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INSIDE

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Bacterial Meningitis: Rarer, in Older Patients, but Equally Deadly

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Safdieh reports no financial relationships to this field of study.

Synopsis: *With the advent of new vaccines, the incidence of bacterial meningitis has declined, particularly in children, but the mortality rate has remained the same.*

Source: Thigpen MC, et al. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med* 2011;364:2016-2025.

BACTERIAL MENINGITIS IS A FEARED MEDICAL ILLNESS THAT HAS A HIGH MORbidity and mortality rate. Meningitis can present at any age group, although the predominant pathogenic organisms do vary by age. Prior studies in the 1970s and 1980s have demonstrated that the most common causes of sporadic community-acquired bacterial meningitis in the United States are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, group B streptococcus (GBS), and *Listeria monocytogenes*. The introduction of the Hib vaccine reduced the overall incidence of bacterial meningitis by 55% by 1995. The authors of this study analyzed incidence patterns of bacterial meningitis in the United States from 1998-2007. A number of public health changes were introduced during the study period, including a meningococcal vaccine, a pneumococcal vaccine, and routine screening of pregnant women for GBS.

Coordinated by the CDC, the study authors reviewed a prospectively collected cohort of cases of bacterial meningitis in an infectious disease surveillance program at a number of geographically dispersed clinical sites, which included almost 8% of the United States population. Only cases of meningitis caused by one of the five organisms listed above were included in the study. The cases through the study period (1998-2007) were analyzed for trends and a latter portion of the group (2003-2007) was also analyzed for detailed epidemiology.

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For the study period, 3188 cases of bacterial meningitis were identified with a mortality rate of 14.8%. The incidence of bacterial meningitis significantly decreased by 31% from the beginning to the end of the surveillance period (2 cases per 100,000 in 1998-1999 down to 1.38 cases per 100,000 in 2006-2007). The median age of patients significantly increased from the beginning to the end of the study period, from 30.3 years to 41.9 years. The overall case fatality rate over the study period remained unchanged. The most common organisms from 2003-2007 were *S. pneumoniae* (58%), GBS (18.1%), *N. meningitidis* (13.9%), *H. influenzae* (6.7%), and *L. monocytogenes* (6.7%). Through the study period, there were 4100 average annual cases of bacterial meningitis in the United States, with 500 annual deaths.

Rates of bacterial meningitis decreased most dramatically among children, causing the median age to rise. Overall, the pathogen with the most dramatic decrease over the study period was *S. pneumoniae*, which the authors suggest is due to pneumococcal vaccination. Of note, the rate of meningitis in children under age 2 months did not decrease, suggesting that GBS surveillance and treatment does not prevent late-onset disease, manifested as meningitis. *L. monocytogenes* did decrease in infants, which correlates with lower rates of maternal listeriosis, likely due to better education and a safer food supply.

■ COMMENTARY

This study demonstrates a number of important points. Bacterial meningitis is certainly becoming rarer over time, due to vaccination as well as better public health measures. Because of the overwhelming success of pediatric vaccines in preventing meningitis, the median age of bacterial meningitis is increasing. It is worth noting that the absolute incidence of bacterial meningitis did decrease in adults older than age 65 in the study period, but not as dramatically as in children. Although bacterial meningitis is less common now than it was in the past, the mortality rate remains unchanged. This is even more important to remember in the setting of declining incidences, as younger physicians may not see as many cases in training and therefore may fail to recognize and rapidly treat patients with meningitis. There is more work to be done, including widespread adoption of the adult pneumococcal vaccine. However, it is certainly encouraging to see the profound positive effects that can occur as a result of public health policies. ■

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Please call **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

Variant Creutzfeldt-Jakob Disease: A Review of 150 Cases

ABSTRACT & COMMENTARY

By John J. Caronna, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Variant Creutzfeldt-Jakob disease usually presents with subtle psychiatric symptoms and there is usually a significant delay in diagnosis.*

Source: Heath CA, et al. Diagnosing variant Creutzfeldt-Jakob disease: A retrospective analysis of the first 150 cases in the U.K. *J Neurol Neurosurg Psychiatry* 2011;82:646-651

In the mid-1990s, variant Creutzfeldt-Jakob disease (vCJD) was recognized as an example of bovine-to-human spread of bovine spongiform encephalopathy (mad cow disease) by ingestion of meat products infected with the pathogenic prion protein. At present, more than 200 probable cases of vCJD have been identified in 11 countries.[1] In all patients, infection occurred either during residence in the UK or through contact with meat products, animals, or animal products exported from the UK. Four cases of vCJD transmitted by blood transfusion have been reported.[2]

The authors undertook a retrospective study of the first 150 cases of vCJD identified in the UK between 1995 and 2005. They systematically analyzed symptoms, signs, and

the diagnostic process with the aim of achieving an earlier diagnosis in future cases of vCJD.

In this series, individuals with vCJD rarely sought medical attention early in the clinical course. The median time from onset to first medical contact was 2.5 months (mean 3.4 months). Early clinical features of vCJD were subtle and of insidious onset. Non-specific psychiatric symptoms — anxiety, irritability, social withdrawal, agitation, and insomnia — dominated the early clinical course. Neurologic features developed early in only a minority of patients, were usually non-specific symptoms such as painful dysesthesias, and were not associated with an abnormal neurological examination. Patients with neurological features or a combination of neurological and psychiatric symptoms presented earlier to a medical practitioner, in comparison with those who had only psychiatric features: neurological onset, 2 months; psychiatric onset, 3.3 months; and combined neurologic and psychiatric symptoms, 1.7 months. At first medical contact, vCJD was not considered as a possible diagnosis in any patient.

The mean time from onset to neurological referral was 7.4 months. In 147 of 150 cases, the mean time from onset to suspected diagnosis of vCJD was 8.9 months and to confirmed diagnosis by current diagnostic criteria (see article) was 10.5 months. In two older patients aged 68 and 74 years not diagnosed in life, vCJD was identified at autopsy. In one case detailed information was not available.

Thirty-eight patients diagnosed within 6 months of onset had both a more rapidly progressive course and earlier objective neurologic signs, which probably led to the earlier diagnosis.

Brain MRI supported the clinical diagnosis of vCJD in 143 of 150 patients. The majority of the negative MRI scans did not include the fluid attenuated inversion recovery (FLAIR) sequence that is most sensitive for identifying hyperintensity of the pulvinar and thalamus that is characteristic of vCJD.

The authors conclude that achieving an early diagnosis of vCJD remains a challenge because of the insidious onset of illness, and the non-specific and mainly psychiatric early clinical features in the majority of cases.

■ COMMENTARY

There is no effective treatment of vCJD whether diagnosed early or late in the clinical course. Fortunately, the number of clinically recognized cases of vCJD is declining: nevertheless, the possibility of unidentified environmental reservoirs for prions in soil and in animals other than cattle suggests that eradication of the disease may not be possible.[1]

Although a diagnosis of vCJD early in the clinical course has little therapeutic benefit for the affected individual, the public health implications of delayed diagnosis are serious. In the present series, 18 patients had 20 surgical procedures after the onset of illness and before vCJD was diagnosed. Four affected individuals donated blood in the early clinical phase of illness. It is unknown whether secondary transmission of vCJD by contaminated surgical instruments and donated blood occurred. The authors have provided an excellent review of the clinical features of vCJD and have underscored the need for clinicians to consider the diagnosis in patients, young or old, presenting with a progressive neuropsychiatric disorder. ■

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REM Sleep Behavior Disorder and Biomarkers of Neurodegenerative Disease

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

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

Synopsis: *Biomarkers for Parkinson's disease and related neurodegenerative diseases occur frequently in patients with idiopathic REM sleep behavior disorder. These include impairment of olfactory and color discrimination, and abnormalities in cerebral blood flow.*

Source: Vendette M, et al. Brain perfusion and markers of neurodegeneration in rapid eye movement sleep behavior disorder, *Movement Disorders* 2011 [Epub ahead of print]; doi: 10.1002/mds.23721.

In recent years, there has been a growing recognition that non-motor manifestations of Parkinson's disease (PD) and related disorders develop years — or decades — before the onset of motor symptoms. This "premotor stage" of PD is characterized by symptoms such as constipation, anxiety, hyposmia, impairment of color discrimination, and sleep disorders. A specific parasomnia — rapid eye movement sleep behavior disorder (RBD) — has been closely associated with synucleinopathies such as PD, diffuse Lewy body disease (DLBD), and multiple system atrophy (MSA).

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*

Are There Sex Differences in the Results from Carotid Endarterectomy and Stenting?

Source: Howard VJ, et al. Influence of sex on outcome of stenting versus endarterectomy: A subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Lancet Neurol* 2011;10:530-537.

CREST FAILED TO DEMONSTRATE ANY SIGNIFICANT DIFFERence in the primary endpoint (composite of stroke, myocardial infarction, or death during the 4-year follow-up period) between carotid artery stenting (CAS) and carotid endarterectomy (CEA) in patients with symptomatic or asymptomatic carotid artery stenosis. A prespecified secondary aim was to examine differences by sex, since previous studies suggested a higher periprocedural complication rate and lower efficacy from these interventions in women compared to men.

Between 2001 and 2008, 2502 patients were randomized to CEA or CAS, and 872 (34.9%) were women. Rates of the primary endpoint for CAS versus CEA in women were 8.9% vs 6.7% (hazard ratio [HR] = 1.35, 0.82 – 2.23). Periprocedural events occurred in 6.8% of women assigned to CAS vs 3.8% of women assigned to CEA (HR = 1.84). The results of CREST supported the findings suggested by previous studies that there is a higher incidence of complications, both periprocedural and long-term, in women who undergo CAS compared to CEA for the treatment of carotid artery stenosis. Complications may be related to the smaller diameter of the internal carotid arteries in women, but other factors may play a role. ■

Intravenous Thrombolysis Is Less Effective in Elderly Patients

Source: Bhatnagar P, et al. Intravenous thrombolysis in acute ischaemic stroke: A systematic review and meta-analysis to aid decision making in patients over 80 years of age. *J Neurol Neurosurg Psychiatry* 2011;82:712-717.

THE PIVOTAL NINDS INTRAVENOUS THROMBOLYSIS TRIAL (*N Engl J Med* 1995) did not include patients ≥ 80 years of age, but recently, many elderly patients are being treated with thrombolytic drugs with increasing frequency, and an age cutoff for thrombolysis has not been defined. Investigators in the UK performed a meta-analysis of 13 published studies, systematically evaluating outcome measures of mortality, functional recovery

RBD is characterized by loss of muscle atonia during REM sleep, with acting out of the dreams (kicking, punching, shouting, etc.) that can lead to injury to the patient or bed partner. RBD may occur in patients with a known neurodegenerative disorder, but also can occur in the absence of detectable motor or cognitive symptoms ("idiopathic RBD"). With long-term follow-up, however, a large percentage of patients with so-called "idiopathic" RBD go on to develop PD or a related disorder.

In this study, the authors examined cerebral blood flow patterns in idiopathic RBD vs healthy controls, and tested the hypothesis that the specific pattern of abnormal perfusion will correlate with the presence of other established biomarkers for PD (impaired olfactory and color discrimination). The study population consisted of 20 patients with idiopathic RBD (confirmed by polysomnography) and 20 healthy control subjects. Each subject underwent a motor examination, color vision discrimination testing (Farnsworth-Munsell test), olfactory discrimination testing (University of Pennsylvania Smell Identification Test-12 items), and resting-state single-photon emission computerized tomography (SPECT) to evaluate cerebral blood flow. Subjects with parkinsonism on examination, and those with known neurodegenerative disorders, were excluded from participation in the study.

In comparison with healthy controls, subjects with RBD had a pattern of cerebral blood flow similar to that of PD, with decreased perfusion of the frontal cortex and medial parietal areas, and increased perfusion of subcortical regions (including the bilateral pons, putamen, and hippocampus). In RBD, there was also a correlation between: (1) reduced perfusion in frontal and occipital regions with impairment in color discrimination, and (2) reduced perfusion in the bilateral anterior hippocampal gyrus with impairment of olfactory discrimination. The findings confirm the association between RBD, abnormal regional cerebral perfusion, and other biomarkers of PD. In addition, they demonstrate a correlation between individual PD biomarkers and specific patterns of abnormal cerebral perfusion.

by modified Rankin scale, and the rate of symptomatic intracranial hemorrrhage (SICH) at 3 months following IV thrombolysis with alteplase in < 80 and ≥ 80-year-old patients with acute ischemic stroke (AIS).

By combining the results of the studies, the overall odds ratio was 2.77 (95% confidence interval [CI] 2.25 to 3.40) for death, 0.49 (95% CI; 0.40 to 0.61) for achieving a favorable outcome, and 1.31 (95% CI; 0.93 to 1.84) for SICH in ≥ 80-year-old patients compared to < 80 years old. Patients > 80 years old appear to have a lower probability of having a favorable outcome and a higher mortality rate compared with patients < 80 years old, but their rate of SICH is not significantly increased. This analysis supports the continued enrollment of elderly patients in clinical trials of thrombolysis and provides risk-benefit information that can be used in the clinical treatment of such patients. ■

Hypertonic Saline in Treatment of Intracerebral Hemorrhage

Source: Wagner I, et al. Effects of continuous hypertonic saline infusion on perihemorrhagic edema evolution. *Stroke* 2011;42: 1540-1545.

Neurological deterioration after intracerebral hematoma (ICH) usually is due to the mass effect of the hematoma with its associated perihematoma edema. Surgical evacuation has not been proven to be better than best medical care, and treatment options are limited. The investigators explored the use of early continuous infusion of hypertonic saline as a treatment modality that might reduce brain edema.

Twenty-six consecutive patients with spontaneous lobar and basal ganglia/thalamic ICH > 30 mL were treated with continuous 3% hypertonic saline infusion to achieve Na of 145 to 155 mmol/L and osmolality of 310-320 mOsmol/kg. Measurements of absolute and relative edema volume were assessed on repeated cranial CT and compared to historical controls (n = 64) from a database with hematoma > 30 mL.

The treatment group had an absolute edema volume that was significantly smaller between day 8 and day 14 and a relative edema volume (absolute edema/hematoma volume) that was smaller between day 2 and day 14. Treated patients had fewer intracranial pressure crises (ICP > 20 mmHg for > 20 min) than the historical controls (12 vs 56) and in-hospital mortality was 11.5% for the group treated with hypertonic saline compared to 25% for the historical controls. This non-randomized, consecutive series suggests that continuous infusion of hypertonic saline may have a beneficial effect on the outcome for patients with ICH, but this must be confirmed by a randomized, controlled clinical trial. ■

■ COMMENTARY

Given the compelling evidence that PD and related disorders begin many years before the onset of motor symptoms, there has been a heightened interest in the identification of biomarkers for PD. Such biomarkers would allow for future neuroprotective treatments to be administered as early as possible in the disease course, prior to the onset of motor symptoms.

In this study, the authors confirm previous observations that RBD is associated with abnormal patterns of cerebral perfusion and other markers of neurodegenerative disease. They also demonstrate a correlation between specific biomarkers (impaired smell and color discrimination, respectively) and the pattern of cerebral perfusion. Further study, including longitudinal analysis, is warranted to identify which biomarker(s) are of greatest clinical utility in predicting the likelihood and time-course for the future development of a neurodegenerative disorder in patients with "idiopathic" RBD. ■

Common Entrapment Neuropathies and Chronic Inflammatory Demyelinating Neuropathy

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: *Entrapment neuropathies are not more common in the setting of chronic inflammatory demyelinating neuropathy and suggest a surgically treatable lesion.*

Source: Rajabally YA, Narasimhan M. Electrophysiologic entrapment syndromes in chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* DOI: 10.1002/mus.22146.

Is chronic inflammatory demyelinating polyneuropathy (CIDP) associated with an increased incidence of multiple entrapment neuropathies at common sites of compression, and, ipso facto, does the presence of multiple entrapment neuropathies at common sites of compression support a diagnosis of CIDP, or assist in differentiating it from other demyelinating neuropathies? To address this question, a prospective study of 31 patients with CIDP was performed to determine if common sites of compression were more likely to be involved than their immediately adjacent segments. All patients fulfilled European Federation of Neurological Societies/Peripheral Nerve Society guidelines for the diagnosis of CIDP.[1] None of the patients gave a history suggestive of pre-existing entrapment neuropathy. Using standard percutaneous recording procedures, bilateral electrodiagnostic studies of the median, ulnar, and peroneal nerves at the wrist, elbow, and fibular head, respectively, were performed, recording at the abductor pollicis brevis, abductor digiti minimi, and extensor digitorum brevis, respectively, and compared to the forearm segments for the median and ulnar nerves, and the below-knee segment for the peroneal nerve. Conduction block was defined as a drop in amplitude of 30% or more on proximal, compared to distal stimulation, and demyelination of a nerve segment was felt to be present if a 25% or more difference in conduction velocity was found between the common entrapment site and the non-entrapment site. Statistical analysis was provided using Fisher's exact test, and t-tests were used to calculate differences of the mean.

No difference in demyelination was found in the median nerve, comparing the common entrapment site at the wrist to its proximal adjacent segment. Interestingly, in both the ulnar and peroneal nerves, there was significantly more frequent demyelination at non-entrapment sites, as measured by conduction velocity, compared to sites more prone to compression neuropathy. With respect to conduction block, no segmental differences were seen in the ulnar nerve, and conduction block was more frequent below the knee than across the fibular head in the peroneal nerve. In CIDP, there is no predilection for demyelination at common entrapment sites, and evidence of such demyelination should suggest a potentially surgically treatable lesion rather than favor a diagnosis of CIDP.

■ COMMENTARY

Voltage-gated Na+ channels (Nav) and ankyrin G, a cytoplasmic protein, are concentrated at nodes of Ranvier. Paranodal proteins include paranodin, also known as Caspr, and contactin. Electron microscopic study of superficial peroneal nerve biopsies obtained from 12 patients with CIDP and 10 with chronic inflammatory axonal polyneuropathy revealed that, compared to controls, CIDP patients demonstrated immunofluorescence of paranodin/Caspr that was more widespread, extending into the internodes, whereas Nav, and KCNQ2, a potassium voltage-gated channel subunit also found in the nodal region, were less altered. Labeling of paranodin was irregular and/or decreased in chronic inflammatory axonal polyneuropathy internodes, whereas control nerves demonstrated Nav restricted to the nodes of Ranvier, flanked by paranodin. These abnormalities are the first such described at the nodes of Ranvier in chronic inflammatory demyelinating or axonal polyneuropathy and may have future value in clinically distinguishing between these disorders.[2] ■

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Are We Close to Understanding the Role of Fingolimod in the Treatment of MS?

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MS

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College

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

Synopsis: *Patients originally on interferon beta-1a in the TRANSFORMS study were re-randomized to either 0.5 or 1.25 mg of fingolimod. There was a reduction in relapse rate and MRI activity in patients that switched to fingolimod without an increase in severe adverse events.*

Source: Khatri B, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: A randomized extension of the TRANSFORMS study. *Lancet Neurol* 2011;10:520-529.

Fingolimod recently was approved by the FDA at the 0.5 mg dose for the treatment of relapsing forms of multiple sclerosis (MS). As a sphingosine 1-phosphate receptor agonist, the adverse event profile differs significantly from current first-line immunomodulatory agents (IMA) used to treat MS, and it still has yet to be determined where this agent will fall within our treatment algorithm. To advance our understanding of fingolimod, patients within the TRANSFORMS core study were enrolled into an extension study for which the clinical benefit and safety of switching to fingolimod from interferon beta-1a (IFN β-1a) was studied.

In the original 12-month study, patients were randomized to receive either IFN β-1a, fingolimod 0.5 mg, or fingolimod 1.25 mg where a significant benefit of both doses of fingolimod compared to IFN β-1a was found by both clinical (relapse rate) and MRI outcomes. In the TRANSFORMS extension study reported here, the patients originally assigned IFN β-1a were re-randomized to receive either 0.5 mg or 1.25 mg of fingolimod, and those patients assigned to fingolimod during the core study remained at the same dose. After an additional 12 months of treatment (months 13-24), the groups were compared by clinical, MRI, and safety measures. There was a 30% and 36% reduction in annualized relapse rate (ARR) in months 13-24 in patients that switched to 0.5 mg and 1.25 mg of fingolimod, respectively. The ARR for months 13-24 in both switched groups was still higher than those patients that remained on fingolimod; therefore, the 24-month (core + extension) ARR for the continuous fingolimod groups remained less than those that switched. Likewise, there was an improvement in new T2 and contrast-enhancing lesions in the switched groups during months 13-24. There was also a reduction in brain atrophy rate in months 13-24 months in patients that switched to fingolimod. However, this rate was lower than the rate found in the patients continuously treated with fingolimod; consequently, the 24-month atrophy rate was similar across groups. There was no difference in disability in the core or extension phases. The adverse event profile in the patients that switched from IFN β-1a to fingolimod was lymphopenia, abnormal hepatic enzyme levels, first dose bradycardia, and three cases of macular edema, all of which were expected. Importantly, the rate of infectious adverse events did not increase with a switch to fingolimod. Adverse events in months 13-24 in the continuously fingolimod-treated patients remained stable.

■ COMMENTARY

The current study demonstrates the clinical and MRI benefits of switching to fingolimod from IFN β-1a without a significant compromise on safety. Given the beneficial treatment affect of fingolimod over IFN β-1a in the core study (0-12 months), it isn't surprising to see a benefit after switching, although the design of this switch study is much preferred to observational studies given that patients are matched and randomly assigned to treatment. However, both phases of the TRANSFORMS study are extremely short; thus we can only state that fingolimod has short-term superiority over IFN β-1a. The lower relapse rate in patients continuously treated with fingolimod compared to those that switched in months 13-24 might indicate that a delay of fingolimod treatment is detrimental, but long-term disability data is required to make that determination. Of note, the immunomodulatory agents have established long-term safety profiles, and we have no long-term safety data on fingolimod or information regarding the effects of chronic lymphopenia induced by this drug. In addition, the long-term infectious and malignancy risks remain to be seen. Thus, as it now stands, the role of fingolimod for the treatment of MS is less likely to be as a first-line treatment, but reserved as an option when patients fail their initial IMA. ■

CME Objectives

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

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

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

79. A 66-year-old woman with hypertension and alcoholism presents to the ER with 1 day of severe headache and neck stiffness. On examination, she is febrile to 38.8º C, has nuchal rigidity, is lethargic but arousable, is oriented to name and place but not time, and is nonlocalizing on motor and sensory examination. Which of the following organisms is the most likely cause of her clinical syndrome?

a. Group B streptococcus
b. *Haemophilus influenzae*
c. *Listeria monocytogenes*
d. *Streptococcus pneumoniae*

80. All of the following suggest a diagnosis of vCJD *except*:

a. new onset of progressive psychiatric symptoms.
b. previous residence in the U.K.
c. burning dysesthesisas.
d. a history of familial dementia.
e. a "pulvinar sign" on MRI/FLAIR sequence.

81. Diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) may be confidently made when:

a. multiple entrapment neuropathies at common sites of compression are found clinically.
b. multiple entrapment neuropathies at common sites of compression are found on nerve conduction studies.
c. Both a and b
d. Neither a nor b

82. All of the following are associated with the subsequent development of Parkinson's disease *except*:

a. REM sleep behavior disorder.
b. decreased regional cerebral blood flow in the putamen.
c. impaired color discrimination.
d. impaired olfactory discrimination.

83. Which of the following is not an adverse event associated with fingolimod?

a. Lymphopenia
b. Flu-like symptoms
c. First dose bradycardia
d. Macular edema
e. Elevation of liver function

84. Periprocedure complications occur more frequently in women who undergo carotid artery stenting, than in men.

a. True
b. False

85. Hypertonic saline treatment improves outcome in patients with intracerebral hematomas.

a. True
b. False

86. Patients with acute ischemic stroke who are ≥ 80 years of age have the same outcome after treatment with alteplase, as those who are < 80 years of age.

a. True
b. False

In Future Issues:

Biomarkers in Alzheimer's Disease

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COPD in Never Smokers

Source: Lamprecht B, et al. *Chest* 2011; 139:752-763.

Unless there is another overt cause, such as occupational exposure to toxic inhalants, we generally expect chronic obstructive pulmonary disease (COPD) to be secondary to cigarette smoking. The pulmonology literature consistently suggests that a substantial minority — at least 20% — is NOT related to cigarette smoking. This multinational survey by Lamprecht et al provides a fresh appraisal of the burden of COPD unrelated to smoking.

The Global Initiative for Obstructive Lung Disease (GOLD) guidelines were used to define COPD through spirometry. Primary cigarette smoking, exposure to secondary smoke, occupational exposure, and biomass exposure (for instance, cooking or home heating using wood, coal, dung, or crop residue) were all queried among 10,000 subjects from 14 countries.

Of the 4291 never smokers, 12.2% fulfilled GOLD criteria for COPD. Of all persons ultimately defined as meeting COPD criteria, just over one-fourth were never smokers. Women were disproportionately represented in the group of persons with moderate-severe COPD. It has been suggested that women may have greater susceptibility both to tobacco smoke as well as other potentially toxic inhalants.

COPD is now the third most common cause of death in America. Pulmonologists have suggested that COPD remains underdiagnosed. Based on these results, the authors suggest that symptomatic persons, even if never smokers, should be screened for COPD. ■

Early Prostate Cancer: Prostatectomy vs Watchful Waiting

Source: Bill-Axelson A, et al. *N Engl J Med* 2011;364:1708-1717.

The management of early prostate cancer (PCA) remains controversial. Although surgical and radiation interventions offer the opportunity for cure, many more men with early PCA die with the disease than from it. Were definitive interventions without risk, there likely would be little discussion about whether to intervene; however, because the potential consequences of intervention are significant (e.g., incontinence, erectile dysfunction), clarification of the risk:benefit ratio is critical.

A randomized multinational study of subjects from Sweden, Finland, and Iceland (n = 695) randomized men < 75 years of age with localized, moderately well to well-differentiated prostate cancer to either radical prostatectomy or watchful waiting. Men were followed for 12.8 years.

At 12.8 years, all-cause mortality was statistically significantly less in the surgery group (166/347) than the watchful waiting group (201/348). Similarly, PCA-related death was superior in the surgically treated group (14.6% vs 20.7%). Benefits were clear from men < 65 years of age, but only a trend toward benefit (results not statistically significant) could be determined from the data in older men, possibly because of the smaller number of men in this age group.

Adverse effects of surgery were substantial. For instance, at 1 year, 32% of men had incontinence and 58% had impotence. Younger men with early PCA appear to enjoy mortality benefit from surgical intervention, though at a substantial adverse event cost. Competing causes of death in older men diminish the relative benefits of surgery. ■

Dietary Vitamin D and Incident Diabetes

Source: Gagnon C, et al. *Diabetes Care* 2011;34:1133-1138.

The beta cells of the pancreas possess a vitamin D receptor, so perhaps we should not be surprised that vitamin D might be associated with diabetes (DM). Preliminary evidence has suggested that dietary vitamin D (VTD) might be associated with risk for DM, but prior to this report, no large population study has provided sufficient information to be definitive.

Gagnon et al researched subjects involved in the AusDiab studies, which included 11,247 noninstitutionalized adults free of DM at baseline who underwent a 75 g oral glucose tolerance test (GTT) at baseline. Five years later about half (6537) of these had a repeat GTT, of which 80% were still not diabetic.

The investigators found a linear relationship between reported dietary VTD and incident DM over a 5-year interval: for every 25 nmol/L increase in VTD, there was a 24% reduced risk of DM. Also studied in this same data set was calcium intake, which did not correlate with incident DM. Subjects in the top quartile of VTD intake enjoyed a 44% risk reduction for incident DM.

Because these are observational data, causation cannot be established. Prospective, randomized, placebo-controlled trials of VTD supplementation will be necessary to confirm the preventive capacity of VTD. ■

Functional Cobalamin Deficiency in Diabetes

Source: Solomon LR. *Diabetes Care* 2011;34:1077-1080.

It has been suggested that as many as 30% of senior citizens have so-called functional cobalamin deficiency (FCD), defined as the presence of elevated metabolites such as methylmalonic acid in the face of ostensibly normal cobalamin levels. Since methylmalonic acid should accumulate primarily in the circumstance of vitamin B12 insufficiency, there appears to be some functional deficiency in cobalamin, manifested as increased levels of methylmalonic acid.

The intersection of diabetes with FCD occurs because previous trials have noted that diabetics comprise up to one-third of subjects experiencing improvements in neuropathic signs with vitamin B12 supplementation, and the vast majority of these subjects (88%) did not have decreased vitamin B12 levels.

To better define the epidemiologic profile of FCD, a retrospective review of patients evaluated for cobalamin deficiency from 1993-2005 characterized levels of cobalamin in relation to methylmalonic acid. Because renal insufficiency is associated with increases in methylmalonic acid, creatinine > 1.4 mg/dL was an exclusion criterion.

Among nondiabetics there was an inverse relationship between methylmalonic acid and cobalamin. Among diabetics, however, increasing cobalamin levels were not associated with decreasing methylmalonic acid, suggesting that there was a relative cobalamin resistance.

Equally noteworthy, neuropathy was much more frequent in persons with elevated methylmalonic acid than without (62% vs 18%) and more than 85% of persons treated with pharmacologic doses of cobalamin experienced improvement in neuropathy.

There is substantial controversy over the existence of functional cobalamin deficiency. Considering that cobalamin supplementation has no known important toxicity, clinicians may wish to re-examine the issue of cobalamin treatment for diabetic subjects with elevated levels of methylmalonic acid, even in the face of normal cobalamin levels. ■

Should Leukotriene Antagonists Have Higher Priority for Asthma Control?

Source: Price D, et al. *N Eng J Med* 2011;364:1695-1707.

Current asthma guidelines suggest that once an asthma patient has progressed to the stage of persistent asthma (even mild-persistent asthma), inhaled corticosteroids (ICS) should be the preferred initial "controller" (maintenance) medication. Nonetheless, comparator trials of leukotriene inhibitors (LKT) with ICS have produced inconsistent findings, sometimes indicating superiority of ICS, but other times suggesting equal efficacy of the two classes. Because concerns about adverse effects of ICS in obstructive airways diseases have persisted for several decades, the absence of similar concerns with LKT agents promotes consideration of how to maximize their positive potential.

Two trials comprise the data reported in this publication. In the first, persons initiating controller therapy for persistent asthma (n = 306) were randomized to either ICS or LKT. In the second trial, asthma subjects who had already received ICS for controller medication but who required advancement of pharmacotherapy (n = 352) were randomized to either LKT or long-acting beta agonist (LABA). The primary outcome was the score on the Mini Asthma Quality of Life Questionnaire at 2 months. Secondary outcomes included the same questionnaire results at 2 years and frequency of asthma exacerbations.

At 2 months, the LKT proved equivalent to ICS as initial therapy, and equivalent to LABA as add-on treatment. At 2 years, although not able to achieve the statistical threshold defining equivalence, the outcomes were very similar. There was no difference in the frequency of exacerbations between LKT and ICS or between LKT and LABA when added to ICS. There was no placebo control in this trial, and the trial was open label. Nevertheless, these data suggest that in a "real world" setting, the efficacy of LKT in asthma may have been underestimated. ■

Selenium Impacts Orbitopathy in Graves Disease

Source: Krassas GE, et al. *N Eng J Med* 2011;364:1920-1931.

Ocular abnormalities associated with Graves disease are sometimes called Graves' orbitopathy (GORB) and occur in as many as half of Graves' disease cases. Treatments for GORB include glucocorticoids and irradiation, but are generally reserved for moderately severe disease. Mild GORB has been shown to spontaneously regress (20%), remain stable/unchanging (65%), or advance (15%). Hence, a safe intervention to prevent advancement of GORB would be desirable. The antioxidant effects of selenium led to consideration of its potential favorable impact upon GORB.

This controlled trial randomized patients (n = 107) to selenium sulfide 100 mcg twice daily or placebo for 6 months. GORB evaluation was done at baseline, 3, 6, and 12 months. The primary outcome was the percentage of patients improving from baseline. The study hypothesis was that active treatment would improve the number of persons with GORB regression by 25%: from 20% (as seen in naturalistic follow-up of untreated GORB) to 45%.

By 6 months, there was a statistically significant improved quality of life and regression of GORB, which was reconfirmed at 12 months. There were no serious adverse effects seen with selenium.

Although it would have been nice to have seen selenium levels before and after treatment, and hopefully a correlation between selenium repletion and outcomes, these preliminary data are still quite supportive of a

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Two New Drugs Approved for Treatment of Hepatitis C

In this issue: Two new drugs for treatment of hepatitis C; NSAIDs and myocardial infarction risk; AIM-HIGH clinical trial stopped; and FDA actions.

Two new drugs for hepatitis C

The FDA has approved two new drugs for the treatment of hepatitis C — the first new drugs to be approved in years. The approvals came within days of each other, pitting the two drugs (and their companies' marketing departments) against each other in this multibillion dollar market. Both drugs are protease inhibitors and both have similar indications. First to be approved was Merck's boceprevir (Victrelis), which is indicated for adults with hepatitis C who still have some liver function and who either have not been treated previously with drug therapy or who have failed drug therapy. Boceprevir is approved for use in combination with peginterferon alpha and ribavirin. The approval was based on two phase 3 clinical trials of 1500 adults in which two-thirds of patients in the boceprevir, interferon, and ribavirin treatment group experienced a significantly increased sustained virologic response at 24 weeks compared to 38% with interferon and ribavirin alone. Boceprevir is taken orally three times a day with food. The second drug approved was Vertex Pharmaceutical's telaprevir (Incivek), which also was approved for patients with hepatitis C who either have not received interferon-based drug therapy or who have not responded adequately to prior therapies. Telaprevir is also approved for use with peginterferon alpha and ribavirin. Approval was based on three phase 3 clinical trials of over 2000 adults. In previously untreated patients, 79% of patients in the telaprevir group experienced a sustained viral response compared to 46% for standard treatment. Most patients experienced virologic response at 24 weeks suggesting that treatment times may be reduced from 48 weeks to 24 weeks. Telaprevir is also taken orally three times a day with food. Both drugs are approved to treat genotype-1, the most common form of hepatitis C and the most difficult to treat. The drugs have similar side effects, which include anemia and serious rashes. Several other drug manufacturers have similar drugs in the pipeline with approval expected within the next year or two. It is estimated that about 170 million people worldwide and 3.2 million Americans are infected with chronic hepatitis C, which is the most common cause of progressive liver disease leading to liver transplant. Telaprevir is expected to cost nearly $50,000 per treatment course, while bocepavir is expected to cost between $26,000 to $48,000 per treatment course depending on the duration. ■

NSAID use in patients with prior MI

A new study points out the risk of nonsteroidal anti-inflammatory drug (NSAID) use in patients who have had a myocardial infarction (MI) — suggesting that even brief use increases the risk for death and recurrent MI. Researchers from Denmark reviewed the records of nearly 84,000 patients who were admitted with first time MI and their subsequent NSAID use. The risk of death and recurrent MI was correlated to the duration of NSAID treatment. From 1997-2006, 42.3% of patients received NSAIDs. There

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were more than 35,000 deaths or recurrent MIs in the cohort of whom 43% had filled a prescription for an NSAID. Use of an NSAID was significantly associated with an increased risk of death or recurrent MI at the beginning of treatment (hazard ratio [HR] 1.45; 95% confidence interval [CI], 1.29 to 1.62) and persisted throughout the NSAID treatment course (HR 1.55; 95% CI, 1.46 to 1.64 after 90 days), returning to baseline soon after stopping the drug. The risk of death or recurrent MI varied with different drugs and was somewhat higher with increased COX-2 selectivity. Diclofenac was associated with the highest risk (HR 3.26; 95% CI, 2.57 to 3.86). Duration of therapy was also reviewed with diclofenac causing an increased risk from the beginning of treatment and persisting throughout the treatment course. Ibuprofen showed an increased risk when used for more than one week, whereas celecoxib showed an increased risk after 14-30 days of treatment. Naproxen was not associated with a statistically significant increased risk of death or MI for the entire treatment duration. The authors conclude that short-term treatment with most NSAIDs is associated with increased cardiovascular risk. This suggests that there is no apparent safe therapeutic window for NSAIDs in patients with prior MI and "challenge the current recommendations of low-dose and short-term use of NSAIDs as being safe" (*Circulation* 2011;123:2226-2235). One interesting aspect of this study was the use of rofecoxib (Vioxx) prior to its withdrawal in 2004. While rofecoxib was found to increase cardiovascular risk (the reason for its withdrawal from the market), it appeared to be no more dangerous than other commonly used NSAIDs and was apparently safer than diclofenac. ■

NHLBI stops AIM-HIGH trial

Niacin may not be effective in preventing cardiovascular disease. The National Heart Lung and Blood Institute (NHLBI) has prematurely stopped the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) clinical trial 18 months earlier than planned. Analysis of the data found that adding high-dose, extended-release niacin to statin treatment in people with heart and vascular disease did not reduce the risk of cardiovascular events. AIM-HIGH participants had well-controlled low-density lipoprotein levels on a statin, however they were at risk of cardiovascular disease due to previous history of cardiovascular disease and a combination of low high-density lipoprotein (HDL) cholesterol and high triglycerides. During the nearly 3 years of the study, patients who took high-dose, extended-release niacin with a statin had increased HDL cholesterol and lower triglyceride levels compared to those who took a statin alone; however, the combination was not effective at reducing fatal or nonfatal heart attacks, strokes, hospitalizations for acute coronary syndrome, or revascularization procedures. There also was a "small and unexplained increase in ischemic stroke rates in the high-dose, extended-release niacin group" that contributed to the decision to halt the trial. Termination of the AIM-HIGH trial was announced by press release from the NHLBI on May 26. ■

FDA actions

The FDA has approved linagliptin for the treatment of type 2 diabetes in adults. The drug is an inhibitor of DPP-4, an enzyme that degrades incretin hormones (GLP-1 and GIP). It is approved for use as a stand-alone therapy or in combination with other drugs for type 2 diabetes including metformin. The approval was based on eight double-blind, placebo-controlled trials of nearly 4000 patients that showed improved blood glucose control compared to placebo. Linagliptin is marketed by Boehringer Ingelheim Pharmaceuticals as Tradjenta.

The FDA has approved rilpivirine, a new non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of adults with HIV-1 infections who are treatment naïve. Rilpivirine is to be used as part of a highly active antiretroviral therapy (HAART). The approval was based on two phase 3 trials of nearly 1400 adults with HIV who were observed for 48 weeks, and an additional 96-week trial in which the drug was compared to efavirenz as part of multidrug combinations. Rilpivirine was found to be comparable to efavirenz with regard to percentage of patients with undetectable HIV viral load. Patients who failed rilpivirine are more likely to develop drug resistance than patients who failed efavirenz. Rilpivirine is marketed by Tibotec Therapeutics as Edurant.

Rosiglitazone (Avandia) remains on the U.S. market, but its days may be numbered. In a new step to restrict use of the drug, the FDA has updated the Risk Evaluation and Mitigation Strategy to include a restricted access in distribution plan. Physicians and patients must enroll in the distribution program in order to receive the drug. Rosiglitazone will no longer be available in commercial pharmacies after mid-November and will only be available by mail order through certified pharmacies. Use of the drug is limited to patients who are currently on rosiglitazone and whose diabetes is not controlled by other treatments and who are unwilling to change to pioglitazone (Actos). ■

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

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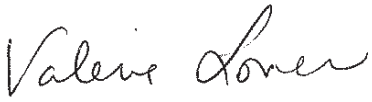

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