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Interleaving deep brain stimulation improves dyskinesias and parkinsonism

Interleaving stimulation has been shown to be most beneficial for dyskinesias and parkinsonism, with minimal improvement in reducing other adverse effects. This conclusion, based on results of a retrospective chart review, was presented at the American Academy of Neurology's 68th Annual Meeting, from April 15 to 21.
▸3

Progressive cerebellar atrophy and anti-NMDA receptor encephalitis

JAMA Neurology

Diffuse cerebral atrophy is reversible and does not imply a poor clinical outcome within the context of anti–NMDA receptor encephalitis. Further studies are warranted to determine whether progressive cerebellar atrophy can serve as a reliable prognostic marker for poor clinical outcome. ▸4

Anticholinergic use and cognition and brain atrophy in cognitively normal older adults

JAMA Neurology

The use of AC medication should be avoided in older adults if a suitable alternative is available due to the associated increase in brain atrophy and clinical signs of cognitive decline. ▸6

High coffee consumption and decreased risk for multiple sclerosis

Journal of Neurology, Neurosurgery, and Psychiatry

The findings are in line with animal research results, and, keeping in mind the limitations intrinsic to this retrospective epidemiology design, suggest a protective role of coffee consumption for development of MS. ▸7

Deep brain stimulation of the ventral tegmental area for refractory chronic cluster headache

Neurology

This study supports that VTA-DBS may be a safe and effective therapy for refractory CCH patients who failed conventional treatments. ▸14

OPINION

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Dr Wolfgang Wick ▸9

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Interleaving deep brain stimulation improves dyskinesias and parkinsonism

Continued from page 1.

"Deep brain stimulation is a well established surgical treatment for advanced movement disorders that are resistant to pharmacological interventions. The electrode most commonly used includes four stimulating contacts. Conventional deep brain stimulation programming involves monopolar (one contact as the negative pole and the battery case as the positive pole) or bipolar (two contacts activated with one being the negative and the other set as the positive pole) stimulation," explains Dr Drew S. Kern of the Movement Disorders Center, University of Colorado, Denver.

"A new programming technique involves interleaving stimulation that provides alternating sequences of stimulation on the same electrode. For example, two contacts can be programmed individually with specific parameters for each. This may reduce adverse effects and improve therapeutic benefit, because stimulation may be directed away from unwanted regions and stimulation of different regions may be programmed to specific optimised parameters. This new and exciting form of programming may further improve patient care but guidance is needed on when to implement interleaving stimulation."

> **"A new programming technique involves interleaving stimulation that provides alternating sequences of stimulation on the same electrode. For example, two contacts can be programmed individually with specific parameters for each**

"Consequently, we reviewed all cases in which interleaving programming was attempted at our hospital. In patients with Parkinson's disease treated with subthalamic deep brain stimulation, three main rationales underlay interleaving: management of dyskinesias, management of other adverse effects, and to improve parkinsonism. Subsequently, we evaluated the clinical efficacy of interleaving in each of these three categories."

Twenty-seven patients with Parkinson's disease underwent interleaving, subthalamic nucleus deep brain stimulation (24 bilateral) and 41% continued on interleaving at their last evaluation. Subanalysis demonstrated three main categories for performing interleaving: management of dyskinesias (n=12), other adverse effects (n=9), and parkinsonism (n=6).

All patients with dyskinesias benefited from interleaving stimulation. Half of the patients, however, discontinued interleaving stimulation due to waning of benefit (n=1), worsened parkinsonism (n=3), or other adverse effects (n=3).

In comparison with the remarkable benefit of interleaving stimulation for dyskinesias, minimal efficacy was observed in other adverse effects. Interleaving was performed to improve other adverse effects: speech difficulty (n=6), dystonia (n=1), pain (n=1), and behavioural problems, specifically impulsivity (n=1). Only one patient with speech difficulty benefited from interleaving.

Interleaving improved parkinsonism in all patients, specifically those with tremor (n=4), gait impairment (n=1), and bradykinesia (n=1). One patient discontinued interleaving stimulation due to stimulation-induced facial contractions.

"The results provide preliminary evidence for interleaving stimulation in subthalamic nucleus deep brain stimulation. Larger, prospective studies are needed, however, to validate our findings, "Dr Kern said,

"Furthermore, the response of interleaving stimulation in other targets including the globus pallidus interna and ventralis intermedius nucleus of the thalamus remains unknown."

Dr Kern concluded that interleaving stimulation was most beneficial for dyskinesias and parkinsonism, with minimal benefit demonstrated for stimulation-induced speech difficulty. ■

Editor's pick

JOURNAL SCAN

The case for restricting corticosteroid use in glioblastoma

Brain: A Journal of Neurology

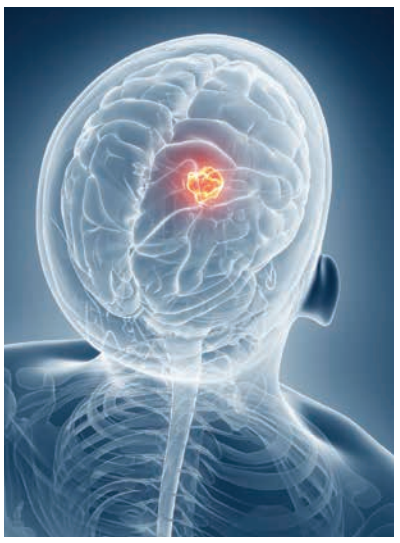
Take-home message

- Steroids are commonly used to treat brain oedema, but questions have been raised about their potential impact on disease and survival in patients with glioblastoma, an effect not studied thoroughly to date. In this study, the authors perform a retrospective analysis of glioblastoma patients in three independent cohorts, assessing the interaction of steroid therapy with survival. They also assess the effects of dexamethasone (DEX), the most commonly used steroid for managing cerebral oedema, on tumour biology and survival in a relevant murine model. There was a negative effect on survival in all three cohorts based on the use of DEX. In a Memorial Sloan Kettering Cancer Center cohort, median survival was 20.6 months in patients not on DEX vs 12.9 months in patients on DEX at the start of radiotherapy. Multivariate analysis identified a persistent independent association with survival after correction for confounders (DEX was used more frequently in patients with lower Karnofsky scores and altered neurological function). In the EORTC NCIC trial, patients on baseline steroids had lower median progression-free survival than patients not on steroids, and the effect remained significant after adjusting for a number of factors. In the German Glioma Network cohort, a worse outcome was seen in patients on steroids, in particular in patients who received gross total resection and were treated with radiotherapy plus chemotherapy. Mouse data confirmed reduced effectiveness of therapy in the context of steroid treatment.
- Taken together, the data suggest that caution should be exercised in treating patients who have glioblastoma with steroids, and alternates should be employed when possible.

Dr Codrin Lungu

Abstract

Glioblastoma is the most common and most aggressive primary brain tumour. Standard of care consists of surgical resection followed by radiotherapy and concomitant and maintenance temozolomide (temozolomide/radiotherapy→temozolomide). Corticosteroids are commonly used perioperatively to control cerebral oedema and are frequently continued throughout subsequent treatment, notably radiotherapy, for amelioration of side effects. The effects of corticosteroids such as dexamethasone on cell growth in glioma models and on patient survival have remained controversial. We performed a retrospective analysis of glioblastoma patient cohorts to determine the prognostic role of steroid administration. A disease-relevant mouse model of glioblastoma was used to characterise the effects of dexamethasone on tumour cell proliferation and death, and to identify gene signatures associated with these effects. A murine anti-VEGFA antibody was used in parallel as an alternative for oedema control. We applied the dexamethasone-induced gene signature to the Cancer Genome Atlas glioblastoma dataset to explore the association of dexamethasone exposure with outcome. Mouse experiments were used to validate the effects of dexamethasone on survival in vivo. Retrospective clinical analyses identified corticosteroid use during radiotherapy as an independent indicator of shorter survival in three independent patient cohorts. A dexamethasone-associated gene expression signature correlated with shorter survival in the Cancer Genome Atlas patient dataset. In glioma-bearing mice, dexamethasone pretreatment decreased tumour cell proliferation without affecting tumour cell viability, but reduced survival when combined with radiotherapy. Conversely, anti-VEGFA antibody decreased proliferation and increased tumour cell death, but did not affect survival when combined with radiotherapy. Clinical and mouse experimental data suggest that corticosteroids may decrease the effectiveness of treatment and shorten survival in glioblastoma. Dexamethasone-induced anti-proliferative effects may confer protection from radiotherapy- and chemotherapy-induced genotoxic stress. This study highlights the importance of identifying alternative agents such as vascular endothelial growth factor antagonists for managing oedema in glioblastoma patients. Beyond the established adverse effect profile of protracted corticosteroid use, this analysis substantiates the request for prudent and restricted use of corticosteroids in glioblastoma.



Corticosteroids Compromise Survival in Glioblastoma *Brain* 2016 Mar 28;[EPub Ahead of Print], KL Pitter, I Tamagno, K Alikhanyan, et al.

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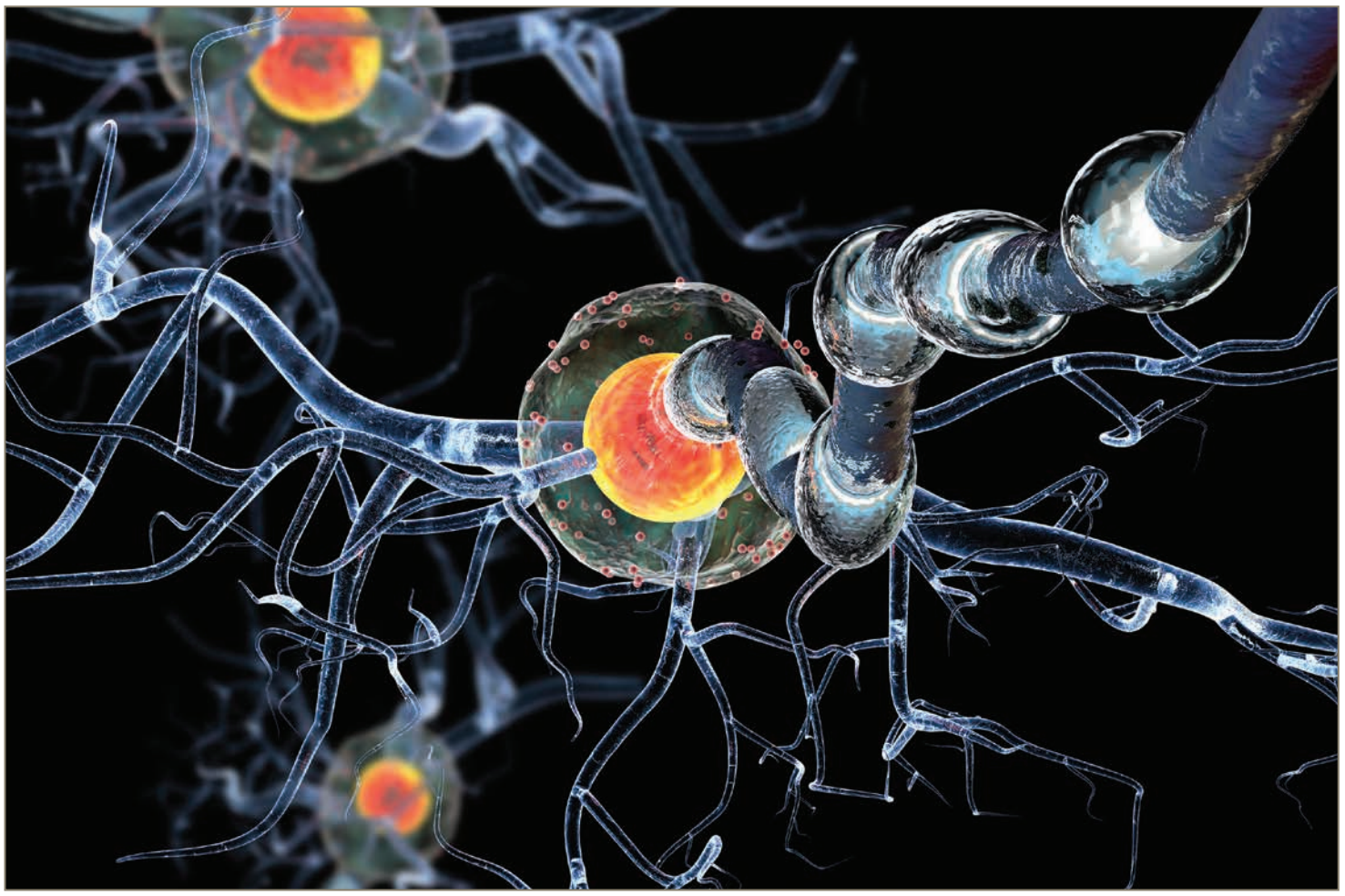
EXPERT OPINION

Treatment options for medication-resistant tremor

By Dr Andres Lozano



Patients who have medication-resistant tremor now have at least four surgical options. The procedures are aimed at modulating the activity of dysfunctional thalamic cortical circuits that are responsible for tremor. Either lesioning or electrical modulation of various targets along this circuit has been used. Deep-brain stimulation (DBS) of the VIM nucleus or its afferent axonal projections has been used extensively.

These same structures can also be targeted by lesioning, and here radiofrequency lesioning or Gamma Knife has been used. The first single-blinded assessment of Gamma Knife thalamotomy for tremor was published by Dr Witjas and colleagues this past November in *Neurology*.

> "Gamma Knife thalamotomy is an option for those patients who either do not want the invasive procedures or who have a contraindication for conventional surgery

A total of 55 patients with either parkinsonian or essential tremor were treated, and the authors report 54.2% in upper limb tremor score. It is reasonable to assume, therefore, that Gamma Knife thalamotomy is an option for patients with tremor that is resistant to medications. The issue is there are now four different procedures to offer, including DBS, Gamma Knife, radiofrequency, and the emergence of a new procedure known as magnetic resonance focused ultrasound (MRgFUS).

It is useful to make an analysis of the pros and cons of Gamma Knife. (See box)

DBS and radiofrequency thalamotomy involve making an opening in the skull and penetrating the brain to the target site. This has the possibility of causing a permanent neurologic deficit related to haemorrhage estimated to be <1%. There is also risk of infection, and the procedures are psychologically perhaps more difficult for the patients to accept as they are considered to be invasive. While there has been no head-to-head comparison of the various techniques, it is generally felt that thalamotomy and DBS can reduce tremor on the order of 80%, which may be in a similar ballpark to the Gamma Knife results reported here.

A fourth player on the horizon is MRgFUS. This has some of the advantages of Gamma Knife while eliminating some of its disadvantages. In particular, it is also noninvasive and involves focusing 1000 beams of ultrasound through the skull to a focal point. There is the possibility of mapping and immediate feedback in that the tremor disappears as a lesion is made in the correct target area. It is the early days of MRgFUS, and whether it will prove to be safe and effective is something that remains to be seen. In the meantime, however, Gamma Knife thalamotomy is an option for those patients who either do not want the invasive procedures or who have a contraindication for conventional surgery (eg, bleeding disorders).

An analysis of Gamma Knife thalamotomy

The pros

- The procedure is "noninvasive." It involves the application of a frame and the delivery of 130 rays of focused radiation to the thalamus.
- There are no incisions involved.
- The procedure can be done on an outpatient basis.

The cons

- Since there is no physiologic mapping, one can never be sure that the correct target has been reached during the treatment.
- There is no immediate feedback that the procedure is effective.
- It is ionising radiation, which may sometimes have unexpected consequences based on the individual's radiobiology.
- There is a possibility of delayed oncogenesis with ionising radiation. Although this risk is probably quite small, there have been reports of glioblastomas many years after acoustic neuroma radiosurgery; however, the cause and effect has never been clearly established in this context.
- The lesions are not adjustable or titratable once the radiation dose is delivered.

Progressive cerebellar atrophy and anti-NMDA receptor encephalitis

JAMA Neurology

Take-home message

- The long-term clinical implications of diffuse cerebral atrophy (DCA) and cerebellar atrophy in patients with anti-NMDA receptor encephalitis were assessed in this study. Although cerebellar atrophy was associated with a poor outcome, other features, including DCA without cerebellar atrophy, serious complications, ventilatory support, and prolonged hospitalisation, were not. Also, DCA was reversible, whereas cerebellar atrophy was not.
- DCA is reversible and does not imply a poor clinical outcome within the context of anti-NMDA receptor encephalitis. Further studies are warranted to determine whether progressive cerebellar atrophy can serve as a reliable prognostic marker for poor clinical outcome.

Dr Josep Dalmau

The current study is based on a thorough and a prolonged follow-up of 15 patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, resulting in three remarkable findings, including:

1. 13/15 patients had very good outcomes despite the severity of the disease (eg, 1 patient was unresponsive for 8 months, and another patient was unresponsive for 18 months);
2. 5 patients developed diffuse cerebral atrophy (DCA), and, of these, 3 started to reverse to normal approximately 1 year after onset and the other 2 patients had associated progressive cerebellar atrophy, which did not reverse to normal; and
3. Poor long-term outcome was associated with cerebellar atrophy but was not associated with DCA, clinical complications, ventilatory support, or prolonged hospitalisation.

Compared with patients who did not have DCA, those with DCA had longer hospitalisations (median, 11.1 vs 2.4 months; P = 0.002), required more frequent ventilatory support (5 of 5 vs 4 of 10 patients; P = 0.04), and developed more serious complications (4 of 5 vs 0 of 10 patients; P = 0.004).

Overall, these findings are paradigm changing and very important to keep in mind when making decisions about the prognosis and treatment of patients with anti-NMDAR encephalitis.

IMPORTANCE Anti-N-methyl-d-aspartate receptor (NMDAR) encephalitis is an immune-mediated disorder that occurs with IgG antibodies against the GluN1 subunit of NMDAR. Some patients develop reversible diffuse cerebral atrophy (DCA), but the long-term clinical significance of progressive brain and cerebellar atrophy is unknown.

OBJECTIVE To report the long-term clinical implications of DCA and cerebellar atrophy in anti-NMDAR encephalitis.

DESIGN, SETTING, AND PARTICIPANTS A retrospective observational study and long-term imaging investigation was conducted in the Department of Neurology at Kitasato University. Fifteen patients with anti-NMDAR encephalitis admitted to Kitasato University Hospital between January 1, 1999, and December 31, 2014, were included; data analysis was conducted between July 15, 2015, and January 18, 2016.

EXPOSURES Neurologic examination, immunotherapy, and magnetic resonance imaging (MRI) studies were performed.

MAIN OUTCOMES AND MEASURES Long-term MRI changes in association with disease severity, serious complications (eg, pulmonary embolism, septic shock, and rhabdomyolysis), treatment, and outcome.

RESULTS The clinical outcome of 15 patients (median age, 21 years, [range, 14–46 years]; 10 [67%] female) was evaluated after a median follow-up of 68 months (range, 10–179 months). Thirteen patients (87%) received first-line immunotherapy (intravenous high-dose methylprednisolone, intravenous immunoglobulin, and plasma exchange alone or combined), and 4 individuals (27%) also received cyclophosphamide; 2 patients (13%) did not receive immunotherapy. In 5 patients (33%), ovarian teratoma was found and removed. Serious complications developed in 4 patients (27%). Follow-up MRI revealed DCA in 5 patients (33%) that, in 2 individuals (13%), was associated with progressive cerebellar atrophy. Long-term outcome was good in 13 patients (87%) and poor in the other 2 individuals (13%). Although cerebellar atrophy was associated with poor long-term outcome (2 of 2 vs 0 of 13 patients; P = 0.01), other features, such as DCA without cerebellar atrophy, serious complications, ventilatory support, or prolonged hospitalisation, were not associated with a poor outcome. Five patients with DCA had longer hospitalisations (11.1 vs 2.4 months; P = 0.002), required ventilatory support more frequently (5 of 5 vs 4 of 10 patients; P = 0.04), and developed more serious complications (4 of 5 vs 0 of 10 patients; P = 0.004) compared with those without DCA. Although DCA was reversible, cerebellar atrophy was irreversible.

CONCLUSIONS AND RELEVANCE In anti-NMDAR encephalitis, DCA can be reversible and does not imply a poor clinical outcome. In contrast, cerebellar atrophy was irreversible and associated with a poor outcome. This observation deserves further study to confirm progressive cerebellar atrophy as a prognostic marker of poor outcome.

Association of progressive cerebellar atrophy with long-term outcome in patients with anti-N-methyl-D-aspartate receptor encephalitis *JAMA Neurol* 2016 Apr 25;[EPub Ahead of Print], T Iizuka, J Kaneko, N Tominaga, et al.

EXPERT OPINION

Top stories in neurovirology

By Dr Avindra Nath

Viruses are considered to be organisms in the external environment and are spread from one animal to another or across species. The reservoir for the virus is always some other living organism. However, some viruses can get incorporated into the chromosome and then get transmitted vertically in the genetic material. Although this fact has been known for quite some time, it has received little attention because these viruses lay dormant in normal adults.

> Since HERV-K belongs to the same family of viruses as HIV, which causes AIDS, one could use a similar approach for developing drugs that would target HERV-K

The human genome has a large number of retroviral sequences. In fact, nearly 8% of the genome is made of retroviral elements. A recent publication by Li et al shows that one of these viruses, termed human endogenous retrovirus K (HERV-K) may play a pathogenic role in amyotrophic lateral sclerosis (ALS).[1] The group found that the virus was activated in the brains of patients with ALS and, under experimental conditions, expression in neurons caused them to die. Further, a transgenic mouse created from one of the genes that encodes the coat protein of the virus developed symptoms and pathological changes classical of ALS. Based on their observations, the authors hypothesised that the virus may get transmitted from neuron to neuron, thus explaining the anatomical spread of the illness.

This observation changes our conventional thinking about how viruses may play a role in neurodegenerative diseases and blurs the line between infections and genetic illnesses. This also opens up new therapeutic possibilities. Since HERV-K belongs to the same family of viruses as HIV, which causes AIDS, one could use a similar approach for developing drugs that would target HERV-K. It may even be useful to determine if some of the approved drugs for treating HIV could be repurposed for controlling HERV-K replication. ■

1. Li W, Lee MH, Henderson L, et al. Human endogenous retrovirus-K contributes to motor neuron disease. Sci Transl Med. 2015;7(307):307ra153.

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JOURNAL SCAN

Association of environmental toxins with amyotrophic lateral sclerosis

JAMA Neurology

Take-home message

- This case-control study determined that persistent environmental pollutants measured in blood were significantly associated with amyotrophic lateral sclerosis and may represent modifiable disease risk factors.

IMPORTANCE Persistent environmental pollutants may represent a modifiable risk factor involved in the gene-time-environment hypothesis in amyotrophic lateral sclerosis (ALS).

OBJECTIVE To evaluate the association of occupational exposures and environmental toxins on the odds of developing ALS in Michigan.

DESIGN, SETTING AND PARTICIPANTS Case-control study conducted between 2011 and 2014 at a tertiary referral centre for ALS. Cases were patients diagnosed as having definitive, probable, probable with laboratory support, or possible ALS by revised El Escorial criteria; controls were excluded if they were diagnosed as having ALS or another neurodegenerative condition or if they had a family history of ALS in a first- or second-degree blood relative. Participants completed a survey assessing occupational and residential exposures. Blood concentrations of 122 persistent environmental pollutants, including organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), and brominated flame retardants (BFRs), were measured using gas chromatography-mass spectrometry. Multivariable models with self-reported occupational exposures in various exposure time windows and environmental toxin blood concentrations were separately fit by logistic regression models. Concordance between the survey data and pollutant measurements was assessed using the nonparametric Kendall τ correlation coefficient.

MAIN OUTCOMES AND MEASURES Occupational and residential exposures to environmental toxins, and blood concentrations of 122 persistent environmental pollutants, including OCPs, PCBs, and BFRs.

RESULTS Participants included 156 cases (mean [SD] age, 60.5 [11.1] years; 61.5% male) and 128 controls (mean [SD] age, 60.4 [9.4] years; 57.8% male); among them, 101 cases and 110 controls had complete demographic and pollutant data. Survey data revealed that reported pesticide exposure in the cumulative exposure windows was significantly associated with ALS (odds ratio [OR] = 5.09; 95% CI, 1.85–13.99; P = .002). Military service was also associated with ALS in 2 time windows (exposure ever happened in entire occupational history: OR = 2.31; 95% CI, 1.02–5.25; P = 0.046; exposure ever happened 10–30 years ago: OR = 2.18; 95% CI, 1.01–4.73; P = 0.049). A multivariable model of measured persistent environmental pollutants in the blood, representing cumulative occupational and residential exposure, showed increased odds of ALS for 2 OCPs (pentachlorobenzene: OR = 2.21; 95% CI, 1.06–4.60; P = 0.04; and cis-chlordane: OR = 5.74; 95% CI, 1.80–18.20; P = 0.005), 2 PCBs (PCB 175: OR = 1.81; 95% CI, 1.20–2.72; P = 0.005; and PCB 202: OR = 2.11; 95% CI, 1.36–3.27; P = 0.001), and 1 BFR (polybrominated diphenyl ether 47: OR = 2.69; 95% CI, 1.49–4.85; P = 0.001). There was modest concordance between survey data and the measurements of persistent environmental pollutants in blood; significant Kendall τ correlation coefficients ranged from -0.18 (Dacthal and "use pesticides to treat home or yard") to 0.24 (trans-nonachlor and "store lawn care products in garage").

CONCLUSIONS AND RELEVANCE In this study, persistent environmental pollutants measured in blood were significantly associated with ALS and may represent modifiable ALS disease risk factors.

Association of environmental toxins with amyotrophic lateral sclerosis *JAMA Neurol* 2016 May 09;[EPub Ahead of Print], FC Su, SA Goutman, S Chernyak, et al.

EXPERT OPINION

Anticholinergic meds and cognition

By Dr Irene Mace Hamrick

A longitudinal study published last month in *JAMA Neurology* collected neuroimaging and cognitive testing results of 451 cognitively intact adults at specific intervals over 32.1 months (range 6–108 months).[1] The mean age of study participants was 73.3 years, and 60 participants had been taking medium- or high-potency anticholinergic medications for a minimum of 1 month. Over the follow-up period, the group exposed to anticholinergic medications had worse outcomes on Wechsler Memory Scale, Trail Making Test Part B, and lower glucose metabolism on PET. MRI showed reduction of brain volume overall and in the hippocampus, along with enlargement of ventricles.

Alzheimer's disease is considered to be a deficit of acetylcholine (ACh), and most medications for the treatment enhance ACh in the brain by inhibiting the enzyme that breaks it down. In contrast, medications that inhibit ACh should not be used in older adults, especially those at risk or with the diagnosis of dementia. Since 1992, the Beers Criteria recommend against the use of anticholinergic medications in older adults. [2,3] More data are emerging that changes associated with anticholinergic medications are permanent, with one study last year showing a 56% increase of dementia and 68% increase of Alzheimer's disease with >1095 cumulative, standardised daily doses.[4]

With the new prospective, additional findings on brain imaging and cognitive testing, what are we to do when patients come to us with insomnia or incontinence that we often treat with anticholinergics? Anticholinergics, such as diphenhydramine, which is in all "PM" over-the-counter products, lose their sleep-inducing efficacy after only 3 nights.[5] Explaining to our patients that sleep needs decrease and sleep gets more fragmented with increasing age can reassure many worries. Lowering the temperature of the bedroom and moving bath time to earlier in the evening gives the brain the signal that it is time to go to sleep as the body temperature drops.

Almost all medications on the market for urge incontinence are anticholinergic, and, yes, antimuscarinics have the same effect on the brain. Kegel exercises, if done often (>45 times daily), are as effective as oxybutynin, even in men.[6] Avoiding bladder irritants such as alcohol, caffeine, and nicotine can prevent incontinence. Many patients restrict their fluid intake in an attempt to avoid bladder accidents or to save trips to the bathroom, and do not feel thirsty due to apoptosis of the thirst centre in the hypothalamus. A concentrated urine is very irritating to the bladder, and increasing fluid intake to at least 2 quarts a day can prevent urge incontinence. Extra efforts on our part can have significant benefits for our patients' brains. ■

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Irene Mace Hamrick MD FAAFP, AGSF is an associate professor, Clinical Health Sciences, Department of Family Medicine, University of Wisconsin; director of geriatrics services, Department of Family Medicine, University of Wisconsin, Madison, Wisconsin

JOURNAL SCAN

Anticholinergic use and cognition and brain atrophy in cognitively normal older adults

JAMA Neurology

Take-home message

- Well over 400 cognitively normal older adults were followed to evaluate the association between use of anticholinergic (AC) medication and cognitive impairment. People taking AC medication (AC+) showed lower scores on immediate-recall memory testing, the Trail Making Test Part B, and tests of executive function than people not taking AC medication (AC–). In addition, neuroimaging revealed a reduction in total cortical volume and temporal lobe cortical thickness and an increase in lateral ventricle and inferior lateral ventricle volumes in AC+ individuals compared with those who were AC–.
- The use of AC medication should be avoided in older adults if a suitable alternative is available due to the associated increase in brain atrophy and clinical signs of cognitive decline.

Dr Irene Mace Hamrick

IMPORTANCE The use of anticholinergic (AC) medication is linked to cognitive impairment and an increased risk of dementia. To our knowledge, this is the first study to investigate the association between AC medication use and neuroimaging biomarkers of brain metabolism and atrophy as a proxy for understanding the underlying biology of the clinical effects of AC medications.

OBJECTIVE To assess the association between AC medication use and cognition, glucose metabolism, and brain atrophy in cognitively normal older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Indiana Memory and Aging Study (IMAS).

DESIGN, SETTING AND PARTICIPANTS The ADNI and IMAS are longitudinal studies with cognitive, neuroimaging, and other data collected at regular intervals in clinical and academic research settings. For the participants in the ADNI, visits are repeated 3, 6, and 12 months after the baseline visit and then annually. For the participants in the IMAS, visits are repeated every 18 months after the baseline visit (402 cognitively normal older adults in the ADNI and 49 cognitively normal older adults in the IMAS were included in the present analysis). Participants were either taking (hereafter referred to as the AC+ participants [52 from the ADNI and 8 from the IMAS]) or not taking (hereafter referred to as the AC- participants [350 from the ADNI and 41 from the IMAS]) at least 1 medication with medium or high AC activity. Data analysis for this study was performed in November 2015.

MAIN OUTCOMES AND MEASURES Cognitive scores, mean fludeoxyglucose F 18 standardised uptake value ratio (participants from the ADNI only), and brain atrophy measures from structural magnetic resonance imaging were compared between AC+ participants and AC- participants after adjusting for potential confounders. The total AC burden score was calculated and was related to target measures. The association of AC use and longitudinal clinical decline (mean [SD] follow-up period, 32.1 [24.7] months [range, 6-108 months]) was examined using Cox regression.

RESULTS The 52 AC+ participants (mean [SD] age, 73.3 [6.6] years) from the ADNI showed lower mean scores on Weschler Memory Scale-Revised Logical Memory Immediate Recall (raw mean scores: 13.27 for AC+ participants and 14.16 for AC- participants; P = 0.04) and the Trail Making Test Part B (raw mean scores: 97.85 seconds for AC+ participants and 82.61 seconds for AC- participants; P = 0.04) and a lower executive function composite score (raw mean scores: 0.58 for AC+ participants and 0.78 for AC- participants; P = 0.04) than the 350 AC- participants (mean [SD] age, 73.3 [5.8] years) from the ADNI. Reduced total cortical volume and temporal lobe cortical thickness and greater lateral ventricle and inferior lateral ventricle volumes were seen in the AC+ participants relative to the AC- participants.

CONCLUSIONS AND RELEVANCE The use of AC medication was associated with increased brain atrophy and dysfunction and clinical decline. Thus, use of AC medication among older adults should likely be discouraged if alternative therapies are available.

Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults *JAMA Neurol* 2016 April 18 [EPub ahead of print]. S Risacher, B McDonald, E Tallman, et al.

JOURNAL SCAN

Brain stimulation and constraint for perinatal stroke hemiparesis

Neurology

Take-home message

- Effective treatments for cerebral palsy (CP) are limited. Hemiparetic CP is a common type, and often results from in-utero or perinatal stroke. Constraint-induced movement therapy (CIMT) and repetitive transcranial magnetic stimulation (rTMS) are therapeutic options based on engaging neuroplasticity. This study is a 2x2 factorial design, randomised, blinded controlled trial in which hemiparetic children aged 6 to 19 years underwent a 2-week goal-directed training camp during which they had daily CIMT, rTMS, both, or neither. Using the Assisting Hand Assessment (AHA) and the Canadian Occupational Performance Measure as primary outcomes, all interventions showed benefit at 1 week to 2 months after the intervention, with some of the benefit waning by 6 months. The addition of rTMS, CIMT, or both doubled the chances of clinically significant improvement, and the effects were additive. The largest improvement was seen with the combined rTMS+CIMT modality, with an improvement of 5.91 AHA units, compared with 0.62 units in patients receiving neither. The therapies were well-tolerated and all participants completed the trial.
- The results show a role for the combined rTMS and CIMT approach for improving therapy-induced functional motor gains in hemiparetic CP.

Dr Codrin Lungu

OBJECTIVE To determine whether the addition of repetitive transcranial magnetic stimulation (rTMS) and/or constraint-induced movement therapy (CIMT) to intensive therapy increases motor function in children with perinatal stroke and hemiparesis.

METHODS A factorial-design, blinded, randomised controlled trial (clinicaltrials.gov/NCT01189058) assessed rTMS and CIMT effects in hemiparetic children (aged 6-19 years) with MRI-confirmed perinatal stroke. All completed a 2-week, goal-directed, peer-supported motor learning camp randomised to daily rTMS, CIMT, both, or neither. Primary outcomes were the Assisting Hand Assessment and the Canadian Occupational Performance Measure at baseline, and 1 week, 2 and 6 months postintervention. Outcome assessors were blinded to treatment. Interim safety analyses occurred after 12 and 24 participants. Intention-to-treat analysis examined treatment effects over time (linear mixed effects model).

RESULTS All 45 participants completed the trial. Addition of rTMS, CIMT, or both doubled the chances of clinically significant improvement. Assisting Hand Assessment gains at 6 months were additive and largest with rTMS + CIMT (β coefficient = 5.54 [2.57-8.51], p = 0.0004). The camp alone produced large improvements in Canadian Occupational Performance Measure scores, maximal at 6 months (Cohen d = 1.6, p = 0.002). Quality-of-life scores improved. Interventions were well tolerated and safe with no decrease in function of either hand.

CONCLUSIONS Hemiparetic children participating in intensive, psychosocial rehabilitation programs can achieve sustained functional gains. Addition of CIMT and rTMS increases the chances of improvement.

CLASSIFICATION OF EVIDENCE This study provides Class II evidence that combined rTMS and CIMT enhance therapy-induced functional motor gains in children with stroke-induced hemiparetic cerebral palsy.

Brain Stimulation and Constraint for Perinatal Stroke Hemiparesis: The PLASTIC CHAMPS Trial *Neurology* 2016 May 03;86(18)1659-1667, A Kirton, J Andersen, M Herrero, A Nettel-Aguirre, L Carsolio, O Damji, J Keess, A Mineyko, J Hodge, MD Hill

NEWS

Long-term treatment benefit seen in relapse-onset MS

Disease-modifying therapy protects against disability accrual over 10-year period

For patients with relapse-onset multiple sclerosis (MS), disease-modifying therapy protects against long-term disability accrual, according to a study published online May 4 in the *Annals of Neurology*.

Vilija G. Jokubaitis, PhD, from the University of Melbourne, and colleagues examined predictors of 10-year expanded disability status scale (EDSS) change after treatment initiation in patients with relapse-onset MS. Patients had remained on injectable therapy for at least one day, and were monitored thereafter on any approved disease-modifying therapy or no therapy. Data were included for 2466 patients who reported post-baseline disability scores during follow-up of at least 10 years.

> "We provide evidence of long-term treatment benefit in a large registry cohort, and provide evidence of long-term protective effects of pregnancy against disability accrual

The researchers found that patients were treated 83 percent of their follow-up time, on average. At 10 years post-baseline, EDSS scores had increased by a median of 1 point. Over 10 years, the annualised relapse rate was predictive of increases in the median EDSS. Greater burden was seen for on-therapy relapses versus off-therapy relapses. There was an independent correlation for cumulative treatment exposure with lower EDSS at 10 years. Over the 10-year observation period, pregnancies were also independently associated with lower EDSS scores.

"We provide evidence of long-term treatment benefit in a large registry cohort, and provide evidence of long-term protective effects of pregnancy against disability accrual," the authors write. "We demonstrate that high-annualised relapse rate, particularly on-treatment relapse, is an indicator of poor prognosis."

Several authors disclosed financial ties to the pharmaceutical industry.

HealthDay

Antihistamine may help reverse optic neuropathy in MS

Vision improvement with clemastine fumarate appears modest but results are promising

Clemastine fumarate partially reverses optic neuropathy in patients with multiple sclerosis, according to a study presented at the annual meeting of the American Academy of Neurology.

The study was small, involving only 50 patients averaging 40 years of age. All had been diagnosed with multiple sclerosis for an average of five years and were also diagnosed with optic neuropathy.

For three months, patients received either the antihistamine or a placebo. The groups were then switched for the last two months of the study. While taking the antihistamine, patients showed a slight improvement in terms of the delays in transmission of signal from the retina to the visual cortex.

> "This study provides a framework for future multiple sclerosis repair studies and will hopefully herald discoveries that will enhance the brain's innate capacity for repair

The findings "are preliminary," study author Ari Green, MD, assistant clinical director of the Multiple Sclerosis Center at the University of California, San Francisco, stressed in a news release from the American Academy of Neurology. "But this study provides a framework for future multiple sclerosis repair studies and will hopefully herald discoveries that will enhance the brain's innate capacity for repair."

HealthDay

JOURNAL SCAN

Metformin and pioglitazone in metabolic syndrome and multiple sclerosis

JAMA Neurology

Take-home message

- The authors of this prospective cohort study evaluated the anti-inflammatory effects of metformin and pioglitazone in 50 multiple sclerosis (MS) patients with coexisting metabolic syndrome (MetS) treated with metformin, pioglitazone, or no treatment. Patients were assessed with brain MRI every 6 months for new T2 or gadolinium-enhancing lesions. Blood samples were also tested for serum leptin, adiponectin, cytokines, and regulatory T cells. At 6 months' follow-up, both the metformin and pioglitazone groups had a significant decrease in lesions visible on MRI compared with the control group. The metformin and pioglitazone groups also had a decrease in serum leptin levels and various cytokines as well as an increase in adiponectin levels and circulating T cells compared with controls.
- Metformin and pioglitazone may be effective for the treatment of inflammation in MS, and this warrants further evaluation and future research.

IMPORTANCE Metabolic syndrome (MetS) is thought to influence several autoimmune diseases, including multiple sclerosis (MS). Anti-inflammatory effects of treatments used for MetS, such as metformin hydrochloride and pioglitazone hydrochloride, have been demonstrated, although clinical evidence supporting use of these treatments in MS is lacking.

OBJECTIVES To determine whether metformin and/or pioglitazone are associated with a reduction in disease activity as measured by brain magnetic resonance imaging in patients with MS and MetS and to evaluate the potential mechanisms underlying this anti-inflammatory effect.

DESIGN, SETTING AND PARTICIPANTS A prospective cohort study was conducted from March 1, 2012, to December 30, 2014, at a private MS referral centre among 50 obese patients with MS who also developed MetS. Twenty patients received metformin hydrochloride, 850 to 1500 mg/d, and 10 patients received pioglitazone hydrochloride, 15 to 30 mg/d; 20 untreated patients served as controls. Groups were comparable in terms of sex, age, body mass index, Expanded Disability Status Scale score, disease duration, annual relapse rate, and treatment status. Patients were followed up for a mean (SD) of 26.7 (2.7) months (range, 24–33 months).

MAIN OUTCOMES AND MEASURES Magnetic resonance imaging of the brain was performed at 6-month intervals, and the presence of new or enlarging T2 lesions or gadolinium-enhancing lesions was registered. Serum leptin and adiponectin levels were measured. The production of cytokines by peripheral blood mononuclear cells was assayed, as were regulatory T-cell numbers and function.

RESULTS Of 50 patients, after 6 months of treatment, 20 patients with MS who were treated with metformin and 10 who received pioglitazone showed a significant decrease in the number of new or enlarging T2 lesions (metformin, 2.5 at study entry to 0.5 at month 24; pioglitazone, 2.3 at study entry to 0.6 at month 24), as well as of gadolinium-enhancing lesions (metformin, 1.8 at study entry to 0.1 at month 24; pioglitazone, 2.2 at study entry to 0.3 at month 24). Compared with controls, both treatments led to a decrease in mean (SD) leptin levels (metformin, 5.5 [2.4] vs 10.5 [3.4] ng/mL, P<0.001; pioglitazone, 4.1 [0.8] vs 11.0 [2.6] ng/mL, P<.001) and increase in mean (SD) adiponectin serum levels (metformin, 15.4 [5.5] vs 4.5 [2.4] µg/mL, P<0.001; pioglitazone, 12.6 [3.6] vs 4.8 [0.6] µg/mL, P<0.001). Mean (SD) number of myelin basic protein peptide–specific cells secreting interferon γ and interleukin (IL)–17 were significantly reduced in patients receiving metformin compared with controls (interferon γ, 30.3 [11.5] vs 82.8 [18.8], P<0.001; IL-17, 212.4 [85.5] vs 553.8 [125.9], P<0.001). Patients treated with pioglitazone showed significant decreases in the mean (SD) number of myelin basic protein peptide-specific cells secreting IL-6 and tumour necrosis factor compared with controls (IL-6, 361.6 [80.5] vs 1130.7 [149.21], P<0.001; tumour necrosis factor, 189.9 [53.4] vs 341.0 [106.0], P<.001). Both metformin and pioglitazone resulted in a significant increase in the number and regulatory functions of CD4+CD25+FoxP3+ regulatory T cells compared with controls (metformin, 6.7 [1.5] vs 2.1 [1.0], P=0.001; pioglitazone, 6.9 [0.8] vs 3.0 [0.8], P=0.001).

CONCLUSIONS AND RELEVANCE Treatment with metformin and pioglitazone has beneficial anti-inflammatory effects in patients with MS and MetS and should be further explored.

Immunologic Effects of Metformin and Pioglitazone Treatment on Metabolic Syndrome and Multiple Sclerosis *JAMA Neurol* 2016 Mar 07;[EPub Ahead of Print], L Negrotto, MF Farez, J Correale

JOURNAL SCAN

High coffee consumption and decreased risk for multiple sclerosis

Journal of Neurology, Neurosurgery, and Psychiatry

Take-home message

- Epidemiological data have suggested a protective effect from coffee consumption in several CNS diseases, most notably Parkinson's disease. Through presumed attenuation of neuroinflammation via adenosine A1 modulation, it has been proposed that caffeine may have a similar protective effect in multiple sclerosis (MS), but prior data have been inconsistent. This is a large study using two populations, one Swedish and one in the US, collecting data on coffee consumption habits and MS diagnosis. The population totalled 2779 MS cases and 3960 controls. Comparing the participants with the highest coffee consumption rates in both studies with those who reported no coffee consumption, the risk of MS appeared to be substantially reduced, with an odds ratio of 0.70 in the Swedish population and 0.69 in the American population. There was also a reduction in odds with increasing coffee consumption.
- The findings are in line with animal research results, and, keeping in mind the limitations intrinsic to this retrospective epidemiology design, suggest a protective role of coffee consumption for development of MS. It is unclear through what mechanism this may be occurring and whether additional confounding factors need to be explored.

Dr Codrin Lungu

OBJECTIVES Previous studies on consumption of caffeine and risk of multiple sclerosis (MS) have yielded inconclusive results. We aimed to investigate whether consumption of coffee is associated with risk of MS.

METHODS Using two population-representative case-control studies (a Swedish study comprising 1620 cases and 2788 controls, and a US study comprising 1159 cases and 1172 controls), participants with different habits of coffee consumption based on retrospective data collection were compared regarding risk of MS, by calculating ORs with 95% CIs. Logistic regression models were adjusted for a broad range of potential confounding factors.

RESULTS Compared with those who reported no coffee consumption, the risk of MS was substantially reduced among those who reported a high consumption of coffee exceeding 900 mL daily (OR 0.70 (95% CI 0.49 to 0.99) in the Swedish study, and OR 0.69 (95% CI 0.50 to 0.96) in the US study). Lower odds of MS with increasing consumption of coffee were observed, regardless of whether coffee consumption at disease onset or 5 or 10 years prior to disease onset was considered.

CONCLUSIONS In accordance with studies in animal models of MS, high consumption of coffee may decrease the risk of developing MS. Caffeine, one component of coffee, has neuroprotective properties, and has been shown to suppress the production of proinflammatory cytokines, which may be mechanisms underlying the observed association. However, further investigations are needed to determine whether exposure to caffeine underlies the observed association and, if so, to evaluate its mechanisms of action.

Time to wake up and smell the coffee? Coffee consumption and multiple sclerosis *J Neurol Neurosurg Psychiatry* 2016;87:5 453; A K Hedström, E M Mowry, M A Gianfrancesco, et al.

Q & A

Personalised medicine in neuro-oncology: current status

In the neuro-oncology space, success in finding individualised targetable mutations has been limited, but with the emergence of the utilisation of immune checkpoint inhibitors, this is about to change, says Dr Minesh Mehta in an interview with Dr Farzanna Haffizulla.

Dr Haffizulla: Let's talk about precision medicine and personalised advances, targeted treatment based on the individual rather than having a blanket standard of care treatment. What are your thoughts, and what are some of the advances to come?

Dr Mehta: Well, obviously, finding specific targets in each individual patient's tumour has become the Holy Grail of oncology, and this has been very successful, in, for example, non-small cell lung cancer. Unfortunately, in the neuro-oncology space, our successes have not been that great in finding individualised targetable mutations, for which specific drugs can be utilised.

This search continues, but there is another direction in which this personalisation of therapy is beginning to emerge, and that's the utilisation of immune checkpoint inhibitors.

Immune checkpoint inhibitors have become the darling child in the oncology world in the last 2 to 3 years, especially with all the dramatic advances in melanoma, and they're beginning to find application in neuro-oncology in new clinical trials and new concepts.

Dr Haffizulla: Matrix metalloproteinase, you mentioned melanoma – I think about that – and isocitrate dehydrogenase (IDH), co-deletions, 1p/19q, et cetera. Can you tell me what else is on the horizon?

Dr Mehta: All of the molecular markers that you mentioned have now been shown to have significant prognostic implications in many brain tumours, and in some situations they're even predictive of therapeutic benefit.

It's quite likely that these molecular markers will become incorporated in the future classifications of brain tumours, moving from histology-based to molecular marker-based classification, and some of them like IDH might even provide us therapeutic avenues using IDH inhibitors in future practice.

> "So, collaboration is important. Making sure the different specialties, not just in neuro-oncology, oncology, radiation oncology, et cetera – imaging – all come together to really have that personalised approach

Dr Haffizulla: Fantastic. I know the World Health Organisation classification scheme that you mentioned is based on the histology, and bringing in the molecular signature of the tumour itself, and using that to further classify these particular tumours, will help, as you said, gear treatment in the correct direction. What are your thoughts on when this is coming out?

Dr Mehta: In particular, for the lower-grade gliomas, the grade II and the grade III gliomas, there is such a confluence in terms of the clinical outcomes for patients with similar molecular patterns that it's very likely that the molecular pattern, rather than the grade, might become the future driver of the newer classification. And such a classification is being worked on as we speak.

Dr Haffizulla: So, collaboration is important. Making sure the different specialties, not just in neuro-oncology, oncology, radiation oncology, et cetera – imaging – all come together to really have that personalised approach.

Are there any other study designs that are being thought up now that might come to fruition a little bit later down the road? Maybe not just using a retrospective review of the clinical trial data that we have now, but taking a new lens, a new approach, to how we've approached some of the clinical trials for brain tumour research.

Dr Mehta: Well, let me give you two examples that I think are about to take off somewhat rapidly in the neuro-oncology space.

The first is really the example of combining immune checkpoint inhibitors with radiation. It turns out that radiation, especially high-dose radiation, can be quite immunogenic by causing tumour cell death, and combining that with an immune checkpoint inhibitor that allows a sustained anti-tumour response to be maintained, might be an innovative therapeutic avenue. Clinical trials based on this concept of combining radiation and immune checkpoint inhibitors are about to be launched, and these might be very intriguing to study.

Dr Haffizulla: I know it's always significantly challenging sometimes to recruit the right number of patients, especially with this disease type. How has it been to collaborate among different groups? With the different clinical trials and the designs that we have today, we need to have some good statistical power.

Dr Mehta: In neuro-oncology where we deal with tumours that are relatively uncommon, compared with many of the other tumours that we see in the oncology space, collaboration is crucial; so, we have mounted transatlantic collaborations among cooperative groups in the US, as well as in Europe, and we're even looking at collaborations across the world to complete some of these trials. ■

Dr Minesh Mehta is professor of radiation oncology; associate director of clinical research, radiation oncology, University of Maryland School of Medicine; medical director, Maryland Proton Treatment Center, Baltimore, Maryland.

Dr Farzanna Haffizulla is national president of the American Medical Women's Association (AMWA) 2014–2015; private practice, Internal Medicine, Davie, Florida.

JOURNAL SCAN

Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma

The New England Journal of Medicine

Take-home message

- This was a multicentre, randomised phase III trial including 251 patients with newly diagnosed low-grade gliomas designed to compare postoperative radiation therapy (RT) alone vs radiation therapy followed by combination chemotherapy with procarbazine, lomustine, and vincristine (RT+PCV).
- At a median follow-up of 11.9 years, the median overall survival was substantially longer in the RT+PCV group compared with those who received only radiation (OS, 13.3 vs 7.8 years). Grade 3 or 4 haematologic adverse events occurred in nearly 50% of patients treated with RT+PCV.

Dr Jeremy Jones

BACKGROUND Grade 2 gliomas occur most commonly in young adults and cause progressive neurologic deterioration and premature death. Early results of this trial showed that treatment with procarbazine, lomustine (also called CCNU), and vincristine after radiation therapy at the time of initial diagnosis resulted in longer progression-free survival, but not overall survival, than radiation therapy alone. We now report the long-term results.

METHODS We included patients with grade 2 astrocytoma, oligoastrocytoma, or oligodendroglioma who were younger than 40 years of age and had undergone subtotal resection or biopsy or who were 40 years of age or older and had undergone biopsy or resection of any of the tumour. Patients were stratified according to age, histologic findings, Karnofsky performance-status score, and presence or absence of contrast enhancement on preoperative images. Patients were randomly assigned to radiation therapy alone or to radiation therapy followed by six cycles of combination chemotherapy.

RESULTS A total of 251 eligible patients were enrolled from 1998 through 2002. The median follow-up was 11.9 years; 55% of the patients died. Patients who received radiation therapy plus chemotherapy had longer median overall survival than did those who received radiation therapy alone (13.3 vs 7.8 years; hazard ratio for death, 0.59; P=0.003). The rate of progression-free survival at 10 years was 51% in the group that received radiation therapy plus chemotherapy versus 21% in the group that received radiation therapy alone; the corresponding rates of overall survival at 10 years were 60% and 40%. A Cox model identified receipt of radiation therapy plus chemotherapy and histologic findings of oligodendroglioma as favourable prognostic variables for both progression-free and overall survival.

CONCLUSIONS In a cohort of patients with grade 2 glioma who were younger than 40 years of age and had undergone subtotal tumour resection or who were 40 years of age or older, progression-free survival and overall survival were longer among those who received combination chemotherapy in addition to radiation therapy than among those who received radiation therapy alone.

Radiation Plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma *N Engl J Med* 2016 Apr 07;374(14)1344–1355, JC Buckner, EG Shaw, SL Pugh, et al.

Future directions for targeted therapies in neuro-oncology

INTERVIEW WITH DR PATRICK Y. WEN

What is the future of neuro-oncology? Dr Wen, director of the Center for Neuro-Oncology at Dana-Farber Cancer Institute and professor of neurology at Harvard Medical School shares his perspective.

Generalised inflammation and brain tumours: is the brain an 'immunosanctuary'?

INTERVIEW WITH DR JEFFREY J RAIZER

Could a drug such as bevacizumab be used in conjunction with immunotherapy to decrease oedema rather than using steroids? Dr Jeffrey Raizer, Director of Medical Neuro-Oncology at Northwestern University, Chicago, explains.

Q & A

Clinical implications of new molecular understanding in glioblastoma

Taking a targeted and molecularly driven immuno-therapeutic approach comes with benefits, says Dr Wolgang Wick in an interview with Dr Farzanna Haffizulla.

Dr Haffizulla: Let's talk more of the personalised approach – looking at molecular targets, understanding the tumours themselves and the antigens that they express, and how we can best direct targeted therapies in different patient populations.

Dr Wick: I think it's very important. It is already an important aspect for radiotherapy; so, we have different responses to radiotherapy. It's an important aspect for all sorts of chemotherapy. It's an important aspect for so-called targeted agents because, if you are really looking at the tumour tissue prior to your targeted approach, you will probably get more out of the treatment than if you take a one-size-fits-all type of approach. Of course, the same assay and the same approach, the same kind of molecular workup could also be used to then identify neoantigens, mutated antigens, which then could be used for targeted and molecularly driven immune therapies. You have an active immunotherapy with a peptide, or with an mRNA, or whatever, and then you have that in combination with a checkpoint inhibitor or something, but you should use that active part in a personalised way and not in a one-size-fits-all approach.

> "If you are really looking at the tumour tissue prior to your targeted approach, you will probably get more out of the treatment than if you take a one-size-fits-all type of approach

Dr Haffizulla: Absolutely. You maximise benefit to the patient, and minimise risk and side effects and adverse events. You know, we could probably even use some of the antigens that are expressed to create vaccines to prevent some of these tumour types.

Dr Wick: It would be great. IDH is a good example. We've actually had our own trial, and we had a very nice publication last year on mutated IDH being used as a peptide vaccine to treat low-grade tumours. This is not quite prevention, but this is – outside the disease of glioblastoma – really in the early stages with the primary treatments, trying to have a maintenance treatment that prevents a low-grade tumour from getting more malignant and recurring.

Dr Haffizulla: Absolutely, because what percentage of the low-grade gliomas convert to glioblastoma? It's about 30% or…?

Dr Wick: Yes. I think it's about that range, but 90% are expressing IDH. I think for those tumours, since it is uniquely expressed, IDH is really an interesting and very smart target to tackle, especially in that disease because it's not directly dividing. There is enough time for an immunotherapeutic response.

Dr Haffizulla: Right. What are your thoughts on the matrix metalloproteinase?

Dr Wick: You mean as a target or as a biomarker?

Dr Haffizulla: As a biomarker.

Dr Wick: It could be a nice biomarker for anti-angiogenic treatments. There will be patients who will benefit from those treatments, but we probably have not been smart enough to identify them, and matrix metalloproteinases in the serum could be one aspect, and one possibility to discover.

Dr Haffizulla: I'm just thinking about us getting signalling prior to the tumour forming. The possible release of other markers that might be out there that we haven't explored yet. Any that you might be working on in your lab, or within research?

Dr Wick: You mean markers prior to the formation of the tumour?

Dr Haffizulla: Prior to the…or the detection, we should say, because a marker could be there, but we may not be able to see it with some of the imaging techniques we have.

Dr Wick: What we are doing is really looking at the serum for non-coding RNAs; so, this is something we are really interested in.

Dr Haffizulla: MicroRNA.

Dr Wick: Yes, microRNA and long non-coding RNA. All the non-coding parts of the genome, which are probably more stably expressed at some stages, and, on the one hand, difficult to detect, but if you have the measures to do the detection, I think it could be something which is really specific for tumour development versus normal brain or other diseases. ■

Scan the QR code with your smartphoe to see the video interview

Dr Wolfgang Wick is division head, neuro-oncology, German Cancer Research Center (DKFZ); program chair, neuro-oncology, National Center for Tumor Diseases; Hertie Professor of Neuro-Oncology and director, National Tumor Center, University of Heidelberg, Heidelberg, Germany.

Dr Farzanna Haffizulla is national president of the American Medical Women's Association (AMWA) 2014–2015; private practice, Internal Medicine, Davie, Florida.

JOURNAL SCAN

Response of recurrent GBM to immune checkpoint inhibition

Journal of Clinical Oncology

Take-home message

- In this study, exome sequencing and neoantigen prediction of 37 biallelic mismatch repair deficiency (bMMRD) cancers were performed to make comparisons with brain neoplasms. The 32 malignant tumours identified were all hypermutant. The mutational load was significantly higher in bMMRD glioblastomas (GBMs) than in other tumours. Additionally, bMMRD GBMs showed neoantigen loads that were 7 to 16 times higher than found in several immunoresponsive tumour types (including melanomas, lung cancers, and microsatellite-unstable gastrointestinal cancers). A pair of siblings with bMMRD GBM experienced clinically significant responses after treatment with nivolumab.
- This study suggests that recurrent GBM may be responsive to immune checkpoint inhibition. The authors suggest that the increasing availability of sequencing technologies may facilitate analysis of mutation burden and neoantigens in ways that may improve treatment of these patients.

Dr Patrick Y. Wen

While there is significant interest in immune checkpoint inhibitors in glioblastomas, the activity of these agents and predictors of response are unknown. There is increasing evidence in other cancers that hypermutated tumours may have a better response. Biallelic mismatch repair deficiency (bMMRD) is a childhood cancer syndrome that often results in glioblastomas characterised by a high mutational burden. In this study, 2 children with bMMRD with recurrent glioblastomas were treated with the anti-PD1 antibody nivolumab and experienced durable and significant responses. This represents one of the first reports of responses of recurrent glioblastoma to immune checkpoint inhibition.

Immune Checkpoint Inhibition for Hypermutant Glioblastoma Multiforme Resulting From Germline Biallelic Mismatch Repair Deficiency *J Clin Oncol* 2016 Mar 21;[EPub Ahead of Print], E Bouffet, V Larouche, BB Campbell, et al.

JOURNAL SCAN

Stereotactic radiosurgery vs whole-brain radiation for brain metastases from breast or non-small cell lung cancer

Cancer

Take-home message

- Patients treated with radiation therapy for brain metastases from NSCLC or breast cancer were evaluated to compare outcomes between treatment with stereotactic radiosurgery (SRS) alone and whole-brain radiation therapy (WBRT). SRS alone was performed in 27.8% of patients with NSCLC and 13.4% of patients with breast cancer. SRS was usually selected for patients with ≤3 metastases and lesions ≤4 cm in size, and these patients achieved longer survival times than those treated with WBRT.
- SRS alone is effective for patients with <4 brain metastases secondary to NSCLC or breast cancer.

Abstract

BACKGROUND The optimal treatment for patients with brain metastases remains controversial as the use of stereotactic radiosurgery (SRS) alone, replacing whole-brain radiation therapy (WBRT), has increased. This study determined the patterns of care at multiple institutions before 2010 and examined whether or not survival was different between patients treated with SRS and patients treated with WBRT.

METHODS This study examined the overall survival of patients treated with radiation therapy for brain metastases from non-small cell lung cancer (NSCLC; initially diagnosed in 2007-2009) or breast cancer (initially diagnosed in 1997–2009) at 5 centres. Propensity score analyses were performed to adjust for confounding factors such as the number of metastases, the extent of extracranial metastases, and the treatment centre.

RESULTS Overall, 27.8% of 400 NSCLC patients and 13.4% of 387 breast cancer patients underwent SRS alone for the treatment of brain metastases. Few patients with more than 3 brain metastases or lesions ≥ 4 cm in size underwent SRS. Patients with fewer than 4 brain metastases less than 4 cm in size (n = 189 for NSCLC and n = 117 for breast cancer) who were treated with SRS had longer survival (adjusted hazard ratio [HR] for NSCLC, 0.58; 95% confidence Interval [CI], 0.38–0.87; P = 0.01; adjusted HR for breast cancer, 0.54; 95% CI, 0.33–0.91; P = 0.02) than those treated with WBRT.

CONCLUSIONS Patients treated for fewer than 4 brain metastases from NSCLC or breast cancer with SRS alone had longer survival than those treated with WBRT in this multi-institutional, retrospective study, even after adjustments for the propensity to undergo SRS.

Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. *Cancer* 18 Apr 2016 [online]; L Halasz, H Uno, M Hughes, et al.

American Academy of Neurology 68th annual meeting

15 –21 APRIL 2016 • VANCOUVER, CANADA

The world's largest gathering of neurologists congregated in Vancouver, Canada to attend the American Academy of Neurology annual meeting with more than 10,000 neurology professionals from across the globe networking and discussing cutting-edge research, and collaborating on education.

Confirmed: the safety of pregnancy in women with epilepsy

Women with epilepsy looking to become pregnant were as likely to become pregnant, took comparable time to become pregnant, and experienced similar outcomes of pregnancy as their healthy peers.

Jacqueline A. French, MD, of New York University Langone Medical Center, New York, explained that she and her team set out to compare time to pregnancy and outcomes (live birth, miscarriage) among women with epilepsy and healthy controls as part of the Women with Epilepsy: Pregnancy Outcomes and Deliveries (WEPOD) study. Studies have suggested women with epilepsy are less fertile than those without the condition.

Dr French said, "Epilepsy is a condition that affects people at all ages. Many women with epilepsy need to navigate their childbearing years. While several studies have addressed pregnancy outcomes, fewer have focused on preconception issues."

The team enrolled and followed women with epilepsy and healthy control, age 18–41 years, who tried to become pregnant within 6 months of discontinuing contraception.

The customised WEPOD electronic diary captured medication use, seizures, sexual activity, and menstrual bleeding. Pregnancy tests were performed if no menses occurred by cycle day 35. Outcomes included the proportion of women who became pregnant and duration from cessation of birth control to pregnancy.

A proportional hazard model was used to evaluate the association between time to pregnancy and certain baseline characteristics. Dr French and colleagues enrolled 88 women with epilepsy and 109 healthy controls with similar demographic characteristics.

In women with epilepsy, 61.4% achieved pregnancy vs 60.6 % for healthy controls (difference not significant). Median time to pregnancy was 6.0 (95% confidence interval: 3.8–10.5) months in women with epilepsy compared to 9.0 (95% confidence interval 6.9–12.9) for healthy controls (difference not significant). Time to pregnancy did not differ across the two groups after controlling for age, body mass index, parity, and race.

Race ($P = 0.0007$) and parity ($P = 0.0083$) were significantly associated with time to pregnancy. A similar proportion of pregnancies ended in miscarriage (12.9% women with epilepsy vs 19.7% controls), live birth (80.0% women with epilepsy and 80.3% controls), or another outcome (5.0% vs 0.0%).

Dr French concluded that women with epilepsy looking to become pregnant were as likely to become pregnant, took comparable time to become pregnant, and experienced similar outcomes of pregnancy as their healthy peers. These findings should reassure women with epilepsy who wish to become pregnant and their clinicians.

She added, "We are so happy to be able to reassure women with epilepsy that their likelihood of conceiving is the same as for women who are not facing these challenges. Their likelihood of miscarriage is no higher either. These are questions and concerns we hear regularly from women with epilepsy." ■

> We are so happy to be able to reassure women with epilepsy that their likelihood of conceiving is the same as for women who are not facing these challenges. Their likelihood of miscarriage is no higher either. These are questions and concerns we hear regularly from women with epilepsy >10

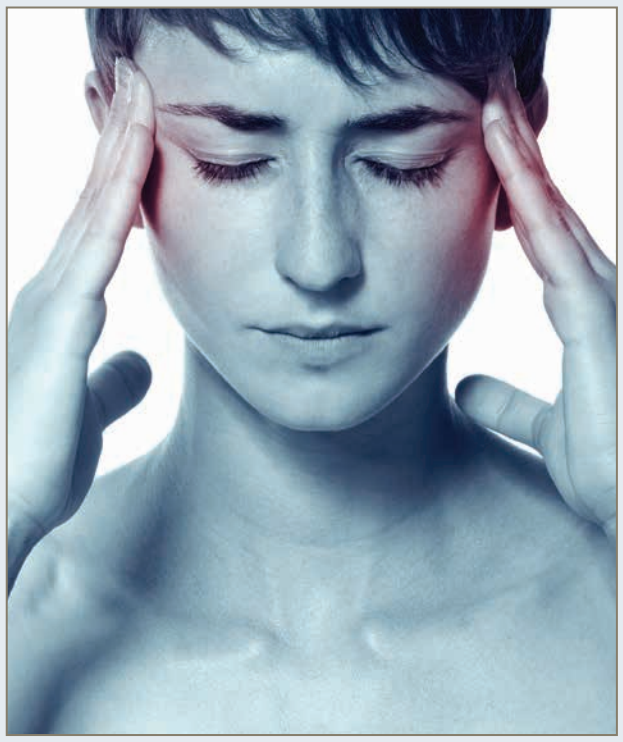
> The study suggests a high possibility of phenotypic and genotypic association between irritable bowel syndrome and primary headache disorders and supports the presence of a shared pathophysiological basis >11

> Methylphenidate may be effective in ameliorating some cognitive deficits in patients with epilepsy, without affecting seizure control >11

Migraine and tension headaches may be genetically linked to irritable bowel syndrome

Migraine and tension-type headaches may share genetic links with irritable bowel syndrome.

Derya Uluduz, MD, of Istanbul University, Turkey, explained that irritable bowel syndrome is the most common gastrointestinal disorder worldwide and affects up to 45 million people in the US. Many sufferers remain undiagnosed and the exact cause is not known. Common symptoms include abdominal pain or cramping, a bloated feeling, gas, diarrhoea, and constipation.



> Irritable bowel syndrome can be defined as migraine of the bowels

Dr Uluduz said, "Since headache and irritable bowel syndrome are such common conditions, and causes for both are unknown, discovering a possible link that could shed light on shared genetics of the conditions is encouraging."

Patients with irritable bowel syndrome display increased hypothalamic gray matter activity, suggesting an association between stress and the hypothalamic-pituitary-adrenal axis. From this perspective, irritable bowel syndrome can be defined as migraine of the bowels.

In patients with irritable bowel syndrome with constipation, serotonin secretion in plasma is decreased. Serotonin signalling is defective in irritable bowel syndrome, with a decrease in mucosal serotonin and immune-reactivity of the serotonin transporter.

The study involved 107 patients with episodic migraine, 53 with tension-type headache, 107 with irritable bowel syndrome and 53 healthy individuals. Participants with migraine and tension headache were examined for symptoms of irritable bowel syndrome and participants with irritable bowel syndrome were asked about headaches.

The frequency of irritable bowel syndrome in migraine patients was found to be twofold compared with episodic tension type headache (54.2% vs 28.3%, $P < 0.05$). Unilaterality and photophobia was more pronounced in migraine patients with irritable bowel syndrome. Migraine was found in 38 patients (35.5%) and episodic tension type headache was found in 24 patients (22.4%) with irritable bowel syndrome.

Comparison of study vs control subjects revealed a significant difference in terms of serotonin transporter intron 2 gene 10/12 vs migraine patients ($P = 0.0247$). When patients with episodic tension type headache and controls were compared, a significant difference in serotonin transporter intron 2 gene 10/12 ($P = 0.0103$) and 12/12 ($P = 0.0043$) genes was observed. When patients with irritable bowel syndrome and controls were compared, a significant difference in terms of 5-HT2A–1438 AA genotype ($P = 0.0005$) was observed.

Dr Uluduz concluded that the study suggested a high possibility of phenotypic and genotypic association between irritable bowel syndrome and primary headache disorders and supports the presence of a shared pathophysiological basis.

She added, "Further studies are needed to explore this possible link. Discovering shared genes may lead to treatment strategies for these chronic conditions." ■

Methylphenidate may ameliorate cognitive deficits in patients with epilepsy

Methylphenidate may be effective in ameliorating some cognitive deficits in patients with epilepsy, without affecting seizure control.

Jesse M. Adams, PhD, of Stanford University, Palo Alto, California, explained that epilepsy, interictal epileptiform discharges, and antiepileptic medications have been associated with cognitive impairments. Beyond reducing seizures or altering the number and types of antiepileptic medications, no validated treatment is available for these impairments.

Methylphenidate is effective for attention deficit/hyperactivity disorder. Since patients with epilepsy suffer attention deficits, Dr Adams and colleagues evaluated methylphenidate for cognitive difficulties in epilepsy in a pilot study.

> Methylphenidate may be effective in ameliorating some cognitive deficits in patients with epilepsy, without affecting seizure control

The team compared cognitive effects of placebo vs methylphenidate in patients with epilepsy. Ten- and 20-mg single dosages were given 1 week apart followed by a 1-month open-label phase.

Recorded measurements in the double-blind portion included the Conners Continuous Performance Task (CPT), Symbol-Digit Modalities Test (SDMT), and Medical College of Georgia Paragraph Memory Test. Adverse events and seizure frequency were monitored. Repeated-measures analyses of variants were performed.

Thirty-five adult patients with epilepsy participated, of whom 31 completed the double-blind portion. Demographics of completers were mean age 35.3 (range 20–60) years, 13 men and 18 women, and a mean of 2.8 seizures per month. Twenty-four patients suffered from focal, six generalised, and one unclassified epilepsy. Mean epilepsy duration was 12.5 years.

Methylphenidate was associated with significantly better performance than placebo on the SDMT ($P = 0.008$), and in the following CPT variables: d ($P = 0.037$), hits ($P = 0.04$), and omissions ($P = 0.034$). Seizure frequency was unchanged.

Adverse events leading to withdrawal included cognitive problems (n=1 on 20 mg), anxiety/agitation (n=1 on 10 mg), and tachycardia (n=1 who received the higher, 40 mg dose). One subject was lost to follow-up after one 20 mg dose without side effects.

Dr Adams concluded that methylphenidate may be effective in ameliorating some cognitive deficits in patients with epilepsy, without affecting seizure control. Additional studies are required to confirm the result. ■

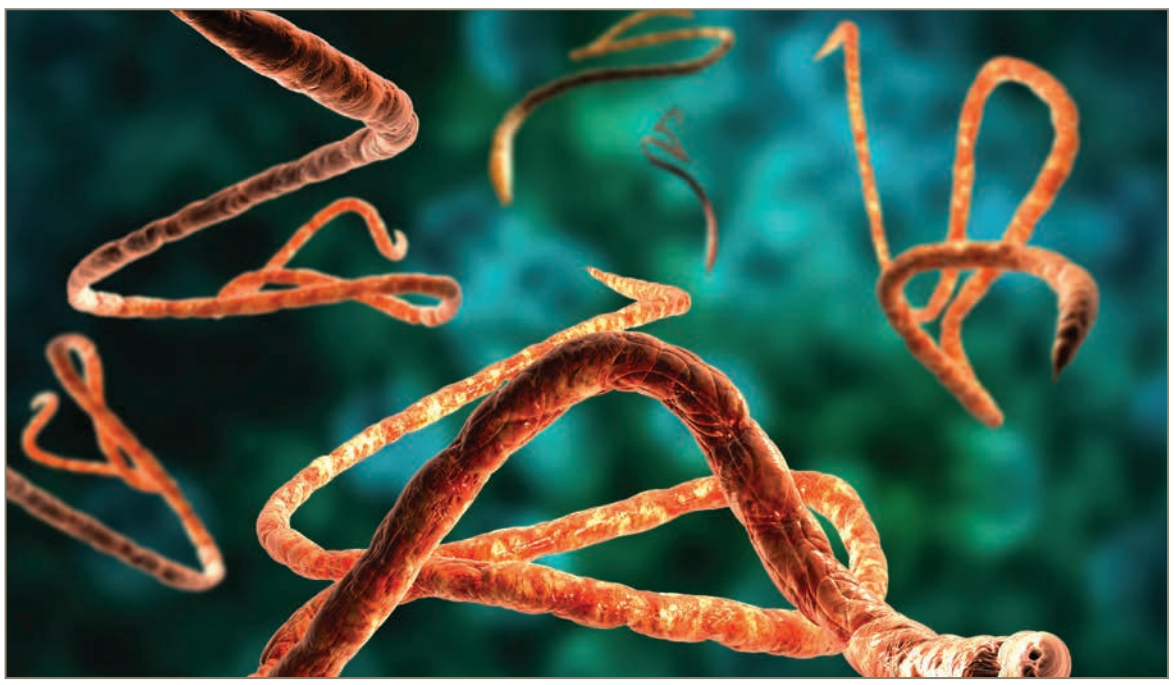
A majority of Ebola virus survivors experience neurological symptoms 6 months after infection

The majority of a cohort of Ebola virus survivors had neurological symptoms more than 6 months after initial infection. The study was part of the larger Partnership for Research on Ebola Virus In Liberia (PREVAIL) III study, which is following patients with prior Ebola virus disease and their close contacts, who serve as controls.

"While an end to the outbreak has been declared, these survivors are still struggling with long-term problems," said Lauren Bowen, MD, of the National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, Maryland.

More than 28,600 people were infected with Ebola in West Africa during the outbreak. Of that number, 11,300 died. In collaboration with the ongoing PREVAIL III natural history study of Ebola survivors, we wanted to find out more about possible continued long-term brain health problems for the more than 17,000 survivors of the infection."

Of 82 Ebola virus disease survivors, the mean age was 34.6 ± 11.0 years. Fifty three percent were female. 69.5% of survivors were admitted to an Ebola treatment unit for more than 14 days.



The most commonly recalled new neurologic symptoms during or after the Ebola treatment unit admission were headache, depressed mood, weakness, myalgia, and memory loss. Severe neurologic manifestations included hallucinations, meningitis, and coma. Severe manifestations were found in half of survivors, and the remaining half displayed moderate manifestations.

The most commonly reported ongoing symptoms were weakness, headache, depressed mood, memory loss, and myalgia. Two patients were actively suicidal and one suffered from active hallucinations.

The most common neurologic findings were abnormalities of eye pursuits and saccades in nearly two thirds of the cohort; tremor and abnormal reflexes, and abnormal sensory findings in one third, and frontal release signs in a sixth. Nearly all survivors had some neurologic disability as measured by the Modified Rankin Scale.

> "Neurologic abnormalities following Ebola virus disease involved subcortical structures, cerebellar pathways, and sensory peripheral nerves and were present in most survivors

Dr Bowen concluded that neurologic abnormalities following Ebola virus disease involved subcortical structures, cerebellar pathways, and sensory peripheral nerves and were present in most survivors.

Evaluations of uninfected contacts of the survivors are ongoing and will allow for additional insight into the neurologic burden of Ebola virus disease. Controls are being evaluated to determine which of these findings is Ebola-specific. Examined participants were seen on only one occasion, so whether symptoms will persist or resolve is not known.

Dr Bowen added, "It is important for us to know how this virus may continue to affect the brain long term." ■

Emotionally abused children may be more likely to experience migraine as adults

Emotionally abused children may be more prone to experience migraines as young adults. The link between migraine and abuse was stronger for emotional abuse than for physical or sexual abuse.

"Emotional abuse showed the strongest link to increased risk of migraine. Childhood abuse can have long-lasting effects on health and well-being," said Gretchen Tietjen, MD, of the University of Toledo, Ohio.

> "People who were emotionally abused were 32% more likely to have migraine than those who were not abused

Dr Tietjen and colleagues assessed emotional abuse by asking, "How often did a parent or other adult caregiver say things that really hurt your feelings or made you feel like you were not wanted or loved?"

The study included data from 14,484 patients age 24 to 32 years. About 14% reported having been diagnosed with migraines. Participants were asked whether they had experienced emotional, physical, or sexual abuse in childhood.

Physical abuse was defined as being hit with a fist, kicked, or thrown down on the floor, into a wall, or down stairs. Sexual abuse included forced sexual touching or sexual relations. About 47% of participants answered yes to having been emotionally, 18% physically, and 5% sexually abused.

Of those diagnosed with migraines, 61% reported having been abused as a child. Of those who never had a migraine, 49% said they were abused. Those who were abused were 55% more likely to experience migraine than those who were never abused after accounting for age, income, race and sex.

Participants who were emotionally abused were 52% more likely to have migraine than those who were not abused, after accounting for other types of abuse as well as age, income, race and sex. In contrast, those who were sexually or physically abused were not significantly more likely to have migraine than people who were not abused.

The relationship between emotional abuse and migraine remained when researchers adjusted the results to take into account depression and anxiety. In that analysis, people who were emotionally abused were 32% more likely to have migraine than those who were not abused.

Dr Tietjen noted an association was shown between childhood emotional abuse, a very common occurrence, and migraine. It did not show cause and effect, though the finding that the likelihood of suffering migraines increases with an increasing number of abuse types suggested causation.

Dr Tietjen concluded, "More research is needed to better understand the relationship between childhood abuse and migraine. This is also something doctors may want to consider when they treat people with migraine." ■

> Neurologic abnormalities following Ebola virus disease involved subcortical structures, cerebellar pathways, and sensory peripheral nerves and were present in most survivors >12

> Daylight savings time transitions were associated with an increased incidence of ischaemic stroke during the **first 2 days** after transitions >13

> Participants who used a computer once per week or more were **42% less** likely to develop memory and thinking problems than those who did not >13

Outdoor light pollution may interfere with sleep

Well-lit neighbourhoods at night may interfere with sleep.

"Our world has become a 24/7 society. We use outdoor lighting, such as streetlights, to be more active at night and to increase our safety and security. The concern is that we have reduced our exposure to darkness and it could be affecting our sleep," said Maurice Ohayon, MD, DSC, PhD, of Stanford University, Stanford, California.

> Excessive exposure to light at night may affect how we function during the day and increase the risk of excessive sleepiness

A total of 15,863 people were interviewed by phone over an 8-year period. They were asked about sleep habits, quality of sleep, and medical and psychiatric disorders.

Using nighttime data from the Defense Meteorological Satellite Program, Dr Ohayon's team looked at how much outdoor light the subjects were exposed to at night. People living in urban areas of 500,000 people or more were exposed to nighttime lights that were three to six times more intense than people living in small towns and rural areas.

The study showed that nighttime light affected sleep duration and was significantly associated with sleep disturbances. People living in more intensely lit areas were 6% more likely to sleep fewer than 6 hours per night than people in less intensely lit areas. People living in more intensely lit areas were more likely to be dissatisfied with their sleep quantity or quality than those in less intensely lit areas, with 29% dissatisfied compared to 16%, respectively.

People with high exposure to light were also more likely to report fatigue than those with low exposure to light: 9% vs 7%, respectively. People with high exposure to light also slept less per night than those with low exposure to light, an average of 412 compared to 402 minutes per night.

In addition, people with high exposure to light were more likely to awaken up confused during the night than those with low exposure to light: 19% experienced this confusion compared to 13%, respectively. They were also more likely to experience excessive sleepiness and impaired functioning, at 6% vs 2%, respectively.

Dr Ohayon concluded that exposure to outdoor nighttime light exposure was strongly associated with changes in sleep habits and impacted daytime functioning, increasing the risk of excessive sleepiness.

"Light pollution can be found in any sizable city in the world. Yet excessive exposure to light at night may affect how we function during the day and increase the risk of excessive sleepiness. If this association is confirmed by other studies, people may want to consider room-darkening shades, sleep masks, or other options to reduce their exposure to light at night," he said. ■

A preliminary study links daylight saving time to stroke risk

Turning the clock ahead or back 1 hour during daylight savings time transitions may be tied to an increased risk of ischaemic stroke, but only temporarily.

"Studies have shown that disruptions in circadian rhythm increase the risk of ischaemic stroke, so we wanted to find out if daylight savings time was putting people at risk," said Jori Ruuskanen, MD, PhD, of the University of Turku, Finland.

Daylight savings time transitions disrupt circadian rhythms and have been shown to shift the pattern of diurnal variation in stroke onset, but effects on the overall incidence of ischaemic stroke are unclear.

Dr Ruuskanen and colleagues looked at a decade (2004–2013) of data on stroke in Finland to calculate the rate of stroke. They compared the rate of stroke in 3033 people hospitalised during the week following a daylight savings time transition to the rate in 11,801 people hospitalised either 2 weeks before or after that week.

The incidence of ischaemic stroke was increased during the first 2 days (incidence ratio 1.08; confidence interval 1.01–1.15, P = 0.020) after transition, but the difference was diluted when observing the whole week (incidence ratio 1.03; 0.99–1.06; P= 0.069). Weekday specific increase was observed on second day (Monday: incidence ratio 1.09; CI 1.00–1.90; P = 0.023) and fifth day (Thursday: incidence ratio 1.11; confidence interval 1.01–1.21; P = 0.016) after transition.

Women were more susceptible to temporal changes after daylight savings time transitions than men, but there no difference in overall risk of ischaemic stroke was observed between genders. Increased risk was seen for patients with malignancy (relative risk 1.25; confidence interval 1.00–1.56; P = 0.047), and advanced age (>65 years) on the first 2 days (relative risk 1.20; confidence interval 1.04–1.38; P = 0.020) and on the second day (relative risk 1.23; confidence interval 1.03–1.47; P = 0.021) after daylight savings time transition. Daylight savings time transition did not affect in-hospital mortality.

> Differences in the effect of daylight savings time transitions may occur depending on age or gender, but no difference was reflected in the overall incidence of ischaemic stroke

Dr Ruuskanen concluded that daylight savings time transitions were associated with an increased incidence of ischaemic stroke during the first 2 days after transitions. Differences in the effect of daylight savings time transitions may occur depending on age or gender, but no difference was reflected in the overall incidence of ischaemic stroke.

She said, "Further studies must now be done to better understand the relationship between these transitions and stroke risk and to find out if there are ways to reduce that risk." ■

Using a computer and participating in social activities appear to reduce risk of memory decline

Keeping the brain active with social activities and using a computer may help older adults reduce their risk of memory and thinking problems.

"Our results show the importance of keeping the mind active as we age. While this study shows only association, not cause and effect, as people age, they may want to consider participating in activities like these because they may keep the mind healthier, longer," said Janina Krell-Roesch, PhD, of the Mayo Clinic, Scottsdale, Arizona.

Dr Krell-Roesch's team reported previously on a cross-sectional association between late-life mentally stimulating activities and decreased odds of mild cognitive impairment. The risk of incident mild cognitive impairment as predicted by late-life mentally stimulating activities, however, is poorly understood.

Dr Krell-Roesch and colleagues followed 1929 people age 70 years and older who were parts of the larger Mayo Clinic Study of Aging in Rochester, Minnesota. Participants had normal memory and thinking abilities at recruitment. They were then followed for an average of 4 years until they developed mild cognitive impairment or remained impairment-free.

In a questionnaire, participants were asked about their engagement in mentally stimulating activities such as computer use, reading, crafting and social activities within 12 months before participation in the study.

The team then determined whether participants who engaged in mental activities at least once per week were at lower risk for new onset of mild cognitive impairment than participants who did not engage in these activities.

Participants who used a computer once per week or more were 42% less likely to develop memory and thinking problems than those who did not. A total of 193 of 1077 people (17.9%) in the computer use group developed mild cognitive impairment, compared to 263 of 852 (30.9%) who did not report computer use.

People who engaged in social activities were 23% less likely to develop memory problems than those who did not engage in social activities. A total of 154 of 767 (20.1%) people in the social activities group developed problems, compared to 302 of 1162 (26.0%) people who did not participate in social activities.

People who reported reading magazines were 30% less likely to develop memory problems. Those who engaged in craft activities were 16% less likely to develop memory problems. Similarly, those who played games were 14% less likely to develop memory problems.

After stratification by apolipoprotein ε4 status, findings remained the same for apolipoprotein ε4 noncarriers. Only computer use, however (hazard ratio 0.65, 95% confidence interval 0.65–0.92) and social activities (hazard ratio 0.62, 95% confidence interval 0.43–0.89) were associated with a decreased risk of incident mild cognitive impairment for APOE epsilon4 carriers.

Dr Krell-Roesch concluded that cognitively normal elderly individuals who engage in specific mentally stimulating activities have a decreased risk of incident MCI. The associations may vary with apolipoprotein ε4 carrier status. ■

MY APPROACH

Success in migraine preventive treatment

Migraine attacks significantly interfere with quality of life despite appropriate use of acute medications. Dr Stephen Silberstein shares his principles which have led to success in preventive treatments.

When do I use migraine preventive treatment? I consider prevention if my patients' migraine attacks significantly interfere with their quality of life despite appropriate use of acute medications; if they have four or more attacks per month or eight or more headache days per month; if acute medications fail or are overused; or if they have hemiplegic migraine, basilar migraine, frequent, prolonged or uncomfortable aura symptoms, or migrainous infarction. I consider a preventive migraine drug successful if it reduces migraine attack frequency or days by at least 50% within 3 months.

Many classes of medications are used for migraine prevention: antiepileptic drugs, antidepressants, beta blockers, calcium channel antagonists, serotonin antagonists, botulinum neurotoxins, NSAIDs, and vitamins. I start with a drug based on its efficacy, adverse events, patient preference, and the presence of any coexistent or comorbid conditions. The preventive drugs with the best-proven efficacy are certain beta blockers, divalproex sodium, and topiramate. An underweight patient would be a candidate for one of the medications that commonly produce weight gain, such as a tricyclic antidepressant; in contrast, I would try to avoid these drugs and consider topiramate when the patient is overweight. Tertiary tricyclic antidepressants that have a sedating effect would be useful at bedtime for patients with insomnia. Older patients with cardiac disease or patients with significant hypotension may not be able to use tricyclic antidepressants, calcium channel blockers, or beta blockers, but could use divalproex sodium or topiramate.

Monotherapy is a treatment goal, and taking advantage of comorbid or coexistent illness may facilitate treatment of both disorders with a single drug. However, therapeutic independence may be needed should monotherapy fail. For example, tricyclic antidepressants are often recommended for patients with migraine and depression. However, appropriate management of depression often requires higher doses of tricyclic antidepressants, which may be associated with more adverse effects. A better approach might be to treat the depression with a selective serotonin reuptake inhibitor or a selective norepinephrine reuptake inhibitor.

When would I stop a preventive medication?

- Preventive migraine therapy should be stopped when the patient develops intolerable adverse events or a severe drug reaction; the drug does not demonstrate even partial efficacy after 2 months of therapy; and disorders such as acute medication overuse have not been eliminated.
- I would also stop the drug if the patient has shown significant benefit. If the headaches are well-controlled for at least 6 months, I slowly taper and, if possible, discontinue the drug. ■

Stephen D. Silberstein MD is professor, Department of Neurology; director, Jefferson Headache Center, Thomas Jefferson University, Philadelphia, Pennsylvania.

Dr Stephen D. Silberstein's principles for successful preventive migraine treatment

- **Start the drug at a low dose** and increase it slowly until therapeutic effects develop, the ceiling dose is reached, or adverse events become intolerable.
- **Give the treatment an adequate trial.** A full therapeutic trial may take 2 to 6 months before the maximal response to a treatment is evident.
- **Set realistic goals.** Success is a 50% reduction in attack frequency or headache days, a significant decrease in attack duration, or an improved response to acute medication.
- **Reevaluate therapy**. Migraine may improve or remit independent of treatment.
- **Involve patients in their care to maximise compliance.** I discuss the rationale for a particular treatment, when and how to use it, and what adverse events are likely. I address patient expectations and set realistic goals. I set realistic expectations regarding adverse events. Most are self-limited and dose-dependent, and patients should be encouraged to tolerate the early adverse events that may develop when a new medication is started.

NEWS

Narrow band of green light may ease migraine symptoms

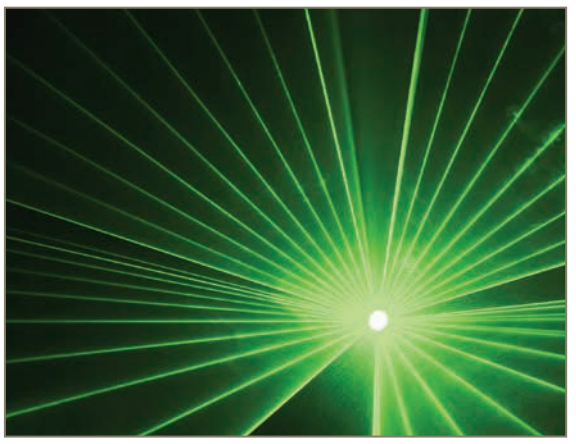
Experimental light therapy finds it can ease photophobia, pain for some patients

A treatment involving a narrow spectrum of low-intensity green light may help ease migraine pain, according to a study published online May 17 in *Brain*.

Rami Burstein, PhD, of the Beth Israel Deaconess Medical Center in Boston, and colleagues exposed 69 migraine patients to different colours of light.

The researchers found that while blue light exacerbated headache pain, a narrow spectrum of low-intensity green light significantly reduced photophobia. In some cases, this green light also reduced migraine pain by about 20 percent.

"Although photophobia is not usually as incapacitating as headache pain itself, the inability to endure light can be disabling," Burstein said in a medical centre news release. "More than 80 percent of migraine attacks are associated with and exacerbated by light sensitivity, leading many migraine sufferers to seek the comfort of darkness and isolate themselves from work, family, and everyday activities." ■



HealthDay

Prevalence of migraine up in patients with cardiac syndrome X

Increased prevalence of migraine in CSX compared with coronary artery disease or healthy controls

The prevalence of migraine headache is elevated in patients with cardiac syndrome X (CSX) compared to patients with coronary artery disease or healthy controls, according to a research letter published in the May 3 issue of the *Journal of the American College of Cardiology*.

In a prospective study, Reza Nemati, MD, from the Bushehr University of Medical Sciences in Iran, and colleagues examined the prevalence of migraine headache in three groups: 50 patients with CSX, 50 patients with coronary artery disease, and 50 healthy controls.

The researchers found that the prevalence of migraine was 60, 16, and 22 percent in CSX patients, the coronary artery disease group, and the healthy control group, respectively ($P < 0.0001$). In women and men with CSX the frequency of migraine headache was 70.4 and 52.2 percent, respectively.

"Our study concluded that CSX may presumably be a manifestation of migraine as another migraine equivalent," the authors write. "After the ongoing evidence on the multifaceted pathophysiology of CSX, it became even more clear that there is a need for a pragmatic approach to education and training of medical practitioners in the management of patients, especially in refractory patients using the current treatment." ■

HealthDay

JOURNAL SCAN

Deep brain stimulation of the ventral tegmental area for refractory chronic cluster headache

Neurology

Take-home message

- A small proportion of patients with chronic cluster headache (CCH) are refractory to medical therapy. In these patients, the pain is debilitating, and the periods of remission are short. In these cases, peripheral nerve stimulation and central neuromodulation have been proposed. This is an uncontrolled, open-label prospective study of deep brain stimulation (DBS) targeting the ventral tegmental area (VTA) in patients with intractable CCH. A total of 21 consecutive patients underwent the therapy under a humanitarian device intervention, using an MRI-guided approach. A high-frequency (185Hz) stimulation regimen was used. Follow-up ranged from 4 months to 5 years, with a median of 18 months. At the last follow-up point, there was an overall 60% improvement in median headache frequency (from 5 to 2 attacks per day) and an improvement in median headache severity of 30% (from 10 to 7 points on the verbal rating scale). There was a concomitant reduction in triptan intake and an improvement in quality-of-life measures. The most notable side-effect was diplopia, a known reversible stimulation-related adverse effect for this stimulation target.
- The data need to be interpreted with caution, as the placebo effect can be very large with these interventions in this patient population, but the results suggest potential efficacy of VTA DBS for intractable CCH, which should be studied further, ideally with a sham stimulation control.

Dr Codrin Lungu

OBJECTIVES To present outcomes in a cohort of medically intractable chronic cluster headache (CCH) patients treated with ventral tegmental area (VTA) deep brain stimulation (DBS).

METHODS In an uncontrolled open-label prospective study, 21 patients (17 male; mean age 52 years) with medically refractory CCH were selected for ipsilateral VTA-DBS by a specialist multidisciplinary team including a headache neurologist and functional neurosurgeon. Patients had also failed or were denied access to occipital nerve stimulation within the UK National Health Service. The primary endpoint was improvement in the headache frequency. Secondary outcomes included other headache scores (severity, duration, headache load), medication use, disability and affective scores, quality of life (QoL) measures, and adverse events.

RESULTS Median follow-up was 18 months (range 4–60 months). At the final follow-up point, there was 60% improvement in headache frequency ($P = 0.007$) and 30% improvement in headache severity ($P = 0.001$). The headache load (a composite score encompassing frequency, severity, and duration of attacks) improved by 68% ($P = 0.002$). Total monthly triptan intake of the group dropped by 57% post-treatment. Significant improvement was observed in a number of QoL, disability, and mood scales. Side effects included diplopia, which resolved in 2 patients following stimulation adjustment, and persisted in 1 patient with a history of ipsilateral trochlear nerve palsy. There were no other serious adverse events.

CONCLUSIONS This study supports that VTA-DBS may be a safe and effective therapy for refractory CCH patients who failed conventional treatments.

CLASSIFICATION OF EVIDENCE This study provides Class IV evidence that VTA-DBS decreases headache frequency, severity, and headache load in patients with medically intractable chronic cluster headaches.

Ventral tegmental area deep brain stimulation for refractory chronic cluster headache *Neurology* 2016;86(18)1676-1682, H Akram, S Miller, S Lagrata, et al.

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