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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Is Stem Cell Transplantation a Viable Treatment Option for CIDP?

By Norman Latov, MD, PhD

Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Latov reports that he receives grant/research support from Grifols; is a retained consultant for CSL Behring and Baxter; and owns stock in Therapath LLC.

SYNOPSIS: In this small, uncontrolled trial, autologous stem cell transplantation appeared to be efficacious for the treatment of patients with refractory CIDP.

SOURCE: Press R, et al. Autologous haematopoietic stem cell transplantation: A viable treatment option for CIDP. *J Neurol Neurosurg Psychiatry* 2014;85:618-624.

The authors describe the results of autologous haematopoietic stem cell transplantation (AHSCT) treatment in 11 consecutive patients with chronic inflammatory demyelinating polyneuropathy (CIDP) refractory to first-line immunomodulatory treatments and one or more second-line treatments. The total median Inflammatory Neuropathy Cause and Treatment Score (INCAT) and Rankin scores improved significantly within 2-6 months after AHSCT. Eight of the 11 patients maintained drug-free remission, but three of the 11 relapsed during the follow-up period, requiring retransplantation with AHSCT in one. Complications occurred following six of the transplantations, but resolved spontaneously or with treatment. The authors conclude that AHSCT can be efficacious in therapy-refractory CIDP, with a manageable complication profile, although randomized controlled trials are needed.

■ COMMENTARY

CIDP is an inflammatory neuropathy that targets the myelin sheaths in the peripheral nerves. First-line therapies include intravenous immunolobulins, corticosteroids, or plasmapheresis, with a reported response rate of 66% to 87%.[1,2,3,4] Those who progress despite first-line treatment are usually offered second-

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line therapies with anti-inflammatory agents, which have not been tested in clinical trials, but can be beneficial in 25% of patients refractory to first-line therapies.[5] In the current cohort, treatments included alemtuzumab, azathioprine, cyclosporine, cyclophosphamide, beta-interferon, mycophenylate motefil, natalizumab, or rituximab.

In those refractory to second-line therapies, hematopoietic stem cell transplantation (HST) has been reported to be beneficial in occasional patients.[6] High-dose cyclophosphamide without stem cell rescue has also been reported to be efficacious in some cases.[7] In general, autologous stem cells are generally preferred to allogenic stem cells as the latter can cause graft-vs-host disease, including CIDP,[8] although relapses are more common following the use of autologous stem cells, possibly due to inclusion of autoreactive lymphocytes.[9] In the current study, three of the 11 patients suffered relapses, with one requiring repeat AHSCT.

The risks associated with AHSCT are mainly due to the severe pancytopenia that follows the bone marrow ablation. In the current study, early complications were seen in six to 12 transplants, and included reactivation of cytomegalovirus or Epstein-Barr virus, bacterial infection with *E. coli*, staphylococci, *Klebsiella*, pseudomonas, alpha Streptococci, or *Clostridium difficile*; hemorrhagic cystitis; pancreatitis; anemia; hypothyroidism; and neutropenia. All, however, resolved spontaneously or with treatment.

A caveat to keep in mind is that there is no definitive test for CIDP, so that other causes for demyelinating polyneuropathy, such as Charcot-Marie Tooth type I, anti-MAG neuropathy, or POEMS syndrome, should be definitively ruled out before proceeding with more drastic treatments. As an example, in a recent trial of CIDP, 17% of the patients were found to have an alternate diagnosis that was only made after the patients failed to respond to standard therapies.[10] ■

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ABSTRACT & COMMENTARY

OnabotulinumtoxinA for Treatment of Chronic Migraines

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: A pooled analysis of four clinical trials concluded that treatment with onabotulinumtoxinA at doses of 75-260 U administered every 12 weeks for up to five treatment cycles was efficacious, safe, and well tolerated for the prophylaxis of headache in adults with chronic migraine.

SOURCE: Diener HC, et al. Pooled analysis of the safety and tolerability of onabotulinumtoxinA in the treatment of chronic migraine. *Eur J Neurol* 2014;21:851-859.

Injection of onabotulinumtoxinA, causing inhibition of the release of acetylcholine at the neuromuscular junction, is an effective treatment for the prophylaxis of headache in patients with chronic migraine (CM). But patients want to know that it is safe and without problem side effects. Diener et al assessed the safety and tolerability of onabotulinumtoxinA in CM prophylaxis in men and women, aged 18-65 years, using data from two exploratory Phase 2 and two Phase 3 (PREEMPT: Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy) double-blind, placebo-controlled trials. The studies shared similar dosing intervals (approximately 12 weeks) with doses between 75 and 260 U. In the PREEMPT 1 and 2 multicenter trials, patients were randomized to either onabotulinumtoxinA (155-195 U) or placebo. Treatments were 31 fixed-site, fixed-dose intramuscular injections across seven specific head/neck muscle areas. An additional 40 U of onabotulinumtoxinA or placebo could be administered using a "follow-the-pain" injection paradigm that varied across treatment visits. The maximum dose was 195 U across 39 sites per treatment cycle. Patients who completed the double-blind phase entered an open-label phase, where they received 155-195 U of onabotulinumtoxinA at 12-week intervals. The majority of patients in the pooled analysis of the four studies received doses between 150-200 U, with an average of 163 U per treatment cycle.

Safety assessments included adverse events (AEs), physical examination, and clinical laboratory tests. OnabotulinumtoxinA was safe and well tolerated, with a low discontinuation rate (3.4%) due to AEs. Approximately 73% of patients who were injected with onabotulinumtoxinA reported at least one AE, most frequently neck pain (13.8% vs 2.4% with placebo). Other AEs that occurred in the pooled analysis more frequently with onabotulinumtoxinA treatment than with placebo were head, neck, or shoulder/upper arm muscular weakness (8.0%); headache (8.0%); facial paresis (8%); musculoskeletal stiffness (6.1%); and eyelid ptosis (4.6%). Weakness generally involved injected or adjacent muscles, but an effect on nearby muscles can occur due to local diffusion. However, distant effects of the intramuscular injection were not reported. Serious AEs (most commonly migraine, pneumonia, uterine leiomyoma, and headache) were infrequent, occurring in 5.4% of patients who received any onabotulinumtoxinA treatment (n = 1997) and 3.0% of patients receiving placebo (n = 1052), and did not appear to be treatment related. The incidence of AEs potentially associated with hypersensitivity was also not considered to be treatment related (2.2% with onabotulinumtoxinA and 2.0% with placebo). The dosing and injection paradigm used in the PREEMPT clinical program (155-195 U) resulted in fewer individual AEs and demonstrated robust long-term (up to 56 weeks) efficacy.

■ COMMENTARY

CM, as defined by the third beta edition of the International Classification of Headache Disorders (ICHD-3 beta), is characterized by headache occurring on ≥ 15 days per month for at least 3 months and the features of migraine headache on at least 8 days per month. Any effective treatment that can decrease the personal and economic disability of CMs has very significant individual and societal benefit. There are very limited prophylactic treatment options for the 1.4-2.2% of the population who suffer specifically from CM; although medications used to decrease the frequency and severity of episodic migraine are commonly used to prevent CM. Topiramate, commonly used for migraine prophylaxis in episodic migraine, was shown in a small pilot study to have more treatment-related AEs, with a higher discontinuation rate, as compared to treatment with onabotulinumtoxinA. The benefit of onabotulinumtoxinA in the prevention of CM has been proven in randomized, double-blind, placebo-controlled trials, with most patients deriving benefit to varying degrees. Any CM trial has logistical challenges, because of the variable nature of the disease itself, with added study design difficulties when using a muscle paralytic agent. True blinding of onabotulinumtoxinA injections is problematic, as lack of the ability to wrinkle the forehead is characteristic of the treatment. However, this potential unblinding of the treatment arm in clinical trials does not negate the clear benefit enjoyed by many patients, both before and after the treatment was approved by the FDA.

Physicians who inject this medication for CM realize the unique aspects of this treatment and may tweak the FDA-recommended injection protocol. The physician's individual injection technique is perfected with experience and patient feedback. After years of treating patients with onabotulinumtoxinA, I inject fewer units into the neck and shoulders of small, thin individuals in order to decrease the risk of neck weakness and pain. Injection higher in the corrugator muscles above the brows, with a small extra dose injected laterally, eliminates cosmetic complaints about asymmetric eyebrows. Some returning patients are adamant about the benefit of their "follow-the-pain" injections, which may be offered when the injections can be performed safely in painful areas of the face and head. Although the treatment is not approved for use in children under the age of 18, I have found efficacy and tolerability with onabotulinumtoxinA injections for chronic migraine in adolescents. The usual experience of neurologists who inject onabotulinumtoxinA is that the treatment is safe and effective, providing a significant measure of relief to many patients suffering from this disabling neurological disorder. ■

ABSTRACT & COMMENTARY

Diffusion Tensor MRI Advances Diagnostic Accuracy in ALS

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: Diffusion tensor magnetic resonance imaging of the brain and spinal cord, which measures the integrity of white-matter fiber tracks, can improve the sensitivity and specificity of amyotrophic lateral sclerosis diagnosis.

SOURCE: Kassubek J, et al. Diffusion tensor imaging analysis of sequential spreading of disease in amyotrophic lateral sclerosis confirms patterns of TDP-43 pathology. *Brain* 2014;137:1733-1740.

Based on 76 autopsies, and using distribution patterns of phosphorylated 43 kDa TAR DNA-binding protein, four neuropathological stages of amyotrophic lateral sclerosis (ALS) have recently been defined by Brettschneider et al.[1] ALS was found to progress in a sequential regional pattern, with stage 1 lesions observed in the agranular motor cortex; brainstem cranial motor nuclei of nerves V, VII, and XII; and in spinal cord anterior horn cells, with stage 2 involvement seen in the prefrontal neocortex (middle frontal gyrus), brainstem reticular formation, precerebellar nuclei, and red nucleus. In stage 3, abnormalities were found in the prefrontal gyrus rectus and orbital gyri, postcentral neocortex, and striatum, and stage 4 changes were seen in anteromedial portions of the temporal lobe, including the hippocampal formation. An in vivo approach to assessing this spread of TDP-43 pathology is measurement of neuro-axonal loss in white matter fiber tracts. Using magnetic resonance imaging (MRI)-based techniques, can the ex vivo staging system be transferred to noninvasive in vivo diagnostics in ALS, thereby permitting in vivo monitoring of disease progression?

To address this question, 111 patients (68 men, 43 women) with clinically definite or probable, mild-to-moderate, sporadic ALS, based on revised El Escorial criteria,[2] underwent clinical and laboratory examination, including MRI imaging using a 1.5T (n = 78) or 3.0T (n = 33) scanner, with 74 healthy, age-matched controls used for comparison. No one in either group had other medical, neurologic, or psychiatric issues. MRI images were examined by a fiber-tracking approach to analyze five tracts-of-interest that represent the white matter correlates of the four stages of ALS: the corticospinal tract (stage 1), the corticorubral and corticopontine tracts (stage 2), the corticostriatal pathway (stage 3), the proximal portion of the perforant path (stage 4), and two reference pathways originating from the corpus callosum and optic tract. Postprocessing and statistical analysis comprised whole brain-based spatial statistics, the t-test, staging categorization of a decision alogorithm, and calculation of axial and radial diffusivity, with false discovery rate corrected at $P < 0.05$.

Using region of interest analysis, ALS patients could be differentiated from controls using the 1.5T MRI with 78% sensitivity and 69% specificity, and using the 3.0T MRI by 82% and 68%, respectively. Tract-wise fractional anisotropy statistics found similar sensitivity and specificity results: 79% and 71% for the former, and 79% and 73% for the latter, respectively. In the entire cohort, distinction between ALS and controls was greatest at stage 1 for the corticospinal tract. Staging pattern identification could be performed at the individual patient level. In ALS, it is possible to image stages of disease in predefined tract structures in vivo using tract of interest-based tensor diffusion MRI technique, permitting in vivo monitoring of disease progression.

■ COMMENTARY

Diffusion tensor imaging (DTI) of the cervical spinal cord in ALS patients may disclose corticospinal abnormalities not seen on conventional MRI. Among 24 patients with probable or definite ALS, conventional cervical spinal cord MRI was unremarkable. In contrast, fractional anisotropy was significantly lower and apparent diffusion coefficient correlates were significantly greater than those of 16 age-matched controls when examining the lateral corticospinal tracts bilaterally. No correlation between abnormal DTI parameters and clinical findings was seen. Quantitative DTI can disclose subtle abnormalities in the lateral corticospinal tracts even in "MRI normal-appearing" cervical spinal cord of ALS patients and may be used to assist in the diagnosis of ALS.[3] ■

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ABSTRACT & COMMENTARY

The Neurophysiological Features of Myoclonus-Dystonia

By Alexander Shtilbans, MD, PhD

Assistant Professor of Neurology, Weil Cornell Medical College

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

SYNOPSIS: Myoclonus-dystonia is characterized by specific neurophysiological dysfunctions that appear to be different from the ones seen in other dystonias.

SOURCE: Popa T, et al. The neurophysiological features of myoclonus-dystonia and differentiation from other dystonias. *JAMA Neurol* 2014;71:612-619.

Myoclonus-dystonia is a movement disorder characterized by a combination of rapid, brief muscle contractures and sustained repetitive movements resulting in abnormal postures. Loss-of-function mutations or deletions in the ε-sarcoglycan (SGCE) gene on chromosome 7 have been implicated in 50% of the cases (DYT 11). The function of SGCE in the brain is presently unknown. Genetic defects in other locations presumably account for the rest of the cases (DYT 15). Aside from the abnormal movements, the patients frequently have psychiatric problems including depression, anxiety, and obsessive-compulsive disorder.

The objective of this study was to evaluate the neurophysiological characteristics of myoclonus dystonia due to SGCE defects. The authors studied 12 myoclonus-dystonia patients from 11 unrelated families with genetic defects in SGCE gene compared with 12 healthy volunteers. The pharmacological treatments of the patients were discontinued at least 1 week prior to the beginning of the study. The patients and controls were assessed by clinical examination and rating, MRI of the brain, and electrophysiological testing including resting motor threshold, active motor threshold, short-interval intracortical inhibition, and short-interval intracortical facilitation. Assessments of the left primary motor cortex excitability using transcranial magnetic stimulation and cerebellar-dependent eye-blink classic conditioning were conducted as well. Electrophysiological data were correlated with clinical scores in the patient group. Contrary to the previous findings in other forms of dystonia, these authors detected low membrane excitability of the corticocortical axons and normal intracortical GABA inhibition. However, there was enhanced responsiveness of the motor cortex to plasticity noted, as well as abnormal response to cerebellar conditioning in the patient group. The authors concluded that cerebellar dysfunction plays a role in pathophysiology of dystonia and that their findings support parasagittal cerebellum involvement in pathogenesis of myoclonus-dystonia, which the authors believe to be different from other types of dystonia based on the neurophysiological characteristics.

■ COMMENTARY

The authors of the current study evaluated neurophysiological features in patients with myoclonus-dystonia harboring a defect in SGCE gene (DYT-11). While the study was small and did not include patients with other genetic defects, such as seen in DYT 15, it was well designed and showed differences in some characteristics from other dystonias. Namely, the patients had low membrane excitability of the corticocortical axons while their intracortical GABA inhibition was normal. Also, myoclonus-dystonia patients showed enhanced tendency of the motor cortex to develop plasticity and cerebellar dysfunction compared to controls. While not much is known about the pathophysiology of myoclonus-dystonia, a possible explanation for these differences could be that abnormalities of myoclonus and dystonia could originate anywhere in the wide functional motor network including sensorimotor cortex, cerebellum, brainstem, and spinal cord, besides basal ganglia. It is still unclear whether the noted changes are causative or compensatory.

Despite the noted cerebellar dysfunction in the patient group as well as in other types of dystonia, the lack of clinical cerebellar signs on exam could be related to distortion of the cerebellar output, which could minimize the clinical picture.

Interestingly, the global disability score had discrepant results between the patient self-rating scores and the ones done by a neurologist. Indeed, the biphasic active motor threshold correlated with the self-rated but not the neurologist-rated global disability score. The authors rightfully argue that the self-rated scores might be more accurate given variations of the patients' symptoms throughout the day.

Overall, the demonstrated neurophysiological differences in patients with myoclonus-dystonia compared to other forms of dystonia are important and warrant further studies in larger and more genetically diverse groups of patients to evaluate the functional significance of these changes, which can help understand the pathophysiology of the disease and lead to effective treatment. ■

ABSTRACT & COMMENTARY

Is Epilepsy Surgery on the Decline?

By Padmaja Kandula, MD

Assistant Professor of Neurology, Comprehensive Epilepsy Center, Weill Cornell Medical College

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

SYNOPSIS: In this 20-year, retrospective study, the authors summarize surgical trends in three major German epilepsy centers and identified a declining prevalence of epilepsy surgery from 1998 to 2008.

SOURCE: Helmstaedter C, et al. Temporal lobe surgery in Germany from 1988 to 2008: Diverse trends in etiological subgroups. *Europ J Neurol* 2014;21:827-834.

Despite class I evidence and subsequent 2013 American Academy of Neurology (AAN) Practice Guidelines advocating early surgery in drug-resistant epilepsy (failure of two anti-epileptic agents), surgery for epilepsy has not increased in the United States over the last two decades. In this present retrospective study, the authors parallel the U.S. experience and summarize the experience of surgical trends in three major German epilepsy centers from 1988 to 2008. In contrast to previous papers, however, surgical trends with regards to other temporal lobe etiologies are taken into consideration.

In total, 2812 patients with temporal lobe epilepsy (TLE) underwent epilepsy surgery in all three centers combined. The authors addressed the number of surgeries over time, duration of epilepsy before surgical intervention, differences in trends between etiologic categories of TLE, and inter-institution variability.

Not surprisingly, with the advent of improved MRI technique, there was a steady increase in epilepsy surgeries for each 4-year epoch from 1988 to 2004, from 296 in the early epoch to more than 700 patients more recently. Correspondingly, there was an increase in patients with hippocampal sclerosis from 30-58% during the years of 1988-2004, with a subsequent plateau in the years thereafter. From 2005 to 2008, there was a subsequent decrease to 600 epilepsy surgeries with relative stability in the prevalence of hippocampal sclerosis (58%).

An interesting observation was the longer duration of epilepsy in patients with hippocampal sclerosis compared to other TLE etiologic subtypes, such as tumors, vascular lesions, and focal cortical dysplasia. In fact, the group with hippocampal sclerosis had continuously increasing age at time of surgery by an average of 7 years over the observed two decades.

■ COMMENTARY

The steady increase of patients with reported hippocampal sclerosis undergoing epilepsy surgery is not surprising. However, the overall decline in epilepsy surgeries with relative stability of the hippocampal sclerosis rate, from 2005-2008, is perplexing. In all three centers, there was a notable trend of increasing age at surgical intervention and increasing duration of epilepsy with an overall fixed rate of hippocampal sclerosis from 2005-2008. Various theories have been proposed to explain this inconsistency. One plausible explanation is the influence of disease-modifying factors such as aggressive treatment of brain infections, febrile seizures, and the advent of second- and third-generation anti-epileptic agents. Although the idea of influencing the natural course of hippocampal sclerosis via better medical care and aggressive pharmacologic treatment is satisfying, without larger population-based studies, no definitive conclusions can be drawn. Resective surgery is well established for the treatment of TLE, but the future of epilepsy treatment is evolving. Currently neurostimulatory treatment is in its infancy, but perhaps the nature of this discussion will become even more varied and intricate over the next two decades with a growing arsenal of treatment options. ■

Atrial Fibrillation and Cryptogenic Stroke: Important New Information

By Matthew E. Fink, MD

Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital

SOURCES: Gladstone DJ, et al, for the EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;370:2467-2477.

Kamel H. Editorial. Heart-rhythm monitoring for evaluation of cryptogenic stroke. *N Engl J Med* 2014;26:2532-2533.

Sanna T, et al, for the CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;370:2478-2486.

Ischemic stroke remains a leading cause of death worldwide, and atrial fibrillation is a major risk factor, increasing the risk of ischemic stroke five-fold in those who have a confirmed diagnosis of atrial fibrillation. Of all ischemic strokes, 20-40% have no identifiable cause and are classified as cryptogenic ischemic strokes. Clinically, it has been suspected that many of these cryptogenic ischemic strokes have the features of cardiogenic embolism, but a clear cause has not been identified, and therefore, the most effective treatment for cardiogenic embolism, full anticoagulation with either warfarin or the newer direct thrombin inhibitors, is not used. If in fact these patients have silent or intermittent atrial fibrillation that has not been identified, they remain at increased risk for recurrent stroke, and standard therapy with antiplatelet medication would be inferior to the use of full anticoagulation. Two recently published randomized trials (CRYSTAL AF and EMBRACE) have shed further light on the value of prolonged cardiac monitoring in patients with cryptogenic stroke, in order to diagnose occult or silent atrial fibrillation.

CRYSTAL AF was a randomized controlled study of 441 patients over the age of 40 who had a transient ischemic attack (TIA) or ischemic stroke of undetermined cause, and had long-term monitoring with an insertable cardiac loop ECG monitor that remained in place for a minimum of 6 months. The control group received 24 hours of ECG monitoring within 90 days of the index event. The primary endpoint was the time to first detection of atrial fibrillation, and defined as an episode > 30 seconds within 6 months. Secondary endpoint was time to first detection of atrial fibrillation within 12 months. At 6 months, atrial fibrillation was detected in 8.9% of patients in the monitored group vs 1.4% of patients in the control group ($P < 0.001$). By 12 months, atrial fibrillation was detected in 12.4% of patients in the monitored group vs 2% of patients in the control group ($P < 0.001$).

EMBRACE was a study of 572 patients 55 years of age or older, without known atrial fibrillation, who had a TIA or cryptogenic ischemic stroke within the previous 6 months and a negative 24-hour ECG monitoring. The patients were then randomized to a second 24-hour monitoring session, or noninvasive ambulatory ECG monitoring with a 30-day event-triggered recorder. The primary endpoint was newly detected atrial fibrillation lasting > 30 seconds within 90 days after randomization. Secondary outcomes included episodes of atrial fibrillation lasting 2.5 minutes or longer and anticoagulation status at 90 days. In the EMBRACE study, atrial fibrillation was detected in 16.1% of the 30-day monitoring group, compared to 3.2% in the control group ($P < 0.001$). Atrial fibrillation lasting 2.5 minutes or longer was present in 9.9% of the intervention group, compared to 2.5% in the control group ($P < 0.001$). By 90 days, oral anticoagulant therapy had been prescribed for more patients who were diagnosed with atrial fibrillation in the monitoring group then in the control group (18.6% vs 11.1%; $P < 0.01$).

Both of these well-designed and well-executed randomized clinical trials clearly demonstrated a significant identification of atrial fibrillation in patients with cryptogenic stroke if they undergo long-term monitoring anywhere from 30 days to 1 year. It is clear from these studies that long-term monitoring should be the standard of care for patients with cryptogenic stroke, although the actual duration of monitoring has yet to be determined. In addition, the best technique for monitoring has not been clearly determined. We should also recognize that the majority of patients do not have atrial fibrillation identified, and therefore we must continue to look for other causes of cryptogenic stroke. Nevertheless, these findings are a major advance in our knowledge and will help to prevent secondary stroke in patients who have cryptogenic ischemic stroke or TIAs. ■

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CME QUESTIONS

1. Which of the following statements is false regarding chronic inflammatory demyelinating polyneuropathy (CIDP)?

a. First-line therapies for CIDP include intravenous immunoglobulin, corticosteroids, and plasmapheresis.

b. Autologous stem cell transplantation is safer than allogeneic stem cell transplantation.

c. Various second-line immunotherapies for CIDP have been proven to be effective in randomized clinical trials.

d. The risks associated with stem cell transplantation are primarily due to pancytopenia and infections.

2. Which is the most common adverse effect noted with intramuscular injection of onabotulinumtoxinA for chronic migraine?

a. Eyelid ptosis

b. Neck pain

c. Headache

d. Shoulder weakness

3. Which of the following statements is true regarding amyotrophic lateral sclerosis (ALS)?

a. With diffusion tensor imaging of the brain, ALS patients may be differentiated from controls using a 1.5T MRI.

b. With diffusion tensor imaging of the brain, ALS patients may be differentiated from controls using the 3.0T MRI.

c. Diffusion tensor imaging of the cervical spinal cord in patients with ALS may disclose corticospinal abnormalities not seen on conventional MRI.

d. All of the above are correct.

e. None of the above are correct.

4. Myoclonus-dystonia syndrome can be easily distinguished from other forms of dystonia.

a. True

b. False

5. Which of the following statements regarding temporal lobe epilepsy is false?

a. Newer anti-epileptic medications are improving the long-term management of patients.

b. The frequency of hippocampal sclerosis as a cause of epilepsy has been declining over time.

c. Temporal lobectomy is an established and effective treatment for anterior temporal localization epilepsy.

d. Other causes of temporal lobe epilepsy include tumors, vascular lesions, and focal cortical dysplasia.

6. In patients with cryptogenic ischemic stroke, which of the following statements is false?

a. Cryptogenic ischemic stroke is defined by the absence of apparent cause or risk factors sufficient to explain the cause.

b. Standard therapy for cryptogenic stroke is antiplatelet medication.

c. If atrial fibrillation is diagnosed, appropriate treatment would be full anticoagulation.

d. All cryptogenic ischemic strokes are caused by cardiogenic embolism.

e. The prevalence of atrial fibrillation increases with increasing age.

[IN FUTURE ISSUES]

Update on Multiple Sclerosis