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Neurology [ALERT®]

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ABSTRACT & COMMENTARY

MRI Investigation of Brain Abnormalities in Friedreich's Ataxia

By Mary L. Vo, MD, PharmD

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Dr. Vo reports she is an advisory board member for CSL Behring, is a consultant and advisory board member for Alexion Pharmaceuticals, and receives grant/research support from Takeda Pharmaceuticals.

SYNOPSIS: Friedreich's ataxia (FRDA) is characterized by progressive weakness, sensory loss, ataxia, and dysarthria starting in childhood. The authors of this MRI-based study demonstrated that structural damage is limited to the spinal cord, red nucleus, and cerebellar peduncles in young FRDA patients, but progresses to widespread cerebral damage in adult FRDA patients.

SOURCE: Rezende TJR, Martinez ARM, Faber I, et al. Developmental and neurodegenerative damage in Friedreich's ataxia. *Eur J Neurol* 2019;26:483-489.

The most common autosomal recessive ataxia, Friedreich's ataxia (FRDA) is caused by a GAA expansion in intron 1 of the FXN gene, resulting in a reduced amount of frataxin protein. Frataxin is essential in the assembly of iron and sulfur cluster molecules needed for energy production and cellular response to oxidative stress. Cells of the central nervous system are particularly vulnerable to the effects of frataxin depletion. FRDA results in progressive weakness, ataxia, speech disturbance, and sensory loss.

The classical form of FRDA manifests prior to age 25 years, and most patients rely on wheelchairs for mobility within 15 years of diagnosis. The neurodegenerative nature of FRDA has been demonstrated by imaging studies showing progressive atrophy of multiple areas of the brain, especially cerebellar dentate nuclei and white and grey matter atrophy of the brainstem, motor cortex, and cerebellum in affected adults. However, there are scarce data describing imaging abnormalities in the pediatric population.

Between 2009 and 2017, 37 patients with confirmed FRDA and 38 healthy controls were recruited from University of Campinas neurogenetics clinic in Brazil. All 37 FRDA patients had the classical form of disease, with onset prior to age 25 years. Of the 37 FRDA patients, 12 were grouped into young FRDA (yFRDA),

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[INSIDE]

Neurology
[ALERT]

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mean age 14 ± 2.7 years, and 25 were in the adult FRDA (aFRDA) group, mean age 28.4 ± 12.2 years. Disease onset occurred at age 9.2 ± 2.6 years in the yFRDA group and 13.5 ± 4.5 years in the aFRDA group. Older FRDA patients tended to have more severe disease, with Friedreich's Ataxia Rating Scale (FARS) III subscore 66.0 ± 18.0 relative to 53.3 ± 15.1 in the yFRDA group. There were no significant differences between GAA1 or GAA2 repeat lengths.

All underwent 3T high-resolution magnetic resonance imaging (MRI) scan of the brain and cervical spinal cord. Multimodal MRI analysis was performed. Investigators also collected detailed clinical and molecular data, including disease onset, duration, GAA repeat length, and FARS score for all subjects. The focus of the study was to explore neuroanatomical differences between yFRDA and aFRDA subjects. Among the yFRDA group, volumetric reduction was limited to the red nuclei compared to controls. In contrast, aFRDA patients had more widespread atrophy in the hippocampi, thalami, red nuclei, and brainstem structures. White matter analysis in the yFRDA group showed increased radial diffusivity in the cerebellar peduncle and volume loss in superior cerebellar white matter tracts compared to healthy controls. The finding of increased cerebellar radial diffusivity directly correlated with disease severity.

Overall, yFRDA patients had limited infratentorial structural damage, whereas supratentorial involvement was found in aFRDA patients. The yFRDA group did not show evidence of supratentorial grey matter atrophy, cortical thinning that has been described in affected adults. Further, the yFRDA group did not demonstrate evidence of white matter injury, including abnormal axial diffusivity and fractional anisotropy, seen in the aFRDA group.

Spinal cord imaging showed reduced spinal cord area among all FRDA subjects compared to healthy controls, consistent with prior neuropathological observations showing that the spinal cord in FRDA patients fails to reach normal size. In contrast to the positive correlation between cord area and age in controls, the yFRDA group showed a progressive decline in cord area with aging. Moreover, there were no significant differences in spinal cord area between the yFRDA and aFRDA groups despite wide differences in mean ages. These findings suggest that the spinal cord involvement seen in FRDA is the result of both impaired development and neurodegeneration.

The current study offers a unique insight into early structural damage in FRDA patients, suggesting that frataxin deficiency can cause impaired brain and spinal cord development, leading to a distinctive neuroanatomical signature where the cervical spinal cord, medulla, inferior cerebellar peduncle, and red nucleus are affected preferentially.

■ COMMENTARY

FRDA is a progressive neurological disease resulting in severe disability and early death. Rezende et al defined a unique neuroanatomical pattern seen in children with early disease and offered valuable insight into the pathophysiology of FRDA. This work underscores the critical need for imaging biomarkers to predict disease progression and serves as an outcome measure for clinical trials. ■

ABSTRACT & COMMENTARY

REM Behavior Disorder, Dementia, and Parkinson's Disease

By Daniel A. Barone, MD, FAASM

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Dr. Barone reports he is on the speakers bureau for Jazz Pharmaceuticals and is a consultant for Molecule Mattress.

SYNOPSIS: In this well-designed prospective cohort study of patients with REM behavior disorder, the investigators reported that 73.5% of patients developed a neurodegenerative disorder after a 12-year follow-up.

SOURCE: Postuma RB, Iranzo A, Hu M, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: A multicentre study. *Brain* 2019;142:744-759.

Idiopathic REM sleep behavior disorder (iRBD) is a well-known early sign of the alpha-synucleinopathies, which include Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). It is characterized by active (sometimes violent) movements during REM sleep and is interpreted as "acting out dreams." As such, the presence of iRBD allows researchers to observe prodromal neurodegenerative states and potentially intervene when neuroprotection becomes available. Postuma et al sought to assess the neurodegenerative disease risk and the predictors of neurodegeneration in a multicenter cohort of patients with iRBD. They included prospective follow-up data from 24 centers of the International RBD Study Group.

In total, 1,280 patients were recruited following a diagnosis of polysomnographically confirmed iRBD without parkinsonism or dementia. The average age was 66.3 ± 8.4 years, and 82.5% of participants were male. Patients underwent motor, cognitive, autonomic, and sensory testing, and were followed prospectively for an average of 4.6 years (range one to 19 years), during which time their risk of dementia and parkinsonism were assessed using Kaplan-Meier analysis. The authors used Cox proportional hazards analysis to predict phenoconversion and a time-to-event analysis to calculate sample size estimates for disease-modifying trials.

The authors reported a conversion rate from iRBD to a neurodegenerative disorder to be 6.3% per year, with 73.5% converting after 12-year follow-up. Abnormal quantitative motor testing significantly increased the phenoconversion rate (hazard ratio [HR], 3.16), as did objective motor examination (HR, 3.03), olfactory deficit (HR, 2.62), mild cognitive impairment (HR, 1.91-2.37), erectile dysfunction (HR, 2.13), motor symptoms (HR, 2.11), an abnormal DaTscan (HR, 1.98), color vision abnormalities (HR, 1.69), constipation (HR, 1.67), REM atonia loss (HR, 1.54), and age (HR, 1.54). By contrast, there was no significant predictive value of sex, daytime somnolence, insomnia, restless legs syndrome, sleep apnea, urinary dysfunction, orthostatic symptoms, depression, anxiety, or hyperechogenicity on substantia nigra ultrasound. Finally, there was a difference in cognitive variables at baseline between those converting to primary dementia vs. those converting to parkinsonism.

Postuma et al also attempted to determine a sample size estimate for neuroprotective trials. Using phenoconversion as a categorical endpoint, the authors found that sample sizes for a two-year trial with HR = 0.5 ranged from 142 to 366 patients per arm. They pointed out that stratification could decrease sample sizes further. Olfaction and the Movement Disorder Society prodromal criteria appeared to be the two most efficient strategies. It is fortunate that the total sample size for a future neuroprotective trial was discovered to be less than the number of participants who were recruited to this current study. This large multicenter study confirmed the high phenoconversion rate from iRBD to an alpha-synucleinopathy, and has provided estimates of the potential predictive value of prodromal markers. This information can be used to stratify patients for neuroprotective trials.

[Patients with a new diagnosis of idiopathic REM sleep behavior disorder should be examined for subtle signs of neurodegenerative disorders.]

■ COMMENTARY

As demonstrated in this large and well-done study, patients with a new diagnosis of iRBD should be examined for existing subtle signs of neurodegenerative disorders. Aside from those studied by Postuma et al, new biomarkers are being developed that could further aid risk stratification and perhaps even therapeutic options. For example, Gámez-Valero et al recently reported that glucocerebrosidase gene variants are found in iRBD patients more frequently compared to controls, and this finding is associated with PD and DLB.[1] Similarly, patients with iRBD recently were found to have increased microglial activation in the substantia nigra along with reduced dopaminergic function in the putamen as detected through PET.[2]

Perhaps the most important opportunity for research in the intersection of sleep medicine and neurology is the potential discovery and testing of a neuroprotective strategy to prevent ongoing neurodegeneration in identified at-risk individuals. This present study, along with others, will provide a much better platform for the understanding and treatment for iRBD and conversion to a more debilitating neurodegenerative disease. To this point, individuals with iRBD are enrolling in the Parkinson's Progression Markers Initiative study,[3] as well other similar prospective cohorts around the world. ■

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1. Gámez-Valero, Iranzo A, Serradell M, et al. Glucocerebrosidase gene variants are accumulated in idiopathic REM sleep behavior disorder. *Parkinsonism Related Dis* 2018;50:94-98.
2. Stokholm MG, Iranzo A, Ostergaard K, et al. Assessment of neuroinflammation in patients with idiopathic rapid-eye-movement sleep behaviour disorder: A case-control study. *Lancet Neurol* 2017;16:789-796.
3. Parkinson's Progression Markers Initiative. Available at: http://www.ppmi-info.org. Accessed April 15, 2019.

ABSTRACT & COMMENTARY

Alcohol Consumption and Migraine

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: In this observational, cross-sectional survey performed via an online questionnaire, researchers confirmed that alcohol consumption is a common trigger for migraine, and red wine is the type of alcohol cited as a trigger most frequently.

SOURCE: Onderwater GLJ, van Oosterhout WPJ, Schoonman GG, et al. Alcoholic beverages as trigger factor and the effect on alcohol consumption behavior in patients with migraine. *Eur J Neurol* 2019;26:588-595.

Migraine is a common disabling primary headache disorder that affects 12% of the population of the western world. As part of their treatment regimen, patients with migraine are advised to identify and avoid triggers. Alcoholic beverages, especially red wine, frequently are included as a top 10 trigger. However, very few, small, retrospective studies focus on alcoholic beverages as potential migraine triggers. Onderwater et al used data from the Leiden University Migraine Neuro-Analysis (LUMINA) project to identify which alcoholic beverages are reported as migraine triggers frequently, to estimate trigger consistency and time to attack onset, and to explore the effect on alcohol consumption.

In this observational study, investigators used cross-sectional data collection via a web-based questionnaire sent by email. All patients with migraine included in LUMINA between February 2008 and January 2013 were sent an alcohol trigger questionnaire. Of 3,785 patients who received the questionnaire, 2,424 (64%) responded. Non-responders were older, had a longer disease duration, and had higher attack frequency and number of migraine days. There was no significant difference in gender or migraine subtype. Data from 2,197 patients were available for analysis.

Overall, 783 (35.6%) patients reported alcohol as a migraine trigger. Of the 1,547 participants with migraine who consumed alcohol, 658 (42.5%) reported that alcohol was a trigger, 694 (44.9%) did not report alcohol as a trigger, and 195 (12.6%) were not sure. Patients who reported alcohol as a trigger were more likely to have migraine without aura, had a higher frequency of attacks, had more migraine days, drank slightly more per occasion, and drank more vodka and significantly less red wine. Red wine was the most frequent beverage specifically mentioned as a migraine trigger, with 512 of 658 (77.8%) alcohol-consuming migraine patients reporting red wine as a trigger. Vodka was the trigger mentioned least frequently, with only 56 of 658 (8.5%) patients reporting vodka as a trigger. Patients estimated that 2.18 ± 1.3 standard glasses of red wine or 2.16 ± 1.9 standard glasses of vodka were required to trigger a migraine. The time of onset was rapid, within three hours, in one-third of the patients. Ninety percent of patients had an onset in less than 10 hours. Of the 650 patients with migraine who did not consume alcohol, 165 (25.8%) stopped consuming alcohol because either it triggered migraines or they were told by others that it could be a potential trigger.

■ COMMENTARY

In this large migraine cohort, Onderwater et al found that alcoholic beverages were reported as a migraine trigger in more than one-third of patients, with red wine as the most frequently mentioned trigger and vodka as the least. The study provides additional support for advising migraine patients to observe if alcoholic beverages, especially red wine, trigger their migraine attacks. Being aware of triggers allows patients to modify their behavior to improve their quality of life. ■

ABSTRACT & COMMENTARY

Avoid Surprise Migraine Triggers

By Dara G. Jamieson, MD

Emeritus Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: The degree of unexpectedness or "surprisal" associated with known migraine triggers is a predictor of headache attacks. Social avoidance behavior is positively correlated with headache disability, pain, and depression, but there is a negative correlation between headache pain endurance and anxiety.

SOURCES: Turner DP, Lebowitz AD, Chtay I, Houle TT. Headache triggers as surprise. *Headache* 2019;59:495-508.

Ruscheweyh R, Pereira D, Hasenbring MI, Straube A. Pain-related avoidance and endurance behaviour in migraine: An observational study. *J Headache Pain* 2019;20:9.

Multiple models have been used to predict triggering and chronification of migraine headaches. Turner et al examined the hypothesis that the surprising aspect of a headache trigger is associated with daily headache activity. They proposed that headache trigger exposure can be characterized based on the degree of "surprise" that the trigger presents to the individual, and that headache attacks are associated with reactions to uncommon or unexpected triggering experiences.

In this prospective cohort study using data from the Headache Prediction Study, Turner et al followed 95 individuals with episodic migraine. They analyzed diary data for daily levels of several common headache triggers: number of caffeinated beverages, number of alcoholic beverages, stress (Daily Stress Inventory), and mood disturbance (Profile of Mood States). The probability of observing variations in each headache trigger was used to estimate the "surprisal" of experiencing each trigger as a predictor of headache attacks. The analysis of statistical interactions between previous and current values of the triggers and the current headache status determined the influence of the degree of surprise in encountering the trigger.

Participants experienced headache attacks on 1,613 of 4,195 days (38.5%). Rare or surprising values were associated with headache activity consistently, and four common headache triggers (caffeine, alcohol, stress, and mood) were found to predict future headache activity. The degree of surprise associated with the trigger correlated with resultant headache activity. Each trigger surprisal was associated with development of a future headache (expressed as a 1 standard deviation change in surprisal). Odds ratios ranged from 1.11 (95% confidence interval [CI], 1.00-1.24) for alcohol to 1.30 (95% CI, 1.14-1.46) for stress. The authors stated that "surprise is not just a change in triggers." They postulated that in the trigger surprise model, the absolute changes in triggers are not as important as the unexpectedness of the changes from their typical levels. So, is avoidance of surprise a reliable method to avoid headache triggering?

In the fear-avoidance model, pain is predicted to evolve from episodic to chronic because of anticipatory fear of the pain and the resultant pain-avoidant behavior. The model is offered as an explanation for chronic musculoskeletal pain in the absence of overt pathology. Also, pain-endurance behavior may exacerbate chronic musculoskeletal pain due to continuous physical overload. The significance of pain-related avoidance and endurance behavior in migraine is less known, despite the prominence of anticipatory anxiety in migraineurs and the frequent need to persevere during the attack.

Ruscheweyh et al administered the Avoidance-Endurance Questionnaire behavioral subscales, the Pain Disability Index (PDI), the Migraine Disability Assessment Scale (MIDAS), and the Hospital Anxiety and Depression Scale (HADS) to 90 episodic and 38 chronic migraineurs, with re-evaluation of 69 of 128 individuals after three to six months. Exercise, relaxation techniques, and preventive treatments also were assessed. At baseline, there was a positive correlation between avoidance (especially social avoidance behavior) and pain and headache disability as assessed by the PDI and MIDAS, respectively. There was a positive correlation between social avoidance and depression ($P = 0.047$) and a negative correlation between endurance and anxiety ($P = 0.013$) on the HADS. Neither avoidance nor endurance was related to headache intensity or frequency or to a diagnosis of episodic vs. chronic migraine.

On follow-up after treatment at the authors' headache center, headache frequency, intensity, and pain-related disability improved significantly; however, avoidance and endurance were unchanged. Distinct characteristics of migraine may not fit into a musculoskeletal model. The authors noted that a difference between musculoskeletal disorders and migraine is that episodic migraine attacks are separated by pain-free episodes. Since physical activity can trigger and exacerbate migraine pain, physical avoidance behavior may be appropriate. Stress, as a powerful migraine trigger, may be exacerbated by increased endurance, which in migraine can range from appropriate tolerance to excessive persistence.

■ COMMENTARY

Migraine sufferers know that headaches occur with change in their triggers, including stress (e.g., stress relief), weather (e.g., barometric pressure changes), sleep (e.g., oversleeping), and estrogen levels (e.g., menstrual and pregnancy-related headaches). However, there may be some benefit to anticipation of the change, as opposed to experiencing a surprising change that appears to exacerbate the migraine-triggering effect. In the fear-avoidance model of headache pain, exaggerated anticipatory anxiety leads to avoidance behavior, with exacerbation of pain and disability, including depression. Since treatment in a headache center achieved improvement in headache frequency and disability in the absence of changes in avoidance or endurance behavior, there may be adaptive benefit to some degree of avoidance of unexpected triggers and to powering through (i.e., enduring) the headache, in combination with appropriate acute and chronic treatments. In the fear-avoidance model, non-threatening or transient pain is associated with less anxiety when accompanied by improved coping mechanisms. With migraine, the combination of surprising triggers and

excessive avoidance, especially social avoidance behavior leading to depression, may lead to enhanced migraine disability and potentially to chronification of migraine. If the trigger with risk of resultant migraine is anticipated with less anxiety, then the headache pain can be confronted and treated appropriately. The teaching points for migraine patients appear to be know your headache triggers and avoid those that you can control, anticipate non-modifiable triggers, and manage all triggers expectantly without socially debilitating avoidant behavior. ■

ABSTRACT & COMMENTARY

MRI of the Brachial and Lumbar Plexus Assists in the Diagnosis of CIDP

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: MRI of the brachial plexus and/or lumbar plexus may be helpful in making a diagnosis of chronic inflammatory demyelinating polyradiculopathy in patients who do not meet the standard criteria. Imaging findings include increased signal intensity, nerve hypertrophy, and nerve contrast enhancement.

SOURCE: Fargeot G, Viala K, Theaudin M, et al. Diagnostic usefulness of plexus magnetic resonance imaging in chronic inflammatory demyelinating polyradiculopathy without electrodiagnostic criteria of demyelination. *Eur J Neurol* 2019;26:631-638.

Proximal and distal symptoms, motor more so than sensory, that are progressive over more than two months, with depressed deep tendon reflexes, elevated cerebrospinal fluid protein with normal cells, and nerve conduction studies demonstrating demyelinating neuropathy, support a clinical diagnosis of chronic inflammatory demyelinating polyradiculopathy (CIDP). Approximately 20% of patients with predominantly axonal loss, proximal demyelination, or primarily sensory involvement lack definite or probable electrodiagnostic criteria for CIDP. Might brachial or lumbosacral plexus magnetic resonance imaging (MRI) allow a diagnosis of CIDP to be made in these instances?

In this retrospective study, Fargeot et al reviewed all patients who underwent brachial or lumbosacral plexus MRI, or both, for possible CIDP at the Bicetre and Pitié-Salpêtrière University Hospitals in Paris, between January 2013 and June 2015. All patients met European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) clinical criteria for CIDP and had undergone nerve conduction studies and needle electromyography, as well as one of either lumbar puncture, nerve biopsy, or somatosensory-evoked potential examination. Laboratory studies included complete blood count, fasting blood glucose, liver and renal function tests, folate and B12 levels, human immunodeficiency virus antibody, serum protein electrophoresis, and antiganglioside and anti-myelin-associated glycoprotein (anti-MAG) antibody determination. Exclusion criteria included patients with hereditary neuropathy, anti-MAG neuropathy, or motor neuropathy with conduction block. Interpretation of the MRI was performed by a neuroradiologist aware of the possibility of CIDP but blinded to all clinical data. The authors performed a statistical analysis using the Wilcoxon-Mann-Whitney test, with categorical variables compared with a chi-squared test, or Fisher's exact test, where warranted. $P < 0.05$ was considered statistically significant.

Among 60 patients who underwent plexus MRI for suspected CIDP, four were excluded because of a diagnosis of motor neuropathy with conduction block or anti-MAG neuropathy made during the study period (n = 2 each). Another eight patients who did not undergo either lumbar puncture, nerve biopsy, or somatosensory-evoked potential examination were excluded. Among the 48 remaining patients, 38 did not meet definite EFNS/PNS electrodiagnostic criteria for CIDP, of which 22 (61%) were purely sensory, six (17%) had distal acquired demyelinating symmetric neuropathy, three each (8% each) had purely motor or focal neuropathy, and two (6%) had multifocal acquired demyelinating sensory and motor neuropathy (Lewis-Sumner syndrome).

Among 10 patients who met electrodiagnostic criteria for CIDP, plexus MRI was abnormal in eight patients (80%), demonstrating increased signal intensity on STIR (8/8), hypertrophy (8/8), and contrast enhancement (2/8). Among 38 patients without definite electrodiagnostic criteria for CIDP, plexus MRI was abnormal in 22 (58%), encompassing increased signal intensity on STIR in 22/22, hypertrophy in 20/22 (91%), and contrast enhancement in 8/22 (36%). MRI findings in these patients were more asymmetric and less diffuse than in

Continued on page 72

Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

Similar Long-term Outcomes for Stenting and Endarterectomy for Carotid Stenosis

SOURCE: Brott TG, Calvet D, Howard G, et al; Carotid Stenosis Trialists' Collaboration. Long-term outcomes of stenting and endarterectomy for symptomatic carotid stenosis: A preplanned pooled analysis of individual patient data. *Lancet Neurol* 2019;18:348-356.

In previous studies, researchers demonstrated that the risk of periprocedural complications, specifically stroke or death, was higher in patients undergoing carotid artery stenting (CAS) compared to carotid endarterectomy (CEA) for treatment of high-grade symptomatic carotid stenosis greater than 70%. However, the long-term consequences are not known. Brott et al attempted to evaluate the long-term efficacy of these procedures by doing a pooled analysis of four large, randomized, controlled trials designed to assess the relative efficacy of CAS vs. CEA for treatment of symptomatic carotid artery stenosis. Individual patient data were pooled from the following four studies: Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial, Stent-Protected Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy trial, the International Carotid Stenting Study, and Carotid Revascularization Endarterectomy versus Stenting trial. (Mas JL, et al. *N Engl J Med* 2006;355:1660-1671. Space Collaborative Group; Ringleb PA, et al. *Lancet* 2006;368:1239-1247. Bonati LH, et al. *Lancet* 2015;385:529-538. Brott TG, et al. *N Engl J Med* 2010;363:11-23.).

The risk of ischemic stroke was assessed starting at 121 days' postprocedure and then at one, three, five, seven, nine, and 10 years after randomization. The primary outcome was a composite risk of stroke or death within 120 days (periprocedure risk) or subsequent stroke that occurred up to 10 years after randomization (postprocedural risk). In the four trials, 4,775 patients were randomly assigned and 99.6% were followed for up to a maximum of 12.4 years. The median length of follow-up across all the studies ranged from two to 6.9 years. One hundred twenty-nine periprocedural events occurred in patients who underwent CEA, and 206 events occurred in those allocated to CAS. This confirms what has been shown in other studies — that periprocedural risk is higher in patients undergoing CAS. Long-term follow-up showed a similar number of ischemic strokes occurring in each group: 57 for those allocated to CAS and 55 in those undergoing CEA. The annual rates of ischemic stroke per person-year were similar in both treatment groups, but the addition of periprocedural risk favored carotid endarterectomy.

If periprocedural risk can be reduced in stenting procedures, then both procedures should be approximately equal in efficacy and longer-term durability. In addition, comorbidities, such as continuing to smoke cigarettes, hypercholesterolemia, and contralateral carotid stenosis all contributed to increasing morbidities. These factors should be assessed in future studies. ■

Transcranial Sonothrombolysis for Acute Ischemic Stroke – Not Yet Ready for Patient Treatment

SOURCE: Alexandrov AV, Kohrmann M, Soinne L, et al. Safety and efficacy of sonothrombolysis for acute ischemic stroke: A multicenter, double-blind, phase 3, randomized controlled trial. *Lancet Neurol* 2019;18:338-347.

Currently, IV alteplase for thrombolysis is the only approved treatment for acute ischemic stroke worldwide. Despite the growing use of mechanical thrombectomy, most stroke centers around the world do not have this capability, and any treatment that might enhance the efficacy of IV thrombolysis would be a welcomed improvement. In a Phase II trial published in 2004 (Alexandrov AV, et al. *N Engl J Med* 2004;351:2170-2178), the use of 2 MHz pulsed Doppler with a portable transcranial Doppler device was shown to double the rate of recanalization of middle cerebral artery occlusions. Investigators then organized a Phase III randomized trial to evaluate the efficacy of this approach.

In this multicenter trial at 76 medical centers in 14 countries, 335 patients were randomly allocated to the intervention group and 341 patients to the control group. The investigators included patients who had an acute ischemic stroke with an NIH stroke scale score of ≥ 10 and who received IV thrombolysis within three hours of symptom onset in North America and 4.5 hours of symptom onset in other countries. The intervention group received active 2 MHz pulsed wave ultrasound for 120 minutes focused on the middle cerebral artery, and the control group received sham ultrasound. The ultrasound was delivered using a specially designed device that kept the ultrasound probe focused on middle cerebral artery without the need for an operator holding the probe. The primary outcome was improvement in the modified Rankin Scale score at 90 days.

The adjusted odds ratio for improvement in the modified Rankin Scale score at 90 days in the intervention group was 1.05 and in the control group 1.24, but these differences were not statistically significant. Adverse events were reported in approximately the same frequency in both groups. The investigators concluded that transcranial Doppler delivery of sonothrombolysis was feasible and safe, but showed no clinical benefit at 90 days. However, the investigators urged continuing investigation of this technology because many centers may not be able to offer thrombectomy. This treatment deserves further investigation and evaluation for potential benefit. ■

Continued from page 70

patients who satisfied electrodiagnostic criteria for CIDP. Following plexus MRI, diagnosis was adjusted in 7/38 (18%) and allowed 7/24 (29%) to be classified as definite CIDP when used as a supportive criterion in conjunction with electrodiagnostic studies. Plexus MRI can be a valuable tool in the diagnosis of CIDP.

■ COMMENTARY

Following treatment for CIDP, determining objective patient improvement may be challenging where variation is minimal or fatigue predominates. Spina et al tested the 6-minute walk test (6MWT) among 42 CIDP patients to determine its sensitivity compared to other clinical outcome measures, including the modified version of the inflammatory neuropathy cause and treatment scale–sensory subscore, the Overall Neuropathy Limitation Scale, the Rasch-built overall disability scale, the modified Rankin Scale, and the Medical Research Council scale. Fatigue was analyzed by comparing first minute vs. the sixth minute velocity during the 6MWT. By using anchor and distribution-based approaches, the Minimal Clinically Important Difference Score (MCID), indicating meaningful clinical change required to consider a patient a responder, was calculated to be 20 meters. Using the 6MWT-MCID with other outcome measures, 74% of patients were identified as responders. Sensitivity of the 6MWT, which also captured fatigue-related changes, was 90%, compared to 77% for other measures. Routine assessment of CIDP patients should include the 6MWT, with MCID to identify responders to therapy set at 20 meters. ■

REFERENCE

1. Spina E, Topa A, Iodice R, et al. Six-minute walk test is reliable and sensitive in detecting response to therapy in CIDP. *J Neurol* 2019;266:860-865.

CME QUESTIONS

1. **Which of the following MRI abnormalities can be seen in a pediatric patient with Friedreich's ataxia?**
   a. Generalized cortical atrophy
   b. Volumetric reduction in the red nucleus
   c. Cerebral hemisphere gray matter injury
   d. Volume loss in cerebral white matter tracts
2. **REM sleep behavior disorder is characterized by which of the following features?**
   a. Morning sleep paralysis
   b. Active movements during REM sleep
   c. Sleep walking
   d. Obstructive sleep apnea
3. **Which of the following statements about alcoholic beverages as a trigger factor for migraine is false?**
   a. Approximately 35% of patients with migraine reported alcohol as a trigger.
   b. Vodka and red wine were equally likely to trigger migraine attacks.
   c. One-third of migraine attacks occurred within three hours of alcohol consumption.
   d. A little more than two standard glasses of red wine or vodka were necessary to trigger an attack.
4. **Migraine triggers should be:**
   a. ignored, as abortive medications are effective for most headache patients.
   b. recognized and managed while minimizing the social effect of trigger avoidance.
   c. avoided by whatever means necessary to prevent headaches.
   d. acknowledged as disability-related occurrences leading to depression and anxiety.

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]

Treatment of Primary Brain Tumors