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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Occipital Nerve Stimulation in Medically Intractable Chronic Cluster Headache

By Alina Masters-Israilov, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Occipital nerve stimulation is an effective and safe treatment that can help reduce attack frequency and intensity in patients with medically intractable chronic cluster headache.

SOURCE: Wilbrink LA, de Coo IF, Doesborg PG, et al. Safety and efficacy of occipital nerve stimulation for attack prevention in medically intractable chronic cluster headache (ICON): A randomised, double-blind, multicentre, phase 3, electrical dose-controlled trial. *Lancet Neurol* 2021;20:515-525.

Cluster headache, a type of trigeminal autonomic cephalalgia, is a disabling primary headache disorder that is more prevalent in men and features severe unilateral periorbital pain associated with ipsilateral autonomic symptoms. Patients can endure up to eight attacks per day, and each attack lasts 15 minutes to three hours. Cluster periods can last weeks and up to three months. However, patients with chronic cluster headache either have no pain-free periods or pain-free periods lasting less than three months.

Treatment of cluster headache often entails acute, bridging, and preventive therapies. Patients who do not respond to or cannot tolerate commonly prescribed preventive treatments, such as verapamil and valproic acid (making up about 15% of patients with chronic cluster headache), are described to have medically intractable chronic cluster headache (MICCH). Occipital nerve stimulation (ONS) has been recommended in the treatment of MICCH. ONS features electrodes that are implanted subcutaneously, bi-occipitally, and connected to an implantable pulse generator (IPG) subcutaneously in the abdominal or gluteal region. ONS may inhibit the trigeminocervical complex in the brainstem, where cervical, somatic trigeminal, and dural trigeminovascular afferents synapse.

This study was an international, multicenter, randomized, double-blinded, electric dose-controlled trial assessing ONS in patients with MICCH. Patients included

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This CME activity is intended for the neurologist. It is in effect for 36 months from the date of the publication.

The Passing of M. Flint Beal, MD

It is with great sadness that I inform our readers of the sudden death of M. Flint Beal, MD, prior editor of *Neurology Alert* and our current peer reviewer.

Dr. Beal, University Professor of Neuroscience in the Feil Family Brain and Mind Research Institute and Professor of Neurology, died at home on June 12, 2021. He was an iconic, internationally recognized leader in neurology and neurogenerative disorders who made invaluable contributions to Weill Cornell Medicine as a scientist, department chair, and mentor.

Dr. Beal was recruited from Harvard Medical School in 1998 as chair of the Department of Neurology and Neuroscience at Weill Cornell Medicine and Neurologist-in-Chief at NewYork-Presbyterian/Weill Cornell Medical Center. He was an outstanding researcher, educator, and clinician who brought high quality and academic strength to the department, and he was greatly respected by colleagues, patients, and students.

Dr. Beal's research focused on the mechanism of neuronal degeneration in Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis. His laboratory worked to develop novel therapeutic interventions for these disorders by combining genetic and pharmacologic approaches. He was recognized for exemplary achievement in his field with numerous honors and was a member of the National Academy of Medicine. He will be greatly missed.

— *Matthew E. Fink, MD, Editor*

had chronic cluster headache; at least four headache attacks per week; were older than 18 years of age; had magnetic resonance imaging (MRI) of the brain within the past year without relevant findings; and had either non-response, intolerance, or contraindication to verapamil and lithium along with non-response, intolerance, or contraindication to methysergide, topiramate, or gabapentin. The study consisted of a 12-week baseline observation period, a device implantation period (using Medtronic Quad Plus), and a 10-day 10% ONS run-in treatment period, followed by 24 weeks of stepwise increase of ONS intensity to an ultimate goal of either 100% or 30% ONS (masked phase), and another 24-week (weeks 25-48), open-label treatment period in which participants received individually optimized open-label ONS. Investigators did not use a 0% setting because both groups had to experience paresthesia to have a valid control group. The primary outcome was change in weekly mean attack frequency (MAF) in weeks 21-24 compared with baseline. Some of the secondary outcomes included the proportion of patients with more than a 50% reduction in MAF at weeks 24 and 48 compared with baseline, mean attack intensity at weeks 21-24 and weeks 45-48, and adverse events. Data were collected during both the follow-up visits every three months and through using web-based diaries.

From Oct. 12, 2010, until Dec. 3, 2017, 150 patients were enrolled from tertiary headache centers, of which 130 were assigned to treatment and ultimately implanted with ONS (65 patients assigned to 100% ONS and 65 patients assigned to 30% ONS). At weeks 21-24, MAF in the total population was 7.38 (interquartile range [IQR], 2.50 to 18.50), which represented a median decrease of -5.21 (IQR, 11.18 to -0.19; $P < 0.0001$) compared to baseline. In the 100% and 30% ONS groups, the median decrease in MAF was -4.08 (-11.92 to -0.25) and -6.50 (-10.83 to -0.08), respectively; there was no difference in MAF decrease between weeks 21 and 24 compared to baseline between these two treatment groups (-2.42; 95% confidence interval, -5.17 to 3.33). Interestingly, the median weekly MAF already was reduced in both treatment groups as early as weeks 1-4 after ONS. In the total study population, approximately half the participants had at least a 50% reduction in MAF at weeks 21-24 and weeks 45-48, and a small percentage of patients (nine patients) were completely pain-free at weeks 21-24. A total

of 129 adverse events occurred with 100% ONS and 95 adverse events occurred with 30% ONS, of which 17 in the 100% ONS group and eight in the 30% ONS group were labeled as serious (for brief hospitalization for hardware-related issues). Nonetheless, most patients reported they would recommend the therapy to other patients. The most common reported side effects were local pain, impaired wound healing, neck stiffness, and hardware damage.

■ COMMENTARY

Both ONS settings of 100% and 30% used in the study showed a significant reduction in attack frequency in patients with MICCH and were safe and well tolerated. This study showed more rapid onset of improvement than shown in similar previous studies, which is important for patients with MICCH who would benefit from rapid relief. Early success of ONS also was shown to be predictive of sustained response at later weeks. An optimal stimulation protocol and trial design to test this new technology should be focused on determining the most effective level of intensity at or below the lowest level that induces paresthesia. It is likely that each patient will have a different level of intensity that results in the effective treatment of headache. ONS may be a more tolerable treatment than some oral medications that have been used historically for cluster headache prevention. ■

ABSTRACT & COMMENTARY

Mortality and Costs of Status Epilepticus

By Pegah Afra, MD

Associate Professor of Neurology, Weill Cornell Medical College; Associate Attending Neurologist; NewYork-Presbyterian Hospital; Adjunct Associate Professor, University of Utah

SYNOPSIS: In an analysis of a large group of patients hospitalized with status epilepticus, based on an administrative database, patients who required a third line of intravenous anesthetic agents had the highest mortality and highest hospital costs.

SOURCE: Guterman EL, Betjemann JP, Aimetti A, et al. Association between treatment progression, disease refractoriness, and burden of illness among hospitalized patients with status epilepticus. *JAMA Neurol* 2021;78:588-595.

Status epilepticus (SE) is a life-threatening condition affecting 12 to 61 cases per 100,000 people.[1-4] SE is treated with benzodiazepines as the first-line antiseizure drug (ASD) followed by intravenous ASDs (i.e., brivaracetam, fosphenytoin, lacosamide, levetiracetam, phenobarbital, phenytoin, and valproic acid).[5] If SE does not abate, treatment is continued with intravenous anesthetics (i.e., etomidate, ketamine, midazolam, methohexital, pentobarbital, propofol, and thiopental).[5] Often, patients with SE require treatment in an intensive care unit (ICU) setting. Additionally, SE can become refractory SE (RSE) when it requires third-line therapy with intravenous anesthetic infusions to achieve seizure control, or super-refractory SE (SRSE) when SE persists after 24 hours of anesthetic infusion or recurs after weaning of intravenous anesthetic agents.[6,7] Therefore, SE often is associated with high morbidity and mortality because of the need for a prolonged ICU stay and mechanical ventilation and its associated medical complications.[6-8] These authors investigated differences in clinical outcomes and costs associated with hospitalization for SE of varying degrees of refractoriness.

In a descriptive cross-sectional study of SE using the Premier Healthcare Database from Jan. 1, 2016, to Dec. 31, 2018, the investigators analyzed 43,988 U.S. hospitalizations (of any age) with a primary or secondary ICD-10 diagnosis of SE. Disease refractoriness was classified as low, moderate, or highly refractory based on the use of intravenous ASDs vs. continuously infused intravenous anesthetics. For example, midazolam would be a first-line therapy if administered as an initial bolus injection, but it would be considered a third-line intravenous anesthetic if administered in the ICU on the same day as an intravenous infusion.

Three cohorts were defined: low refractory SE was treatment with none or one intravenous ASD and no third-line intravenous anesthetic; moderate refractory SE was defined as treatment with more than one intravenous ASD and no third-line intravenous anesthetic; and highly refractory SE was defined as treatment with at least one intravenous ASD and at least one third-line intravenous anesthetic. Outcome measures were discharge disposition, need for mechanical ventilation, adverse events, hospital and ICU length of stay (LOS), and cost. A series of pairwise comparisons was done between different groups (basic SE characteristics and outcome data) using a bootstrap-based analysis of variance for parametric data, Kruskal-Wallis tests for nonparametric data, and χ^2 tests for categorical data.

From the included 43,988 U.S. SE hospitalizations, 22,851 patients (51.9%) were male with mean age 49.9 years (95% confidence interval, 49.7 to 50.1 years). There were 14,694 admissions (33.4%) for low refractory SE, 10,140 (23.1%) for moderate refractory SE, and 19,154 (43.5%) for highly refractory SE. Overall

in-hospital mortality was 11.2%, with the highest mortality rates in highly refractory SE (18.9%) compared with moderate refractory SE (6.3%) and low refractory SE (4.6%). The *P* value was < 0.001 for all comparisons. Median hospital LOS was five days (interquartile range [IQR], 2 to 10 days) with a greater length of stay in highly refractory SE (eight days; IQR, 4 to 15 days) compared with moderate refractory SE (four days; IQR, 2 to 8 days) and low refractory SE (three days; IQR, 2 to 5 days). Patients with highly refractory SE had greater hospital costs, with median costs of $25,105 (mean, $41,858; standard deviation [SD], $59,063) in the high refractory SE cohort, $10,592 (mean, $18,328; SD, $30,776) in the moderate refractory SE cohort, and $6,812 (mean, $11,532; SD, $17,228) in the low refractory SE cohort.

■ COMMENTARY

This study describes the range of morbidity, mortality, and costs associated with SE, with the burden increasing with the higher level of refractoriness. The three cohorts of low, moderate, and highly refractory SE were based on medication treatment and only approximate clinically defined early SE, RSE, and SRSE. About 43.5% of inpatients with SE required more antiseizure and anesthetic medications as a result of refractory disease. They also had higher clinical and financial costs and a higher mortality rate of 18.9% (which was more than 10% higher than moderate and low refractory SE). Patients with high refractory SE also had a longer hospital stay, and, therefore, higher total costs for acute hospitalization. ■

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ABSTRACT & COMMENTARY

Functional Cognitive Disorder: An Important Condition for Neurologists to Recognize

By Lisa Ravdin, PhD

Associate Professor of Neuropsychology in Neurology

SYNOPSIS: Functional cognitive disorder (FCD) is a term that can be used to describe cognitive difficulties that are present where there is no biologic cause, but a lack of consensus in diagnostic criteria limits its use in clinical practice and research. Ball and colleagues proposed an operational definition for FCD as the cognitive phenotype of functional neurological disorder.

SOURCES: Ball HA, McWhirter L, Ballard C, et al. Functional cognitive disorder: Dementia's blind spot. *Brain* 2020;143:2895-2903.

Kapur N, Kemp S, Baker G. Functional cognitive disorder: Dementia's blind spot. *Brain* 2021;144:e37.

Subjective cognitive complaints that present without an identifiable cause or objective evidence of impairment are commonly observed and may present at greater rates in older adults. The term functional cognitive disorder (FCD) has been used to describe unexplainable persistent cognitive complaints and can be seen as a cognitive variant of the broader term, functional neurological disorder (FND). The authors of this article convey that internal inconsistency is at the core of the diagnosis of FCD, which is present when the individual's subjective sense of cognitive dysfunction is discrepant with intact objective test scores, presentation, and independence in activities of daily living, as well as a collateral's report reflecting reduced concern compared to that reported by the affected person. In FCD, there is variability in performance within a particular cognitive domain where an individual shows "the ability to perform a task well at certain times, but with significantly impaired ability at other times, particularly when the task is the focus of attention." This is not simply normal variability where performance fluctuates over time as in cognitive disorders that have waxing and waning symptoms. Internal inconsistency needs to be seen within a particular cognitive domain. This also is discrepant from individuals who intentionally perform poorly and fail effort testing (i.e., malingerers).

FCD is common in clinical practice but is rarely diagnosed as such. Patients with subjective cognitive complaints with no identifiable neurologic disorder often are diagnosed with mild cognitive impairment (MCI) or subjective cognitive decline. The authors contend that FCD terminology also could be useful to de-emphasize the expectation that these subjective cognitive complaints necessarily progress to dementia. Importantly, definitions of FCD lack consensus, and the unclear trajectory of these symptoms, as well as the likelihood of comorbidity with underlying neurodegenerative processes, precludes its common use and understanding in clinical and research settings. The authors propose an operational definition for FCD as the cognitive phenotype of FND.

In a letter to the editor, Kapur and colleagues indicated that some of the main points raised in the formulation of the FCD definition proposed by Ball et al are potential sources of confusion. Specifically, differentiating between internal and external inconsistency and its applicability to the diagnosis is questioned. These authors pointed out that use of this definition does not account for naturally occurring neurologic presentations that have features of inconsistency. It is suggested that this definition of FCD has an overreliance on internal inconsistency. Further, these authors recognized that the neuropsychological evaluation examines patterns on cognitive testing, and these exams do, in fact, include consideration of non-organic factors in the interpretation of neurocognitive data, including fluctuating attention, alertness, effort, and environmental factors, both within and between cognitive domains.

■ COMMENTARY

It is not uncommon for individuals to present with cognitive complaints even when there is no biologic evidence that meets the threshold of a diagnosable disorder. This often is labeled as MCI. When used in this manner, MCI is a term that does not convey diagnostic specificity, essentially creating a blind spot in discriminating subjective vs. objective cognitive compromise. The neuropsychological evaluation can help to identify patient-specific factors that contribute to cognitive complaints as well as interpret patterns of performance that can be useful in examining subjective vs. objective cognitive concerns. Patients with cognitive complaints may benefit from evidence-based interventions that target factors that create or amplify the experience of cognitive dysfunction, such as depression, anxiety, sleep problems, substance use, stress, and chronic pain. ■

ABSTRACT & COMMENTARY

Is it Chronic Inflammatory Demyelinating Polyneuropathy or Charcot-Marie-Tooth Disease?

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Charcot-Marie-Tooth disease may be confused with chronic inflammatory demyelinating polyneuropathy, resulting in inappropriate and hazardous treatments. Age at onset < 40 years, a family history of neuropathy, absence of nerve hypertrophy on magnetic resonance imaging, and poor response to intravenous immune globulin treatment should prompt a genetic evaluation.

SOURCE: Hauw F, Fargeot G, Adams D, et al. Charcot-Marie-Tooth disease misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy: An international multicentric retrospective study. *Eur J Neurol* 2021; Jun 1. doi:10.1111/ENE.14950. [Online ahead of print].

Chronic inflammatory demyelinating polyneuropathy (CIDP) and Charcot-Marie-Tooth disease (CMT) overlap. CIDP is an acquired, immune-mediated, inflammatory demyelinating neuropathy, classically manifesting as a symmetric motor-predominant neuropathy with proximal and distal weakness, responsive to immunomodulatory therapy, whereas CMT encompasses a group of genetic neuropathies, usually demyelinating in nature, with predominantly distal weakness, not amenable to specific treatment. CMT occasionally is misdiagnosed as CIDP. Which features might suggest a diagnosis of CMT rather than CIDP, and thus prevent inappropriate treatment?

Using European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria for the diagnosis of CIDP, an observational retrospective study was undertaken among 16 university hospitals in France, Switzerland, and Belgium to identify patients with definite or probable CIDP and to determine how many were misdiagnosed CMT patients. Among 1,104 CIDP patients, detailed data were collected on 56 patients whose CIDP diagnosis was challenged. CMT was considered, based on family history, pes cavus, electrodiagnostic (EDX) findings, and lack of response to intravenous immune globulin (IVIG) treatment. EDX studies were performed on both the upper and lower extremities,

using standard methodology, with skin temperature kept between 32° C and 34° C. Conduction block required a 50% drop in proximal negative peak compound muscle action potential amplitude, as per EFNS/PNS criteria. Additional paraclinical investigations included serum antiganglioside antibody measurement, cerebrospinal fluid (CSF) analysis, magnetic resonance imaging (MRI) of the brachial and lumbosacral plexus, nerve biopsy, and genetic analysis, comprising *PMP22* gene deletion/duplication analysis. If *PMP22* was negative, further analysis was performed with a panel of 127 genes involved in hereditary neuropathies in 20 patients, and a panel of 76 genes in five patients. CMT patients misdiagnosed as CIDP were compared to a group of 35 CIDP patients diagnosed using EFNS/PNS criteria, randomly selected among CIDP patients followed at Bicêtre University Hospital and Pitié-Salpêtrière University Hospital, Paris, France. Statistical analysis comprised the Wilcoxon-Mann-Whitney test, Chi-squared test, and Fisher test, with significance set at 0.05.

Among 1,104 patients diagnosed initially with definite or probable CIDP based on EFNS/PNS criteria, CMT was suspected in 56 patients (5%) and genetically confirmed in 35 patients (3.2%). Median age at onset in these 35 misdiagnosed patients was 39 years (range, 4 to 60 years), with onset before age 15 years in five patients (14%), and before age 40 years in 18 patients (51%). Consanguinity was present in four patients (11%), with a family history of neuropathy or an associated autoimmune condition in eight patients (23%). Pes cavus was present in 20 patients (57%), cranial nerve involvement in six patients (17%), upper limb onset in 16 patients (46%), and asymmetric onset in four patients (11%). Progressive neuropathy was present in 32 patients (91%) and a relapsing-remitting course was present in three patients (9%). Challenge to the CIDP diagnosis was suggested by a family history in six patients (17%), EDX findings in three patients (9%), lack of response to IVIG in two patients (6%), pes cavus in one patient (3%), and a combination of these in 19 patients (54%). Among 33 patients treated with IVIG, seven were considered to be responsive. *PMP22* gene mutations were found in 12 patients (34%), MPZ gene mutations were found in 11 patients (31%), and 10 miscellaneous CMT gene mutations were found in the remaining 12 patients (34%). Compared to typical CIDP patients, CMT patients misdiagnosed as CIDP had earlier onset, often younger than age 40 years (18 vs. 2), often with childhood onset (7 vs. 0), with more frequent initial muscle atrophy and motor impairment at diagnosis. Proximal conduction block was less frequent in CMT, as was response to IVIG treatment. CSF protein above 0.5 g/L and MRI plexus abnormalities were more frequent in CIDP.

■ COMMENTARY

The diagnosis and treatment of CIDP has been updated recently by the EFNS/PNS and may further improve differentiating CIDP from CMT.[1] At least two motor and two sensory nerves must be abnormal for a diagnosis of typical CIDP. An ultrasound demonstrating nerve enlargement in at least two sites in proximal median nerve segments or the brachial plexus may assist in diagnosis. If diagnostic criteria are met using clinical and EDX studies, neither CSF analysis nor nerve biopsy is necessary. First-line treatments strongly recommended by the task force include corticosteroids or IVIG, with IVIG recommended over plasma exchange because of its ease of administration. Subcutaneous IVIG is equivalent to IVIG for maintenance therapy but perhaps less so for induction treatment. Methotrexate, interferon beta 1a, and fingolimod are contraindicated in CIDP, whereas azathioprine, mycophenolate mofetil, or cyclosporine may be considered as alternatives to IVIG or as corticosteroid-sparing agents. Cyclophosphamide, cyclosporine, or rituximab may be considered for CIDP patients who are refractory to first-line therapy. ■

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ABSTRACT & COMMENTARY

Localized Slow Wave Sleep in the Awake but Inattentive Brain

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Electroencephalogram studies of humans during periods of "mind wandering" and "mind blanking" have shown regional changes that suggest parts of the brain may be asleep while other areas are activated.

SOURCE: Andrillon T, Burns A, Mackay T, et al. Predicting lapses of attention with sleep-like slow waves. *Nat Commun* 2021;12:3657.

With every hour spent awake over the course of a day, our "sleep pressure" mounts. It has been believed that falling asleep is the only way for the brain to restore homeostatic balance. However, more recent research suggests that even while awake, localized areas of the brain can rest. This process has been well documented using depth electrodes in rodents and it has been demonstrated to a lesser extent on surface electroencephalogram (EEG) in humans. When local sleep occurs, a specific signature is observed on EEG, showing regional zones of high amplitude slow waves (delta frequency), closely mimicking deep (stage 3), non-rapid eye movement (REM) sleep. Importantly, this pattern is distinct from drowsiness, in which more global changes occur on EEG. The drowsy state more closely resembles stage 1 sleep — showing a global dampening rather than a rise in EEG amplitude and showing brain wave frequencies in the low alpha to upper theta range, rather than 1 Hz to 3 Hz delta waves.

Behaviorally, local sleep may be associated with lapses of attention. When subjects are asked to stay on task, especially a boring one, their mind may turn inward, wandering into unrelated thoughts or even becoming vacant entirely. In this current study, states of mind wandering (MW) and mind blanking (MB) are distinguished from the fully attentive state of being "on-task" (ON). Both MW and MB are found to be different from ON, but more importantly, MW and MB are shown to be distinct from each other.

Participants (n = 32) were placed in a dimly lit room and asked to perform go/no-go tasks. In one paradigm, they were shown a series of faces and asked to press a button for all neutral faces (go) and avoid this response (no go) for any smiling faces. Similarly, they were shown digits (one through nine) and asked to press the button for any digit (go) that was not the digit three (no go). The task was interrupted at random intervals during which participants also were asked whether they felt they were "task focused" (ON) or whether they were "off task," either focusing on some other thoughts (MW) or focusing on nothing (MB). Also, they rated their level of vigilance on a scale between one (extremely sleepy) to four (extremely alert).

The results of this investigation showed that there was more inattention in the MB state, since misses were recorded when go responses were required. Reaction time also was slowed. By contrast, the MW state suggested hyperarousal, with an increase in false alarm activations when no-go responses were required. Reaction times were shortened correspondingly. Overall, MB was a sluggish mental state, while MW suggested impulsivity.

The investigators also used larger pupil size as a measure of vigilance. While both MW and MB showed smaller pupils than ON, there was no difference when MW and MB were compared directly. This occurred despite the observation that subjects reported they were more vigilant when in MW.

However, more striking were the EEG data. When MW was compared to ON, there was an increase in high amplitude slow frontal lobe activity. This possibly suggests that in MW, the frontal lobe is downregulated, shifting focus and allowing the mind to wander off topic. MB also showed this frontal lobe activity, but, in addition, it showed slow wave activity in central-parietal areas, suggesting a more widespread distribution of sleep-like brain waves. When comparing MW and MB, frontal lobe high-amplitude activity was more pronounced with MW, and parietal waves were more pronounced with MB. This parietal activity, with a sharp upward deflection, followed by a wider downward wave, had the morphology of K-complexes as seen in stage 2 non-REM sleep.

In their discussion, the authors noted that their findings are robust and consistent over three complementary parameters — behavioral (false activations and misses), phenomenological (subject reporting of MW and MB), and physiological (EEG). Attentional lapses, thus, were dichotomized into two distinct footprints. One showed false activations (impulsivity), MW, and impaired frontal lobe function (with high-amplitude slow wave mimicking sleep). The other showed misses (sluggish mentation), MB, and parietal slow waves, which mimicked stage 2 sleep.

■ COMMENTARY

It has been proposed that sleep allows for the clearance of toxic proteins (amyloid beta, among others) from the brain by enhancing the so-called "glymphatic" system. During deep sleep, there can be increased drainage of cerebrospinal fluid through channels in perivascular spaces and through widened gap junctions. Crucially, if focal slow wave EEG patterns can occur even in the waking state, as this paper suggests, it can be concluded that areas of the brain may rest and become restored even without the occurrence of sleep. As the authors noted, local sleep is achieved when attention is "turned inward" rather than focused on the external world. It could perhaps be suggested that meditation (which has been part of the human experience since 5,000 years BCE) might help to achieve this. By either letting the mind wander or by wiping our thoughts clean entirely, we actually may produce similar restoration of neural homeostatic balance as if we were actually asleep.

One weakness of this study is that it does not address REM, a state of cortical activation during sleep (dreaming) that also is thought to be a crucial restorative stage. Following sleep deprivation, not only slow wave sleep but also REM can be observed to rebound. REM is a

mixed state, since there is muscle relaxation but also upregulation of the sympathetic nervous system, with increases in heart and respiratory rates. If the concept of "daydreaming" were true to its name, it is possible that while some areas are slowed (such as the frontal lobe in MW), deep brain regions known to be involved in REM — such as the so-called peduncular pontine reticular formation — enter an activated state. ■

CME INSTRUCTIONS

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CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

CME QUESTIONS

1. **Occipital nerve stimulation had which of the following effects on patients with chronic cluster headaches?**
   a. No benefit at 30% of maximum stimulation
   b. Benefit only when given at 100% of maximum stimulation
   c. Reduced weekly mean attack frequency at both 30% and 100% stimulation
   d. Intolerable side effects
2. **Which of the following groups of patients has the highest mortality rate from status epilepticus (SE)?**
   a. Highly refractory SE
   b. Good response to first-line therapy
   c. Moderate refractory SE
   d. Low refractory SE
3. **The human electroencephalogram shows which of the following changes during periods of inattention (mind wandering)?**
   a. Generalized slowing, in the 1 Hz to 3 Hz range
   b. High-amplitude slow-wave activity in the frontal lobes
   c. Normal posterior alpha-rhythms
   d. Parietal lobe slow waves
4. **Compared to typical chronic inflammatory demyelinating polyneuropathy (CIDP) patients, Charcot-Marie-Tooth patients misdiagnosed as CIDP:**
   a. have a later age of onset, older than age 40 years.
   b. have less frequent initial muscle atrophy and motor impairment at diagnosis.
   c. demonstrate proximal conduction block more frequently.
   d. are less responsive to intravenous immune globulin treatment.
5. **The experience of subjective cognitive complaints indicates the presence of an underlying neurologically based disorder.**
   a. True
   b. False