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Miller Fisher Syndrome vs Bickerstaff Brainstem Encephalitis: What Is the Difference?

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: *Sera from patients with Bickerstaff brainstem encephalitis demonstrate the ability to disrupt the blood-brain barrier; sera from Miller Fisher syndrome do not.*

Source: Saito K, et al. Blood-brain barrier destruction determines Fisher/Bickerstaff clinical phenotypes: An in vitro study. *J Neurol Neurosurg Psychiatry* 2013;84:756-765.

Characterized by ophthalmoplegia, ataxia, altered consciousness, and hyper-reflexia, Bickerstaff brainstem encephalitis (BBE) shares features with Miller Fisher syndrome (MFS), including a history of preceding infection, spontaneous recovery, response to plasma exchange or intravenous immunoglobulin, the presence of serum IgG anti-GQ1b antibodies, and cerebrospinal fluid cytoalbuminogenic dissociation. Could these disorders form a spectrum of an anti-GQ1b antibody syndrome, with MFS the peripheral nervous system analog and BBE the central nervous system counterpart, and if so, what might explain the variable clinical expression? Might differences in breakdown of the blood-brain and blood-nerve barriers be responsible?

To address these questions, acute-phase sera were obtained within 3 weeks of symptom onset, from hospitalized patients with MFS (n = 10) and BBE (n = 11) throughout Japan. Anti-GQ1b antibodies were detected in 8/11 BBE sera and 9/10 MFS sera. Sera of eight healthy individuals served as normal controls. Immortalized human brain microvascular endothelial cells and peripheral nerve microvascular endothelial cells were incubated with these sera to determine how blood-brain and blood-nerve barrier function was impaired as a consequence, by evaluating transendothelial electrical resistance and expression of tight junction proteins,

including claudin-5 and occludin. Statistical analysis encompassed ANOVA and the Mann-Whitney U test, with $P < 0.05$ considered statistically significant.

Following exposure to BBE sera, but not MFS sera, human brain microvascular endothelial cells demonstrated significantly decreased transendothelial electrical resistance, not influenced by the presence or absence of anti-GQ1b antibodies. BBE sera, but not MFS sera, decreased claudin-5 protein expression, but not occludin, in brain microvascular endothelial cells, and increased mRNA expression of matrix metallopeptidase 9 (MMP-9) and matrix metallopeptidase 2 (MMP-2). MMP-9 secretion, but not MMP-2, was also increased by BBE sera, but not by MFS sera, in brain microvascular endothelial cells. No correlation was found between MMP-9 concentration and change in transendothelial electrical resistance. TNF-alpha neutralizing antibody reversed the blood-brain barrier disruption of brain microvascular endothelial cells induced by BBE sera. Blood-brain and blood-nerve barrier function were unaffected by purified IgG obtained from BBE or MFS sera, and peripheral nerve microvascular endothelial cells were similarly unaffected by MFS or BBE sera. Only BBE sera, and not MFS sera, disrupt and reduce blood-brain barrier function. Purified IgG from these sera does not cause blood-brain barrier disruption, and the presence of anti-GQ1b antibodies seems not to contribute to this disruption, suggesting that humoral factors other than IgG antibodies, including anti-GQ1b, play the significant role. Alteration of the blood-brain barrier may explain the central nervous system dysfunction in BBE and it may be mediated by upregulated matrix metallopeptidases.

■ COMMENTARY

Anti-GQ1b antibodies are also found in patients who do not fulfill criteria for MFS but who have either acute ataxia or ophthalmoparesis with cerebrospinal fluid cytoalbuminogenic dissociation. Isolated, unilateral cranial neuropathies are also reported, and in one study of 100 patients with isolated abducens palsy, 25% were positive for anti-GQ1b antibodies.[1] Pharyngeal-cervical-brachial weakness, affecting oropharyngeal, neck, and shoulder muscles, associated with areflexia is another syndrome associated with anti-GQ1b antibodies. Recurrent episodes are rare but described. ■

Reference

1. Tatsumoto M, et al. Isolated abducens nerve palsy as a regional variant of Guillain-Barre syndrome. *J Neurol Sci* 2006;243: 35-38.

Fibromuscular Dysplasia and Childhood Stroke

ABSTRACT & COMMENTARY

By Sotirios Keros, MD, PhD

Instructor, Department of Pediatrics, Division of Pediatric Neurology, Weill Cornell Medical College

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

Synopsis: *Childhood fibromuscular dysplasia is a fairly distinct entity from the typical adult form, and the "string of beads" finding on angiography is relatively uncommon.*

Source: Kirton A, et al. Fibromuscular dysplasia and childhood stroke. *Brain* 2013;136(Pt 6):1846-1856.

Arteriopathies are a major cause of stroke in childhood and typically are associated with poor outcomes. Fibromuscular dysplasias (FMD) represent a distinct group of arteriopathy, with the classic medial fibroplasia form typified by refractory hypertension, renal artery involvement, and stroke with a "string of beads" appearance on angiography. Diagnosis of childhood FMD, however, is difficult due to many non-classic presentations.

In this retrospective case study, the authors searched for cases from two Canadian stroke registries, as well from a PubMed search. Inclusion criteria were children (newborns to age 18) who had an arterial stroke associated with

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

either pathologic or radiographic evidence of FMD or renal arteriopathy. Eighty-one cases were discovered, with most strokes classified as arterial ischemic strokes or transient ischemic attack (81%), hemorrhagic stroke (16%), or both (2.5%). Of these 81 cases, 27 represented pathologically proven FMD, primarily identified by either autopsy or by biopsies of the renal or temporal arteries. Nineteen of these proven cases had sufficient detail to identify a specific pathological subtype, with 17 classified as intimal fibroplasia and two as medial hyperplasia. The remaining eight cases had pathological changes throughout all three layers of the arterial wall and were unclassifiable. The median age at onset of symptoms was 7 years (range 2 months to 16 years), with one-third presenting during the first year of life. Seventy percent of the cases presented with neurologic complaints, primarily motor deficits (65%) or seizures (33%). While 82% of the pathologically proven cases were found to have a confirmed stroke, 19% had a transient ischemic attack as their only clinical neurologic finding at presentation.

The results of cerebrovascular imaging were available in 19 children in the pathologically proven group, with only six (31%) of those cases reporting a string of beads type appearance. In these six cases, five had an unclassifiable pathology while the remaining child had intimal fibroplasia. Of the 13 cases without a string of beads appearance, nine (64%) were described as showing focal stenosis, segmental stenosis, or occlusion. Seven of these nine had intimal fibroplasia. Moyamoya syndrome was diagnosed in 33% in the pathologically proven group. Renal arteriopathy was present in 15 (56%) cases and all had documented hypertension, with 88% of these cases reporting abnormal renin or aldosterone levels. Twenty-one of the 27 had investigations for systemic arteriopathy, and 16 of these reported abnormalities in noncerebral or renal arteries such as the aortic (50%), celiac/mesenteric (43%), coronary (43%), peripheral (21%), pulmonary (14%), splenic (14%), external carotid (8%), and hepatic/pancreatic (8%) arteries.

Various medical and surgical treatments were reported in these patients, including corticosteroids, antithrombotic or antiplatelet therapies, renal angioplasty, nephrectomy, and cerebral revascularization. Overall, treatment reporting was limited, and did not allow for outcomes comparisons. In all cases with outcome data, 37% were classified by the authors as "good" with the remaining 63% classified as "poor." Nine of 27 patients had a recurrence of ischemic stroke at a median interval of 29 months. There were 12 deaths (44%).

The 27 cases in the pathologically proven group were compared to 31 cases of clinically diagnosed FMD. Among the statistically significant findings, the children in the clinically diagnosed group were less likely to present in the first year of life (9% vs 33%). They were more likely to present with neurologic symptoms (95% vs 70%), have a string of beads appearance on angiography (74% vs 22%), and have unilateral disease (86% vs 19%). The clinically diagnosed group was less likely to have a poor outcome (32% vs 63%), have recurrence (8% vs 36%), or to die (4% vs 44%). There were no cases of hemorrhagic stroke in this group. In a subset analysis of all 15 postpubertal cases, no differences were found in the variables that are associated with the typical adult FMD.

■ COMMENTARY

There are obvious limitations inherent in any analysis of retrospective cases taken from multiple registries and literature reviews. Despite this, the authors find many important, novel differences between pathologically proven FMD and the suspected cases. It is clear that the absence of the typical string of beads finding does not rule out FMD in children and that pathologic confirmation is necessary for diagnosis. In addition, a string of beads type finding is present in other relatively common childhood arteriopathies, such as transient cerebral arteriopathy, whose clinical characteristics overlap closely with the suspected FMD group, suggesting that FMD may not be the correct diagnosis for many of those cases. The authors suggest that the best available angiography be performed in all unexplained cases of childhood stroke, including renal and other systemic arteries. Intimal fibroplasia and ischemic stroke with recurrence were common in the childhood FMD, all of which are rare in adult disease. This suggests that prepubertal FMD is a fairly distinct entity. Given the high incidence of ischemic stroke and recurrence, primary and secondary prevention, such as antiplatelet therapy, should be strongly considered. ■

Glucocerebrosidase Mutations in Dementia with Lewy Bodies

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is on the speakers bureau and advisory board for Allergan and Teva; speakers bureau for Boehringer-Ingelheim, GlaxoSmithKline, and Novartis; advisory board for Merz; and is a consultant for Gerson Lehman Group and Guidepoint Global.

Synopsis: *This multicenter study compared genotype data to establish that mutations in the glucocerebro-*

By Matthew E. Fink, MD, *Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital*

Clopidogrel Added to Aspirin Reduces Ischemic Stroke Risk after TIA or Minor Stroke

Sources: Wang Y, et al. for the CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *New Engl J Med* 2013;369:11-19.

Hankey G. Dual antiplatelet therapy in acute transient ischemic attack and minor stroke. Editorial. *New Engl J Med* 2013;369:82-83.

Stroke commonly occurs during the first few weeks or months after a transient ischemic attack (TIA) or minor stroke, and the investigators of the CHANCE trial (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) tested the potential benefits and risks of adding clopidogrel to aspirin to provide greater protection against subsequent stroke than aspirin alone. In a randomized, double-blind, placebo-controlled trial at 114 centers in China, 5170 patients were randomly assigned within 24 hours of the acute event to either aspirin at 75 mg per day plus placebo for 90 days or clopidogrel (initial dose of 300 mg followed by 75 mg per day for 90 days) plus aspirin at a dose of 75 mg per day for the first 21 days. The primary outcome was stroke (ischemic or hemorrhagic) during 90 days of follow-up in an intention-to-treat analysis. Differences were assessed using a random-effects, Cox proportional-hazards model.

Stroke occurred in 8.2% of patients in the clopidogrel-aspirin group compared to 11.7% of those in the aspirin group (hazard ratio, 0.68; 95% confidence interval, 0.57-0.81; $P < 0.001$). Significant hemorrhage occurred in seven patients (0.3%) in the clopidogrel-aspirin group and in eight (0.3%) in the aspirin-alone group. Hemorrhagic stroke occurred in 0.3% in each group. The aspirin-clopidogrel group had a 32% reduction in risk of recurrent stroke at 90 days, compared to aspirin alone, with no increase in risk of hemorrhagic

sidase (GBA1) gene are a risk factor for developing dementia with Lewy bodies.

Source: Nalls MA, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. *JAMA Neurol* 2013;70: 727-735.

Mutations in the glucocerebrosidase gene (GBA1) have long been established to cause Gaucher's disease. However, multiple studies have now demonstrated that GBA1 mutations are a significant risk factor for Parkinson's disease (PD) and are associated with a higher incidence of cognitive changes and earlier disease onset. The primary objective of this study was to establish whether mutations in the GBA1 gene are a risk factor for developing dementia with Lewy bodies (DLB). This international, multicenter analysis was undertaken to further evaluate the relationship between GBA1 mutations and risk of DLB, and to compare with Parkinson's disease dementia (PDD). Eleven centers with previous experience in GBA1 genotyping contributed data for the study, which were analyzed at the National Institutes of Health. Included subjects met McKeith criteria for DLB or the Movement Disorders Task Force criteria for PDD. Cases examined comprised 721 with DLB, 151 with PDD, and 1962 controls. Ascertainment of mutations varied by site. Full sequencing of all GBA1 exons was performed in 80.6% DLB samples, 66.2% PDD samples, and 30.8% control samples. Remaining samples underwent screening for either 5-10 mutations (13% DLB, 33.1% PDD, 18.9% controls) or up to four mutations (6.4% DLB, 0.7% PDD, 50.3% controls). Of the subjects included, 34.5% and 36% were women (DLB and PDD, respectively), whereas 52.8% of the controls were women. Control subjects' mean age at examination was less than that for DLB and PDD (DLB: 75 years, PDD: 76 years, controls: 65 years). Subjects self-reported European descent in 98-100% cases, and less than 1% of patients were of Ashkenazi Jewish or Asian descent. Data aggregated from all sites revealed that DLB subjects were approximately eight times more likely than controls to carry a GBA1 mutation (odds ratio [OR], 8.28). Subjects considered to have PDD were found to have a slightly lower association (OR, 6.48). Logistic regression models adjusted for site found an OR of 8.66 for DLB and 3.82 for PDD. Further analysis revealed a significant association between earlier ages of disease onset in subjects with GBA1 mutations, and cases with GBA1 mutation developed symptoms approximately 5 years earlier than those without ($P < 0.001$).

■ COMMENTARY

PD associated with GBA1 mutations is likely associated with a higher incidence of dementia, and findings

complications. However, it is premature to generalize these findings outside of the Chinese population, since there is a much higher rate of intracranial atherosclerosis in the Chinese population, and other associated risk factors (hypertension, smoking, hyperlipidemia) occur at different frequencies than in North America and Europe. ■

Women Are at Greater Risk of Dying from Stroke Than Men

Source: Zhou G, et al. Sex differences in stroke case fatality: A meta-analysis. *Acta Neurol Scand* 2013;128:1-8.

THERE IS ONGOING CONTROVERSY REGARDING GENDER disparity in stroke treatment and outcomes. Many small studies suggest that women have worse outcomes than men after stroke, and some authors have suggested that women are less likely to receive thrombolysis or other interventions than men. However, there is a dearth of large, population-based studies that have examined gender differences in treatment and outcome. Zhou et al investigated sex differences in stroke case fatality in all published studies based on a comprehensive meta-analysis. A systematic search of all published databases was made for papers published from 1992 through 2009, groups were pooled, and a random effects model was used to find sex differences in cases of fatality of stroke with a Mantel-Haenzel method. A meta-regression analysis was also performed.

Thirty six population-based studies, along with three randomized clinical trials (RCTs), representing 125,227 men and 115,511 women, were included and analyzed. For the pooled group, there was an overall hazard risk of 1.13 for women compared to men. In the RCTs subgroup, there was a hazard risk of 1.27 for women and in the population-based studies a risk of 1.12. Although these data support the hypothesis that stroke case fatality is higher in women, more large, multicenter clinical trials are needed to determine this with more certainty. ■

from this study extend this concept to DLB. Combined genotyping results in this multicenter study find that risk for DLB is approximately eight times higher in subjects with GBA1 mutations compared with controls. This finding is important in understanding genetics of the "alpha-synucleinopathies," and once again underscores the overlap between PD and DLB. It also highlights the advantage of a collaborative approach. There are several fundamental weaknesses of this study, however. Most importantly, there was considerable variation in the methods used for mutation analysis. Efforts were made to adjust for this in the statistical analysis, but this makes interpretation of the results far more difficult. Also, some sites did not include control cases, and some cases relied on clinical diagnosis while pathology was available for others. Examination of results by site in fact reveals considerable variation, although all demonstrated a positive association. As noted above, there are differences in age and gender between the DLB/PDD and control groups. Finally, it would be interesting to see how these findings compare to other ethnic groups. At this time, genetic testing is not routinely recommended in patients presenting with parkinsonism, but as we move toward this potential, this and similar studies will be critically important. Moreover, a better understanding of genetic mechanisms underlying the development of parkinsonism may provide novel therapeutic targets, and the finding of GBA1 association with PD, PDD, and DLB newly establishes the importance of lysosomal function in these challenging disorders. ■

Is Tumefactive Demyelination Different from MS?

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MPH

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Gauthier reports she receives research support from EMD Serono, Biogen Idec, and Novartis Pharmaceuticals, and is on the speakers bureau for Biogen Idec and Teva Neurosciences.

Synopsis: *Patients presenting with tumefactive demyelinating lesions have MRI characteristics indistinguishable from a primary central nervous system tumor. Many patients go on to have relapsing-remitting disease and may have recurrence of tumefactive lesions.*

Source: Nagappa M, et al. Tumefactive demyelination: Clinical, imaging, and follow-up observations in thirty-nine patients. *Acta Neurol Scand* 2013;128:39-47.

LARGE, ATYPICAL DEMYELINATING LESIONS ON MRI CAN BE difficult to distinguish between primary central nervous system tumors and are referred to as "tumefactive" demyelinating lesions. Our understanding of these lesions and how they relate to multiple sclerosis (MS) has been described in only a few key publications. The largest series was reported by Lucchinetti et al, in which the clinical and MRI features of 168 patients with biopsy-proven tumefactive demyelinating disease were described.[1] That report highlighted that the majority of these patients went on to have a typical relapsing course of MS and therefore presented a broader spectrum of the disease. In this current study by Nagappa et al, the authors similarly describe a cohort of patients with tumefactive demyelinating disease.

Thirty-nine patients with a monophasic or relapsing-remitting neurologic illness, an intracranial "mass" lesion > 2 cm suggestive of demyelination, and/or clinical-radiological resolution following steroid therapy were diagnosed as having a tumefactive demyelinating lesion. Categorization for lesion site/number, edema pattern, and enhancement pattern were based on previously published criterion.[1] The most common presenting symptoms were hemiparesis, cerebellar symptoms, and signs of increased intracranial pressure (headache, vomiting, papilledema, and altered sensorium). Seizures and aphasia, which are uncommon for a typical MS relapse, were noted to occur in a small number of patients. The most commonly involved sites on MRI were frontal lobe, parietal lobe, and corpus callosum; in addition, only a minority had a solitary lesion (35.8%). The most common pattern of enhancement was partial ring enhancement; however, complete ring, patchy, uniform, and lack of enhancement also were found. A moderate level of edema (extending 1-3 cm from the lesion) was present in about one-third of the patients with the remaining having minimal or no edema. The results of 19 biopsies revealed typical cellular infiltrates of acute demyelinating lesions, well demarcation of myelin loss, and a relative preservation of axons. Limited follow-up of 13/22 monophasic patients over a mean of 8.3 months revealed that complete neurological recovery occurred in only 53.5%. Serial imaging in only eight monophasic patients revealed significant resolution in 75% of patients. However, two had evidence of new demyelinating lesions. Of the 17 with a relapsing-remitting course, 10 were reported to have relapse symptoms prior to the presentation, although never given the diagnosis of MS. Twelve of these patients were followed for a mean of 37.8 months, and within this time, 13 relapses occurred. Interestingly, MRI revealed new tumefactive lesions for 10 of these subsequent relapses and 60% occurred in the same location. All but one patient received steroids and three patients required additional treatment with plasmapheresis. There were no distinguishing features between the monophasic and relapsing-remitting subgroups.

■ **COMMENTARY**

We tend to approach patients with tumefactive demyelinating lesions differently, but in fact, these types of lesions fall within the clinical spectrum of MS. Is there any way to spare a patient a brain biopsy? Interestingly, in both this series and that reported by Lucchinetti, the majority of patients had multiple lesions; thus, with this feature, as well as any history of prior relapse, there should be a suspicion for demyelination and an attempt to avoid a biopsy.

What should we expect from these patients moving forward? Unfortunately, the main limitation of this study was the limited follow-up, especially within the monophasic group. The majority of the patients who presented with a first episode in the series published by Lucchinetti went on to have MS. Therefore, I suspect that the number considered monophasic for this study is overestimated. Interestingly, in this study, there were recurrences of tumefactive lesions, and even more intriguing is that they occurred within the same region. Lucchinetti reported that the presence of tumefactive lesions (including the small minority with recurrence of these lesions) did not dictate a worse disease course as compared to a population-based matched MS cohort. In summary, it appears that tumefactive lesions occur as part of MS and must be considered when facing potential biopsy for a cranial lesion and once identified, treated as typical MS. ■

Reference

1. Lucchinetti CF, et al. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. *Brain* 2008;131(PT 7):1759-1775.

Is Chronic Cerebrospinal Venous Insufficiency Implicated in the Pathogenesis of MS?

ABSTRACT & COMMENTARY

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *In this case-control study, the authors report that there is no difference in the prevalence of chronic cerebrospinal venous insufficiency in patients with multiple sclerosis vs non-multiple sclerosis participants.*

Source: Barreto AD, et al. Chronic cerebrospinal venous insufficiency: Case-control neurosonography results. *Ann Neurol* 2012 Dec 13; DOI: 10.1002/ana.23839 [Epub ahead of print].

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. The exact etiology triggering the disease has not been elucidated. In a study published in 2009, Zamboni et al put forth the hypothesis that chronic cerebrospinal venous outflow impairment was a potential cause for the pathogenesis of MS and they reported that patients benefit from procedures to correct this obstruction.[1] They defined criteria for diagnosis of what was termed "chronic cerebrospinal venous insufficiency or CCSVI." In the wake of this report, widespread dissemination through social networks and websites on the Internet triggered tremendous interest among MS patients. Numerous MS patients sought and underwent diagnostic procedures for the detection of CCSVI, and many of them went on to have endovascular corrective procedures. These surgical interventions have not been without harmful effects, including death from intracranial hemorrhage. In light of the interest generated by the hypothesis that CCSVI was the underlying cause of MS, and endovascular procedures to correct CCSVI were touted as a cure for MS, several independent studies were undertaken to investigate this hypothesis. The present study examines this hypothesis.

In this single-center, prospective, case-control study, 276 subjects participated, including 206 MS patients and 70 non-MS participants, including healthy volunteers and patients with other neurologic diseases. A certified neurosonologist who was blinded to the diagnosis performed the sonography tests. Extracranial and intracranial vessels were imaged. They included the internal jugular and vertebral veins and the deep cerebral veins. After acquisition of the images and flow velocity data, it was analyzed in a blinded manner without prior knowledge of the study subjects' diagnosis or any other information that could potentially bias the assessment. The mean age of the MS patients was 48.3 ± 9.9 years, while that of the non-MS participants was 44.3 ± 11.8 years ($P < 0.007$). Among MS patients, the mean disease duration from onset of symptoms was 13.7 ± 10 years, and the mean Expanded Disability Status Scale was 2.6 ± 2.0.

The participants were assessed to determine if they met the criteria for CCSVI and if there was a specific pattern seen in patients with MS. According to the diagnostic criteria proposed by Zamboni, patients need to meet at least two of five criteria to have a diagnosis of CCSVI. The five diagnostic criteria were based on extracranial reflux, intracranial reflux, B-mode jugular stenosis, detection of flow by Doppler in jugular and vertebral veins, and upright vs supine cross-sectional area in the jugular veins, respectively. In the present study, 82/276 (29.7%) subjects fulfilled at least one of the Zamboni criteria. There was no difference in the proportion of patients who met the criteria in either group, MS patients vs non-MS participants. There was also no statistically significant difference between MS (3.88%) and non-MS (7.14%) subjects who met at least two criteria ($P = 0.266$). The proportion of subjects with 0, 1, or 2 criteria did not differ significantly across the groups. The authors concluded that there was no difference in the incidence of venous outflow patterns among MS and non-MS subjects, and the study did not demonstrate any association between CCSVI and MS.

■ COMMENTARY

CCSVI has received immense attention as a plausible cause for MS, and despite the lack of proven efficacy, numerous patients have undergone endovascular procedures to correct CCSVI. Since the publication of Zamboni's initial reports, multiple centers have investigated a potential association between CCSVI and MS, and some centers have even conducted clinical trials evaluating outcomes af-

ter corrective procedures for CCSVI in patients with MS. A tremendous amount of resources have been spent testing this hypothesis. None of these studies have demonstrated a causative association or therapeutic benefit from surgical interventions. The present study adds to the overwhelming evidence that CCSVI is not implicated in the pathogenesis of MS. Our experience with this hypothesis has highlighted the need for the MS community to approach theories, without clear scientific basis, with great caution and deter patients from undergoing often expensive and potentially hazardous procedures without any proven benefit. ■

Reference

1. Zamboni P, et al. Chronic cerebrospinal venous insufficiency in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2009;80:392-399.

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

1. Bickerstaff brainstem encephalitis is similar to Miller Fisher syndrome in all of the following *except*:
a. presence of anti-GQ1b antibody.
b. presence of cerebrospinal fluid cytoalbuminogenic dissociation.
c. presence of altered consciousness.
d. history of preceding infection.
e. may respond to plasma exchange or intravenous immunoglobulin.

2. Which of the following statements is true regarding childhood fibromuscular dysplasia?
a. The intimal fibroplasia form is rare.
b. Recurrence risk of ischemic stroke is higher than in adults with fibromuscular dysplasia.
c. Recurrence risk of ischemic stroke is lower than in adults with fibromuscular dysplasia.
d. The string of beads appearance on angiography is common.

3. Mutations in GBA1 appear to increase the risk of developing all of the following *except*:
a. Parkinson's disease.
b. Gaucher disease.
c. Alzheimer's disease.
d. Dementia with Lewy bodies.
e. Parkinson's disease with dementia.

4. Which of the following is a characteristic of the enhancement pattern of a tumefactive demyelinating lesion on MRI?
a. No enhancement
b. Patchy enhancement
c. Partial ring enhancement
d. Complete ring enhancement
e. All of the above

5. Which of the following statements is *not* true about multiple sclerosis?
a. Multiple sclerosis is a chronic inflammatory disease of the central nervous system.
b. Chronic cerebrospinal venous insufficiency (CCSVI) has been proven as a cause of multiple sclerosis.
c. Endovascular treatment of CCSVI has resulted in fatal complications.
d. Endovascular treatment of CCSVI has not resulted in improved outcomes for patients with multiple sclerosis.

6. Aspirin, given alone, is better than aspirin combined with clopidogrel in reducing the risk of stroke after a transient ischemic attack.
a. True
b. False

7. Men are more likely to die after a stroke than women.
a. True
b. False

In Future Issues:

Restless Legs Syndrome

Clinical Briefs in Primary Care™

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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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Continuing Warfarin for Pacemaker/ICD Implantation is Safer Than Bridging

Source: Birnie DH, et al. *N Engl J Med* 2013;368:2084-2093.

The decision process to determine the optimal scheduling of antithrombotic therapy in the perioperative period is complex. The most recent AT9 CHEST guidelines suggest discontinuation of warfarin 5 days prior to pacemaker/implantable cardioverter-defibrillator (PCM-ICD) implantation, complemented with heparin bridging. This method is somewhat unwieldy, expensive, and has not been confirmed by a large, randomized trial as optimizing risk reduction. During transition from warfarin to heparin, an interval of increased risk for thromboembolism occurs in some, and the use of heparin has also been shown to frequently be associated with device-pocket hematoma.

In the Bridge or Continue Coumadin for Device Surgery Randomized Controlled trial, 681 PCM-ICD patients were randomized to continued warfarin or heparin bridging. Patient selection criteria also included high baseline annual thromboembolism risk (≥ 5%). The primary outcome of the trial was incidence of significant device-pocket hematoma (DPH), which can result in prolongation of hospitalization, need to stop anticoagulation, or additional surgery.

There was a dramatic difference in risk for the DPH primary endpoint between subjects continued on warfarin uninterrupted (3.5%) and subjects randomized to heparin bridging (16%). Risk reduction through continuation of warfarin was not associated with any increased incidence of major surgical adversities compared with bridging. Continuation of warfarin, uninterrupted, was associated with more than 80% reduction in risk of DPH compared to bridging, while not compromising other measures of safety. ■

Bariatric Surgery Impact on Cholesterol Metabolism

Source: Benetti A, et al. *Diabetes Care* 2013;36:1443-1447.

Bariatric surgery techniques are often described as restrictive (e.g., gastric banding) or diversionary (e.g., biliointestinal bypass). While diversionary surgery (DIV) is associated with greater weight loss and more rapid metabolic changes than restrictive surgery (RES), the greater simplicity and reversibility of the latter are pertinent in selecting which intervention is preferred.

Although the impact of bariatric surgery on diabetes has been much publicized, the impact of bariatric surgery on cholesterol is less well recognized. To date, most of the favorable impact on cholesterol has been attributed to weight loss. Over the long term, DIV is associated with greater weight loss than RES. However, since DIV and RES are associated with similar overall weight loss during the first postoperative 6 months, one could compare cholesterol metabolism of the two types of surgery independent of weight loss.

Benetti et al compared cholesterol metabolism in DIV with RES (n = 20). They found that with DIV, reduced cholesterol absorption produced a decrease in LDL and non-HDL, associated with enhanced catabolic LDL receptor activity in the liver.

Because metabolic changes in both groups in reference to glucose, insulin, insulin resistance, and weight loss were similar, the authors suggest that these favorable cholesterol metabolic changes are induced specifically with DIV, and because weight loss over the specified interval was essentially equivalent, the changes in lipids are not fully explained by weight loss. ■

The Do-it-Yourself Diabetes Diagnosis Kit

Source: Bethel MA, et al. *Diabetes Care* 2013;36:1483-1488.

In the last decade, the threshold for diagnosis of diabetes has expanded to lower levels of fasting glucose, inclusion of reference laboratory A1c, and refinement of the definitions of prediabetes. Use of the oral glucose tolerance test (OGTT) appears to be less and less necessary, considering the relative convenience of other diagnostic tests. Could a self-administered OGTT change the balance and be a positive addition to the diagnostic portfolio?

Bethel et al report on a self-administered OGTT home use kit (SmartGRA) used by 30 diabetic and non-diabetic subjects. The kit includes instructions to guide the user through the process of timed capillary glucose measurement as well as a wireless data recorder for glucose levels, the results of which are *not* visible to the user (glucose measurements are wirelessly transmitted to the clinic for evaluation).

Was self OGTT accurate? In a word,

yes. Comparison of OGTT reports generated by SmartGRA vs office-based testing found comparable reproducibility of results. Although the results of home OGTT tended to overestimate glucose levels compared to the reference laboratory, this emerged as a problem with device calibration, which should be able to be remediated. Overall, subjects found the device easy to use.

As a proof-of-concept trial, these results lend credence to the idea that OGTT — generally conceded to be sufficiently unwieldy so that other diagnostic tests are preferred — might merit reconsideration if a well-calibrated, similarly patient-friendly device comes to market. ■

Low Creatinine Excretion Associated with Mortality in Type 2 Diabetes

Source: Sinkeler SJ, et al. *Diabetes Care* 2013;36:1489-1494.

Creatinine excretion (CER), as measured by the 24-hour urinary excretion of creatinine, has recently been noted to be associated with increased mortality, both in persons with underlying renal disease and the general population. CER reflects overall lean muscle mass, so that declines in CER may simply reflect deconditioning, loss of muscle mass, cachexia, malnutrition, etc., each of which may have a negative impact on mortality.

Sinkeler et al report on data accrued from two previously completed trials of angiotensin receptor blockers in diabetic nephropathy: Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan trial and the Irbesartan Diabetic Nephropathy trial. Twenty-four hour urinary CER was measured at baseline for the majority (n = 2360) of participants. Since mortality data from both trials are available, the relationship between CER and mortality can be evaluated.

Across the population studied, each halving decrement of CER was associated with a doubling of mortality risk. Since the primary association of CER is with muscle mass, the authors pose the interesting question of whether efforts expended to improve muscle mass, such as enhanced exercise and nutrition, might favorably effect mortality in this population. ■

Diabetes and Cognitive Function

Source: Spauwen PJJ, et al. *Diabetes Care* 2013;36:1554-1561.

The relationship between vascular disease and type 2 diabetes is consistent: Risk for microvascular events (retinopathy, neuropathy, and nephropathy) and macrovascular events (stroke and MI) is increased compared to non-diabetics. Additionally, when diabetics suffer macrovascular events, the consequences are typically more severe than similar events in non-diabetics.

The etiology of cognitive impairment is often multifactorial, including vascular insufficiency. Diabetics have a higher prevalence of cognitive impairment than non-diabetics, but the rate of cognitive decline in diabetics has not been studied.

The Maastricht Aging Study is comprised of 10,396 adults residing in the province of Limburg, the Netherlands. A sample from this population (n = 1290) underwent extensive neuropsychological testing at baseline, 6 years, and 12 years. At baseline, approximately 5% of the population had type 2 diabetes, with an incidence of an additional 5% over subsequent 6-year intervals.

When compared with controls, diabetics had a significant rate of cognitive decline over 6 and 12 years. Even when adjusted for variables that are more commonly comorbid in diabetics (hypertension, dyslipidemia, obesity), the acceleration in cognitive decline was greater in diabetics. As might be intuitive, diabetics with baseline cognitive impairment progressed at a more rapid rate than those without. Whether any specific intervention among diabetics (e.g., better control of glucose, lipids, blood pressure) might ameliorate the exaggerated rate of cognitive decline remains to be determined. ■

Benefits of Screening for Lung Cancer with Low-Dose CT

Source: The National Lung Screening Trial Research Team. *N Engl J Med* 2013;368:1980-1991.

Lung cancer (LCA) is responsible for more deaths than any other cancer worldwide. The burgeoning growth of smoking in developing countries suggests that this dismaying fact is unlikely to diminish in the foreseeable future. Clinical trials of screening for LCA through chest x-ray (CXR) did not show improved outcomes, likely because of its relatively poor discriminative ability in early disease.

The National Lung Screening Trial enrolled smokers and ex-smokers with at least a 30 pack-year history. Participants were randomized to an annual low-dose CT × 3 (n = 26,714) or standard chest x-ray (n = 26,035).

A positive radiographic finding on at least screening was seen in three times as many CT screenees as chest x-ray (27.3% vs 9.2%). LCA was diagnosed in 1.1% of the CT group vs 0.7% in the CXR group.

Screening for LCA was found to reduce LCA-related mortality by 20% and all-cause mortality by 7%.

Most of the abnormalities detected by low-dose CT screening were benign, so that the positive-predictive value for a positive CT was only 3.8% (i.e., about 4% of study subjects with any positive suspicious finding on CT turned out to have LCA). Reassuringly, repeatedly negative low-dose CT had a negative predictive value of 99.9% (i.e., essentially no one who had negative sequential CT screening was diagnosed with LCA during the screening and follow-up period). ■

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PHARMACOLOGY WATCH

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Prostate Medications and Cancer Risks — New Evidence

In this issue: Risk of high-grade prostate cancers; clopidogrel and stroke risk; antibiotics and statins; and FDA actions.

Prostate cancer risk and 5-ARIs

The 5-alpha reductase inhibitors (5-ARI) finasteride (Proscar) and dutasteride (Avodart) are used to treat lower urinary tract symptoms in men. They are known to reduce prostate-specific antigen (PSA) levels and there was hope that they may also reduce the incidence of prostate cancer. But in two large trials, PCPT (finasteride) and REDUCE (dustasteride), despite a nearly 25% reduction in the overall rate of prostate cancer, the risk for high-grade prostate cancers was increased (Gleason score 8-10). Debate has raged for the last several years about the significance of these findings and whether the increase was real or spurious due to detection bias. A new study from Sweden attempts to clarify this issue. Using the National Prostate Cancer Register along with prescription data, nearly 27,000 cases of prostate cancer were identified along with some 134,000 matched controls. More than 7800 men were exposed to a 5-ARI, including 1500 with prostate cancer and 6300 controls. As noted in previous studies, the risk of prostate cancer decreased with increasing duration of use of a 5-ARI. With 3 years of treatment, the risk of prostate cancer was 28% lower in the treatment group (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.59-0.89; $P < 0.001$ for trend). The reduction was seen primarily for Gleason score 2-6 and score 7 tumors ($P < 0.001$ for trend for both). However, as opposed to previous studies, the risk for higher grade tumors was not significantly increased, although the risk was not decreased either. By 3 years, the OR was 1.23 (95% CI, 0.90-1.68; $P = 0.46$ for trend), but did not reach statistical significance. The ORs for shorter exposures were 0.96 for 0-1 year exposure, 1.07 for 1-2 years, and 0.96 for 2-3 years. The authors conclude that men treated with a 5-ARI for lower urinary tract symptoms had a lower risk of prostate cancer with Gleason scores 2-7 and no evidence of increased risk of Gleason score 8-10 of cancers up to 4 years of treatment (*BMJ* 2013;346:f3406). The FDA issued a safety warning in 2011 regarding finasteride and dutasteride and the risk of high-grade prostate cancers and it is unlikely that this study alone will reverse that, but it is reassuring for the millions of men who take these drugs for lower urinary tract symptoms. ■

Clopidogrel could reduce stroke risk

Adding clopidogrel to aspirin in patients with minor stroke or a transient ischemic attack (TIA) may help reduce the risk of stroke within the next 90 days, according to a new study from China. In a randomized, double-blind, placebo-controlled trial, nearly 5200 patients were seen within 24 hours after onset of minor ischemic stroke or high-risk TIA and randomized to a combination of clopidogrel with aspirin or aspirin alone. The combination group was given clopidogrel at an initial dose of 300 mg followed by 75 mg per day for 90 days along with aspirin 75 mg per day for the first 21 days, while the aspirin alone group got placebo plus aspirin 75 mg for 90 days. The primary outcome was stroke (isch-

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emic or hemorrhagic) during 90 days of follow-up in an intention-to-treat analysis. Stroke occurred in 8.2% of the clopidogrel-aspirin group as compared to 11.7% in the aspirin alone group (hazard ratio 0.68; 95% CI, 0.57-0.81; $P < 0.001$). Moderate or severe hemorrhage occurred in seven patients in the clopidogrel-aspirin group and eight in the aspirin alone group. The rate of hemorrhagic stroke was the same (0.3%) in both groups. The authors conclude that among patients with TIA or minor stroke who are seen within the first 24 hours of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the next 90 days. The combination does not increase the risk of hemorrhagic stroke or hemorrhage (*N Engl J Med* published online June 26, 2013). An accompanying editorial states that this trial "proves the concept that dual platelet therapy can be more effective than single platelet therapy in preventing early recurrent stroke in patients with acute symptomatic atherothrombosis...," and also shows that dual platelet therapy can be given without excess harm in patients with acute focal brain ischemia. There is slight concern that the results may not apply to non-Chinese patients with different forms of underlying arterial disease (*N Engl J Med* published online June 26, 2013). ■

Antibiotic coprescription and statins

Use caution if you prescribe clarithromycin or erythromycin to patients on statins. Both drugs (but not azithromycin) inhibit cytochrome P450 isoenzyme 3A4, which can increase blood concentrations of statins, especially atorvastatin, simvastatin, and lovastatin. Researchers from Canada looked at the records of continuous statin users who were prescribed clarithromycin (n = 72,591) or erythromycin (n = 3267) with azithromycin use as a comparator (n = 68,478). The risk of hospitalization for rhabdomyolysis within 30 days was the main outcome. Although the absolute risk was low, concomitant use of clarithromycin/erythromycin with atorvastatin, simvastatin, or lovastatin was associated with a higher rate of hospitalization with rhabdomyolysis, especially in those with acute kidney injury. There was also an increase in all-cause mortality when the drugs were combined (absolute risk for rhabdomyolysis 0.02%, with acute kidney disease 1.26%, all-cause mortality 0.25%, relative risks 2.17, 1.78, and 1.56, respectively). These data suggest that coprescription of clarithromycin or erythromycin with a statin that is metabolized by CYP3A4 (atorvastatin, simvastatin, and lovastatin) increases the risk of statin toxicity (*Ann Intern Med* 2013;158:869-876). ■

FDA actions

The FDA has approved paroxetine for the treatment of hot flashes (vasomotor symptoms) associated with menopause. Paroxetine is a selective serotonin reuptake inhibitor (SSRI) and has the same active ingredient in the antidepressant Paxil. It is the first non-hormone based drug approved for this indication. The safety and efficacy of the drug was established in two randomized, double-blind, placebo-controlled trials of 1175 postmenopausal women with moderate-to-severe hot flashes that showed paroxetine was more effective in relieving symptoms than placebo. This new form of paroxetine contains 7.5 mg of the drug and is dosed once daily at bedtime. Paroxetine for depression and other psychiatric indications is dosed at 10-40 mg. All forms of paroxetine carry a boxed warning about increased risk of suicide. There is also concern about reduced effectiveness of tamoxifen if both medications are taken together. Paroxetine 7.5 mg for hot flashes is marketed by Noven Therapeutics as Brisdelle.

The FDA has approved a new formulation of selegiline — a once-daily, orally dissolving tablet — for the treatment of Parkinson's disease (PD) in patients who are losing responsiveness to levodopa/carbidopa. Most PD patients start treatment with levodopa/carbidopa, but for many, the effectiveness wanes with increasing "off" periods during which time symptoms worsen. In clinical trials, the new combination of selegiline reduced "off" periods by an average of 2.2 hours per day compared to 0.6 hours for placebo. The dissolvable tablet uses a new system that delivers more drug at a lower dose. The drug company claims this results in fewer side effects. Selegiline, a monoamine oxidase (MAO) inhibitor, has been available as a generic and also as the branded drugs Eldepryl and Zelapar. Like other MAO inhibitors, it can cause severe, even fatal, reactions if given in combination with certain other drugs including meperidine, tramadol, SSRIs, TCA antidepressants, and the over-the-counter medication dextromethorphan. The new orally dissolving selegiline is marketed by Valeant Pharmaceuticals as Zelapar.

The FDA has approved the TNF blocker golimumab for the treatment of ulcerative colitis. The drug was previously approved to treat rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The approval for ulcerative colitis was based on two studies of more than 800 patients, one group had failed other treatments and the other group were responders who were evaluated for maintenance. In both groups, golimumab was superior to placebo. Golimumab is marketed by Janssen Biotech as Simponi. ■