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Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Neuroimmunology and Movement Disorders: When Should We Test for Autoantibodies?

By Claire Henchcliffe, MD, PhD

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Dr. Henchcliffe reports she is a consultant for ACADIA Pharmaceuticals and US WorldMeds.

SYNOPSIS: Autoantibody-associated neurological disorders can mimic neurodegenerative and other movement disorders, but are likely under-diagnosed, resulting in missed treatment opportunities. This review is a "must read" for all neurologists.

SOURCE: Balint B, Vincent A, Meinck HM, et al. Movement disorders with neuronal antibodies: Syndromic approach, genetic parallels, and pathophysiology. *Brain* 2018;141:13-36.

Balint et al tackled an expanding and rapidly developing field, linking neuroimmunology and presence of specific autoantibodies to movement disorders. The concept is highly familiar, and has been well described in movement disorders such as Sydenham chorea, stiff person syndrome, and paraneoplastic cerebellar degeneration. The authors make the case that anti-neuronal antibody-associated syndromes likely are under-recognized and both under- and mis-diagnosed.

When should the clinical features of movement disorders lead the clinician to suspect an autoimmune etiology? Balint et al proposed a syndromic approach that takes into account the primary movement disorder type, such as dystonia, myoclonus, etc., together with age at onset, "red flags," and associated features such as encephalopathy and seizures. This then would prompt identification of a panel of candidate autoantibodies for testing. In the first part of their review, Balint et al extensively

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described and summarized anti-neuronal, anti-glial, and anti-ganglioside antibodies occurring in association with movement disorders that are classified by phenomenology: chorea/dyskinesia, dystonia, myoclonus, parkinsonism, ataxia, sleep movement disorders, tremor, neuromyotonia/myokymia, paroxysmal dyskinesia, and stiff person disorders. The authors provided extensive examples to support their approach. As an example of effects of age at onset, anti-NMDAR antibody-associated encephalitis is more likely to manifest as a movement disorder in children, and anti-D2R antibodies associated with chorea and other symptoms are seen only in children. Uncharacteristic findings on imaging also may prompt further work-up; for example, in a patient with chorea, the presence of cognitive decline and MRI FLAIR hyperintensities would suggest testing for anti-CV2/CRMPS antibodies. Atypical localization of symptoms also may be a red flag (for example, hemidystonia or craniocervical dystonia in children with NMDAR antibodies). Sometimes, however, there may be little to provide the alert, and the authors provided the example of encephalopathy associated with anti-LGI1- and CASPR2-antibody mimicking Creutzfeldt-Jakob disease, which even may have a "cortical ribbon" visualized on MRI.

A second table that listed relative frequency of antibody findings in clinical practice adds context. For example, of multiple autoantibodies associated in the literature with cerebellar ataxia, certain ones are extremely rare to date (such as anti-AP3B2/Nb: single case; ARHGAP26/Ca: six cases), whereas others (anti-Yo or anti-Zic4) are more common. Finally, the authors reviewed the fascinating area of sleep behavior disorders, highlighted in this review as part of IgLON5-antibody-linked neurodegeneration. This tauopathy, associated with presence of IgLON5 antibodies, may begin with sleep disorder but progress to a constellation of symptoms, ultimately suggestive of progressive supranuclear palsy or multiple system atrophy.

■ COMMENTARY

Movement disorders arise from multiple etiologies, and a great deal of focus in our sub-specialty has been placed on neurodegenerative and genetic etiologies. Now, however, the clinician is faced with an expanding list of associated autoantibodies including a subset associated with paraneoplastic disease. Balint et al highlighted heterogeneous and overlapping clinical manifestations that may mimic neurodegenerative, genetic, infectious, and other movement disorders. Using phenomenology as a starting point will be extremely useful in the immediate future to the clinician faced with unusual movement disorders or movement disorders associated with "red flags," such as rapid progressive, an odd combination of symptoms, or presence of autoimmune disorders in the family. On a practical level, it will help "flag" patients for more extensive testing and more frequent follow-up, and if testing reveals the presence of the suspected antibodies, this may open the path to data-driven and targeted treatment. However, this is a young field, and access to specific tests may be limited, there is variability in testing between facilities, and, importantly, the resulting treatments may depend on expert opinion rather than clinical trials. Nonetheless, this paper will serve as a platform upon which to build and as an outstanding reference for clinical practice and teaching in the immediate future. Moreover, it conceptually adds to the drive for precision medicine approaches in neurology and in movement disorders as a whole. ■

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ABSTRACT & COMMENTARY

Targeting Hypersensitive Corticostriatal Terminals to Treat Restless Legs Syndrome

By Daniel A. Barone, MD, FAASM

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

SYNOPSIS: Based on this innovative study using optogenetic microdialysis, the mechanisms underlying restless legs syndrome include dopamine-mediated hypersensitivity of corticostriatal neurons to glutamate release.

SOURCE: Yepes G, Guitart X, Rea W, et al. Targeting hypersensitive corticostriatal terminals in restless legs syndrome. *Ann Neurol* 2017;82:951-960.

Restless legs syndrome (RLS) is a common neurologic disorder characterized by a rest-induced, movement-responsive, nocturnal urge to move the legs. Often, it is associated with periodic leg movements during sleep (PLMS) and hyperarousal. Altered dopamine function plays a major role in PLMS symptomatology, supported by the therapeutic response to L-dopa and dopamine receptor agonists (i.e., pramipexole and ropinirole), as well as the biochemical changes related to the dopamine system. Additionally, it appears that glutamate mechanisms are involved in both PLMS and the hyperarousal component of RLS, supported by the efficacy of ligands of the α2δ subunits of calcium channels (i.e., gabapentin, pregabalin) on these symptoms, the subunits being localized preferentially in neuronal glutamate terminals.

Yepes et al reported two major aims: to demonstrate a previously hypothesized increased sensitivity of corticostriatal glutamatergic terminals in the rodent with brain iron deficiency (BID) (a pathogenetic model of RLS), and to determine whether the glutaminergic terminals could be a target for drugs effective in RLS, particularly the dopamine agonists (pramipexole and ropinirole) and α2δ ligands (gabapentin).

The authors used optogenetic-microdialysis, which is a technique involving the use of light to control cells in living tissue, typically neurons that have been genetically modified to express light-sensitive ion channels. This technique allows the measurement of the extracellular concentration of glutamate on local light-induced stimulation of corticostriatal glutamatergic terminals. This method also allows analysis of the effect of local perfusion of compounds within the same area being sampled for glutamate.

Rodents with BID showed hypersensitivity of corticostriatal glutamatergic terminals; that is, they required a lower frequency of optogenetic stimulation to induce glutamate release. In both the hypersensitive and control glutamatergic terminals, the authors demonstrated that the terminals were targets for locally perfused pramipexole, ropinirole, and gabapentin, as they all significantly counteracted optogenetically induced glutamate release. Furthermore, using selective antagonists, the authors demonstrated that there was involvement of dopamine D4 and D2 receptor subtypes in the effects of pramipexole.

The authors concluded that hypersensitivity of corticostriatal glutamatergic terminals can comprise a major mechanism of RLS symptoms. They went on to point out that selective D4 receptor agonists, by specifically targeting these terminals, should provide a new efficient treatment with fewer secondary effects.

■ COMMENTARY

This is scientifically sound study, and although done in rodents, the potential clinical implications in humans are quite robust. Others have studied dopamine, iron, and opioid systems extensively to identify the physiological mechanisms underlying RLS, and although no singular model has sufficed, this paper sheds light on a new approach. The α2δ ligands (gabapentin and pregabalin) already have been presumed to decrease glutamatergic neurotransmission and, thus, treat RLS. However, the ability of the dopamine agonists pramipexole and ropinirole to modulate the function of corticostriatal glutamatergic terminals implies a conceptual change in their presumed therapeutic mechanism. Dopamine D2SR and D4R are the D2-like receptor subtypes preferentially localized in corticostriatal glutamatergic terminals and involved in a direct modulation of striatal glutamate release. The implication is that more selective D2SR and D4R agonists could be potential medications for RLS. D4R agonist is more likely to be effective because it is more selectively expressed by corticostriatal neurons, and activation of D2LR might contribute to unwanted side effects in RLS, such as augmentation).

Decreased iron concentrations in the substantia nigra can precipitate RLS, as it is one of the primary brain

regions in which dopamine-producing cells reside, and an inverse relationship has been demonstrated between iron concentrations in the substantia nigra and the severity of RLS symptoms. This study demonstrated that BID in rodents results in hypersensitive corticostriatal terminals, which show an increased sensitivity to depolarization-induced glutamate release. Prior studies have shown a higher prevalence of RLS symptoms in conditions that compromise iron availability, but most patients with RLS do not have systemic iron deficiency. Very little is known regarding how iron is regulated by the blood-brain barrier or by the different cells within the brain, or how a brain region can be low in iron yet other organs in the body have normal levels.

Opiate medications are considered alternative treatment for RLS, but the precise mechanisms by which they improve RLS are not well understood. Opiate receptors have been identified in the dorsal horn and are likely involved in regulating incoming nociceptive sensory information, as well as in brainstem areas (periaqueductal grey and in the basal ganglia), which could be sites involved in improvement of symptoms. Neither improvement in iron stores nor the use of opiate medications have clear mechanisms to explain RLS and the improvement of symptoms through their application, yet these interventions do tend to work. Although the authors have made a step forward in our understanding of RLS, there remains much to be discovered. ■

ABSTRACT & COMMENTARY

Functional Imaging Studies in Parkinson's Disease

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: A meta-analysis of 142 studies demonstrated that functional imaging studies in Parkinson's disease using tracers for aromatic acid decarboxylase showed smaller defects compared to those using tracers targeting dopamine transport and VMAT2. Symptom severity correlated linearly with dopamine neuron loss as determined by these imaging studies.

SOURCE: Kaasinen V, Vahlberg T. Striatal dopamine in Parkinson disease: A meta-analysis of imaging studies. *Ann Neurol* 2017;82:873-882.

Kaasinen et al assessed 1,520 papers obtained through a PubMed search using various search terms, including dopamine, Parkinson's disease (PD), parkinsonism, PET, and SPECT. Out of these 1,520 papers, 142 studies were included in this analysis if they met the following inclusion criteria: human PET or SPECT study; aromatic l-amino decarboxylase (AADC), vesicular monoamine transporter 2 (VMAT2), or dopamine transporter (DAT) tracer was used; idiopathic Parkinson's disease patients were compared with healthy controls; and binding was reported as a mean for both PD and healthy controls in at least one striatal region. Twelve studies were excluded because of repetition of subjects. There were 157 separate PD samples in these 142 studies. The total number of PD patients was 3,605 and the total number of healthy controls was 2,352. Of these 142 studies, 67 were AADC studies, 64 were DAT studies, and 11 were VMAT2 studies. All of the studies demonstrated a 13.2% to 77% lower binding of AADC, DAT, and VMAT2 in PD patients compared with controls. In order of effect size from most to least, the posterior putamen showed the most effect size, then the entire putamen, followed by the anterior putamen, and lastly the caudate nucleus. The defect in AADC was consistently smaller than the defects in VMAT2 or DAT. The correlation between disease severity and dopamine loss was linear and this correlation was strongest in the caudate compared to the putamen. The longitudinal studies (total of 18; 3 AADC studies, and 15 DAT studies) had inconsistent results but suggested a negative exponential progression of dopamine loss.

■ COMMENTARY

Dopaminergic functional imaging has been used in research for nearly 30 years. This study confirms the relationship between dopamine loss and disease severity. The strengths of this meta-analysis include the large number of studies and subjects. Publication bias was not found to be significant. However, important considerations need to be noted. Different methods and machines can provide varying results that can contribute to the stark contrast between neuropathology showing a lack of dopamine fibers and imaging, which shows a reduction in fibers by 50%. In addition, PD has varying subtypes that also may contribute to the large range in reduction in

binding of AADC, VMAT2, and DAT. Along these lines, the search terms included atypical parkinsonisms, and these imaging modalities cannot accurately distinguish between PD and the atypical Parkinson patients. Thus, the inclusion of atypicals in these studies can lead to varying binding reduction. Although the imaging modalities can help correlate disease severity and neuronal loss at a single time point, longitudinal analysis was found to be inconsistent. Thus, these functional imaging studies still are not reliable biomarkers of PD. Further research into the type of tracer and target is required to establish functional imaging as a reliable biomarker. ■

ABSTRACT & COMMENTARY

Myasthenia Gravis, MuSK, and Pregnancy

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: Myasthenia gravis increases both maternal and fetal complications and mortality during pregnancy, but the MuSK-antibody variant appears less morbid, based on this small retrospective series of 17 patients.

SOURCE: Santos E, Braga A, Gabriel D, et al. MuSK Myasthenia gravis and pregnancy. *Neuromuscul Disord* 2017; Nov. 28. https://doi.org/10.1016/j.nmd.2017.11.014. [Epub ahead of print].

Pregnancy is not contraindicated in women with myasthenia gravis (MG), but carries a 40% risk of exacerbation during pregnancy, an additional 30% risk in the puerperium, maternal mortality of 40/1,000 live births, and perinatal mortality 68/1,000 births.[1] How safe is pregnancy for prospective mothers with muscle-specific tyrosine kinase (MuSK) antibody-positive MG?

In this retrospective, multicenter, cohort study, 17 MuSK-MG pregnant women, 13 with more than one pregnancy, were identified among seven hospitals in northern Portugal. Diagnosis of MuSK-MG was based on clinical presentation, electrodiagnostic testing, and positive antibody titers, with clinical status, including refractory MG, based on Myasthenia Gravis Foundation of America guidelines. Following informed consent, data were collected on all patients. Age of MG onset was 34.5 years, of which 46.2% were refractory. Other autoimmune conditions were present in 23%, including thyroid disease, sacroiliitis, and anti-phospholipid syndrome. MG occurred either before (n = 4) or after (n = 23) pregnancy, with no instance of MG-onset during or within the six-month postpartum period.

Among patients who became pregnant after MG onset (n = 4), none experienced myasthenic crisis during pregnancy, none suffered a miscarriage, and there were no cases of fetal akinesia, hydramnios, or intrauterine growth retardation. Two patients delivered preterm, at 35 and 37 weeks, respectively, due to membrane rupture, and two underwent cesarean delivery, one by choice and one for obstetric reasons. Among patients who became pregnant before MG onset (n = 23), there were similarly no instances of fetal akinesia, hydramnios, or intrauterine growth retardation, but three ended in miscarriage, two in one patient with anti-phospholipid syndrome and one of unknown cause. Neither group experienced preeclampsia, stillbirths, or birth defects, and none fulfilled criteria for low neonatal birth weight, although compared to babies born to mothers before MG onset, those born to mothers after MG onset had lower birth weight. Among the neonates, there was one case of neonatal MG lasting three weeks in a full-term baby with an Apgar of 9/10, delivered by cesarean delivery under general anesthesia. In the 12-month postpartum period, all babies developed normally.

Pregnancy does not precipitate MuSK-MG, nor does MuSK-MG negatively affect pregnancy. Newborn weight may be lower than expected, but does not fulfill criteria for low birth weight.

■ COMMENTARY

When choosing immunosuppressive agents for women of childbearing age with myasthenia gravis (MG), always discuss the possibility of pregnancy. Oral pyridostigmine is safe but not intravenously, as it may precipitate uterine contractions. Where immunosuppression is warranted, corticosteroids at the lowest effective dose are the agent of choice. Although retrospective studies suggest they increase the incidence of cleft palate when used during the first trimester, recent studies show no such increase, although they may increase the risk of gestational diabetes, infection, and preterm deliveries. IVIG and PLEX frequently have been used during pregnancy for a variety of autoimmune conditions and generally are well tolerated.

Hence, they may be used for MG crisis or severe MG during pregnancy, but the risks and benefits to mother and fetus must be weighed carefully. Immunosuppression other than corticosteroids is best avoided during pregnancy, although recent international consensus guidelines propose that azathioprine and cyclosporine are relatively safe in pregnancy for MG when corticosteroids do not adequately control symptoms or are not tolerated. If a pregnancy is incidentally discovered while a patient is taking nonsteroidal immunosuppression, one must consider the possibility that drug withdrawal may be too late to avoid teratogenesis.[2] ■

REFERENCES

1. Plauche WC. Myasthenia gravis in mothers and their newborns. *Clin Obstet Gynecol* 1991;34:82-99.
2. Edmundson C, Guidon AC. Neuromuscular disorders in pregnancy. *Semin Neurol* 2017:37:643-652.

ABSTRACT & COMMENTARY

Pain in Anti-MAG Neuropathy

By Russell L. Chin, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Most patients with anti-MAG neuropathy complain of painful paresthesias or dysesthesias, but unlike diabetic neuropathy, these symptoms are not severe and do not affect quality of life as much as motor weakness.

SOURCE: Rajabally YA, Delmont E, Hiew FL, et al. Prevalence, correlates and impact of pain and cramps in anti-MAG neuropathy: A multicenter European study. *Eur J Neurol* 2018;25:135-141.

Anti-MAG neuropathy is associated with an IgM monoclonal gammopathy and manifests typically as a slowly progressive, symmetric, predominantly sensory neuropathy affecting distal lower more than upper extremities. Sensory loss, involving all modalities, typically occurs earlier than weakness, which eventually develops in most patients in the distal extremities. Unlike chronic inflammatory demyelinating polyneuropathy, proximal strength typically is spared. Hand tremor may develop later in the disease course. Demyelinating features are noted by electromyography/nerve conduction studies in more than 90% of patients, particularly severely prolonged distal motor latencies and severe conduction velocity slowing, while conduction block is uncommon. Widening of myelin lamellae can be noted on ultrastructural examination of the nerve. No significant benefit from plasmapheresis, steroids, intravenous immunoglobulin, chlorambucil, or other immunosuppressive agents has been found. Rituximab has been reported to be beneficial[1]; however, clinical trials have been negative. Longer duration studies with adequate outcome measures may be necessary.[2]

In this study, pain of any type was reported in 80% of clinically stable patients with anti-MAG neuropathy. Paresthesiae/dysesthesiae were the most common pain subtypes. Cramps involving the lower extremities were reported in 64% (35/55) of patients, with concomitant upper extremity involvement in 29% (10/35). Correlation analyses showed multiple positive associations between pain severity and cramp severity, location, and frequency with various measures of quality of life and disability.

■ COMMENTARY

Pain typically is associated more with diabetic and amyloid neuropathies because of small fiber sensory involvement. It also is reported with demyelinating neuropathy, such as Guillain-Barré syndrome, presumably because of direct inflammation of nerve roots. Rajabally et al highlighted the fact that pain also may be a prominent but under-recognized feature of inflammatory, immune-mediated neuropathies such as anti-MAG neuropathy, in particular.[3]

In this study, dysesthesias/paresthesias were present in more than 70% of patients. Although these symptoms generally are not considered painful by physicians or patients, they were associated independently with some measures of fatigue and a poorer quality of life. As would be expected, other types of pain (such as burning, pressing, or paroxysmal pain) also correlated positively with other quality-of-life metrics.

Cramps were described in the lower extremities more frequently, but hand involvement (specifically the severity and frequency of cramps) was most relevant to disability and quality of life. A beneficial role for physiotherapy was suggested by the finding of inverse correlations between: 1) cramp severity and level of physiotherapy, and 2) cramps interfering with sleep and level of physiotherapy.

This article raises awareness of the high frequency of pain and cramps that might affect quality of life in anti-MAG neuropathy. Non-drug treatments, such as physiotherapy for cramps, may be helpful and should not be neglected. Any treatment interventions will

need to affect quality of life measures positively to be meaningful for the patient. ■

REFERENCES

1. Svahn J, Petiot P, Antoine JC, et al. Anti-MAG antibodies in 202 patients: Clinicopathological and therapeutic features. *J Neurol Neurosurg Psychiatry* 2017; Oct. 25. doi: 10.1136/jnnp-2017-316715. [Epub ahead of print].
2. Pruppers MH, Merkies IS, Notermans NC. Recent advances in outcome measures in IgM-anti-MAG+ neuropathies. *Curr Opin Neurol* 2015;28:486-493.
3. Pazzaglia C, Briani C, Nobile-Orazio E, et al. Occurrence and characterization of pain in immune-mediated neuropathies: A multicenter prospective study. *Eur J Neurol* 2011;18:177-183.

ABSTRACT & COMMENTARY

Serum Tau as a Reliable Biomarker of Outcome After Cardiac Arrest

By Halinder S. Mangat, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Currently, there are no reliable and readily available biomarkers to assist in determining prognosis for neurological recovery after cardiac arrest, but serum tau measurements hold promise for the future.

SOURCE: Mattsson N, Zetterberg H, Nielsen N, et al. Serum tau and neurological outcome in cardiac arrest. *Ann Neurol* 2017;82: 665-675.

Prognostication after cardiac arrest remains a challenge, with most biomarker tests for extent of neural injury having variable sensitivity and specificity. Mattsson et al used a novel single molecule detection assay to quantify serum tau in patients from the Target Temperature Management (TTM) after cardiac arrest trial, which examined the outcomes in patients treated to 33° or 36°C after cardiac arrest.[1] Blood samples were collected from 819 patients at 29 European centers, of whom 689 were eligible for this sub-study. Outcomes were assessed at six months using the Cerebral Performance Categories (CPC) scale.

The mean age of patients was 64 years, 81% were male, and the mean return of spontaneous circulation (ROSC) time was 31 minutes, after 73% received bystander CPR. Higher tau was associated with older age, longer ROSC, and absence of bystander CPR. There were no longitudinal differences in serum tau between 33° and 36°C groups with poor outcome. Overall differences between groups were smaller than that between patients with good (CPC 1-2) and poor (CPC 3-5) outcomes.

Poor outcomes correlated with elevated tau levels drawn within 24 hours of cardiac arrest, and differences in tau between groups increased at 48 hours; 72 hours and later samples had greater sensitivity for poor outcomes. In the CPC 1 group, serum tau decreased significantly between time points (24, 48, 72 hours), while it increased in CPC 4 and 5. Low levels of tau were correlated with lower CPC, and similar correlations also were seen with the modified Rankin Scale. In prognostic accuracy, ROSC analyses at different time points were identical, and false-positive rate of 2% at 72 hours provided a sensitivity of 66%. Adding tau to clinical information improved prediction with AUC of 0.94 in logistic regression models of poor outcome. Models comparing clinical information with NSE or tau yielded similar AUC, as did models including all three.

■ COMMENTARY

In the search for additional and improved biomarkers, the authors must be commended on this sub-study from the TTM trial. In this study, serum tau showed good correlation with poor outcome after cardiac arrest regardless of therapeutic temperature target, with the best sensitivity seen with high serum levels at 72 hours in CPC 3-5 group. The specificity and sensitivity were 91% and 71%, respectively, at a false-positive rate of 5% at 72 hours. The accuracy was slightly higher for tau compared to NSE. The use of the test in conjunction with clinical data can improve prognostication at 72 hours and may assist in identifying patients who are unlikely to benefit from prolonged intensive care compared to patients who are more likely to survive.

The study has been well performed as part of a multicenter trial and was powered adequately for detection of poor outcomes with tau levels. Temperature management was not found to be a confounder.

One of the critical needs in neuroprognostication is to discover a biomarker that not only has high specificity and sensitivity, but also can be performed readily at any hospital, since cardiac arrest is a ubiquitous

illness seen at hospitals globally. The currently used assay is not commercially available and is semi-automated. However, advances in technology likely can deliver this for commercial use.

The promise of tau as a biomarker of severe brain injury also has been demonstrated recently in traumatic brain injury.[2] Different forms of tau, such as phospho-tau, also may be promising, and although not ready for clinical use, do hold the hope of a biomarker for acute brain injury, regardless of etiology. ■

REFERENCES

1. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. *N Engl J Med* 2013;369: 2197-2206.
2. Rubenstein R, Chang B, Yue JK, et al. Comparing plasma phospho-tau, total tau, and phospho tau-total tau ratio as acute and chronic traumatic brain injury biomarkers. *JAMA Neurol* 2017;74: 1063-1072.

CME QUESTIONS

1. **Which of the following is correct about autoantibody-associated movement disorders?**
   a. Presence of IgLON5 antibodies causes a synucleinopathy, leading to MSA-like symptoms.
   b. The presence of anti-neuronal antibodies usually is indicated by abnormal findings on neuroimaging.
   c. Autoantibodies have been associated with several movement disorders but always in association with encephalopathy.
   d. Tauopathy associated with presence of IgLON5 antibodies is associated with sleep movement disorders.
2. **Which of the following medications may be effective in the treatment of restless legs syndrome?**
   a. Pramipexole
   b. Ropinirole
   c. Iron supplements
   d. Gabapentin
   e. All of the above
3. **Which of the following is *not* true regarding the results of the study of functional imaging in Parkinson's disease?**
   a. Caudate had the most severe binding reduction.
   b. There were 11 VMAT2 studies.
   c. The correlation between disease severity and dopamine loss was strongest in the caudate nucleus.
   d. AADC binding defect was consistently smaller than the other two targets.
4. **Compared to pregnant women without myasthenia gravis, pregnant women with muscle-specific tyrosine kinase (MuSK)-positive myasthenia gravis:**
   a. have an increased risk of still birth.
   b. have an increased risk of pre-eclampsia.
   c. have an increased risk of birth defects.
   d. All the above are true.
   e. None of the above are true.
5. **Anti-MAG neuropathy is *not* associated with which of the following?**
   a. Pain and cramps
   b. Demyelinating changes on EMG/NCS
   c. IgG monoclonal gammopathy
   d. Responsiveness to intravenous immunoglobulin
   e. Distal weakness and tremor
6. **Elevated serum tau levels after cardiac arrest correlate with a worse neurological outcome.**
   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]

Special Report from the International Stroke Conference