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A monthly survey of developments in neurologic medicine

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INSIDE

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Epilepsy and Sleep Apnea

ABSTRACT & COMMENTARY

By Charles Pollak, MD

Professor of Clinical Neurology, Weill Cornell Medical College;

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

Synopsis: *Obstructive sleep apnea may be both a cause and a consequence of uncontrolled epileptic seizures.*

Sources: Malow BA, Foldvary-Schaefer N, Vaughn BV, et al. Treating obstructive sleep apnea in adults with epilepsy: a randomized pilot trail. *Neurology* 2008;71:572-577; Foldvary-Schaefer N, Stephenson L, Bingaman W. Resolution of obstructive sleep apnea with epilepsy surgery? Expanding the relationship between sleep and epilepsy. *Epilepsia* 2008; 49:1457-1459.

IT IS WELL KNOWN TO NEUROLOGISTS THAT CONVULSIVE SEIZURES ARE more likely to occur during REM (rapid eye movement) or deep non-REM sleep, so much so that sleep is used as an activating condition in the diagnostic electroencephalography (EEG) laboratory. At the same time, sleep deprivation is a potent activator of seizures and of status epilepticus. The relationship of seizures to sleep, therefore, is complex.

The two papers cited above illustrate this complexity. Foldvary-Schaefer et al report the case of an 18-year-old epileptic man with interictal epileptiform discharges (IEDs) that were markedly activated in sleep. Subdural and depth electrode recordings from the left frontal and temporal lobes showed interictal discharges and three seizure types: behavioral arrest with and without automatisms, loss of contact with chin twitching and head jerks, and arousal from sleep with grimacing and head clonic activity. He underwent a premotor frontal lobotomy. In four postoperative years, he has had only five seizures despite the reduction of antiepileptic drugs. At the time of presentation, he reported daytime sleepiness and snoring and was found to have moderate obstructive sleep apnea (apnea-hypopnea index = 24 apneas or hypopneas per hour, not temporally related to epileptiform activity).

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Use of continuous positive airway pressure (CPAP) resulted in abolition of apneas. Remarkably, not only was the apnea-hypopnea index (AHI) normal postoperatively, but the spike rate also was markedly reduced compared to the preoperative baseline.

Previously, small case series have shown that treatment of obstructive sleep apnea (OSA) may reduce seizures, possibly by reducing sleep-wake transitions and correcting sleep deprivation; however, amelioration of OSA following curative epilepsy surgery has never before been reported. The authors were unable to explain this outcome of surgery, though they speculated that the abundant interictal discharges and seizures prior to surgery might have affected upper airway control during sleep in a vulnerable patient.

The second study, by Malow et al, was described as a pilot study meant to provide critical information for planning a trial to test the hypothesis that treating OSA in epileptic patients would improve seizure control. Because 30% of patients with epilepsy continue to have seizures despite antiepileptic drugs (AEDs), eliminating factors such as sleep deprivation that may promote seizures could provide important new strategies for seizure control. Epileptic subjects selected for this study had to have two or more seizures a month after optimization of AEDs, as well as coexisting OSA.

Those subjects meeting criteria for OSA after two nights of polysomnography were randomly assigned to either therapeutic or sham-CPAP treatments. Sham CPAP was accomplished by providing a CPAP machine modified to include a large hidden leak in the exhaust port of the mask to disperse the therapeutic pressure. The sham treatment provided normal blower noise and airflow resistance, making the patient's experience similar to that of therapeutic CPAP. Subjects assigned to sham CPAP slept with the sham CPAP for two consecutive nights. Those assigned to therapeutic CPAP were titrated to the pressure needed to resolve their apneas and hypopneas. Therapeutic or sham treatment was then continued at home for 10 additional weeks. The second night of therapeutic CPAP was found to be significantly more effective in reducing AHI than the sham CPAP. It was not significantly more effective in reducing seizures; however, a greater reduction of seizures was observed in the therapeutic group.

■ COMMENTARY

We must be cautious about drawing conclusions from the finding by Foldvary-Schaefer et al that curative epilepsy surgery in one patient resulted in an apparent resolution of sleep apnea. For one thing, the length of follow-up was not clear. We are told only that a follow-up polysomnogram 6 months postoperatively showed the AHI to be normal (1.1 events/hour). The mechanisms by which apneas were controlled are not known. It also is not clear whether the improvement lasted longer than 6 months, when a follow-up polysomnogram was done. The apneas and hypopneas had been occurring at a rate of 24 per hour and were easily controlled by a CPAP pressure of only 5 cm of water.

Malow et al billed their study as a "pilot" that provided information regarding the feasibility of a planned comprehensive trial to test the hypothesis that treating OSA in patients with epilepsy improves seizure control. Had the difference in seizure rate between therapeutic and sham CPAP groups been statistically significant, I suspect that this study of 68 subjects for which 865 candidates were screened would have been portrayed as solid evidence for detecting and treating sleep disorders such as OSA in epileptic patients. Instead, the need for a larger sample is evidence that the effect of OSA on seizure frequency is rather modest.

Taken together, these interesting studies contribute to our appreciation of the complexity of the relationship between sleep disorders and seizures. We may anticipate further exploration of this area, with clinical benefits as a likely result. ■

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Questions & Comments
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Chronic Migraine: Recognition, Prevention, and Treatment

ABSTRACT & COMMENTARY

By Dara G. 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 speaker's bureau for Boehringer Ingelheim and Merck.

Synopsis: *Increased migraine attack frequency and overuse of acute medication, especially barbiturates and opiates, are risk factors for the chronification of migraine, which occurs in up to 2% of individuals.*

Sources: Bigal ME, Serrano D, Reed M, et al. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. *Neurology* 2008;71:559-566; Bigal ME, Serrano D, Buse D, et al. Acute migraine medications and evolution from episodic to chronic migraine: A longitudinal population-based study. *Headache* 2008;48:1157-1168; Silberstein S, Diener HC, Lipton R, et al. Epidemiology, risk factors, and treatment of chronic migraine: a focus on topiramate. *Headache* 2008;48:1087-1095.

CHRONIC DAILY HEADACHE IS A HETEROGENEOUS GROUP of headache disorders characterized by headaches on ≥15 days per month for more than three months. Chronic or transformed migraine, a subtype of chronic daily headache, has a prevalence of up to 2% of individuals, predominantly women, in the United States. Bigal et al used longitudinal data from the American Migraine Prevalence and Prevention (AMPP) study to evaluate the disease burden, diagnosis, and risk factors associated with chronic migraine. Analysis of the AMPP study found that patients with chronic migraine reported significantly more missed days of work and family activities than did patients with episodic migraine. While the majority of the chronic migraine sufferers (87.6%) sought care to discuss their headaches with a health professional, migraine-specific acute treatments were used by less than a third of chronic migraineurs and less than half were satisfied with their acute therapies. Only a third of chronic migraineurs were using preventive medications.

Data from the AMPP study was used to assess the role of specific classes of acute medications in the chronification of migraine. Adjustment was made for risk factors for headache progression, such as gender, headache frequency and severity, and prevention medication use. Of 8219 individuals with episodic migraine in 2005, 209 (2.5%) had developed transformed migraine by 2006. Baseline increased headache frequency was a risk factor for transformed migraine. Individuals who used medications containing barbiturates (OR = 2.06, 95% CI = 1.3-3.1) or opiates (OR = 1.98, 95% CI = 1.4-2.2) were at increased risk of transformed migraine. A dose-response relationship was found for use of barbiturates. Use of triptans (OR = 1.25, 95% CI = 0.9-1.7) at baseline was not associated with prospective risk of transformed migraine. Overall, NSAIDs (OR = 0.85, 95% CI = 0.63-1.17) were not associated with transformed migraine. NSAIDs appeared to be protective against transition to transformed migraine in migraineurs with less than 10-14 headache days per month, but were associated with an increased risk of transition to transformed migraine at high levels of monthly headache days. The risk of migraine chronification was greater in women than in men, even controlling for triptan use and headache frequency. The authors concluded that episodic migraine sufferers develop transformed migraine at the rate of 2.5% per year. Any use of barbiturates and opiates, but not triptans, was associated with increased risk of chronic migraine. NSAIDs were protective at low headache frequency, but increased the risk of transformation at high headache frequency.

Multiple medications, including topiramate, have been found to be effective and safe for preventive treatment for episodic migraine. These medications also may be used to decrease the frequency and severity of chronic migraine. Two randomized, double-blind, placebo-controlled, multicenter trials investigating the efficacy and safety of topiramate in the treatment of patients with chronic migraine found that topiramate at a dose of 100 mg daily reduced the number of headache days and the use of acute medications.

■ COMMENTARY

Migraine can evolve from an episodic annoyance to a chronic disability, a process that often is abetted by well meaning but misguided health care providers who provide inappropriate quantities of non-specific acute pain medications. The recognition of the potential dangers of excessive acute medication use, especially with barbiturates and opiates, and the appropriate use of preventative medications in patients with frequent migraines, can decrease the incidence of chronic migraine. Prevention of the excess use of acute pain

medication in combination with the use of daily prophylactic medication, such as topiramate, can decrease the disability of chronic migraine. ■

How the Cerebellum Affects Dystonia

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports that she is on the speaker's bureau for GlaxoSmithKline, Teva, Boehringer Ingelheim, Schwarz Pharma, and Allergan.

Synopsis: *Two animal models of dystonia reveal that cerebellar activity influences abnormal involuntary dystonic movements, and implicate dysfunction of a cerebellar-striatal network in the development of dystonia.*

Source: Neychev VK, Fan X, Mitev VI, et al. The basal ganglia and cerebellum interact in the expression of dystonic movement. *Brain* 2008;131(Pt 9):2499-2509.

THE AUTHORS CHOSE TWO ANIMAL MODELS OF DYSTONIA in which to investigate whether cerebellar activity either causes, or influences expression of, a dystonic phenotype. First, they examined a genetic model of dystonia, tottering mutant mice. The tottering mutant phenotype arises from a *Cacna1a* gene point mutation that impairs activity of CaV2.1 (P/Q type) calcium channels. In these mice, secondary up-regulation of L-type calcium channels in the cerebellum leads to spontaneous paroxysmal dystonia, and attacks also can be induced by caffeine. Cerebellectomies, confirmed at post-mortem, were performed under anesthesia on tottering mice (n=5); motor outcomes were compared with tottering mice subjected to sham surgery, in which the cerebellum was exposed surgically, but no tissue was excised (n=5). After cerebellectomy, tottering mice had no more spontaneous or caffeine-induced paroxysmal dystonic spells, whereas the control sham-operated group continued to have typical paroxysmal attacks.

Next, tottering mice were subjected to striatal lesions by 6-hydroxydopamine (6OHDA) or quinolinic acid (QA). This increased dystonic spell frequency and duration when compared with controls. Consistent with this finding, microdialysis demonstrated decreased intrastriatal dopamine levels associated with dystonia. The second set of experiments made use of a pharmacologic model of dystonia. Here, kainic acid (KA) was injected into cerebellar cortex of normal mice, an approach that is known to result in generalized dystonia. Kainic acid injections made to cerebellum in mice that had previously undergone striatal 6OHDA or QA lesions resulted in much more severe dystonia. Moreover, KA injection to the cerebellum resulted in significantly lower striatal dopamine levels, as measured by microdialysis.

■ COMMENTARY

Dystonia is an involuntary movement disorder involving abnormal sustained muscle contractions with spread of activity into neighboring muscles not usually involved that often results in twisting movements. The majority of cases of dystonia are idiopathic, and incidence of primary generalized dystonia is estimated in one study to be 3.4 per 100,000 individuals and the incidence of of primary focal dystonia (such as torticollis, blepharospasm, and writer's cramp) to be 29.5 per 100,000 individuals. Traditional teaching has focused upon basal ganglia dysfunction in the etiopathogenesis of dystonia. In fact, this has been the basis for the highly successful surgical treatment of dystonia by deep brain stimulation of the globus pallidus pars interna.

The present study, however, supports the emerging understanding that cerebellar structures play an important role in this disorder. Using two very distinct mouse models of dystonia, the authors have succeeded in demonstrating that both the dystonic phenotype and striatal dopamine levels are affected by cerebellar inputs. Inevitably, the use of animal models has limitations in translation to human disease and its treatment. With regard to the models chosen here, the *Cacna1a* gene can cause paroxysmal dystonia in humans and mice, but also can lead to cerebellar atrophy, ataxia, and epilepsy, making results more complicated to interpret. Interpretation of lesional models also is hampered by our ability to characterize their functional, as opposed to structural, effects. Nonetheless, an important role for the cerebellum in cases of human dystonia is supported by reports of familial dystonia with prominent cerebellar atrophy, of dystonia associated with cerebellar stroke, and with the finding of significant cerebellar atrophy in one study of patients with writer's cramp. Improved understanding of this circuitry may well expand our options for treatment, both pharmacologically and surgically. ■

Monitoring Response to Antiplatelet Therapy: A Role in Neurointerventional Procedures?

ABSTRACT & COMMENTARY

By Dana Leifer, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Leifer reports she is involved with grants/research support for Neurobiological Technologies and ImaRx and is on the speaker's bureau for Bristol-Myers Squibb and Sanofi Aventis.

Synopsis: *Platelet function testing identifies patients who do not respond to antiplatelet therapy and are at increased risk for acute stent thrombosis after neurointerventional procedures.*

Source: Lee DH, Avat A, Morsi H, et al. Dual antiplatelet therapy monitoring for neurointerventional procedures using a point-of-care platelet function test: a single-center experience. *AJNR Am J Neuroradiol* 2008; 29:1389-1394.

ANTIPLATELET THERAPY IS THE KEY MEDICAL THERAPY for prevention of ischemic stroke for most patients and is essential for preventing thrombosis after angioplasty and stenting in the cerebrovascular, coronary, and peripheral vascular circulations. Despite the use of antiplatelet therapy, many patients who are treated only medically have recurrent ischemic events, and stent thrombosis remains a significant problem after endovascular procedures. A growing body of evidence suggests that resistance to antiplatelet therapy is a significant part of the problem.

The incidence of recurrent ischemia and death appears to be between 2 and 9 times more frequent in patients who are resistant to antiplatelet therapy.[1,2] The use of assays to identify resistant patients and then to guide changes in therapy has been limited, however, because traditional assays of response to antiplatelet therapy have been time-consuming and dependent on the availability of skilled laboratory technicians. Several point-of-care systems have now been developed that are easier to use and make it practical to assess response to antiplatelet agents such as aspirin and clopidogrel.

Lee et al have now examined resistance to aspirin and clopidogrel in patients undergoing neurointerventional procedures. They used one of the newer assay systems (VerifyNow; Accumetrics). Previous work with this assay demonstrated that patients with coronary artery disease and aspirin resistance were more likely to have cardiovascular death or coronary or cerebrovascular ischemic events than aspirin-responsive patients (15.6% vs. 5.3%, $P<0.001$).[3]

Lee et al studied 98 patients who underwent neurointerventional procedures during which stenting was planned. Two patients were resistant to aspirin and 42 were resistant to clopidogrel. Stents were placed in 63 patients. The main finding of the study was that acute stent thrombosis developed in 3 of the 42 clopidogrel-resistant patients, but in none of the clopidogrel responders. Stent thrombosis did not occur in aspirin-resistant patients, but, as noted above, there were only 2 aspirin-resistant patients in the study.

The investigators state that the "preferred" regimen was aspirin 325 mg/day and clopidogrel 75 mg/day after a 300 mg load for 5 to 10 days before the procedure, but it is not stated how many patients actually received this regimen. Twenty-nine of the 42 patients who were resistant to clopidogrel received an extra 300 mg dose, and assays were repeated 30 minutes later in 10 of these, 3 of whom were clopidogrel-responsive on the repeat test. Of note, 2 of the cases of stent thrombosis were among the 29 patients who received an extra dose of clopidogrel, and neither of these patients responded to clopidogrel on repeat testing. However, repeat testing may have been done too quickly for the extra dose to have its maximal effect on the assay.

The investigators also tried to identify factors that predicted a response to clopidogrel. Multivariate analysis suggested that response to clopidogrel was inversely related to patient weight and not independently related to other factors. In particular, duration of treatment prior to the procedure was not related to response.

■ COMMENTARY

The results suggest that measurement of resistance to antiplatelet therapy before neurointerventional procedures may identify patients at increased risk for intraprocedural thrombosis. The paper raises the possibility that extra doses of antiplatelet therapy that convert resistant patients into responders may improve their outcome, but the paper does not answer this question. Additional studies to address this question and to investigate the potential benefits of monitoring antiplatelet medication in other cerebrovascular disorders are needed and may lead to improved outcomes. ■

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2. Gum PA, Kottke-Marchant K, Welsh PA, et al. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. *J Am Coll Cardiol* 2003;41:961-965.
3. Chen WH, Cheng X, Lee PY. Aspirin resistance and adverse clinical events in patients with coronary artery disease. *Am J Med* 2007;120:631-635.

Getting Toes To Go Up

ABSTRACT & COMMENTARY

By Michael Rubin, MD, FRCP(C)

Professor of Clinical Neurology, Weill Cornell Medical College.

Dr. Rubin reports he is involved with grants/research support for Pfizer and on the speaker's bureau for Athena Diagnostics.

Synopsis: *The Babinski sign continues to be a valid bed-side test for pyramidal tract lesions.*

Source: Singerman J, Lee L. Consistency of the Babinski reflex and its variants. *Eur J Neurol* 2008;15:960-964.

Joseph Francois Felix Babinski, a French neurologist of Polish descent, first described the phenomenon of the upgoing toe to the French Biological Society in 1896. By applying a noxious stimulus to the sole of the foot (a pinprick), he noted hallux dorsiflexion contralateral to pyramidal tract lesions, even in patients unable to voluntarily extend their toes. Improvement of the technique, by firmly stroking the lateral aspect of the sole, was reported in a second paper, that same year, by the same author, in the same journal.[1] Oppenheim (1902) noted that firmly stroking the medial tibia could produce the same result; Gordon (1905) demonstrated that firm calf pressure did the same; and Chaddock (1911) added his own version, labeled the external malleolar sign, that is elicited by stroking the skin inferior to the lateral malleolus. How reliable are these various techniques, both compared to each other and when used by different examiners?

Between November 2006 and March 2007, 23 inpatients with a variety of neurological disorders, most commonly stroke, and 11 non-neurological inpatients serving as controls, were examined by six neurologists who each performed the Babinski, Oppenheim, Gordon, and Chaddock maneuvers on all subjects in a blinded fashion: patients were entirely hidden behind a curtain with only their feet exposed. Written and diagrammatic instructions were given to each examiner to maintain consistency but each could use their own tools to elicit the response (e.g., end of reflex hammer, ignition key of a Bentley). Re-examination of 6 subjects was performed one week later to determine intra-observer consistency. Each neurologist interpreted his/her own findings, repeating the test as often as needed. Equivocal responses were rejected. The kappa statistic was used for statistical analysis.

Not surprisingly, the Babinski reflex demonstrated the highest inter-observer consistency, with a kappa value indicative of moderate to substantial agreement. It was followed, in order, by the Chaddock, Oppenheim, and Gordon reflexes, all of which had kappa values indicative of fair to moderate agreement. Intra-observer consistency was best achieved by the Gordon reflex, followed by the Chaddock, Oppenheim, and Babinski reflexes. Amongst all responses, the Babinski and Chaddock were the most reliable pair and would be recommended as the preferred set at the bedside.

■ COMMENTARY

Read about the Babinski sign and discover its remarkable history in the *Puerto Rico Health Science Journal*.[2] Reported in a paralyzed animal by Czech anatomist and physiologist Jiri Prochaska as early as 1784, interpreted as a spinal reflex by Hall (1833) and Brigham (1840), and associated with hemiparesis by Karl Wernicke (1874), Babinski nevertheless merits the eponym as he was the first to interpret its clinical relevance and correlate it with central nervous system pathology. As the favorite student of Charcot, this is particularly remarkable, as the teacher rarely examined his patients. He maintained that the neurological examination had little to add to the medical history; however, his pupil was exceptional at clinical observation and will forever be remembered as demonstrating the significance of physical diagnosis. "Rabbi Hanina said: From my teachers I learned much, from my colleagues still more, but from my students most of all" (Babylonian Talmud, Tractate Ta'anit 7a). ■

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2. Brau C, Brau RH. Babinski's signe de l'eventail: a turning point in the history of neurology. *P R Health Sci J* 2008;27:103-105.

Use of Anti-angiogenic Agents in Glioblastoma Treatment

ABSTRACT AND COMMENTARY

By Adília Hormigo, MD, PhD

Assistant Professor of Neurology, Weill Cornell Medical College,

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

Synopsis: *The anti-angiogenic monoclonal antibody, bevacizumab, shows great promise in the treatment of malignant gliomas.*

Source: Ali SA, McHayleh WM, Ahmad A, et al. Bevacizumab and irinotecan therapy in glioblastoma multiforme: a series of 13 cases. *J Neurosurg* 2008;109:268-272.

GLIOBLASTOMA (GBM) IS ONE OF THE MOST COMMON of the primary brain tumors and has a median survival of 12-14 months. At recurrence, the median survival is 3-6 months, with less than 10% having a progression-free survival of 6 months.

In this study, the authors used bevacizumab plus irinotecan to treat 13 patients with GBM who had failed initial standard treatment of resection followed by radiotherapy with concurrent chemotherapy or who had tumor progression or recurrent disease after multiple treatment regimens. They treated 9 patients with bevacizumab at a dose of 5 mg/m^2 every 2 weeks and irinotecan at a dose of 125 mg/m^2 every week for 3 weeks followed by one week off. Four patients were treated with bevacizumab 10 mg/m^2 with irinotecan at 125-250 mg/m^2 every 2 weeks. Six patients (46%) had a clinical response. By imaging criteria, 10 patients (77%) had a partial response, defined as >50% reduction in edema and enhancement, along with a 25% reduction in total tumor mass. Three patients (23%) had stable disease. Median time to progression was 24 weeks and median overall survival was 27 weeks. The authors reported nonfatal intracranial hemorrhage in two patients and deep venous thrombosis in another.

■ COMMENTARY

The results of this observational study support prior data that showed benefit of bevacizumab in combination with irinotecan or other agents for treatment of patients with GBM and recurrent disease. This suggests that bevacizumab, a monoclonal antibody that neutralizes vascular endothelial growth factor, is the key drug in these regimens and supports further trials using anti-angiogenic compounds in the treatment of GBM. The drug is generally well tolerated and the studies reveal a positive effect on survival. Potential serious complications are intracerebral hemorrhage and stroke, and over time some patients may develop hypertension and proteinuria with renal dysfunction. The MRI responses were remarkable, with rapid reduction in tumor mass in the responders. However, in patients on bevacizumab who have a clinical deterioration and increased hyperintensity on FLAIR (fluid attenuation inversion recovery) but a sustained reduction in contrast-enhancement on MRI, the MRI has to be interpreted with caution since it can be difficult to determine if this represents tumor growth or tissue necrosis. MRI has limitations in evaluating therapeutic response to biological agents. In some of the cases, non-enhancing tumor developed rapidly and raises the question of whether bevacizumab has a role in the development of more aggressive tumor. The results of future trials will determine whether anti-angiogenic agents should be administered concurrently with the standard treatment of radiotherapy combined with chemotherapy. ■

References

1. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007;25:4722-4729.
2. Pope WB, Lai A, Nghiemphu P, et al. MRI in patients with high-grade gliomas treated with bevacizumab and chemotherapy. *Neurology* 2006;66:1258-1260.

CME Questions

5. Which of the following statements is correct about dystonia?

a. Primary, but not secondary, dystonia involves basal ganglia dysfunction.
b. Dystonia exclusively involves non-dopaminergic striatal inputs.
c. Most cases of dystonia arise from secondary causes.
d. Cerebellar input can modulate striatal dopamine levels and affect dystonic movements.
e. Evidence for cerebellar influence on dystonic symptoms derives exclusively from animal models.

6. The most reliable set of reflexes to perform in attempting to elicit an upgoing toe is:

a. Chaddock and Oppenheim.
b. Gordon and Chaddock.
c. Babinski and Chaddock.
d. Babinski and Oppenheim.
e. Babinski and Gordon.

7. Which of the following is true about the use of bevacizumab in the treatment of glioblastoma (GBM)?
a. Bevacizumab is an epidermal growth factor receptor tyrosine kinase inhibitor.
b. In general, MRI of patients treated with bevacizumab shows no response to the treatment.
c. Bevacizumab was used in the current study in newly diagnosed GBM.
d. Bevacizumab is a neutralizing monoclonal antibody against vascular endothelial growth factor.

8. Which of the following is most likely to promote the evolution from episodic to chronic migraine?
a. Sumatriptan
b. Butalbital/acetaminophen/caffeine
c. Ibuprofen
d. Naproxen sodium
e. Rizatriptan

9. What percentage of patients undergoing neurointerventional procedures were resistant to aspirin?
a. 2%
b. 9%
c. 18%
d. 43%

10. What percentage of patients undergoing neurointerventional procedures were resistant to clopidogrel?
a. 2%
b. 9%
c. 18%
d. 43%

11. What was the rate of intraprocedural thrombosis in the clopidogrel resistant group?
a. 0%
b. 3%
c. 7%
d. 25%

Answers: 5. d; 6. c; 7. d; 8. b; 9. a; 10. d; 11. c

CME Objectives

The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs;

• To discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

In Future Issues:

Treatment of Neurocysticercosis

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
VOLUME 13, NUMBER 10 PAGES 19-20 OCTOBER 2008

The Obesity-Sexual Health Relationship

Source: Esposito K, et al. Obesity and sexual dysfunction, male and female. *Int J Impot Res* 2008;20:358-365.

The established causal relationship between endothelial dysfunction and erectile dysfunction (ED) provides mechanistic insight into an obesity-sexual health linkage. Obesity is associated with an increased incidence of diabetes, dyslipidemia, and hypertension, all of which contribute to endothelial dysfunction. Both the 9-year follow up of the Massachusetts Male Aging Study and the 25-year follow up of the Rancho Bernardo Study found overweight to be an independent risk factor for ED, essentially doubling the odds ratio. Although correlation with BMI is strong, it appears to be central adiposity (aka visceral adiposity) that is most strongly related to endothelial dysfunction.

The relationship between obesity in women and sexual health is both less well studied, and not as easily explained. Available data suggest that disorders of arousal, lubrication, and orgasm are more common in overweight and obese women, although sexual desire disorders (e.g., hypoactive sexual desire disorder) and sexual pain disorders (e.g., dyspareunia) are not. In contrast to men, in whom body fat distribution is relevant, it is BMI alone which shows best correlation in women. Interestingly, scores on the Female Sexual Function Index (FSFI) correlate with BMI in women with prevalent sexual dysfunction, but do not show this same correlation in unselected healthy populations.

Women with metabolic syndrome score lower on the FSFI than matched controls, although a plausible putative relationship remains to be established.

Interventions targeting weight reduction have been promising: An exercise/diet program in men has been shown to improve erectile function, and a 2-year study of the Mediterranean diet in women improved FSFI scores. Improved sexual health may be another reason to advocate healthful diet and exercise for our patients. ■

Body Composition and Treatment of Hypogonadism

Source: Svartberg J, et al. Testosterone treatment in elderly men with subnormal testosterone levels improves body composition and BMD in the hip. *Int J Impot Res* 2008;20:378-387.

The Tromso study is an ongoing health survey of men who live in the municipality of Tromso, Norway. In 2001, men aged 60-80 years (n=335) with hypogonadism (HGO) were identified and matched with eugonadal age-matched controls; in 2005, these hypogonadal men were enrolled in a 1-year testosterone treatment intervention.

At baseline, HGO subjects had a greater percentage of fat mass, including visceral, subcutaneous, and total fat mass, than their matched controls. Fasting glucose, 2-hour glucose levels, and triglycerides were also higher in the HGO group, reflecting a correspondingly higher level of insulin resistance.

The testosterone treatment intervention was carried out in 69 men of the HGO group. Treatment produced an increase in fat-free mass, a decrease in fat mass, and a decrease specifically in total abdominal adipose tissue. As in prior trials, testosterone replacement increased bone mineral density, predominantly in the hip. Metabolic defects seen in HGO were not corrected by testosterone replacement. Testosterone replacement has numerous favorable effects on body composition in hypogonadal men. ■

Changing Metrics for Diabetes Management

Source: Nathan DM, et al. Translating the A1C assay into estimated average glucose values. *Diabetes Care* 2008;31:1473-1478.

The conceptualization of hemoglobin A1c levels (A1c) as a marker of adequacy of diabetes control has remained elusive for many of our patients. Since blood glucose is measured typically (in the United States) in mg%, and numbers typically range from 100 and higher, the concept that an A1c of 7.0 somehow corresponds to good glucose control is not surprisingly an item of potential disconnect.

Nathan et al performed an international multicenter study utilizing the combination of continuous glucose monitoring with A1c levels in subjects (n=507) with type 1 diabetes, type 2 diabetes, and non-diabetics.

Subjects underwent continuous glucose monitoring with a Medtronic device that performs serum glucose determinations every 5 minutes. This was performed for 2 days at baseline, then every 4 weeks for 12 weeks. At the same time, subjects performed an 8-point fingerstick glucose panel. All told, each subject completed approximately 2700 glucose readings during the 3-month period.

The linear regression relationship between A1c and average glucose was established to be the same in both normal and diabetic individuals. An A1c of 7 correlates

with an average glucose of 154 mg%. For each incremental increase of 1 unit in A1c, average glucose increased by approximately 30 mg%. Adoption of the average glucose metric might simplify our patients' understanding of goals in diabetes. ■

Which Is Best for Weight Loss: Low Carb, Low Fat, or Mediterranean?

Source: Shai I, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008;359:229-241.

In overweight individuals, the single most critical marker of success is simply reduction of weight. On the other hand, proponents of diets that specifically target individual dietary components, such as carbohydrate or fat, point to putative benefits of specific restrictions. If weight loss is the ultimate arbiter of success, it remains unclear which dietary plan is the best. To date, the best evidence for endpoint reduction resides with the Mediterranean diet in secondary prevention of cardiovascular events: A greater than 70% relative risk reduction has been demonstrated (superior, literally, to that obtained with statins in a similar setting).

A two-year trial randomized obese (BMI = 31 kg/m^2) subjects to either a fat-restricted, carbohydrate-restricted, or Mediterranean diet. Patients received intensive instruction from dietitians. The low-fat and Mediterranean diets each provided 1500 kcal/d (women) or 1800 kcal/d (men). The low-carbohydrate diet did not have an absolute calorie limit; instead, subjects were restricted to a maximum intake of 120 g/d carbohydrate.

At two years, the low-carbohydrate and Mediterranean diets produced a 5.5 kg and 4.6 kg weight loss, respectively. The low-fat diet resulted on a 2.9 kg weight loss. The authors suggest that either of the two more successful diets might be appropriate; since the Mediterranean diet provided better glycemic control, and the low-carbohydrate diet resulted in better lipid effects, individual choice of diet could be informed by baseline risk factors. ■

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Influenza Vaccine Efficacy in Senior Citizens

Source: Jackson ML, et al. Influenza vaccination and risk of community-acquired pneumonia in immunocompetent elderly people: A population-based, nested case-control study. *Lancet* 2008;372:398-405.

Influenza vaccination (FluVax) is multi-intentioned: reduction in incidence of influenza, reduction of influenza-related morbidities (e.g., pneumonia, heart failure), reduction of transmission to others, and ultimately, since influenza-related deaths number more than 15,000 every year, reduction in mortality. Even though most clinicians consider the value of FLUVax to be a given, controversy still exists about the relative merits of FLUVax.

The study population addressed in the communication by Jackson et al is composed of immunocompetent community-dwelling elders age 65-94 years in Washington state (n=53,929). Persons who had a history of cancer, chronic renal disease, or prescriptions for immunosuppressive medications were excluded (as non-immunocompetent). The object of the study was to discern whether FLUVax reduced cases of community acquired pneumonia (CAP) in vaccinated groups. Extensive evaluation of both recorded diagnoses, as well as review of chest X-rays to confirm the presence of pneumonia in both inpatients and outpatients, strengthened the accuracy of pneumonia diagnosis.

During the influenza season of three consecutive years (2001-2003), the odds ratio for pneumonia among vaccinated versus non-vaccinated individuals was 1.04 (i.e., a slightly greater, though not statistically significant, increased risk). These data do not confirm a statistically significant reduction in pneumonia in immunocompetent senior citizens through influenza vaccine. ■

Best Combination Therapy for Symptomatic Relief in COPD

Source: Rabe KF, et al. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. *Chest* 2008;134:255-262.

There are no disease-modifying pharmacotherapies for COPD. That is, although bronchodilators, anticholinergic agents, and inhaled corticosteroids improve FEV1 and reduce symptoms, decline in pulmonary function continues unabated and lung function returns promptly once medication is stopped.

Overall, in COPD anticholinergic therapy (e.g., ipratropium, tiotropium) provides greater improvements in pulmonary function than beta-adrenergic therapy or inhaled corticosteroids. Combination therapy (anticholinergic + beta agonist or beta agonist + inhaled steroid) is more effective than either monotherapy. Which combination therapy is to be preferred has not yet been established.

Patients with moderate COPD were randomized to receive 6 weeks of either tiotropium + formoterol or salmeterol + fluticasone. At the end of this time period, an assessment of lung function over a 12-hour period was performed. The endpoint was the area-under-the-curve of pulmonary function for 12 hours at end of study.

The tiotropium + formoterol combination was statistically significantly superior to the salmeterol + fluticasone combination; for instance, the mean difference in FEV1 was 78 mL (p = 0.0006). Need for use of rescue medications was the same for both groups.

At least over the short term, the bronchodilator combination of tiotropium + formoterol provides superior improvements in bronchodilation compared to salmeterol + fluticasone. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Gender Differences with Anticoagulation Discontinuation

In this issue: Some women with DVT may stop warfarin after six months; Vytorin and cancer; preventing recurrent stroke; and FDA news.

When is it safe to stop anticoagulation after an unprovoked venous thromboembolism? A new study suggests that women with minimal risk factors may safely stop anticoagulation after 6 months of therapy, although the same may not be true for men. Canadian researchers randomized 646 patients with a first, unprovoked major venous thromboembolism and followed them for 4 years. Data were collected for 69 potential predictors of recurrent venous thromboembolism while patients were taking oral anticoagulants and a multi-variable analysis of predictor variables was performed. Men had a 13.7% annual risk of recurrence after discontinuing oral anticoagulation and there was no combination of clinical predictors that could identify a low-risk subgroup of men. In women, 52% had zero or one of the following risk factors: hyperpigmentation, edema or redness of either leg, d-dimer ≥ 250 mcg/L while taking warfarin, body mass index ≥ 30 kg/m^2, or age ≥ 65 years. These women had an annual risk of recurrent thromboembolism of 1.6% (95% CI, 0.3% to 4.6%). Women who had two or more of these risk factors had an annual risk of 14.1%. The authors conclude that women with zero or one risk factor may safely discontinue oral anticoagulant therapy after 6 months of therapy following their first unprovoked venous thromboembolism; however, this conclusion does not apply to men (*CMAJ* 2008;179:417-426). An accompanying editorial points out that patients with the first episode of unprovoked venous thromboembolism have a high rate of recurrence if they stop anticoagulation therapy — about 10% in the first year. Current guidelines from the American College of Chest Physicians recommend lifetime therapy for patients with a first episode of proximal deep venous thrombosis or pulmonary embolism provided that good anticoagulant monitoring is achievable and indefinite treatment is consistent with patient preferences. This study identifies a large group of women who may safely stop anticoagulation after 6 months although the authors do recommend further validation (*CMAJ* 2008; 179:401-402).

FDA Announces Vytorin Investigation

The news keeps getting worse for Merck/Schering-Plough, the distributor of Vytorin®: The FDA has announced that it will investigate a report from the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis) of the possible association between the use of Vytorin and increased incidence of cancer. The SEAS trial was designed to see if Vytorin, a combination of simvastatin and ezetimibe, would reduce cardiovascular events in patients with aortic stenosis. In a July press

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release, the company reported on preliminary data which showed that the trial did not show benefit for the primary endpoint of aortic-valve related major cardiovascular events, but did show that a larger percent of subjects treated with Vytorin were diagnosed with, and died from, all types of cancer compared to placebo during the 5-year study. There was improvement in the secondary endpoint of ischemic events (15.7% vs 20%) but no benefit in other secondary endpoints. The number of cancers was 105 (11.1%) in the Vytorin group vs 70 (7.5%) in the control group (P = 0.01), and the number of cancer deaths was 39 (4.1%) in the Vytorin group vs 23 (2.5%) in the control group (HR 1.67; 95% CI, 1.00 to 2.79; P = 0.05). The FDA is also looking at interim data from two large ongoing trials of Vytorin, the Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) which, so far, have not shown an increased risk of cancer associated with Vytorin. The SHARP trial should be completed in 2010, while the IMPROVE-IT trial should be finished in 2012. Initial data from the SEAS trial were presented in the recent news conference; full results were published at www.nejm.org (DOI: 10.1056/NEJMao0804602) on Sept. 2, 2008. The FDA says its investigation will take at least 6 months from the date of publication.

PRoFESS Trial Shows No Stroke Benefit

The recently published PRoFESS trial failed to show benefit of two strategies for preventing recurrent strokes. In the first arm of the study, the angiotensin-receptor blocker (ARB) telmisartan was compared to placebo in more than 20,000 patients with ischemic stroke. Patients were randomized to telmisartan 80 mg daily or placebo and followed for a mean follow-up of 2.5 years. Mean blood pressure was 3.8/2.0 mmHg lower in the telmisartan group; however, there was no difference in the rate of recurrent stroke (8.7% telmisartan vs 9.2% placebo [HR 0.95; 95% CI, 0.87 to 1.01; P = 0.11). The rate of new onset diabetes was 1.7% in the treatment group and 2.1% in the placebo group (P = 0.10). The authors conclude that therapy with telmisartan initiated soon after an ischemic stroke did not significantly lower the rate of recurrent stroke, diabetes, or major cardiovascular events. The second wing of the study compared aspirin plus 200 mg of extended release dipyridamole (Persantine®) twice daily vs clopidogrel (Plavix®) 75 mg daily in the same patient group. After a mean of 2.5 years of follow-up recurrent stroke occurred in 9% of patients receiving aspirin and dipyridamole and 8.8% of patients receiving clopidogrel (HR 1.01; 95% CI, 0.92 to 1.11). The secondary outcomes of stroke, myocardial infarction, or death from vascular causes occurred in 13.1% of both groups. The authors conclude that there is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke (*N Engl J Med*, published on-line at www.NEJM.org, Aug. 27, 2008).

FDA Actions

The FDA has issued a warning regarding the use of simvastatin in patients who are taking amiodarone. More than 20 mg of simvastatin plus amiodarone puts patient at higher risk for rhabdomyolysis since amiodarone inhibits CYP 3A4, one of the enzymes that metabolizes simvastatin. The simvastatin labeling has contained a warning regarding concomitant use with amiodarone since 2002; however, the FDA continues to receive reports of rhabdomyolysis associated with use of the two drugs. Physicians are also urged to tell their patients to report any unexplained muscle pain, tenderness, or weakness while taking the drugs. Other risks for rhabdomyolysis associated with statins include advanced age, uncontrolled hypothyroidism, and renal impairment.

There should be plenty of flu vaccine this fall. The FDA has announced the approval of six manufactures including GlaxoSmithKline, ID Biomedical, MedImmune, Novartis, Sanofi Pasteur, and CSL Limited. The vaccine will again be a trivalent vaccine comprised of two influenza A viruses and one influenza B virus. All three strains are new this year, an unusual occurrence as usually only one or two strains are updated each year.

The FDA issued an alert in October 2007 regarding exenatide (Byetta®) and the risk of acute pancreatitis. Since then, 6 more cases of hemorrhagic or necrotizing pancreatitis have been reported to the FDA associated with use of the drug, including two deaths. Exenatide is an injectable incretin mimetic used to treat type 2 diabetes. The FDA is recommending that exenatide should be stopped immediately if pancreatitis is suspected. Currently there is no patient profile which would predict increased risk of pancreatitis. Amylin Pharmaceuticals, the manufacture of exenatide, is working with the FDA on new labeling regarding the risk of hemorrhagic or necrotizing pancreatitis. ■