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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Is Pediatric-onset Multiple Sclerosis a Neurodegenerative Disorder?

By Eric Mallack, MD, MBE, and Barry E. Kosofsky, MD, PhD

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Drs. Mallack and Kosofsky report no financial relationships relevant to this field of study.

SYNOPSIS: Pediatric-onset multiple sclerosis (onset less than age 18) compromises age-expected brain growth, thus implicating the neurodegenerative component of multiple sclerosis as an early-onset process, which may have diagnostic and potentially therapeutic implications for affected individuals.

SOURCE: Aubert-Broche B, et al. Onset of multiple sclerosis before adulthood leads to failure of age-expected brain growth. *Neurology* 2014;83:2140-2146.

Multiple sclerosis (MS) is traditionally understood as a focal, inflammatory, demyelinating disease of the central nervous system. MS has also been recently characterized as having a neurodegenerative component, as evidenced by progressive deep gray matter atrophy in adult-onset MS. In a parallel manner, reduced thalamic and whole brain volumes have been demonstrated in pediatric-onset MS (onset prior to age 18). In this study, the authors pursued longitudinal MR-based volumetric analyses to compare the growth trajectory of the brain, including deep grey structures — thalamus, putamen, caudate, and globus pallidus — by comparing regional brain volumes in patients with pediatric and adolescent-onset MS with age-matched controls. The relative contribution of "T2 lesion burden" and the timing of the onset of puberty to brain growth was also investigated. The authors hypothesized that identification of the differences in the growth curves would determine whether differences in regional brain

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volumes could be attributed to failure of brain growth, progressive brain atrophy, or both. As such, this study was pursued to demonstrate the possibility of the early onset of a regional neurodegenerative component in pediatric MS patients.

A total of 185 MRI scans of 36 pediatric MS patients (mean age of first scan = 14 years old) was compared with a control group (NC) of 25 age-matched pediatric patients (mean age of first scan = 16 years). The MS group had a mean of 5.1 scans over a range of 1 and 8 years from first to last scan. The NC group was scanned twice at an interval from 1 to 2 years from the first scan for a total of three scans. The same MR scanner was used for both groups. A normative brain growth reference data set was used from the publically available NIH-funded MRI Study of Normal Brain Development (NIHPD) for which mean age of first scan = 11 years, with subsequent scans obtained at 2- to 3-year intervals.

Low T2 lesion burden was arbitrarily chosen as 0.35% of normalized brain volume. Puberty was defined as age onset 11 years old —arbitrarily chosen to understand the effect of disease onset before and after that time — which is the average age for boys and girls.

The study revealed no significant difference between regional brain volumes of the NC group and the NIHPD group, thus indicating that the NC group was representative of the larger sample population of the NIHPD group. The MS brain and thalamic brain volume curves were significantly attenuated, as compared to the NIHPD group. There was no discontinuity in whole or regional brain volumes before vs after age 11 in pediatric MS patients, indicating no effect of puberty on longitudinal brain growth.

T2 lesion burden between brain, caudate, putamen, and globus pallidus volumes did not differ between MS patients who had an inter-scan lesion-to-brain ratio exceeding 0.35% vs MS patients with low lesion-to brain ratios < 0.35%. However, higher lesion load, not specific to the thalamus, was significantly associated with smaller thalamic volumes over time.

■ COMMENTARY

The onset of MS during childhood and adolescence significantly inhibits normal brain and thalamic growth. Additionally, there is progressive loss of brain and thalamic volume over time, implicating a component of brain atrophy. Thus, the neurodegenerative aspect of MS is not a late-onset complication. Rather, it is at play early on in patients with pediatric and adolescent-onset MS. The attenuated growth and subsequent thalamic atrophy in this population is consistent with thalamic atrophy seen in adult-onset MS, thus proving its higher sensitivity and vulnerability to the disease process across all ages. This becomes even more salient in patients with higher overall T2 lesion burden, as that independently correlates with thalamic atrophy, irrespective of lesion location. Presumably this reflects the predominant subcortical localization of MS lesions and the coordinate volumetric changes attributable to the thalamus as the "relay" for ascending projections to cortex.

For the pediatric neurologist, this study reframes how one should think about pediatric MS patients. The approach to treatment should be two-pronged and proceed in tandem. One should symptomatically treat the inflammatory state, but the other should also include treatment goals for both short- and long-term neuroprotection and neuro-repair in the effort to maximize the long-term cognitive outcome of pediatric MS patients with active disease.

For the adult neurologist, the study reframes how one should think about adults with early-onset MS as they transition from pediatric to adult medical management. Treatment of an acute flare with drugs targeted to prevent secondary flare may not fully cover the treatment scope of the disease. By the time they have stepped into the adult clinic, patients with pediatric- and adolescent-onset MS may have already undergone a significant, albeit potentially treatable, amount of neuro-degeneration. As the brain becomes less "plastic" over time, early and aggressive treatment of both the inflammatory and neurodegenerative components of MS will be imperative in patients affected with MS at younger ages. ■

ABSTRACT & COMMENTARY

Autologous Hematopoietic Stem Cell Transplant for Relapsing-Remitting MS

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal is on the speakers bureau for Biogen Idec, Teva Pharmaceuticals, Genzyme Corp., and Acorda Therapeutics.

SYNOPSIS: Interim analysis at 3 years post-treatment of a study of high-dose immunosuppression and autologous hematopoietic stem cell transplant for relapsing remitting-multiple sclerosis demonstrates sustained disease control but also shows potential risks associated with this treatment.

SOURCE: Nash RA, et. al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for relapsing-remitting multiple sclerosis (HALT-MS): A 3-year interim report. *JAMA Neurol* 2015;72:159-169.

Relapsing-remitting multiple sclerosis (RRMS) is characterized by a predominantly inflammatory early phase with a transition to a largely neurodegenerative secondary progressive phase. Immunomodulating treatment works best in the relapsing phase with limited benefit in the secondary phase. At present, there are 10 FDA approved treatments for relapsing MS. Each of these has varying levels of efficacy and immunosuppressive effects and their own unique benefits/risk profile. However, despite the availability of these multiple medications, many patients remain treatment refractory. Moreover, these treatments (with perhaps the exception of alemtuzumab) need to be continued to maintain disease control, raising the issues of compliance and potential risk of side effects/adverse events associated with their continuous use. Hence, a potent short-term treatment that induces sustained long-term benefit is of immense interest in the treatment of MS. Autologous hematopoietic stem cell transplantation has been explored for MS for several years. Based on data from these early pilot trials, it appears that it can have a significant benefit in relapsing MS but not have a meaningful benefit in progressive MS. Taking into consideration these findings, the present study was designed.

High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplantation for Relapsing-Remitting Multiple Sclerosis (HALT-MS) is an ongoing, single-arm, 5-year study. Eligible subjects were RRMS patients between 18-60 years of age, who had expanded disability status scale (EDSS) of 3 to 5.5 at baseline, disease duration < 15 years, and at least two relapses in the preceding 18 months. Peripheral blood stem-cell mobilization was achieved with filgrastim. High-dose BEAM chemotherapy regimen included carmustine, etoposide, cytarabine, and melphalan. Oral prednisone was administered during mobilization to reduce risk of relapses and during stem cell transplantation. Clinical evaluations including EDSS, Multiple Sclerosis Impact Scale, and MS Functional Composite were performed at baseline, months 6 and 12, and annually thereafter. Between annual visits, patients were contacted by phone and, in the event of neurologic symptoms, they were brought in for an evaluation. Brain MRI was performed at screening, week 6, month 6, month 12, and annually thereafter.

Twenty-four patients received high-dose immunosuppressive therapy followed by autologous hematopoietic stem cell transplantation (HDIT/HCT). The median disease duration was 4.9 years and median EDSS was 4.5. The primary study endpoint was the time-to-treatment failure defined by death from any cause, or disease progression as evidenced by increase in EDSS, relapse, or two or more gadolinium-enhancing or new T2 lesions on brain MRI a year or more after HDIT/HCT. At 3 years, the probability of event-free survival was 78.4%. EDSS improved after HDIT/HCT with a median change of -0.5 at 3 years. One patient had a relapse during mobilization. Within 3 years, none of the patients developed gadolinium-enhancing lesions other than one patient who was non-complaint with prednisone prophylaxis during mobilization and had an MS relapse associated with gadolinium-enhancing lesions. Brain volume between baseline and month 6 was decreased but appeared to have stabilized afterward. All patients experienced a grade 3 or 4 adverse event, which is severe, life-threatening, or disabling, as defined by the National Cancer Institute Common Terminology Criteria for Adverse events. Most of these were expected hematological/gastrointestinal or infectious events and were reversible or treatable. There were two deaths. One death was due to disease progression at 2.5 years post HDIT/HCT and another was due to worsening pre-existing asthma at 3.5 years. Severe disease progression and death following hematopoietic stem-cell transplantation has been reported elsewhere as well.

■ COMMENTARY

This small, single-arm study demonstrates that high-dose immunosuppressive therapy followed by autologous hematopoietic stem cell transplantation can have sustained significant benefit in RRMS. However, it also highlights the risks associated with this treatment. The study also has limitations including a small number of patients, open-label nature, unblended evaluation, and the infrequent follow-up visits. Based on these preliminary results, it appears to be an option worth further exploration for highly active MS. However, when considering its potential role in this population, one would need to weigh its benefits vs risks against currently FDA-approved agents that would generally be considered for highly active MS, especially natalizumab and alemtuzumab. We will learn further about the long-term outcome from immunosuppressive therapy followed by autologous hematopoietic stem cell transplantation at the completion of this study after a total of 5 years of follow-up. ■

ABSTRACT & COMMENTARY

'The Butterfly Effect' Explains Weather Triggering of Migraine

By Dara Jamieson, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: For about 13% of patients with migraine, a change in weather may be a trigger for some headaches; however, there is no specific perturbation in meteorological measures that is likely to predict a headache.

SOURCE: Hoffmann J, et al. The influence of weather on migraine – are migraine attacks predictable? *Ann Clin Transl Neurol* 2015;2:22-28.

In 2011, Hoffmann et al published a pilot analysis of the headache diaries of 20 Berlin migraineurs, correlating migraine attack frequency and severity to atmospheric air pressure, temperature, and relative air humidity. In six patients, the attack prevalence and pain intensity were associated with a lower temperature and higher humidity. As an expansion on this earlier data, the headache diaries of 100 migraineurs were retrospectively examined by the same investigators to assess the correlation of headaches with change in weather. Weather data included hourly recordings of atmospheric pressure, temperature, and relative humidity in years 2006 and 2007. These three weather measures, in 4-hour intervals over 12 consecutive months, and their variation within the 24 hours preceding a migraine attack, as noted in the patient diaries, were analyzed. For migraineurs showing a positive correlation between the meteorological measures and headache attacks, logistic regression analysis was used to assess the predictability of a migraine attack based on the meteorological information. Small monthly variations in migraine frequency were noted, with more events recorded in January, May, and July and fewer headaches noted in the months of November, August, and March. Migraines were slightly more likely to occur on Tuesday and Wednesday, than on Sunday. Migraines were twice as likely to occur in the early morning between 4 a.m. and 8 a.m., as compared to later in the evening between 8 p.m. and midnight. Because the pooled analysis for the 100 patients did not reveal a significant correlation between the meteorological variables and migraines, the patients' diaries were analyzed individually. Significant migraine correlation with weather was found in 13 patients; however, significant values in the weather parameters or their changes did not follow a predictable pattern. The correlation between migraines seemed to be with a perturbation in the weather pattern, rather with than any specific increase or decrease in the specific meteorological measures. Even in weather-sensitive migraineurs, a migraine attack could not be consistently predicted based on the weather patterns measured in this study.

■ COMMENTARY

Migraine is a complex brain disorder, with episodic head pain that can occur spontaneously or can be triggered by environmental conditions that reflect the individual predilections of patients. Some triggers are endorsed by many patients (e.g., alcohol) and others are unique to the point of oddness (e.g., leather shoes). Frequently, patients report a correlation between migraine headaches and change in weather. In a review published in 2013, appropriately entitled "Migraine and triggers: Post hoc ergo propter hoc?" Hoffman and Recober reviewed the available literature and concluded that the "clinical and experimental data seem to indicate that in a subgroup of migraineurs, the incidence of migraine attacks may be associated with low temperature, high relative humidity, and low atmospheric pressure."[1] However, Hoffman and his colleagues based this conclusion on their small pilot study published in 2011,[2] whose early results did not predict the less conclusive results of their recent analysis of more data. This current study found a relatively small

percentage (13%) of migraineurs had weather sensitivity, without a reliable forecast of the specific directions of the change that was likely to trigger an attack.

Despite much patient headache diary documentation and physician questioning about triggers of migraine attacks, the vast majority of headaches are triggered by what I characterize as "chaos in the universe." But, the effect of weather perturbations on migraine headaches is best described by the "butterfly effect," whereby a small change in the initial conditions leads to a complex sequence of events that eventually produces a significantly different outcome. Had the butterfly not flapped its wings when and where it did, the tornado, days later, might not have achieved its eventual strength and location. Weather changes do not cause the migraine headache to occur, and the headache might have occurred even without the atmospheric pressure, temperature, and humidity changes. However, there is some weather contribution to the characteristics and timing of a particular migraine headache, with a stronger influence in certain inexplicably vulnerable migraineurs. The obvious problem for the weather-sensitive headache sufferers is that the lack of predictability means that migraineurs get asked about a weather trigger, but nobody tells them what to do about it. ■

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2. Hoffmann J, et al. Weather sensitivity in migraineurs. *J Neurol* 2011;258:596-602.

ABSTRACT & COMMENTARY

Update in Treating Neuropathic Pain

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: In an exhaustive review of the literature with a meta-analysis, the following medications were found to be most efficacious in the treatment of neuropathic pain: gabapentin, pregabalin, serotonin-noradrenaline reuptake inhibitors including duloxetine or venlafaxine, and tricyclic antidepressants.

SOURCE: Finnerup NB, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol* 2015;14:162-173.

Which agents are most efficacious for the treatment of neuropathic pain? Given new drug treatments, novel methods of delivering old ones, and new clinical trials, meta-analysis and systematic review of the literature was undertaken by Finnerup et al to address this question.

Adhering to the 23-item AGREE II: Appraisal of Guidelines for Research and Evaluation, for reporting and evaluating health care recommendations, the authors conducted a literature review using PubMed, Medline, the Cochrane Central Register of Controlled Trials, and Embase, searching from January 1966 to April 2013. Published reviews and reference lists of selected papers were additionally gathered, as were primary registries in the World Health Organization Network and those approved by the International Committee of Medical Journal Editors. PubMed and the ClinicalTrials.gov website searches brought the study up to date as of January 31, 2014. Inclusion criteria comprised patients of any age with neuropathic pain, defined as pain caused by a lesion affecting the somatosensory nervous system, including diabetic or non-diabetic painful neuropathy, post-herpetic neuralgia, post-amputation, post-traumatic, or post-surgical neuropathic pain, plexus avulsion injuries and complex regional pain syndrome type 2, central post-stroke pain, spinal cord injury pain, and multiple sclerosis-associated pain. As they do not meet the current definition of neuropathic pain, complex regional pain syndrome type 1, low back pain without radicular pain, fibromyalgia, and atypical face pain were excluded. Interventions studied included systemic or topical treatments, and single-administration treatments with long-term efficacy. Studies that were randomized, double-blind, or placebo-controlled, with parallel group or crossover study designs, were included, but studies published only as abstracts were excluded, as were studies in which the primary outcome included a score for paraesthesia only or pain and paraesthesia. Final recommendations were made using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) classification. Numbers needed-to-treat (NNT) for 50% pain reduction, calculated with the fixed-effects Mantel-Haenszel method, was the primary effect measure, with secondary outcome being the difference in pain intensity.

Among 1634 records screened, 1361 were excluded

by abstract, leaving 273 full-text articles assessed for eligibility; 229 of these articles or trials were ultimately incorporated for meta-analysis. Based on GRADE, strong first-line recommendations could be given for gabapentin, pregabalin, serotonin-noradrenaline reuptake inhibitors including duloxetine or venlafaxine, and tricyclic antidepressants. Weak second-line recommendations were given for capsaicin 8% patches, lidocaine patches, and tramadol, with third-line recommendations for botulinum toxin A (subcutaneously) and strong opioids, including sustained release oxycodone and morphine. Given these findings, a revision of current recommendations for control of neuropathic pain should be considered.

■ COMMENTARY

Multiple mechanisms, at both the level of the peripheral and central nervous systems, appear to underlie neuropathic pain, suggesting that simultaneous targeting may improve treatment outcome. Inconsistent results from the few clinical trials undertaken using drug combinations, including morphine and gabapentin, gabapentin and nortriptyline, pregabalin and duloxetine, and doxepin and capsaicin, have been disappointing, but this option requires further investigation.[1] ■

REFERENCE

1. Eisenberg E, Suzan E. Drug combinations in the treatment of neuropathic pain. *Curr Pain Headache Rep* 2014;18:463; DOI 10.1007/s11916-014-0463-y.

ABSTRACT & COMMENTARY

Restless Legs Syndrome and Post-polio Syndrome

By Alexander Shtilbans, MD, PhD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Restless legs syndrome is prevalent in patients with post-polio syndrome and is associated with decreased quality of life and fatigue.

SOURCE: Romigi A, et al. Restless legs syndrome and post polio syndrome: A case-control study. *Eur J Neurol* 2015;22:472-78.

Restless leg syndrome (RLS) is a sensorimotor disorder characterized by a distressing urge to move the legs and occasionally the arms, usually accompanied by an uncomfortable sensation of pain in the affected body parts, mostly the legs. The sensations occur particularly in the evening or at night and are relieved by movements. RLS can be primary or secondary due to metabolic abnormalities. The pathophysiology of primary RLS is still poorly understood, but is thought to be related, at least in part, to dysfunction of central dopaminergic system, iron metabolism, and opioid neurotransmission. Secondary RLS is classically associated with iron deficiency anemia, pregnancy, or uremia in end-stage renal disease. Post-polio syndrome (PPS) affects patients with a history of acute poliomyelitis and is characterized by worsening muscle weakness and new and progressive generalized fatigue affecting quality of life of the patients.

The authors of this paper conducted a case-control, cross-sectional study aimed to investigate the prevalence of RLS, fatigue, and daytime sleepiness in patients with PPS compared to controls.

In this trial, 78 patients with PPS and 90 control subjects matched by age and sex were screened. Exclusion criteria for both groups were secondary forms of restless leg syndrome as well as current treatment with clonazepam, dopamine agonists, antidepressant medications, or neuroleptics. The study consisted of collection of demographic data and face-to-face evaluation by a sleep neurologist who administered a questionnaire and performed a clinical examination. In particular, severity of fatigue was assessed using a fatigue severity scale, and health-related quality-of-life was evaluated by a short-form health survey. Stanford Sleepiness Scale was used to evaluate daytime sleepiness. Patients and controls were categorized into four subgroups: patients with PPS without RLS, patients with PPS and RLS, controls without RLS, and controls with RLS.

The results showed that of the 66 enrolled PPS patients, 42 (63.6%) experienced RLS symptoms. None of them had RLS prior to PPS onset. Of the 80 recruited health controls, six subjects (7.5%) were affected by RLS. Based on this, calculated odds ratio (OR) of RLS in PPS patients was 21.5, and was statistically significant. Both men and women with PPS had similar ORs for RLS. Fatigue severity scale scores were higher in PPS patients affected by RLS compared to PPS patients who didn't have RLS. There was no significant difference in daytime sleepiness measures. Health-related quality of life scores were lower in PPS/RLS patients. The authors

didn't find any correlation between RLS rating scale and Medical Research Council strength rating scores and PPS duration.

Overall, the authors concluded that patients with PPS have high prevalence of RLS, suggesting significant comorbidity between PPS and RLS. They also hypothesized that both conditions could have a common pathological process, such as central nervous system inflammation. Alternatively, the diencephalon-spinal dopaminergic pathway could be an anatomical entity involving both RLS and PPS. The authors further suggested that PPS can be considered a possible cause of secondary form of RLS.

■ COMMENTARY

The authors of the current case-control study evaluated the prevalence of RLS among a group of patients with history of PPS compared to healthy controls. Besides establishing the prevalence to be 63.6%, the authors found a high correlation of fatigue and decreased quality of life with increased OR of having RLS in patients' group. The authors argue that fatigue may be partially related to occurrence and severity of RLS. They further hypothesized that RLS could represent a possible cause for the circadian fatigue seen in PPS.

This study is one of the first to be conducted to evaluate the prevalence of RLS in PPS patients. It was well designed, but the PPS group had slightly more women compared to the control group. In addition, subjects taking clonazepam, dopamine agonists, antidepressants, or neuroleptics were excluded from the study, while the authors didn't say anything about those taking opioids or gabapentin enacarbil extended-release, which are routinely prescribed for patients with RLS. This omission could have altered the calculated prevalence of RLS in both groups. Other limitations included a lack of population-based sampling and evaluation of other comorbidities. Nonetheless, PPS can be considered a possible cause of the secondary form of RLS. ■

Neurology [ALERT™]

Stroke Alert

By Matthew E. Fink, MD

Intracranial Clot Extraction Results in Better Outcomes than Intravenous Thrombolysis Alone

Sources: Berkhemer OA, et al. for the MR CLEAN investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11-20. DOI: 10.1056/NEJMoa1411587

Goyal M, et al, for the ESCAPE trial investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *New Engl J Med* 2015;372:1019-1030. DOI: 10.1056/NEJMoa1414905.

Campbell BC, et al, for the EXTEND-IA investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *New Engl J Med* 2015;372:1009-1018. DOI: 10.1056/NEJMoa1414792.

In last month's *Neurology Alert*, we briefly mentioned the studies reported at the International Stroke Conference that showed dramatic improvements in neurological outcome and survival using the latest intracranial clot retrieval devices. This month, we will discuss three studies that have been recently published in the New England Journal of Medicine — MR CLEAN, ESCAPE, and EXTEND — regarding intracranial clot extraction for acute ischemic stroke.

In MR CLEAN, 500 patients from 16 medical centers in the Netherlands were enrolled and randomized to usual care vs intracranial clot extraction. Eligible patients had a proximal arterial occlusion in the anterior cerebral circulation confirmed by vessel imaging that could be treated intra-arterially within 6 hours of symptom onset. The primary outcome was the modified Rankin scale score in 90 days. Mean age of the patients was 65 years, and 89% were treated with intravenous alteplase before randomization. Retrieval stents were used and 81.5% of the patients assigned to intra-arterial treatment. The adjusted odds ratio for a good functional outcome was 1.67 (95% confidence interval [CI], 1.21-2.30). There was an absolute difference of 13.5 percentage points in favor of functional independence (modified Rankin score 0-2) in the interventional group (32.6% vs 19.1%). There was no significant difference in mortality or the occurrence of symptomatic intracerebral hemorrhage between the two groups of patients.

In the ESCAPE trial, participants with acute ischemic stroke in the anterior circulation with a demonstrated proximal vessel occlusion were included up to 12 hours after symptom onset. Patients with a large infarct core or poor collateral circulation on CT and CT angiography were excluded. The primary outcome was the score on the modified Rankin scale at 90 days.

The trial was stopped early because of efficacy. At 22 centers around the world, 316 participants were enrolled and 238 received intravenous alteplase before any interventions. The median time from study CT to the first reperfusion in the interventional group was 84 minutes. The rate of functional independence (90-day modified Rankin score of 0-2) was improved with the intervention (53% vs 29%, $P \leq 0.001$). The primary outcome measure favored the intervention group with an odds ratio of 2.6. The intervention was associated with reduced mortality compared to the control group, but there was no significant difference in the rate of symptomatic intracerebral hemorrhage.

Finally, in the EXTEND-IA trial, patients were randomly assigned to receive standard intravenous alteplase, with or without endovascular thrombectomy, using the SOLITAIRE FR stent retriever. Patients were enrolled if they presented within 4.5 hours after onset of ischemic stroke symptoms. All patients had occlusion of the internal carotid or middle cerebral artery and evidence of salvageable brain tissue with a small ischemic core, based on CT perfusion imaging. The primary outcomes were reperfusion in 24 hours and early neurological improvement (8-point reduction on the NIHSS or score = 0 to 1 at day 3). Secondary outcomes included the modified Rankin scale score at 90 days. The trial was stopped early because of efficacy after 70 patients had undergone randomization. The percentage of ischemic territory that had undergone reperfusion in 24 hours was greater in the endovascular therapy group compared to the alteplase only group, and endovascular therapy, initiated at a median of 210 min., increased early neurological improvement at 3 days (80% vs 37%, $P = 0.002$). More patients had improved functional outcome and 90 days (71% vs 40%). There were no differences in rates of death or symptomatic intracerebral hemorrhage.

All three of these well-designed and executed studies support the efficacy of intracranial artery clot extraction for patients with acute ischemic stroke, who have 1) proven major vessel occlusion, 2) short time interval between onset of symptoms and start of the procedure, and 3) use of the most advanced technological devices. Improved technology and patient selection played a major role in determining the success of these trials, and these rules should be applied when making treatment decisions for our own patients. These studies, and others, are heralding a new era in ischemic stroke therapy. ■

CME QUESTIONS

1. **Which of the following statements support the concept that MS is a "neurodegenerative disorder"?**
   a. Pediatric MS patients have less brain and thalamic growth than do normal controls.
   b. Adult MS patients develop thalamic atrophy.
   c. Adult MS patients develop late-life brain atrophy.
   d. Adult MS patients develop late-life cognitive impairments.
   e. All of the above
2. **Which of the following is NOT a complication of autologous hematopoietic stem cell transplantation for the treatment of RRMS?**
   a. Severe leukopenia
   b. Severe opportunistic infections
   c. Severe gastrointestinal disturbances
   d. Peripheral neuropathy
   e. Death
3. **When are migraines most likely to occur?**
   a. Between 4 am to 8 a.m.
   b. From 8 p.m. to midnight
   c. On Sundays in March
   d. In the afternoons in November
   e. Under the harvest moon
4. **Based on extensive review of the literature, and using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) classification, which of the following appears to have the best chance of success in treating neuropathic pain?**
   a. Gabapentin
   b. Capsaicin cream
   c. Lidocaine patches
   d. Tramadol
   e. All of the above are equally efficacious
5. **Which of the following is a secondary cause of restless legs syndrome?**
   a. Iron deficiency
   b. Pregnancy
   c. End-stage renal disease
   d. Post-polio syndrome
   e. All of the above
6. **Success in intracranial arterial clot extraction for acute ischemic stroke depends on all of the following except:**
   a. rapid institution of therapy.
   b. careful patient selection with proven large artery occlusion.
   c. use of the most efficacious clot extraction device.
   d. skill and experience of the interventionalist.
   e. use of intravenous thrombolysis.

[IN FUTURE ISSUES]

Neurologic Sleep Disorders