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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Guillain-Barré Syndrome in the Elderly

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: Guillain-Barré syndrome in the very old (> 80 years of age) results in more severe disease with poorer recovery.

SOURCE: Peric S, Berisavac I, Tamas OS, et al. Guillain-Barré syndrome in the elderly. *J Peripher Nerv Syst* 2016;21;105-110.

Guillain-Barré syndrome (GBS) affects all ages, men more than women, with a lifetime risk of one in 1,000. Overall incidence of GBS increases by 20% for every decade of life after 10 years of age, although some studies have shown an incidence drop after age 80 years. Is the disease more severe in the elderly?

In this retrospective analysis of hospital records between 2009-2013, with 2014 data entered prospectively, the authors reviewed all GBS cases evaluated in seven tertiary healthcare centers in three countries: Serbia, Republic of Srpska, and Montenegro. Based on World Health Organization guidelines, 60 years of age was the cutoff between young and old, with 61-80 years of age designated young-old, and older than 80 years designated old-old. Standard criteria were used to diagnose GBS, and the GBS disability scale was used to assess disability. Statistical analysis comprised the Kolmogorov-Smirnov, chi-square, Mann-Whitney U, and Student's *t* tests, with statistical significance set at 0.05.

Over the six-year study period, 403 GBS patients were included for analysis, including 250 who were younger than 60 years of age and 153 who were older than 60 years of age. Respiratory infections or a diarrheal illness preceded GBS onset in one-third and one-fifth of cases, respectively, within a mean of 12 days prior to onset, with no significant difference appreciated between the age groups with respect to antecedent events. Frequency of prior medical illness was similar in both groups, though a history of malignancy was thrice as common in older patients. Acute inflammatory demyelinating polyneuropathy was the most common GBS variant

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Weill Cornell Medical College
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[INSIDE]

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[ALERT]

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in both age groups, but acute motor and sensory axonal neuropathy (AMSAN) was twice as common in older patients, 12% vs. 6% of all GBS cases. Elevated cerebrospinal fluid protein was less common in the older group, but hyponatremia was more common, as was severe disability, seen in 72% of the older group at nadir, compared to 42% of the younger patients. Both groups tolerated intravenous immunoglobulin or plasma exchange, or both, with similar frequencies of side effects. Non-responders comprised 5% of both groups. Comparing the old-old to the young-old, bulbar symptoms and comorbidities were more common in the old-old, 50% vs. 19%, and 100% vs. 66%, respectively. On discharge, 67% of the old-old had severe disability, compared to 37% of the young-old. No significant difference between the older groups was seen with respect to the frequency of AMSAN. Elderly patients, especially those older than 80 years of age, developed more severe GBS with slower recovery compared to those younger than 60 years.

■ COMMENTARY

At the other end of the age spectrum, children with GBS do well, but GBS may be a difficult diagnosis to make in this age group. Comparing preschool children, younger than six years of age, to those between the ages of 6-18 years, 68% of preschoolers are misdiagnosed, compared to 21% of older children, with misdiagnoses including tonsillitis, meningitis, myopathy, discitis, rheumatic disorders, and coxitis. Although both groups delayed seeing their pediatrician by a median of five days, delay in correct diagnosis was significantly longer in younger than in older children, three days compared to zero days. Older children presented with classical symptoms, facilitating diagnosis, where preschoolers refused to walk and complained of leg pain, delaying diagnosis. Diagnosis of GBS in preschoolers is a challenge.[1] ■

REFERENCE

1. Roodbol J, de Wit MC, Walgaard C, et al. Recognizing Guillain-Barre syndrome in preschool children. *Neurology* 2011;76;807-810.

ABSTRACT & COMMENTARY

For Migraine Pain, Green Light May Give Relief

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a consultant for Bayer and Boehringer-Ingelheim.

SYNOPSIS: Migraine-related photophobia appears to originate in cone-driven retinal pathways and is then mediated by thalamic neurons. Green light causes less stimulation than other colors.

SOURCE: Noseda R, Bernstein CA, Nir RR, et al. Migraine photophobia originating in cone-driven retinal pathways. *Brain* 2016;139:1971-1986.

In the throes of their untreated migraine headaches, 41 migraine patients completed psychophysical assessments of the effects that different colors of light had on their pain intensity, throbbing, and associated muscle tenderness, as well as on the location of the migraine pain. The patients initially were questioned about these migraine characteristics in an unlit room to establish a baseline to compare the same characteristics when exposed to lights of different wave lengths. The migraineurs were positioned in front of a full-field ganzfeld ColorDome (Diagnosys LLC), with the light on at the lowest intensity initially and then with incremental increases every 30 seconds, from just above dark to the light of an office. The light changed from white, to blue, to green, to amber, and then to red. While looking at the light, the participants rated their headache severity, the site of the pain, and the new onset of throbbing and/or muscle tenderness. Electroretinograms (ERGs) in 46 patients recorded the response of both the cone and rod systems using a corneal recording electrode. Nine flashes of light at one-second intervals, in a series of three, were averaged for the light-adapted, single-flash, cone ERG. For the light-adapted, 30 Hz, flicker cone ERG, 150 flashes of light were delivered over five seconds. Dark-adapted, rod ERG used nine dim light flashes of each color without

background illumination. Color-specific visual evoked potentials (VEPs) were recorded in 46 participants, with only 28 waveforms showing clearly identifiable N1, P1, N2, and P2 deflections. Peaks of N2 and P2 were used to compare VEP response to photic stimulation flashed in the sequential colors. Patient recordings were supplemented with rat studies to assess the role of subcortical pathways in response to color stimulation. Multi-unit in vivo recordings from the rat thalamus evaluated the electrophysiological response to different light colors.

Assessing intensity, location, throbbing, and muscle tenderness, green light exacerbated migraine headaches significantly less than did white, blue, amber, or red light. Increased intensity of light increased pain severity, but exposure to green light reduced pain intensity in about 20% of the patients. Throbbing, muscle tenderness, and spread of the pain from the original sight were less with white and green light than with the other light colors. Differences in ERG response suggested that activation of cone-mediated, but not of rod-mediated, retinal pathways factored into the different light sensitivity between green and the other colors. The P2 amplitude response, but not the N2 amplitude values, on VEPs, was significantly less with green light stimulation, as compared to other colors. Recordings from rat thalami showed that increased neuronal activity was associated with exposure to blue and white light, but not with exposure to green light.

These results from ERG, VEP, and thalamic recordings suggest that exposure to green light is less irritating to migraine sufferers than is exposure to light of other colors. Green light activated cone-driven retinal pathways to a lesser extent than did white, blue, and red light. Thalamic neurons in the rat were most responsive to blue light and least responsive to green light. Migraine photophobia may originate in the retina and may be mediated by the thalamus, rather than other cortical pathways.

■ COMMENTARY

The authors stated that migraine headache is uniquely exacerbated by light. However, while photophobia is very frequently associated with migraine headaches, discomfort associated with light also is associated with other headache types, both primary and secondary. The interplay between cone-driven retinal pathways, light-sensitive trigeminovascular thalamic neurons, and the cortex that seems to mediate photophobia also may factor into light sensitivity with other causes of headache. This study appears to resolve the question of what exactly is photophobia during a migraine. Is it a heightened perception of light intensity (i.e., lights appear brighter) or is it, as the investigation seems to indicate, a light-induced increase in head pain? Further investigation of migraine subtypes, as well as other headache types, is needed to investigate potential differences in the definition of photophobia with different headache etiologies.

Migraine suffers seem to have a unique sensitivity to light even between headaches. They may wear sunglasses not only when suffering from a headache, but also while pain-free, including indoors or on cloudy days. Comparing results of ERG and VEP studies in episodic migraine sufferers not during a headache to the results in non-migraneurs may reveal that a unique retinal and cortical response to light is a function of the propensity to migraine, rather than of the headache itself.

These intriguing results may have eventual therapeutic benefit. Some migraineurs report headaches triggered by bright light exposure, as well as headache associated with sensitivity to light. Glasses that filter out the photophobic wavelengths and allow in only green light may reduce headache triggering, as well decrease the pain of the actual headache. Looking at life through green-colored glasses may be another lifestyle adjustment for migraine sufferers. ■

ABSTRACT & COMMENTARY

What is the End Game in Creutzfeldt-Jakob Disease Progression?

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: Cerebellar and psychiatric symptoms at diagnosis of Creutzfeldt-Jakob disease may portend a higher risk for more rapid development of akinetic mutism.

SOURCE: Nakatani E, Kanatani Y, Kaneda H, et al. Specific clinical signs and symptoms are predictive of clinical course in sporadic Creutzfeldt-Jakob disease. *Eur J Neurol* 2016; May 24. doi:10.1111/ene.13064 [Epub ahead of print].

Creutzfeldt-Jakob disease (CJD) is a rare but devastating cause of rapidly progressive dementia. It can be sporadic (sCJD), genetic/familial, iatrogenic, or variant, with the sporadic type being the most common. CJD can

manifest with a variety of symptoms, including cognitive impairment, myoclonus, visual perceptual problems, cerebellar dysfunction, psychiatric dysfunction, and pyramidal or extrapyramidal involvement. Once symptoms develop, progression to disability and death is quite rapid with median disease duration of five months. Prognostic factors that predict a somewhat longer survival time include female gender, younger age at diagnosis, and certain laboratory findings, including elevated CSF 14-3-3 protein, pseudo-periodic EEG complexes, and heterozygosity (MV) at codon 129 of the prion protein. However, when initiating therapy and when considering enrollment into trials, death may not be the most reasonable endpoint, as enrolling patients too late into the course of the disease may mask any potential benefit. A more reasonable measurable endpoint may be akinetic mutism, and this study evaluated the prognostic factors that predict the risk for the development of akinetic mutism.

Nakatani et al reviewed all cases of probable and definite CJD reported to the Japanese health ministry from 2003-2008. Probable sCJD was diagnosed in patients with progressive dementia with at least two of the four clinical signs or symptoms: *myoclonus, visual or cerebellar disturbance, pyramidal or extrapyramidal dysfunction, or akinetic mutism*, a typical EEG with generalized triphasic periodic complexes at approximately one per second, or a positive 14-3-3 assay of the CSF and death in less than two years. Definite sCJD cases were defined as those with a confirmed pathological diagnosis at autopsy or biopsy. The authors excluded from analysis any patients who manifested with akinetic mutism as a presenting symptom, since the purpose of the study was to determine prognostic features for the development of akinetic mutism. The authors then performed multivariate analysis to determine prognostic factors for akinetic mutism as well as to determine the disease course from onset to the development of akinetic mutism.

The analysis included 455 cases of CJD. Sixty-one percent of patients were women. Median age at diagnosis was 70 years. Median time from symptoms to diagnosis was 1.2 months. Ninety-three percent of patients demonstrated typical EEG findings and 93% of patients demonstrated typical MRI hyperintensities. Of the patients tested, 81% had elevated CSF 14-3-3 protein levels. The most common presenting symptoms included cerebellar (50.8%), psychiatric (50.4%), visual (44.8%), pyramidal (32.1%), extrapyramidal (29.2%), and myoclonus (28.7%).

In the cohort, the cumulative incidence of akinetic mutism at 3, 6 and 12 months after diagnosis of sCJD was 67.8%, 78.6%, and 85.7%, respectively. Median time to the development of akinetic mutism was 1.5 months. In multivariate analysis, only the presence of cerebellar (hazard ratio, 2.15) or psychiatric symptoms (hazard ratio, 1.5) at disease onset was significantly correlated with the development of akinetic mutism. The median times to the development of akinetic mutism in patients with psychiatric symptoms and cerebellar disturbance, cerebellar disturbance only, psychiatric symptoms only, and neither condition were 0.99, 1.51, 1.88, and 2.93 months, respectively. Additionally, the authors determined that the presence of cerebellar disturbance at the time of diagnosis was predictive of future development of myoclonus, pyramidal and extrapyramidal dysfunction, and visual disturbance.

■ COMMENTARY

This study provides some previously unknown insights into the clinical course of CJD, specifically the relationship between the symptoms at disease onset and the subsequent disease course. The major finding of this study is the strong correlation between the onset with cerebellar (and less so psychiatric) symptoms and the more rapid development of akinetic mutism. It is worth recalling that there is no effective therapy for CJD at this time. Clinical trials for CJD are critically important, and if akinetic mutism will be used as an endpoint in these trials, then the factors that predict higher risk for the development of akinetic mutism will be important to understand. Additionally, for the practicing neurologist, it is helpful to know that patients who manifest with cerebellar symptoms are at higher risk for earlier development of this end-stage manifestation of CJD. ■

ABSTRACT & COMMENTARY

Structural and Functional Imaging 'Phenotypes' in Refractory Temporal Lobe Epilepsy Patients

By Kimberly Pargeon, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Using high-resolution 3-T magnetic resonance imaging, temporal lobe epilepsy-hippocampal sclerosis showed significant preoperative ipsilateral volume loss, T2 hyperintensity, and mean diffusivity increases across all subfields, with the greatest effects seen anteriorly. However, temporal lobe epilepsy-gliosis showed increased volume in the dentate gyrus bilaterally, and more focal and subtle increases in T2 intensity and mean diffusivity.

SOURCE: Bernhardt BC, Bernasconi A, Liu M, et al. The spectrum of structural and functional imaging abnormalities in temporal lobe epilepsy. *Ann Neurol* 2016;80:142-153.

Temporal lobe epilepsy (TLE) is the most common cause of refractory epilepsy in adults, with up to 20% of patients having continued seizures, despite adequate trials of antiepileptic medications.[1] Many of these patients may be appropriate surgical candidates with either standard anterior temporal lobectomy or selective amygdalohippocampectomy, but the success of surgery is highly dependent on the presurgical evaluation, which is aimed at accurately identifying the epileptogenic zone and predicting postoperative complications. This process can include both structural and functional imaging.[1]

The most common pathological finding in refractory TLE is hippocampal sclerosis (TLE-HS), characterized radiographically by hippocampal atrophy, increased T2 signal, and increased tissue diffusivity. These imaging markers are notably absent in up to half of patients, sometimes leading to delays in surgery, and even when surgery is performed, postoperative seizure recurrence may be higher. For these patients, there may be no apparent cell loss, but instead there may be isolated gliosis (TLE-G). There also seems to be some mounting evidence that TLE is associated with abnormalities in functional network connections, particularly one called the default mode network (DMN), involving areas of the temporal, parietal, and frontal lobes, and appearing to play a role in internal thought processing.[2]

The goal of the present study was to identify unique structural and functional imaging "phenotypes" in patients with clearly defined TLE-HS and TLE-G. Thirty-nine consecutive medically refractory TLE patients treated from 2008 to 2014 were selected from a hospital database in Montreal. All patients underwent a research-dedicated high-resolution 3T brain MRI, had a selective amygdalohippocampectomy with a clear pathological diagnosis, and did not have an alternate etiology for their refractory TLE. Based on histopathology, 20 patients had hippocampal sclerosis (TLE-HS) and 19 patients had only gliosis (TLE-G). The groups were comparable in age, epilepsy duration, age at seizure onset, monthly seizure frequency, and seizure semiologies. However, TLE-HS had a tendency for a higher prevalence of febrile seizures, more male subjects, more generalized tonic-clonic seizures, and a higher, though nonsignificant, rate of postoperative seizure freedom.

The authors gave a detailed description of the MRI acquisition, preprocessing, subfield mapping, and final analyses. For all comparisons, the hippocampus was divided into three consistently identifiable subfields, specifically CA1-3, CA4-dentate gyrus (DG), and subicular complex. Each group was compared to a control group (sex- and age-matched) and then to one another. Relative to controls, the primary finding was that TLE-HS typically presented with significant and only ipsilateral hippocampal *atrophy* affecting *all* subfields, whereas TLE-G presented with *increased* volumes within the CA4-DG bilaterally. TLE-HS also showed marked bilateral increases in T2 intensity and mean diffusivity (MD) with the highest effects in the ipsilateral CA1-3 and CA4-DG, whereas TLE-G showed subtler ipsilateral increases. When comparing the groups, the TLE-HS still showed significant ipsilateral atrophy and MD increases across *all* fields, but the T2 increases were only seen in the anterior ipsilateral CA1-3 subfield.

When evaluating hippocampal functional connectivity, TLE-G showed only subtle disruptions, which were localized to the subiculum. However, TLE-HS demonstrated significant "reconfigurations" of hippocampal networks, typically with decreased connectivity between areas of the DMN, including connections to the ipsilateral anterior and dorsal medial prefrontal cortex. In addition, patients with higher hippocampal T2 signal and atrophy seemed more likely to have associated "functional disconnections" from key structures in this so-called DMN.

■ COMMENTARY

Per the authors, "best practice" radiological studies can fail to show a pathological lesion in up to 50% of patients. Thus, the primary goal of this study was to determine "phenotypes" associated with two of the more common pathological diagnoses in TLE from high-resolution imaging. As described above, the authors were able to delineate some clear structural and functional imaging characteristics associated with TLE-HS with subtler findings associated with TLE-G. Prior to surgery, this type of detailed analysis could be used to determine the potential histopathological diagnosis. This could be applied in imaging "negative" cases, which may represent early or subtle instances of TLE-HS. Findings could then be used to determine treatment options and to better predict postoperative prognosis. In addition, as the authors mention, in instances where histopathology may be unobtainable, such as with thermal ablation, these techniques could possibly be used instead.

However, there are some drawbacks. First, this type of "research-dedicated" imaging would not be readily available in all locations. In addition, the analysis, including

the preprocessing and subfield mapping, would not be a service provided by all radiology departments and likely would be performed by the treating team. Although these analyses usually utilize freely available software, they often are complicated, multi-step processes and can lead to errors. Finally, insurance companies do not support some types of specialized imaging, including some functional imaging. Regardless of its present clinical applicability, this study sheds some interesting light on the idea of TLE as a heterogeneous disorder, likely representing a "spectrum." ■

REFERENCE

1. Stylianou P, Hoffmann C, Blat, Harnof S. Neuroimaging for patient selection for medial temporal lobe epilepsy surgery: Part 1 structural neuroimaging. *J Clin Neurosci* 2016;23:14-22.

ABSTRACT & COMMENTARY

Stiff-Person Spectrum Disorder: What Can Antibody Profiles Tell Us?

By Claire Henchcliffe, MD, PhD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is on the speakers bureau and advisory boards for Teva, IMPAX, and ACADIA, and receives grant/research support from Biogen and Kaneka.

SYNOPSIS: This retrospective study of 121 patients with stiff-person spectrum disorder extensively examined antibody correlates of clinical features. Anti-GAD65 antibodies were highly associated with typical stiff-person syndrome, and anti-GlyR antibodies with SPS-plus. However, presence of anti-GAD antibodies predicted worse outcome than presence of antiGlyR antibodies, independent of clinical subtype.

SOURCE: Martinez-Hernandez E, Arino H, McKeon A, et al. Clinical and immunologic investigations in patients with stiff-person spectrum disorder. *JAMA Neurol* 2016;73:714-720.

Stiff-person spectrum disorder (SPSD) was first reported by Moersch and Woltman in 1956 as stiff man syndrome, but it is now understood to present as a spectrum of conditions, ranging from segmental (stiff-limb syndrome, SLS) through to severe (progressive encephalomyelitis with rigidity and myoclonus, PERM) forms. Martinez-Hernandez and colleagues describe 121 patients with SPSD together with results of comprehensive antibody testing in this retrospective study, with the aims of dissecting out clinic-immunological associations and suggesting prognostic factors. Patients were classified into four groups: 1) stiff-person syndrome (SPS) with classic truncal rigidity and spasms (n = 50); 2) SLS with distal limb rigidity causing abnormal hand or foot postures (n = 24); 3) SPS-plus, with symptoms including myoclonus, seizures, brainstem dysfunction, and others (n = 37); and 4) overlap syndromes that included ataxia (n = 6), limbic encephalitis (n = 1), and epilepsy (n = 3) in combination with SPS or SLS. Antibodies to eight targets on inhibitory synapses were examined in paired serum-CSF (n = 65), serum-only (n = 50), or CSF only (n = 6), with targets as follows: GAD65, glycine receptor alpha1 subunit (GlyR), amphiphysin, gephyrin, GABAa receptor (GABAaR), dipeptidyl peptidase protein 6 (DPPX), and glycine transporter 1 and 2. Patients had a median age of symptom onset of 51 (interquartile range 40-61) years, and 62% were women. Antibodies to inhibitory synapses were commonly detected (67% total), including GAD65 (43%); GlyR (20%); and GABAaR, amphiphysin, or DPPX (4% combined). A minority of patients had more than one antibody detected. Interestingly, of the 33% without identified antibodies, three had serum antibodies to unidentified epitopes in live neuronal cultures. A major finding was the strong association of certain clinical features with specific antibodies. Classic SPS was much more likely in GAD65-positive or antibody negative cases, whereas SPS-plus (with a more aggressive presentation) was more likely in those with GlyR antibodies. However, those with GlyR antibodies had superior clinical outcomes than those with GAD65 antibodies or those who were antibody-negative.

■ COMMENTARY

This is a remarkable study that provides comprehensive antibody profiling in a rare disorder: one estimate of incidence is that it affects one in a million. It highlights the variable nature of SPSD, making it sometimes difficult to diagnose, and of the patients included in this study, less than half had typical SPS. The major finding of this study is that the types of antibodies present may predict outcome. In particular the presence of GAD65 and GlyR has different implications. There was preferential association of GAD65 with typical SPS, and of GlyR with SPS-plus, but presence of either antibody had associations with prognosis independent of the type of syndrome. Specifically, although those with GlyR antibodies had more severe symptoms at diagnosis, they had better outcomes than those with GAD65 antibodies. Although the major finding focuses on the two most common antibodies, anti-GAD76 to anti-GlyR, it is helpful in the clinic to

know that other antibodies to inhibitory synapses were rarely detected (4% for GABAaR, amphiphysin, or DPPX), and none of the samples tested had antibodies to gephyrin, GlyT1 or GlyT2). This suggests that GAD65 and GlyR testing is sufficient in the majority of cases, along with amphiphysin in given its association with breast and lung cancer. The study, of course, is subject to referral bias and given its retrospective nature there could be other factors at play in the antibody associations determined. Therefore, it will be necessary to dig deeper. Nonetheless, if presence of anti-GAD vs. anti-GlyR antibodies turns out to be a true predictor of prognosis, it will greatly help clinical management and patient counseling. ■

Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

Ticagrelor vs. Aspirin for Secondary Stroke Prevention — About the Same!

SOURCE: Johnstone SC, Amarenco P, Albers GW, et al for the SOCRATES Steering Committee and Investigators. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med* 2016;375:35-43.

After ischemic stroke and transient ischemic attack, the risk of subsequent ischemic events is high during the first 90 days after the index event. The standard secondary preventive treatment has been a daily dose of aspirin. However, the benefit of this treatment, on a long-term basis, is only about a 20% lower rate of recurrent stroke compared to no preventive therapy. Therefore, other therapies have been sought that are more effective. Ticagrelor is an antiplatelet agent that reversibly binds and inhibits the P2Y12 receptor on platelets and is direct acting, and theoretically, should be more effective than either clopidogrel or aspirin. This trial was designed to test the effectiveness of secondary prevention with ticagrelor vs. aspirin.

An international double-blind, controlled trial was performed in 674 centers in 33 countries, and enrolled 13,199 patients with nonsevere ischemic stroke or transient ischemic attack. If subjects did not have a cardioembolic stroke, they were randomly assigned within 24 hours after symptom onset, in a 1:1 ratio, to receive either ticagrelor or aspirin daily, for days 2 through 90. The primary endpoint was the time to occurrence of stroke, myocardial infarction, or death within 90 days. During the 90 days of treatment, the primary endpoint occurred in 6.2% of patients treated with ticagrelor vs. 7.5% of patients treated with aspirin (hazard ratio, 0.89; 95% confidence interval, 0.78-1.0; 95% confidence interval, 0.78-1.01; $P = 0.07$). There was no difference in major bleeding episodes nor any difference in the incidence of intracranial hemorrhage.

In this trial, ticagrelor was not found to be superior to aspirin in reducing the rate of stroke, myocardial infarction, or death within 90 days, but there was a trend toward a reduced rate of ischemic stroke, that did not reach statistical significance. ■

In Patients with Intracerebral Hemorrhage, Intensive Lowering of Blood Pressure Does Not Improve Outcome

SOURCE: Qureshi AI, Palesch YY, Barsan WG, et al for the ATTACH-2 Trial Investigators. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 2016; DOI: 10.1056/NEJMoa1603460 [Epub ahead of print].

After spontaneous intracerebral hemorrhage, there is a severe hypertensive response that may be associated with hematoma expansion and increased mortality. The INERACT-2 study (*N Engl J Med* 2013;368:2355-2365) looked at the effectiveness of blood pressure reduction within six hours after symptom onset, to a target systolic blood pressure of < 140 mmHg. There was no significant difference in neurological outcome or mortality, compared to patients who were treated with a target systolic blood pressure of < 180 mmHg. The ATTACH-2 trial was designed to determine if even more rapid lowering of blood pressure, within 4.5 hours of onset of symptoms, and a target blood pressure of < 120 mmHg, would result in an improved rate of death or disability at three months.

Of 1,000 participants with a mean systolic blood pressure of 200 ± 27 mmHg at baseline, 500 were assigned to intensive treatment and 500 to standard treatment. Enrollment was stopped because of futility after an interim analysis. The primary outcome of death or disability was observed in 38.7% of the participants in the intensive treatment group and 37.7% of participants in the standard treatment group, after adjustment for age, initial Glasgow Coma Scale score, presence or absence of intraventricular hemorrhage, and other premorbid factors. The rate of renal adverse events, within seven days after randomization, were significantly higher in the intensive treatment group than in the standard treatment group. In conclusion, intensive treatment of patients with intracerebral hemorrhage to achieve a target systolic blood pressure < 120 mmHg did not result in a lower rate of death or disability, but did result in an increased rate of renal adverse events. ■

CME QUESTIONS

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CME QUESTIONS

1. **With respect to Guillain-Barre syndrome (GBS), which statement is correct?**
   a. GBS does not occur in the very old population, i.e., those older than 80 years of age.
   b. Elderly patients develop more severe GBS with slower recovery, compared to younger patients.
   c. GBS is very easy to diagnose in preschoolers who present with leg pain and refusal to walk.
   d. Elevated cerebrospinal fluid protein is never seen in older patients with GBS.
   e. None of the above statements are true.
2. **Filtering out all but which color light appears to reduce photophobia and migraine headache intensity?**
   a. Red
   b. White
   c. Blue
   d. Green
   e. Amber
3. **Strong predictors for early akinetic mutism in patients with Creutzfeldt-Jakob disease include which of the following?**
   a. Behavior disorders at onset
   b. Generalized triphasic periodic EEG complexes
   c. Cerebellar findings at onset
   d. Myoclonus
   e. Both a and c
4. **Which of the following is not a typical radiographic feature of hippocampal sclerosis in patients with refractory temporal lobe epilepsy?**
   a. Increased T2 signal
   b. Hippocampal atrophy
   c. Increased volume in the dentate gyrus
   d. Increased mean diffusivity
5. **The presence of GAD65 antibodies in stiff-person spectrum disorders (SPSD) is associated with which of the following?**
   a. Typical stiff-person syndrome presenting with axial involvement, muscle spasms, and compromised axial posture
   b. Superior clinical outcome when compared to cases with presence of anti-GlyR antibodies
   c. More severe symptoms at time of diagnosis than SPSD associated with GlyR antibodies
   d. Co-occurrence of other antibodies to inhibitory synapse in the majority of cases
6. **For secondary prevention of ischemic stroke, ticagrelor is better than aspirin.**
   a. True
   b. False
7. **Intensive and rapid lowering of systolic blood pressure after intracerebral hemorrhage results in better outcomes.**
   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 Multiple Sclerosis