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INSIDE

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Brain Biopsies in Normal Pressure Hydrocephalus and the Subsequent Diagnosis of Alzheimer's Disease

ABSTRACT & COMMENTARY

By Michael Lin, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Many patients who are shunted for normal pressure hydrocephalus have Alzheimer's pathology, and many go on to develop Alzheimer's disease.*

Sources: Leinonen V, et al. Amyloid and tau proteins in cortical brain biopsy and Alzheimer's disease. *Ann Neurol* 2010;68:446-453.

Hamilton R, et al. Lack of shunt response in suspected idiopathic NPH with AD pathology. *Ann Neurol* 2010;68:535-540.

McKhann G, Mayeux R. Brain drain: A bottom-up approach to normal pressure hydrocephalus. *Ann Neurol* 2010;68:415-417.

A FRUSTRATING ASPECT OF DIAGNOSTIC CRITERIA FOR NEURODEGENERATIVE dementias is the lack of biological testing. For the most common dementia, Alzheimer's disease (AD), diagnosis is purely clinical, based on time course, severity, and memory-dominant cognitive profile. For the much rarer illness, normal pressure hydrocephalus (NPH), diagnosis is based primarily on the clinical triad involving gait, cognition, and bladder control, together with hydrocephalus on imaging. Laboratory testing based on the biology of disease currently is not part of diagnostic criteria for either illness. However, surgical treatment of suspected NPH affords the opportunity for brain biopsy, which then can be correlated with subsequent outcomes. Two articles[1,2] and an accompanying editorial[3] in the Oct. 2010 issue of *Annals of Neurology* consider such biopsies in suspected NPH, taken at the time of intraventricular pressure monitoring or shunt insertion, and the subsequent clinical diagnosis of AD.

The work by Leinonen and colleagues is the largest study to date of

brain biopsies and subsequent outcomes. Over 15 years, 433 patients with at least 1 symptom of NPH and hydrocephalus on imaging underwent intraventricular pressure monitoring at the Kuopio University Hospital in Finland, and were followed clinically for a median 4.4 years. Right frontal biopsies were obtained at the time of monitoring, and immunostained with antibodies against Aβ and hyper-phosphorylated tau (HPτ). Of the 433 patients, 10% were Aβ+/HPτ+, 33% were Aβ+/HPτ-, and 57% were Aβ-/HPτ- (a single Aβ-/HPτ+ case was excluded). Subsequent development of clinical AD occurred in 81% of the Aβ+/HPτ+ cases, 33% of the Aβ+/HPτ- cases, and 5% of the Aβ-/HPτ- cases. Substantial fractions of all groups also developed non-AD dementias or mild cognitive impairment. Thus, the presence of both Aβ and tau pathology strongly predicted development of AD (OR 68 vs. Aβ-/HPτ-). Aβ alone also significantly predicted subsequent AD but less strongly (OR 11 vs. Aβ-/HPτ-). Of note, shunting was still of benefit even in patients with AD pathology on biopsy. Patients in both Aβ+/HPτ+ and Aβ+/HPτ- groups were shunted based on ICP monitoring criteria not described, and 75% of patients in each group improved, including patients who subsequently developed clinical AD.

Hamilton and colleagues at the University of Pennsylvania studied a smaller group of 47 patients with at least 2 symptoms of NPH and hydrocephalus on imaging. All were shunted and underwent brain biopsy, and 30 were eventually followed. Patients with moderate to severe AD pathology on biopsy had significantly worse cognition than those without pathology, and only 2 of 8 patients with moderate to severe pathology were improved 4 months after shunting, compared to 18 of 22 patients with no or mild pathology.

■ COMMENTARY

That the presence of AD pathology correlates with subsequent diagnosis of AD clearly makes sense. At the same time, these studies also raise many questions. For one, not all cases with AD pathology subsequently developed clinical AD. Indeed, even at autopsy, AD pathology may be present without any cognitive impairment. It is possible that this phenomenon may be purely a matter of limited follow-up—given enough time all such patients might develop clinical symptoms. However, the question would then still remain, what factors allow some subjects to maintain cognition longer? Thus, even the ultimate biologic testing, brain biopsy, is limited by our understanding of disease biology. Our understanding of NPH is similarly limited, particularly with respect to predicting success from shunting. The study by Hamilton suggests that success is likelier in the absence of other explanatory pathologies; however, using physiologic criteria based on ICP monitoring, Leinonen found benefit independent of subsequent AD diagnosis.

These studies suggest that biological testing can improve both diagnosis and therapy. The next step in improving our understanding of these diseases is clearly to make aggressive, systematic use of newer methodologies, including CSF and brain Aβ and tau measurements and amyloid imaging, and to incorporate them into studies with long-term clinical follow-up. ■

References

1. Leinonen V, et al. Amyloid and tau proteins in cortical brain biopsy and Alzheimer's disease. *Ann Neurol 2010;*68:446-453.
2. Hamilton R, et al. Lack of shunt response in suspected idiopathic NPH with AD pathology. *Ann Neurol 2010;*68:535-540.
3. McKhann G, Mayeux R. Brain drain: A bottom-up approach to normal pressure hydrocephalus. *Ann Neurol 2010;*68:415-417.

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Primary Small-vessel Central Nervous System Vasculitis in Children

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 speaker's bureau for Boehringer Ingelheim and Merck.

Synopsis: *Brain biopsy is necessary to make the diagnosis of small-vessel primary angiitis of the central nervous system in children, prior to treatment with steroids and immunosuppressant medications.*

Source: Elbers J, et al. Brain biopsy in children with primary small-vessel central nervous system vasculitis. *Ann Neurol* 2010;68:602-10.

Hunder G, et al. Primary central nervous system vasculitis: Is it a single disease? *Ann Neurol* 2010;68:573-574.

Hutchinson C, et al. Treatment of small vessel primary CNS vasculitis in children: An open-label cohort study *Lancet Neurol* 2010;9; 1078-1084.

Friedman N. Small vessel childhood primary angiitis of the CNS: First steps toward a standardised treatment regimen. *Lancet Neurol* 2010;9;1042-1044.

PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM (PACNS) is an immune-mediated inflammatory process directed toward blood vessels of the CNS. The disease is recognized in adults, but also has been associated with variable clinical and radiological presentations, and devastating neurological consequences in children.

Elbers et al. characterized the clinical and histopathological features of brain biopsies, obtained through extended burr holes, in a total of 13 children (aged 5 to 17 years) with small-vessel PACNS of childhood (SVcPACNS) from 1998 to 2008 at a single center. Presenting features included seizures (85%), headache (62%), and cognitive decline (54%). Inflammatory markers were elevated in 12 of 13 children. All patients had some abnormality (e.g., increased opening pressure, pleocytosis, or increased protein) on CSF analysis. MRIs showed T2 hyperintensities in multiple or diffuse locations in most, but not all, scans; no scans showed restricted diffusion. All children with diagnostic biopsies had negative cerebral angiography, ruling out large vessel PACNS. Brain biopsy confirmed SVcPACNS in 11 patients with intramural lymphocytic infiltrate; two had only nonspecific perivascular inflammation. All 6 non-lesional biopsies from the non-dominant frontal lobe yielded a diagnosis of SVcPACNS. Lack of specific histological features correlated with prolonged time to biopsy, prior steroid treatment, and inadequate specimen sampling.

The authors concluded that in children presenting with new onset severe headaches, seizures, or cognitive decline, the diagnosis of SVcPACNS confirmed by a brain biopsy should be considered. Although non-lesional biopsies may succeed in yielding the diagnosis, lesional biopsies increase diagnostic accuracy. Steroid treatment prior to biopsy and inadequate biopsy sampling may obscure the diagnosis.

Hutchinson et al. evaluated a treatment protocol and described the long-term neurological outcomes in a single-center open-label cohort study of children with biopsy-proven SVcPACNS. Median age at diagnosis was 9.8 years (range 5.5–17.8 years) and median follow-up was 33 months (range 1–86 years). Induction therapy with steroids and pulses of intravenous cyclophosphamide was followed by maintenance therapy with either azathioprine or mycophenolate mofetil. Clinical and neurological assessments, quality-of-life measures, and laboratory markers were performed at baseline, 3, 6, 9, 12, 18, and 24 months, then yearly. Brain imaging was performed at baseline, 6, 12, 18, and 24 months. The pediatric stroke outcome measure (PSOM) score at 24 months measured neurological outcome. Of 19 children who met the inclusion criteria, 14 completed induction and received maintenance therapy with azathioprine (n = 9) or mycophenolate mofetil (n = 5). Of 13 patients who completed 24 months' follow-up, nine had a good neurological outcome by PSOM. Eight of 19 patients experienced disease flares. Four patients achieved remission of disease off medication.

The authors concluded that this treatment protocol of immunosuppressive therapy may improve long-term neurological outcome in children with SVcPACNS. Because of adverse events and neurological flares associated with azathioprine treatment, mycophenolate mofetil is the preferred maintenance medication. Appropriate diagnosis of children with this disorder is crucial because good neurological outcome may be achieved with standardized treatment.

■ COMMENTARY

These papers, and their accompanying editorials, emphasize that PACNS is a disease of any age, including children. Vasculitis involving small vessels of the CNS is difficult to diagnose with neuroimaging techniques or other non-invasive testing. Diffuse or multifocal MRI abnormalities, without clear foci of ischemia or infarction, overlap with other neurological disorders. Small vessel disease is usually angiographically negative. Spinal fluid is non-specific. Only brain biopsy can diagnose SVcPACNS, which appears to be a low-risk, but high-yield, procedure. Unfortunately, none of these pediatric cases was analyzed for vascular amyloid deposition which may be found on biopsy of PACNS in adults. While treatment with immunosuppressant medication in children (i.e., steroids and pulses of intravenous cyclophosphamide followed by maintenance therapy with mycophenolate mofetil) may have long-term consequences, the neurological damage of SVcPACNS warrants aggressive treatment and close follow-up. ■

Cyclosporine A for Duchenne Muscular Dystrophy

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: *Unfortunately, cyclosporine treatment had no effect on muscle power in children with Duchenne muscular dystrophy.*

Source: Kirschner J, Schessl J, Schara U, et al. Treatment of Duchenne muscular dystrophy with ciclosporin A: A randomised, double-blind, placebo-controlled multicentre trial. *Lancet Neurol* 2010;9:1053-1059.

DUCHENNE MUSCULAR DYSTROPHY (DMD), AN X-LINKED DISease affecting 1 in 3,500 newborn boys, causes progressive skeletal muscle weakness, cardiomyopathy, and ventilatory failure, resulting in wheelchair-dependence by age 12 years and death by age 35 years in virtually all. Glucocorticoids improve muscle strength and have extended the expected lifespan past 20 years, but side effects limit their long-term use. Might lifespan be improved by administering cyclosporine?

Between January 2004 and 2007, DMD ambulatory patients, 5 years of age or older, followed through the German Muscular Dystrophy Network, were recruited into a multicenter, randomized, double-blinded, placebo-controlled trial comparing 3 months of oral cyclosporine A (3.5–4.0 mg/kg per day) vs. placebo. Following 3 months of treatment, prednisone, 0.75 mg/kg, was added, administered orally in an alternating fashion, 10 days on, followed by 10 days off, for an additional 12 months. DMD diagnosis was based on the clinical picture, elevated serum creatine kinase level, and results of muscle biopsy or genetic testing. Patients were excluded if they were previously treated with steroids, or had received clenbuterol or other sympathomimetics in the previous 3 months. Outcome measures, performed at baseline and at months 3, 9, and 15, included manual muscle testing as measured by the extended version of the Medical Research Council (MRC) score, and quantitative muscle testing using the Citec handheld dynamometer. Functional outcome measures included the time to stand up from a supine position, and the time to walk 10 m independently. Statistical analysis used a linear regression model with baseline value, treatment group, age, and trial site as covariates, and an additional posthoc supportive analysis, using a mixed regression model. Kaplan-Meier estimation and log-rank tests, and Cox proportional hazards regression models were applied where indicated. Though Novartis Pharma AG provided funding, they played no role in study design, data collection, analysis, or interpretation, or in writing the paper.

Among 77 patients who received cyclosporine A and 76 placebo patients, no improvement in muscle strength was appreciated in the treatment group over placebo. Nor did the addition of intermittent prednisone to cyclosporine for 1 year prove beneficial. None of the outcome measures was shown to be significantly different between treatment groups. Adverse events were seen in the same frequency in both groups. Cyclosporine A is safe but provides no tangible clinical benefit in DMD.

■ **COMMENTARY**

Focusing on cardiac function may provide an alternate avenue for improving life expectancy in DMD. Usually evident after the first decade, the incidence of conduction defects, and dilated and hypertrophic cardiomyopathy, increases with age, as do arrhythmias including atrial flutter, frequent premature atrial and ventricular beats, and ventricular arrhythmias, which itself may be a risk factor for sudden death. Up to 20% of DMD patients experience a cardiac death, a number expected to rise as respiratory complications are being more successfully managed. ACE inhibitors delay the onset and progression of ventricular dysfunction and, in the DMD mouse model, appear to bulk up muscle. Research in this direction is clearly warranted. ■

Lacosamide as Adjunctive Therapy in Nonconvulsive Status Epilepticus

ABSTRACT & COMMENTARY

By Padmaja Kandula, MD

Assistant Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Medical College of Cornell University

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

Synopsis: *The authors report a small, retrospective case series using low-dose intravenous lacosamide in the successful, adjunctive treatment of nonconvulsive status epilepticus.*

Sources: Koubeissi MZ, et al. Efficacy and safety of intravenous lacosamide in refractory nonconvulsive status epilepticus. *Acta Neurol Scand* DOI: 10.1111/j.1600-0404.2010.01430.x _ 2010.

Although overt convulsive status epilepticus has deservedly received wide spread attention due to systemic complications, nonconvulsive status epilepticus (NCSE) has become increasingly recognized in both comatose and noncomatose patients. As such, the ideal medication for nonconvulsive status should be intravenous, relatively free of drug interactions, and non-sedating. Lacosamide, already approved for adjunctive partial seizures in adults, meets the above three criteria, suggesting a potential role in the treatment of nonconvulsive status.

The authors of this paper report on their experience with intravenous lacosamide in the treatment of NCSE. The records of all patients with refractory nonconvulsive status epilepticus were reviewed at University Hospitals Case Medical Center (Cleveland). Four patients were identified who were treated with lacosamide and underwent continuous video EEG monitoring. EEG traces were blindly reviewed to confirm onset and offset of nonconvulsive status. Both general and neurologic examinations were performed before and after administration of intravenous lacosamide. All four patients were found to have medically resistant focal NCSE despite treatment with varying doses and combinations of lorazepam, levetiracetam, fosphenytoin, and enteral pregabalin. Intravenous lacosamide was administered between 3 and 50 hours after known diagnosis of NCSE. Side effects were recorded by patient-reported diary. Pre- and post-PR intervals were calculated after infusion of lacosamide.

Patient #1 presented with new onset prolonged convulsion and subsequent depressed mental status despite 2 mg of lorazepam and 1,000 mg fosphenytoin. Continuous electroencephalographic recording (cEEG) revealed nearly continuous left hemispheric ictal activity. An additional 2 g of levetiracetam and enteric 300 mg pregabalin were administered. Ictal activity persisted nearly 24 hours later, prompting intravenous infusion with low-dose (50 mg) lacosamide. There was electrographic cessation of ictal activity nearly 30 minutes after intravenous infusion. The patient returned to baseline neurologic status with eventual 100 mg twice daily maintenance dosing of lacosamide. No seizure recurrence occurred during subsequent 48 hour cEEG recoring.

Patient #2 presented with new onset symptomatic right hemispheric seizures in the setting of an acute right subdural hemorrhage. Two milligrams of lorazepam and three grams of intravenous levetiracetam were administered without seizure cessation. Subsequently, 100 mg of iv lacosamide was infused with reduction of electrographic seizures from 5 per hour to 1 every 2 hours. Intravenous maintenance lacosamide was escalated to 200 mg twice daily with improvement in seizure frequency to 3 per day.

Patient #3 presented initially with new onset seizures and electroclinical correlate in the setting of atypical recurrent right fronto-parietal meningioma. Seizures were characterized initially by focal facial clonic movements, vocalizations, and excessive salivation. Low-dose levetiracetam was initiated at 500 mg twice daily. Electroclinical seizures were replaced with electrographic seizures (recorded on cEEG) without clinical correlate from the right frontocentral region. Ictal activity persisted despite 4 mg of intravenous lorazepam and further escalation of levetiracetam to 4 grams per day. After a 15-minute infusion of 100 mg of intravenous lacosamide, complete cessation of ictal activity was noted.

Patient #4 presented with left hemibody clonic movements in the setting of a remote right sided hemorrhagic stroke. The patient was given rapid sequence lorazepam (6 mg), followed by fosphenytoin load, and increase in maintenance levetiracetam. Intravenous lacosamide was added after failure to control seizures, with cessation of ictal events within 2 hours of intravenous lacosamide infusion. The patient remained seizure-free on adjunctive maintenance lacosamide of 100 mg bid.

■ COMMENTARY

Similar to levetiracetam, lacosamide is relatively free of drug interactions and has a good safety profile, both useful qualities in treating critically ill patients in a timely fashion. Although the preliminary experience of these

authors is optimistic, only patient #4 truly met criteria for refractory partial non-convulsive status. Patients #1 and #2 received suboptimal benzodiazepine therapy. Patients #2 and #3 received subsequent levetiracetam, instead of the usual hydantoin load after benzodiazepine treatment.

Despite the obvious small numbers in this retrospective clinical case series, it is interesting that sustained cessation of ictal activity occurred in all 4 patients with a modest dose of lacosamide, suggesting that agents with different mechanisms of action may be useful in combating partial status. There is accumulating evidence at the receptor level that as time marches on, GABAergic mechanisms fail and seizures become drug-resistant, further emphasizing the waning utility of benzodiazepine effectiveness at the $GABA_A$ receptor over time.

Further large-scale studies are needed to define lacosamide's role in nonconvulsive status epilepticus. Lacosamide, with a novel mechanism of action and favorable pharmacokinetics, potentially may be useful in nonconvulsive status, particularly where it is desirable to avoid mechanical intubation. ■

Excessive Sleepiness and Narcolepsy: Clues from Genetics and Polysomnography

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical Center

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

Synopsis: *The accurate diagnosis of narcolepsy requires detailed history as well as physiological and genetic testing.*

Source: Morrison I, et. al. Diagnosing narcolepsy with cataplexy on history alone: Challenging the International Classification of Sleep Disorders (ICSD-2) criteria. *European J Neurol* 2010 doi:10.1111/j.1468-1331.2010.03223.x. Goel N, et. al. DQB1*0602 predicts interindividual differences in physiologic sleep, sleepiness, and fatigue. *Neurology* 2010;75:1509-1519.

A CLINICAL DIAGNOSIS OF NARCOLEPSY IS MADE BASED ON a history of excessive daytime somnolence (EDS), sleep paralysis, and hypnagogic hallucinations. Given these features, narcolepsy then can be categorized into two groups based on the presence or absence of cataplexy. This categorization has important implications in terms of making a definitive diagnosis. If cataplexy is absent, then a sleep study—overnight polysomnogram (PSG) followed by a multiple sleep latency test (MSLT)—is required to confirm a diagnosis. In contrast, when cataplexy is present, the International Classification of Sleep Disorder (ICSD-2) allows for the diagnosis of narcolepsy without further study and states that a PSG and MSLT "should whenever possible" be performed.

There is considerable overlap between the symptoms described by narcoleptics and normal people. Sleep paralysis can be present as an isolated parasomnia and EDS can be multifactorial in nature, most prominently occurring as a result of unrecognized sleep disordered breathing. More importantly, the diagnosis of narcolepsy carries important implications in terms of treatment, most notably being long term therapy with amphetamines. These drugs carry the potential for abuse, or may be desirable as performance enhancers in otherwise normal people. There is the potential to "fake" cataplexy, with drop attacks occurring on a volitional basis.

The present study by Morrison et al., an extended case series, examined five individuals previously diagnosed with narcolepsy with cataplexy. Three cases were diagnosed by a primary care physician and two by a neurologist. None had prior sleep studies. When formally studied, no subject had an MSLT diagnostic of narcolepsy. One patient attempted to simulate rapid eye movement sleep (REM) by rolling her eyes. Three of five patients refused to accept that they were not narcoleptic. One patient did admit to "embellishing her history." As the authors note, while a constellation of spells of transient muscle weakness precipitated by emotion, EDS, vivid dreams, and hallucinations around sleep are compelling features in making a diagnosis of narcolepsy, data from PSG and MSLT can contradict the clinical picture. Furthermore, all five cases were studied genetically as well and none had the HLA DQB1*0602 allele. While this allele can be absent in 30%-50% of cases of narcolepsy without cataplexy, it should be positive in nearly 100% of patients with classic narcolepsy and cataplexy. As the authors note, measurement of CSF hypocretin levels (not done here) could provide additional diagnostic clarification.

In the second study referenced here, Goel et al examine whether DQB1*0602 status in a set of normal subjects, without a sleep disorders diagnosis, is correlated with sleep, subjective reports, and neurobehavioral measures. There were 92 DQB1*0602 negative and 37 DQB1*0602 positive subjects. Each subject was studied for two 10-hour baseline nights, followed by a Partial Sleep Deprivation (PSD) paradigm of 5 nights, with only 4 hours of total time in bed.

DQB1*0602 positive subjects were subjectively sleepier and more fatigued at baseline. On an objective test of sleepiness (the ability to resist sleep),

however, DQB1*0602 positive subjects did not differ from DQB1*0602 negative subjects. The authors used spectral analysis of EEG to average delta activity across the night, defined as slow wave energy (SWE). This SWE can be understood as an overall homeostatic pressure to sleep. This SWE was lower in the positive subjects, although this was not a consistent finding in all EEG leads. SWE would be expected to decline over the course of the night, as sleep is accrued. This decline was seen in both groups, but was more prominent in positive subjects. Following PSD, both positive and negative subjects demonstrated a comparably greater sleep drive (increased SWE during the night), but positive subjects still had higher subjective reports of sleepiness and fatigue. Cognitive performance declined in both groups due to sleep deprivation and was not more severe in positive subjects.

During PSD, DQB1*0602 subjects showed a greater decrease in REM sleep latency compared to negative subjects. This tendency toward a shortened REM sleep latency, while not equivalent to the sleep onset REM seen in narcoleptics, may represent a suggestion of a shared trait between these DQB1*0602 subjects and narcoleptic patients.

■ COMMENTARY

Although all differences were not statistically significant, in general, the quality of sleep achieved by DQB1*0602 positive subjects overall was poorer, with difficulty staying asleep (more awakenings and wake after sleep onset) and less stage 3 sleep on PSG, during baseline and PSD. These data suggest that the DQB1*0602 positivity in normal subjects may be a marker for reduced homeostatic sleep pressure during sleep as well as associated with some features of narcolepsy, such as fragmentation of sleep architecture and a complaint of excessive daytime sleepiness. These data are suggestive that DQB1*0602 positivity may identify a subset of individuals who are not infrequently encountered in clinical practice—people who are sleepy during the day and complain of wakefulness at night.

The studies of Morrison and Goel, while very different in their subject populations and methodology, emphasize that accurate diagnosis of sleep disorders requires a combination of detailed and extensive history taking, neurophysiological study (polysomnography), and adjunctive testing such as the use of genetic markers or possibly hormone levels. ■

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

- 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.

CME Questions

33. All of the following are true regarding dementia *except*:

a. NPH and Alzheimer's disease may coexist.

b. In biopsies taken at time of shunting, about 40% of NPH patients have some Alzheimer's pathology.

c. Most patients with Alzheimer's pathology develop Alzheimer's disease.

d. All patients with Alzheimer's pathology develop Alzheimer's disease.

34. Primary small-vessel central nervous system vasculitis in children and adolescents:

a. can be diagnosed based on its characteristic appearance on cerebral angiography.

b. should be treated with azathioprine for maintenance therapy.

c. has a uniformly poor neurological prognosis even with appropriate treatment.

d. rarely can be diagnosed by a non-lesional brain biopsy.

e. should be diagnosed by brain biopsy prior to treatment with intravenous steroids.

35. In Duchenne muscular dystrophy, cyclosporine A treatment:

a. improves strength better than placebo.

b. prolongs life better than placebo.

c. improves strength better than placebo when added to prednisone.

d. carries a significant risk of side effects, making it contraindicated despite its benefits.

e. appears to be of no clinical benefit over placebo.

36. Lacosamide has been proven to be efficacious in the treatment of status epilepticus.

a. True

b. False

37. Which of the following statements about narcolepsy is *not* correct?

a. Clinical criteria include excessive daytime sleepiness, sleep paralysis, and hypnagogic hallucinations.

b. Narcolepsy may occur with or without cataplexy.

c. Patients who have narcolepsy with cataplexy carry the DQB1*0602 gene.

d. Polysomnography is not needed to make a narcolepsy diagnosis.

e. Patients may pretend to have narcolepsy as part of drug-seeking behaviors.

38. Dabigatran, in a comparative randomized clinical trial with warfarin, failed to reduce stroke incidence in patients with atrial fibrillation.

a. True

b. False

39. Carotid endarterectomy in asymptomatic patients has a modest benefit and should only be performed with low perioperative risk.

a. True

b. False

Answers: 33. d, 34. e, 35. e, 36. b, 37. d, 38. b, 39. a.

Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, *MD, Interim Chair and Neurologist-in-Chief, Director, Division of Stroke & Critical Care Neurology, Weill Cornell Medical College and New York Presbyterian Hospital*

Predicting Risk of Perioperative Death or Stroke After Carotid Endarterectomy in Asymptomatic Patients

Source: Calvillo-King, L, et.al. Predicting risk of perioperative death and stroke after carotid endarterectomy in asymptomatic patients: Derivation and validation of a clinical risk score. *Stroke* 2010;41:2786-2794.

Three quarters of the 117,000 carotid endarterectomies (CEA) performed in the United States every year are in patients who are asymptomatic. The benefits are small, and randomized trials have shown that CEA reduced the absolute risk of stroke or death by about 6% over 5 years. Therefore, current guidelines state that CEA should be performed on an asymptomatic patient only if the operative risk is less than 3%. The investigators set out to identify preoperative risk factors that would allow prediction of surgical risk, by reviewing 6,553 asymptomatic Medicare beneficiaries in New York State who underwent CEA. The following eight items were significant multivariable predictors of perioperative events and formed the basis of a "CEA-8 Clinical Risk Score": (1) female sex (OR = 1.8), (2) nonwhite race (OR = 1.8), (3) severe disability (OR = 3.7), (4) congestive heart failure (OR = 1.6), (5) coronary artery disease (OR = 1.6), (6) valvular heart disease (OR = 1.5), (7) history of prior stroke or TIA, and (8) nonoperated carotid stenosis > 50% (OR = 1.8). The combined score stratified patients with a risk of stroke or death from 0.6% to 9.6%. ■

Dabigatran Is as Effective as Warfarin in Preventing Stroke in Patients with Atrial Fibrillation

Source: Diener HC, et. al. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurology* 2010;9:1157-1164.

In the randomised evaluation of long-term anticoagulation Therapy (RE-LY) trial, dabigatran reduced the occurrence of both stroke and hemorrhage, compared to warfarin, in 18,113 patients with atrial fibrillation. In this subgroup analysis of patients who had a previous stroke or TIA, the investigators followed 1,195 patients who were in the 110 mg dabigatran group, and 1,233 patients who were in the 150 mg dabigatran group for a median duration of 2.0 years (IQR 1.14–2.86). Stroke or systemic embolism occurred in 65 patients (2.78% per year) on warfarin compared with 55 patients (2.32% per year) on 110 mg dabigatran (RR = 0.84) and 51 patients (2.07% per year) on 150 mg dabigatran (RR = 0.75). The rate of major bleeding was significantly lower on the 110 mg dose of dabigatran, and similar on the 150 mg dose, when compared to warfarin. The effects of dabigatran compared to warfarin were not significantly different between patients who had previous stroke or TIA and the other patients in the RE-LY trial. ■

In Future Issues:

The Lastest in Parkinson's Disease

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, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Have people with HTN reduced salt intake?

Source: Ayala C, et al. Actions taken to reduce sodium intake among adults with self-reported hypertension. *J Clin Hypertens* 2010;12:793-799.

The most recent advice from the U.S. Department of Agriculture (2005) recommends that the general population of adults not consume > 2300 mg/day of sodium, and that persons with hypertension (HTN) consume ≤ 1500 mg/day. In contrast to these recommendations, NHANES data from 2005-2006 indicate that U.S. adults consume essentially 1.5 times the recommended ceiling. One would hope that with all the health information available to consumers that persons with HTN would be particularly attuned to restricting their sodium intake, especially as awareness and treatment of HTN have increased over the last two decades.

The HealthStyles survey is sent annually to thousands of randomly selected homes in the United States by an international research organization. Surveys in 2005 (n = 6168) and 2008 (n = 7000) from non-pregnant adults who self-identified as hypertensive and also as having received advice from their clinician to reduce salt intake were analyzed for responses to questions about their sodium habits.

Over the 3-year interval, the percentage of adults who reported reading food labels increased from 49.1% to 53.0%; persons who reduced the amount of sodium in their diet increased from 48.3% to 56.6%. Overall, women more often read food labels than men, and blacks more often than Hispanics or whites.

Lifestyle intervention can have a meaningful impact on an individual- or population-wide basis. Although it is encouraging to note that a majority of adults with HTN currently do read food labels for sodium content, and have reduced their sodium intake, there remains much room for more widespread adoption of such potentially healthful habits. ■

The P450 system and CV outcomes with clopidogrel

Source: Pare G, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *N Engl J Med* 2010;363:1704-1714.

A great deal of controversy has surrounded the clinical relevance of the P450 system and efficacy of clopidogrel. The basic story line is as follows: To reduce CV events in persons with atrial fibrillation or post-ACS, clopidogrel must reduce platelet aggregation. This inhibition of platelet aggregation (IPA) is dependent not upon clopidogrel itself, but on a metabolite of clopidogrel, which is generated through the CYP2C19 pathway. In vitro, it is clear that genetic variations in CYP2C19 activity can impact IPA: Loss-of-function genetic alleles have been shown to produce reduced IPA in vitro. Similarly, things that block activity of the CYP2C19 system also reduce IPA in vitro. End of story? Not so fast.

Initial retrospective studies reported a concerning increase in events in person on clopidogrel who were concomitantly receiving CYP2C19-inhibiting proton pump inhibitors. Two subsequent prospective analyses, however, failed to demonstrate reduced efficacy when clopidogrel and PPI were used concomitantly.

This study compared CV outcomes in post-ACS or atrial fibrillation subjects (total n = 5059) who had undergone genetic testing and been found to have a variety of genetic CYP2C19 loss-of-function variants. No meaningful impact of CYP2C19 genotype upon CV outcomes (or bleeding risk) was found.

For the time being, use of CYP2C19 genotyping does not seem to help us decide how to better provide IPA for our patients. Whether this reflects inaccuracy of currently available testing methods, recognition that other forces are at play beyond simple aggregation of platelets, or other as-yet undefined issues remains to be determined. ■

Risk assessment for bleeding during warfarin therapy

Source: Pisters R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation. *Chest* 2010;138:1093-1100.

The CHADS2 score has proven to be very useful in stratifying risk of stroke for patients with atrial fibrillation (AF). The risk reduction for stroke provided by warfarin anticoagulation in AF is about 66%. Yet, at lower baseline risks (e.g., CHADS2 score 0-1), the risk of bleeding starts to counterbalance stroke risk reduction. To date, there has been no comparably simple tool to predict risk of bleeding while on warfarin.

HAS-BLED incorporates seven readily available risk factors to predict bleeding risk from warfarin in persons with AF with the following number of points: hypertension (1 point), abnormal renal/hepatic

function (1 point each), stroke (1 point), bleeding history/diathesis (1 point), labile INR (1 point), elderly > 65 (1 point), and drugs/alcohol use (1 point each). Whenever the HAS-BLED score is greater than the CHADS score, bleeding risk may outweigh clinical benefit. Clinicians may want to consider refining their bleeding risk prediction for patients with potential indications for warfarin based upon the HAS-BLED stratification tool. ■

Coenzyme Q10 for Peyronie's disease

Source: Safarinejad MR. Safety and efficacy of coenzyme Q10 supplementation in early chronic Peyronie's disease. *Int J Impot Res* 2010;22:298-309.

Peyronie's disease is an uncommon penile fibrotic disorder that most commonly affects young and middle-aged men. It is characterized by pain, deformity, or decreased capacity for intromission as a result of penile angulation. In contrast to chordee, the congenital abnormality in which ventral penile tissue defects prevent full expansion of the underside of the penis, resulting in a downward curvature upon erection, Peyronie's disease is an acquired fibrosis of the penis, which results in thickened penile plaques that prevent full erection. In whatever area of the penis such fibrotic plaques occur, that area will be unable to achieve full dilation and erection, resulting in angulation of the penis. There is no uniformly effective treatment for Peyronie's disease, although surgical correction is often effective.

Fibrotic plaque analysis in Peyronie's disease has demonstrated early oxidative inflammation, followed by creation of fibrotic scar. Since coenzyme Q10 has been shown to have antioxidant capacity, a clinical trial of its efficacy in early Peyronie's was intuitively appealing.

Men with early Peyronie's disease (n = 186) were randomized to coenzyme Q10 300 mg/day or placebo for 24 weeks. At trial end, there was a statistically significant reduction in plaque size, penile curvature, and improvement in sexual function in the active treatment group. Because coenzyme Q10 is a very well tolerated intervention with no known serious adverse effects (there were no reported drug-related adverse events or discontinuations), it offers a promising alternative for persons with Peyronie's disease. ■

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Impact of using A1c to diagnose pre-diabetes

Source: Mann DM, et al. Impact of A1c screening criterion on the diagnosis of pre-diabetes among U.S. adults. *Diabetes Care* 2010;33:2190-2195.

The dramatic increase in type 2 diabetes (DM2) seen in the last decade is predictably going to become even more evident: Although 24 million Americans currently have DM2, more than twice as many have pre-diabetes (p-DM2). Historically, persons with p-DM2 who are untreated progress to frank DM2 at a rate of 7%-10% per year.

Until 2010, p-DM2 was diagnosed based upon the presence of either impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both. Since 2010, the ADA has indicated that an A1c of 5.7%-6.4% qualifies as p-DM2. This tool has been welcomed by the primary care community because it does not require fasting, and can be obtained during any routine office visit. The limitation of A1c, however, is that it does not necessarily capture all the persons who would have been identified had either a fasting blood glucose or postprandial glucose (or both) been obtained; data from NHANES indicate that a substantial number of persons with IFG will not have an abnormal A1c, and vice versa. For instance, of 51.7 million NHANES subjects with IFG, only 23 million have an A1c that meets p-DM2 criteria.

All of the diagnostic markers for p-DM2 are used in an effort to identify the pathophysiologic derangements at a point in time where intervention might change disease progression. IFG, IGT, and A1c identify overlapping, but not identical, populations. Because clinicians will commonly have access to fasting glucose levels obtained concomitantly with other labs (e.g., CMP), it appears that few cases of p-DM2 will be missed by utilizing an A1c measurement. ■

Should tiotropium be a maintenance asthma medication?

Source: Peters SP, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010; 363:1715-1726.

Traditional maintenance pharmacotherapy for persistent asthma includes inhaled corticosteroids (ICS), leukotriene modulators, and—when used concomitantly with ICS—long-acting beta agonists (LABA). Except for the acute care setting, anticholinergic treatment, like tiotropium (TIO) has been generally thought of as a treatment for COPD rather than asthma.

Peters et al performed a double-blind, crossover trial in asthmatics (n = 210) who were poorly controlled on ICS alone. As add-on treatment, patients were randomized to tiotropium (ICS + TIO), the long-acting beta agonist salmeterol (ICS + LABA), or a doubling of ICS (ICS + ICS).

ICS + TIO was found to be superior to ICS + ICS for morning peak expiratory flow (the primary endpoint of the trial). ICS + TIO was demonstrated to be noninferior to ICS + LABA for morning peak expiratory flow, prebronchodilator FEV1, and proportion of asthma-control days (the secondary endpoint of the trial). These results support the consideration of TIO as a maintenance medication for asthma when used in conjunction with ICS. Because the study duration was brief (14 weeks), the durability of anticholinergic treatment for asthma—for instance, is TIO useful in preventing asthma exacerbations?—remains to be determined. ■

PHARMACOLOGY WATCH

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

Rivaroxaban: Another Warfarin Replacement

In this issue: Rivaroxaban may be dabigatran's first competitor; a new way to measure non-adherence to medication therapy; FDA Actions.

Another Warfarin Replacement on Horizon

Just as Boehringer Ingelheim begins marketing dabigatran (Pradaxa®) as a replacement for warfarin, a competitor drug may be on the horizon. As reported at the American Heart Association (AHA) meetings in November, rivaroxaban, an oral drug factor Xa inhibitor, is as effective as warfarin at preventing stroke and blood clots in patients with nonvalvular atrial fibrillation.

The ROCKET AF study (Stroke Prevention Using the Oral Direct Factor Xa Inhibitor Rivaroxaban Compared With Warfarin in Patients with Nonvalvular Atrial Fibrillation) looked at more than 14,000 patients with atrial fibrillation. Patients were randomized to warfarin or rivaroxaban (20 mg/day). The time in therapeutic range for warfarin was 57.8%. With a primary endpoint of stroke and non-CNS systemic embolism, rivaroxaban was associated with a rate of 1.71 events per 100 patient-years vs 2.16 for warfarin (P = 0.015 for superiority and P < 0.001 for non-inferiority). On an intention to treat (ITT) basis, event rates were 2.12 for rivaroxaban vs 2.42 for warfarin (P = 0.117). There were 55 intracranial bleeds with rivaroxaban compared with 84 with warfarin (P = 0.019). Rivaroxiban also showed numerically fewer MIs (0.91 vs 1.12 per 100 person-years; P = 0.12). All-cause mortality was 1.87 in the rivaroxaban group vs 2.21 in the warfarin group (P = 0.073). In the ITT analysis, mortality was 4.52 vs 4.91 (P = 0.152), respectively.

This study (presented at the American Heart Association Scientific Sessions; Chicago, IL; Nov. 15, 2010) was the seventh Phase III trial in the development of rivaroxaban, with other studies evaluating the drug for prevention and treatment of venous thromboembolism, indications that Bayer and Johnson & Johnson have already filed with the FDA. It is also expected that a new drug application will be filed soon for the prevention of stroke in patients with nonvalvular atrial fibrillation. Like dabigatran, rivaroxaban requires no monitoring and has few drug interactions. Rivaroxaban has the advantage of being dosed once a day compared to twice-daily dosing for dabigatran. ■

Non-adherence: A New Way to Measure

A new study examines drug adherence in an interesting way — by looking at the rate of prescriptions abandoned at the pharmacy. Traditional non-adherence studies have looked at refill rates, pill counting, and patient reports of medication use. But prescriptions abandoned at the pharmacy represent a potential opportunity to intervene and improve adherence at the very onset of the prescribing process.

Researchers used the CVS pharmacy database to evaluate more than 10 million prescriptions

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filled by more than 5 million patients. The overall abandonment rate was 3.27%, although nearly half of those were eventually filled by the same drug or a similar drug within 30 days. Not surprisingly, patients were least likely to abandon opiate prescriptions, and were most likely to abandon expensive prescriptions. Prescriptions with a copayment of $40-$50 and those with a copayment of more than $50 were 3.4 times and 4.68 times more likely to be abandoned, respectively, than prescriptions with no copayment ($P <$ 0.001 for both comparisons). New users of medications were more likely to abandon prescriptions than prevalent users, and prescriptions that were delivered to the pharmacy electronically were 1.64 times more likely to be abandoned than those that were not electronic ($P < 0.001$); however, they were unable to determine whether written prescriptions were never delivered to the pharmacy by patients.

The authors concluded that prescription abandonment represents an important opportunity to intervene and improve adherence (*Ann Intern Med* 2010;153:633-640). An accompanying editorial points out that the rate of abandonment in this study was actually quite low. Others studies have suggested that 17%-20% of patients do not pick up new prescriptions, and 8% of patients' prescriptions are denied by health plans. Physicians and pharmacists are urged to remain mindful that costs are an important barrier to adherence and that lower cost alternatives should be prescribed "whenever feasible" (*Ann Intern Med* 2010;153:680-681). ■

FDA Actions

The FDA has asked the manufacturers of propoxyphene-containing pain medications (Darvon®, Darvocet®, and generics) to withdraw them from the market. The withdrawal is based on new data showing the drugs are associated with serious and fatal heart arrhythmias. Health care professionals are advised to stop prescribing propoxyphene and patients are asked to contact their health care providers to discuss switching to other pain medications. Propoxyphene has been the target of consumer groups for more than 30 years because of evidence of poor efficacy in treating pain and a high level of side effects including falls. ■

The FDA has approved duloxetine (Cymbalta®) for the treatment of chronic musculoskeletal pain. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, was previously approved for treating depression, generalized anxiety disorder, diabetic neuropathy, and fibromyalgia. The new indication for musculoskeletal pain includes low back pain and osteoarthritis. The expanded indication was based on the results of four double-blind, placebo-controlled trials, which showed that patients treated with duloxetine had significantly greater pain reduction than those patients treated with placebo. Duloxetine is marketed by Eli Lilly and Company. ■

The FDA has approved lurasidone for the treatment of schizophrenia in adults. The drug is classified as an atypical antipsychotic, and like other drugs in this class, carries a boxed warning regarding an increased risk of death associated with off-label use to treat behavioral problems in older adults with dementia. Common adverse reactions include drowsiness, feelings of restlessness, nausea, agitation, and Parkinsonian symptoms such as bradykinesia, tremor, and muscle stiffness. Lurasidone will be marketed by Sunovion Pharmaceuticals as Latuda™. ■

The FDA has approved a new injectable cephalosporin, ceftaroline, to treat community-acquired bacterial pneumonia (CABP) and bacterial skin infections, including those caused by methicillin-resistant *Staphylococcus aureus*. Ceftaroline was approved based on data from four studies that showed the drug to be as effective as ceftriaxone for the treatment of CABP and as effective as vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections. The recommended dose for patients with normal renal function is 600 mg given as a one-hour IV infusion every 12 hours. Ceftaroline is marketed by Forest Laboratories as Telflaro™. ■

The FDA's Vaccines and Related Biological Products Advisory Committee has recommended an expanded indication for Gardasil®, Merck's quadravalent human papillomavirus vaccine to prevent anal intraepithelial neoplasia and anal cancer in males and females ages 9-26. The approval was based on a phase III double-blind, placebo-controlled trial in which more than 4000 males were randomized to receive the three-dose vaccine or placebo. There was a significant reduction in the rate of anal intraepithelial neoplasia or anal cancer, especially in men who have sex with men. The vaccine is already approved for prevention of genital warts and cervical, vulvar, and vaginal cancer in females ages 9-26 and prevention of genital warts in males ages 9-26. ■

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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.

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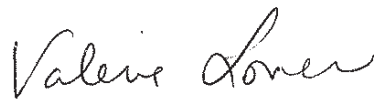

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