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INSIDE

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Spreading Depolarisations After TBI: A Clinical Context

ABSTRACT & COMMENTARY

By Halinder S. Mangat, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Spreading depolarisations following severe traumatic brain injury are associated with a poor outcome. They serve to cause secondary injury and energy imbalance. This mechanism might provide a target for therapeutic intervention.*

Source: Hartings JA, et al. Spreading depolarisations and outcome after traumatic brain injury: A prospective observational study. *Lancet Neurol* 2011;10:1058-1064.

THIS STUDY REVEALS THE ASSOCIATION OF TWO TYPES OF SPREADING DEPOlarisations — cortical spreading (CSD) and isoelectric spreading (ISD) — with poor clinical outcome in patients with traumatic brain injury (TBI).[1] The former occur in the background of baseline cortical electrical activity and the latter in isoelectric cortex, which is thought to be penumbral tissue.

The study included 109 patients with acute TBI who required surgical intervention. A majority of the patients suffered subdural hematomas and parenchymal contusions. Traumatic subarachnoid hemorrhage (tSAH) was frequently associated with these injuries. Patients were managed according to TBI guidelines. After the surgical evacuation of the lesion, an electrode strip was placed over the cortical surface on viable but frequently edematous or contused cortex with minimal tSAH. The electrocorticography was continued for a maximum of 7 days.

The study recorded 1328 depolarisations in 58 (56%) patients. Of these 38 had CSD only and 20 had at least one ISD, with or without CSD. Nineteen percent of patients who had no depolarisations had an unfavorable outcome by eGOS. However, 53% with CSD and 85% with ISD had unfavorable outcome. Eleven patients with depolarisations also had seizures.

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No individual covariate of outcome was associated with depolarisations.

■ COMMENTARY

Spreading depolarisations are a spectrum of electrophysiological phenomena, which involve waves of depolarizing activity over injured and penumbral neurons, and were first described by Leao in 1944.[2] These waves have since been better characterized, and the COSBID group has also reported their presence in other neurological illnesses.[3] This is the first study demonstrating the clinical impact of spreading depolarisations on patient outcome.

There are numerous mechanisms of neuronal injury associated with spreading depolarisations such as calcium influx, loss of ionic gradients, and neuronal swelling. These are also accompanied by a vascular response, which may be of three possible types: none, transient hyperemia (physiological hyperdynamic response), or vasoconstriction causing hypoperfusion (inverse hemodynamic response).[4] When the inverse response propagates with the depolarization wave, it is called cortical spreading ischemia. While in healthy cortex the depolarisations cause limited vascular disturbances lasting 10 minutes, in injured cortex they may be self-perpetuating and long-lasting (up to 100 mins). An inverse hemodynamic response causes further ischemia, which may then generate more depolarisations, causing a vicious cycle. In SAH, CSD result in cellular hypoxia, probably by both reducing supply and increasing consumption.[5] In addition to local hemodynamic disturbances, CSD also causes glucose depletion even in the presence of a hyperemic response.[6]

These cellular phenomenon result in further metabolic insult to the neuronal cells likely affecting recovery in the penumbral region and causing further necrosis in vulnerable areas.

In the present study, every effort was made to avoid any confounding factors. The electrodes used are similar to the ones used in epilepsy localization and are not thought to cause cortical irritation. They can capture electrical activity within a distance of 5 cm.

Spreading depolarisations are a novel pathophysiological mechanism associated with secondary insults and poor outcome after TBI. However, causation, as the authors state, can only be proven if therapeutic interventions to modify the depolarisations result in improved outcome. Also, a non-invasive method of monitoring for and identifying depolarisations will make it easier to study its effects. Surely, this will be an area of active research in the coming years. ■

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Brain Involvement in Neuromyelitis Optica — An Evolving Concept

ABSTRACT & COMMENTARY

By Jai S. Perumal, MD

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Dr. Perumal is a consultant for Biogen Idec, and is on the speakers bureau for Teva and Biogen Idec.

Synopsis: *Based on a retrospective study of 34 patients, the authors report that clinical manifestations of brain involvement are not uncommon in the neuromyelitis optica spectrum of disorders.*

Source: Chan KH, et al. Brain involvement in neuromyelitis optica spectrum disorders. *Arch Neurol* 2011;68:1432-1439.

NEUROMYELITIS OPTICA (NMO) IS AN INFLAMMATORY disease of the central nervous system that preferentially affects the optic nerves and spinal cord. Classic NMO or Devic's disease is characterized by recurrent episodes of optic neuritis (ON) and transverse myelitis (TM). In earlier descriptions of NMO, lack of cerebral involvement was considered a characteristic feature, but brain abnormalities, both clinical and radiologic, are being increasingly recognized. This, along with the identification of the serum NMO IgG antibody, resulted in revision of the earlier criteria for NMO. The NMO IgG antibody, which is potentially pathogenic and has high specificity, has broadened the definition of conditions falling under the umbrella of NMO, and at present, patients with isolated ON or TM who have the NMO IgG antibody are classified as having an NMO Spectrum Disorder (NMOSD).

In the present study, Chan et al report clinical manifestations of brain involvement including brainstem encephalitis in patients with NMOSD. This was a retrospective study of 34 patients with NMOSD. Patients had brain and spine MRIs at the time of their relapses and yearly for up to 3 years after their diagnosis. Clinical manifestations of brain involvement and brain lesions on MRI were analyzed. Of the 34 patients, 20 (59%) had brain involvement either clinically or radiologically on MRI. Eleven patients (32%) had clinical manifestations of brain involvement. Eight of these patients (24%) had brainstem encephalitis. The symptoms of brain involvement in these NMOSD patients included vomiting, vertigo, hiccups, diplopia, trigeminal neuralgia, dysphagia, visual field deficits, motor and sensory symptoms, and cognitive impairment. Nineteen (56%) patients had brain lesions in MRI. Among these patients, the most frequently involved site of brain lesions was the brain stem, which was seen in 15 (44%) patients. The authors conclude that brain involvement is common in patients with NMOSD and symptomatic brainstem lesions are not infrequent.

■ COMMENTARY

Our understanding of NMOSD has grown immensely in the past few years leading to the recognition of NMO as distinct from multiple sclerosis (MS). The discovery of the highly specific serum NMO IgG antibody has expanded our knowledge of the immunopathogenesis and the identification of the NMO spectrum of disorders. This distinction is significant not just in understanding the underlying pathology but also in terms of treatment selection and prognosis. Patients having an NMOSD typically do not respond to disease-modifying treatments used for MS, but need immunosuppressive agents to control their disease. In determining prognosis in a patient who develops ON or TM and who does not have MS, the presence of serum NMO IgG antibody predicts a higher risk of recurrence compared to a patient who does not have the antibody. Therefore, initiation of immunosuppressive treatment may be warranted at the time of the initial event in these patients.

In earlier criteria proposed for NMO in 1999, one of the absolute requirements was the absence of symptoms from CNS involvement outside of the optic nerves and spinal cord. But after increasing recognition of asymptomatic brain lesions on MRI and clinical symptoms from brain involvement, the revised criteria proposed in 2006 reflected this fact. The current criteria for a diagnosis of NMO requires the presence of ON and TM and two out of the three supportive criteria: (1) MRI evidence of a contiguous spinal cord lesion extending three or more vertebral segments, (2) initial brain MRI not diagnostic for MS, and (3) NMO IgG seropositivity.

The present study adds credence to these criteria and is in accordance with earlier reports of symptomatic brain involvement, which can be present in about 60% of patients with NMO spectrum disorder. The authors further highlight the frequent involvement of the brain stem leading to brainstem encephalitis. Recognition that brain involvement does not exclude a diagnosis of NMOSD in patients who otherwise meet the criteria will result in accurate diagnosis and prompt initiation of appropriate therapy. ■

Plasma Exchange for Steroid-Unresponsive Optic Neuritis

ABSTRACT & COMMENTARY

By Marc Dinkin, MD

Assistant Professor of Ophthalmology, Weill Cornell Medical College

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

Synopsis: *This study shows improvement in visual acuity in some patients with steroid-unresponsive optic neuritis, but it is not clear if plasma exchange accounts for this improvement.*

Stroke Alert: A Review of Current Clinical Stroke Literature

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.

Daytime Sleepiness as a Stroke and Cardiac Risk Factor

Synopsis: *Excessive daytime sleepiness appears to be an important risk factor for stroke. It is unknown whether this is related to obstructive sleep apnea or other mechanisms.*

Source: Blechier M, et al. Excessive daytime sleepiness and vascular events. The Three City Study. et al. *Ann Neurol Online* Oct. 31, 2011. DOI: 10.1002/ana.22656.

Excessive daytime sleepiness (EDS) is a common complaint in clinical practice. Not only does it have a direct impact on quality of life and productivity, it may have direct effects on morbidity and mortality. EDS has been shown to increase the risk of stroke and to a lesser degree coronary heart disease (CHD) in middle-aged populations and in the elderly, and it has been shown to impact cardiovascular risk, particularly in women. EDS may be a product of insufficient sleep duration or an underlying sleep disorder, most notably concomitant obstructive sleep apnea (OSA). Sleep deprivation has been shown to increase sympathetic drive, with elevated levels of catecholamines, and also results in endothelial cell dysfunction and systemic inflammation.

In the current report, from the French Three City Study (Bordeaux, Dijon, and Monpelier), 9294 elderly patients (age > 65) from the community were selected and given a face-to-face questionnaire. EDS was rated by subjects as occurring never, rarely, regularly, or frequently. Subjects also rated their sleep quality and the presence or absence of insomnia. Sleep duration was not reported. Outcomes at 2 years included CHD (angina, myocardial infarction, or cardiac related death) and stroke (classified as ischemic, hemorrhagic, or unspecified).

Results of the study showed a nearly two-fold (hazard ratio [HR] 1.92) increased risk of a combined endpoint of CHD and stroke. For stroke alone, there was a HR of 2.24, which was statistically significant, and for CHD, the HR was 1.70, which did not reach significance. Of note, the relationship between EDS and stroke applied roughly equally to ischemic compared with hemorrhagic strokes.

Source: Roesner S, et al. Treatment of steroid-unresponsive optic neuritis with plasma exchange. *Acta Neurol Scand* 2011; DOI: 10.1111/j.1600-0404.2011.01612.x.

Neuro-ophthalmologists encounter a great many conditions where diagnosis is firm, but treatments are of questionable value. Optic neuritis, an inflammatory demyelinating condition resulting in loss of visual acuity and loss of fields and color vision, is no exception, since more than 95% of patients improve to an acuity of > 20/40 at 1 year, whether or not they are treated with intravenous steroids or placebo. Indeed, the results of the Optic Neuritis Treatment Trial (ONTT) indicated that IV steroids resulted only in a speedier recovery of vision, without a significant difference in the end result.[1] Nevertheless, IV methylprednisolone is commonly prescribed for acute optic neuritis, in part because it is felt that there may be a subset of patients too small to have affected the results of the ONTT for whom treatment is a game changer. The 5% of patients who did not improve to > 20/40 in the ONTT represents a group of patients whose outcome might be improved with more aggressive treatments early on, and some of those may eventually be found to have neuromyelitis optica (NMO).

The study by Roesner and colleagues focused on "steroid-unresponsive optic neuritis," defined here to include patients who received 3-5 days of 1 g of IV methylprednisolone at onset, and a second cycle of 2 g per day for 3-5 days 2 weeks later, without recovery to above 50% acuity in at least one eye. Building on a few prior studies that have shown plasma exchange (PE) to be of some benefit in patients with multiple sclerosis (MS) or severe optic neuritis, the authors performed a retrospective analysis of 23 patients with steroid-unresponsive optic neuritis who received plasma exchange. Ten patients had relapsing-remitting MS, one had NMO, and 12 presented with a clinically isolated syndrome of optic neuritis.

The authors found that 11/23 patients (48%) showed a significant improvement, five of whom improved to 30-85% of normal, and six who improved to > 85%. Overall, among the nearly half of the group that appeared to respond, acuity improved from a mean of 16% prior to PE to 45% afterwards and to 60% at the first follow-up visit (average 50 days after PE). There were a few cases of benign hypotension, but no serious side effects were reported.

Stroke Alert (continued)

There were no data in this study regarding OSA, but there was no interaction between the presence of frequent or regular snoring or BMI and the vascular endpoints. As the authors acknowledge, obesity and snoring are less reliable predictors of OSA in the elderly than in younger people. Also, the relationship between EDS and vascular events was not modified by the presence or absence of insomnia, cognitive dysfunction, use of hypnotics, or depression with early morning awakening. In the absence of data on sleep itself, these variables might serve as surrogate markers to quantify sleep quality and duration.

Importantly, hypertension was a major modifying factor. When the population was split into subjects with or without hypertension at baseline, a relationship between EDS and vascular events was only demonstrated in the hypertensive group. As the authors note, hypertension is, in part, the result of sympathetic hyperactivity in EDS subjects and is such a powerful vascular risk factor on its own that it would likely mask any independent relationship between EDS and vascular events.

Among the 5262 participants who underwent B-mode ultrasound of the carotid arteries, those with EDS had higher carotid plaque burden. Adjustment for this subclinical atherosclerosis, however, did not modify the relationship between EDS and vascular events. Of note, obstructive sleep apnea is known to be associated with increased carotid plaque burdens as well.

■ COMMENTARY

Because EDS was based solely on patient reports, there may be some patients who are misclassified, especially since more objective measures, such as the Epworth Sleepiness Scale, were not performed. As the authors note, subjects may not have been able to differentiate between sleepiness and fatigue.

A clear limitation of this study is the absence of data on sleep duration and OSA. Because OSA is a potent risk factor for hypertension as well as vascular events and EDS, it may be an important unifying diagnosis in a significant subset of these subjects.

It is not clear from this study or from previous reports why EDS appears to be a more potent risk factor for stroke than CHD. This may relate to the extremely powerful relationship between hypertension and stroke and could have important therapeutic implications. While EDS is multifactorial, requiring a complex set of behavioral and pharmacological interventions, the diurnal hypertension that results from EDS is an extremely modifiable stroke risk factor. ■

■ COMMENTARY

This is an important study in that it is the largest review to date of plasmapheresis for steroid-unresponsive optic neuritis, and offers some encouragement that this treatment may affect the outcome in this subset of patients. As the authors correctly conclude, however, while the improvement in their population "might be due to PE," it is difficult to draw any firm conclusions. The study is retrospective, there is no placebo arm, and the outcomes are not rigorously compared to the natural history of patients with steroid-unresponsive optic neuritis who recently received a second course of IV steroids and are at a mean of 31 days out from their acute episode. The authors argue that patients with optic neuritis typically experience a rapid recovery within 2 weeks of symptom onset, suggesting that their patient group would not have likely improved during the time period observed without the addition of PE. However, in the ONTT, some patients experienced recovery of visual acuity between 1 and 3 months, which is the precise time that this cohort was followed. In fact, if one limits their observations to the group of patients who did not recover within the first month, as was done here, then the *majority* of those patients will go on to show significant improvement in the coming months, since 95% of patients reach a final acuity of 20/40 by one year. Among the patients in this study who showed improvement to 85% or more, it should be noted that only two patients improved to that degree within the 7 days following plasmapheresis (two others reached 85% at a 3 week follow-up and another at 180 days). Therefore, a PE effect based on improvement during the treatment cannot be concluded.

This study could have been strengthened by an analysis of other markers of optic nerve function such as low contrast visual function, color vision, and visual field perimetry. The authors might have discovered a higher rate of improvement if these modalities were included, although any such improvement would also be limited by the lack of a control group or comparison with the natural history of similar patients.

There is ample reason to suspect that PE may affect the outcome of some patients with demyelinating events, since a subset of patients show histopathological evidence of intra-lesion antibody and complement deposition. As the consequence of poorly recovered optic neuritis may include low vision and a profound change in quality of life, a large prospective, double-blind, placebo-controlled

trial of plasmapharesis in patients without early improvement is warranted. Such a study should preferably include a multi-modality comparison of visual function including visual fields and color testing, as well as a comparison of axonal loss as reflected in retinal nerve fiber layer thinning measured by optical coherence tomography. ■

Reference

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Predicting Outcome after Epidural Steroid Injection

ABSTRACT & COMMENTARY

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: *Response to treatment of unilateral lumbar radiculopathy can be predicted by an abnormal needle EMG in the appropriate root distribution.*

Source: Annaswamy TM, et al. Needle electromyography predicts outcome after lumbar epidural steroid injection. *Muscle Nerve* 2011: 10 OCT 2011 11:07AM EST | DOI:10.1002/mus.22320

CAN NEEDLE ELECTROMYOGRAPHY (EMG) BE USED AS AN independent predictor of beneficial outcome to epidural steroid injection in patients with lumbosacral radiculopathy? To address this question, 89 patients with lumbosacral radiculopathy, 79 men and 10 women, were consecutively enrolled in this hospital-based, outpatient, prospective study. Lumbosacral radiculopathy was defined as either: (A) radiating pain in an L4, L5, or S1 nerve root distribution, (B) motor, sensory, or deep tendon reflex abnormalities on neurological examination in an L4, L5, or S1 nerve root distribution, or (C) magnetic resonance imaging evidence of L4, L5, or S1 nerve root impingement. Exclusionary criteria included pregnancy, anticoagulation, allergy to steroids or bupivicaine, homelessness, and the inability to travel to appointments or converse in English. All patients underwent intralaminar steroid and bupivicaine injection under fluoroscopic guidance, with needle placement confirmed using contrast dye. The primary objective was to determine if an abnormal EMG, indicative of lumbosacral radiculopathy and defined as positive waves or fibrillation potentials in a myotomal distribution, predicted pain relief from epidural steroid injection. Secondary objectives assessed whether other factors were predictive of pain relief following epidural steroid injection, including age, sex, smoking history, work status, body mass index, self-rating pain disability questionnaires encompassing psychosocial and functional disability sub-scores, and alcohol use. Statistical analysis included post-hoc Tukey multiple comparisons and simple linear regression.

Of 89 enrollees, 19 dropped out due to non-compliance (n = 11), refusal to continue or discovery of alternate diagnosis (n = 3 each), and spontaneous improvement or relocation to another facility (n = 1 each). All enrollees fulfilled either the history or examination criteria for lumbosacral radiculopathy, or both. MRI was never the sole criteria for study inclusion. EMG data were available and complete for 80 subjects, of which 42 were indicative of lumbosacral radiculopathy, 25 were normal, and 13 were equivocal. Of these 80, a first epidural steroid injection was performed on 78, and a second was performed on 43, either before or after a follow-up visit that occurred, on average, 126 days later. Significantly greater improvement was found in the abnormal EMG group, compared to the normal EMG group, in patient disability pain questionnaire scores, in both its psychosocial and functional subscores, and in the numerical rating pain scale. Abnormal needle EMG findings of lumbosacral radiculopathy is an independent predictor of and can identify those patients more likely to benefit from epidural steroid injection.

■ COMMENTARY

Is interlaminar epidural injection, depositing steroids in the posterior epidural space, or transforaminal epidural injection, depositing steroids in the anterior epidural space, the favored route for unilateral radicular pain? Usually, half the dose of steroid is used in the latter method compared to the former. Among 64 chronic radiculopathy patients treated in a randomized, prospective study, both methods were equally efficacious, 39% and 38% respectively, in providing significant improvement over a 6-month period, as measured by visual analog scale pain scores and functional capacity using the Owestry scale.[1] Apparently, epidural injection may work from either approach. ■

Reference

1. Rados I, et al. Efficacy of interlaminar vs transforaminal epidural steroid injection for the treatment of chronic unilateral radicular pain: Prospective, randomized study. *Pain Med* 2011;12:1316-1321.

A New Look at an Old Medication for Migraine Headaches — Is It Worth It?

ABSTRACT & COMMENTARY

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a retained consultant for Boehringer Ingelheim, Merck, and Ortho-McNeil, and is on the speakers bureau for Boehringer Ingelheim.

Synopsis: *Dihydroergotamine, in a longer 5-day intravenous protocol for refractory primary headache appears to be efficacious, but this older medication needs to be compared directly to newer migraine treatments.*

Source: Nagy AJ, et al. Intravenous dihydroergotamine for inpatient management of refractory primary headaches. *Neurology* 2011;77:1827-1832. Epub 2011 Nov 2.

The outcome and side effects of intravenous dihydroergotamine (IV DHE) in disabling primary headache disorders was assessed as a function of dosing in 163 patients who were admitted to the National Hospital for Neurology and Neurosurgery, London, from 2003 to 2004. Their headache diagnoses were assigned according to the International Classification of Headache Disorders, 2nd edition (ICHD-II). The patients were contacted months after discharge by telephone to review their response to therapy. Patients were asked to provide an overall assessment of the therapy's benefit as mild, moderate, or excellent. Of the patients interviewed, 114 had chronic migraine, 38 had cluster headache, and 11 had new daily persistent headache (NDPH). The mean time to follow-up for the entire cohort was 11 months. Total DHE dosage ranged from 8.25 to 11.25 mg over the admission. For the patients with migraine (n = 114), 84 of 113 (74%) reported at least some subjective benefit, with half reporting moderate or excellent overall benefit. Along with DHE treatment, overuse of acute pain medications was treated. In the 114 migraine patients treated with DHE, preventive medications to decrease the frequency and severity headaches were started in 81 patients. For patients with cluster headaches, 29 (76%) felt that the DHE had been beneficial overall, with half of that group regarding it as moderately beneficial or excellent. In patients with new persistent daily headache, only those with migrainous symptoms responded and in that group the response was less robust compared with that seen in the chronic migraine cohort. Side effects noted with DHE included: nausea (94 patients causing cessation of the medication in 6 patients), leg cramps (46 patients), limb pain (26 patients), chest tightness (5 patients), diarrhea (19 patients), constipation (5 patients), and abdominal cramps (16 patients).

The authors opined that repetitive IV DHE treatments are both effective and well-tolerated for the inpatient management of medically refractory primary headache, including chronic migraine and cluster headaches. They concluded that these data support increasing the dose of DHE to 11.25 mg over 5 days, as compared to shorter courses, based on increased pain-free responses. The authors note a number of caveats, including the lack of placebo control arm, the lack of use of migraine disability tools, and the possible improvement due to the regulation of headache medicines and the inpatient environment.

■ COMMENTARY

Parenteral DHE has been used for decades to treat acute primary headaches. New methods of delivery (nasal, oral inhalation) and revised protocols have led to a resurgence of interest in this highly effective medication, which has

been eclipsed by new acute and preventive medications, including triptans.

The usual inpatient protocol for IV DHE in refractory migraine is 2 days. The authors reviewed data using a longer duration of treatment and advocated a 5-day intravenous protocol with a single medication, as opposed to a shorter "cocktail" approach with multiple parenteral and oral medications. However, the authors' conclusions on efficacy are based on uncontrolled, retrospective data and further verification is needed before their protocol should supplant customary treatments. The method by which the self-reported, patient satisfaction data were collected was neither specified nor validated. This longer IV DHE protocol has not been compared to the more commonly used shorter protocol or to IV valproate sodium, which has been shown to be as effective as IV DHE for refractory migraine. The use of DHE precludes the use of triptans within 24 hours, delaying DHE's use in patients who have used triptans prior to admission. The longer intravenous protocol necessitates a longer hospitalization than may be necessary to achieve pain relief, so the extra time and expense of the longer protocol need to be justified. ■

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 Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

1. Spreading cortical depolarizations following acute brain injury may be responsible for secondary ischemic damage.

a. True
b. False

2. Which of the following is NOT a diagnostic criteria for NMOSD?

a. Optic neuritis and transverse myelitis are present.
b. Isolated optic neuritis may occur.
c. Positive antibodies for NMO IgG.
d. Brain MRI not diagnostic for multiple sclerosis.

3. Which of the following statements is false about optic neuritis?

a. Optic neuritis usually recovers spontaneously.
b. Intravenous corticosteroids speeds recovery of optic neuritis.
c. Optic neuritis may be an isolated event, or part of multiple sclerosis.
d. Neuromyelitis optica never presents with isolated optic neuritis.
e. Neuromyelitis optica may respond to plasma exchange.

4. Interlaminar and transforaminal epidural steroid injection are equally efficacious for unilateral radicular pain.

a. True
b. False

5. Which of the following statements is true?

a. Intravenous DHE used for 5 days was found to be superior to intravenous valproate for treatment of refractory migraine.
b. Intravenous DHE decreases headache duration and severity in new persistent daily headache.
c. Chest pain is the most common side effect noted with intravenous DHE.
d. At least half of patients with refractory cluster headache reported benefit from intravenous DHE.

6. Excessive daytime sleepiness may be a modifiable stroke risk factor.

a. True
b. False

In Future Issues: Update on Epilepsy

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Barrett's Esophagus: What's the Risk?

Source: Hvid-Jensen F, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* 2011;365:1375-1383.

FOR UNKNOWN REASONS, ADENOCARcinoma of the esophagus (E-ca) is experiencing the most rapid increase of any known cancer in the United States. Although the absolute incidence of E-ca pales next to lung, prostate, or breast cancer, the inexplicable proliferation of this cancer has spurred increased scrutiny of at-risk individuals. Barrett's esophagus, which is felt to represent an attempt at protective epithelial remodeling in response to the trauma of acid exposure, occurs in as many as 10% of individuals undergoing endoscopy for symptoms of GERD. Once Barrett's is identified, consensus group guidelines suggest ongoing surveillance, despite the absence of outcomes trials indicating that such surveillance improves survival.

The Danish Pathology Registry and Cancer Registry provide an opportunity to review data accrued for the entire population of Denmark. Follow-up of persons with Barrett's esophagus (n = 11,029) over a median of 5.2 years of observation identified 197 cases of E-ca, for an annual incidence of 0.12%. Likelihood of developing E-ca was increased in persons with higher degrees of dysplasia. Based on these data, the authors suggest that ongoing surveillance of Barrett's esophagus might wisely be limited to those with demonstrated dysplasia, since the incidence of E-ca in persons without dysplasia was so very low. ■

Life Expectancy: The Japanese Are #1

Source: Murray CJ. Why is Japanese life expectancy so high? *Lancet* 2011; 378:1124-1125.

EVEN THOUGH JAPAN SPENDS ESSENTIALLY half of what the United States spends on health care (8.5% of their gross domestic product vs 16.4% of ours), they have ranked No. 1 in life expectancy for 30 years. To what might we attribute their success?

That Japan provides universal health coverage can certainly be responsible for a portion of their favorable outcomes, but other factors are also at play. For instance, Japanese public health programs to reduce salt intake and become more aggressive about blood pressure control are credited with substantial reductions in stroke. Indeed, such Japanese hypertension programs have evoked a substantial decline in blood pressure among the population as a whole, especially in women (the gender in which successful blood pressure control is conspicuously less prominent in the United States).

Although it is difficult to measure the direct impact of one additional factor — educational attainment — on health, epidemiologic surveys do consistently indicate a linear relationship between education and positive health outcomes. The generally high educational attainment among Japanese may be a critically important factor.

Current health trends suggest that Japan may not stay in the No. 1 slot: Inadequate tobacco control and a rising BMI among the population, unless counteracted, may incur similar health decrements as have been seen in other nations. ■

The Calcium/Cardiovascular Disease Link

Source: Sabanayagam C, Shankar A. Serum calcium levels and hypertension among U.S. adults. *J Clin Hypertens* 2011;13:716-721.

THE RELATIONSHIP BETWEEN CALCIUM INtake — through diet and/or supplements — and vascular health is complex. Some recent epidemiologic surveys have found a positive association between calcium supplements and adverse cardiovascular (CV) outcomes, as well as vascular calcification (i.e., more CV disease and calcification with calcium supplementation than without). Because hypertension (HTN) is the most common vascular antecedent to adverse CV events, investigation of the relationship of calcium to blood pressure (BP) is pertinent.

The National Health and Nutrition Examination Survey (NHANES) has published cross-sectional data from diverse populations throughout the United States for more than 30 years. The authors obtained data from the NHANES population (n = 12,403) of adults over age 20 seeking to examine the relationship between serum calcium levels and BP.

Persons in the highest quartile of serum calcium were 1½ times more likely to have HTN than those in the lowest quartile. Even when adjusted for age, race, alcohol, body mass index, cholesterol, C-reactive protein, glomerular filtration rate, serum albumin, vitamin D,

and phosphorus, the relationship between calcium and BP remained.

Several mechanisms through which calcium might incur increased risk of HTN have been offered, including a direct vascular effect, parathyroid activity, and renal vasoconstriction. Before concluding that calcium is simply a "bad guy," it is important to recognize that several reports have shown that *dietary* calcium is *inversely* related to HTN. ■

What Factors Lead to Acquisition of *Clostridium difficile*?

Source: Loo VG, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *N Engl J Med* 2011;365:1693-1703.

The toxicity associated with intestinal habitation by *Clostridium difficile* ranges from asymptomatic colonization to life-threatening infection. In the United States, *C. difficile* is the most common cause of health care-associated diarrhea. Although the association of *C. difficile* with use of antibiotics and/or hospitalization is clear and well established, why certain individuals fall prey to infection/colonization — whereas most do not — remains ill-defined.

Loo et al performed a prospective study of patients admitted to Canadian hospitals over 15 months (n = 4143). Subsequent to hospital admission, *C. difficile* infection was identified in 2.8% (n = 117) and colonization in 3% (n = 123); excluded from these numbers were the 4.4% of individuals who were already *C. difficile* colonized upon admission.

As has been noted in previous observational studies, older age, antibiotic use, and use of proton pump inhibitors (PPI) or histamine-type 2-receptor antagonists (H2RA) were each associated with *C. difficile* colonization and infection. The mechanism by which PPI/H2RA use is associated with *C. difficile* remains speculative, but is attributed to disturbance of bacterial flora. Whether more restraint in use of antibiotics, PPI, or H2RA medications will reduce the incidence of serious *C. difficile* infections remains to be determined. ■

The Relationship Between Sleep and Hypertension

Source: Bansil P, et al. Associations between sleep disorders, sleep duration, quality of sleep, and hypertension: Results from the National Health and Nutrition Examination Survey, 2005 to 2008. *J Clin Hypertens* 2011;13:739-743.

It is probably obstructive sleep apnea (OSA) with which clinicians most familiarly associate hypertension (HTN). Indeed, some recent trials have found a remarkably high prevalence of previously unsuspected OSA in persons with resistant HTN. What about other sleep variances, such as persons with sleep movement disorders (e.g., restless legs, sleep apnea), short sleep (< 7 hrs/night), or poor sleep? The authors report on data obtained through the most recent National Health and Nutrition Examination Survey obtained through direct interview with 10,308 adults.

Overall, persons with HTN were statistically significantly more likely to have a sleep disorder than normotensive individuals (11% vs 6%). "Poor sleep" did not appear to be a relevant factor, but less than 7 hours of sleep nightly was. No gender or ethnicity differences were detected.

In contrast to prior data sets, this study did not find a consistent relationship specifically with sleep disorders and HTN. Rather, it was in persons who reported both a sleep disorder *and* short sleep that risk of HTN rose steeply: this combination was associated with more than a doubling of risk. Finally, the authors also note that more than two-thirds of persons with sleep problems had not discussed their issues with a health professional. ■

DPP4 Inhibitors are Associated with Reduced Risk of Hip Fracture

Source: Monami M, et al. Dipeptidyl peptidase-4 inhibitors and bone fractures: A meta-analysis of randomized clinical trials. *Diabetes Care* 2011;34:2474-2476.

In an era where concern about adverse consequences of pharmacotherapy on bone health are prominent — proton pump inhibitors associated with increased risk of hip fracture, bisphosphonates associated with an increased risk of spiral femoral fractures, and even thiazolidinediones noted to increase fracture risk — a more sanguine headline is certainly welcome.

The dipeptidyl peptidase-4 inhibitors (DPP-4) currently include three agents: sitagliptin, saxagliptin, and linagliptin, each of which provides a fairly similar degree of glucose reduction. The physiologic activity of GLP-1 (the primary pathway through which DPP-4 treatment enhances glucose control) includes activation of osteoblasts and inhibition of osteoclasts. Animal studies have shown that DPP-4 agents actually increase bone density, but no large, long-term clinical trial has confirmed a relationship between DPP-4 and fractures in humans.

Monami et al performed a meta-analysis on trials of DPP-4 inhibitors lasting 6 months or longer from which data on fractures was able to be extracted. Based on 28 trials of DPP-4 treatment (n = 11,880) vs comparator (n = 9175), the odds ratio for fracture was 40% less in persons receiving DPP-4 than in comparator. DPP-4 appear to have a protective effect on bone. ■

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Rivaroxaban Now Approved for Stroke Prevention

In this issue: New indication for rivaroxaban; new study on warfarin testing; medications causing adverse drug events; niacin as an add-on therapy; and FDA actions.

Rivaroxaban for atrial fibrillation patients

Rivaroxaban (Xarelto), Janssen Pharmaceutical's once-a-day oral Xa inhibitor, has been approved for reducing the risk of stroke in patients with atrial fibrillation. The drug was previously approved for prophylaxis of deep vein thrombosis in patients undergoing hip or knee replacement. Rivaroxaban is the second "non-warfarin" oral anticoagulant to be approved for this indication after the direct thrombin inhibitor dabigatran (Pradaxa). The approval was based on the ROCKET AF trial, a double-blind, randomized, noninferiority comparative trial with warfarin, which showed a rate of stroke or systemic embolism of 2.1% per year for rivaroxaban and 2.4% per year for warfarin. The study looked at 14,000 patients over 700 days of follow-up. Rates of major and non-major bleeding were the same with the two drugs, although the rate of intracranial hemorrhage was lower for rivaroxaban while the rate of GI bleeding was lower with warfarin. ROCKET AF showed noninferiority of rivaroxaban vs warfarin but not superiority (*N Engl J Med* 2011;365:883-891). The approval sets up a major marketing showdown between Janssen and Boehringer Ingelheim, the manufacturer of dabigatran, for this multibillion dollar market. Meanwhile, Pfizer and Bristol-Myers Squibb are jointly developing a third drug — apixaban, also a factor Xa inhibitor — which is undergoing an "accelerated review" by the FDA with approval likely in March 2012. All three drugs have the potential disadvantage of the lack of an antidote, a problem that seems to be plaguing dabigatran with more than 250 fatal bleeding episodes reported worldwide since the drug was approved in 2010. A recent report suggests that prothrombin complex concentrate may be an effective reversal agent for rivaroxaban but not dabigatran (*Circulation* 2011;124:1573-1579). ■

Warfarin testing every 12 weeks?

One of the major disadvantages of warfarin over the newer anticoagulants is the need for frequent prothrombin time monitoring and dose adjustment. Most guidelines recommend a maximum interval of 4 weeks between testing. A new study suggests that stable patients may be safely tested at 12-week intervals. A total of 226 patients who were on a stable dose of warfarin for at least 6 months were assigned to testing every 4 weeks, while the other half had blood tests done every 4 weeks, but sham INRs within the target range were reported for two of the three 4-week periods. The percentage of time in the therapeutic range was 74.1% in the 4-week group compared with 71.6% in the 12-week group (noninferiority $P = 0.020$ for a 7.5% point margin). Patients in the 12-week group had fewer dose changes and secondary outcomes, including major bleeding, thromboembolism, and death that were no different between the two groups. The authors conclude that assessment of warfarin dosing every

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12 weeks seems to be safe and noninferior to assessment every 4 weeks, although they recommend further study (*Ann Intern Med* 2011;155:653-659). This study is important given the marked cost differential between warfarin and dabigatran or rivaroxaban. Some patients, especially if they pay for their own medications, may opt to remain on warfarin if they are on a stable dose, especially if they only require testing four times a year. ■

Adverse drug events in the elderly

Although low cost, warfarin remains one of the most dangerous medications in common usage. In fact, hospitalizations for adverse events in the elderly are much more likely to be caused by commonly used medications, such as warfarin, rather than medications classified as high risk in the elderly, according to a new study from the CDC. Researchers used a national database of adverse drug events from 2007-2009 to estimate the frequency and rates of hospitalization after emergency department visits for adverse events in older adults to assess the risk of specific medications causing this hospitalization. It is estimated that adverse drug events led to nearly 100,000 hospitalizations during the 2-year period with nearly half among adults 80 years of age or older. Nearly two-thirds of the hospitalizations were due to unintentional overdoses. Four medications or medication classes were implicated alone or in combination in 67% of hospitalizations including warfarin (33.3%), insulins (13.9%), oral antiplatelet agents (13.3%), and oral hypoglycemic agents (10.7%). High-risk medications were implicated in only 1.2% of hospitalizations. The authors suggest that efforts to promote the safe management of antithrombotic and antidiabetic agents have the potential to substantially reduce harm to our older patients (*N Engl J Med* 2011;365:2002-2012). This study points out that we may be spending too much effort in managing "high-risk" medications in the elderly, while warfarin alone is responsible for a third of medication-related hospitalizations. ■

Is it time to retire niacin?

An editorial published online in the *New England Journal of Medicine* asks, "Niacin at 56 Years of Age — Time for an Early Retirement?" Retirement may be the logical next step after publication of the AIM-HIGH trial (see *Pharmacology Watch* July 2011), the National Heart Lung and Blood Institute's trial comparing niacin plus intensive statin therapy with intensive statin therapy alone in patients with established cardiovascular disease. The study was halted early when it was found that the addition of 1500-2000 mg of niacin per day to simvastatin, despite significantly raising HDL levels an average of 7 points, had no effect on the primary endpoint, which was a composite of the rate of death from coronary artery disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for acute coronary syndrome, or symptom-driven coronary or cerebral revascularization (primary endpoint 16.4% niacin group, 16.2% placebo group; $P = 0.79$) (*N Engl J Med* published online November 15, 2011). The accompanying editorial suggests there is lack of evidence to support niacin as an add-on therapy in patients with cardiovascular disease who have well-controlled LDL cholesterol levels. Additionally, long-acting niacin is relatively expensive and frequently causes flushing — two additional factors that argue against continued use of the drug except, perhaps, in patients who are intolerant of statins (*N Engl J Med* published online November 15, 2011). ■

FDA actions

The news isn't much better for fenofibrate. The FDA has issued a safety communication for the cholesterol lowering medication stating that the drug may not lower the risk of major cardiovascular events based on data from the ACCORD Lipid trial. ACCORD (similar in design to AIM-HIGH) evaluated the efficacy and safety of fenofibrate plus simvastatin vs simvastatin alone in patients with type 2 diabetes. There was no significant difference in the risk of experiencing a major adverse cardiac event between the two groups, and women may have even experienced an increase in the risk for major adverse cardiac events with combination therapy vs simvastatin alone. The FDA is requiring the manufacturer of Trilipix brand fenofibric acid to conduct a clinical trial to evaluate the cardiovascular effects of the drug in patients at high risk for cardiovascular disease who are already taking statins (www.fda.gov/Drugs/DrugSafety/ucm278837.htm).

The FDA has approved a new formulation of zolpidem for treatment of insomnia in patients who wake up in the middle of the night and have difficulty returning to sleep. Zolpidem, originally marketed as Ambien and now available as a generic, is a short-acting hypnotic. The new product is a lower dose sublingual formulation that comes in a 1.75 mg dosage recommended for women and 3.5 mg for men. The lower dose for women is recommended because women clear the drug more slowly than men. It can be used if the patient has at least 4 hours of bedtime remaining. Zolpidem sublingual is marketed by Transcept Pharmaceuticals as Intermezzo. ■

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- 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.

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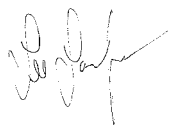

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