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Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Steroid Treatment Regimens for Chronic Inflammatory Demyelinating Polyneuropathy

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports no financial relationships relevant to this field of study.

SYNOPSIS: In the United States, first-line treatment for chronic inflammatory demyelinating polyneuropathy (CIDP) is intravenous immunoglobulin (IVIG). Authors of this retrospective survey from Europe found that corticosteroid treatment had similar efficacy as IVIG and should be considered as first-line therapy for CIDP.

SOURCE: van Lieverloo GGA, Peric S, Doneddu PE, et al. Corticosteroids in chronic inflammatory demyelinating polyneuropathy: A retrospective, multicentre study, comparing efficacy and safety of daily prednisolone, pulsed dexamethasone, and pulsed intravenous methylprednisolone. *J Neurol* 2018;265:2052-2059.

Glucocorticoids, intravenous immunoglobulin (IVIG), and plasma exchange are the mainstays of therapy for chronic inflammatory demyelinating polyneuropathy (CIDP), with the initial choice among them decided by availability, disease severity, venous access, treatment side effects, cost, and concurrent illness. When disease is mild with minimal effect on quality of life or function, treatment may not even be necessary. If glucocorticoids are contraindicated, alternative immunosuppressant agents include azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, rituximab, or tacrolimus. When corticosteroids are administered, various regimens may be offered. Which regimen is most effective and safe for CIDP?

Data on treatment-naïve CIDP patients were collected retrospectively from 2000 until 2018 from three centers in Europe, including Serbia, The Netherlands, and Italy, where corticosteroids were considered first-line treatment. All patients satisfied European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) criteria for definite, probable, or possible CIDP, and were treated with either oral prednisone or prednisolone, 1-1.5 mg/kg/d for six weeks followed by a taper over at least eight months; oral dexamethasone 40 mg/d for four days, monthly for six months; or intravenous (IV) methylprednisolone, 500 mg/d for four days, with at least two further courses at 1-2 g/month, depending on disease severity. Any patient who did not

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improve on the regimen was given IVIG. The primary outcome was improvement in motor or sensory impairment as measured by the treating neurologist and/or Rankin scale, with no further need for treatment. Any patient who received IVIG was considered a nonresponder. The secondary outcome was the remission rate, defined as treatment-free stable or improving clinical status, with relapse defined as any setback requiring treatment. Statistical analysis comprised the Fisher-Freeman-Halton *t* test, one-way ANOVA, two-tailed *t* test, and Kruskal-Wallis tests, as applicable, with post hoc analyses also encompassing the Mann-Whitney *U* test. Statistical significance was defined as $P < 0.05$.

Among 196 screened patients, 125 received corticosteroids alone and were included in the study, of which 54% (n = 67) were treated with daily oral prednisone, 30% (n = 37) with oral dexamethasone, and 17% (n = 21) with IV methylprednisolone. Corticosteroid treatment resulted in a 60% (n = 75) response rate overall, with no significant difference between the three treatment regimens. Fifty-seven percent improved with either oral prednisone or IV methylprednisolone, and 68% improved following oral dexamethasone. Among the 75 responders, 61% (n = 46) remained in remission over a median follow-up of 55 months. Of the 29 patients who relapsed, 69% (n = 20) did so within six months following treatment cessation. Corticosteroids resulted in a 33% probability of five-year remission, with severe adverse events occurring in two patients (severe hypertension and myocardial infarction in one each) and moderate adverse events in 8% (n = 10), including glaucoma, hypertension, de novo diabetes, depression, Cushingoid appearance, and gastrointestinal complaints. Corticosteroids resulted in an improvement in 60%, with remission in 61% of responders, and any modality of administration was equally efficacious and safe.

■ COMMENTARY

Recently described in patients with inflammatory neuropathies, IgG autoantibodies caspr and neurofascin-155 are associated with the subacute onset of severe motor weakness and poor response to IVIG, with the latter autoantibody additionally associated with debilitating tremor of cerebellar origin. Anti-neurofascin IgM autoantibodies have been reported in 8% of patients with inflammatory neuropathy but also in 5% with idiopathic neuropathy. In a recent report, IgM autoantibodies against neurofascin-155, in titers ranging from 1:100 to 1:400, were detected by ELISA in five patients, four with CIDP, three of whom also presented with tremor and one with Guillain-Barré syndrome. Electrodiagnostic studies were consistent with demyelinating neuropathy, although nerve biopsies showed axonal injury in three and demyelination only in one. IgM neurofascin-155 autoantibodies may be worth testing in patients with inflammatory neuropathies, but their pathogenic role remains to be determined.[1] ■

REFERENCE

1. Doppler K, Stengel H, Appeltshauser L, et al. Neurofascin-155 IgM autoantibodies in patients with inflammatory neuropathies. *J Neurol Neurosurg Psychiatry* 2018; Jun 26. doi:10.1136/jnnp-2018-318170. [Epub ahead of print].

ABSTRACT & COMMENTARY

Ibudilast Shows Promise for the Treatment of Progressive MS

By Jai S. Perumal, MD

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Dr. Perumal reports she is a consultant for Genzyme and Biogen.

SYNOPSIS: A Phase II trial of ibudilast in progressive multiple sclerosis demonstrated a decreased rate of brain atrophy when compared to placebo.

SOURCE: Fox RJ, Coffey CS, Conwit R, et al; for the NN102/SPRINT-MS Trial Investigators. Phase 2 trial of ibudilast in progressive multiple sclerosis. *N Engl J Med* 2018;379:846-855.

Although incredible advancements have been made in the treatment of multiple sclerosis (MS) over the past 30 years, and new therapies have made a significant impact on relapsing-remitting disease (RRMS), the treatment of progressive MS remains challenging. Recent research into the potential underlying pathological processes has shed some light on why medications that predominantly work on the peripheral immune system may not be that effective in progressive MS. Researchers have reported that the inflammatory injury in progressive MS may be caused more by resident immune cells within the central nervous system rather than the influx of immune cells from the periphery, like in RRMS. A better understanding of these mechanisms has helped advance the search for an effective treatment for progressive MS. Given this scenario, the results of the recent Phase II study of ibudilast in progressive MS show promise and are encouraging.

Ibudilast is a phosphodiesterase inhibitor currently available in Japan for the treatment of asthma and post-stroke dizziness. It has inhibitory effects on macrophage migration inhibitory factor and toll-like receptor 4, which have been found to be increased in the cerebrospinal fluid of patients with progressive MS. Ibudilast also can cross the blood-brain barrier. The results of an earlier clinical trial of ibudilast in RRMS showed that it seemed to have a positive effect on the rate of brain atrophy and evolution of T1 hypointensities rather than on the development of new T2 lesions. These observations, along with the known mechanism of action of ibudilast, provided the rationale for exploring this medication in the treatment of progressive MS.

Fox et al conducted this Phase II study of ibudilast in progressive MS through NeuroNEXT, an NIH-sponsored consortium of several neurologic institutions in the United States, with the goal of facilitating faster and more efficient clinical treatment trials in neurology. They randomized 255 patients from 28 U.S. sites in a 1:1 ratio to ibudilast or placebo. The dose of ibudilast was 100 mg/day. Inclusion criteria were progressive (secondary or primary) MS patients between 21 to 65 years of age with an expanded disability status scale (EDSS) range of 3.0-6.5 who demonstrated disease progression in the preceding two years. Disease progression was defined as one of the following: 0.5-point increase in EDSS or a 20% increase in either the 25-foot timed-walk or nine-hole peg test. Concurrent treatment with beta-interferon or glatiramer acetate was allowed. The primary endpoint was the rate of brain atrophy as measured by the brain parenchymal fraction. The main secondary outcomes included change in diffusion tensor imaging in the pyramidal tracts, change in magnetization transfer ratio in normal appearing brain tissue, and thickness of retinal nerve fiber layer as measured by optical coherence tomography. Eight patients in the ibudilast group and three patients in the placebo group withdrew before at least one post-baseline MRI was obtained and were excluded; thus, 244 patients were included in the analysis.

The rate of change in brain volume decreased by 48% in patients taking ibudilast vs. placebo. The rate of change in brain parenchymal fraction was -0.0010 (95% confidence interval [CI], -0.0016 to -0.0004) per year in the ibudilast group and -0.0019 (95% CI, -0.0025 to -0.0013) per year in the placebo group. The secondary outcomes tended to be positive toward ibudilast as well, but there were limitations to their interpretations. There were no opportunistic or serious infections associated with ibudilast. The ibudilast group had a higher incidence of gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain), headache, and depression. There were no other safety concerns during the trial.

■ COMMENTARY

The results of this Phase II trial suggest that ibudilast may be effective as a potential treatment for progressive MS. This trial, taken together with an earlier study using ibudilast to treat RRMS, seems to demonstrate that its effect on brain atrophy progression may be separate from any anti-inflammatory effect on new lesion formation. Based on what we now know to be potential disease pathology in progressive MS and the mechanism of action of this medication, ibudilast treatment could have a significant effect on disease processes specific to progressive MS. Further trials are needed to study this drug in progressive MS to examine clinical disability outcomes. A challenge for MS treatment trials is the appropriate endpoints and methods to assess disability, which need to be designed carefully during plans for Phase III trials for ibudilast. ■

ABSTRACT & COMMENTARY

Cerebellar Atrophy May Contribute to Cognitive Impairment in FTD

By Makoto Ishii, MD, PhD

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Dr. Ishii reports no financial relationships relevant to this field of study.

SYNOPSIS: In this cross-sectional study, researchers identified distinct patterns of cerebellar atrophy and its association with cognitive dysfunction in the frontotemporal dementia syndromes.

SOURCE: Chen Y, Kumfor F, Landin-Romero R, et al. Cerebellar atrophy and its contribution to cognition in frontotemporal dementias. *Ann Neurol* 2018;84:98-109.

Frontotemporal dementias (FTDs) are neurodegenerative disorders consisting of three primary clinical syndromes: behavioral-variant (bvFTD), semantic dementia (SD), and primary progressive nonfluent aphasia (PNFA). bvFTD is characterized by personality and behavioral changes, while SD and PNFA primarily affect language. FTDs lead to significant atrophy in the frontal and temporal lobes; however, atrophy in other brain regions, including the cerebellum, has been reported. The cerebellum is well known for its role in motor coordination and planning, but accumulating evidence suggests that the cerebellum also may be involved in cognition. Therefore, Chen et al sought to establish the changes in cerebellar gray matter integrity in bvFTD, SD, and PNFA subjects and to determine the association of cerebellar atrophy with the main cognitive domains.

Study participants included patients diagnosed with FTD (45 bvFTD, 29 SD, and 23 PNFA) from the Frontotemporal Dementia Research clinic in Sydney, Australia. Control subjects included 35 age-, sex-, and education-matched healthy elders without known psychiatric or neurodegenerative disorders or genetic mutations for FTD. All participants underwent extensive testing in the major cognitive domains (attention and processing speed, working memory, language-motor, language-semantics, visuospatial function, episodic memory, executive function, and emotional processing). The researchers obtained whole-brain 3T MRI and analyzed three-dimensional T1-weighted sequences with voxel-based morphometry (VBM). They also obtained mean intensity values of cerebellar grey matter, which then were correlated with cognitive performance across the main cognitive domains.

For all study subjects, there were no differences in demographic characteristics except disease duration, with SD patients having a longer duration than bvFTD or PNFA. On general cognitive testing, as expected, FTD patients scored worse than controls, with SD patients doing worse than bvFTD and PNFA. Disease severity based on the Frontotemporal Dementia Rating Scale was the worst in bvFTD compared to SD and PNFA groups. Neuropsychological testing revealed the typical patterns expected for the FTD syndromes, with bvFTD impaired on all measures except language-motor. The SD group was impaired on attention and processing speed, working memory, language-semantics, and emotion processing. The PNFA group was impaired on attention and processing speed, working memory, language-motor, and executive function.

A VBM analysis of the whole-brain MRI revealed typical canonical patterns of atrophy specific to each FTD syndrome. In bvFTD, there was widespread bilateral intensity reduction primarily in the frontal and temporal lobes. In SD, there was a left greater than right anterior temporal lobe atrophy. In PNFA, there was a left greater than right inferior frontoinsular region atrophy. All three FTD syndromes showed reduced cerebellar grey matter intensity compared to controls. When each FTD syndrome was compared separately, specific atrophy patterns were noted. In bvFTD, there was widespread bilateral intensity reduction involving most lobules and the vermis. In SD, there were more focal changes bilaterally in lobules VI, Crus I, and Crus II. In PNFA, a significant intensity decrease was found bilaterally in Crus I, Crus II, and lobule VIIb and in the right lobule VI. Across all FTD patients, there was overlapping atrophy in Crus I, Crus II, and lobule VI bilaterally.

Interestingly, there were significant correlations between cerebellar atrophy and cognitive scores, which showed a distinct pattern among the FTD syndromes. Comparing bvFTD and controls, attention and processing speed and working memory were correlated with cerebellar atrophy, while visuospatial function and language-motor correlated with cerebellar atrophy in SD and PNFA, respectively. When all participants were included in the analysis, working memory was found to correlate significantly with right cerebellar lobule VI, Crus I, and Crus II.

■ COMMENTARY

The main results from this paper suggest that cerebellar atrophy in FTDs can affect select cognitive domains, and that cerebellar atrophy is not simply due to global brain neurodegeneration but is specific to FTDs. These authors provided strong additional evidence for the role of the cerebellum in cognition; however, there were significant limitations that need to be addressed. First, replication is needed in additional cohorts to verify these results. Additionally, since FTD was diagnosed clinically, the use of FTD biomarkers (e.g., tau positron emission tomography), once validated, would be essential to avoid possible misclassification of patients in future studies. Furthermore, longitudinal studies in FTD patients examining the changes in the cerebellum as cognition declines over time would provide stronger evidence for cerebellar atrophy contributing to cognitive decline. Investigating cerebellar structural changes over time also would identify specific atrophy patterns in the cerebellum, which could provide further evidence that cerebellar atrophy is not simply a consequence of global brain atrophy. This study also

cannot establish causality or identify the mechanisms underlying cerebellar atrophy. It is plausible that loss of cortical neurons feeds back to the cerebellum to cause atrophy. Alternatively, there may be specific neurodegenerative processes that occur in the cerebellum independent of those in the cortex. Longitudinal functional connectivity studies and mechanistic studies using cellular and animal models would be useful to address these questions. Finally, studies investigating the cerebellum and its role in other behaviors affected in FTD, such as empathy and eating behavior, are needed. Although significant work needs to be done, additional research building on this important study could further advance our understanding of the cerebellum in nonmotor function. ■

ABSTRACT & COMMENTARY

Primary Headaches: Look, Listen, and Diagnose Rather Than Image

By Dara G. Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports no financial relationships relevant to this field of study.

SYNOPSIS: The diagnosis of primary headache disorders by a computerized and clinical paradigm can predict a baseline prevalence of intracranial abnormalities on brain imaging. Some historical "red flags" in children with headaches, including morning headaches and occipital pain, are not associated with increased intracranial abnormalities.

SOURCES: Wang R, Liu R, Dong Z, et al. Unnecessary neuroimaging for patients with primary headaches. *Headache* 2018; Aug 23. doi: 10.1111/head.13397. [Epub ahead of print].

Irwin SL, Gelfand AA. Occipital headaches and neuroimaging in children. *Curr Pain Headache Rep* 2018;22:59.

Tsze DS, Ochs JB, Gonzalez AE, Dayan PS. Red flag findings in children with headaches: Prevalence and association with emergency department neuroimaging. *Cephalalgia* 2018; Jan 1. doi: 10.1177/0333102418781814. [Epub ahead of print].

Brain imaging often is used to differentiate between primary headaches without specific neuroimaging correlates and secondary headaches due to visible brain lesions. However, the ubiquity of headaches necessitates a parsimonious approach to brain imaging. The study from Wang et al at the Headache Center of the Chinese People's Liberation Army General Hospital was designed to verify that primary headache patients do not need neuroimaging. Brain imaging was obtained in 1,070 healthy controls (345 male, aged 40.18 ± 12.46 years) and 1,070 primary headache patients (345 male, aged 40.05 ± 12.30 years) diagnosed by computerized clinical decision support systems (CDSS) and correlating clinical assessment. The CDSS is an interactive decision support system using computer software and International Classification of Headache Disorders criteria to diagnose based on clinical data.

The primary headache diagnosis, without "red flags" by history or abnormality on examination, was confirmed by a headache specialist. Primary headaches were migraine (62%), tension-type (32%), trigeminal autonomic cephalalgias (5%), and other (1.5%). In each group, 382 participants underwent computed tomography (CT) scans and 688 underwent magnetic resonance imaging (MRI) scans based on individual non-neurological considerations. The neuroimaging findings were classified as significant abnormalities, nonsignificant abnormalities, or normal. Significant abnormalities were defined as neoplastic disease, hydrocephalus, vascular malformations (aneurysms, arteriovenous malformations, dural fistula, and/or cavernous angiomas), Chiari malformations, intracranial hemorrhages, and acute infarcts. White matter lesions, commonly seen in migraineurs, were not considered a significant finding. The rate of significant abnormalities, which were noted only on the MRI scans, was not significantly different in the primary headache group (four patients or 0.58%: two hydrocephalus, two nose/throat tumors) compared to the healthy controls (five controls or 0.73%: two cerebral infarction, one acoustic schwannoma, two cavernous angiomas). The authors concluded that with the possible exception of the very rare diagnosis of retinal migraine, neuroimaging is not necessary for patients with the presumed diagnosis of primary headaches.

Headaches in children are especially concerning to physicians and parents, so neuroimaging often is used for reassurance that the primary headache diagnosis is correct. The authors of two recently published articles evaluated the role of neuroimaging in children with headache. In a prospective cohort study, Tzse et al evaluated the prevalence of historical "red flags" and their association with intracranial abnormalities in 224 healthy children aged 2 to 17 years who were evaluated for headaches in the emergency department (ED). The ED physicians

completed standardized forms to document headache characteristics and associated symptoms, along with examination findings. At least one presumed historical "red flag" was found in 87.9% of the children, including headache upon awakening from sleep (34.8%), headache noted with or soon after awakening in the morning (39.7%), and headaches increasing in frequency, duration, and severity (40%, 33.1%, and 46.3%). Children who were not imaged in the ED received a four-month telephone follow-up. In the 33% of children who received ED neuroimaging, the prevalence of emergent, serious, and incidental intracranial abnormalities was 1%, 1.5%, and 7%, respectively. Fifty-two of the 55 (94.5%) children who underwent ED neuroimaging for a documented reason (as opposed to "no specified reason") were noted to have historical red flags, such as headaches on awakening from sleep (46.1%), headaches with or soon after morning awakening (26.9%), or headaches of increasing frequency (19.2%). The authors concluded that while historical red flags are common in children presenting with headaches to the ED, their presence is associated with a low risk of emergent intracranial abnormalities.

Occipital head pain in children has been considered a red flag to indicate a secondary headache. Irwin's review of the medical literature determined that 0 to 4.1% of children with occipital headaches and normal neurological examinations have significant findings on neuroimaging. Migraine was the most likely etiology for occipital headaches, which are noted in up to 20% of children with headaches. Occipital headaches in neurologically normal children are no more likely to be associated with intracranial pathology than headaches localized to other cranial locations.

■ COMMENTARY

The question "Is brain imaging needed to diagnose a headache?" plagues patients, parents, physicians, and payers. Clearly, an associated abnormality on neurological examination dictates brain imaging. The more common and more complicated scenario involves a seemingly characteristic history of a primary headache disorder, a normal neurological examination, and a patient skeptical of the proffered diagnosis. Wang et al used a "belt-and-suspenders" approach to diagnose primary headache disorders and then image both headache patients and headache-free controls, finding no difference in significant brain lesions. The value of clinical and computer diagnostic skills is reassuring, but the authors emphasized the importance of time and expertise in obtaining a detailed neurological history and in performing an appropriate neurological examination prior to deciding that imaging is not indicated. Historically, imaging advocated with some types of primary headaches, such as side-locked headaches including trigeminal autonomic cephalgias and cluster headaches.

This study and personal experience indicate that even with these side-locked headaches, imaging adds little to diagnostic accuracy if the history is characteristic and the examination is normal. Some pediatric red flags, such as morning and occipital headaches, appear to be of little significance and should no longer elicit a knee-jerk response to image. A detailed history, an appropriate examination, and a thoughtful approach should lead to a focused approach to ordering brain imaging studies in patients with headaches. However, if brain imaging is deemed appropriate, then an MRI scan, as opposed to a CT scan, generally should be obtained. ■

BRIEF REPORTS

Recent Advances in Sleep Medicine

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Segal reports no financial relationships relevant to this field of study.

Does CPAP Improve the Sex Lives of People With Obstructive Sleep Apnea?

SOURCE: Jara SM, Hopp ML, Weaver EM. Association of continuous positive airway pressure treatment with sexual quality of life in patients with sleep apnea: Follow-up study of a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg* 2018;144:587-593.

When faced with the possibility of continuous positive airway treatment (CPAP) therapy for obstructive sleep apnea (OSA), patients commonly balk, especially if they fear that this potentially unromantic therapy will affect their sex life adversely. This report from Jara et al suggests otherwise. Data were derived from a 25-point Snore Outcome Scale (SOS), which included two sex-related options: "Because of medical problem, unable to have sexual relations" and "Lack of desire for sexual relations." This was scored on a 0-5 scale (with 5 being worst). Specifics regarding sexual function were limited, as data were derived from only these two points on a general scale (the SOS-25) rather than a predetermined sex-specific questionnaire. The cohort included 182 participants (63% men) with severe OSA. There was a significant improvement in SOS score of -0.7 among CPAP users compared with -0.1 among nonusers. This effect persisted in a multivariate analysis. However, in a

specific subgroup analysis using only gender, the benefit was restricted to women. There was a 1.3-point improvement in women (95% confidence interval [CI], 0.5-2.18), but only a 0.16-point difference in men (95% CI, -0.26 to 0.58). The authors did not provide any theories to explain this sex difference.

■ COMMENTARY

Among men using CPAP, prior noncontrolled case series have suggested an improvement in sexual function, although primarily among subjects who reported prior sexual difficulties. Although hormonal effects have been implicated in OSA, it never has been confirmed that low testosterone is a consequence of sleep-disordered breathing or that testosterone can rise with the use of CPAP. However, factors that clearly can improve with CPAP, such as weight gain and poor sleep quality, have shown a definite relationship to testosterone levels.

Among women, other studies have contradicted this study, failing to show improvements in sexual function or distress with CPAP use. Taking a more granular approach than merely two questions from the SOS-25, other studies used detailed female-specific scales of sexual function, distress, and overall satisfaction. ■

Dimethyl Fumarate Holds Promise for the Treatment of OSA

SOURCE: Braley TJ, Huber AK, Segal BM, et al. A randomized, subject and rater-blinded, placebo-controlled trial of dimethyl fumarate for obstructive sleep apnea. *Sleep* 2018;41. doi: 10.1093/sleep/zsy109.

Inflammation may be both a downstream effect of OSA as well as a contributor to OSA severity. Proinflammatory cytokines are elevated in the serum of patients with OSA, a process that specifically may be driven by the nuclear transcription factor NFκB. Furthermore, inflammation repeatedly has been implicated as a driving factor in the consequences of OSA, such as cardiovascular disease and stroke. Previous studies of OSA in patients with rheumatological disease have shown than biologics such as the TNF-inhibitor etanercept (Enbrel) may ameliorate OSA. Braley et al randomized patients to the multiple sclerosis (MS) drug dimethyl fumarate (DMF; Tecfidera). Previous observational studies among MS patients with OSA had shown improvements in respiratory status among those treated with DMF compared with matched MS patients who were not on immunomodulatory therapy. In this study of neurologically normal patients, 50 subjects were randomized to DMF (n = 35) or placebo (n = 15), in a planned 2:1 ratio. All of the patients either were unwilling or unable to use CPAP and had moderate to severe OSA (apnea hypopnea index on average of 27 events per hour). There was an improvement in the hypopnea index of 3.1 among treated patients, compared with a 10-point worsening in the placebo group (absolute difference = 13.1; P = 0.033). There were favorable trends, but no significant effect of DMF on cytokine levels (TNF, IL-10, IL-13) and no specific relationship between cytokines and clinical outcomes. In an interesting exploratory analysis of NFκB levels, the authors found a correlation between levels of this transcription factor and subjects whose OSA was affected most favorably by DMF therapy.

■ COMMENTARY

Although the effects of DMF did not eradicate OSA, this pharmacological therapy has promise, especially among the large subset of patients who cannot comply with CPAP therapy. ■

Sleep Disruptions Are Common in Hospitalized Patients

SOURCE: Wesselius HM, van den Ende ES, Alsma J, et al. Quality and quantity of sleep and factors associated with sleep disturbance in hospitalized patients. *JAMA Intern Med* 2018;178:1201-1208.

Poor sleep among hospitalized patients adversely affects their well-being and more importantly may lead to unfavorable medical outcomes. Wesselius et al studied 2,005 patients using sleep diaries and sleep-related questions from the validated PROMIS (patient-reported outcomes measurement information system) questionnaire. Using "flash mob" methodology, data from a single day, Feb. 22, 2017, were collected throughout the Netherlands, using word of mouth and social media to create the cohort. Sleep on the previous night of the patient's hospitalization was compared to habitual sleep at home during the month before the hospitalization. Total sleep time in the hospital decreased by 83 minutes on average, compared to sleep at home. The average number of awakenings was 3.3 in the hospital compared with two at home. Patients woke up 44 minutes earlier in the hospital compared with their usual wake-up time. Patients reported that 70% of awakenings could be attributed to "hospital staff," with a variety of other factors, such as noise of other patients, medical devices, pain, and toilet visits, noted.

■ COMMENTARY

Both the public and medical professionals recognize that patients "can't get a good night's sleep in the hospital." Although the findings of this study support this contention, the magnitude of these effects (e.g., less than a 1.5 hour decrease in overall sleep and less than an hour earlier wake-up time) actually are less than one might expect. While beeping monitors and other noise disruptions were noted, planned interruptions of sleep by staff for vital sign checks or blood draws may represent modifiable low-hanging fruit for improvement. ■

Poor Sleep Can Lead to Accelerated Atherosclerosis

SOURCE: Dominguez Rodriguez F, Fernandez Alvira JM, Fernandez Friera L, et al. Association of actigraphy-measured sleep parameters and subclinical atherosclerotic burden: The PESA study. *Eur Heart J* 2018;39(Suppl 1):P2466.

Insufficient and poor quality sleep can lead to significant medical complications including atherosclerotic disease. Dominguez Rodriguez et al studied 2,974 patients in the Progression and Early Detection of Subclinical Atherosclerosis (PESA) cohort. Subjects were screened using 2D/3D ultrasound in the carotid, abdominal aorta, and iliofemoral arteries. A coronary artery calcium score on CT also was calculated. Movement sensors (actigraphy) were used to measure sleep duration during a one-week period.

Actigraphy is a useful surrogate for more invasive types of sleep monitoring such as polysomnography. Subjects were stratified into four groups: markedly short sleep (< 6 hours), short sleep (6-7 hours), average reference (7-8 hours), and long sleep (> 8 hours). Sleep duration of less than six hours was associated with a mildly increased odds of atherosclerosis on ultrasound, although not on cardiac calcium (odds ratio [OR], 1.27; 95% CI, 1.06-1.52). Subjects with the most fragmented sleep (bottom 20%) had an increased risk of atherosclerosis as well (OR, 1.35; 95% CI, 1.05-1.65). The diagnosis of metabolic syndrome also was made more frequently in the subjects with short or disrupted sleep.

■ COMMENTARY

This research corroborates prior data, although some previous studies have suggested a more complex U-shaped curve, putting both short sleepers and excessively long sleepers at risk for atherosclerotic disease. Regardless, these data provide further support for the importance of sleep in the optimization of medical outcomes. ■

CME QUESTIONS

1. **Which is the best way to administer corticosteroids to patients with chronic inflammatory demyelinating polyneuropathy?**
   a. Oral prednisone or prednisolone, 1-1.5 mg/kg/d for six weeks followed by a taper over at least eight months
   b. Oral dexamethasone 40 mg/d for four days, monthly for six months
   c. Intravenous methylprednisolone, 500 mg/d for four days, with at least two further courses at 1-2 g/month, depending on disease severity
   d. All the above regimens are equally efficacious

2. **Which of the following statements regarding multiple sclerosis (MS) is false?**
   a. Primary progressive MS has a clinically benign course.
   b. Secondary progressive MS results in significant disability.
   c. Anti-inflammatory treatments are effective only in relapsing-remitting MS.
   d. Relapsing-remitting MS results in brain atrophy after many years, despite current treatments.

3. **Based on a recent study of frontotemporal dementia (FTD) patients, which of the following is false regarding cerebellar atrophy and FTD?**
   a. The cerebellar atrophy pattern was exactly the same among the three FTD syndromes (behavioral variant, semantic dementia, and primary progressive nonfluent aphasia).
   b. The cerebellar atrophy pattern in behavioral variant FTD patients was associated with attention and processing speed and working memory.
   c. The cerebellar atrophy pattern in semantic dementia patients was associated with visuospatial function.
   d. The cerebellar atrophy pattern in primary progressive nonfluent aphasia patients was associated with language-motor function.

4. **Which historical red flag is most likely to correlate with a significant neuroimaging abnormality?**
   a. Occipital head pain in a child
   b. Headache present on awakening
   c. Headache noted in the morning after awakening
   d. Headache associated with transient monocular vision loss

5. **Obstructive sleep apnea may result in sexual dysfunction.**
   a. True
   b. False

6. **Chronic sleep disorders are a risk factor for the development of atherosclerosis.**
   a. True
   b. False

7. **Dimethyl fumarate, a treatment for multiple sclerosis, does not affect sleep disorders.**
   a. True
   b. False

[IN FUTURE ISSUES]

Memory Disorders