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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Zika Virus Infection and Guillain-Barré Syndrome: The Evidence Grows

By Joseph E. Safdieh, MD

Vice Chair and Associate Professor, Weill Cornell Medical College

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

SYNOPSIS: A recent Zika outbreak in Colombia was associated with a significant increase in Guillain-Barré syndrome (GBS) rates, with laboratory evidence of definite or probable Zika infection in more than half of the GBS cases.

SOURCE: Parra B, Lizarazo J, Jimenez-Arango JA, et al. Guillain-Barre syndrome associated with Zika virus infection in Colombia. *N Engl J Med* 2016;375:1513-1523.

Zika virus is a mosquito-born flavivirus that has recently emerged in Central and South America as well as the Caribbean and southern parts of the United States. Although humans typically are infected with Zika via a mosquito bite, Zika virus can be transmitted from an infected human to an uninfected human via sexual contact. Much attention has been paid to the Zika virus-associated microcephaly in children born to some mothers infected during pregnancy. During an earlier Zika virus outbreak in French Polynesia, there was an indication of an association with Guillain-Barré syndrome (GBS). As Zika has moved through the Americas, surveillance for GBS cases has been set up in a number of countries to document the case rate and to determine association with recent Zika virus infection. This paper presents data from the GBS surveillance program in Colombia.

Colombia reported its first case of Zika virus infection in October 2015, and by January 2016, cases were reported in most regions of the country. At the same time, hospitals were noting an uptick in the number of patients diagnosed with GBS. Surveillance of GBS cases was set up to track the number of GBS cases, the

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clinical features, and the laboratory testing to assess for recent or current Zika virus infection. GBS cases were diagnosed based on Brighton criteria. For Brighton criteria, level 1 requires both abnormal nerve conduction (NCS) studies and cerebrospinal fluid (CSF) cytoalbuminologic dissociation, level 2 requires either NCS or CSF abnormalities, and level 3 is based on clinical features alone without support from testing. Zika virus infection was categorized as definite (confirmed by Zika RNA-PCR in serum, urine, or CSF), probable (positive CSF and/or serum ELISA for flavivirus with negative Dengue serologies), or suspected (supportive clinical syndrome without supportive testing). Supportive clinical symptoms of Zika are quite nonspecific and include rash, fever, conjunctivitis, arthralgia, myalgia, and periarticular edema.

Parra et al reported on the results of GBS surveillance in Colombia from January through March 2016. Of note, 270 cases of GBS were reported throughout the country over these three months, as compared to an estimated baseline in Colombia of 250 cases per year. Sixty-eight GBS patients presented to the specialized centers that were involved for the purposes of this study. Of the 68 cases, 82% fulfilled Brighton criteria level 1 or 2 for the diagnosis of GBS. The majority of the patients had a typical ascending limb weakness pattern, with 50% developing bifacial paresis. A small number of cases of Miller Fisher variant also occurred. Median age of the patients was 47 years, with 56% male predominance. Eighty-two percent of those who underwent lumbar puncture demonstrated elevated CSF protein, with median CSF white blood cell count of 0 per CC. Seventy-eight percent of those who underwent electrophysiologic testing demonstrated features consistent with acute inflammatory demyelinating polyradiculopathy. Most patients were treated with intravenous immunoglobulin. Thirty-one percent of the patients required mechanical ventilation, and three patients died.

Of the 68 GBS patients included in this analysis, 97% had a recent illness suspicious for Zika virus infection in the previous four weeks. These symptoms lasted a median of four days and occurred a median of seven days before GBS symptom onset. Forty-two of the 68 patients with GBS underwent diagnostic testing for Zika virus. On laboratory testing, 17 (25%) of the patients had definite Zika infection, 18 (26%) of the patients had probable Zika infection, and the rest were considered suspected cases. Of note, 16 of the 17 patients with definite Zika virus demonstrated positive PCR in the urine, but only three in the CSF and one in the serum. Of the patients with definite and probable Zika infection, two developed GBS symptoms at the same time as the Zika symptoms, 20 (48%) patients developed GBS symptoms immediately after Zika infection with no post-Zika recovery period, and the remainder of the patients developed GBS with a more typical post-infectious course.

■ COMMENTARY

This is an important study because it offers more evidence of a possible connection between Zika virus and the development of GBS. Although it cannot be stated with certainty that Zika can trigger GBS, the evidence in this study, in addition to the previously described GBS outbreak after Zika infection in French Polynesia, lends further support to the association. It is worth noting that more than half of the GBS cases in this cohort had definite or probable Zika exposure. It is interesting that in some of the GBS cases, the symptoms developed either concurrently or immediately following the Zika symptoms, suggesting a possible parainfectious pathogenesis. This is distinct from the usual post-infectious temporal onset of GBS in patients with other known triggers such as *Campylobacter jejuni*. It is not known if the Zika virus is directly pathogenic to peripheral nervous system structures.

The symptoms, signs, and diagnostic testing findings in Zika-associated GBS are similar to the GBS typically seen in traditional clinical settings. The paper does not provide follow-up on outcomes, but it would be important to know whether these patients responded to therapy. Zika virus cases transmitted via mosquito vector already have been reported in Florida and Texas. Sexually transmitted cases of Zika have been reported in multiple states. U.S. neurologists should be familiar with the possible association between Zika and GBS and should ask about recent travel history (of the patient and any sexual partners) when encountering a patient with GBS. ■

ABSTRACT & COMMENTARY

Electrical Brain Stimulation for Primary Progressive Aphasia

By Douglas Labar, MD, PhD

Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In this pilot study, transcranial direct current stimulation appeared to improve some aspects of verbal object identification and naming in a small number of patients with primary progressive aphasia.

SOURCE: Teichmann M, Lesoil C, Goddar J, et al. Direct current stimulation over the anterior temporal areas boosts semantic processing in primary progressive aphasia. *Ann Neurol* 2016;80:693-707.

Transcranial direct current stimulation (tDCS) delivers stimulation via conducting sponges affixed to the patient's skull. A steady state current is passed through the scalp and skull and into the brain. The resultant changes in resting membrane potentials alter neuronal firing rates, thus influencing brain function. Historically, current has been passed through large brain regions, often in a multilobar fashion from hemisphere to hemisphere. Recent technical advances have allowed more selective stimulation of topographically discrete zones. This permits isolation of unique cortical functions for detailed investigation.

One such small cortical area of interest is the temporal lobe tip. This area can be targeted for excitatory (anodal) or inhibitory (cathodal) focal stimulation. In primary progressive aphasia (PPA) patients, the left temporal tip shows hypoactive metabolism, on positron emission tomography (PET). Thus, it may be hypothesized that excitatory anodal tDCS of the left temporal tip may improve language function in PPA. Furthermore, inhibitory cathodal stimulation of the right temporal tip may reduce its interference with left side function, restoring interhemispheric balance, and in turn improving language.

In 2016, Teichmann et al treated 12 PPA patients with tDCS. Patients were tested before and after single 20-minute sessions of active or sham tDCS. Several features of the research were designed to segregate specific from nonspecific treatment effects. Patients were selected for the presence of very focal (and testable) deficits, which is a characteristic of the semantic variant of PPA. Clinical evaluation employed tests involving materials matching. Presented items for the matching tasks were subdivided into living (e.g., animals) vs. nonliving (e.g., inanimate objects) items, and into visual vs. verbal modalities. Normal control subjects were included to eliminate any performance changes that might not be related to treating the PPA.

In the verbal modality, which covered the most important deficits in these patients, left-excitatory plus right-inhibitory tDCS improved post-stimulation performance. In the visual modality, there were no changes due to stimulation. When the testing material was in the verbal modality and the living category, right-side inhibitory tDCS, but not left-side excitatory tDCS, improved performance. There were no nonspecific tDCS-associated changes in overall cognitive and attentional functions.

■ COMMENTARY

This study design and results by Teichmann et al demonstrated a thoughtful application of our knowledge concerning tDCS physiological effects to a disease state's physiological functional disturbances. Most likely, excitatory stimulation, to antagonize the patients' depressed cortical activity state (as demonstrated on their baseline PET scans), truly led to improved verbal semantic function. This leads to the interesting concept of selecting and targeting brain illnesses and treatments based on baseline imaging functional assessments, such as the baseline hypometabolic temporal tips, seen in the patients in this study.

However, it is not just the location and nature of the brain hypofunction treated in this study that is of interest. The authors provided evidence that an imbalance between hemispheres, and an intervention to help re-establish appropriate interhemispheric balance, were significant operative components in producing a good outcome. This is an example of an evolution into neurological assessments and treatments directed toward restoring and maintaining critical neural networks and balances, as opposed to focusing on the discrete functions of isolated brain nuclei or fiber pathways.

This study may have several avenues for follow-up research. Do the abnormalities on baseline PET scans improve in parallel with the improvements in semantic functions? Finally, the durability of the effects would be of interest. Is tDCS somehow temporarily boosting

neural function, which then returns to baseline? Or are the effects more long-lasting? Were the latter true, this would be of considerable interest for future clinical applications. ■

ABSTRACT & COMMENTARY

Bull's-eye Sign in Parsonage-Turner Syndrome

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: High-resolution MRI of peripheral nerves can help make an accurate diagnosis of the Parsonage-Turner syndrome by revealing a bull's-eye sign in cross-sectional images of the nerve.

SOURCE: Sneag DB, Saltzman EB, Meister DW, et al. The MRI bullseye sign: An indicator of peripheral nerve constriction in Parsonage-Turner syndrome. *Muscle Nerve* DOI: 10.1002/mus.25480. [Epub ahead of print].

Localization of the lesion in neuralgic amyotrophy, also known as Parsonage-Turner syndrome (PTS), can be challenging. Differentiating upper trunk plexopathy from C5-6 radiculopathy, or lower trunk plexopathy from C8-T1 radiculopathy, and particularly identifying mononeuropathy as due to PTS, is difficult electrodiagnostically when sensory nerve conduction studies or needle electromyography are normal. In addition, cervical magnetic resonance imaging (MRI) may cloud the diagnosis by demonstrating multilevel foraminal stenosis. Torsion, or hourglass constrictions (HGCs), of a peripheral nerve have been found during surgery in PTS patients with mononeuropathy, but have been rarely identified by MRI. Recent technological advances, including software and surface coil developments, have enabled high-resolution peripheral nerve MRI to detect focal fascicular abnormalities of nerves both at the plexus and extra-plexus levels. By identifying hourglass constrictions in PTS, MRI may be rendered more sensitive in diagnosing this disorder, and differentiating it from radiculopathy or mononeuropathy from other causes.

Six patients (four men and two women), mean age 43.3 years, with PTS based on history, clinical examination, and electrodiagnostic findings underwent 3.0 Tesla MRI of the brachial plexus, arm, elbow, and/or forearm, as indicated by the clinical findings, followed by surgical exploration. MRI studies were interpreted prior to surgery by a single radiologist specialized in peripheral nerve MRI, and nerve constriction was defined as a > 75% focal caliber change of the nerve trunk and/or individual nerve fascicle. All patients were found to have HGCs of affected nerves, and thus surgery focused on the site of identified constriction, with all patients undergoing neurolysis, and in one patient, nerve transfer. Surgery was performed a mean 12.4 months after symptom onset, and in all cases, only after electrodiagnostic studies confirmed absent or minimal recovery in these patients, affecting the suprascapular, radial, and axillary nerves, and the anterior interosseous nerve and pronator teres fascicles of the median nerve trunk.

Among 11 affected nerves, 23 constriction sites were identified. Within each nerve or fascicle, an average of 2.3 sites of constriction were seen, and all but two were associated with a bull's-eye sign within 2 cm proximal to the narrowing, manifested as a central hypointensity, encircled by peripheral signal hyperintensity, on intermediate-weighted fast spin echo or fat-suppressed imaging, or both, orthogonal to the nerve's longitudinal axis. Surgery confirmed the site of nerve constriction, but no definitive extrinsic cause was found to explain the narrowing. High-resolution MRI may play a more pivotal role in PTS diagnosis by identifying HGCs of affected nerves.

■ COMMENTARY

With an incidence as high as 1/1000, affecting men twice as often as women of all ages, and recurring in at least 25% of idiopathic cases, the pathophysiology of neuralgic amyotrophy, or PTS, remains unknown, encompassing infectious or immune triggers (10% may have concomitant hepatitis E virus infection in the acute phase of PTS), mechanical causes (10% are reportedly preceded by excessive arm exercise), and genetic factors. When presenting with the typical history of extreme shoulder or arm pain followed hours to days later by muscle weakness and appropriate focal clinical findings, diagnosis may be made in the office. Often, neurologists rely on electrodiagnostic studies (NCS/EMG) to confirm the diagnosis but low sensitivity and sampling error diminish the diagnostic value. MRI demonstration of the bull's-eye sign appears to accurately localize hourglass constrictions and, although the cause is unknown, is supportive of a diagnosis of PTS. ■

ABSTRACT & COMMENTARY

How Useful is Amyloid PET Imaging in the Diagnosis of Dementia?

By Michael T. Lin, MD, PhD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

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

SYNOPSIS: In a prospective, observational study in multiple centers in Italy, amyloid PET imaging was shown to be negative in 35% of patients who met clinical criteria for a diagnosis of Alzheimer's disease.

SOURCES: Boccardi M, Altomare D, Ferrari C, et al. Assessment of the incremental diagnostic value of florbetapir F18 imaging in patients with cognitive impairment: The incremental diagnostic value of amyloid PET with [18F]-florbetapir (INDIA-FBP) study. *JAMA Neurol* 2016;73:1417-1424.

Caselli RJ, Woodruff BK. Clinical impact of amyloid positron emission tomography — is it worth the cost? *JAMA Neurol* 2016;73: 1396-1398.

Amyloid plaques are a defining pathological hallmark of Alzheimer's disease (AD), the most common cause of cognitive impairment with aging, but they are microscopic and, until recently, were not readily detectable pre-mortem. In 2012, the FDA approved the first PET ligand, florbetapir, for detecting amyloid plaques in the living brain. Since then florbetaben and flutemetamol have also become commercially available. Unfortunately, amyloid PET scans are very expensive (~$5,000), and Medicare does not pay for it, arguing that it makes little practical difference and is not worth the cost (multiplied by the high incidence and prevalence of AD with aging), particularly in the absence of any effective therapy for AD. The recently published Incremental Diagnostic Value of Amyloid PET with [18F]-Florbetapir (INDIA-FBP) study and accompanying editorial addressed this issue of cost-effectiveness, looking at the effect of amyloid PET results on diagnosis, diagnostic confidence, and drug treatment.

The INDIA-FBP study is an open-label, multicenter study conducted in 18 AD evaluation units in northern Italy. Patients were eligible if they were between ages 50 and 85 years, had a pre-scan diagnostic confidence of AD between 15% and 85%, had at worst moderate dementia, had no contraindications to PET scan, and had no prior participation in a trial of an anti-amyloid agent. The authors estimated that these criteria selected 14-27% of new patients referred to their memory clinics. All eligible patients were consecutively enrolled. Subjects underwent routine evaluation by the local dementia expert (neurologist or geriatrician) as well as florbetapir amyloid PET. Prior to and immediately after disclosure of PET results, the local experts were asked to formulate their diagnosis, rate their confidence that the cognitive impairment was due to AD, and decide drug treatment. Pre- and post-disclosure diagnoses, confidence, and treatment plans were compared.

From Aug. 5, 2013, to Dec. 31, 2014, 228 consecutively eligible subjects were enrolled. Prior to disclosure of amyloid PET results, 165 were diagnosed with AD and 63 with a non-AD condition (37 with frontotemporal degeneration [FTD], 26 with other [largely vascular and Lewy body dementia]).

Of the 165 subjects with a pre-scan diagnosis of AD, a substantial proportion (35%) had a discordant PET result (amyloid negative), and in the majority (79%) of these cases, the diagnosis was changed to a non-AD condition. In the 21% of cases in which the diagnosis remained AD despite the negative PET result, the pre-scan confidence in the AD result was higher, suggesting that the presentation was very typical of AD. The authors noted that this false-negative rate (35% x 21% = 7%) matches the approximate sensitivity of florbetapir compared to autopsy (92%).

Of the 63 subjects with a pre-scan diagnosis of a non-AD condition, nearly half (48%) had a discordant PET result (amyloid positive). This proportion was similar in the 37 subjects diagnosed with FTD (48.6% were amyloid positive) and the 26 subjects diagnosed with some other condition (46.2% were amyloid positive). In the prescan-FTD/amyloid-positive subjects, 72% had their diagnosis changed to AD, consistent with the ability of AD to mimic FTD. However, in the pre-scan-non-FTD/amyloid-positive subjects, only 25% had their diagnosis changed to AD, consistent with the known high co-occurrence of AD pathology with vascular dementia and Lewy body dementia at autopsy.

Finally, AD treatment (cholinesterase inhibitors and memantine) was initiated in 65% of patients who were amyloid positive but not previously on AD treatment, and AD treatment was withdrawn in 33% of patients who were amyloid negative and previously receiving treatment.

■ COMMENTARY

These results show that even among dementia experts there can be substantial discordance between biomarker results and clinical impression of AD, and that amyloid PET results can make a substantial difference in diagnosis and AD drug treatment plan. Presumably, the discordance would be even larger with general neurologists or internists. A similar study is underway in the United States (Imaging Dementia--Evidence for Amyloid Scanning [IDEAS] study, www.ideas-study.org).

Although encouraging, it remains to be seen whether amyloid PET results make a difference in long-term outcomes, such as caregiver burden, healthcare utilization, and overall costs. In the absence of strongly effective therapy, it is arguable whether a difference in treatment with cholinesterase inhibitors and memantine is clinically significant. In their editorial, Caselli and Woodruff mentioned circumstances in which the economic justification might be clearer (e.g., applying for disability in someone still working), but these are highly selected circumstances. However, the field is rapidly evolving, with new biomarkers and new therapies that may actually modify the course of disease.[1] Thus, the cost-benefit analysis must be continually reassessed. ■

REFERENCE

1. Sevigny J, Chiao P, Bussiere T, et al. The antibody aducanumab reduces Aß plaques in Alzheimer's disease. *Nature* 2016;537:50-56.

ABSTRACT & COMMENTARY

Rituximab Treatment in Neuromyelitis Optica Spectrum Disorders

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal reports she receives grant/research support from Genzyme Corp., and is on the speakers bureau for Biogen Idec, Genzyme Corp., Acorda Therapeutics, and Teva Pharmaceuticals.

SYNOPSIS: Based on a meta-analysis and review of rituximab use in the treatment of neuromyelitis optica spectrum disorders, the authors reported that rituximab was efficacious in reducing relapse rate and disability, but cautioned about potential side effects and adverse events, especially when considering rituximab as first-line therapy.

SOURCE: Damato V, Evoli A, Iorio R. Efficacy and safety of rituximab therapy in neuromyelitis optica spectrum disorders. A systematic review and meta-analysis. *JAMA Neurol* 2016;73:1342-1348.

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system that preferentially affects the optic nerves and spinal cord. Classic NMO or Devic's disease is characterized by concurrent episodes of optic neuritis (ON) and transverse myelitis (TM). NMO spectrum disorder (NMOSD) is diagnosed in patients with isolated ON or TM who have the NMO IgG (aquaporin -4) antibody, which is potentially pathogenic and has high specificity for this group of diseases. NMO was accepted as a distinct entity from multiple sclerosis (MS) after the discovery of the aquaporin-4 antibody in 2004. The aquaporin-4 test is > 80% sensitive and > 99% specific for NMOSD. This distinction of NMOSD from MS is important, as the disease course and treatment options for this disease are different from that of MS.

There are no FDA-approved treatments for NMOSD. Traditionally, relapses are treated with a course of intravenous steroids and steroid-refractory relapses are treated with intravenous immunoglobulin (IVIg) or plasmapheresis (PLEX). Long-term disease-modifying treatments that have been used in NMOSD include pulse corticosteroids, IVIg, azathioprine, mycophenolate mofetil, and rituximab. Rituximab, a monoclonal anti-CD 20 antibody, increasingly is being used in the treatment of NMOSD and often is considered a first-line therapy for this disease.

Given this scenario, the authors conducted a systematic review and meta-analysis of all published data on the use of rituximab in NMOSD to evaluate the safety and efficacy in this disease. To identify the studies, the authors conducted a search of MEDLINE, Cochrane Central Register of Controlled Trials, and clinicaltrials.gov databases using the terms, neuromyelitis optica and rituximab or Devic's disease and rituximab. Out of 119 records that were identified, using their selection criteria, 46 studies were included in the analysis. The analysis was restricted to publications in English, studies with more than two patients, and patients who met the strict criteria for NMOSD.

The combined data set of all the studies included 438 patients. The mean age was 32 years (range 2-77 years), 83.7% were AQP4-IgG positive, the mean disease duration at time of first rituximab infusion was 50 months (range 1.5-276 months), and the mean follow-up after

rituximab infusion was 27.5 months (range 3-272 months). In 57 patients (13%), rituximab was the first-line therapy, and the remainder of patients had tried one or more alternate options before rituximab treatment was initiated. Various regimen of rituximab were used, including 375 mg/m^2 weekly for four weeks, 1 gram every two weeks for two courses, 500 mg/weekly for two weeks, and others regimens.

When efficacy was evaluated, the mean risk reduction on annualized relapse rate was 0.79 (95% confidence interval [CI], -1.09 to -0.50). The mean reduction in Expanded Disability Status Scale score (from studies where it was reported) was 0.64 (95% CI, -1.18 to -0.10). Among the variables that were analyzed, shorter disease duration alone had a positive effect on magnitude of efficacy. Adverse events were reported in 26% of patients. These included infusion-related reactions (10.3%), infections (9.1%), persistent leukopenia (4.6%), and development of posterior reversible leukoencephalopathy (two patients, 0.5%). The severity and nature of the infections was not specified in this analysis, but none of the patients were reported to have developed progressive multifocal leukoencephalopathy (PML). Seven (1.6%) deaths were reported, but the causes of death not specified and the authors noted that the cause of death could have been the severity of the patients' disease itself and not necessarily related to rituximab therapy.

■ COMMENTARY

Based on this comprehensive review, it appears that rituximab is effective in reducing relapses and decreasing risk of disability in patients with NMOSD. There are side effects and adverse events associated with this treatment, including infusion-related reactions and infec-

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Neurology [ALERT®]

Stroke Alert

By Matthew E. Fink, MD

Migraine and Stroke: Data Are Accumulating

SOURCE: Androulakis XM, Kodumuri N, Giamberardino LD, et al. Ischemic stroke subtypes and migraine with aura in the ARIC study. *Neurology* 2016;87:2527-2532.

The Atherosclerosis Risk in Communities study (ARIC) is a prospective, longitudinal community-based cohort study that started in 1993, and followed all vascular events including stroke for the subsequent 20 years. At time of enrollment, patients had to be in the age group of 45-64 years, and the mean age of the patients was 59 years at the third clinical visit of follow-up. All strokes are classified as either cardioembolic, lacunar, or thrombotic. Of 12,758 participants, there were 1,622 migraineurs. When compared to non-headache patients, there was a significant association between those patients who had migraine with visual aura and ischemic stroke, with a hazard ratio (HR) = 1.7 (95% confidence interval [CI], 1.2-2.6; *P* = 0.008). Migraine without visual aura was not significantly associated with ischemic stroke compared to non-headache participants. Among the three stroke types categorized in this study, migraine with visual aura was significantly associated only with cardioembolic stroke (HR, 3.7; 95% CI, 1.6-8.7; *P* = 0.003). The relationship between migraine and stroke is controversial, and findings vary across different population studies. This study shows a strong association between cardioembolic ischemic stroke and migraine with visual aura, but it does not explain the pathophysiology and mechanism for this association. It is proposed by the authors that migraine may predispose to atrial fibrillation, but this is a purely speculative mechanism. ■

U.S. Mortality from Subarachnoid Hemorrhage Declining

SOURCE: Mackey J, Khoury JC, Alwell K, et al. Stable incidence but declining case-fatality rates of subarachnoid hemorrhage in a population. *Neurology* 2016;87:2192-2197.

Aneurysmal subarachnoid hemorrhage continues to be one of the most morbid stroke subtypes with a continuing high mortality. However, in most advanced centers around the world, mortality has been declining, but this has not been documented in the United States. The investigators analyzed data that was collected prospectively from a series of stroke registries during five discrete annual time periods, beginning in 1988 and ending in 2010. The incidence of SAH in the five study periods (age-, race-, and sex-adjusted to the 2000 U.S. population) was 8.8 (95% confidence interval, 6.8-10.7), 9.2 (7.2-11.2), 10.0 (8.0-12.0), 9.0 (7.1-10.9), and 7.7 (6.0-9.4) per 100,000, respectively; the trend in incidence rates from 1988 to 2010 was not statistically significant (*P* = 0.22).

During these time intervals, advanced neurovascular imaging, endovascular coiling, and neurologic intensive care unit availability increased significantly over time. All-cause, five-day mortality declined from 32% to 18%, 30-day mortality declined from 46% to 25%, and 90-day mortality declined from 49% to 29%, from 1988 to 2010, and these changes were statistically significant. The investigators attributed the decline in mortality to advances in medical and surgical therapies, changes in triage of patients directly to specialized centers, and the emergence of neurocritical care units at hospitals that care for such patients. The findings in this Greater Cincinnati/Northern Kentucky region study are consistent with published reports from Western Europe and Japan. ■

Continued from page 39

tions. However, the nature and severity of the infections were not specified, and no case of PML was reported. Although a few fatalities were reported in the studies, the causes of death were not mentioned, and they could have been due to the consequences from severe disease and not necessarily due to therapy. It also appears that early treatment with rituximab was associated with better outcomes. Since NMOSD is often characterized by severe relapses, which can lead to permanent residual disability, early prevention of these relapses would have the greatest effect on morbidity and quality of life. Rituximab appears to be a good choice as a first-line treatment in NMOSD, but one would need to proceed with caution and monitor patients closely for any potential adverse event. ■

CME QUESTIONS

1. **The relationship between Zika virus infection and Guillain-Barré syndrome (GBS) is characterized by which of the following observations?**
   a. GBS rarely follows Zika virus infection.
   b. GBS following Zika infection shows cerebrospinal fluid pleocytosis.
   c. GBS following Zika infection occurs more quickly than classic GBS.
   d. GBS following Zika infection was reported only in Colombia.
   e. GBS following Zika infection does not show slowing of nerve conductions.
2. **Transcranial direct cortical stimulation is an FDA-approved technology for treating cognitive impairments, such as aphasia.**
   a. True
   b. False
3. **The bull's-eye sign on MRI:**
   a. accurately localizes hourglass constrictions.
   b. is seen with brachial plexopathy from a wide variety of causes.
   c. is diagnostic of hereditary brachial plexopathy.
   d. is diagnostic of radiation-induced brachial plexopathy.
4. **Amyloid PET imaging of patients given a clinical diagnosis of Alzheimer's disease (AD) revealed which of the following?**
   a. Clinical diagnosis and imaging were concordant more then 90% of the time.
   b. Thirty-five percent of clinically diagnosed AD patients had negative amyloid PET scans.
   c. Use of amyloid PET had no effect on treatment decisions.
   d. Amyloid PET imaging rarely has false negatives.
   e. Amyloid PET imaging is covered by Medicare insurance.
5. **Which of the following statements about NMOSD is false?**
   a. Clinical criteria include optic neuritis and/or transverse myelitis.
   b. Immunotherapies used to treat multiple sclerosis are FDA approved to treat NMOSD.
   c. Most patients with NMOSD are older than 50 years of age.
   d. More than 80% of NMOSD patients are AQP4-IgG antibody positive.
   e. In this meta-analysis, rituximab was effective in reducing relapses in NMOSD patients.
6. **Common migraine is a risk factor for ischemic stroke.**
   a. True
   b. False
7. **Aneurysmal subarachnoid hemorrhage continues to have a 30-day mortality of almost 50%.**
   a. True
   b. False

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.

[IN FUTURE ISSUES]

Update on Brain Tumor Treatment