RELIAS MEDIA

Vol. 38, Issue 4, December 2018
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Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Comparison of Two Apheresis Techniques for Treating Relapses in Neuromyelitis Optica Spectrum Disorders

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal reports she is a consultant for Genzyme and Biogen.

SYNOPSIS: Based on a large study of patients in a national registry, investigators reported similar efficacy when comparing the two apheresis techniques: plasma exchange vs. immunoadsorption for the treatment of relapses in NMOSD. Early initiation of apheresis was associated with better outcomes.

SOURCE: Kleiter I, Gahlen A, Borisow N, et al. Apheresis therapies for NMOSD attacks: A retrospective study of 207 therapeutic intervention. *Neurol Neuroimunol Neuroinflamm* 2018;5:e504. doi:10.1212/NXI.0000000000000504.

Neuromyelitis optica spectrum disorders (NMOSD) are characterized by attacks of optic neuritis and/or transverse myelitis. The relapses of NMOSD generally are more severe than those in multiple sclerosis and often are refractory of intravenous (IV) steroids. Accumulation of disability in NMOSD tends to occur from residual deficits from relapses rather than from a progressive disease course. Hence, prevention of and optimal treatments for relapses are of utmost importance in decreasing the accrual of long-term disability. Apheresis is used frequently to treat NMOSD relapses refractory to IV steroids or even as the first-line treatment. Kleiter et al sought to compare plasma exchange (PE) vs. immunoadsorption (IA) to determine if one technique was superior to the other.

The analysis included 207 relapses that occurred in 105 NMOSD patients. Data collected in the

Financial Disclosure: *Neurology Alert*'s Editor in Chief Matthew Fink, MD; Peer Reviewer M. Flint Beal, MD; Executive Editor Leslie Coplin; Editor Jonathan Springston; and Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

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Neurology Alert (ISSN 0741-4234) is published monthly by Relias Learning, 111 Corning Road, Suite 250, Cary, NC 27518-9238. Periodicals postage paid at Cary, NC, and additional mailing offices. POSTMASTER: Send address changes to *Neurology Alert*, Relias Learning, 111 Corning Road, Suite 250, Cary, NC 27518-9238.

GST Registration Number: R128870672.

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German registry of NMOSD patients (NEMOS database) were reviewed. Apheresis treatment was used as first-line therapy in 72 instances, second-line therapy in 98, and third-line or later in 37. In the study, 192 relapses were treated with PE and 38 with IA. Median time to initiation of apheresis was one day when it was the first treatment, 11.5 days when it was the second treatment, and 15.5 days when it was the third treatment. Apheresis treatment had to be at least three sessions.

The outcome measure was recovery from the relapse measured immediately after completion of therapy. The results were categorized as complete recovery, partial recovery, and no recovery.

Both PE and IA were equally effective for treating NMOSD relapses. Patients had at least partial recovery with the use of either apheresis therapy. Forty percent of patients achieved complete recovery when apheresis was started within days 0-2 of symptom onset; after that, treatment response declined in a stepwise manner with longer duration to treatment initiation. No patient achieved complete recovery when apheresis was started 20 days or more after symptom onset.

The strongest predictors of response to treatment were the use of apheresis as the initial treatment for the relapse, the time to treatment from symptom onset, and the presence of aquaporin-4 antibodies. Monofocal relapses were more likely to have a better response when compared to multifocal ones, and a younger age was associated with better recovery as well. Factors that did not appear to affect recovery were the type of apheresis treatment, gender, disease duration, or the disease-modifying treatment the patient was on at the time of the relapse.

Study limitations included the retrospective nature of the analysis, the time of determination of the outcome measure (immediately at the cessation of apheresis treatment, which could have prevented assessment of delayed recovery), and the lower number of patients who received IA compared to PE. The disease-modifying treatments that the patients were on was not specified in the study. This is a potential factor that could influence recovery. However, the long-term disease-modifying treatments these patients were on did not seem to affect the recovery outcome measured.

[Given the often-severe nature of NMOSD relapses and the high incidence of refractoriness to conventional IV steroid treatment, it is imperative that more effective treatments like apheresis be initiated as soon as possible after symptom onset to prevent permanent residual disability from these relapses.]

■ COMMENTARY

Kleiter et al provided valuable information pertaining to the treatment of NMOSD. Based on this analysis, it appears that both types of apheresis treatments are equally effective for recovery from relapses in NMOSD. The study results demonstrated factors that influence recovery, and, most importantly, emphasized that early initiation of apheresis was the strongest predictor of response.

Given the often-severe nature of NMOSD relapses and the high incidence of refractoriness to conventional IV steroid treatment, it is imperative that more effective treatments like apheresis be initiated as soon as possible after symptom onset to prevent permanent residual disability from these relapses. ■

ABSTRACT & COMMENTARY

Zika-associated vs. Non-Zika Guillain-Barré Syndrome

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Guillain-Barré syndrome associated with Zika virus is similar to non-Zika virus cases in terms of severity of illness and prognosis around long-term recovery and disability.

SOURCE: Dirlikov E, Major CG, Medina NA, et al. Clinical features of Guillain-Barré syndrome with vs without Zika virus infection, Puerto Rico, 2016. *JAMA Neurol* 2018;75:1089-1097.

Transmitted by mosquitoes, Zika virus (ZIKV) is an arthropod-borne virus (arbovirus) that is related to other flaviviruses, including dengue, yellow fever, and West Nile. Approximately 20% of patients experience nonspecific manifestations of infection, including low-grade fever, rash, arthralgias, or conjunctivitis. More serious neurologic complications include congenital microcephaly, encephalitis, meningoencephalitis, transverse myelitis, and Guillain-Barré syndrome (GBS). Can GBS associated with ZIKV be differentiated from GBS that is not associated?

ZIKV disease was reported by the Department of Health, San Juan, Puerto Rico, in December 2015, with the first case of GBS in a patient with prior ZIKV infection confirmed in January 2016. In February 2016, public health surveillance was implemented to identify cases of GBS prospectively and test patients for ZIKV, dengue virus, and chikungunya virus. In October 2016, GBS case reporting was made compulsory. Between February and April 2017, all 57 nonspecialized hospitals and two rehabilitation centers in Puerto Rico provided lists of patients hospitalized in 2016 with a diagnostic code of GBS in their medical record. Confirmation of the diagnosis of GBS was performed by medical record review and encompassed clinical presentation, electrodiagnostic studies, cerebrospinal fluid analysis, and absence of an alternative neurologic diagnosis. Telephone interviews were conducted six months following illness onset to determine the extent of long-term disability using the modified Rankin scale, Overall Disability Sum score, and Facial Disability Index. A statistical analysis encompassed Pearson $\chi 2$ test, Fisher exact test, and $\chi 2$ partitioning to compare categorical variables, with the median two-sample test used to compare continuous variables. $P < 0.05$ was considered statistically significant.

Among 135 cases of suspected GBS reported by healthcare professionals in 2016, 98 (72.7%) were confirmed GBS, eight (5.9%) suspected GBS, and 29 (21.5%) non-GBS. Among 181 patients identified by diagnostic code, 100 (55.2%) already had been found through passive public health surveillance. Of the remainder, 25 (34.7%) were confirmed GBS cases, four (5.6%) were suspected GBS, and 43 (59.7%) were non-GBS. The researchers identified 123 confirmed GBS cases, of which 68 (55.3%) were male, with an overall median age of 54 years. ZIKV infection was confirmed in 66.4% of those tested (71 of 107).

Compared to GBS cases without evidence of ZIKV infection, ZIKV GBS cases were of similar age, although they more often were female. Antecedent illness was reported equally in both groups, but antecedent rash and arthralgia were more frequent in the ZIKV GBS group. Duration of hospitalization, medical complications, mortality rate, and frequency of intravenous immunoglobulin administration were similar in both groups, but those with ZIKV more often were admitted to the ICU and required mechanical ventilation, and were more likely to have facial weakness and paresthesiae, dysphagia, and shortness of breath. At clinical nadir, modified Rankin and Hughes Disability scores were comparable, as were median disability scores at six months, although ZIKV GBS patients reported long-term facial difficulties, including abnormal tearing and drinking from a cup, more often.

■ COMMENTARY

First isolated from a febrile macaque monkey in 1948 in the Zika forest of Uganda (hence its name), ZIKV was an unimportant human pathogen until a 2007 outbreak of what initially was thought to be dengue virus on the island of Yap in Micronesia. It turned out to be ZIKV confirmed

by reverse transcriptase PCR. GBS cases then were reported in a 2013-2014 outbreak in French Polynesia, and ZIKV became hyperendemic in some South American areas in 2015. Transmitted by the bite of an infected *Aedes* species mosquito, humans and monkeys appear to be the only viable vertebral hosts for ZIKV, but it also may be transmitted perinatally, presumably through the placenta, as well as by a blood-borne route and via breast milk and semen. ■

ABSTRACT & COMMENTARY

Idiopathic Adult-onset Laryngeal Dystonia

By Harini Sarva, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Researchers demonstrated that isolated laryngeal dystonia in an Italian population can spread to contiguous regions, thus expanding knowledge of dystonia spread and phenomenology of this rare form of dystonia.

SOURCE: Esposito M, Fabbrini G, Ferrazzano G, et al. Spread of dystonia in patients with idiopathic adult-onset laryngeal dystonia. *Eur J Neurol* 2018;25:1341-1344.

Spread of focal dystonia has been described with limb dystonia, cervical dystonia, and blepharospasm. However, the frequency of spread of laryngeal dystonia has not been well described because of mixed population reports. This retrospective study of laryngeal dystonia obtained from the Italian Dystonia Registry reported that of 71 adults with laryngeal dystonia, 79% were women, the mean age of dystonia onset was in the sixth decade, and 84% had the adductor form of laryngeal dystonia.

Fifty subjects had focal laryngeal onset. Among the other 21 subjects, eight had onset in the cranial region, 10 in the neck, and three in the upper limb, with spread to the larynx. Among the fifty with laryngeal onset, 32% spread to a contiguous body region (11 to the neck and five to cranial regions). Thirty-four continued to have isolated laryngeal dystonia over a long period of follow-up, ranging from one to 56 years. For those whose dystonia spread from the larynx, contiguous regions were affected within the first year of dystonia onset. In general, when found in those with other body parts affected, laryngeal dystonia was found most commonly with cervical dystonia and less commonly with upper limb dystonia. None were DYT-1 positive.

■ COMMENTARY

Adult-onset laryngeal dystonia is a rare form of isolated, action-specific dystonia. When it occurs, it affects women more commonly and begins in the sixth decade. Adductor spasm is the most common form. Esposito et al reviewed data from a large dystonia registry comprising subjects from 37 institutions in Italy. The results provide insight into the frequency of spread as well as common phenomenology, allowing clinicians to better counsel patients regarding dystonia spread. However, since participants were from a single ethnic population, it may be difficult to extrapolate these results to other ethnic populations. In addition, all subjects were referred by movement disorders centers; thus, referral bias is an issue. In addition, other dystonia genes known to cause laryngeal dystonia, such as THAP1, TUB4, and GNAL, were not tested. As clinical variability is common among the genetic dystonias, not knowing the complete genetic results further limits

the generalizability of these results. Adult-onset laryngeal dystonia can spread to contiguous body regions, but further study is needed to confirm this observation in other ethnic populations as well as in genetically confirmed DYT-1 isolated dystonias. ■

ABSTRACT & COMMENTARY

Are Women More Prone to Brain Injury Than Men When Playing Soccer?

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: Repeated subconcussive injuries to the brain, such as "heading" the ball in soccer, result in more severe injury and slower recovery in women compared to men.

SOURCE: Rubin TG, Catenaccio E, Fleysher R, et al. MRI-defined white matter microstructural alteration associated with soccer heading is more extensive in women than men. *Radiology* 2018;289:478-486.

Soccer is a sport with a known risk for concussion from player-to-player collision, falls, and repeated "heading" — using the head to deflect the ball in play. Although heading-related impacts have been considered subconcussive, heading is associated with acute central nervous system symptoms. Cumulative heading is associated with cognitive dysfunction and microstructural alteration of white matter on imaging from diffusion-tensor imaging (DTI), similar to that seen with traumatic axonal injury. Female athletes are at greater risk than male athletes for poor outcome after acute traumatic brain injury, including concussion; it is uncertain if this is due to women being more likely to report symptoms when compared with men or is due to a different pathophysiological response to trauma. Neuroimaging can provide an objective means to characterize subclinical variation in brain structure and functioning following head trauma.

To test the hypothesis that DTI would reveal sex-based differences in the association of repetitive head trauma by comparing the microstructural alteration of white matter in the brain, Rubin et al conducted a prospective study comparing female and male amateur soccer players. Each female athlete was paired with a male athlete within two years of her age and with the closest match with respect to reported 12-month heading exposure. A final cohort of 49 men and 49 women, with a median total soccer heading events per year of 487 and 469, respectively, completed the study.

Investigators performed whole-brain MRI with DTI on each patient. They performed whole-brain voxel-wise analysis of white matter fractional anisotropy (FA) using the Automatic Registration Toolbox VANCOVA module to fit a linear regression for FA. Among men, the authors identified three regions in which a greater number of heading events was associated with significantly lower FA: the genu and splenium of the corpus callosum and the pons. In women, the authors identified seven regions in which greater heading was associated with significantly lower FA: the genu of the corpus callosum, left occipital, right parietal and right orbitofrontal white matter, left superior longitudinal fasciculus, right cingulum and right cerebral peduncle. In men, the left temporal white matter showed a significantly higher FA with greater heading exposure. In women, a single location in the left frontal white matter showed a significantly higher FA with greater heading exposure.

[This study provides preliminary radiographic evidence of changes in the brain microstructure to support the observed differences between men and women in response to repeated heading.]

Women consistently showed a greater number and volume of regions with a significant association of heading with lower FA. Heading also was associated with changes in radial diffusivity, mean diffusivity, and axial diffusivity in both men and women. Greater heading exposure was associated

with lower white matter axial diffusivity over great volume in men than in women.

■ COMMENTARY

This study provides preliminary radiographic evidence of changes in the brain microstructure to support the observed differences between men and women in response to repeated heading. Women may be more sensitive than men to the effects of heading at the level of tissue microstructure, with FA the most prevalent indicator of microstructural alteration. Greater heading exposure was associated with lower FA. Lower FA may be indicative of chronic traumatic axonal injury. By identifying risk factors for the development of cumulative injury, including gender, one potentially could develop prevention techniques before long-term sequela develop. ■

Neurology [ALERT®] Stroke Alert

A Biomarker to Help With Neurologic Prognosis After Cardiac Arrest

By Matthew E. Fink, MD, Editor

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

Dr. Fink reports he is a retained consultant for Procter & Gamble and Pfizer.

SOURCE: Moseby-Knappe M, Mattsson N, Nielsen N, et al. Serum neurofilament light chain for prognosis of outcome after cardiac arrest. *JAMA Neurol* 2018; Oct. 29. doi:10.1001/jamaneurology.2018.3223. [Epub ahead of print].

Determining the prognosis of neurological outcome after cardiac arrest is notoriously difficult. It usually is performed in a multimodal fashion and includes the clinical examination, electroencephalogram, somatosensory evoked potentials, brain imaging, and biochemical markers. The most commonly studied blood-based biomarkers after brain injury are S100 and neuron-specific enolase, but neither has shown high accuracy in predicting prognosis. Neurofilament light chain (NFL) is a new potential biomarker, for which elevated levels in the spinal fluid or blood indicate axonal injury in several neurological diseases.

Moseby-Knappe et al used an ultrasensitive assay to quantify serum and cerebrospinal fluid levels in patients who suffered cardiac arrest. They analyzed levels in 782 unconscious patients who had out-of-hospital cardiac arrest. Measurements were analyzed at 24, 48, and 72 hours after cardiac arrest. The main outcome measures were poor neurological outcome at six months of follow-up, defined by the Cerebral Performance Category Scale as category 3 (severe cerebral disability), category 4 (coma), or category 5 (brain death). Of 782 eligible patients, 717 were included, with 80.9% men, and a median age of 65 years. At six months, 360 patients (50.2%) had poor neurological outcomes. Median serum NFL levels were significantly higher in patients with poor outcomes vs. good outcomes at 24 hours, 48 hours, and 72 hours. The NFL measurements showed a high overall performance and high sensitivities and specificities (69% sensitivity with 98% specificity at 24 hours). The serum NFL levels had greater performance than other biochemical serum markers (tau, neuron-specific enolase, and S100). At comparable specificities, serum NFL had greater sensitivity for poor outcomes compared to other diagnostic tests such as electroencephalogram, somatosensory evoked potential, head CT, and neurological examination. The authors concluded that measurement of serum NFL is highly predictive of long-term poor neurological outcome 24 hours after cardiac arrest and may be a helpful complement to other tests used to predict neurological prognosis. ■

Oral Anticoagulant-associated ICH

By Matthew E. Fink, MD, Editor

SOURCE: Tsivgoulis G, Wilson D, Katsanos AH, et al. Neuroimaging and clinical outcomes of oral anticoagulant-associated intracerebral hemorrhage. *Ann Neurol* 2018; Sep. 26. doi:10.1002/ana.2542. [Epub ahead of print].

Intracerebral hemorrhage (ICH) is the most dangerous and feared complication of oral anticoagulation and leads to a high mortality. Although the incidence is declining because of improved treatment of hypertension, the overall number of cases is rising because of more widespread use of antithrombotic medications to respond to the increasing prevalence of atrial fibrillation. In recent years, clinicians have started treating patients more often with non-vitamin K antagonist oral anticoagulants (NOAC-ICH) as opposed to vitamin K antagonists (VKA-ICH), such as warfarin, and debate has continued about the relative risk of hemorrhage with these two classes of oral anticoagulants.

Tsivgoulis et al performed a systematic review to evaluate the relative risk of hemorrhage associated with these two classes of medications. They looked at individual patient data in cohort studies that compared clinical and radiographic outcomes between NOAC-ICH and VKA-ICH patients. The primary outcome measure was 30-day all-cause mortality. They assessed all outcomes in multivariate regression analyses that were adjusted for age, sex, ICH location, and intraventricular hemorrhage extension. They examined seven eligible studies, which comprised 219 patients with a NOAC-ICH and 831 patients with VKA-ICH (mean age, 77 years; 52.5% females). The 30-day mortality was similar between both groups (24.3% vs. 26.5%; hazard ratio, 0.94). However, in multivariate analyses adjusted for cofounders, NOAC-ICH was associated with a lower NIH stroke scale score on admission, a lower likelihood of a severe stroke on admission, and a smaller baseline hematoma volume. The two groups did not differ in the likelihood of small hematoma less than 30 cm^3, the risk of hematoma expansion, in-hospital mortality, functional status at discharge, or functional status at three months.

The authors concluded that although functional outcome at discharge, one month, or three months was comparable between the two groups, patients treated with a NOAC had smaller baseline hematoma volumes and less severe acute stroke syndromes on admission to the hospital. ■

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CME QUESTIONS

1. **In the study by Kleiter et al, which of the following was *not* associated with better recovery from relapses in neuromyelitis optica spectrum disorders?**
   a. Initial treatment with apheresis
   b. Time to apheresis treatment
   c. Presence of aquaporin-4 antibodies
   d. Type of apheresis treatment

2. **Compared to Guillain-Barré syndrome that is not associated with Zika virus, Guillain-Barré syndrome that is associated with Zika virus:**
   a. more often has facial involvement.
   b. more often has dysphagia.
   c. more often has shortness of breath.
   d. All of the above

3. **Which of the following is true about laryngeal dystonia?**
   a. It is not seen commonly with cervical dystonia.
   b. Mean age of onset is in the third decade of life.
   c. Thirty-two percent of focal-onset laryngeal dystonia in this cohort spread to contiguous regions.
   d. It is commonly seen with upper limb dystonia.

4. **Observed sex differences between men and women with repetitive heading injuries include all but which of the following?**
   a. Female athletes are at greater risk than male athletes for poor outcome after acute traumatic brain injury.
   b. Female athletes are more likely to experience a delayed return to normal activities after concussion when compared with men.
   c. Fractional anisotropy is higher following acute head trauma.
   d. Fractional anisotropy is lower in the setting of chronic traumatic brain injury.

5. **Intracerebral hemorrhage associated with non-vitamin K antagonist oral anticoagulants carries a higher mortality than intracerebral hemorrhage associated with warfarin.**
   a. True
   b. False

6. **Twenty-four hours after cardiac arrest, if a patient remains in a coma, neurological prognosis can be determined with near-certainty by using currently available diagnostic tests.**
   a. True
   b. False

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

[IN FUTURE ISSUES]

Advances in Epilepsy Treatment