). At the time of tumor progression, no patients had purely intracanalicular tumors; seven (19%) demonstrated primarily cystic tumor growth; two (5%) had associated brainstem edema; and 14 (38%) had varying degrees of brainstem compression on imaging, which was not different from controls. Table II summarizes the clinical characteristics of patients at the time of salvage surgery with comparison to matched controls. Patients presenting for salvage therapy had poorer hearing compared to matched controls ($P = 0.001$); otherwise, there were no differences between groups prior to microsurgery.

Surgical Salvage

Operative data are summarized in Table III. Previously radiated patients underwent either a translabyrinthine (14; 38%) or retrosigmoid (23; 62%) approach for surgical salvage. Eighteen (49%) patients underwent gross total, 10 (27%) near total, and nine (24%) subtotal resection. The most common indication for near- or subtotal resection was to preserve facial nerve integrity. In contrast, the majority of matched controls underwent GTR (30; 81%), a difference that was statistically significant ($P = 0.01$).

Intraoperative facial nerve electroprognostic testing was performed using proximal minimum stimulation thresholds or the supramaximal stimulation technique described previously.[14] Facial nerve dissection was noted to be subjectively more difficult secondary to adherent and or poorly defined surgical planes at the nerve–tumor interface. The facial nerve was anatomically intact at the end of the operation in 95% (35) of cases following radiation and in 100% of all control subjects. In two previously irradiated cases, the anatomical continuity of the facial nerve was lost while dissecting thinly splayed nerve fibers. The single patient with a nongrowing tumor who underwent salvage surgery for intractable trigeminal neuralgia experienced symptom resolution following surgery.

Complications

The rate of postoperative cerebrospinal fluid (CSF) leak requiring reoperation in radiated cases was 11% (n = 4). One case occurred in a delayed fashion over 12 months following surgery and developed subsequent meningitis, requiring return to the operating room. Two additional cases of early postoperative CSF wound leaks from the craniotomy incision occurred and were successfully managed with suture reinforcement of the skin closure. One patient with prior radiation (3%) suffered brainstem stroke following salvage surgery, with residual neurologic deficits including mild hemiparesis and ataxia, but currently lives independently, whereas none of the control subjects experienced postoperative stroke. Overall complication rates were not significantly different compared to matched controls (Table III).

Facial Nerve Function and Tumor Control Following Salvage Surgery

The median length of radiologic follow-up after salvage surgery was 26.4 months (range 3–114 months), which was not statistically significantly different than duration of follow-up for controls ($P = 0.7$). At last follow-up, no recurrences in cases of GTR, or progressive growth of tumor remnants in less than GTR resection cases, were diagnosed on imaging in either group. Facial nerve outcomes are summarized in Table IV and Figure 2. At last follow-up, good facial nerve function (HB I-II) was observed in 27 (73%) of the patients who underwent primary radiation therapy compared to 28 (76%) controls ($P = 0.8$). Notably, when only analyzing patients with normal preoperative facial nerve function, excluding the two study subjects with post-SRS facial nerve paresis, 27 of 35 (77%) retained good long-term postoperative facial nerve function following salvage surgery. After adjusting for age, tumor size, extent of resection, and duration of follow-up using logistic regression modeling, there was no difference in rate of satisfactory facial

TABLE IV.
Surgical outcomes. Postoperative House-Brackmann Score

Feature	Primary RT* n (%)	Matched Control n (%)	*P* Value
I–II	27 (73%)	28 (76%)	
III–IV	8 (22%)	8 (22%)	0.8
V–VI	2 (5%)	1 (3%)	

*Includes two patients who had preoperative facial nerve paresis following prior radiation therapy.
RT = radiotherapy.

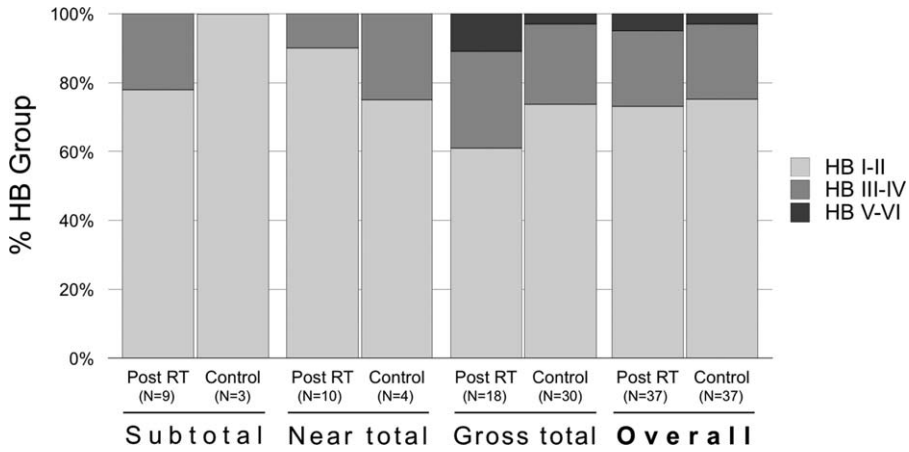

Fig. 2. Comparison of facial nerve outcomes between study and control subjects by extent of resection

nerve outcome (HB I-II) between study and control subjects (Table V).

DISCUSSION

We present a large multicenter case-control study comparing outcomes between postradiated sporadic VS and nonradiated control subjects. Among 37 sporadic VSs that failed primary SRS, our data demonstrate that approximately 77% of patients with normal preoperative facial nerve function retained good (HB I or II) function after salvage surgery, and GTR can be achieved in at least half of the cases. Overall, the rate of long-term facial nerve paresis was similar to a size-matched control population of primary VS; however, the rate of less-than-complete resection was significantly higher in the postradiation group.

In 2005, Friedman et al. similarly reviewed a series of 38 patients (28 sporadic, 10 NF2) who received salvage microsurgery following failed primary radiation therapy compared to a historical nonradiated control group matched according to age and tumor size.[7] Similar to the current study, they found that the rate of gross total resection was lower in the irradiated group (78.9% vs. 97.4%); however, in contrast they found that facial nerve outcomes were poorer than age- and size-matched nonradiated controls (37% vs. 70% HB I or II). The latter discrepancy may be partly explained by several differences between study populations. In our study, the majority of patients (95%) underwent Gamma Knife (Elekta Instruments AB) radiosurgery after the year 2000 using current low-dose treatment parameters. In contrast, the study from the House Ear Clinic spanned the years between 1985 and 2004 and included heterogeneous radiation delivery: gamma knife, linear accelerator (LINAC), and proton beam. Their median length of follow-up was 15 months compared to 26 months. Finally, 10 of the 38 patients had NF2. Patients with NF2-associated VS are known to have poorer postoperative facial nerve outcomes compared to patients with sporadic VS.[15] In 2011, Friedman et al. reported an updated institutional experience, including 17 NF2 patients and 56 sporadic VSs, advocating for partial or near-total resection when required in order to preserve facial nerve integrity.[6] In this updated series, 79.5% received GTR and 20.5% received partial resection. Overall, 65% of patients had postoperative HB grade I or II function; 57% following gross total resection compared to 92% following partial resection. Anatomical continuity of the facial nerve was lost in 10 (13.7%) cases. A control group was not included in this latter analysis.

In 2012, Gerganov et al. also found a much higher rate of poor facial nerve function (43% HB gr 3–6) after salvage surgery in patients who had prior radiation compared to nonradiated controls (30% HB gr 3–6). Gross total resection was performed in all but one control case.[9] In 2013, Husseini et al. compared surgical outcomes of 15 patients who had prior radiation therapy (13 sporadic, 2 NF2) to a control group consisting of 15 nonradiated VSs matched according to age, tumor size, and surgical approach.[8] Overall, 13 (87%) previously irradiated VSs were managed with gross total resection. The facial nerve was anatomically preserved in 14 of 15 cases, but only four of 13 (31%) patients who had HB grade I or II function preoperatively maintained HB I or II function following salvage surgery. None of the patients in any of these series experienced recurrence following salvage surgery, regardless of extent of

TABLE V.
Multivariate Logistic Regression Analysis Investigating Independent Associations With Good Postoperative Facial Nerve Outcome (HB I-II).

Variable	Odds Ratio (95% CI)	*P* Value
Study vs. control subjects	0.61 (0.18–2.04)	0.424
Presurgical tumor size	0.69 (0.33–1.45)	0.332
Age	0.94 (0.87–1.01)	0.079
Extent of resection GTR vs. STR	0.18 (0.02–1.37)	0.097
Extent of resection NTR vs. STR	0.67 (0.07–6.67)	0.730
Length of follow-up after salvage	0.92 (0.74–1.14)	0.436

CI = confidence interval; GTR = gross total resection; HB = House-Brackmann; NTR = near total resection; STR = subtotal resection.

resection, although follow-up in all these series is limited. Together, these data demonstrate that in many cases incomplete tumor resection is required in order to preserve facial nerve integrity, and that more aggressive resection is associated with poorer postoperative facial nerve function.

In a previous study, the authors found that at 3, 5, and 10 years following SRS for treatment of sporadic VS, 45%, 52%, and 77% of patients developed nonserviceable hearing, respectively.[16] In the current study, 15 of 17 (88%) patients with serviceable hearing prior to SRS lost useful hearing at a median of 40 months following treatment, which is even greater than prior estimates.[16–19] The higher percentage of cases that lost serviceable hearing following radiation in the current study is most likely attributable to the added effects of tumor growth.[16–20] The small number of patients with preoperative serviceable hearing in our study precluded analysis of hearing preservation surgery after failed radiation therapy; however, this would seem like an unrealistic goal in most cases.[8]

The merit of gross total tumor resection in the setting of recurrent VS has been a subject of ongoing debate.[6,8] Our data suggest that gross total tumor resection is less frequently achievable in previously radiated tumors compared to nonradiated controls. We acknowledge that our GTR rate of 49% seems low for the patients presented here. However, we want to emphasize that we are very stringent about not considering NTR in which there is no residual tumor visible on the 3-month follow-up MRI as a complete resection. If we were to include NTR and GTR together, the rate would be 76%. Irradiation inevitably delivers a minimum of the prescribed marginal dose to the facial nerve–tumor plane, leading to formation of adhesions and poor surgical planes. As a general strategy, our group enters surgical salvage cases with the intent to remove the tumor in its entirety; however, we utilize intraoperative impression and results of intraoperative electroprognostic testing to assist in determining when less-than-complete resection should be performed in order to preserve facial nerve integrity.[14] The limited cumulative data suggest that short- and intermediate-term tumor control is good even following subtotal resection. Long-term data will be required to ascertain the risk of delayed recurrence.

Theoretically, reirradiation carries an increased risk of cranial neuropathy, hydrocephalus, and radiation-induced cerebral edema or necrosis. Furthermore, tumors that initially fail radiation therapy may be considered more radioresistant and less likely to respond to additional radiation treatment. Despite these considerations, preliminary data suggest that retreatment with low-dose SRS is well tolerated and provides tumor control in the majority of cases.[21–23] Until more data are available documenting the long-term safety and efficacy of this strategy, the authors favor microsurgical salvage in most cases.

With the increasing number of VS cases worldwide receiving primary radiation therapy, and the ongoing trend toward dose deescalation to limit treatment morbidity, our ability to manage radiation failure is becoming increasingly relevant.[3] In the authors' experience, approximately 6% of patients who receive primary SRS experience treatment failure at 5 to 7 years following radiation.[12,24] This number may be greater for cystic, large, or rapidly growing tumors—or in cases where less than 12 Gy to the tumor margin is prescribed.[2,25–27] Data regarding the utility of radiation therapy for treatment of residual progressive disease following subtotal resection is mixed. Several studies have demonstrated that the results following subtotal resection are on par with primary radiation treatment.[28,29] However, in a recent preliminary report of a large prospective multicenter study, Monfared et al. found that four of 11 (36%) cases failed salvage radiation therapy, leading to the conclusion that radiation control of growing tumor remnants following microsurgery is suboptimal.[30]

Our study has several strengths and limitations. We included a relatively large and homogenous cohort of sporadic VS and excluded patients with NF2 given the significant difference in tumor biology and behavior. Control subjects, matched by age, tumor size, and center, were included for comparison. Additionally, patients were included from two separate institutions on separate continents to try and reduce surgeon specific biases. Finally, both institutions have a strong track record of utilizing SRS and microsurgery in the management of VS. Limitations include retrospective review of data, which carries a risk of selection bias, heterogeneous and incomplete data points, and inconsistent follow-up. When previous SRS has failed, much longer follow-up is necessary to truly determine the fate of tumor remnants following less than GTR.

CONCLUSION

Microsurgical resection of VS following SRS is technically challenging. Nevertheless, facial nerve preservation with effective tumor control remains an attainable goal in most patients. Intraoperative surgical judgment about when to perform less than GTR and how to maximize tumor removal in such cases remains extremely important and is very difficult to objectify.

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BIBLIOGRAPHY

1. Carlson ML, Tveiten OV, Driscoll CL, et al. Long-term quality of life in patients with vestibular schwannoma: an international multicenter cross-sectional study comparing microsurgery, stereotactic radiosurgery, observation, and nontumor controls. *J Neurosurg* 2015;122:833–842.
2. Carlson ML, Link MJ, Wanna GB, Driscoll CL. Management of sporadic vestibular schwannoma. *Otolaryngol Clin N Am* 2015;48:407–422.
3. Carlson ML, Habermann EB, Wagie AE, et al. The Changing Landscape of Vestibular Schwannoma Management in the United States--A Shift Toward Conservatism. *Otolaryngology Head Neck Surg* 2015;153:440–446.
4. Jacob JT, Pollock BE, Carlson ML, Driscoll CL, Link MJ. Stereotactic radiosurgery in the management of vestibular schwannoma and glomus jugulare: indications, techniques, and results. *Otolaryngol Clin N Am* 2015;48:515–526.
5. Society LGK (2014) Leksell Gamma Knife: Indications Treated 1986 to 2013 (68%–100% of sites reporting). Leksell Gamma Knife Society. Available at: https://http://www.lgksociety.com/uploads/media/1968-2013-statistics-report.pdf. Last accessed 1 January 2015.
6. Friedman RA, Berliner KI, Bassim M, et al. A paradigm shift in salvage surgery for radiated vestibular schwannoma. *Otol Neurotol* 2011;32:1322–1328.
7. Friedman RA, Brackmann DE, Hitselberger WE, Schwartz MS, Iqbal Z, Berliner KI. Surgical salvage after failed irradiation for vestibular schwannoma. *Laryngoscope* 2005;115:1827–1832.

8. Husseini ST, Piccirillo E, Taibah A, Almutair T, Sequino G, Sanna M. Salvage surgery of vestibular schwannoma after failed radiotherapy: the Gruppo Otologico experience and review of the literature. *Am J Otolaryngol* 2013;34:107–114.
9. Gerganov VM, Giordano M, Samii A, Samii M. Surgical treatment of patients with vestibular schwannomas after failed previous radiosurgery. *J Neurosurg* 2012;116:713–720.
10. Committee on Hearing and Equilibrium guidelines for the evaluation of hearing preservation in acoustic neuroma (vestibular schwannoma). *Otolaryngol Head Neck Surg* 1995;113:179–180.
11. House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Head Neck Surg* 1985;93:146–147.
12. Pollock BE, Link MJ, Foote RL. Failure rate of contemporary low-dose radiosurgical technique for vestibular schwannoma. *J Neurosurg* 2009; 111:840–844.
13. Carlson ML, Van Abel KM, Driscoll CL, et al. Magnetic resonance imaging surveillance following vestibular schwannoma resection. *Laryngoscope* 2012;122:378–388.
14. Schmitt WR, Daube JR, Carlson ML, et al. Use of supramaximal stimulation to predict facial nerve outcomes following vestibular schwannoma microsurgery: results from a decade of experience. *J Neurosurg* 2013; 118:206–212.
15. Mahboubi H, Maducdoc MM, Yau AY, et al. Vestibular schwannoma excision in sporadic versus neurofibromatosis type 2 populations. *Otolaryngol Head Neck Surg* 2015;153:822–831.
16. Carlson ML, Jacob JT, Pollock BE, et al. Long-term hearing outcomes following stereotactic radiosurgery for vestibular schwannoma: patterns of hearing loss and variables influencing audiometric decline. *J Neurosurg* 2013;118:579–587.
17. Yang I, Sughrue ME, Han SJ, et al. A comprehensive analysis of hearing preservation after radiosurgery for vestibular schwannoma: clinical article. *J Neurosurg* 2013;119(suppl):851–859.
18. Roos DE, Potter AE, Zacest AC. Hearing preservation after low dose linac radiosurgery for acoustic neuroma depends on initial hearing and time. *Radiotherapy Oncol* 2011;101:420–424.
19. Hasegawa T, Kida Y, Kato T, Iizuka H, Yamamoto T. Factors associated with hearing preservation after gamma knife surgery for vestibular schwannomas in patients who retain serviceable hearing. *J Neurosurg* 2011;115:1078–1086.
20. Aoyama H, Onodera S, Takeichi N, et al. Symptomatic outcomes in relation to tumor expansion after fractionated stereotactic radiation therapy for vestibular schwannomas: single-institutional long-term experience. *Int J Radiat Oncol Biol Phys* 2013;85:329–334.
21. Kano H, Kondziolka D, Niranjan A, Flannery TJ, Flickinger JC, Lunsford LD. Repeat stereotactic radiosurgery for acoustic neuromas. *Int J Radiat Oncol Biol Phys* 2010;76:520–527.
22. Yomo S, Arkha Y, Delsanti C, Roche PH, Thomassin JM, Regis J. Repeat gamma knife surgery for regrowth of vestibular schwannomas. *Neurosurgery* 2009;64:48–54; discussion 54–45.
23. Liscak R, Vladyka V, Urgosik D, Simonova G, Vymazal J. Repeated treatment of vestibular schwannomas after gamma knife radiosurgery. *Acta Neurochir* 2009;151:317–324; discussion 324.
24. Varughese JK, Wentzel-Larsen T, Pedersen PH, Mahesparan R, Lund-Johansen M. Gamma knife treatment of growing vestibular schwannoma in Norway: a prospective study. *Int J Radiat Oncol Biol Phys* 2012;84:e161–e166.
25. Niu NN, Niemierko A, Larvie M, et al. Pretreatment growth rate predicts radiation response in vestibular schwannomas. *Int J Radiat Oncol Biol Phys* 2014;89:113–119.
26. Lall RR LR, Schumacher A, McCaslin A, Kalapurakal J, Chandler JP. Very low dose stereotactic radiosurgery for vestibular schwannoma. *J Neurol Surg B* 2014;75–A117.
27. Milligan BD, Pollock BE, Foote RL, Link MJ. Long-term tumor control and cranial nerve outcomes following gamma knife surgery for larger-volume vestibular schwannomas. *J Neurosurg* 2012;116:598–604.
28. Pollock BE, Link MJ. Vestibular schwannoma radiosurgery after previous surgical resection or stereotactic radiosurgery. *Prog Neurol Surg* 2008; 21:163–168.
29. Pollock BE, Lunsford LD, Flickinger JC, Clyde BL, Kondziolka D. Vestibular schwannoma management. Part I. Failed microsurgery and the role of delayed stereotactic radiosurgery. *J Neurosurg* 1998;89:944–948.
30. Monfared A, Corrales E, Theodosopoulos P, et al. Facial nerve outcome and tumor control rate as a function of degree of resection in treatment of large acoustic neuromas: preliminary report of the Acoustic Neuroma Subtotal Resection Study. *Neurosurgery* 2015. Epub ahead of print.

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Long-term Outcomes After Middle Fossa Approach for Traumatic Facial Nerve Paralysis

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Objectives: Controversy exists regarding the role of surgery for patients with skull base trauma and facial paralysis. Our goal is to report the long-term outcomes of early facial nerve decompression and repair via the middle fossa (MF) approach for patients with traumatic paralysis.
Study Design: Retrospective case series.
Setting: Academic medical center.
Patients: There were 18 patients who met surgical criteria: immediate complete paralysis, greater than 90% degeneration on electroneurography (ENoG), and no voluntary electromyography (EMG) potentials within 14 days after trauma and 1 year minimum follow-up.
Intervention: MF approach for traumatic facial paralysis and for irreversible injuries nerve grafting was performed.
Main Outcome Measure: Long-term facial function, hearing results, and surgical complications.
Results: At MF decompression, 11 patients had an anatomically intact facial nerve. Of these patients with intact nerves, 72.7% obtained normal to near normal facial function (HB I or II) at 1 year: 27.3% to HB I, 45.5% to HB II, and 27.3% to HB III. At surgery, seven patients were found to have injuries that required nerve grafting and 100% improved to HB III. For all patients, facial nerve function significantly improved after surgery ($p < 0.01$). The average difference in pure tone average and word recognition after surgery was $+2.9$ dB and $+3.3\%$, respectively ($p = 0.44$; $p = 0.74$). Minor, transient complications occurred in three patients and an abscess required drainage in one patient, but no other major complications.
Conclusion: In our series, all patients with traumatic complete paralysis and poor facial prognosis achieved a long-term outcome of HB III or better after MF approach for decompression and repair of the facial nerve. **Key Words:** Facial nerve decompression—Facial nerve repair—Long-term outcomes—Middle fossa approach—Surgical criteria—Temporal bone fracture—Traumatic facial nerve paralysis.

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Traumatic facial nerve paralysis can result from many blunt and penetrating injuries to the temporal bone. The most common causes of temporal bone fractures are motor vehicle accidents, recreational activities, falls, or assaults and can result in stretching, compression, or transection of the facial nerve (1,2). These patients with significant skull base trauma causing facial nerve paralysis often have multiple, complex medical issues, which makes their management challenging.

One of the most devastating aspects of temporal bone trauma is paralysis of the facial nerve, which occurs in 7 to 10% of cases (3). Some patients with posttraumatic facial paralysis may recover normal or near normal facial function with observation or medical management alone, including steroids to minimize posttraumatic neural edema. If the onset of facial nerve dysfunction was delayed from the traumatic incident, then the prognosis is excellent (4–6). However, a subset of patients who have immediate-onset, complete facial nerve paralysis after a skull base trauma are at risk for a poor long-term outcome. The long-term consequences of facial paralysis result in functional limitations, are emotionally distressing, and have significant psychosocial implications (7). Patients who are high risk for poor outcomes, as determined by electrodiagnostic testing, may benefit from surgical management (8–10).

Appropriate surgical candidates after temporal bone trauma have poor long-term prognosis of their facial nerve function. Coupling a function-based clinical evaluation, the House-Brackmann (HB) facial nerve grading system, with electrodiagnostic testing has been effective in determining long-term prognosis (11,12). Specifically, electroneurography (ENoG) and voluntary electromyography (EMG) can provide prognostic information when there is complete paralysis (HB VI) on clinical exam (13). Patients with any posttraumatic facial movement rarely need surgical intervention and several studies show that patients with <90% degeneration on their ENoG testing have excellent long-term outcomes, with

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all patients regaining normal or near normal facial function (HB I or II) (3,11,14). Patients with immediate-onset complete facial paralysis (HB VI) that persists, show >90% degeneration on ENoG, and have absent volitional nerve activity on EMG, have a poor chance of recovery if observed or managed medically (15).

The site of facial nerve injury in patients with traumatic paralysis after a temporal bone fracture is peri-geniculate in approximately 90% of cases (16,17). In addition, the meatal foramen and labyrinthine segment have been shown to be the narrowest portion of the bony facial canal and common sites of electric conduction blockage due to significant edema or bone fragments, which can result in constriction and injury of the intratemporal facial nerve (18,19). Therefore, any surgical intervention should address these sites. When hearing is intact, the middle fossa (MF) approach provides optimal access the meatal foramen, labyrinthine segment, and peri-geniculate areas (20,21). Alternatively, if irreversible hearing loss has occurred after trauma, a translabyrinthine approach may be used.

Published rates of facial nerve recovery vary between surgical intervention and observation, (3,9,10,22–29) and the evidence for the role of surgery for traumatic facial nerve paralysis was recently found to be inconclusive by a systematic review (4). The current body of literature is heterogeneous and lacks standardization, with incomplete data reporting, varying surgical criteria, and erratic electrical testing. Length of follow-up and type of surgery performed are also important variables that vary significantly in the currently published studies. Understanding of the natural history of traumatic paralysis in patients with poor prognosis after clinical evaluation and electrical testing is limited; however, designing a study with matched controls would be difficult to conduct ethically because when a patient reaches the electrodiagnostic criteria in the setting of trauma, it would be unethical to withhold treatment. In this situation, these patients are at high-risk of complete nerve section that will likely not improve without intervention, therefore, surgical treatment is appropriate and necessary, but the effectiveness of MF decompression and repair is not fully defined.

Timing for surgical decompression is controversial. Several studies indicate surgery should be performed within 6 days to 2 weeks of the trauma (10,30–32), whereas, others suggest that good facial nerve outcomes can be achieved regardless of the timing of surgery, as long as it is performed within the first 3 months (22,31). In certain cases in which damage to the nerve is irreversible, nerve grafting with an autologous donor nerve may be performed in conjunction with decompression surgery. Many recipients of nerve grafting can recovery facial nerve function of a HB III, but this is the best reported HB score obtainable (33). For patients undergoing MF surgery, preserving hearing and perioperative morbidity is a significant concern, and many studies document the safety of this procedure (22,34–36).

This study aims to describe the outcomes of early surgical decompression via the MF approach and repair for traumatic facial nerve paralysis in patients with poor facial nerve prognosis in an unmatched series of patients. We also report the long-term postoperative outcomes of the MF facial nerve decompression with and without nerve grafting, particularly in regards to long-term facial function outcomes, safety, and hearing results.

MATERIALS AND METHODS

With Institutional Review Board approval, we searched our database for patients who underwent a MF craniotomy for the diagnosis of temporal bone fracture and facial paralysis. Patients with temporal bone fractures and facial paralysis treated by other surgical approaches were not included. The medical records of 23 consecutive patients treated from 1996 to 2014 at the University of Utah Hospital were retrospectively reviewed. There were five patients who were lost to follow-up within 1 year after surgery or did not meet the inclusion criteria and were excluded. All patients had immediate-onset, complete facial paralysis (HB VI), underwent a computed tomographic (CT) scan, and then underwent ENoG testing. If the patients had >90% degeneration on ENoG testing, no voluntary EMG motor unit potentials, and presented within 14 days of the traumatic facial nerve paralysis, then surgical decompression via the MF approach with possible facial nerve repair was recommended.

For patients electing to have surgical decompression, a standard MF approach to the internal auditory canal (IAC) was performed. The facial nerve was identified in the lateral IAC, exposed from the labyrinthine segment and meatal foramen to the geniculate ganglion and a portion of the tympanic segment. The temporal bone fracture was identified, explored, and the facial nerve was fully exposed on either side of the fracture. For decompression, the fibrous ligament at the meatal foramen of the fallopian canal and exposed nerve sheath (epineurium) was incised. For irreversible injuries, nerve grafting was performed. A mastoidectomy was performed if exposure of the descending segment of the facial nerve was necessary. The nerve was cut back to healthy ends and then a great auricular nerve graft, or in one case a sural nerve graft, was harvested, trimmed, reversed, and placed into position spanning the gap between the ends. A sutureless repair was performed if feasible.

The patient's clinical course was followed, which included: HB grade, pre- and postoperative hearing results with a 4-frequency pure-tone average (PTA) using 0.5, 1, 2, and 3 kHz and word recognition score (WRS), and both immediate postoperative and long-term complications. Final HB grade was assessed at the clinic visit at 1 year after surgery, and the final hearing result was assessed at a clinic visit between 3 months and 1 year after surgery. Hearing outcomes compared the preoperative bone PTA and the postoperative air PTA because all patients had a significant preoperative conductive hearing loss and, thus, preoperative inner ear function was compared with their postoperative hearing result. The results were compiled and statistically analyzed with the chi-square test and regression analysis: including p values, a best-fit linear trendline, and R^2 value. The House-Brackmann (HB) facial nerve grading system is an ordinal variable and appropriate ordinal

linear regression analysis was performed to assess differences in outcome with timing of surgical intervention (37–38).

RESULTS

There were 18 patients who met inclusion criteria. The average patient age at the time of surgical decompression was 28 years and 72.2% of patients were men. Temporal bone CT scan demonstrated 94.4% of patients had otic capsule-sparing fractures and 5.6% had otic capsule-violating fractures. An isolated MF approach was performed on nine patients, whereas, nine patients had combined MF and transmastoid exposure. An anatomically intact facial nerve was identified in 11 patients and an irreversible nerve injury, which required nerve grafting was identified in seven patients. The average duration of follow-up was 36 months. The mechanisms of injury are summarized in Table 1 and the location of facial nerve injury diagnosed intraoperatively in Table 2.

For patients who underwent MF decompression and an intact facial nerve was identified ($n = 11$), 72.7% regained normal or near normal facial function (HB I or II) within 1 year after surgery. Of these patients with intact nerves, 27.3% improved to normal (HB I), 45.5% improved to near normal (HB II), and all remaining patients, 27.3%, improved to a HB III (Fig. 1). At surgery, seven patients were found to have injuries that required nerve grafting, and all seven (100%) improved to HB III. For all patients, facial nerve function significantly improved after surgery ($p < 0.01$). There was no difference in final facial nerve outcome depending on the patient's sex, side of paralysis, ENoG degeneration, or type of temporal bone fracture. In the subset of patients with an intact facial nerve at decompression, the single patient older than 60 years had a HB III facial outcome.

The average time from onset of traumatic facial paralysis to MF decompression with or without nerve grafting was 12.4 days (range: 9–14 days; median: 12 days). Analyzing the final facial nerve grade for patients that did not require nerve grafting based on the number of days from the beginning of facial paralysis to surgical decompression demonstrated a moderate positive correlation ($R^2 = 0.55$; $p < 0.01$) (Fig. 2). Regression analysis with a best-fit linear line shows a statistically significant improvement in final HB grade the earlier the decompression was performed.

Due to significant preoperative conductive hearing losses, the preoperative bone PTA was compared with the postoperative air PTA to illustrate their preoperative inner ear function and their postoperative hearing result. Results of patients' hearing tests are summarized in Table 3. The average difference in pure tone average and word recognition after surgery was +2.9 dB and +3.3%, respectively ($p = 0.44$; $p = 0.74$) and 1 of 18 patients experienced a significant change in final hearing results (>8 dB loss or >8% decrease in WRS).

According to a standardized classification of surgical complications (39), minor complications (Grade I) occurred in 16.7% of patients, including vertigo, autophony, and tinnitus, and all resolved by 3 months after surgery. One patient developed a surgical wound infection and abscess, 9 days postoperatively, which required an incision and drainage and IV antibiotics (Grade III). There were no other major complications.

TABLE 1. *Mechanisms of injury of the temporal bone fracture*

Motor vehicle	66.7%
Falls	11.1%
Water skiing	5.6%
ATV	5.6%
Mining	5.6%
Snowmobile	5.6%

TABLE 2. *Location of the facial nerve injury diagnosed intraoperatively*

Peri-geniculate	66.7%
Tympanic segment	22.2%
Mastoid segment	11.1%
Labyrinthine segment	5.6%

DISCUSSION

Most patients with traumatic facial paralysis can recover normal facial function with conservative treatments such as observation or steroids, however, a fraction of patients are at increased risk for permanent facial nerve dysfunction. Identifying these high-risk patients requires a clinical exam with complete facial paralysis (HB VI) identified immediately after the injury that is not recovering, electrodiagnostic testing with ENOG showing >90% degeneration, and EMG with absent voluntary potentials. This subset of patients is at increased risk for a poor long-term outcome and benefit from decompression surgery to identify those with an irreversibly injured facial nerve. This procedure is also therapeutic to those patients with bony fragments and significant edema constricting the facial nerve because alleviating this impingement allows the facial nerve to recover.

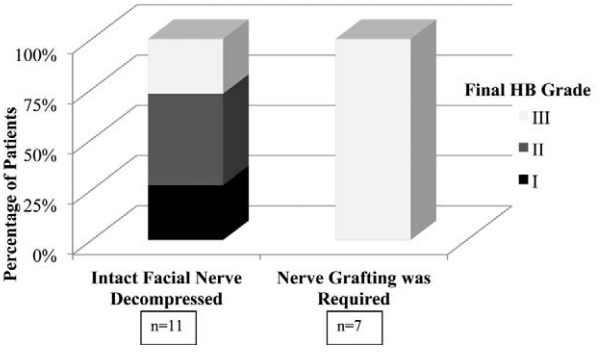

FIG. 1. Final facial nerve HB grade in patients with an intact facial nerve after MF decompression compared with patients requiring nerve grafting.

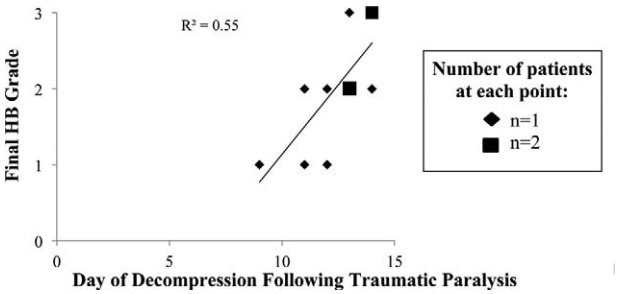

FIG. 2. Final facial nerve HB grade based on the day of decompression after traumatic paralysis for patients that did not require nerve grafting.

The type of surgery performed varies depending on the site of temporal bone fracture and the likely site of facial nerve injury. The perigeniculate region is the site in-which the facial nerve is most often damaged and the meatal foramen and labyrinthine segment are the narrowest portion of the bony facial canal. These areas are most commonly accessed through a MF approach, if hearing preservation is desired (8,17,16). MF decompression and repair of the facial nerve has been offered to patients at risk for a poor long-term outcome with good results in published series, 66.7 to 100% of patients improved to normal or near normal facial function (HB I or II) (3,9,10,22–29), compared with a 53% rate of recovery for patients who were observed (40).

Data on patient's recovery without surgery in the setting of traumatic paralysis with poor prognosis on electrical testing is lacking, but our results demonstrate 7 of 18 patients (38.9%) meeting electrodiagnostic criteria were diagnosed intraoperatively with irreversible facial nerve injuries. This shows that these patients, who are at high-risk of having a nerve transection and long-term complete paralysis (HB V or VI), therefore, surgical treatment is recommended in every case and definitely appropriate. Designing a study with matched controls to test these patients' recovery without surgery would be unethical because it would involve withholding a treatment that is known to be effective.

The current study supports MF facial nerve decompression and repair in patients with traumatic facial nerve paralysis who are at high-risk for a poor long-term facial nerve outcome. In this group of patients that met the electrodiagnostic criteria for severe dysfunction and were surgically decompressed within 14 days from their trauma, the course of the facial nerve was evaluated. Those patients with an intact facial nerve (n = 11) had a 72.7% rate of regaining normal or near normal facial function (HB I or II) within 1 year after surgery. For those patients with irreversible injuries (n = 7), nerve grafting was performed and all of these patients achieved a HB III, which is consistent with the reported literature (33,41).

Timing from the onset of facial paralysis to decompression surgery was important for patients in the current study. Regression analysis showed a statistically significant improvement in final HB grade the earlier the decompression was performed. All patients in the current study underwent decompression surgery within 14 days and those who were operated on earlier had the best long-term outcomes. Fisch initially recommended immediate decompression within 6 to 10 days, if electrical criteria were met (10,30). Hato et al. (31) also looked at timing of surgery for a traumatic facial nerve paralysis and demonstrated there was a 93% rate of a good recovery (HB I and II) if they underwent decompressive surgery within 2 weeks versus only a 63% rate of achieving good recovery if they underwent surgery after 2 weeks. Other studies have not supported these findings (22,23). Thus, there is controversy regarding the timing for decompression surgery and facial nerve repair, however, surgical intervention for traumatic facial nerve paralysis is recommended within 14 days of the injury if surgical criteria is met, but, patients who present after this time frame and meet surgical criteria, may still benefit from decompression.

Our results are limited due to an absence of control patients and that reported data to indicate how these patients with poor prognosis on electrical testing would do without decompressive surgery is limited. Patients with irreversible injuries would likely have devastating long-term facial paralysis with little to no recovery of facial function, however, the remaining patients may improve with conservative measures and the rate of recovery is not well known. In addition, there may be selection bias in our study, because patients medically stable enough to be worked-up and undergo early decompression surgery within 14 days may have less severe skull base trauma and facial nerve injuries.

Reviewing one's own results can be quite educational (and sometimes humbling). The senior author (CS) previously felt that the timing of the treatment of traumatic facial paralysis was not critical. His previous primary surgical goal was to identify and treat neural injury, rather than perform facial nerve decompression, as is done in Bell's palsy. Based on the results of this study, we will now manage patients with a complete immediate facial paralysis from temporal bone fracture and who meet electrical testing result criteria, with the goal to operate as soon as they are medically stable.

For patients who experience facial nerve paralysis secondary to temporal bone trauma and have poor

TABLE 3. *Results of patients' hearing tests*

	Average	Range	Difference in preop to postop
Preop air PTA	57.9 dB	25–100 dB	–
Preop bone PTA	20.4 dB	4–39 dB	–
Postop air PTA	23.3 dB	5–55 dB	+2.9 dB ($p = 0.44$)
Postop bone PTA	21.2 dB	5–40 dB	+0.8 dB ($p = 0.63$)
Preop WRS	88.1%	12–100%	–
Postop WRS	91.4%	12–100%	+3.3% ($p = 0.74$)

prognosis, MF decompression offers good long-term facial nerve outcomes. In cases with irreversible facial nerve injury, nerve grafting offers beneficial results when performed with MF decompression. Surgery should ideally be performed within 14 days of the onset of traumatic facial nerve paralysis, however, patients who present after this time frame and meet surgical criteria, may still benefit from decompression. Decompression in patients over 60 years should be performed to identify those patients with irreversible injuries, but these patients may not improve as much as their younger counterparts. In summary, MF decompression and repair is safe, effective, and provides good long-term facial nerve outcomes in patients with traumatic facial nerve paralysis and poor prognosis on electrical testing.

CONCLUSION

In this series, all patients with traumatic complete paralysis and poor facial prognosis on electrical testing achieved a long-term outcome of HB III or better after MF approach for decompression and repair of the facial nerve. Surgical criteria for decompression includes immediate-onset, complete paralysis (HB VI), >90% degeneration on ENoG, and absent voluntary EMG potentials. When a patient is stable after trauma, surgery is ideally performed within 14 days of trauma, with earlier decompression showing the best results. The current study further supports the safety and efficacy of the MF approach, demonstrating long-term facial nerve outcomes of HB III or better and minimal morbidity in these high-risk trauma patients with facial paralysis.

REFERENCES

1. Blake DM, Tomovic S, Jyung RW. Temporal bone fracture. *Ear Nose Throat J* 2014;93:16–25.
2. Johnson F, Semaan MT, Megerian CA. Temporal bone fracture: evaluation and management in the modern era. *Otolaryngol Clin North Am* 2008;41:597–618.
3. Brodie HA, Thompson TC. Management of complications from 820 temporal bone fractures. *Am J Otol* 1997;18:188–97.
4. Nash JJ, Friedland DR, Boorsma KJ, Rhee JS. Management and outcomes of facial paralysis from intratemporal blunt trauma: a systematic review. *Laryngoscope* 2010;120:1397–404.
5. Maiman DJ, Cusick JF, Anderson AJ, Larson SJ. Nonoperative management of traumatic facial nerve palsy. *J Trauma* 1985;25:644–8.
6. Adour KK, Boyajian JA, Kahn ZM, Schneider GS. Surgical and nonsurgical management of facial paralysis following closed head injury. *Laryngoscope* 1977;87:380–90.
7. Ho AL, Scott AM, Klassen AF, Cano SJ, Pusic AL, Van Laeken N. Measuring quality of life and patient satisfaction in facial paralysis patients: a systematic review of patient-reported outcome measures. *Plast Reconstr Surg* 2012;130:91–9.
8. Gordin E, Lee TS, Ducic Y, Arnaoutakis D. Facial nerve trauma: evaluation and considerations in management. *Craniomaxillofac Trauma Reconstr* 2015;8:1–13.
9. Lambert PR, Brackmann DE. Facial paralysis in longitudinal temporal bone fractures: a review of 26 cases. *Laryngoscope* 1984;94:1022–6.
10. Fisch U. Facial paralysis in fractures of the petrous bone. *Laryngoscope* 1974;84:2141–54.
11. Fisch U. Prognostic value of electrical tests in acute facial paralysis. *Am J Otol* 1984;5:494–8.
12. Gantz BJ, Gmuer AA, Holliday M, Fisch U. Electroneurographic evaluation of the facial nerve. Method and technical problems. *Ann Otol Rhinol Laryngol* 1984;93:394–8.
13. House JW, Brackmann DE. Facial nerve grading system. *Otolaryngol Head Neck Surg* 1985;93:146–7.
14. Sillman JS, Niparko JK, Lee SS, Kileny PR. Prognostic value of evoked and standard electromyography in acute facial paralysis. *Otolaryngol Head Neck Surg* 1992;107:377–81.
15. Fisch U. Current surgical treatment of intratemporal facial palsy. *Clin Plast Surg* 1979;6:377–88.
16. Coker NJ, Kendall KA, Jenkins HA, Alford BR. Traumatic intratemporal facial nerve injury: management rational for preservation of function. *Otolaryngol Head Neck Surg* 1987;97:262–9.
17. Coker NJ. Management of traumatic injuries to the facial nerve. *Otolaryngol Clin North Am* 1991;24:215–27.
18. Ge XX, Spector GJ. Labyrinthine segment and geniculate ganglion of facial nerve in fetal and adult human temporal bones. *Ann Otol Rhinol Laryngol Suppl* 1981;90:1–12.
19. Yamamoto E, Fisch U. Experimentally induced facial nerve compression in cats. *Acta Otolaryngol* 1975;79:390–5.
20. House WF. Surgical exposure of the internal auditory canal and its contents through the middle cranial fossa. *Laryngoscope* 1961;71:1363–85.
21. House WF. Middle cranial fossa approach to the petrous pyramid. Report of 50 cases. *Arch Otolaryngol* 1963;78:460–9.
22. Ulug T, Arif Ulubil S. Management of facial paralysis in temporal bone fractures: a prospective study analyzing 11 operated fractures. *Am J Otolaryngol* 2005;26:230–8.
23. Quaranta A, Campobasso G, Piazza F, Quaranta N, Salonna I. Facial nerve paralysis in temporal bone fractures: outcomes after late decompression surgery. *Acta Otolaryngol* 2001;121:652–5.
24. Brodsky L, Eviatar A, Daniller A. Post-traumatic facial nerve paralysis: three cases of delayed temporal bone exploration with recovery. *Laryngoscope* 1983;93:1560–5.
25. Yetiser S, Hidir Y, Gonul E. Facial nerve problems and hearing loss in patients with temporal bone fractures: demographic data. *J Trauma* 2008;65:1314–20.
26. Darrouzet VDJ, Liguoro D, Truilhe Y, De Bonfils C, Bebear JP. Management of facial paralysis resulting from temporal bone fractures: our experience in 115 cases. *Otolaryngol Head Neck Surg* 2001;125:77–84.
27. Cannon CR, Jahrsdoerfer RA. Temporal bone fractures. Review of 90 cases. *Arch Otolaryngol* 1983;109:285–8.
28. Nosan DK, Benecke JE Jr, Murr AH. Current perspective on temporal bone trauma. *Otolaryngol Head Neck Surg* 1997;117:67–71.
29. Tos M. Course of and sequelae to 248 petrosal fractures. *Acta Otolaryngol* 1973;75:353–4.
30. Fisch U. Management of intratemporal facial nerve injuries. *J Laryngol Otol* 1980;94:129–34.
31. Hato N, Nota J, Hakuba N, Gyo K, Yanagihara N. Facial nerve decompression surgery in patients with temporal bone trauma: analysis of 66 cases. *J Trauma* 2011;71:1789–93.
32. Alford BR, Sessions RB, Weber SC. Indications for surgical decompression of the facial nerve. *Laryngoscope* 1971;81:620–35.
33. Ozmen OA, Falcioni M, Lauda L, Sanna M. Outcomes of facial nerve grafting in 155 cases: predictive value of history and preoperative function. *Otol Neurotol* 2011;32:1341–6.
34. Quist TS, Givens DJ, Gurgel RK, Chamoun R, Shelton C. Hearing preservation after middle fossa vestibular schwannoma removal: are the results durable? *Otolaryngol Head Neck Surg* 2015;152:706–11.
35. Cannon RB, Gurgel RK, Warren FM, Shelton C. Facial nerve outcomes after middle fossa decompression for Bell's palsy. *Otol Neurotol* 2015;36:513–8.

36. Shelton C, Brackmann DE, House WF, Hitselberger WE. Middle fossa acoustic tumor surgery: results in 106 cases. *Laryngoscope* 1989;99:405–8.
37. McCullah P. Regression models for ordinal data. *J R Stat Soc Ser B* 1980;42:109–42.
38. Agresti A. *Analysis of Ordinal Categorical Data*, Second Edition. New Jersey: John Wiley & Sons, Inc; 2010. pp. 44–80.
39. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.
40. Turner JWA. Facial palsy in closed head injuries. *Lancet* 1944;246:756–7.
41. Falcioni M, Taibah A, Russo A, Piccirillo E, Sanna M. Facial nerve grafting. *Otol Neurotol* 2003;24:486–9.

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Cochlear Implantation Versus Auditory Brainstem Implantation in Bilateral Total Deafness After Head Trauma: Personal Experience and Review of the Literature

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Objective: To determine the effectiveness of cochlear implant (CI) in hearing restoration after temporal bone (TB) fractures and investigate the adequacy of auditory brainstem implant (ABI) indication for TB fractures.
Study Design: Retrospective clinical study; a systematic review of the literature in PubMed was also performed to identify all published cases of bilateral TB fractures or bilateral deafness after head trauma treated by means of CI or ABI.
Settings: Quaternary otology and skull base surgery referral center.
Patients: Eleven consecutive patients presented with bilateral severe-to-profound sensorineural hearing loss after head trauma.
Interventions: CI as primary intervention or following a previous treatment.
Main Outcome Measures: CI performances were evaluated in the auditory-only condition in both closed-set and open-set formats.
Results: Fourteen CI were placed, 11 as primary treatment and 3 after ABI failure. At the last follow-up, all patients gained useful open-set speech perception. In secondary CI, all patients obtained better auditory results with the CI if compared with ABI. CI performance did not decrease with time in any case.
Conclusion: Cochlear implantation after TB fractures has proved to have excellent audiometric results. The aim of the initial evaluation of a patient with bilateral anacoustic ears from head trauma should always be to rehabilitate their hearing with a CI. The incidence of labyrinthitis ossificans, negative electrophysiologic testing, the risk of postoperative meningitis or facial nerve stimulation should not be the determinant factors that favor ABI placement. **Key Words:** Auditory brainstem implant—Cochlear implant—Head trauma—Temporal bone fracture.
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Temporal bone (TB) fractures occur in 22% of head traumas. The fracture line may involve functionally important structures, including the fallopian canal, the internal auditory canal (IAC) and the anterior and posterior labyrinth. Otic capsule involvement arguably carries a high risk of severe loss of cochlear and vestibular function (1). Bilateral TB fractures with otic capsule involvement expose patients to a high risk of bilateral deafness and meningitis. Hearing loss may also follow traumatic head injury without evidence of fractures (2). Cochlear implants (CI) have been used as effective means for hearing rehabilitation in patients with TB fractures and head trauma related sensorineural hearing loss (SNHL) (3–8). However, some authors choose auditory brainstem implants (ABI) in bilateral TB fractures treatment, even when CI placement is possible. (9).

Reasons for considering bilateral TB fractures as extended indications for ABI are unsatisfactory CI results because of possible cochlear nerve damage, labyrinthitis ossificans, or facial nerve stimulation (10–13). Another reported drawback is that CI surgery could be challenging because of displaced fracture lines than may impede electrode insertion (6). Furthermore, some authors state that transverse fractures may lead to loss of spiral ganglion cells over time (14), and progressive decrease of CI results.

Feasibility of CIs depends on three factors: 1) patency and integrity of the cochlea, 2) integrity of cochlear nerve, and 3) functional neural connection between these 2 entities.

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Patients with bilateral severe-to-profound SNHL should primarily undergo clinical and radiologic evaluation aiming for CI placement, leaving ABI as a second option (9). In addition, CIs give better and more predictable results than ABI (15).

The aim of this study was to report the authors' experience on the management of bilaterally deaf patients after head trauma; summarize current results reported in the literature; and discuss the role of ABI in this setting, previous experience, results, and possible indications.

MATERIALS AND METHODS

This retrospective study was approved by the local institutional review board; all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Patients were included if they presented with bilateral severe-to-profound SNHL after head trauma (with or without radiologic evidence of TB fracture) and were treated with a CI as primary or secondary modality.

Patients' charts and imaging data were systematically reviewed for causes of deafness, fracture location, cochlear patency, and IAC integrity, together with hearing performance and treatment results.

Systematic review of the literature in PubMed was performed to identify all the cases of bilateral TB fracture, or patients bilaterally deafened by head trauma, treated by means of CI or ABI. Filters were ''human'' and language ''English, Spanish, Italian, French.''

Postoperative auditory performances were evaluated in the auditory-only condition in both closed- set (vowel identification) and open-set formats (bisyllabic word recognition, sentence recognition, and common phrase comprehension) with monitored live voice through the sound field at a level of 70 dB sound pressure level. Hearing results are reported as measured at the last available follow-up visit. The protocol used for audiologic evaluation is described elsewhere (16).

RESULTS

Patients

A total of 11 patients fitting inclusion criteria were identified. There were 8 men and 3 women, with an average age at implantation of 51 years (range, 19–62 yr). In total, 14 CI were placed, 11 as primary treatment, and 3 as secondary treatment after ABI failure. All patients underwent high-resolution computed tomography scan (HRCT) of the TB, and magnetic resonance imaging (MRI) was obtained in 9 of 11 patients. Complete clinical management data and audiologic results are presented in Tables 1 and 2.

Fractures

HRCT scan showed bilateral TB fractures in 6 patients (54.5%), unilateral fracture in 3 patients (27%), and no fracture lines in 2 patients (18%). When analyzing the structures involved by the fracture line, the vestibule was affected in 80% (12/15) cases, the cochlea in 40% (6/15) cases, jugular foramen in 26% (4/15) cases, semicircular canals in 20% (3/15) cases, and IAC in 6% (1/15) case (Figs. 1, 2, and 3).

Patients Primarily Treated With CI

Eight patients (D–K) received CI as the primary and only treatment. To prevent the risk of meningitis, a subtotal petrosectomy was performed with all implantations in which a fracture line in the otic capsule was evident. We did not encounter any difficulties while inserting the electrodes. There was 1 case of preoperative meningitis (patient G). A preoperative cerebrospinal fluid leak occurred in 1 patient that was successfully surgically treated (patient E). All patients were enrolled in the *Streptococcus pneumonie.* vaccination program (Table 1).

One patient (patient D) received bilateral simultaneous cochlear implantation, and 2 patients (patients G and I) received bilateral staged implantation.

All patients obtained open-set abilities.

Patients Previously Treated With an ABI

Three patients (patients A, B, and C) had been previously treated in another center with an ABI; these patients were evaluated for the poor results obtained with their brainstem implants. A comprehensive radiologic evaluation was performed; MRI confirmed the presence and continuity of VIII cranial nerve bilaterally and complete cochlear patency in at least 1 side in the 3 cases. On these basis, they underwent insertion of CI on the contralateral side to the ABI (2 cases; patients A and C) and ipsilateral to the ABI (1 case; patient B) (Table 2; Fig. 4).

All 3 patients obtained better auditory results with the CI if compared with the ABI (Fig. 5). Only patient B had a poor result with CI (30% of open set speech recognition), but it was still superior to the ABI outcomes.

Stability of Audiologic Results With Time

Figure 6 compares audiologic CI results for each patient at 6 months and at the last available follow-up, showing that CI performance does not decrease with time in fractured ears. Mean follow-up is 53 months (range, 16–156 mo).

Systematic Review of the Literature: CI for Hearing Restoration in Head Trauma

Tables 3 and 4 summarize literature review results for CI in patients bilaterally deafened by head trauma. Table 3 shows fracture location, side of implantation, and detailed hearing results for the largest series of CI. Table 4 shows the same data for the most recent case reports, which are also mentioned along the discussion of this article. There is 1 case of bilateral simultaneous CI (17) and 2 cases of bilateral staged CI (3,18).

CI results are tough to summarize because of the heterogeneity of auditory evaluation tests, but the most patients achieved satisfactory results both objectively and subjectively.

Systematic Review of the Literature: ABI for Hearing Restoration in Head Trauma

After detailed revision of the articles retrieved by PubMed search engine, only 3 reports (10–12) were identified wherein

TABLE 1. *Summary of patients primarily treated with cochlear implant in our centers*

Patient	Fig	Hearing status and etiology	Fracture location (computed tomographic scan)	Magnetic resonance imaging	Treatment	Results (VI:BWR:SR:C) (Last follow-up)	Complications
D	1C	Bilateral anacoustic Head trauma	R: Vestibule L: Vestibule	Bilateral cochlear patency and intacts cochlear nerves	Bilateral simultaneous CI + bilateral SP	At 31 mo[a] 100:85:100:100	No
E	1D	Bilateral anacoustic Head trauma with rhinoliquorrhea and bilateral sudden HL 15 days later	R: Vestibule and SCC L: Vestibule and SCC	Bilateral cochlear patency and intact cochlear nerves	CI left side + SP	At 60 mo 100:80:100:100	No
F		Profound bilateral SNHL Head trauma	R: Extralabyrinthine (JF) L: Extralabyrinthine (JF)	Bilateral cochlear patency and intact cochlear nerves	CI right side + SP	At 48 mo 100:100:100:100	No
G	1A 3	Bilateral anacoustic Head trauma	R: C, V, SCC L: No visible fracture	Bilateral cochlear patency and intact cochlear nerves	CI left side Staged CI right side + SP	At 156 mo[a] 100:100:100:100	No
H		Bilateal profound SNHL Head trauma	R: No visible fracture L: No visible fracture	Bilateral cochlear patency and intact cochlear nerves	CI left side	At 58 mo 94:40:74:65	No
I		Left anacoustic Right profound SNHL Head trauma	R: JF, V and C L: JF, V and C	Bilateral cochlear patency and intact cochlear nerves	CI left side + SP Staged CI right side + SP	Left CI (16 mo) 100:60:77:60 Right CI (activation) 80:30:47:35 Both CIs (at right CI activation) 90:35:76:80	No
J	2	Bilateral anacoustic Head trauma	R: No visible fracture L: C, V, IAC Partial cochlear obliteration on the left side	NA	CI right side	At 68 mo 100:65:94:75	No
K		Bilateral profound SNHL After trauma progressive SNHL	R: C, V L: Vestibule	NA	CI right side + SP	At 54 mo 100:75:79:80	No

Pt indicates patient; Fig, figure; VI, vowel identification; BWR, bisyllabic word recognition; SR, sentence recognition; C, common phrases comprehension; R, right; L, left; CI, cochlear implant; SP, subtotal petrosectomy; HL, hearing loss; SCC, semicircular canals; JF, jugular foramen; SNHL, sensorineural hearing loss; V, vestibule; C, cochlea; IAC, internal auditory canal; NA, not available.
[a]With both CIs.

TABLE 2. *Summary of patients previously treated with uuditory brainstem implant in another center*

Pt	Fig	Hearing status and etiology	Fracture location (CT scan)	MRI	First treatment	First treatment results	Second treatment	Second treatment results (VI:BWR:SR:C) last follow up
A		R: Anacoustic Post-meningitis deafness in childhood L: Anacoustic Head trauma in 2006	R: No visible fracture L: Vestibule	Cochlear patency on the right side and partial obliteration on the left side Bilateral intact cochlear nerves	ABI left side in 2006 (other department)	Free-field PTA 55 dB WR 35% with visual and auditory stimulation 6 active electrodes Progressive decrease of results until no use of ABI	CI right side + SP (Parma University 2009)	At 24 months NA:90:90:NA Telephone use
B	4B	Profound bilateral SNHL Head trauma	R: No visible fracture L: No visible fracture	Cochlear patency on the right side and total obliteration on the left side Bilateral intact cochlear nerves	ABI right side 2001 (other department)	After one year 45% open-set SR Progressive decrease of results until no use of ABI	CI right side + SP 2008 (Gruppo Otologico)	At 48 months 0:0:30:0 No telephone use
C	1B 4A	Profound bilateral SNHL Head trauma	R: Promontory L: Vestibule	Bilateral cochlear patency and bilateral intact cochlear nerves	ABI right side 2000 (other department)	After three months 20% open-set SR No use of ABI	CI left side + SP 2010 (Gruppo Otologico)	At 24 months 100:55:69:70 Telephone use with family

Pt indicates patient; Fig, figure; CT, computed tomography; MRI, magnetic resonance imaging; VI, vowel identification; BWR, bisyllabic word recognition; SR, sentence recognition; C, common phrases comprehension; R, right; L, left; ABI, auditory brainstem implant; PTA, pure tone average; WR, word recognition; CI, cochlear implant; SP, subtotal petrosectomy; NA, not available; SNHL, sensorineural Hearing loss.

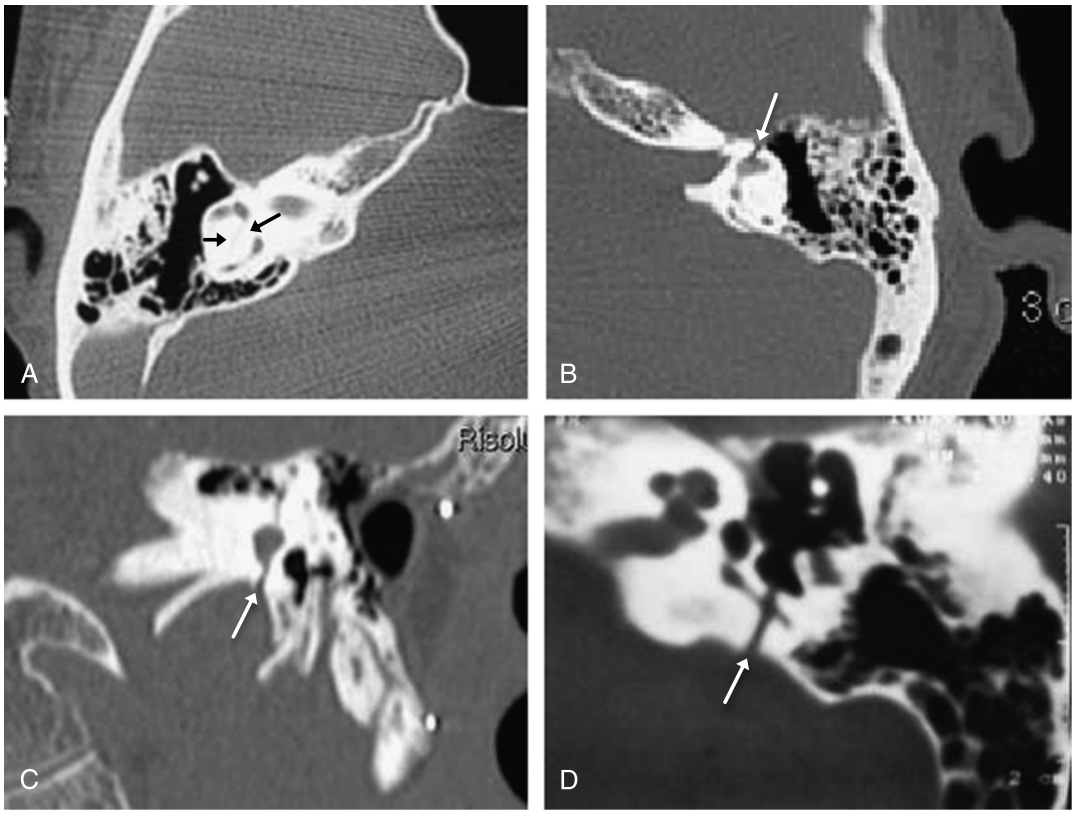

FIG. 1. *A*, CT scan, axial view, right ear. Labyrinthine fracture involving the lateral semicircular canal (*black arrows*). *B*, CT scan, axial view, left ear. Labyrinthine fracture involving the vestibule (*white arrow*). *C*, CT scan, coronal view, left ear. Labyrinthine fracture involving the vestibule (*white arrow*). *D*, CT scan, axial view, left ear. Labyrinthine fracture involving the posterior semicircular canal (*white arrow*).

a total of 7 patients were implanted with an ABI after traumatic deafness. In these series, at 1-year follow-up, 3 patients (50%) failed to achieve satisfactory open set sentence recognition. In the other 3 patients, auditory-alone-mode open-set sentence recognition was 45%, 60%, and 100%, respectively. The authors reported no complications after ABI placement.

Figure 7 illustrates auditory sentence recognition score for ABI and CI for all patients for which numeric data were available in literature review, a clear advantage can

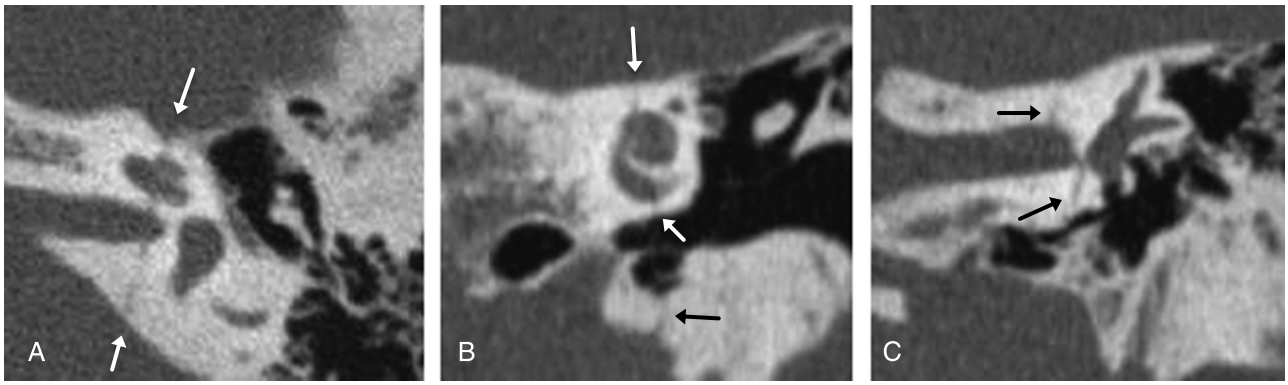

FIG. 2. CT scan of patient J, left ear. *A*, Axial view at the level of the cochlea and IAC showing labyrinthine fracture involving basal and middle turn of the cochlea and IAC fundus (*white arrows*). *B*, Coronal view at the level of the cochlea where it can be appreciated with mayor detail involvement of the basal and middle turns of the cochlea (*white arrows*). The fracture line extends to the hypotympanum (*black arrow*). *C*, Coronal view at the level of the IAC and vestibule showing the fracture line crossing perpendicular to the IAC fundus (*black arrows*).

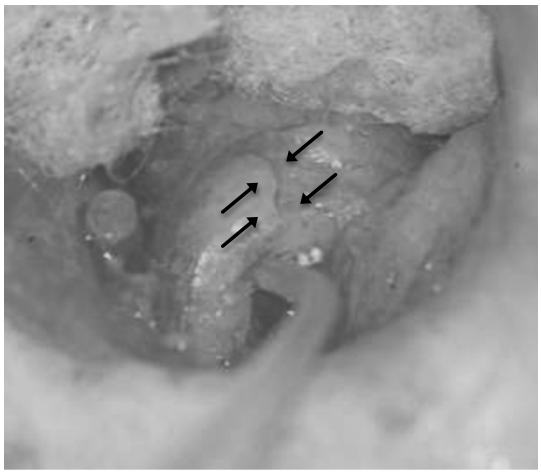

FIG. 3. Right ear. Surgical picture showing CI electrode insertion through RW. Note the fracture line involving the promontory (*black arrows*). CI, cochlear implant; RW, round window.

be observed for CI. This graph must be interpreted with caution because of the heterogeneity of auditory tests between series. Detailed information of each series is

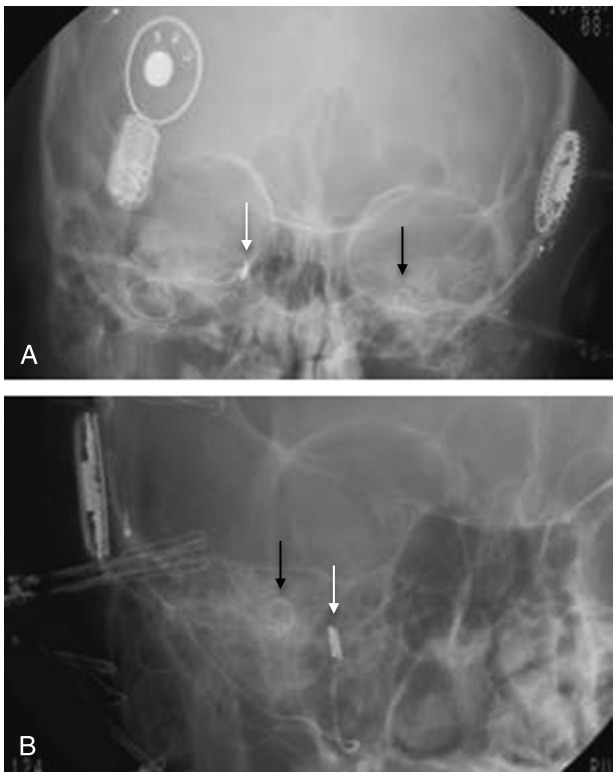

FIG. 4. *A*, X-ray of patient C, showing ABI on the right side (*white arrow*) and CI on the left side (*black arrow*). *B*, X-ray of patient B, showing ABI (*white arrow*) and CI (*black arrow*) on the right side. ABI, auditory brainstem implant. CI, cochlear implant.

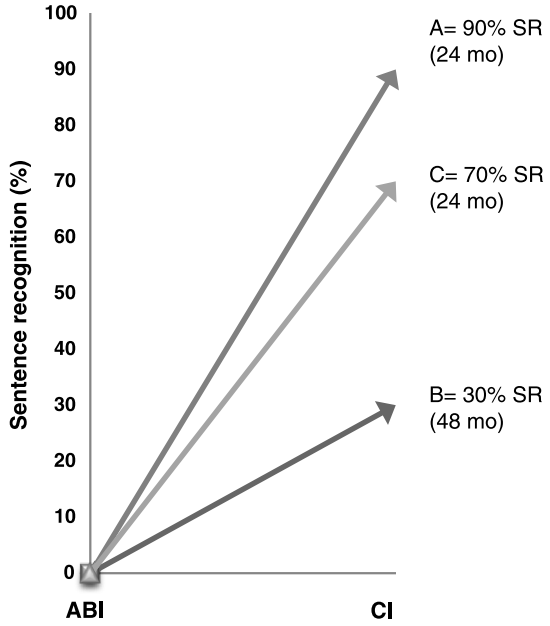

FIG. 5. Open set sentence recognition line plots of patients A, B, and C after first treatment with ABI placed in another department and improvement after second treatment with CI in our department (follow-up). SR, sentence recognition.

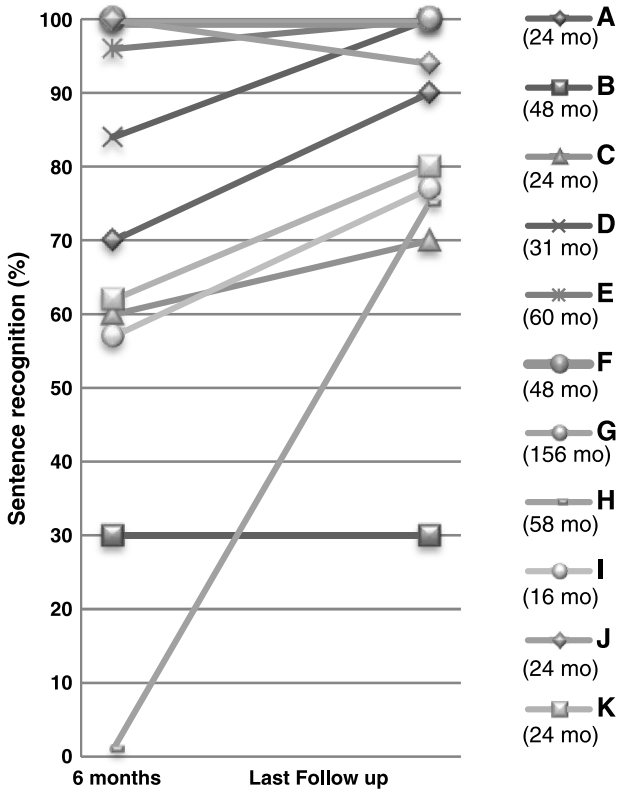

FIG. 6. Stability of audiologic results with time. Open set sentence recognition (SR%) for all the patients at 6 months and at last available follow-up, showing that CI results do not decrease with time. Mean follow-up is 53 months. Last follow-ups are specified below every patient legend in brackets. Mo, months.

TABLE 3. *Review of the literature on the largest series of patients treated with cochlear implantation after bilateral traumatic deafness*

Series (Ref.)	No. of implants	Case	Right ear	Left ear	Treatment	Results (follow-up)
Hagr, 2011 (3)	6	1	Fracture involving cochlea	Fracture involving vestibule	Bilateral staged CI	70% SR[a] (18 mo) Full-time user
		2	Fracture involving vestibule	Fracture involving vestibule	Left CI	90% SR[a] (24 mo)
		3	Fracture involvingotic capsule	Fracture involving otic capsule	Left CI (another centre)	40% SR (36 mo)
		4	Fracture involving cochlea	Fracture involving cochlea	CI (side NS)	SR NS (follow-up NS) Full-time user
		5	No visible fracture	Fracture involving otic capsule	Right CI	70% SR[a] (18 mo)
Greenberg et al., 2010 (4)	11	1	Transverse fracture	Transverse fracture	Right CI	22% CID (12 mo)
		2	No visible fracture	Transverse fracture	Left CI	16% CID (12 mo)
		3	Transverse fracture	Transverse fracture	Left CI	73% CID (12 mo)
		4	No visible fracture	Transverse fracture	Right CI	92% CID (12 mo)
		5	Transverse fracture	No visible fracture	Left CI	NA
		6	No visible fracture	No visible fracture	Right CI	NA
		7	No visible fracture	No visible fracture	Right CI	NA
		8	Transverse fracture	Transverse fracture	Right CI	100% CID (12 mo)
		9	No visible fracture	Transverse fracture	Right CI	88% CID (12 mo)
		10	Transverse fracture	Transverse fracture	Right CI	NA
		11	No visible fracture	No visible fracture	Right CI	100% CID (12 mo)
Serin et al., 2009 (5)	5	1	Transverse fracture involving vestibule	Extralabyrinthine fracture	Left CI	100% 3-syll WR (12 mo) 92% SR open set
		2	No visible fracture	No visible fracture	Right CI	96% 3-syll WR (12 mo) 96% SR open set
		3	Transverse fracture involving vestibule	Transverse fracture involving vestibule	Right CI	100% 3-syll WR (12 mo) 88% SR open set
		4	Transverse fracture involving vestibule	Transverse fracture involving vestibule	Right CI	96% 3-syll WR (12 mo) 84% SR open set
		5	Transverse fracture involving vestibule + cochlea	Transverse fracture involving vestibule + cochlea	Left CI	84% 3-syll WR (12 mo) 80% SR open set
Camilleri et al., 1999 (20)	7	1	No visible fracture	No visible fracture	Right CI	61% BKB (9 mo)
		2	TB fracture, location NS	TB fracture, location NS	Right CI	95% BKB (9 mo)
		3	Fracture involving promontory	No visible fracture	Right CI	68% BKB (9 mo)
		4	Skull base fracture No visible TB fracture	Skull base fracture No visible TB fracture	Right CI	100% BKB (9 mo)
		5	Skull base fracture No visible TB fracture	Skull base fracture No visible TB fracture	Right CI	90% BKB (9 mo)
		6	Skull fracture, location NS	Skull fracture, location NS	Right CI	44% BKB (9 mo)
		7	No visible fracture	Labyrinthine fracture	Right CI	56% BKB (9 mo)

NS indicates not specified; CID, Central Institute for the Deaf Sentence score; NA, not available; 3-syll, trisyllabic; WR, word recognition; BKB, Bamford, Kowal and Bench sentence test; TB, temporal bone.
[a]Reported by the patient.

TABLE 4. *Review of the literature on the most recent case reports of patients treated with cochlear implantation after traumatic bilateral deafness*

Case report	No. of implants	Ref.	Right ear	Left ear	Treatment	Results (follow-up)
Chen and Yin, 2012	1	(6)	Fracture involving cochlea	Fracture involving cochlea	Right CI	Able to use telephone WRS and SRS NS
Zanetti et al., 2010	2	(17)	Fracture involving vestibule	Fracture involving vestibule	Bilateral simultaneous CI	100% WRS[a] (18 mo) 100% SRS[a] (18 mo)
Chung et al., 2010	2	(18)	Labyrinthine fracture involving promontory	Labyrinthine fracture	Bilateral staged CI	RCI: 100% WRS (2 mo) PTA 32 dB LCI: WRS NS PTA 36 dB
Shin et al., 2008	1	(7)	Fracture involving cochlea	Fracture involving cochlea + IAC	Right CI	70% SRS[b] (18 mo)
Simons et al., 2005	1	(8)	Fracture through the otic capsule involving vestibule and PSC	Fracture trough the otic capsule	Left CI	CID 174/200 (6 mo)

WRS indicates word recognition score open set; SRS, sentence recognition score open set; NS, not specified; RCI, right cochlear implant; LCI, left cochlear implant; PTA, pure tone average; dB, decibels; IAC, internal auditory canal; PSC, posterior semicircular canal.

[a]With both CIs.

[b]Understands 70% of the conversation with his/her family.

given in Tables 3 and 4 and in reference (10) for ABI auditory evaluation.

DISCUSSION

Temporal bone fractures occur from high-energy impacts, mainly but not exclusively from car accidents. Various mechanisms have been described in which the forces involved in a temporal bone trauma can account for the auditory damage: 1) direct injury to the acoustic nerve; 2) direct injury to the otic capsule with disruption of the membranous labyrinth, vascular vasospasm, thrombosis, or hemorrhage into the inner ear; 3) perilymphatic fistula; and 4) occlusion of the vestibular aqueduct by the fracture line, with secondary endolymphatic hydrops (19). In addition, 5) pressure waves can be transmitted through the cranial skeleton directly to the cochlea, resulting in damage to the organ of Corti and concussion of the temporal bone without appreciable fracture lines (2).

Cochlear implantation has been demonstrated to be effective for hearing rehabilitation in patients with bilateral TB fractures (3–7,17,18,20). It remains the standard hearing rehabilitation treatment for TB fractures without compromise of the cochlear nerve, with hearing results comparable to other etiologies of deafness (4,20). Results of cochlear implantation remain widely superior and more predictable than ABI results, regardless of the cause of deafness (9). After revising our own experience and performing an extensive literature review, we have found that the hearing outcomes from cochlear implantation in bilateral deafness after head trauma are clearly superior to ABI results. Only in cases where direct trauma to the cochlear nerve is the pathologic mechanism producing hearing loss, rehabilitation with a CI may be unsuccessful. However, total deafness from bilateral cochlear nerve trauma is exceptionally unlikely (21).

Traditionally, the standard indication for ABI was patients aged older than 12 years with neurofibromatosis Type 2 (22). In 2004, Colletti et al. (10) published the first and only series in the literature on ABI to restore hearing after TB trauma. Since then, other authors have also mentioned this possible indication (8,13,17). Recently, it was also included in a consensus statement from a multicenter report of ABI paediatric implantation (23).

Some authors (10,13) suggest an ABI as the treatment of choice in cases of bilateral TB fracture with avulsion of both cochlear nerves. It is questionable whether this severity of traumatism is compatible with life. There is not a single case in the literature of bilateral cochlear nerve

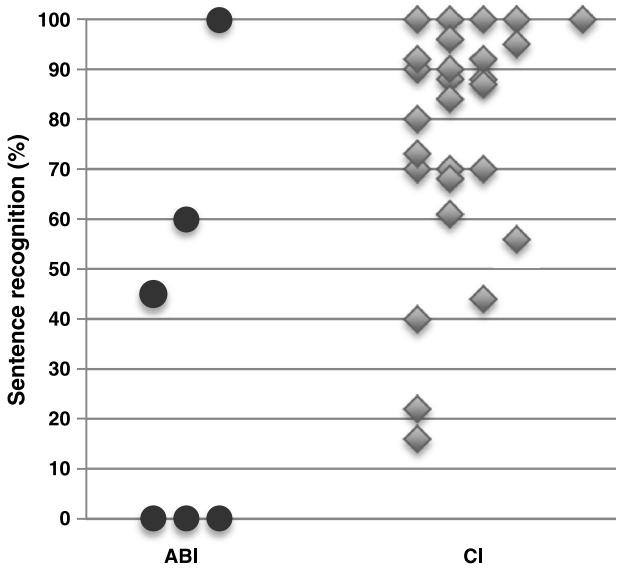

FIG. 7. Comparison of sentence recognition (SR) scores (%) in patients treated with ABI versus CI. For auditory evaluation tests, see references (3–8, 10, 17, 18, and 20).

avulsion after trauma, and the patients that have received an ABI after head trauma (10) had bilaterally intact auditory nerves on MRI, as the authors themselves reported. Only 1 case has been reported with unilateral traumatic avulsion of the VIIth and VIIIth nerve complexes (24). The authors hypothesized that it was the age of the child (3.5 yr) and the immaturity of the skull that permitted lateral displacement of the petrous bone in the occipital trauma, without lethal or serious brain injuries.

Another clinical situation is when the fracture line extends very close or compromises the IAC. In cases of bilateral TB fracture, if there is a radiologic suspicion of extension of the fracture line to the IAC on one side, a CI can be placed on the contralateral side (7) before considering insertion of an ABI. This will provide better hearing outcome. In our series of 15 fractured inner ears, we had only 1 case (6%) of unilateral involvement of the IAC (Fig. 2), this patient was implanted on the contralateral side with satisfactory results. There are no case reports in the literature of bilateral TB fractures involving both IACs.

If a lesion of the VIIIth cranial nerve is suspected, heavily T2-weighted MRI sequences should be obtained (i.e., fast imaging employing steady-state acquisition sequence [FIESTA]). MRI is very sensitive in detecting nerve compression secondary to hematoma, nerve transaction, or axonal injury. Moreover, the FIESTA sequence generates very high signals from tissues with large T2/T1 ratios, making it an ideal scan for cranial nerve assessment at the cerebellopontine angle and IAC (24).

The role of electrophysiologic testing to predict the presence and function of the cochlear nerve prior to CI placement has been largely debated. Positive promontory stimulation test (PST) is correlated with superior speech perception after cochlear implantation, but the absence of PST response does not necessarily indicate the absence of VIIIth cranial nerve function (25,26).

In the presence of bilateral labyrinthine fractures with normal cochlear nerves on MRI, some authors (10) advocate for the insertion of an ABI instead of a CI on the basis of a negative round window test (RWT). They state that this test is more sensitive than promontory stimulation test (PST). This fact that has not been demonstrated in scientific research (27).

To date, the minimum number of ganglion cells required for successful cochlear implantation is still unknown. There has not been any correlation found between the number of surviving ganglion cells and the performance of a CI (28). Postmortem studies show that as few as 3,000 surviving ganglion cells in patients that had useful auditory sensation after cochlear implantation (29).

Similarly, the minimum number of ganglion cells needed to obtain a positive response in PST is unknown. It is possible that the remaining ganglion cells after a TB trauma cannot elicit a response in PST but could be enough for successful cochlear implantation. Therefore, the only reliable way to determine if cochlear implantation will provide benefit is to perform the CI procedure.

We believe that in patients deafened after TB trauma, without evidence of cochlear nerve damage on MRI, it is not indicated to place an ABI based exclusively on the absence of response on electrophysiologic testing. This is a negative result is not demonstrative of the absence of cochlear nerve function (25,26).

Another issue to be considered after a TB fracture is the risk of cerebrospinal fluid (CSF) leak and meningitis. This risk ranges from 2% to 40% for a CSF leak and 12% to 15% for meningitis, depending on the structures involved by the fracture line (30,31). A fracture violating the otic capsule creates a communication between the central nervous system and the middle ear. It is known that the bone of the otic capsule does not heal by callous formation but with a thin layer of fibrous tissue that constitutes the new barrier between the central nervous system and the extradural space (32). Theoretically, this leaves the patient with a permanent risk of CSF leak and meningitis (33).

Some authors (10) advocate that the risk of meningitis precludes placing an electrode inside the cochlea in the presence of fractures crossing the labyrinth. They consider it safer to place an ABI by means of a retrosigmoid approach. However, if there is an active CSF leak, this risk of meningitis can be diminished by using a subtotal petrosectomy (30,33,34) in association with CI insertion. In accordance with these authors, we prefer to perform a double blind sac closure of the external auditory canal, with sealing of the eustachian tube and obliteration of the middle ear cavity with autologous abdominal fat.

Another complication that has been described associated with cochlear implantation in fractured cochleae is a higher incidence of facial nerve stimulation. Camilleri et al. (20) reported this complication in 2 of 7 patients with CI after TB fracture. It is assumed to be caused by electrode stimulation of the facial nerve in the area of geniculate ganglion through the low resistance of the fracture line. In contrast, from our series of 8 cochlear implantations in fractured temporal bones, we had no incidence of facial nerve stimulation; this is consistent with reports by other groups (3,4). In the majority of cases, this complication can be solved by programming adjustments (20) and should not be considered an argument in favor of ABI placement.

One possible mechanism hampering CI insertion may be ossification of the cochlea after trauma (10). As soon as the patient is medically stable, cochlear patency should be evaluated, similar to meningitis patients (9). From reviewing the literature, the incidence of labyrinthitis ossificans after temporal bone fracture and the period needed for new bone formation is relatively unknown (3,7).

Among our 15 fractured inner ears, imaging showed total cochlear obliteration in 1 case and partial obliteration in 2 cases. These patients were implanted on the contralateral side.

Hagr (3) found no cases of labyrinthitis ossificans on MRI from a series of 5 patients with bilateral temporal bone fractures.

Camilleri et al. (20) in his series of 7 patients implanted with CI after bilateral TB fracture, observed unilateral partial obliteration of the basal turn of the cochlea in 2 patients and unilateral total obliteration in 1 patient. The 2 patients with partial obliteration were successfully implanted

and benefited from a CI. The patient with the total obliteration had to be explanted because poor CI performance and facial nerve stimulation. An implantation was then performed on the contralateral side, achieving a satisfactory result. None of these patients had any indication for an ABI.

Greenberg et al. (4) with a total of 13 patients with a CT proven TB fracture, found unilateral labyrinthitis ossificans in 1 patient and bilateral labyrinthitis ossificans in another patient (17.6% incidence of labyrinthitis ossificans in fractured cochleae). The patient with unilateral labyrinthitis ossificans was successfully implanted; no abnormal intraoperative findings were reported. He had a poor outcome with the CI and was lost to follow-up. The patient with bilateral labyrinthitis ossificans was judged not to be suitable candidate for implantation because of the severity of his brain injuries and subsequent cognitive deficit.

It is our belief that the correct indication for an ABI in advanced cochlear obliteration is if no lumen is found after a drill-out attempt (35).

The only case described in the literature of complete bilateral cochlear ossification was assessed only by means of CT scan. Moreover, because of his brain sequelae, this patient was not considered candidate for implantation. Therefore, this indication of ABI remains theoretical.

The idea that fractures involving the cochlea may present with difficult CI electrode insertion because of distorted anatomy and fracture line displacement is widely reported in the literature. In this report, we have 6 cases of fractured cochleae, four of them underwent CI placement (patients G and K single-sided and patient I bilaterally). We did not encounter any difficulty during CI insertion (Fig. 3), and patients achieved sentence recognition ranging from 70% to 100% (mean follow-up of 75 mo; range, 16–156 mo). In a literature review, we identified 6 cases with fractures involving the cochlea being implanted ipsilaterally; authors report successful CI insertion and similar results to our series, ranging from 70% to 100% for sentence recognition (3,5–7,18).

Fractures that damage the cochlea may lead to the loss of spiral ganglion cells over time. (14). Some authors state that these secondary postganglionic injuries could cause the CI to fail (6) or decrease the results with the passage of time. The risk of osteoneogenesis, after hemorrhage in the cochlea, has also been postulated as other possible mechanism of decreased CI performance (10). In contrast to these observations, we have not experienced a decrease in the hearing performance in any of our patients with the passage of time (Fig. 6).

CONCLUSION

Cochlear implantation after TB fractures has proven to have excellent audiometric results. These results are clearly superior to ABI and comparable with other etiologies of deafness. The aim of the initial evaluation of a patient with bilateral anacoustic ears from head trauma should always be to rehabilitate their hearing with a CI. The incidence of labyrinthitis ossificans, negative electrophysiologic testing, the risk of postoperative meningitis, or facial nerve stimulation should not be the determinant factors that favor ABI placement. If cochlear nerve damage is suspected on MRI, cochlear implantation should be performed on the contralateral side. Therefore, ABI may be indicated in TB fractures when cochlear implantation has failed to provide a hearing benefit or CI insertion was not successful because of cochlear ossification. In addition, brainstem implants may have a theoretical role in patients with petrous bone fractures associated with transection of both cochlear nerves. As far as we know, such cases have never been described in the literature and probably are not compatible with life. After literature review and our own experience of 30 years of being a quaternary otologic referral center, we have not identified a single case in which an ABI was a correct indication for hearing restoration after a bilateral TB fracture.

REFERENCES

1. Little SC, Kesser BW. Radiographic classification of temporal bone fractures: clinical predictability using a new system. *Arch Otolaryngol Head Neck Surg* 2006;132:1300–4.
2. Hough JV, Stuart WD. Middle ear injuries in skull trauma. *Laryngoscope*1968;78:899–937.
3. Hagr A. Cochlear implantation in fractured inner ears. *J Otolaryngol Head Neck Surg* 2011;40:281–7.
4. Greenberg S, Shipp D, Lin V, et al. Cochlear implantation in patients with bilateral severe sensorineural hearing loss after major blunt head trauma. *Otol Neurotol* 2010;32:48–54.
5. Serin G, Derinsu U, Sari M, et al. Cochlear implantation in patients with bilateral cochlear trauma. *Am J Otol* 2010;31:350–5.
6. Chen ZN, Yin SK. Cochlear implantation in a patient with bilateral temporal bone fractures resulting from temporomandibular joint surgery. *Chin Med J (Engl)* 2012;125:4160.
7. Shin JH, Park S, Baek S, et al. Cochlear implantation after bilateral transverse temporal bone fractures. *Clin Exp Otorhinolaryngol* 2008;1:171–3.
8. Simons JP, Whitaker ME, Hirsch EB. Cochlear implantation in a patient with bilateral temporal bone fractures. *Otolaryngol Head Neck Surg* 2005;132:809–11.
9. Merkus P, Di Lella FD, Di Trapani GD. Indications and contraindications of auditory brainstem implants: systematic review and illustrative cases. *Eur Arch Otorhinolaryngol* Doi:10.1007/s00405-013-2378-3. 2013 Feb 13.
10. Colletti V, Carner M, Miorelli V, et al. Auditory brainstem implant in posttraumatic cochlear nerve avulsion. *Audiol Neurootol* 2004; 9:247–55.
11. Colletti V, Carner M, Miorelli V, et al. Auditory brainstem implant (ABI): new frontiers in adults and children. *Otolaryngol Head Neck Surg* 2005;133:126–38.
12. Colletti V, Shannon R, Carner M, et al. Outcomes in nontumor adults fitted with the auditory brainstem implant: 10 years' experience. *Otol Neurotol* 2009;30:614–8.
13. Sennaroglu L, Ziyal I. Auditory brainstem implantation. *Auris Nasus Larynx* 2012;39:439–50.
14. Morgan WE, Coker NJ, Jenkins HA, et al. Histopathology of temporal bone fractures: implications for cochlear implantation. *Laryngoscope* 1994;104:426–32.
15. Sanna M, Di Lella F, Guida M, et al. Auditory brainstem implants in NF2 patients: results and review of the literature. *Otol Neurotol* 2012;33:154–64.
16. Vincenti V, Pasanisi E, Guida M, et al. Hearing Rehabilitation in Neurofibromatosis Type 2 Patients: Cochlear versus Auditory Brainstem Implantation. *Audiol Neurotol* 2008;13:273–80.

17. Zanetti D, Campovecchi CB, Pasini S. Binaural cochlear implantation after bilateral temporal bone fractures. *Int J Audiol* 2010;49:788–93.
18. Chung J, Shin M, Min H, et al. Bilateral cochlear implantation in a patient with bilateral temporal bone fractures. *Am J Otol* 2011;32:256–8.
19. Lyos AT, Marsh MA, Jenkins HA, et al. Progressive hearing loss after transverse temporal bone fracture. *Arch Otolaryngol Head Neck Surg* 1995;121:795–9.
20. Camilleri AE, Toner JG, Howarth KL, et al. Cochlear implantation following temporal bone fracture. *J Laryngol Otol* 1999;113:454–7.
21. Merkus P, Free RH, Sanna M. Auditory brainstem implant indications. *Auris Nasus Larynx* 2013;40:113–4.
22. Kuchta J. Twenty-five years of auditory brainstem implants: perspectives. *Acta Neurochir Suppl* 2007;97:443–9.
23. Sennaroglu L, Colleti V, Manrique M. Auditory Brainstem Implantation in Children and Non-Neurofibromatosis Type 2 Patients: A Consensus Statement. *Otol Neurotol* 2011;32:187–91.
24. Corrales CE, Monfared A, Jackler RK. Facial and vestibulocochlear nerve avulsion at the fundus of the internal auditory canal in a child without a temporal bone fracture. *Otol Neurotol* 2010;31:1508–10.
25. Song MH, Kim SC, Kim J, et al. The cochleovestibular nerve identified during auditory brainstem implantation in patients with narrow internal auditory canals: can preoperative evaluation predict cochleovestibular nerve deficiency? *Laryngoscope* 2011;121:1773–9.
26. Kuo SC, Gibson WP. The role of promontory stimulation test in cochlear implantation. *Cochlear Implants Int* 2002;3:19–28.
27. Kileny PR, Zwolan T, Zimmerman-Phillips S, et al. A comparison of round window and transtympanic promontory electrical stimulation in cochlear implant candidates. *Ear Hear* 1992;13:294–9.
28. Nadol JB, Eddington DK. Histopathology of the inner ear relevant to cochlear implantation. *Adv Otorhinolaryngol* 2006;64:31–49.
29. Linthicum FH, Fayad J, Otto SR. Cochlear implant histopathology. *Am J Otol* 1991;12:245–311.
30. Magliulo G, Ciniglio M, Iannella G, et al. Petrous bone fractures violating otic capsule. *Otol Neurotol* 2012;33:1558–61.
31. Brodie HA, Thompson TC. Management of complications from 820 temporal bone fractures. *Am J Otol* 1997;18:188–97.
32. Pearlmann HB. Process of healing in injuries of the capsule of labyrinth. *Arch Otolaryngol* 1939;29:287–305.
33. Fisch U, Mattox D. Subtotal petrosectomy. In: *Microsurgery of the Skull Base*. New York, NY: Thieme Publishers, 1988:4–68.
34. Free RH, Falcioni M, Di Trapani G, et al. The role of subtotal petrosectomy in cochlear implant surgery—a report of 32 cases and review on indications. *Otol Neurotol* 2013;34:1033–40.
35. Sanna M, Khrais T, Guida M, et al. Auditory brainstem implant in a child with severely ossified cochlea. *Laryngoscope* 2006;116:1700–1703.

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Audiometric Outcomes in Pediatric Temporal Bone Trauma

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Abstract

Objective. To characterize pediatric temporal bone trauma, focusing on audiometric outcomes.

Study Design. Case series with chart review.

Setting. Tertiary care children's hospital.

Subjects and Methods. Cases were reviewed of children (<18 years) presenting over a 3-year period with computed tomography–proven temporal bone fracture and audiology examination. All scans were read by a neuroradiologist and reviewed by a pediatric otolaryngologist. Demographics, fracture pattern, and audiometric data were recorded.

Results. Fifty-eight patients (60 fractures) met inclusion criteria. The majority (93%) were otic capsule–sparing fractures. The types and severity of hearing loss were significantly different between the 2 fracture patterns. Based on pure-tone average, all otic capsule–violating fractures had abnormal initial audiograms; 75% of these losses were severe. Approximately half (54%) of otic capsule–sparing fractures had abnormal initial audiograms; a majority were mild losses (85%). All classifiable losses in otic capsule–violating cases were of mixed type, whereas the majority (75%) of losses in otic capsule–sparing cases were conductive. Regardless of classification, 72% of patients with otic capsule–sparing fractures and initially abnormal audiograms improved to normal levels at a mean of 48 days posttrauma; this increased to 83% when only conductive losses were considered.

Conclusions. Hearing loss type and severity differ in otic capsule–sparing and otic capsule–violating temporal bone fractures. A majority of children with otic capsule–sparing fractures and associated hearing loss improve to normal levels in about 6 weeks, especially if the original loss is classified as solely conductive. Children who do not improve within this time frame may warrant early investigation into surgically correctable causes.

Keywords

temporal bone fracture, otic capsule–violating, otic capsule–sparing, conductive hearing loss, sensorineural hearing loss, mixed hearing loss

Temporal bone fractures are the most common type of skull base fracture in pediatric trauma.[1] The potential complications associated with temporal bone fractures are myriad, including facial nerve paresis and other cranial nerve palsies, sensorineural hearing loss (SNHL), conductive hearing loss (CHL), balance disturbances, tinnitus, cerebrospinal fluid leaks, meningocele, encephalocele, cholesteatoma, and meningitis.[2] Additionally, fractures of the skull base are potentially fatal. Head injury is one of the leading causes of death in the pediatric age group.[1]

Although temporal bone trauma and its related effects are common among pediatric patients, literature regarding audiometric outcomes in this age group is lacking. Additionally, many protocols used to manage the aforementioned complications are derived from adult patient experience.[1] Aspects of temporal bone and other skull base trauma may be fundamentally different among younger patients due to differing skull flexibility.[3]

Hearing loss is a common consequence of temporal bone trauma that may have special implications in the pediatric population. Thirty-one percent of children with even unilateral SNHL have been shown to ''experience scholastic or behavioral problems at school.''[4] Early recognition of hearing loss, especially in children, is imperative and can greatly decrease associated morbidity.[5]

Historically, temporal bone fractures have been described in terms of the fracture axis in relation to the long axis of the petrous bone, as either transverse or longitudinal. Even when an oblique category is included, this system insufficiently describes many clinically observed fractures.[6] Additionally, this system correlates poorly with clinical outcomes.[7,8] For these reasons, multiple other classification

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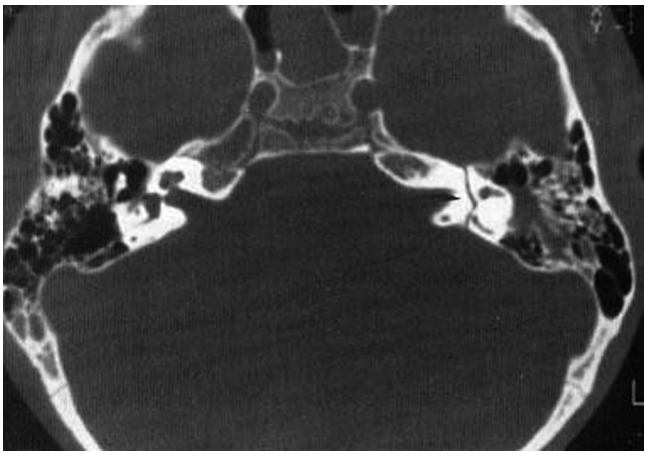

Figure 1. Otic capsule–violating fracture: representative axial computed tomography image.

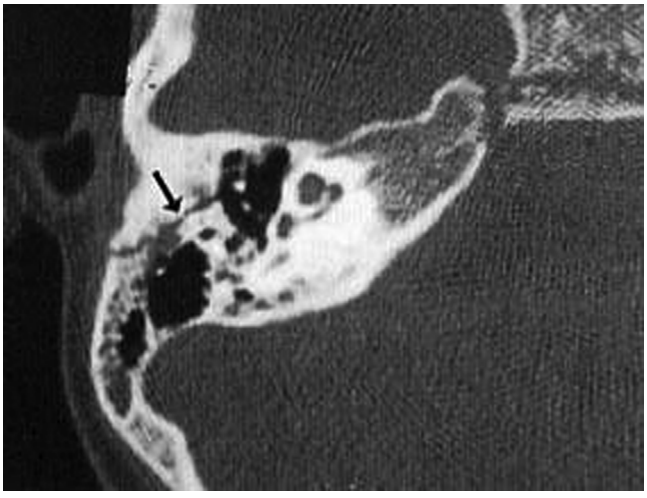

Figure 2. Otic capsule–sparing fracture: representative axial computed tomography image. Arrow points to the fracture line.

schemes have been proposed. Kelly and Tami introduced ''otic capsule–violating'' (OCV) versus ''otic capsule–sparing'' (OCS) terminology in 1994 (**Figures 1** and **2**).[9] In multiple studies, this classification scheme has been more predictive of several fracture-associated deficits, including facial nerve injury, SNHL, and cerebrospinal fluid leak.[6-8,10,11]

Early recognition of temporal bone trauma and its potential otologic complications are essential, especially in the pediatric population. Despite its importance, there is a relative paucity of literature on the subject. This study seeks to characterize pediatric temporal bone trauma with a focus on the natural history of associated audiometric outcomes.

Methods

Ethical Considerations

This study was approved by the University of Pittsburgh Institutional Review Board (protocol PRO13050454).

Study Cohort

We conducted a retrospective analysis of medical records and computed tomography images at a tertiary care academic children's hospital. Potential subjects included all children aged 1 month to 17 years presenting from 2010 to 2013 with maxillofacial trauma. Patients were included if they had temporal bone fracture on computed tomography and at least 1 posttrauma audiometric examination. Clinical data collected included baseline demographics, mechanism of injury, fracture pattern, audiometric data (posttrauma and follow-up, if available), and time to follow-up. All computed tomography scans were read by a neuroradiologist and reviewed by a pediatric otolaryngologist to confirm the presence of temporal bone fracture and classify the fracture(s) if present. Fracture pattern classification was based on OCS versus OCV scheme.[9]

An audiogram or otoacoustic emission (OAE) examination was performed on all patients included in this study. OAE examination was performed on children who could not undergo traditional audiogram due to young age or severity of injury and associated mental status changes. From raw audiometric data, hearing loss was categorized as sensorineural, conductive, mixed, or unclassified. Hearing loss was categorized as unclassified if only OAE data or only air thresholds were available. A pure-tone average (PTA) was recorded on all patients when possible; this was calculated by obtaining the mean value of air and/or bone thresholds at 500, 1000, and 2000 Hz. An air-bone gap >10 dB between air and bone PTA levels was considered abnormal. Hearing loss was deemed mild (PTA, 16-40 dB), moderate (PTA, 40-60 dB), or severe (PTA, >60 dB).

Statistical Analysis

Categorical variables were described as proportions, and continuous variables were described with mean and standard deviation. Measures of association between categorical variables were completed via Fisher's exact test. One-way analysis of variance was used to test continuous variables. Statistical significance was considered at $P < .05$. All tests were 2-sided.

Results

Demographics

There were 280 patients with maxillofacial trauma considered for inclusion. Of these, 58 patients (60 fractures) met inclusion criteria. Most patients who were excluded had other craniofacial fractures but not temporal bone fractures. The majority (62%, n = 36) were male, and most (86%, n = 50) were Caucasian. The mean age of our population was 8.6 $\pm$ 4.9 years (**Table 1**). The most common mechanism of injury was fall (47%; **Figure 3**).

Nearly all fractures were OCS (93%, n = 56), while the remainder (7%, n = 4) were OCV. All OCV fractures in this series violated the cochlea. Three fractures involved the vestibule and basal turn of the cochlea and round window. The fourth OCV fracture transected the cochlea. Almost all

Table 1. Baseline Demographic and Fracture Characteristics Based on Fracture Pattern.[a]

	All	OCS	OCV	*P* Value
Fracture	60	56 (93)	4 (7)	—
Age, y, mean ± SD	8.6 ± 4.9	8.5 ± 4.9	10.8 ± 4.6	.379
Male sex	36 (62)	32 (59)	4 (100)	.1426
Race				
Caucasian	50 (86)	46 (85)	4 (100)	1.000
African American	6 (10)	6 (11)	0	1.000
Hispanic	2 (3)	2 (4)	0	1.000
Sidedness				
Left	22 (38)	20 (37)	2 (50)	.6298
Right	34 (59)	32 (59)	2 (50)	1.000
Bilateral	2 (3)	2 (4)	0	1.000

Abbreviations: OCS, otic capsule–sparing; OCV, otic capsule–violating.
[a]Values presented as n (%), except for age.

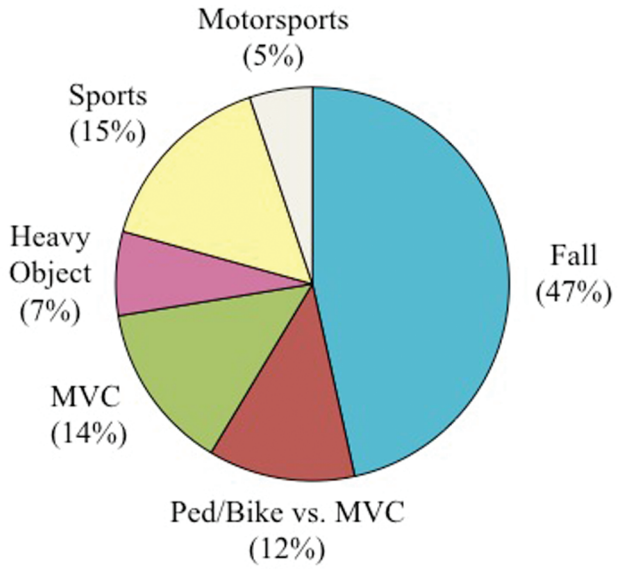

Figure 3. Mechanism of injury associated with pediatric temporal bone fracture. MVC, motor vehicle collision; ped, pedestrian.

patients (97%, n = 56) had unilateral fractures; 2 patients (3%) had bilateral fractures. Of the unilateral fractures, 22 (38%) were left-sided, and 34 (59%) were right-sided. Each patient with bilateral fractures showed only OCS fracture patterns (**Table 1**).

Audiometric Data

Based on PTA or OAM testing, 34 (57%) of the initial post-trauma audiometric evaluations were abnormal. Approximately half (54%, n = 30) of the OCS fractures were associated with abnormal audiometric evaluations, while all 4 OCV fractures had abnormal initial audiograms (100%, n = 4; **Table 2**).

The most common hearing loss type in OCS fractures was CHL (47%, n = 14), followed by unclassified (40%, n = 12), SNHL (10%, n = 3), and mixed (3%, n = 1). In contrast, OCV fractures were associated with mixed losses (50%, n = 2) and unclassified losses (50%, n = 2). The proportion of mixed losses seen in OCS and OCV fractures was significantly different (*P* = .031; **Table 2**, **Figure 4**).

A majority (73%, n = 22) of losses associated with OCS fractures were mild, followed by moderate (10%, n = 3) and severe (3%, n = 1). Only OAE data were available for 13% (n = 4); thus, the severity of the associated hearing losses was unclassified. Only 1 (25%) OCV fracture was associated with a mild hearing loss. The remaining 3 (75%) OCV fractures were associated with severe losses. The proportion of severe hearing losses seen in OCS and OCV fractures varied significantly (*P* = .0026; **Table 2**, **Figure 4**).

Follow-up Data

Follow-up audiometric data were available for 25 fractures (23 patients). Two fractures were OCV and 23 were OCS, yielding a follow-up rate of 41% for OCS fractures and 50% for OCV. A large proportion of patients with initially abnormal audiograms were lost to follow-up (41%, n = 14), including 2 patients with initially severe losses. Neither of the OCV fractures had hearing improvement on follow-up testing. In fact, hearing declined for both these patients. In contrast, a majority of losses associated with OCS fractures were noted to improve to normal levels. Of the 23 OCS fractures for which follow-up data were available, 18 were associated with initially abnormal audiologic examination. The majority (72%, n = 13) improved to PTA ≤20 in a mean of 46.0 ± 15.9 days. When only conductive losses were considered, 10 of 12 (83%) of those with initially abnormal examination results improved to PTA ≤20 in that same time frame (**Table 2**).

Discussion

In this retrospective analysis of pediatric trauma patients at a tertiary referral center, we identified that the type and severity of hearing loss differ in OCS and OCV temporal bone fractures. OCV fractures tend to be associated with

Table 2. Initial and Follow-up Audiometric Outcomes Based on Fracture Pattern.[a]

	All	OCS	OCV	*P* Value
Fracture	60	56 (93)	4 (7)	—
Abnormal audio	34 (57)	30 (54)	4 (100)	.1258
Type of hearing loss				
Conductive	14 (41)	14 (47)	—	.1261
Sensorineural	3 (9)	3 (10)	—	1.000
Mixed	3 (9)	1 (3)	2 (50)	.0307
Unclassified	14 (41)	12 (40)[b]	2 (50)[b]	1.000
Hearing loss severity				
Mild	23 (68)	22 (73)	1 (25)	.0889
Moderate	3 (9)	3 (10)	—	1.000
Severe	4 (12)	1 (3)	3 (75)	.0026
Unclassified	4 (12)	4 (13)[c]	—	1.000
Follow-up audio available	25 (42)	23 (41)	2 (50)	1.000
Improvement from abnormal to normal on follow-up[d]	13 of 20 (65)	13 of 18 (72)	0 of 2 (0)	.1105
Conductive losses	10 of 12 (83)	10 of 12 (83)	—	
Other types	3 of 8 (38)	3 of 6 (50)	0 of 2 (0)	

Abbreviations: OCS, otic capsule–sparing; OCV, otic capsule–violating.
[a]Values presented as n (%).
[b]Otoacoustic emissions or due to lack of bone lines.
[c]Otoacoustic emissions.
[d]Improvements occurred at a mean of 46 ± 15.9 days.

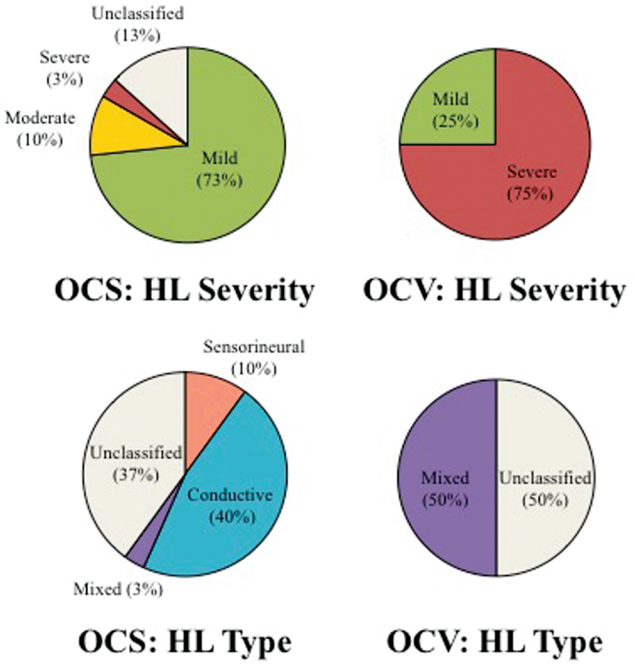

Figure 4. Severity and type of hearing loss (HL) based on fracture pattern. OCS, otic capsule–sparing; OCV, otic capsule–violating.

severe, mixed hearing losses. Although OCS fractures are often associated with no measureable hearing loss, those that are tend to be associated with mild, conductive losses. Hearing losses, especially conductive losses, associated with OCS fractures tend to resolve over the course of about 6 weeks (**Table 2**).

In this study, most fractures were unilateral and OCS (**Table 1**). In adult population reports, 9% to 20% of temporal bone fractures are bilateral.[2] The bilateral prevalence is lower here (3%). In the same vein, the prevalence of all skull base and maxillofacial fractures seems to be lower in children than adults.[1,3,12] Though speculation, this may be related to greater skull flexibility and impact absorption in children.[3] Pediatric craniofacial anatomy is fundamentally different, with developing paranasal sinuses and prominent buccal fat pads. Varying fracture rates between pediatric and adult populations may also relate to a different mechanism of injury pattern in children.[12]

The mechanism of injury distribution in this study was similar to that seen in prior pediatric skull base trauma literature, with falls as the leading cause (**Figure 3**).[1,3,6] A majority of patients in this study were Caucasian males, reflecting a possible tendency for males to engage in more active and reckless behavior (**Table 1**). Motor vehicle accidents are still the leading cause of adult temporal bone fractures, but that prevalence is decreasing.[2,3,13] It has been postulated that this decrease may be related to stricter safety regulations involving airbags and seatbelts.[1] There may be a similar and stronger effect in the pediatric population given rigorous standards for car seats and child restraint devices.

Similar to this study, a previous work showed that most hearing losses associated with OCS fractures were conductive.[6] Whereas a majority of OCV fracture-associated hearing losses were classified as sensorineural in a prior study, we found that most classifiable losses in OCV fractures are mixed (**Table 2**, **Figure 4**).[6] The difference here may be

related to the difficulty in obtaining bone conduction data in this population; it is possible that some conductive components are missed when bone lines cannot be obtained due to patient cooperation or altered mental status associated with injury. Additionally, the mechanisms of injury associated with the OCV fractures in this study tended to be more severe. It seems reasonable to suspect that bloody debris in the canal or hemotympanum could have accounted for some of the CHL in the setting of the overall severity of these patients' injuries. The small number of OCV fractures in this study, however, prohibits drawing any conclusions about this finding of mixed hearing loss.

It has been generally concluded that most trauma-associated CHLs resolve with time. In 1 study, 77% of adults with traumatic CHL improved without surgical intervention.[13] Our findings confirm this and extend to a pediatric population. A majority of the persistent CHLs resulting from temporal bone trauma are reportedly related to ossicular injury or discontinuity.[6] In fact, 1 of the patients in our review who had persistent CHL following OCS temporal bone fracture had documented ossicular discontinuity requiring eventual tympanoplasty. Regarding potential operative intervention for traumatic CHL, it has been suggested in the adult literature that conservative management is appropriate initially and that surgical exploration is indicated only when the loss persists for 4 to 6 months.[2,13] In the pediatric population studied here, we found that a majority of CHLs associated with temporal bone fracture improved to normal levels within 6 weeks (**Table 2**). Given this finding, it could be argued that those children who do not improve to near-normal hearing levels within that time frame warrant further investigation into potential issues that may be surgically corrected. These patients may benefit from intervention earlier than the 4- to 6-month time point suggested in the adult literature.

Limitations

There are several limitations to this study. First, our sample size is relatively small, likely due to the rare incidence of temporal bone fractures. Furthermore, the tertiary referral setting in a single geographic location limits generalizability to other health care settings. There were a large number of unclassified hearing losses in this study. Occasionally, young age or clinical condition precluded the ability to obtain a traditional audiogram. With OAE data in these cases, we were unable to determine the severity or type of loss, unlikely affecting the overall results, as the number of OAE examinations in this study was small. More frequently, however, the available traditional audiograms were missing bone conduction data, presumably due to a lack of cooperation among many of the young patients as well as periaural tenderness resulting from the trauma. Furthermore, the child's clinical condition may have precluded complete audiologic evaluation, particularly if there was neurologic injury. In these instances, the type of hearing loss could not be defined. Finally, a large portion of our population was lost to follow-up. Many of these patients had more devastating, concurrent neurologic injury that could explain some of the poor follow-up. Additionally, this could be related to more local follow-up for referred patients or simply due to resolution of symptoms.

Conclusions

Although audiometric outcomes are difficult to study in the pediatric population, this study suggests that hearing loss type and severity differ in pediatric OCS and OCV temporal bone fractures. Furthermore, the natural history of hearing deficits favor short-term resolution, and those with persisting deficits should be evaluated for surgically amenable causes. Patients and families should be counseled about the strict need for further follow-up given the potential long-term consequences of neglected hearing losses.

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Author Contributions

Amy Schell, study design, data collection, analysis and interpretation of data, drafting of manuscript; **Dennis Kitsko**, study design, data collection, manuscript revision.

Disclosures

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References

1. Perheentupa U, Kinnunen I, Grenman R, et al. Management and outcome of pediatric skull base fractures. *Int J Pediatr Otorhinolaryngol*. 2010;74:1245-1250.
2. Johnson F, Semaan MT, Megerian CA. Temporal bone fracture: evaluation and management in the modern era. *Otolaryngol Clin North Am*. 2008;41:597-618.
3. Kang HM, Kim MG, Hong SM, et al. Comparison of temporal bone fractures in children and adults. *Acta Otolaryngol*. 2013; 133:469-474.
4. Brookhouser PE, Worthington DW, Kelly WJ. Unilateral hearing loss in children. *Laryngoscope*. 1991;101:1264-1272.
5. Bowman MK, Mantle B, Accortt N, et al. Appropriate hearing screening in the pediatric patient with head trauma. *Int J Pediatr Otorhinolaryngol*. 2011;75:468-471.
6. Dunklebarger J, Branstetter B, Lincoln A, et al. Pediatric temporal bone fractures: current trends and comparison of classification schemes. *Laryngoscope*. 2014;124:781-784.
7. Ishman SL, Friedland DR. Temporal bone fractures: traditional classification and clinical relevance. *Laryngoscope*. 2004;114: 1734-1741.
8. Little SC, Kesser BW. Radiographic classification of temporal bone fractures: clinical predictability using a new system. *Arch Otolaryngol Head Neck Surg*. 2006;132:1300-1304.
9. Kelly KE, Tami TA. Temporal bone and skull trauma. In: Jackler RK, Brackmann DE, eds. *Neurotology*. St Louis, MO: Mosby; 1994:340-360.

10. Brodie HA, Thompson TC. Management of complications from 820 temporal bone fractures. *Am J Otol*. 1997;18:188-197.
11. Dahiya R, Keller JD, Litofsky NS, et al. Temporal bone fractures: otic capsule sparing vs otic capsule violating clinical and radiographic considerations. *J Trauma*. 1999;47:1079-1083.
12. Muñante-Cárdenas JL, Olate S, Asprino L, et al. Pattern and treatment of facial trauma in pediatric and adolescent patients. *J Craniofac Surg*. 2010;22:1251-1255.
13. Grant JR, Arganbright J, Friedland DR. Outcomes for conservative management of traumatic conductive hearing loss. *Otol Neurotol*. 2008;29:344-349.

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Pediatric temporal bone fractures: A case series

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ABSTRACT

Objectives: Temporal bone fractures are relatively common findings in patients with head trauma. The aim of this study was to evaluate the characteristics of temporal bone fractures in the pediatric population.
Study design: Retrospective case series. Tertiary care pediatric academic medical center.
Methods: The medical records of patients aged 18 years or less diagnosed with a temporal bone fracture at the Montreal Children's Hospital from January 2000 to August 2014 were reviewed. Patient demographics, clinical presentation, mechanism of injury and complications were analyzed. Imaging studies and audiograms were also evaluated.
Results: Out of 323 patients presenting to the emergency department with a skull fracture, 61 presented with a temporal bone fracture. Of these, 5 presented with bilateral fractures. 47 patients had associated fractures, and 3 patients deceased. We observed a male to female ratio of 2.8:1, and the average age was 9.5 years. Motor vehicle accidents were the primary mechanism of injury (53%), followed by falls (21%) and bicycle or skateboard accidents (10%). The most common presenting signs included hemotympanum, decreased or loss of consciousness, facial swelling and nausea and vomiting. 8 patients had otic involvement on computed tomography scans, and 30 patients had documented hearing loss near the time of accident with a majority being conductive hearing loss. 17 patients underwent surgical management of intracranial pressure.
Conclusion: In children, fractures of the temporal bone were most often caused by motor vehicle accidents and falls. It is common for these patients to have associated fractures.
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1. Introduction

Temporal bone fractures are of special interest for clinicians given that they can translate into an array of complications, and that they usually arise from high impact trauma [1].

The temporal bones are complex structures forming part of the lateral skull base. They are each made up of five parts: the styloid, tympanic, squamous, mastoid and petrous portions [2]. The temporal bones articulate with other cranial bones and form part of the middle and posterior fossae. Important neural and vascular components such as the vestibulocochlear nerve, facial nerve, internal carotid artery and jugular vein, have part of their trajectories though this bone. They also contain the sensory organs of hearing and balance; the cochlea and vestibule [3]. As such, trauma to this intricate area can lead to a variety of clinical presentations including hearing loss, hemotympanum, loss of consciousness, tympanic membrane perforation, otorrhagia, facial nerve injury, cerebrospinal fluid (CSF) leakage, ecchymosis of the post-auricular skin (Battle sign) and periorbital area (raccoon sign) [4–6].

A limited amount of articles regarding temporal bone fractures in children are available in the current literature. The aim of this study was to evaluate the characteristics of temporal bone fractures in patients aged 18 years or less in a pediatric tertiary care hospital setting.

2. Methods

2.1. Ethical approval

Ethical approval for this study was obtained from the pediatric research ethics committee at the McGill University Health Centre. Study number 11-731-PED.

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2.2. Study subjects

A retrospective chart review was performed for patients aged 18 years or less presenting to the Montreal Children's Hospital (Montreal, QC, Canada), a tertiary care pediatric hospital, from January 2000 to August 2014, for a base of skull fracture. The charts were then reviewed in order to identify patients with temporal bone fractures specifically. Data such as demographics, clinical presentation, mechanism of injury and complications were analyzed. Signs and symptoms included hemotympanum, otorrhea (CSF, blood), Battle sign, raccoon eyes, amnesia, tympanic membrane perforation, CSF rhinorrhea, dizziness, tinnitus, vertigo, otalgia, facial swelling, mastoid swelling, headache, level of consciousness at the time of presentation and amnesia.

Complications included facial nerve injury (paresis or paralysis), hearing loss, and intracranial injuries. Associated skull fractures were also described. A head computed tomography confirming the fracture at the time of the injury was another inclusion criterion for selecting patients. Hearing assessments following the injury, including pure-tone audiometry or otoacoustic emissions, were evaluated when performed, as well as documented facial nerve function in medical records. Cases were excluded from analysis when relevant clinical or imaging data was missing.

3. Results

The search for base of skull fractures from January 2000 to August 2014 yielded a total of 323 patients. Of these, 61 patients presented with temporal bone fractures, and 5 of these patients presented with bilateral temporal bone fractures. Patient demographics are presented in Table 1. The majority of patients were male and age of injury ranged from the time of birth until 17 years of age. The mean age was 9.5 years and the median was 10 years.

3.1. Mechanisms of injury

Mechanisms of injury were varied and included motor vehicle accidents (MVA), falls, accidents while biking, skateboarding, tobogganing or skiing, assaults, an animal bite and presence at birth (Table 2). Of these, MVAs were responsible for 53% of the fractures (Fig. 1). Approximately one third of the MVAs occurred while the patient was on an all-terrain vehicle (ATV), driving or as a passenger (32.3%). The criminal code of Canada considers ATVs, snowmobiles, scooters and golf carts as "motor vehicles", for this reason, accidents that occurred while driving (or as a passenger) of these vehicles were included in the MVA category. If a patient was involved in a car collision, the accident was included as an MVA regardless of whether the patient was performing another activity at the time (i.e. riding a bicycle, skateboarding). A total of sixteen patients were implicated in an automobile accident with 5 of these patients being involved in a car collision. Seven patients were hit by an automobile while riding their bicycles or while skateboarding; of these, only 2 were wearing helmets. Four patients were pedestrians.

Thirteen patients had a temporal bone fracture as a result of a fall. The height from which the patients fell varied from 40 cm up to falling from a third floor. Two patients fell off a shopping cart and one fell down the stairs. Five patients were assaulted with a resultant hit to the head with a rock, a baseball bat, hitting their head against a wall or by being physically pushed to the ground. Six patients fell off their bicycles or skateboards and 5 of them were not wearing helmets as documented in the patients' charts. Other less frequent mechanisms of injury are described in Table 2.

Table 1
Patient demographics.

Patients (n)	61
Temporal bone fractures	66
Bilateral fractures	5
Age	
Range	Birth – 17
Mean ± SD	9.5 ± 5.0
Median	10
Male/female	45/16
Deceased	3

Table 2
Mechanisms of injury.

Mechanisms of injury	# of patients
Motor vehicle accident	32
Motor vehicle	16
ATV	10
Scooter	2
Golf cart	3
Snowmobile	1
Fall	13
Bicycle/skateboard	6
Assault	5
Other	5
Dog bite	1
Present at birth (pond fracture)	1
Fall of cement wall	1
Tobogganing	1
Skiing (struck a tree)	1

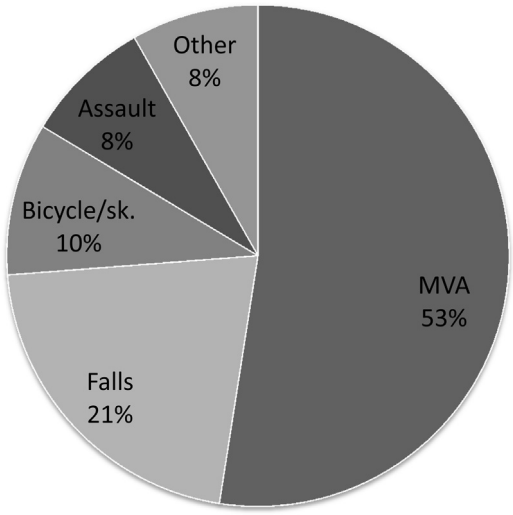

Fig. 1. Pediatric temporal bone fractures: mechanisms of injury.

3.2. Clinical presentation

Ten patients arrived at the tertiary care pediatric medical center already intubated. The most common findings on clinical presentation were the presence of hemotympanum, loss of consciousness and a decreased Glasgow coma scale (GCS) score. Headaches and nausea and/or vomiting were predominant clinical manifestations. Twelve patients also described experiencing hearing loss. Multiple lacerations, drainage of liquid from the ear, otorrhagia, CSF otorrhea, mastoid tenderness, dizziness or confusion were also observed. Other classical physical findings of basilar skull fractures such as raccoon eyes, CSF rhinorrhea and Battle sign were infrequent (see Fig. 2).

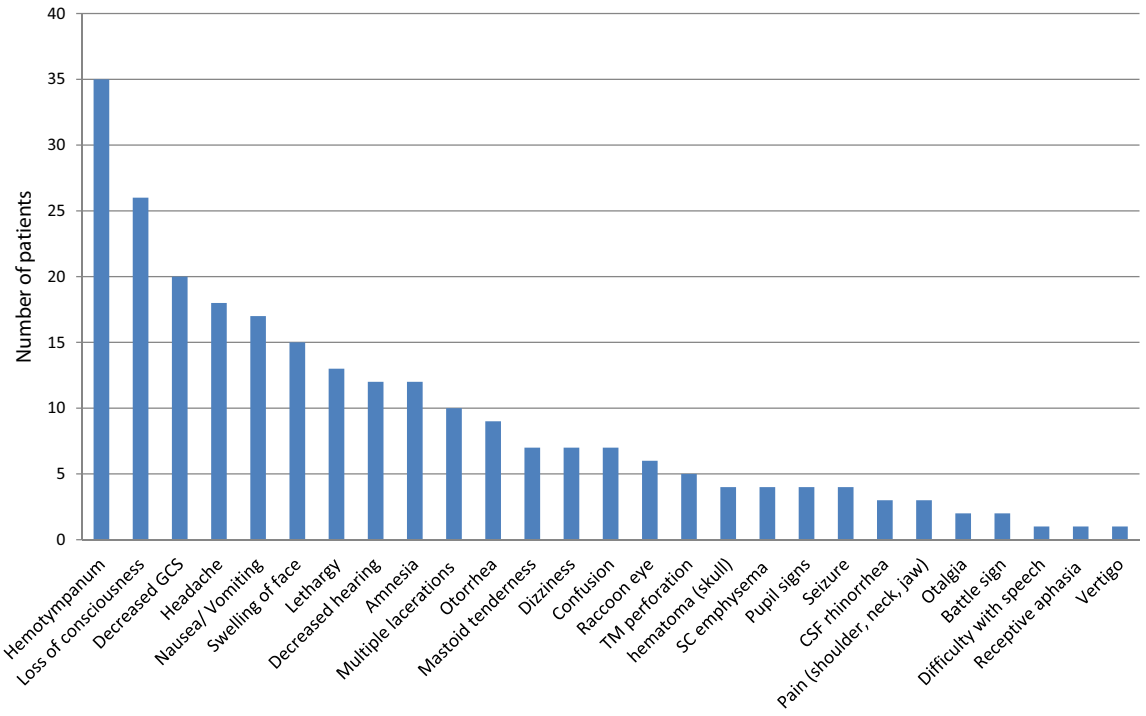

Fig. 2. Pediatric temporal bone fractures: clinical presentations.

3.3. Associated fractures

Multiple fractures were observed to be associated with temporal bone fractures in this study group. The most commonly encountered were parietal and sphenoid bone fractures. Other fractures included frontal, mandible, maxillary, nasal bones and unspecified facial bones. Eight patients also presented with lambdoid suture diastasis (see Fig. 3).

3.4. Complications and associated injuries

Complications included facial nerve injury, hearing loss and intracranial injuries. Only three patients presented with facial asymmetry on physical examination, with one patient having a documented transient facial nerve paresis.

While 12 patients described hearing loss as a clinical symptom, hearing testing performed shortly following the incident demonstrated that 30 patients actually had hearing loss of which 14 presented with mild, 10 with moderate, 1 with severe and 2 with profound hearing loss with audiometry testing. The other 3 patients failed otoacoustic emissions. Nine patients did not have documented audiogram or otoacoustic emission testing. In total, 106 ears were evaluated for hearing impairment: 70 ears showed no hearing loss, 29 were consistent with a conductive hearing loss (CHL), 5 presented with a sensorineural hearing loss (SNHL) and 2 were mixed. Follow-up was not consistent. Of the information available, 2 patients that failed the otoacoustic emissions initially, passed at 1 week, and 3 months follow up. One patient with profound SNHL did not exhibit any change at 2 week follow up. 5 patients with mild (3 CHL, 2 SNHL) and one with moderate CHL recovered their hearing at 1–2 months follow up. 2 patients with moderate CHL presented with mild CHL at 1 week, and 1 year follow up. One patient with mild CHL remained with the same diagnosis at 3 months follow up.

Following computed tomography scanning of these patients, various intracranial complications were observed, of which pneumocephalus was the most common as evidenced in 23 patients. Parenchymal contusion and intracranial hemorrhaging were also frequently observed. Seven patients presented with either midline shift or transtentorial herniation (Table 3).

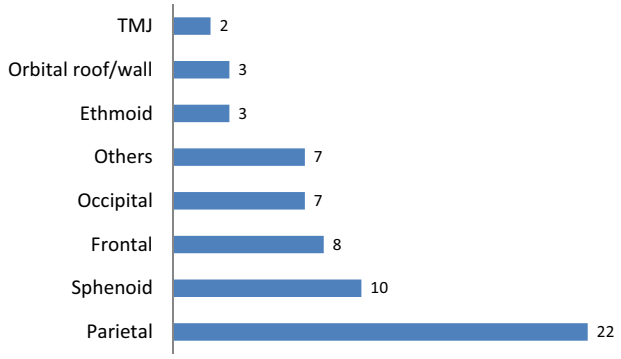

Fig. 3. Temporal bone fractures: associated fractures.

3.5. Temporal bone fracture types

Based on the traditional classification of temporal bone fractures, 35.9% of the fractures were longitudinal, 10.6% were transverse and 53.9% were mixed. Based on the newer classification established by Little et al. [7], 9 fractures were otic capsule involving.

Table 3
Computed tomography findings associated with temporal bone fractures in the pediatric population.

Finding	# of patients
Pneumocephalus	23
Parenchymal contusion	22
Subarachnoid hemorrhage	13
Subdural hemorrhage	13
Epidural hemorrhage	12
Midline shift	7
Transtentorial herniation	7

Recently, Kang et al. developed a classification based on the involvement of the four parts of the temporal bone (squamous, tympanic, mastoid, and petrous) [8]. We also evaluated this classification and found that fractures involving one part represented 37.9%, involving two parts in 25.9%, involving 3 parts in 24.1%, and involving all 4 parts in 12% of the fractures. Of the areas compromised, the most frequently compromised was the mastoid part (47%), followed by the squamous part (38%), the tympanic part (25%) and finally, the petrous part (12%).

4. Discussion

Temporal bone fractures usually arise from high impact trauma, and since it is a complex structure relating to important neurovascular constituents, it is important to evaluate its impact on the pediatric population. Following a review of all the cases of temporal bone fractures during a 14 year span at a pediatric tertiary care center, we evaluated 66 temporal bone fractures. The median age of the children was 10 years with 74% being male patients.

The predominant mechanisms of injury were consistent with the literature with 53% of the cases resulting from a MVA followed by falls [8–10]. Interestingly, in our population, MVA involving less common vehicle types resulted in 48.2% of the accidents, and included ATVs, scooters, golf carts and snowmobiles. Two children died as a result of a MVA. Special precautions should be taken when children are exposed to such vehicles. Also, of the traditional MVA, 7 children were hit while riding a bicycle, and of these, 5 were not wearing helmets. Educating children and their parents in proper behavior and techniques for safe bicycling is also extremely important.

Hemotympanum and loss of consciousness or decreased Glasgow scale and headache were the most frequent findings at initial presentation. Other otological findings were less frequent with 12 patients referring decreased hearing, 9 patients had otorrhea, 5 had tympanic membrane perforations, 2 had otalgia and 1 had vertigo.

Because pediatric temporal bones are more flexible [11] and have decreased mineralization that may protect the otic capsule, it is expected that the incidence of SNHL would be lower in this population [12]. Our results demonstrated that only 5 ears developed SNHL, that 29 ears presented with a CHL and two were mixed. Also, it has been previously described that patients presenting with an otic capsule involving fracture were more likely to develop SNHL, facial nerve injury and cerebrospinal fluid otorrhea [7]. Our results did not evidence such findings, although, of the 5 patients presenting with SNHL, 2 had otic capsule involvement. Findings concerning hearing varied tremendously. It is difficult with this data to make any strong conclusions regarding pediatric temporal bone fractures and hearing loss. Presentations varied from normal hearing to profound SNHL, and recovery for the patients that did present some degree of hearing loss also varied at different follow up periods. It is important to consider that not all patients that present hearing loss in a hearing test will report it as a clinical sign. Therefore, it is of importance for all patients suffering a temporal bone fracture to undergo a formal hearing test, and to follow up as it has been observed that even mild losses may not be recovered. Three patients developed facial nerve paresis.

78% of the patients had additional skull fractures of which parietal, sphenoid, frontal followed by occipital fractures were the most frequent; similar to previously published data [12]. Interestingly, 8 patients had only the squamous part of the temporal bone compromised, however, of these patients, one developed SNHL and 5 had intracranial injuries consisting of parenchymal contusion (1), subarachnoid hemorrhage (2), epidural hemorrhage (2) and subdural hemorrhage (1). None of these children developed facial nerve injury. Patients with isolated fractures of the squamous portion of the temporal bone are at risk of developing intracranial injuries [5].

Intracranial injuries were common with pneumocephalus, parenchymal contusion and intracranial hemorrhaging being the most frequently observed. Intracranial hemorrhage was observed in 62% of the patients and included subarachnoid (21.3%), subdural (21.3%) and epidural hemorrhage (19.6%). Results were comparable to a previously published series of pediatric temporal bone fractures in which 38% of the patients had a subdural hemorrhage, 16% of patients had a subarachnoid hematoma and 13% had an epidural hemorrhage [12].

5. Conclusion

Considering our results, pediatric temporal bone fractures were more common in males and resulted most frequently from MVA and falls. Associated skull fractures and intracranial injuries were commonly found and the most prevalent clinical presentation included hemotympanum, decreased or loss of consciousness and headache. Approximately half of the patients presented with hearing loss, which in the majority, was conductive. Facial nerve injury was rare. Fracture of the squamous part of the temporal bone is associated with intracranial injury and otic involving fractures were infrequent.

Conflict of interest

The authors declare that they have no conflicts of interest.

References

[1] L.W. Travis, R.L. Stalnaker, J.W. Melvin, Impact trauma of the human temporal bone, J. Trauma 17 (1977) 761–766.
[2] J.M. Collins, A.K. Krishnamoorthy, W.S. Kubal, M.H. Johnson, C.S. Poon, Multidetector CT of temporal bone fractures, Semin. Ultrasound CT MR 33 (2012) 418–431.
[3] M. Sanna, T. Khrais, Temporal Bone: A Manual for Dissection and Surgical Approaches, Thieme, New York, 2006.
[4] H.A. Brodie, T.C. Thompson, Management of complications from 820 temporal bone fractures, Am. J. Otol. 18 (1997) 188–197.
[5] D. Lee, C. Honrado, G. Har-El, A. Goldsmith, Pediatric temporal bone fractures, Laryngoscope 108 (1998) 816–821.
[6] N. Munir, R. Clarke, Ear, Nose and Throat at a Glance, John Wiley & Sons, 2012.
[7] S.C. Little, B.W. Kesser, Radiographic classification of temporal bone fractures: clinical predictability using a new system, Arch. Otolaryngol. Head Neck Surg. 132 (2006) 1300–1304.
[8] H.M. Kang, M.G. Kim, S.H. Boo, K.H. Kim, E.K. Yeo, S.K. Lee, et al., Comparison of the clinical relevance of traditional and new classification systems of temporal bone fractures, Eur. Arch. Otorhinolaryngol. 269 (2012) 1893–1899.
[9] W.T. Williams, B.Y. Ghorayeb, J.W. Yeakley, Pediatric temporal bone fractures, Laryngoscope 102 (1992) 600–603.
[10] J. Dunklebarger, B. Branstetter 4th, A. Lincoln, M. Sippey, M. Cohen, B. Gaines, et al., Pediatric temporal bone fractures: current trends and comparison of classification schemes, Laryngoscope 124 (2014) 781–784.
[11] H.M. Kang, M.G. Kim, S.M. Hong, Comparison of temporal bone fractures in children and adults, Acta Otolaryngol. 133 (2013) 469–474.
[12] S. Ort, K. Beus, J. Isaacson, Pediatric temporal bone fractures in a rural population, Otolaryngol. Head Neck Surg. 131 (2004) 433–437.

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Clinical Efficacy of Electroneurography in Acute Facial Paralysis

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The estimated incidence of acute facial paralysis is approximately 30 patients per 100000 populations annually. Facial paralysis is an extremely frightening situation and gives extreme stress to patients because obvious disfiguring face may cause significant functional, aesthetic, and psychological disturbances. For stressful patients with acute facial paralysis, it is very important for clinicians to answer the questions like whether or not their facial function will return to normal, how much of their facial function will be recovered, and how long this is going to take. It is also important for clinicians to treat the psychological aspects by adequately explaining the prognosis, in addition to providing the appropriate medical treatment. For decades, clinicians have used various electrophysiologic tests, including the nerve excitability test, the maximal stimulation test, electroneurography, and electromyography. In particular, electroneurography is the only objective measure that is useful in early stage of acute facial paralysis. In this review article, we first discuss the pathophysiology of injured peripheral nerve. And then, we describe about various electrophysiologic tests and discuss the electroneurography extensively. **J Audiol Otol 2016;20(1):8-12**

KEY WORDS: Acute facial paralysis · Electrophysiological test · Electroneurography · Electromyography.

Introduction

Acute facial paralysis is an acute peripheral facial weakness of various etiologies and its diagnosis can be established without difficulty in patients with unexplained unilateral isolated facial weakness. However, bilateral facial paralysis is more difficult to be notified than unilateral involvement because bilateral facial paralysis makes symmetric weakness. The onset is sudden and symptoms typically peak within a few hours to days. The most common cause of acute onset unilateral peripheral facial weakness is Bell's palsy. Other etiologies include viral infection (herpes zoster virus, human immunodeficiency virus), Guillain-Barre syndrome, autoimmune disease, Lyme disease, Kawasaki disease, head or ear trauma, temporal bone fracture, barotrauma, acute or chronic otitis media, cholesteatoma, sarcoidosis, Melkersson-Rosenthal syndrome, and cerebrovascular accident [1].

Most facial weakness is apparent to a clinician as well as a patient. Its clinical diagnosis is based on both static and dynamic facial analysis during physical examination, and attempts have been recently made to standardize an objective measurement of facial function, for example, digital photographic and videographic interactive computer systems [2-5]. Several systems of clinical measurement of facial nerve function have been devised, but since the mid-1980s, the House-Brackmann grading system has been most widely accepted and endorsed by the American Academy of Otolaryngology-Head and Neck Surgery. However, in this grading system, regional descriptions of facial paralysis within each grade can overlap and lead to confusion in determining the appropriate grade. Therefore, modified House-Brackmann grading system [1] is made, focusing major functional criteria of the House-Brackmann system (absolute movement, synkinesis, eye closure, asymmetry at rest, and absolute paralysis). One of the limitations of both grading systems is the inadequacy

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to stratify the degree of degeneration or reflect the prognosis of facial paralysis.

For decades, clinicians have searched the prognostic tests of sufficient accuracy for acute facial paralysis. Since Esslen [6] introduced the use of electroneurography (ENoG) in the early 1970s, the prognosis of facial paralysis has been predicted based mainly on various electrophysiologic tests, including the nerve excitability test, the maximal stimulation test, ENoG, and electromyography (EMG). In particular, ENoG can determine the percentage of degenerating nerve fibers in early phase of acute facial paralysis. Various studies [7-11] have shown that ENoG can be used to predict the prognosis of acute facial paralysis and May and Shambaugh [12] reported that degeneration ≤ 25% within the first 2 weeks of onset indicated a satisfactory recovery of the facial function in 98% of Bell's palsy cases.

This review article stated the clinical efficacy, advantages and disadvantages of ENoG as the prognostic test of acute facial paralysis. It also described the comparison with other electrophysiological test, including nerve excitability test (NET), maximal stimulation test (MST), and EMG.

Review

Why is the electrophysiological test important?

Facial paralysis can leave aesthetic and functional sequelae to patients and it is very important to patients as well as clinicians to choose the best treatment options and determine its prognosis. However, subjective judgment such as the House-Brackmann grading system cannot give enough or objective information on the paralysis status, especially with regard to the treatment and prognosis. Therefore, objective recording and measuring the degree of neural degeneration and resultant myopathy have been used to determine the physiologic degree of nerve injury and predict the prognosis.

Electrophysiological test is one of supportive tools for the diagnosis of neural-muscular system but not a method to diagnose the disease or confirm the etiology. Before the electrophysiological tests, the history of the facial paralysis and physical examination are preceded and considered to interpret the results of electrophysiological tests. The purposes of electrophysiological tests are to localize the lesion site along the nerve, determine the severity of the injury, and differentiate whether an injured nerve is still degenerating or regenerating.

The pathophysiology of peripheral nerve after the injury

To understand the concept of peripheral neural injury, we should understand what happens after the injury of peripheral nerve. After the injury of peripheral nerve, pathophysiologic changes depend on the severity of the injury as well as the proximity of the injured segment to the cell body. After mild injury like neuropraxia, focal demyelination and remyelination occur. However, retrograde degeneration and regeneration of the axon occur in the case of severer injury. In mild injury, the regenerative and repair processes begin almost immediately, but nerve regeneration begins only after Wallerian degeneration has run its course in severer injury.

Degeneration of the injured nerve

Before regeneration of nerve fibers can occur, a series of degenerative processes must take place. Transection of the axon divided the nerve into proximal segment connecting to a cell body and distal one. Two segments retract in the direction opposite to the transection site each other and two axonal stumps become to be swollen because of accumulation of the cytoskeleton elements along fast axonal transport and slow axoplasmic flow. Within 24 hours post-injury, the nucleus migrates to the periphery of the cell and Nissl granules, rough endoplasmic reticulum, breaks up and disperses (chromatolysis). This chromatolysis ends in 10−21 days after the injury. Within 3 days post-injury, axonal sprout starts to grow from proximal stump and the rate of axonal regeneration is generally estimated to be 1 mm per day. Within 24 hours post-injury, Wallerian degeneration of axon and myelin sheath occur and Schwann cells proliferate. In Wallerian degeneration, the primary change is physical fragmentation of both axons and myelin sheath and both neurotubules and neurofilaments become disarrayed. By 48 to 96 hours post-injury, axonal continuity is lost and nerve conduction is lost. Myelin disintegration lags slightly behind that of axons but is well advanced by 36 to 48 hours. Disintegrated debris of axon and myelin sheath is removed by phagocytosis of macrophages within 12−14 days post-injury. Schwann cell plays a key role in Wallerian degeneration. It becomes active within 24 hours post-injury, divides rapidly into differentiated daughter cells, and upregulates the gene expression for proteins to assist in the degeneration and repair process. Initial role of Schwann cell is to help removal of degenerated debris of axon and myelin sheath. Schwann cell and macrophage work together for phagocytosis and clear the site of injury in a process that requires 2 week to 3 months [13-16]

Regeneration of the nerve

Regenerative and repair processes begin almost immediately, although regeneration of the severer injured nerve begins only after Wallerian degeneration has run along the nerve. For more severe nerve injuries more than 3rd degree of Sunder-

land classification (neurotmesis of Seddon classification), endoneurial tube is disrupted and axon cannot regenerate into its original sheath. Proliferated Schwann cells form cytoskeleton framework (Bungner band) connecting both ends of transected nerve. The earliest signs of nerve regeneration are visible changes in the cell body that mark the reversal of chromatolysis. The metabolic machinery of the cell body is reprogrammed to produce proteins and lipid needed for axonal regrowth during the regeneration process. Both fast and slow axoplasmic transports supply the cytoskeletal materials from the cell body to the sites of axonal regeneration but this process results in swelling of both stumps of transected nerve within several hours post-injury. Axonal regrowth begins as early as 24 hours post-injury. During regeneration, axonal regrowth may be impeded by fibrous tissues and regenerated nerve with myelin sheath can make scar neuroma. Multiple axon sprouts may enter into each endoneurial sheath, even in milder injuries, that do not involve destruction of the sheath itself. However, only one axon sprout becomes to be myelinated. Sometimes, axon sprout may enter into endoneurial tube other than its own. If one axon sprout enters into endoneurial sheath other than its own, we called it as "simple misdirection". If multiple branches of one axon sprout enter into endoneurial sheath other than its own, we called it as "complex misdirection". Clinical examples of complex misdirection are synkinesis and mass movement. Axon sprout which does not enter into any endoneurial sheath becomes atrophic and breaks down [17,18].

The pathophysiologic concept of peripheral neural injury

To interpret the results of electrophysiological tests, we should understand the pathophysiologic concept on the degree of neural injury. In 1943, Seddon [19] described three basic types of peripheral nerve injury that include neuropraxia, axonotmesis, and neurotmesis (Fig. 1). In 1951, Sunderland [20] expanded Seddon's classification to five degrees of peripheral nerve injury (Fig. 1). The 1st degree is essentially the same as neuropraxia of Seddon classification. The 2nd degree is same as axonotmesis of Seddon classification. The 3rd degree is axonotmesis as well as the disruption of endoneurium (intact epi- and perineurium). The 4th degree is axonotmesis, as well as the disruption of endo- and perineurium (intact epineurium). The 5th degree is same as neurotmesis of Seddon classification (complete transection). Sunderland classification is more suitable for the acute traumatic facial paralysis and Seddon classification is for acute inflammatory facial paralysis, such as Bell's palsy. Neuropraxia means local injury of myelin with the axon still intact and functional and is considered as a temporary paralysis of the nerve fiber. So, the nerve action potential can propagate along the nerve in the case of neuropraxia (Seddon classification) or 1st degree injury (Sunderland classification). Major weakness of electrophysiological tests is that they cannot differentiate between axonotmesis and neurotmesis (Seddon classification) or between 2nd to 4th degree injuries (Sunderland classification).

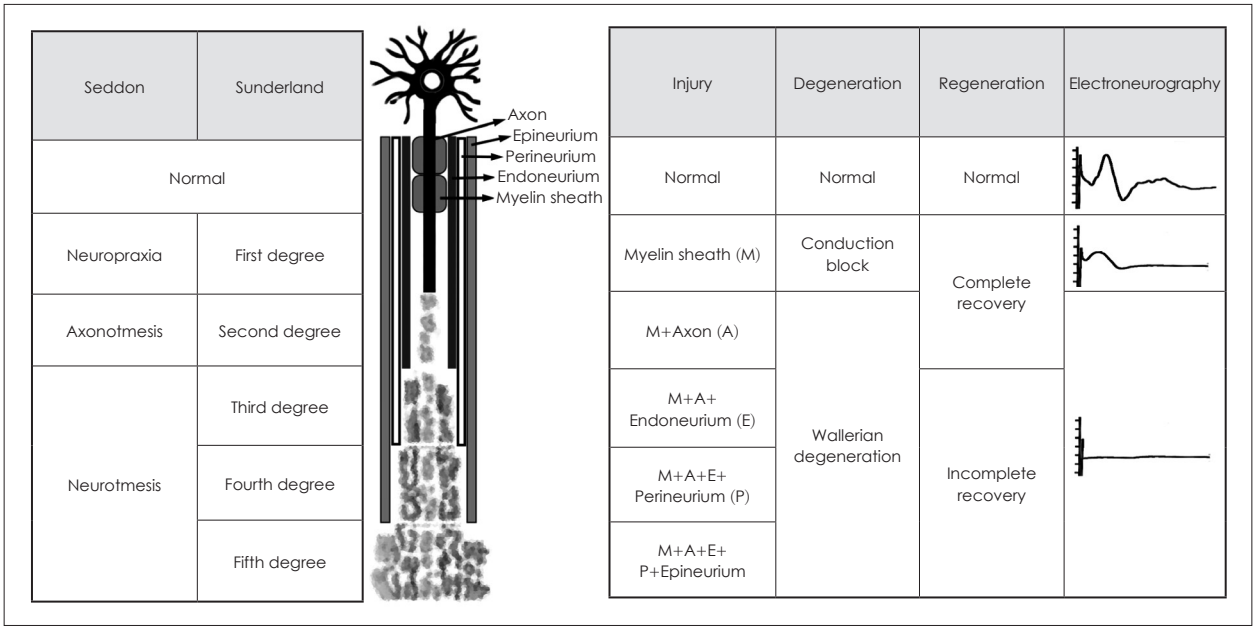

Fig. 1. Overview of Seddon and Sunderland classifications.

Which electrophysiological tests are used to evaluate the facial nerve?

NET, MST, ENoG and EMG are representative electrophysiological tests, which have been widely used clinically. Among these, NET and MST involve the examiner's visual evaluation of electrically-elicited facial movement. Therefore, these two tests have possible subjectivity. NET is the oldest and best known electrophysiological test with well-established clinical efficacy, introduced by Laumans and Jongkees in 1963 [21]. During this test, the lowest current eliciting a facial twitch is defined as the threshold of excitation and the difference in thresholds between the two sides is calculated. During MST, facial movement of the paralyzed side is compared with that of the normal side at the level of maximal stimuli (current level at which the greatest amplitude of facial movement is seen at the normal side). Contrary to NET, MST and ENoG, EMG is the sole electrophysiological test which is very useful after loss of nerve excitability and completeness of degeneration. After 2 to 3 weeks after acute facial paralysis, tests of electrical stimulation (NET, MST, and ENoG) are no longer useful. After 10 to 14 days post-onset, fibrillation potentials or positive sharp waves seen on EMG can confirm the degeneration of facial nerve. In addition, polyphasic reinnervation potentials more useful, which may be seen as early as 4 to 6 weeks after the onset of paralysis.

What is the ENoG?

The ENoG records compound muscle action potential (CMAP) of facial muscle, which is elicited electrically. The facial nerve is stimulated transcutaneously at the stylomastoid foramen using a bipolar stimulating electrode. Responses to maximal electrical stimulation of the two sides recorded electrically by the second bipolar electrode pair placed in several sensory regions of facial nerve branches and compared between both sides. Contrary to NET or MST, ENoG calculates electrically-evoked responses objectively for the amplitude of electrically-evoked response is measured in mV.

Typically, ENoG is delayed until 72 hours post-onset of paralysis because it takes some 72 hours for Wallerian degeneration to propagate from intratemporal portion (injured site) to portion distal to the stylomastoid foramen (electrically-stimulated site during ENoG). Other end of the timing window is the 21 day post-onset of paralysis. After this time, the nerve excitability is lost and the nerve degeneration is completed. In addition, ENoG may be interfered by possible collateral nerves which are regenerated after 2 weeks post-onset. Clinicians should keep in mind that ENoG should be performed for the first time at about 72 hours post-onset and again at 3 to 5 day intervals until a trend and confirmation can be determined. It is good to test the patient serially until a plateau can be determined.

The factors influencing the test results are 1) electrical impedance between electrodes and skin, 2) conduction velocity of the facial nerve, 3) transmission velocity at the junction of neuromuscular junction, 4) propagation velocity along the facial muscle, 5) the degree of synchrony of the facial muscle fibers, and 6) the population of facial nerve fibers still intact. Other factors include sweat and oil status of the skin, diameter of the electrodes, distance between electrodes, location of the electrodes, pressure on the electrodes, skin impedance, and response of the masseter muscles [22,23]. When proper ENoG response is not elicited, clinicians should consider 1) whether or not the electrodes are detached, 2) whether or not the stimulating electrode is malfunctioning, 3) whether or not the facial nerve is totally degenerated, or 4) whether or not the trigeminal nerve is stimulated.

During analysis of ENoG results, latency is not important. Of primary importance is the amplitude of CMAP of the facial nerve. The percentage response of ENoG is defined as a percentage of the amplitude of the paralyzed side divided by the amplitude of the normal side. Alternatively, percentage degeneration is calculated by 1 minus percentage response. The test-retest variability of ENoG amplitude is 6−20% [22,24]. ENoG test-retest variability between sides is known to be 3−20% in normal healthy subjects and asymmetry more than 30% is considered as a clinically significant difference [25].

The major advantage of ENoG is its usefulness to predict the prognosis in early stage of acute facial paralysis. Because conduction block and axonal degeneration progress together in Bell's palsy, ENoG has the advantage of evaluating the portion of the axons which are not degenerated. Esslen [26] and Fisch [27] demonstrated that in the cases with Bell's palsy of 95% degeneration, the prognosis for return of facial nerve function was greatly reduced, with a 50% chance of unfavorable recovery. May, et al. [8] reported the results of ENoG performed within the first 10 days after onset in cases with complete paralysis, which showed that percentage response of less than 10% was highly correlated with incomplete recovery, whereas percentage degeneration of less than 25% has a 98% chance of a satisfactory recovery. Fisch [28] stated that percentage degeneration of 95% within 2 weeks gave a 50% chance of a poor recovery and more gradual decrease in ENoG amplitude was related with a much better prognosis.

As mentioned above, it is important to repeat ENoG until a trend and confirmation can be determined. For example, in the case with percentage degeneration of 50% but complete palsy, we can draw that this facial paralysis may result from conduction block and the prognosis may be excellent. ENoG

is useful to predict the prognosis only during the first 2 weeks after the onset. After then, accurate prediction using ENoG is difficult because the regeneration process already begins at the proximal end or the collateral neural circuit can develop from a healthy nerve around a degenerated nerve.

Conclusion

ENoG is considered the most valuable test to predict the prognosis and its main indication is acute complete facial paralysis. Both the percentage degeneration and rate of degeneration are prognostic indicators. In Bell's palsy, percentage degeneration of more than 90% within 14 days post-onset of complete paralysis indicates poor prognosis in more than 50% of cases.

Although electrophysiological tests provide useful neurophysiological information and serve as a guide to the management of acute facial paralysis, they have some limitations. They cannot distinguish between axonotmesis and neurotmesis and are not useful in cases of incomplete paralysis. In addition, they cannot give any useful information within first 72 hours after the onset.

Conflicts of interest

The author has no financial conflicts of interest.

REFERENCES

1) Mattox DE. Clinical disorders of the facial nerve. In: Flint PW, Haughey BH, Lund VJ, Niparko JK, Richardson MA, Robbins KT, et al., editors. Cummings Otolaryngology: Head & Neck Surgery. 6th ed. Philadelphia, PA: Elsevier Science Health Science;2014. p.2617-28.
2) Linstrom CJ. Objective facial motion analysis in patients with facial nerve dysfunction. Laryngoscope 2002;112(7 Pt 1):1129-47.
3) Neely JG, Wang KX, Shapland CA, Sehizadeh A, Wang A. Computerized objective measurement of facial motion: normal variation and test-retest reliability. Otol Neurotol 2010;31:1488-92.
4) Frey M, Tzou CH, Michaelidou M, Pona I, Hold A, Placheta E, et al. 3D video analysis of facial movements. Facial Plast Surg Clin North Am 2011;19:639-46, viii.
5) Hadlock TA, Urban LS. Toward a universal, automated facial measurement tool in facial reanimation. Arch Facial Plast Surg 2012;14: 277-82.
6) Esslen E. Electrodiagnosis of facial palsy. In: Miehlke A, editor. Surgery of the Facial Nerve. Philadelphia, PA: W.B. Saunders;1973. p.45-51.
7) Thomander L, Stälberg E. Electroneurography in the prognostication of Bell's palsy. Acta Otolaryngol 1981;92:221-37.
8) May M, Blumenthal F, Klein SR. Acute Bell's palsy: prognostic value of evoked electromyography, maximal stimulation, and other electrical tests. Am J Otol 1983;5:1-7.
9) Fisch U. Prognostic value of electrical tests in acute facial paralysis. Am J Otol 1984;5:494-8.
10) Sillman JS, Niparko JK, Lee SS, Kileny PR. Prognostic value of evoked and standard electromyography in acute facial paralysis. Otolaryngol Head Neck Surg 1992;107:377-81.
11) Smith IM, Maynard C, Mountain RE, Barr-Hamilton R, Armstrong M, Murray JA. The prognostic value of facial electroneurography in Bell's palsy. Clin Otolaryngol Allied Sci 1994;19:201-3.
12) May M, Shambaugh GE. Facial nerve paralysis. In: Paparella MM, Shumrick DA, Gluckman JL, Meyerhoff W, editors. Otolaryngology. 3rd ed. Philadelphia, PA: W.B. Saunders;1991. p.1106.
13) Sunderland S, Bradley KC. Endoneurial tube shrinkage in the distal segment of a severed nerve. J Comp Neurol 1950;93:411-20.
14) Kreutzberg GW, Schubert P. Volume changes in the axon during regeneration. Acta Neuropathol 1971;17:220-6.
15) May M. Anatomy of the facial nerve (spatial orientation of fibers in the temporal bone). Laryngoscope 1973;83:1311-29.
16) Sunderland S. The anatomy and physiology of nerve injury. Muscle Nerve 1990;13:771-84.
17) Campbell WW. Evaluation and management of peripheral nerve injury. Clin Neurophysiol 2008;119:1951-65.
18) Fisch U, Felix H. On the pathogenesis of Bell's palsy. Acta Otolaryngol 1983;95:532-8.
19) Seddon HJ. Three types of nerve injury. Brain 1943;66:238-87.
20) Sunderland S. A classification of peripheral nerve injuries producing loss of function. Brain 1951;74:491-516.
21) Laumans EP, Jongkees LB. On the prognpsis of peeripheral facial paralysis of endotemporal origin. Ann Otol Rhinol Laryngol 1963; 72:621-36.
22) Hughes GB, Nodar RH, Williams GW. Analysis of test-retest variability in facial electroneurography. Otolaryngol Head Neck Surg 1983;91:290-3.
23) Gantz BJ, Gmuer AA, Holliday M, Fisch U. Electroneurographic evaluation of the facial nerve. Method and technical problems. Ann Otol Rhinol Laryngol 1984;93(4 Pt 1):394-8.
24) Coker NJ. Facial electroneurography: analysis of techniques and correlation with degenerating motoneurons. Laryngoscope 1992;102: 747-59.
25) Raslan WF, Wiet R, Zealear DL. A statistical study of ENoG test error. Laryngoscope 1988;98(8 Pt 1):891-3.
26) Esslen E. The acute facial palsies: investigations on the localization and pathogenesis of meato-labyrinthine facial palsies. Berlin: Springer-Verlag;1976.
27) Fisch U. Maximal nerve excitability testing vs electroneuronography. Arch Otolaryngol 1980;106:352-7.
28) Fisch U. Surgery for Bell's palsy. Arch Otolaryngol 1981;107:1-11.

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Selected Section Materials by Author

Section 5: Rhinology and Allergic Disorders

Adappa ND, Zhang Z, Palmer JN, et al. The bitter taste receptor T2R38 is an independent risk factor for chronic rhinosinusitis requiring sinus surgery. *Int Forum Allergy Rhinol*. 2014; 4(1):3-7. EBM level NA

Baguley C, Brownlow A, Yeung K, et al. The fate of chronic rhinosinusitis sufferers after maximal medical therapy. *Int Forum Allergy Rhinol*. 2014; 4(7):525-532. EBM level 3

Bleier BS, Castelnuovo P, Battaglia P, et al. Endoscopic endonasal orbital cavernous hemangioma resection: global experience in techniques and outcomes. *Int Forum Allergy Rhinol*. 2016; 6(2):156-161. EBM level 4

Brietzke SE, Shin JJ, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2014; 151(4):542-553. EBM level 3

DeConde AS, Mace JC, Alt JA, et al. Investigation of change in cardinal symptoms of chronic rhinosinusitis after surgical or ongoing medical management. *Int Forum Allergy Rhinol*. 2015; 5(1):36-45. EBM level 2

Dixon BJ, Daly MJ, Chan H, et al. Augmented real-time navigation with critical structure proximity alerts for endoscopic skull base surgery. *Laryngoscope*. 2014; 124(4):853-859. EBM level NA

Garneau J, Ramirez M, Armato SG 3rd, et al. Computer-assisted staging of chronic rhinosinusitis correlates with symptoms. *Int Forum Allergy Rhinol*. 2015; 5(7):637-642. EBM level 3

Han JK. Subclassification of chronic rhinosinusitis. *Laryngoscope*. 2013; 123 Suppl 2:S15-S27. EBM level 2b

Harvey RJ, Parmar P, Sacks R, Zanation AM. Endoscopic skull base reconstruction of large dural defects: a systematic review of published evidence. *Laryngoscope*. 2012; 122(2):452-459. EBM level 3

Hauser LJ, Ir D, Kingdom TT, et al. Investigation of bacterial repopulation after sinus surgery and perioperative antibiotics. *Int Forum Allergy Rhinol*. 2015; 6(11):34-40. EBM level 2b

Henkin RI, Schultz M, Minnick-Poppe L. Intranasal theophylline treatment of hyposmia and hypogeusia: a pilot study. *Arch Otolaryngol Head Neck Surg*. 2012; 138(11):1064-1070. EBM level 2

Hopkins C, Rimmer J, Lund VJ. Does time to endoscopic sinus surgery impact outcomes in chronic rhinosinusitis? Prospective findings from the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis. *Rhinology*. 2015; 53(1):10-17. EBM level 2c

Hox V, Maes T, Huvenne W, et al. A chest physician's guide to mechanisms of sinonasal disease. *Thorax*. 2015; 70(4):353-358. EBM level 4

Leong SC. The clinical efficacy of surgical interventions for empty nose syndrome: a systematic review. *Laryngoscope*. 2015; 125(7):1557-1562. EBM level 3

Li JT, Bernstein DI, Calderon MA, et al. Sublingual grass and ragweed immunotherapy: clinical considerations-a PRACTALL consensus report. *J Allergy Clin Immunol*. 2016; 137(2):369-376. EBM level 1a

Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. 2013; 309(12):1278-1288. EBM level 1a

Selected Section Materials by Author

Luk LJ, Steele TO, Mace JC, et al. Health utility outcomes in patients undergoing medical management for chronic rhinosinusitis: a prospective multiinstitutional study. *Int Forum Allergy Rhinol*. 2015; 5(11):1018-1027. EBM level 2

Macdonald KI, Wright ED, Sowerby LJ, et al. Squeeze bottle versus saline spray after endoscopic sinus surgery for chronic rhinosinusitis: a pilot multicentre trial. *Am J Rhinol Allergy*. 2015; 29(1):e13-e17. EBM level 1

Mener DJ, Lin SY. Improvement and prevention of asthma with concomitant treatment of allergic rhinitis and allergen-specific therapy. *Int Forum Allergy Rhinol*. 2015; 5 Suppl 1:S45-S50. EBM level 4

Oakley GM, Curtin K, Orb Q, et al. Familial risk of chronic rhinosinusitis with and without nasal polyposis: genetics or environment. *Int Forum Allergy Rhinol*. 2015; 5(4):276-282. EBM level 3

Orlandi RR, Smith TL, Marple BF, et al. Update on evidence-based reviews with recommendations in adult chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2014; 4 Suppl 1: S1-S15. EBM level NA

Poetker DM. Oral corticosteroids in the management of chronic rhinosinusitis with and without nasal polyps: risks and benefits. *Am J Rhinol Allergy*. 2015; 29(5):339-342. EBM level 5

Smith KA, French G, Mechor B, Rudmik L. Safety of long-term high-volume sinonasal budesonide irrigations for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016; 6(3):228-232. EBM level 3

Soudry E, Wang J, Vaezeafshar R, et al. Safety analysis of long-term budesonide nasal irrigations in patients with chronic rhinosinusitis post endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2016; doi:10.1002/alr.21724 [Epub ahead of print]. EBM level 3

Stachler RJ. Comorbidities of asthma and the unified airway. *Int Forum Allergy Rhinol*. 2015; 5 Suppl 1:S17-S22. EBM level 4

Suzuki S, Yasunaga H, Matsui H, et al. Complication rates after functional endoscopic sinus surgery: analysis of 50,734 Japanese patients. *Laryngoscope*. 2015: 125(8):1785-1791. EBM level 2

Tajudeen BA, Arshi A, Suh JD, et al. Importance of tumor grade in esthesioneuroblastoma survival: a population-based analysis. *JAMA Otolaryngol Head Neck Surg*. 2014; 140(12):1124-1129. EBM level NA

Varvyanskaya A, Lopatin A. Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2014; 4(7):533-541. EBM level 1

Section 6: Laryngology, Voice Disorders, and Bronchoesophagology

Branco A, Todorovic Fabro A, Gonçalves TM, Garcia Martins RH. Alterations in extracellular matrix composition in the aging larynx. *Otolaryngol Head Neck Surg*. 2015; 152(2):302-307. EBM level 4

Croake DJ, Stemple JC, Uhl T, et al. Reliability of clinical office-based laryngeal electromyography in vocally healthy adults. *Ann Otol Rhinol Laryngol*. 2014; 123(4):271-278. EBM level 3

D'Anza B, Knight J, Greene JS. Does body mass index predict tracheal airway size? *Laryngoscope*. 2015; 125(5):1093-1097. EBM level 4

Djukic V, Milovanovic J, Jotic AD, Vukasinovic M. Stroboscopy in detection of laryngeal dysplasia: effectiveness and limitations. *J Voice*. 2014; 28(2):262.e13-262.e21. EBM level 3a

Selected Section Materials by Author

Domer AS, Leonard R, Belafsky PC. Pharyngeal weakness and upper esophageal sphincter opening in patients with unilateral vocal fold immobility. *Laryngoscope*. 2014; 124(10):2371-2374. EBM level 4

Gelbard A, Francis DO, Sandulache VC, et al. Causes and consequences of adult laryngotracheal stenosis. *Laryngoscope*. 2015; 125(5):1137-1143. EBM level 4

Jetté ME, Gaumnitz EA, Birchall MA, et al. Correlation between reflux and multichannel intraluminal impedance pH monitoring in untreated volunteers. *Laryngoscope*. 2014; 124(10):2345-2351. EBM level 1b

Kavitt RT, Yuksel ES, Slaughter JC, et al. The role of impedance monitoring in patients with extraesophageal symptoms. *Laryngoscope*. 2013; 123(10):2463-2468. EBM level 2b

Kettunen WW, Helmer SD, Haan JM. Incidence of overall complications and symptomatic tracheal stenosis is equivalent following open and percutaneous tracheostomy in the trauma patient. *Am J Surg*. 2014; 208(5):770-774. EBM level 3

Kocdor P, Siegel ER, Tulunay-Ugur OE. Cricopharyngeal dysfunction: a systematic review comparing outcomes of dilatation, botulinum toxin injection, and myotomy. *Laryngoscope*. 2016; 126(1):135-141. EBM level 2a

Koszewski IJ, Hoffman MR, Young WG, et al. Office-based photoangiolytic laser treatment of Reinke's edema: safety and voice outcomes. *Otolaryngol Head Neck Surg*. 2015; 152(6):1075-1081. EBM level 4

Kraft SM, Sykes K, Palmer A, Schindler J. Using pulmonary function data to assess outcomes in the endoscopic management of subglottic stenosis. *Ann Otol Rhinol Laryngol*. 2015; 124(2):137-142. EBM level 4

Lee YC, Lee JS, Kim SW, et al. Influence of age on treatment with proton pump inhibitors in patients with laryngopharyngeal reflux disease: a prospective multicenter study. *JAMA Otolaryngol Head Neck Surg*. 2013; 139(12):1291-1295. EBM level 4

Li M, Chen S, Wang W, et al. Effect of duration of denervation on outcomes of ansa-recurrent laryngeal nerve reinnervation. *Laryngoscope*. 2014; 124(8):1900-1905. EBM level 4

Miles A, McMillan J, Ward K, Allen J. Esophageal visualization as an adjunct to the videofluoroscopic study of swallowing. *Otolaryngol Head Neck Surg*. 2015; 152(3):488-493. EBM level 4

Moawad FJ, Veerappan GR, Dias JA, et al. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. *Am J Gastroenterol*. 2013; 108(3):366-372. EBM level 1b

Paddle PM, Mansor MB, Song PC, Franco RA Jr. Diagnostic yield of computed tomography in the evaluation of idiopathic vocal fold paresis. *Otolaryngol Head Neck Surg*. 2015; 153(3):414-419. EBM level 4

Peng KA, Feinstein AJ, Salinas JB, Chhetri DK. Utility of the transnasal esophagoscope in the management of chemoradiation-induced esophageal stenosis. *Ann Otol Rhinol Laryngol*. 2015; 124(3):221-226. EBM level 4

Reichel O, Dressel H, Wiederänders K, Issing WJ. Double-blind, placebo-controlled trial with esomeprazole for symptoms and signs associated with laryngopharyngeal reflux. *Otolaryngol Head Neck Surg*. 2008; 139(3):414-420. EBM level 1

Reiter R, Pickhard A, Sander S, Brosch S. Prognostic relevance of mucosal waves in patients with unilateral vocal fold paralysis. *Ann Otol Rhinol Laryngol*. 2016; 125(4):331-335. EBM level 4

Richards AL, Sugumaran M, Aviv JE, et al. The utility of office-based biopsy for laryngopharyngeal lesions: comparison with surgical evaluation. *Laryngoscope*. 2015; 125(4):909-912. EBM level 4

Rosow DE, Sulica L. Laryngoscopy of vocal fold paralysis: evaluation of consistency of clinical findings. *Laryngoscope*. 2010; 120(7):1376-1382. EBM level 2

Simpson CB, May LS, Green JK, et al. Vibratory asymmetry in mobile vocal folds: is it predictive of vocal fold paresis? *Ann Otol Rhinol Laryngol*. 2011; 120(4):239-242. EBM level 4

Spataro EA, Grindler DJ, Paniello RC. Etiology and time to presentation of unilateral vocal fold paralysis. *Otolaryngol Head Neck Surg*. 2014; 151(2):286-293. EBM level 4

Taylor SC, Clayburgh DR, Rosenbaum JT, Schindler JS. Clinical manifestations and treatment of idiopathic and Wegener granulomatosis-associated subglottic stenosis. *JAMA Otolaryngol Head Neck Surg*. 2013; 139(1):76-81. EBM level 4

Verma SP, Dailey SH. Office-based injection laryngoplasty for the management of unilateral vocal fold paralysis. *J Voice*. 2014; 28(3):382-386. EBM level 4

Wu AP, Sulica L. Diagnosis of vocal fold paresis: current opinion and practice. *Laryngoscope*. 2015; 125(4):904-908. EBM level 5

Yamauchi A, Yokonishi H, Imagawa H, et al. Vocal fold vibration in vocal fold atrophy: quantitative analysis with high-speed digital imaging. *J Voice*. 2015; 29(6):755-762. EBM level 2

Youssef TF, Ahmed MR. Treatment of clinically diagnosed laryngopharyngeal reflux disease. *Arch Otolaryngol Head Neck Surg*. 2010; 136(11):1089-1092. EBM level 1

Zeigler A, Verdolini Abbott K, Johns M, et al. Preliminary data on two voice therapy interventions in the treatment of presbyphonia. *Laryngoscope*. 2014; 124(8):1869-1876. EBM level 2b

Section 7: Neoplastic and Inflammatory Diseases of the Head and Neck

Agrawal A, Civantos FJ, Brumund KT, et al. [$^{(99m)}$Tc]Tilmanocept accurately detects sentinel lymph nodes and predicts node pathology status in patients with oral squamous cell carcinoma of the head and neck: results of a phase III multi-institutional trial. *Ann Surg Oncol*. 2015; 22(11):3708-3715. EBM level 1

Andtbacka RH, Agarwala SS, Ollila DW, et al. Cutaneous head and neck melanoma in OPTiM, a randomized phase 3 trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor for the treatment of unresected stage IIIB/IIIC/IV melanoma. *Head Neck*. 2016; 38(12):1752-1758. EBM level 2

Badran K, Jani P, Berman L. Otolaryngologist-performed head and neck ultrasound: outcomes and challenges in learning the technique. *J Laryngol Otol*. 2014; 128(5):447-453. EBM level 3

Busch EL, Zevallos JP, Olshan AF. Gastroesophageal reflux disease and odds of head and neck squamous cell carcinoma in North Carolina. *Laryngoscope*. 2016; 126(5):1091-1096. EBM level 3

Selected Section Materials by Author

Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2012; 83(1): 209-216. EBM level 1

Cheung PK, Chin RY, Eslick GD. Detecting residual/recurrent head neck squamous cell carcinomas using PET or PET/CT: systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2016;154(3):421-432. EBM level 2

Choby GW, Kim J, Ling DC, et al. Transoral robotic surgery alone for oropharyngeal cancer: quality-of-life outcomes. *JAMA Otolaryngol Head Neck Surg*. 2015; 141(6):499-504. EBM level 4

Durham AB, Lowe L, Malloy KM, et al. Sentinel lymph node biopsy for cutaneous squamous cell carcinoma on the head and neck. *JAMA Otolaryngol Head Neck Surg*. 2016; 142(12):1171-1176. EBM level 4

Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg*. 2010; 34(1):28-35. EBM level 2

Kumar B, Cipolla MJ, Old MO, et al. Surgical management of oropharyngeal squamous cell carcinoma: survival and functional outcomes. *Head Neck*. 2016; 38 Suppl 1:E1794-1802. EBM level 3

Lang BH, Ng SH, Lau LL, et al. A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. *Thyroid*. 2013; 23(9):1087-1098. EBM level 1

Lang BH, Wong IO, Wong KP, et al. Risk of second primary malignancy in differentiated thyroid carcinoma treated with radioactive iodine therapy. *Surgery*. 2012; 151(6):844-850. EBM level 2

Mazzaglia PJ. Surgeon-performed ultrasound in patients referred for thyroid disease improves patient care by minimizing performance of unnecessary procedures and optimizing surgical treatment. *World J Surg*. 2010; 34(6):1164-1170. EBM level 3

Mehta V, Nathan CA. What is the role of sentinel lymph node biopsy in early-stage oral cavity carcinoma? *Laryngoscope*. 2016; 126(1):9-10. EBM level 4

Morris LG, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. *Thyroid*. 2013; 23(7):885-891. EBM level 1

Oltmann SC, Schneider DF, Chen H, Sippel RS. All thyroid ultrasound evaluations are not equal: sonographers specialized in thyroid cancer correctly label clinical N0 disease in well differentiated thyroid cancer. *Ann Surg Oncol*. 2015; 22(2):422-428. EBM level 3

Papagerakis S, Bellile E, Peterson LA, et al. Proton pump inhibitors and histamine 2 blockers are associated with improved overall survival in patients with head and neck squamous carcinoma. *Cancer Prev Res (Phila)*. 2014; 7(12):1258-1269. EBM level 3

Peng KA, Kuan EC, Unger L, et al. A swallow preservation protocol improves function for veterans receiving chemoradiation for head and neck cancer. *Otolaryngol Head Neck Surg*. 2015; 152(5): 863-867. EBM level 3

Reeve BB, Cai J, Zhang H, et al. Factors that impact health-related quality of life over time for individuals with head and neck cancer. *Laryngoscope*. 2016; 126(12):2718-2725. EBM level 4

Rettig EM, D'Souza G, Thompson CB, et al. Health-related quality of life before and after head and neck squamous cell carcinoma: analysis of the Surveillance, Epidemiology, and End Results-Medicare Health Outcomes Survey linkage. *Cancer*. 2016; 122(12):1861-1870. EBM level 4

Ryu IS, Roh JL, Kim JS, et al. Impact of (18)F-FDG PET/CT staging on management and prognostic stratification in head and neck squamous cell carcinoma: a prospective observational study. *Eur J Cancer*. 2016; 63:88-96. EBM level 2

Schilling C, Stoeckli SJ, Haerle SK, et al. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. *Eur J Cancer*. 2015; 51(18):2777-2784. EBM level 2

Sethugavalar B, Teo MT, Buchan C, et al. Impact of prophylactic gastrostomy or reactive NG tube upon patient-reported long term swallow function following chemoradiotherapy for oropharyngeal carcinoma: a matched pair analysis. *Oral Oncol*. 2016; 59:80-85. EBM level 3

Taghipour M, Sheikhbahaei S, Marashdeh W, et al. Use of 18F-fludeoxyglucose-positron emission tomography/computed tomography for patient management and outcome in oropharyngeal squamous cell carcinoma: a review. *JAMA Otolaryngol Head Neck Surg*. 2016; 142(1):79-85. EBM level 3

Ward MC, Adelstein DJ, Bhateja P, et al. Severe late dysphagia and cause of death after concurrent chemoradiation for larynx cancer in patients eligible for RTOG 91-11. *Oral Oncol*. 2016; 57:21-26. EBM level 3

Yimaer W, Abudouyimu A, Tian Y, et al. Efficacy and safety of vascular endothelial growth factor receptor tyrosine kinase inhibitors in the treatment of advanced thyroid cancer: a meta-analysis of randomized controlled trials. *Onco Targets Ther*. 2016; 9:1167-1173. EBM level 1

Section 8: Otology and Neurotology

Ahsan SF, Seidman M, Yaremchuk K. What is the best imaging modality in evaluating patients with unilateral pulsatile tinnitus? *Laryngoscope*. 2015; 125(2):284-285. EBM level 5

Briggs R, Van Hasselt A, Luntz M, et al. Clinical performance of a new magnetic bone conduction hearing implant system: results from a prospective, multicenter, clinical investigation. *Otol Neurotol*. 2015; 36(5):834-841. EBM level 2b

Cannon RB, Thomson RS, Shelton C, Gurgel RK. Long-term outcomes after middle fossa approach for traumatic facial nerve paralysis. *Otol Neurotol*. 2016; 37(6):799-804. EBM level 4

Chang TP, Lin YW, Sung PY, et al. Benign paroxysmal positional vertigo after dental procedures: a population-based case-control study. *PLOS One*. 2016; 11(4):e0153092. EBM level 3

Crowson MG, Patki A, Tucci DL. A systematic review of diuretics in the medical management of Ménière's disease. *Otolaryngol Head Neck Surg*. 2016; 154(5);824-834. EBM level 3

Crowson MG, Ramprasad VH, Chapurin N, et al. Cost analysis and outcomes of a second-look tympanoplasty-mastoidectomy strategy for cholesteatoma. *Laryngoscope*. 2016; 126(11):2574-2579. EBM level 4

Dieterich M, Obermann M, Celebisoy N. Vestibular migraine: the most frequent entity of episodic vertigo. *J Neurol*. 2016; 263 Suppl 1:S82-S89. EBM level 5

Selected Section Materials by Author

Finbow J, Bance M, Aiken S, et al. A comparison between wireless CROS and bone-anchored hearing devices for single-sided deafness: a pilot study. *Otol Neurotol*. 2015; 36(5):819-825. EBM level 2

Friedland DR, Tarima S, Erbe C, Miles A. Development of a statistical model for the prediction of common vestibular diagnoses. *JAMA Otolaryngol Head Neck Surg*. 2016; 142(4):351-356. EBM level 4

Goebel JA. 2015 Equilibrium Committee Amendment to the 1995 AAO-HNS Guidelines for the Definition of Ménière's Disease. *Otolaryngol Head Neck Surg*. 2016; 154(3):403-404. EBM level 5

Gürkov R, Pyykö I, Zou J, Kentala E. What is Ménière's disease? A contemporary re-evaluation of endolymphatic hydrops. *J Neurol*. 2016; 263 Suppl 1:S71-S81. EBM level 5

Hobson CE, Moy JD, Byers KE, et al. Malignant otitis externa: evolving pathogens and implications for diagnosis and treatment. *Otolaryngol Head Neck Surg*. 2014; 15(1):112-116. EBM level 4

Kerckhoffs KG, Kommer MB, van Strien TH, et al. The disease recurrence rate after the canal wall up or canal wall down technique in adults. *Laryngoscope*. 2016; 126(4):980-987. EBM level 3

Lee DH. Clinical efficacy of electroneurography in acute facial paralysis. *J Audiol Otol*. 2016; 20(1):8-12. EBM level 5

Loh S, Loh WS. Malignant otitis externa: an Asian perspective on treatment outcomes and prognostic factors. *Otolaryngol Head Neck Surg*. 2013; 148(6):991-996. EBM level 3

Madani G, Connor SE. Imaging in pulsatile tinnitus. *Clin Radiol*. 2009; 64(3):319-328. EBM level 5

Marino R, Lampacher P, Dittrich G, et al. Does coupling and positioning in vibroplasty matter? A prospective cohort study. *Otol Neurotol*. 2015; 36(7):1223-1230. EBM level 2

McRackan TR, Wilkinson EP, Brackmann DE, Slattery WH. Stereotactic radiosurgery for facial nerve schwannomas: meta-analysis and clinical review. *Otol Neurotol*. 2015; 36(3):393-398. EBM level 3

Medina M, Di Lella F, Di Trapani G, et al. Cochlear implantation versus auditory brainstem implantation in bilateral total deafness after head trauma: personal experience and review of the literature. *Otol Neurotol*. 2014; 35(2):260-270. EBM level 4

Migirov L, Wolf M, Greenberg G, Eyal A. Non-EPI DW MRI in planning the surgical approach to primary and recurrent cholesteatoma. *Otol Neurotol*. 2014; 35(1):121-125. EBM level 4

Rah YC, Han JJ, Park J, et al. Management of intractable Ménière's disease after intratympanic injection of gentamicin. *Laryngoscope*. 2015; 125(4):972-978. EBM level 4

Roland JT Jr, Gantz BJ, Waltzman SB, et al. United States multicenter clinical trial of the cochlear nucleus hybrid implant system. *Laryngoscope*. 2016; 126(1):175-181. EBM level 2b

Schell A, Kitsko D. Audiometric outcomes in pediatric temporal bone trauma. *Otolaryngol Head Neck Surg*. 2016; 154(1):175-180. EBM level 4

Sladen DP, Frisch CD, Carlson ML, et al. Cochlear implantation for single-sided deafness: a multicenter study. *Laryngoscope*. 2017; 127(1):223-228. EBM level 4

Selected Section Materials by Author

Sood AJ, Lambert PR, Nguyen SA, Meyer TA. Endolymphatic sac surgery for Ménière's disease: a systematic review and meta-analysis. *Otol Neurotol*. 2014; 35(6):1033-1045. EBM level 3a

Tarazi AE, Al-Tawfiq JA, Abdi RF. Fungal malignant otitis externa: pitfalls, diagnosis, and treatment. *Otol Neurotol*. 2012; 33(5):769-773. EBM level 4

Waissbluth S, Ywakim R, Al Qassabi B, et al. Pediatric temporal bone fractures: a case series. *Int J Pediatr Otorhinolaryngol*. 2016; 84:106-109. EBM level 4

Wanna GB, Sweeney AD, Haynes DS, Carlson ML. Contemporary management of jugular paragangliomas. *Otolaryngol Clin North Am*. 2015; 48(2):331-341. EBM level 3

Wegner I, van Waes AMA, Bittermann AJ, et al. A systematic review of the diagnostic value of CT imaging in diagnosing otosclerosis. *Otol Neurotol*. 2016; 37(1):9-15. EBM level 3

Weinreich H, Carey JP. Prevalence of pulsatile tinnitus among patients with migraine. *Otol Neurotol*. 2016, 37(3):244-247. EBM level 4

Wise SC, Carlson ML, Tveiten ØV, et al. Surgical salvage of recurrent vestibular schwannoma following prior stereotactic radiosurgery. *Laryngoscope*. 2016; 126(11):2580-2586. EBM level 3

Zeitler DM, Dorman MF, Natale SJ, et al. Sound source localization and speech understanding in complex listening environments by single-sided deaf listeners after cochlear implantation. *Otol Neurotol*. 2015; 36(9):1467-1471. EBM level 2

Section 5: Rhinology and Allergic Disorders

Olfaction

Henkin RI, Schultz M, Minnick-Poppe L. Intranasal theophylline treatment of hyposmia and hypogeusia: a pilot study. *Arch Otolaryngol Head Neck Surg*. 2012; 138(11):1064-1070. EBM level 2

Nasal Cavity

Leong SC. The clinical efficacy of surgical interventions for empty nose syndrome: a systematic review. *Laryngoscope*. 2015; 125(7):1557-1562. EBM level 3

Paranasal Sinuses

Adappa ND, Zhang Z, Palmer JN, et al. The bitter taste receptor T2R38 is an independent risk factor for chronic rhinosinusitis requiring sinus surgery. *Int Forum Allergy Rhinol*. 2014; 4(1):3-7. EBM level NA

Baguley C, Brownlow A, Yeung K, et al. The fate of chronic rhinosinusitis sufferers after maximal medical therapy. *Int Forum Allergy Rhinol*. 2014; 4(7):525-532. EBM level 3

Brietzke SE, Shin JJ, Choi S, et al. Clinical consensus statement: pediatric chronic rhinosinusitis. *Otolaryngol Head Neck Surg*. 2014; 151(4):542-553. EBM level 3

DeConde AS, Mace JC, Alt JA, et al. Investigation of change in cardinal symptoms of chronic rhinosinusitis after surgical or ongoing medical management. *Int Forum Allergy Rhinol*. 2015; 5(1):36-45. EBM level 2

Garneau J, Ramirez M, Armato SG 3rd, et al. Computer-assisted staging of chronic rhinosinusitis correlates with symptoms. *Int Forum Allergy Rhinol*. 2015; 5(7):637-642. EBM level 3

Han JK. Subclassification of chronic rhinosinusitis. *Laryngoscope*. 2013; 123 Suppl 2:S15-S27. EBM level 2b

Hauser LJ, Ir D, Kingdom TT, et al. Investigation of bacterial repopulation after sinus surgery and perioperative antibiotics. *Int Forum Allergy Rhinol*. 2015; 6(11):34-40. EBM level 2b

Hopkins C, Rimmer J, Lund VJ. Does time to endoscopic sinus surgery impact outcomes in chronic rhinosinusitis? Prospective findings from the National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis. *Rhinology*. 2015; 53(1):10-17. EBM level 2c

Hox V, Maes T, Huvenne W, et al. A chest physician's guide to mechanisms of sinonasal disease. *Thorax*. 2015; 70(4):353-358. EBM level 4

Luk LJ, Steele TO, Mace JC, et al. Health utility outcomes in patients undergoing medical management for chronic rhinosinusitis: a prospective multiinstitutional study. *Int Forum Allergy Rhinol*. 2015; 5(11):1018-1027. EBM level 2

Macdonald KI, Wright ED, Sowerby LJ, et al. Squeeze bottle versus saline spray after endoscopic sinus surgery for chronic rhinosinusitis: a pilot multicentre trial. *Am J Rhinol Allergy*. 2015; 29(1):e13-e17. EBM level 1

Oakley GM, Curtin K, Orb Q, et al. Familial risk of chronic rhinosinusitis with and without nasal polyposis: genetics or environment. *Int Forum Allergy Rhinol*. 2015; 5(4):276-282. EBM level 3

Orlandi RR, Smith TL, Marple BF, et al. Update on evidence-based reviews with recommendations in adult chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2014; 4 Suppl 1: S1-S15. EBM level NA

Poetker DM. Oral corticosteroids in the management of chronic rhinosinusitis with and without nasal polyps: risks and benefits. *Am J Rhinol Allergy*. 2015; 29(5):339-342. EBM level 5

Smith KA, French G, Mechor B, Rudmik L. Safety of long-term high-volume sinonasal budesonide irrigations for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016; 6(3):228-232. EBM level 3

Soudry E, Wang J, Vaezeafshar R, et al. Safety analysis of long-term budesonide nasal irrigations in patients with chronic rhinosinusitis post endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2016; 6(6):568-572. EBM level 3

Suzuki S, Yasunaga H, Matsui H, et al. Complication rates after functional endoscopic sinus surgery: analysis of 50,734 Japanese patients. *Laryngoscope*. 2015: 125(8):1785-1791. EBM level 2

Tajudeen BA, Arshi A, Suh JD, et al. Importance of tumor grade in esthesioneuroblastoma survival: a population-based analysis. *JAMA Otolaryngol Head Neck Surg*. 2014; 140(12):1124-1129. EBM level NA

Varvyanskaya A, Lopatin A. Efficacy of long-term low-dose macrolide therapy in preventing early recurrence of nasal polyps after endoscopic sinus surgery. *Int Forum Allergy Rhinol*. 2014; 4(7):533-541. EBM level 1

Advanced Techniques

Bleier BS, Castelnuovo P, Battaglia P, et al. Endoscopic endonasal orbital cavernous hemangioma resection: global experience in techniques and outcomes. *Int Forum Allergy Rhinol*. 2016; 6(2):156-161. EBM level 4

Dixon BJ, Daly MJ, Chan H, et al. Augmented real-time navigation with critical structure proximity alerts for endoscopic skull base surgery. *Laryngoscope*. 2014; 124(4):853-859. EBM level NA

Harvey RJ, Parmar P, Sacks R, Zanation AM. Endoscopic skull base reconstruction of large dural defects: a systematic review of published evidence. *Laryngoscope*. 2012; 122(2):452-459. EBM level 3

Allergy

Li JT, Bernstein DI, Calderon MA, et al. Sublingual grass and ragweed immunotherapy: clinical considerations-a PRACTALL consensus report. *J Allergy Clin Immunol*. 2016; 137(2):369-376. EBM level 1a

Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. JAMA. 2013; 309(12):1278-1288. EBM level 1a

Selected Section Materials by Topic

Asthma

Mener DJ, Lin SY. Improvement and prevention of asthma with concomitant treatment of allergic rhinitis and allergen-specific therapy. *Int Forum Allergy Rhinol*. 2015; 5 Suppl 1:S45-S50. EBM level 4

Stachler RJ. Comorbidities of asthma and the unified airway. *Int Forum Allergy Rhinol*. 2015; 5 Suppl 1:S17-S22. EBM level 4

Section 6: Laryngology, Voice Disorders, and Bronchoesophagology

Neurolaryngology: Injection and Diagnostics

Domer AS, Leonard R, Belafsky PC. Pharyngeal weakness and upper esophageal sphincter opening in patients with unilateral vocal fold immobility. *Laryngoscope*. 2014; 124(10):2371-2374. EBM level 4

Li M, Chen S, Wang W, et al. Effect of duration of denervation on outcomes of ansa-recurrent laryngeal nerve reinnervation. *Laryngoscope*. 2014; 124(8):1900-1905. EBM level 4

Paddle PM, Mansor MB, Song PC, Franco RA Jr. Diagnostic yield of computed tomography in the evaluation of idiopathic vocal fold paresis. *Otolaryngol Head Neck Surg*. 2015; 153(3):414-419. EBM level 4

Spataro EA, Grindler DJ, Paniello RC. Etiology and time to presentation of unilateral vocal fold paralysis. *Otolaryngol Head Neck Surg*. 2014; 151(2):286-293. EBM level 4

Wu AP, Sulica L. Diagnosis of vocal fold paresis: current opinion and practice. *Laryngoscope*. 2015; 125(4):904-908. EBM level 5

Stroboscopy

Djukic V, Milovanovic J, Jotic AD, Vukasinovic M. Stroboscopy in detection of laryngeal dysplasia: effectiveness and limitations. *J Voice*. 2014; 28(2):262.e13-262.e21. EBM level 3a

Reiter R, Pickhard A, Sander S, Brosch S. Prognostic relevance of mucosal waves in patients with unilateral vocal fold paralysis. *Ann Otol Rhinol Laryngol*. 2016; 125(4):331-335. EBM level 4

Rosow DE, Sulica L. Laryngoscopy of vocal fold paralysis: evaluation of consistency of clinical findings. *Laryngoscope*. 2010; 120(7):1376-1382. EBM level 2

Simpson CB, May LS, Green JK, et al. Vibratory asymmetry in mobile vocal folds: is it predictive of vocal fold paresis? *Ann Otol Rhinol Laryngol*. 2011; 120(4):239-242. EBM level 4

Office-Based Procedures

Croake DJ, Stemple JC, Uhl T, et al. Reliability of clinical office-based laryngeal electromyography in vocally healthy adults. *Ann Otol Rhinol Laryngol*. 2014; 123(4):271-278. EBM level 3

Koszewski IJ, Hoffman MR, Young WG, et al. Office-based photoangiolytic laser treatment of Reinke's edema: safety and voice outcomes. *Otolaryngol Head Neck Surg*. 2015; 152(6):1075-1081. EBM level 4

Richards AL, Sugumaran M, Aviv JE, et al. The utility of office-based biopsy for laryngopharyngeal lesions: comparison with surgical evaluation. *Laryngoscope*. 2015; 125(4):909-912. EBM level 4

Verma SP, Dailey SH. Office-based injection laryngoplasty for the management of unilateral vocal fold paralysis. *J Voice*. 2014; 28(3):382-386. EBM level 4

Aging Larynx

Branco A, Todorovic Fabro A, Gonçalves TM, Garcia Martins RH. Alterations in extracellular matrix composition in the aging larynx. *Otolaryngol Head Neck Surg*. 2015; 152(2):302-307. EBM level 4

Lee YC, Lee JS, Kim SW, et al. Influence of age on treatment with proton pump inhibitors in patients with laryngopharyngeal reflux disease: a prospective multicenter study. *JAMA Otolaryngol Head Neck Surg*. 2013; 139(12):1291-1295. EBM level 4

Yamauchi A, Yokonishi H, Imagawa H, et al. Vocal fold vibration in vocal fold atrophy: quantitative analysis with high-speed digital imaging. *J Voice*. 2015; 29(6):755-762. EBM level 2

Zeigler A, Verdolini Abbott K, Johns M, et al. Preliminary data on two voice therapy interventions in the treatment of presbyphonia. *Laryngoscope*. 2014; 124(8):1869-1876. EBM level 2b

Esophageal Dysphagia

Kocdor P, Siegel ER, Tulunay-Ugur OE. Cricopharyngeal dysfunction: a systematic review comparing outcomes of dilatation, botulinum toxin injection, and myotomy. *Laryngoscope*. 2016; 126(1):135-141. EBM level 2a

Miles A, McMillan J, Ward K, Allen J. Esophageal visualization as an adjunct to the videofluoroscopic study of swallowing. *Otolaryngol Head Neck Surg*. 2015; 152(3):488-493. EBM level 4

Moawad FJ, Veerappan GR, Dias JA, et al. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. *Am J Gastroenterol*. 2013; 108(3):366-372. EBM level 1b

Peng KA, Feinstein AJ, Salinas JB, Chhetri DK. Utility of the transnasal esophagoscope in the management of chemoradiation-induced esophageal stenosis. *Ann Otol Rhinol Laryngol*. 2015; 124(3):221-226. EBM level 4

Esophagopharyngeal Reflux

Jetté ME, Gaumnitz EA, Birchall MA, et al. Correlation between reflux and multichannel intraluminal impedance pH monitoring in untreated volunteers. *Laryngoscope*. 2014; 124(10):2345-2351. EBM level 1b

Kavitt RT, Yuksel ES, Slaughter JC, et al. The role of impedance monitoring in patients with extraesophageal symptoms. *Laryngoscope*. 2013; 123(10):2463-2468. EBM level 2b

Reichel O, Dressel H, Wiederänders K, Issing WJ. Double-blind, placebo-controlled trial with esomeprazole for symptoms and signs associated with laryngopharyngeal reflux. *Otolaryngol Head Neck Surg*. 2008; 139(3):414-420. EBM level 1

Youssef TF, Ahmed MR. Treatment of clinically diagnosed laryngopharyngeal reflux disease. *Arch Otolaryngol Head Neck Surg*. 2010; 136(11):1089-1092. EBM level 1

Tracheobronchial Disorders

D'Anza B, Knight J, Greene JS. Does body mass index predict tracheal airway size? *Laryngoscope*. 2015; 125(5):1093-1097. EBM level 4

Gelbard A, Francis DO, Sandulache VC, et al. Causes and consequences of adult laryngotracheal stenosis. *Laryngoscope*. 2015; 125(5):1137-1143. EBM level 4

Kettunen WW, Helmer SD, Haan JM. Incidence of overall complications and symptomatic tracheal stenosis is equivalent following open and percutaneous tracheostomy in the trauma patient. *Am J Surg*. 2014; 208(5):770-774. EBM level 3

Kraft SM, Sykes K, Palmer A, Schindler J. Using pulmonary function data to assess outcomes in the endoscopic management of subglottic stenosis. *Ann Otol Rhinol Laryngol*. 2015; 124(2):137-142. EBM level 4

Taylor SC, Clayburgh DR, Rosenbaum JT, Schindler JS. Clinical manifestations and treatment of idiopathic and Wegener granulomatosis-associated subglottic stenosis. *JAMA Otolaryngol Head Neck Surg*. 2013; 139(1):76-81. EBM level 4

Section 7: Neoplastic and Inflammatory Diseases of the Head and Neck

Head and Neck Ultrasound

Badran K, Jani P, Berman L. Otolaryngologist-performed head and neck ultrasound: outcomes and challenges in learning the technique. *J Laryngol Otol*. 2014; 128(5):447-453. EBM level 3

Mazzaglia PJ. Surgeon-performed ultrasound in patients referred for thyroid disease improves patient care by minimizing performance of unnecessary procedures and optimizing surgical treatment. *World J Surg*. 2010; 34(6):1164-1170. EBM level 3

Oltmann SC, Schneider DF, Chen H, Sippel RS. All thyroid ultrasound evaluations are not equal: sonographers specialized in thyroid cancer correctly label clinical N0 disease in well differentiated thyroid cancer. *Ann Surg Oncol*. 2015; 22(2):422-428. EBM level 3

Application of PET/CT/MRI in Management of Head and Neck Cancer

Cheung PK, Chin RY, Eslick GD. Detecting residual/recurrent head neck squamous cell carcinomas using PET or PET/CT: systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2016; 154(3):421-432. EBM level 2

Ryu IS, Roh JL, Kim JS, et al. Impact of ^{18}F-FDG PET/CT staging on management and prognostic stratification in head and neck squamous cell carcinoma: a prospective observational study. *Eur J Cancer*. 2016; 63:88-96. EBM level 2

Taghipour M, Sheikhbahaei S, Marashdeh W, et al. Use of ^{18}F-fludeoxyglucose-positron emission tomography/computed tomography for patient management and outcome in oropharyngeal squamous cell carcinoma: a review. *JAMA Otolaryngol Head Neck Surg*. 2016; 142(1):79-85. EBM level 3

Complications: Dysphagia Prevention and Management After Therapy for Head and Neck Cancer

Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2012; 83(1): 209-216. EBM level 1

Peng KA, Kuan EC, Unger L, et al. A swallow preservation protocol improves function for veterans receiving chemoradiation for head and neck cancer. *Otolaryngol Head Neck Surg*. 2015; 152(5): 863-867. EBM level 3

Ward MC, Adelstein DJ, Bhateja P, et al. Severe late dysphagia and cause of death after concurrent chemoradiation for larynx cancer in patients eligible for RTOG 91-11. *Oral Oncol*. 2016; 57:21-26. EBM level 3

Management of Thyroid Nodules and Thyroid Malignancy

Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg*. 2010; 34(1):28-35. EBM level 2

Lang BH, Ng SH, Lau LL, et al. A systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. *Thyroid*. 2013; 23(9):1087-1098. EBM level 1

Lang BH, Wong IO, Wong KP, et al. Risk of second primary malignancy in differentiated thyroid carcinoma treated with radioactive iodine therapy. *Surgery*. 2012; 151(6):844-850. EBM level 2

Morris LG, Sikora AG, Tosteson TD, Davies L. The increasing incidence of thyroid cancer: the influence of access to care. *Thyroid*. 2013; 23(7):885-891. EBM level 1

Lymphatic System: Sentinel Node Biopsy

Agrawal A, Civantos FJ, Brumund KT, et al. [$^{(99m)}$Tc]Tilmanocept accurately detects sentinel lymph nodes and predicts node pathology status in patients with oral squamous cell carcinoma of the head and neck: results of a phase III multi-institutional trial. *Ann Surg Oncol*. 2015; 22(11):3708-3715. EBM level 1

Durham AB, Lowe L, Malloy KM, et al. Sentinel lymph node biopsy for cutaneous squamous cell carcinoma on the head and neck. *JAMA Otolaryngol Head Neck Surg*. 2016; 142(12):1171-1176. EBM level 4

Mehta V, Nathan CA. What is the role of sentinel lymph node biopsy in early-stage oral cavity carcinoma? *Laryngoscope*. 2016; 126(1):9-10. EBM level 4

Schilling C, Stoeckli SJ, Haerle SK, et al. Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. *Eur J Cancer*. 2015; 51(18):2777-2784. EBM level 2

Quality of Life

Reeve BB, Cai J, Zhang H, et al. Factors that impact health-related quality of life over time for individuals with head and neck cancer. *Laryngoscope*. 2016; 126(12):2718-2725. EBM level 4

Rettig EM, D'Souza G, Thompson CB, et al. Health-related quality of life before and after head and neck squamous cell carcinoma: analysis of the Surveillance, Epidemiology, and End Results-Medicare Health Outcomes Survey linkage. *Cancer*. 2016; 122(12):1861-1870. EBM level 4

Sethugavalar B, Teo MT, Buchan C, et al. Impact of prophylactic gastrostomy or reactive NG tube upon patient-reported long term swallow function following chemoradiotherapy for oropharyngeal carcinoma: a matched pair analysis. *Oral Oncol*. 2016; 59:80-85. EBM level 3

Treatment Modalities Update: Robotic Surgery

Choby GW, Kim J, Ling DC, et al. Transoral robotic surgery alone for oropharyngeal cancer: quality-of-life outcomes. *JAMA Otolaryngol Head Neck Surg*. 2015; 141(6):499-504. EBM level 4

Kumar B, Cipolla MJ, Old MO, et al. Surgical management of oropharyngeal squamous cell carcinoma: survival and functional outcomes. *Head Neck*. 2016; 38 Suppl 1:E1794-1802. EBM level 3

Treatment Modalities Update: Immunotherapy

Andtbacka RH, Agarwala SS, Ollila DW, et al. Cutaneous head and neck melanoma in OPTiM, a randomized phase 3 trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor for the treatment of unresected stage IIIB/IIIC/IV melanoma. *Head Neck*. 2016; 38(12):1752-1758. EBM level 2

Yimaer W, Abudouyimu A, Tian Y, et al. Efficacy and safety of vascular endothelial growth factor receptor tyrosine kinase inhibitors in the treatment of advanced thyroid cancer: a meta-analysis of randomized controlled trials. *Onco Targets Ther*. 2016; 9:1167-1173. EBM level 1

Inflammatory: GERD Role in Cancer Development and Prevention

Busch EL, Zevallos JP, Olshan AF. Gastroesophageal reflux disease and odds of head and neck squamous cell carcinoma in North Carolina. *Laryngoscope*. 2016; 126(5):1091-1096. EBM level 3

Papagerakis S, Bellile E, Peterson LA, et al. Proton pump inhibitors and histamine 2 blockers are associated with improved overall survival in patients with head and neck squamous carcinoma. *Cancer Prev Res (Phila)*. 2014; 7(12):1258-1269. EBM level 3

Section 8: Otology and Neurotology

Migraine and Vertigo

Chang TP, Lin YW, Sung PY, et al. Benign paroxysmal positional vertigo after dental procedures: a population-based case-control study. *PLOS One*. 2016; 11(4):e0153092. EBM level 3

Dieterich M, Obermann M, Celebisoy N. Vestibular migraine: the most frequent entity of episodic vertigo. *J Neurol*. 2016; 263 Suppl 1:S82-S89. EBM level 5

Friedland DR, Tarima S, Erbe C, Miles A. Development of a statistical model for the prediction of common vestibular diagnoses. *JAMA Otolaryngol Head Neck Surg*. 2016; 142(4):351-356. EBM level 4

Ménière's Disease

Crowson MG, Patki A, Tucci DL. A systematic review of diuretics in the medical management of Ménière's disease. *Otolaryngol Head Neck Surg*. 2016; 154(5);824-834. EBM level 3

Goebel JA. 2015 Equilibrium Committee Amendment to the 1995 AAO-HNS Guidelines for the Definition of Ménière's Disease. *Otolaryngol Head Neck Surg*. 2016; 154(3):403-404. EBM level 5

Gürkov R, Pyykö I, Zou J, Kentala E. What is Ménière's disease? A contemporary re-evaluation of endolymphatic hydrops. *J Neurol*. 2016; 263 Suppl 1:S71-S81. EBM level 5

Rah YC, Han JJ, Park J, et al. Management of intractable Ménière's disease after intratympanic injection of gentamicin. *Laryngoscope*. 2015; 125(4):972-978. EBM level 4

Sood AJ, Lambert PR, Nguyen SA, Meyer TA. Endolymphatic sac surgery for Ménière's disease: a systematic review and meta-analysis. *Otol Neurotol*. 2014; 35(6):1033-1045. EBM level 3a

Pulsatile Tinnitus

Ahsan SF, Seidman M, Yaremchuk K. What is the best imaging modality in evaluating patients with unilateral pulsatile tinnitus? *Laryngoscope*. 2015; 125(2):284-285. EBM level 5

Madani G, Connor SE. Imaging in pulsatile tinnitus. *Clin Radiol*. 2009; 64(3):319-328. EBM level 5

Weinreich H, Carey JP. Prevalence of pulsatile tinnitus among patients with migraine. *Otol Neurotol*. 2016, 37(3):244-247. EBM level 4

Acute Otitis Externa

Hobson CE, Moy JD, Byers KE, et al. Malignant otitis externa: evolving pathogens and implications for diagnosis and treatment. *Otolaryngol Head Neck Surg*. 2014; 15(1):112-116. EBM level 4

Loh S, Loh WS. Malignant otitis externa: an Asian perspective on treatment outcomes and prognostic factors. *Otolaryngol Head Neck Surg*. 2013; 148(6):991-996. EBM level 3

Tarazi AE, Al-Tawfiq JA, Abdi RF. Fungal malignant otitis externa: pitfalls, diagnosis, and treatment. *Otol Neurotol*. 2012; 33(5):769-773. EBM level 4

Cholesteatoma

Crowson MG, Ramprasad VH, Chapurin N, et al. Cost analysis and outcomes of a second-look tympanoplasty-mastoidectomy strategy for cholesteatoma. *Laryngoscope*. 2016; 126(11):2574-2579. EBM level 4

Kerckhoffs KG, Kommer MB, van Strien TH, et al. The disease recurrence rate after the canal wall up or canal wall down technique in adults. *Laryngoscope*. 2016; 126(4):980-987. EBM level 3

Migirov L, Wolf M, Greenberg G, Eyal A. Non-EPI DW MRI in planning the surgical approach to primary and recurrent cholesteatoma. *Otol Neurotol*. 2014; 35(1):121-125. EBM level 4

Sensorineural Hearing Loss

Briggs R, Van Hasselt A, Luntz M, et al. Clinical performance of a new magnetic bone conduction hearing implant system: results from a prospective, multicenter, clinical investigation. *Otol Neurotol*. 2015; 36(5):834-841. EBM level 2b

Roland JT Jr, Gantz BJ, Waltzman SB, et al. United States multicenter clinical trial of the cochlear nucleus hybrid implant system. *Laryngoscope*. 2016; 126(1):175-181. EBM level 2b

Conductive and Mixed Hearing Loss

Marino R, Lampacher P, Dittrich G, et al. Does coupling and positioning in vibroplasty matter? A prospective cohort study. *Otol Neurotol*. 2015; 36(7):1223-1230. EBM level 2

Wegner I, van Waes AMA, Bittermann AJ, et al. A systematic review of the diagnostic value of CT imaging in diagnosing otosclerosis. *Otol Neurotol*. 2016; 37(1):9-15. EBM level 3

Single-Sided Deafness

Finbow J, Bance M, Aiken S, et al. A comparison between wireless CROS and bone-anchored hearing devices for single-sided deafness: a pilot study. *Otol Neurotol*. 2015; 36(5):819-825. EBM level 2

Sladen DP, Frisch CD, Carlson ML, et al. Cochlear implantation for single-sided deafness: a multicenter study. *Laryngoscope*. 2017; 127(1):223-228. EBM level 4

Zeitler DM, Dorman MF, Natale SJ, et al. Sound source localization and speech understanding in complex listening environments by single-sided deaf listeners after cochlear implantation. *Otol Neurotol*. 2015; 36(9):1467-1471. EBM level 2

Temporal Bone and Skull Base Lesions

McRackan TR, Wilkinson EP, Brackmann DE, Slattery WH. Stereotactic radiosurgery for facial nerve schwannomas: meta-analysis and clinical review. *Otol Neurotol*. 2015; 36(3):393-398. EBM level 3

Wanna GB, Sweeney AD, Haynes DS, Carlson ML. Contemporary management of jugular paragangliomas. *Otolaryngol Clin North Am*. 2015; 48(2):331-341. EBM level 3

Wise SC, Carlson ML, Tveiten ØV, et al. Surgical salvage of recurrent vestibular schwannoma following prior stereotactic radiosurgery. *Laryngoscope*. 2016; 126(11):2580-2586. EBM level 3

Skull Base and Ear Trauma

Cannon RB, Thomson RS, Shelton C, Gurgel RK. Long-term outcomes after middle fossa approach for traumatic facial nerve paralysis. *Otol Neurotol*. 2016; 37(6):799-804. EBM level 4

Medina M, Di Lella F, Di Trapani G, et al. Cochlear implantation versus auditory brainstem implantation in bilateral total deafness after head trauma: personal experience and review of the literature. *Otol Neurotol*. 2014; 35(2):260-270. EBM level 4

Schell A, Kitsko D. Audiometric outcomes in pediatric temporal bone trauma. *Otolaryngol Head Neck Surg*. 2016; 154(1):175-180. EBM level 4

Waissbluth S, Ywakim R, Al Qassabi B, et al. Pediatric temporal bone fractures: a case series. *Int J Pediatr Otorhinolaryngol*. 2016; 84:106-109. EBM level 4

Facial Nerve

Lee DH. Clinical efficacy of electroneurography in acute facial paralysis. *J Audiol Otol*. 2016; 20(1):8-12. EBM level 5

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