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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

REM Behavior Disorder as a Predictor of Parkinson's Disease: A Clinical and PET Imaging Study

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: In a carefully executed study of REM behavior disorder patients compared to controls and those with Parkinson's disease, a distinct anatomic-metabolic pattern was observed using FDG-PET imaging.

SOURCE: Wu P, et al. Consistent abnormalities in metabolic network activity in idiopathic rapid eye movement sleep disorder. *Brain* 2014;137:3122-3128.

Dream enactment during sleep is known as rapid eye movement (REM) behavior disorder (RBD). In the absence of physiological muscle paralysis during REM, patients may punch, kick, or otherwise destroy property during their dreams. This can be hazardous to themselves and their bed partners. More importantly, RBD has been linked to neurodegenerative diseases, specifically the α-synucleinopathies (Parkinson's disease [PD], Lewy body dementia [LBD], and multiple system atrophy [MSA]). However, this association remains unexplained and raises multiple questions. Why does RBD predict PD? What exactly is the risk for PD in a patient with sporadic RBD? And what is the meaning of incidental muscle activity in REM sleep during a polysomnogram (REM sleep without atonia, RSWA) in a patient who is otherwise asymptomatic?

Prior research has shown that while patients are in the midst of dream enactment, supplementary motor area (SMA) activity can be demonstrated on FDG-PET, which is absent in controls. In this study, Wu and

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his colleagues studied a cohort of Chinese patients to identify a pattern on positron emission tomography (PET) termed rapid eye movement sleep behavior disorder-related pattern (RBD-RP). This pattern was identified as separate and distinct from the Parkinson's disease-related pattern (PD-RP) previously defined by this group. The neuro-anatomy associated with these patterns is complex, but distinct from one another. RBD-RP shows increased activity in the pons, thalamus, medial frontal and sensorimotor areas, hippocampus, supramarginal and inferior temporal gyri, and posterior cerebellum, with decreased activity in occipital and superior temporal regions. PDRP shows relative increases in sensorimotor, pallido-thalamic, pontine, and cerebellar metabolism, with decreased activity in premotor and posterior parietal-occipital metabolism. The PD-RP distribution has been previously shown to highly correlate with idiopathic PD compared to controls.

This study included 21 newly recruited RBD patients, as well as previously identified patients with RBD (presumably in more advanced stages), and PD patients and healthy controls. PD patients included those with hemi-Parkinsonism (Hoehn and Yahr Stage 1) and moderate PD (Hoehn and Yahr Stage 2-3). The RBD-RP on PET showed a 95% sensitivity and specificity for this diagnosis ($P < 0.0001$) compared to controls. There was some overlap between the RBD-RP pattern and the PD pattern, more prominent in the hemi-PD patients compared to the moderate PD patients. This is consistent with the clinical evolution of RBD — it appears prior to PD or very early in the course of the disease. Conversely, the PD-RP pattern was more prominently seen in moderate PD patients compared to hemi-PD or RBD. This again suggests more of a similarity between RBD and early PD as opposed to PD in its more advanced stages.

Only 48% of the RBD patients included in this study showed polysomnographic evidence of increased motor activity on EMG (measured in the upper or lower extremities or in the chin), while the remainder of the cohort had only a positive history of dream enactment behavior. While this may be viewed as a weakness of the study, it is more consistent with clinical observations. The majority of patients with RBD in practice are identified by history not by polysomnogram.

■ COMMENTARY

It still remains unknown how many RBD patients will go on to develop PD or any other α-synucleinopathy. It also remains unknown whether there are any variations in the diagnostic criteria, severity, or time course of RBD that would improve this prognostication. This clinical and PET study is an important first step toward understanding the anatomical substrate of RBD and its relationship to PD. ■

ABSTRACT & COMMENTARY

The Clinical Spectrum of Encephalitis

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: The majority of cases of encephalitis are viral or autoimmune, and factors associated with a poor prognosis include coma and need for mechanical ventilation.

SOURCES: Singh TD, et al. The spectrum of acute encephalitis: Causes, management and predictors of Outcome. *Neurology* 2015;84:1-8.
Sonneville R, et al. Clinical spectrum and outcomes of patients with encephalitis requiring intensive care. *Eur J Neurol* 2015;22:6-16.

Encephalitis is a serious neurologic condition caused by acute inflammation of the brain. Patients typically present acutely with any combination of confusion, fever, seizures, headache, focal neurologic deficits, and abnormal involuntary movements.

Diagnosis is typically made by cerebrospinal fluid (CSF) analysis and serologic studies on CSF and blood. Neuroimaging and electroencephalogram can sometimes assist in making the diagnosis. The acute treatment of suspected encephalitis includes antiviral therapy and aggressive supportive care, including management of intracranial hypertension, if significant cerebral edema is present. The most common cause of encephalitis is viral infection, but over the past decade there has been a rapidly increasing recognition of immune-mediated causes, including both paraneoplastic and non-paraneoplastic antibodies.

Neurologists are often called to assist in the diagnosis of encephalitis, especially when the etiology is not readily apparent on standard workup. Because encephalitis is relatively rare (0.07-12.6 cases per 100,000), large case series, accumulated over a number of years, are necessary to recognize causes and outcomes. The two studies summarized here are both rigorous, detailed, retrospective reviews of patients diagnosed with encephalitis over the prior 10 or more years. Both papers assessed the causes of encephalitis, demographic factors, outcomes, and prognostic factors. The American study, performed at the Mayo Clinic, reviewed all cases of encephalitis from 2000-2012, and the European study, performed at a Parisian hospital, reviewed all cases of encephalitis requiring ICU care from 1991-2012.

In the American study, the authors identified 198 patients over a decade. There was no clear gender predilection and the median age was 58 years. Forty-eight percent of the patients were determined to have viral encephalitis, 22% autoimmune, and 30% unknown or other etiology. Within the viral encephalitis group, 38.9% were caused by herpes simplex virus, 23% by varicella zoster virus, 19% by West Nile virus, 6% by Epstein-Barr virus, and 3% by HIV. Within the autoimmune group, the most common autoantibodies identified were NMDA (24.4%) and voltage-gated potassium channel (24.4%). Good outcomes (modified Rankin score 0-2) occurred in 50% of the viral encephalitis group, 40% of the autoimmune encephalitis group, and 54% of the group with undetermined etiologies. Prognostic factors that were associated with poor outcome included coma (odds ratio [OR], 5.06), mechanical ventilation (OR, 3.44), immune-compromised state (OR, 2.79), acute thrombocytopenia (OR, 2.36), and older age (OR, 2.28). Overall mortality rate was 9%.

In the European study, 279 patients were identified over 20 years. Causes included infectious/viral in 53%, immune mediated in 15%, and undetermined in 32%. Of note, there was a higher incidence of cases of autoimmune encephalitis in the 2002-2012 patients compared to the 1991-2001 patients. Good outcomes (modified Rankin scale) occurred in 75% of patients. Mortality rate was 17%. The authors performed a multivariate analysis and determined that prognostic factors for poor outcome included coma (OR, 7) and aspiration pneumonia (OR, 4). Other significant but less robust prognostic factors included lower body temperature, elevated CSF protein levels, and delayed ICU admission. The most common causes of infectious encephalitis in this cohort included tuberculosis and herpes simplex virus.

[These studies summarize recent large cohorts of patients with encephalitis and allow clinicians to more accurately diagnose and care for these patients.]

■ COMMENTARY

Despite being done on different continents, these studies share some striking similarities that allow for more significant generalizability of the findings. In both studies, infectious causes accounted for about half of the cases of encephalitis, with autoimmune causes accounting for 15-22% of cases. Both studies also clearly demonstrated that coma is a very poor prognostic factor in encephalitis cases. Of note, only the American study found an association of poor prognosis with older age. Also, tuberculosis was a common cause of encephalitis in the European cohort (23% overall), but was not noted in the American cohort. It is interesting to note as well that delayed ICU admission was an independent predictor of poor prognosis, suggesting that early ICU care may improve the prognosis of encephalitis. One caveat to note is that retrospective prognostic data must always be applied cautiously in the clinical setting so as to avoid the problem of the "self-fulfilling prophecy" in which a patient with presumed poor prognostic factors is not treated aggressively, resulting in a bad outcome.

Encephalitis is an important diagnosis to recognize and treat in a rapid and efficient manner. These studies are important because they summarize recent large cohorts of patients with encephalitis, allowing the clinician to use these data to more accurately diagnose and care for patients with encephalitis. ■

ABSTRACT & COMMENTARY

Progesterone in Acute Traumatic Brain Injury: No Protection Offered

By Halinder S. Mangat, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Administration of progesterone after acute traumatic brain injury does not improve neurological outcome nor reduce mortality.

SOURCES: Wright DW, et al. Very early administration of progesterone for acute traumatic brain injury (ProTECT III trial). *N Engl J Med* 2014;371:2457-2466.
Skolnick BE, et al. A clinical trial of progesterone for severe traumatic brain injury (SYNAPSE trial). *N Engl J Med* 2014;371:2467-2476.

The ProTECT trial studied the benefit of parenteral progesterone administered within 4 hours after moderate or severe non-penetrating traumatic brain injury (TBI).[1] In the study, 882 patients were randomized 1:1. The two groups were similar in demographics, cause, and severity of injury. Progesterone was administered as a continuous infusion over 96 hours. Based on severity of injury, mortality and functional outcome (measured by GOS-E) were similar in the two groups. Incidence of thrombophlebitis was slightly higher in the group receiving progesterone; this was the most commonly observed adverse effect.

The SYNAPSE trial enrolled only patients with severe non-penetrating TBI.[2] Progesterone was administered within 8 hours, and the infusion continued for 120 hours. In this trial, 1195 patients were randomized. GOS (and GOS-E) outcomes and mortality were similar in the two groups. Dose of progesterone was identical in the two trials and was weight-based.

■ COMMENTARY

TBI remains a major global health problem, exacting a huge social and economic price. However, in spite of significant advances in the management of severe TBI, there is no pharmacological agent that has been shown to treat the deleterious effects of TBI and improve outcome. The Brain Trauma Foundation has developed guidelines for the management of severe TBI.[1] The main tenets of the guidelines are reduction of intracranial pressure and ensuring adequate cerebral perfusion while avoiding hypoxia and hypotension. There is scant Level I evidence supporting the various interventions even though several randomized clinical trials have been conducted to evaluate a variety of therapies, including steroids and hypothermia.

Progesterone has been shown to have a multitude of neurotrophic effects while limiting toxic neuronal injury by blocking excitotoxic pathways. Importantly, Phase 2 trials showed significant reduction in mortality as well as improvement in functional outcome in patients who received progesterone after suffering a TBI.

Both the trials were based on the Phase 2 PROTECT data for dosing and duration of treatment.[2] Supporting data were also available from another single-center trial.[3] While patients were treated within 4 hours in the PROTECT trial, patients in the SYNAPSE trial were treated within 8 hours. Yet, the outcomes were similar in the two trials and comparable to placebo therapy. No benefit was seen with progesterone therapy.

While pilot data seemed to suggest benefit, the size of the ProTECT Phase 2 trial was small, enrolling a total of 50 patients. The statistical significance of the mortality benefit was not very robust, while patients with moderate injury had improved functional outcome. Meanwhile, the trial by Xiao et al enrolled 159 patients and demonstrated improved functional outcome. However, the differences in the mortality and GOS at 3 and 6 months were marginal, while the differences in Functional Independence Measure (FIM) scores were more pronounced at 6 months. The targeted 50% favorable outcome in the current trials appears over-reaching based on these data. In addition, the mortality in the pilot trial placebo group patients was significantly higher than that in the current trials, as well as mortality documented from retrospective cohort studies.[4] This may also partly explain the loss of the earlier-observed marginal mortality benefit. Many of the beneficial mechanisms of progesterone were studied in rodents and extrapolated to benefit humans also. No data in large animals were available. We have learned from past failed trials that rodent data do not translate to benefit in human trials.

Many of the above-cited points are also emphasized in the editorial accompanying the articles.[5] Failed Phase 3 trials must make us look very closely at pilot data. The

editorial cites unrecognized bias and modest benefit in pilot data. Whether this is due to single-center data or increasing need for a therapy to improve outcome after TBI, it needs to be minimized.

In summary, these trials demonstrate the failure of progesterone to provide benefit in improving outcome after TBI. Nevertheless, we must learn that to avoid failure in future trials, robust pilot trials must be undertaken, demonstrate significant benefit, and perhaps be preceded by preclinical data from large animals. We must avoid letting our enthusiasm cloud our judgments and observations. ■

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ABSTRACT & COMMENTARY

Predicting Efficacy of IVIG in CIDP

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 a retrospective chart review of 281 treatment-naïve patients with chronic inflammatory demyelinating polyradiculoneuropathy, lack of response to intravenous immunoglobulin was predicted by 1) presence of painful neuropathy and 2) strength differences between arm and leg muscles.

SOURCE: Kuitwaard K, et al. Intravenous immunoglobulin response in treatment-naive chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Neurosurg Psychiatry* 2014;0:1-6. doi:10.1136/jnnp-2014-309042

Glucocorticoids, intravenous immune globulin (IVIG), and plasma exchange are equally efficacious for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP), each having its own advantages and disadvantages. Although expensive and sometimes limited in availability, depending on manufacturer supply and accessibility to specialized centers, IVIG and plasma exchange offer more rapid improvement for CIDP than do steroids, but are less likely to induce remission. As an alternative, steroids are inexpensive, yet associated with multiple clinically significant side effects. Can neurologists predict which CIDP patient is less likely to respond to IVIG, thereby avoiding its cost and inconvenience?

Medical records of treatment-naive CIDP patients seen between 1980 and 2011 at Erasmus MC, University Medical Center, Rotterdam, the Netherlands, and London Health Sciences Center, London, Ontario, Canada, were retrospectively reviewed. Clinical diagnostic criteria for typical or atypical CIDP, as determined by the European Federation of Neurological Societies/Peripheral Nerve Society, were fulfilled in all. Exclusionary criteria included patients with chronic acquired or hereditary neuropathy, multifocal motor neuropathy, recurrent Guillain-Barré syndrome, and those with an IgM monoclonal gammopathy of undetermined significance (MGUS) if they also demonstrated antibodies against myelin-associated glycoprotein. IVIG 2 g/kg was the initial therapy in all patients, with fresh frozen plasma used prior to IVIG availability. Improvement of at least 1 grade on the modified Rankin scale was considered clinically significant. Statistical analysis comprised the $\chi 2$ test, Fisher's exact test, and the Mann-Whitney U test, with a two-sided P value < 0.05 considered significant.

Among 281 treatment-naive CIDP patients given one course of IVIG, encompassing 179 males and 102 females, with 13 patients under age 18 years, 76% (n = 214) improved, with no significant difference appreciated between adults and children and no correlation between response and patient age. Among IVIG non-responders, plasma exchange and steroids resulted in subsequent improvement in 66% and 58%, respectively, with a total of 79% improving after either or both. Remission was achieved after a single IVIG course in 16% (n = 14). Response to IVIG was positively associated with the absence of pain, equivalent arm and leg weakness, absence of MGUS, and absence of other autoimmune

disease in univariate analysis, and positively associated with the absence of pain and the presence of equivalent arm and leg weakness in multivariate analysis. Pain or a difference in weakness between arms and legs were not associated with response to steroids. Pain or a difference in weakness in arms and legs may be signs of an IVIG non-responder.

■ COMMENTARY

What is/are the antibody target(s) in CIDP? Contactin-2, a neuronal membrane protein that functions as a cell adhesion molecule, and connexin 32, one of a family of transmembrane proteins that forms paranodal gap junctions and mutation of which results in X-linked Charcot-Marie-Tooth disease, have been suggested as potential target antigens in peripheral nervous system demyelination. Antibodies to contactin-2 have been reported in patients with multiple sclerosis. Nevertheless, sera from 45 CIDP patients, five multifocal motor neuropathy patients and four with combined central demyelination and CIDP failed to show binding for either antigen using an anti-human fluorescent antibody.[1] But the search for the immune target in CIDP will continue. ■

REFERENCE

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ABSTRACT & COMMENTARY

Statins and the Neuromuscular System

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: Statins inhibit the function of 3-hydroy-3-methylglutaryl coenzyme A reductase and are widely used for risk reduction of cardiovascular and cerebrovascular disease. It is estimated that about 10% of patients will discontinue statins due to muscle-related symptoms.

SOURCE: Argov Z. Statins and the neuromuscular system: A neurologist's perspective. *Eur J Neurol* 2015;22:31-36.

In this review, Argov summarizes the common clinical scenarios (in decreasing order of frequency) encountered by the neurology consultant: 1) asymptomatic creatine kinase (CK) elevation, generally not more than five times the upper limit of normal (or <1000 IU/L); 2) myalgias, usually with an elevated CK; 3) persistent muscle symptoms and elevated CK despite cessation of statin; 4) necrotizing autoimmune myopathy; and 5) rhabdomyolysis.

Older women with a low body mass index and systemic disease (such as renal insufficiency, liver disease, hypothyroidism, or diabetes) may be at greater risk for statin intolerance. The pathogenesis of statin-induced myopathy is unknown, but some hypotheses include muscle membrane defects due to low cholesterol, inhibition of protein prenylation, induction of pro-apoptotic pathways, impaired mitochondrial function with low coenzyme Q, or induction of an autoimmune process. The latter is supported by the identification of autoantibodies against HMGCR, found in a minority of patients with necrotizing autoimmune myopathy.

Statins should be withdrawn in the setting of severe myalgia and weakness, but not necessarily for asymptomatic CK elevations less than five times the upper limit of normal or the pretreatment level. When lipid lowering is essential, rechallenging with a different statin, every-other-day dosing, or selection of a different lipid-lowering agent (e.g., cholesterol absorption inhibitor) are potential treatment strategies. In patients with existing myopathies or myasthenia gravis, statin use is not automatically contraindicated, but should be monitored carefully.

■ COMMENTARY

This is a succinct review of a very relevant topic for the neurology consultant, given the ubiquity of statin use and frequency of muscle-related symptoms. Fortunately, most patients tolerate the medication and have resolution of myalgias and CK elevations within weeks of treatment cessation. Should symptoms persist or worsen, referral to a neuromuscular expert is warranted to exclude an immune-mediated necrotizing myopathy for which aggressive immunomodulatory therapy is required.

The evidence for a statin-induced peripheral neuropathy is controversial, and the incidence is likely very low. Earlier reports that suggested a 4- to 14-fold increased risk of developing polyneuropathy have not been supported by clinical experience or in any rigorous case-control studies. ■

Stroke Alert

By Matthew E. Fink, MD

Intra-arterial Clot Extraction with Retrievable Stent Is Effective and Safe

SOURCE: 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.

In the March 2013 issue of *Neurology Alert*, we provided a special report on the highly publicized studies reported at the 2013 International Stroke Conference that failed to show a benefit of intra-arterial therapies and clot extraction, compared to the standard of care, which, at that time, was intravenous thrombolysis. In our editorial, we commented that the studies were performed with first-generation devices and after long time intervals, and that it was our expectation that as the technology improved, so would the results.

Therefore, we were not surprised when the MR CLEAN study was published recently in the *New England Journal of Medicine*. This was a randomized trial of intra-arterial treatment following standard of care (IV thrombolysis) compared to standard of care alone. Eligible patients had proximal arterial occlusion in the anterior circulation that was confirmed on arterial imaging, and they were treated with intra-arterial clot extraction within 6 hours of symptom onset. The primary outcome measures were the modified Rankin score at 90 days, and the odds ratio measured the likelihood that intra-arterial treatment would lead to a lower Rankin score compared to standard of care alone.

The study was performed at 16 medical centers in the Netherlands, and 500 patients were enrolled and randomized to the treatment arm or the control arm. A total of 445 patients, or 89%, were treated with intravenous alteplase before randomization, and retrievable stent technology was used in 190 of 233 patients assigned to the intra-arterial treatment arm. Intra-arterial treatment could involve thrombus retraction, aspiration, wire disruption, or use of a retrievable stent. The adjusted odds ratio, which measured the likelihood that intra-arterial treatment would lead to lower modified Rankin scores, was 1.67 (95% confidence interval, 1.21-2.30) in favor of intra-arterial therapy. The rate of functional independence, determined by a modified Rankin score of 0 to 2, favored intra-arterial intervention (32.6% vs 19.1%). There was no significant difference in the incidence of symptomatic intracerebral hemorrhage or a difference in mortality between the two groups. The investigators' conclusion was that intra-arterial therapy performed within 6 hours of stroke onset, in patients with proximal intracranial occlusion, showed improvement and benefit to a greater degree than patients treated with standard therapy, intravenous thrombolysis.

Other ongoing studies using intra-arterial retrievable stents have also been in progress, and several of them have been put on hold while the full analysis of the MR CLEAN study is completed. It is our opinion that these studies are likely to show a benefit, and that intra-arterial clot retrieval therapy will become the standard of care for patients who have large vessel arterial occlusions in the setting of ischemic stroke. ■

In Asian Patients, Intracranial Atherosclerosis Is Associated with More Severe White Matter Hyperintensities

SOURCE: Park JH, et.al. Association of intracranial atherosclerotic stenosis with severity of white matter hyperintensities. *Eur J Neurology* 2015;22: 44-52.

White matter hyperintensities (WMHs) are commonly seen on magnetic resonance imaging scans of elderly people, and are pathologically correlated with myelin pallor, loss of myelin and axons, and gliosis. Many of these lesions are related to cerebral ischemia and are more common in patients with vascular risk factors, particularly hypertension, and cerebrovascular disease. WMHs have been associated with cognitive dysfunction, dementia, depression, psychosis, gait impairment, falls, and hand incoordination, and they are also associated with a markedly increased risk of future symptomatic stroke. The relationship between extracranial and intracranial atherosclerosis and WMHs is uncertain, and this investigation attempts to provide further information of this relationship.

Park et al performed a cross-sectional study of 679 consecutive Korean patients with acute ischemic stroke (mean age = 67.8 years) who underwent brain MRI/MR angiography. Severity of deep WMHs (d-WMHs, n = 560) and periventricular WMHs (p-WMHs, n = 590) was rated separately and compared across three groups: intracranial atherosclerotic stenosis (ICAS , n = 318), extracranial atherosclerotic stenosis (ECAS, n = 71), and no cerebral atherosclerotic stenosis (NCAS, n = 290). Significant stenosis was defined as ≥ 50% for both ICAS and ECAS.

The ICAS group showed a higher d-WMH/p-WMH score than both the ECAS and the NCAS groups ($P < 0.001$ for all). Patients with higher scores of d-WMH/p-WMH had a higher incidence of ICAS ($P < 0.001$ for all), but not of ECAS or NCAS. In this Asian/Korean ischemic stroke population, intracranial stenosis was associated with a higher number of WMHs. With the known increased prevalence of intracranial atherosclerosis in the Asian population, this study highlights an important consequence, WMHs, which may have important clinical implications. ■

CME QUESTIONS

1. **Which of the following statements about REM behavior disorder (RBD) is true.**
   a. RBD is a rare complication of obstructive sleep apnea.
   b. RBD is "dream enactment" during sleep and may cause physical injury.
   c. RBD is a precursor of Parkinson's disease.
   d. RBD only occurs in older adults.

2. **Which of the following is *false* about encephalitis?**
   a. Most cases of encephalitis are caused by viral infections.
   b. The most ominous clinical sign in a patient with encephalitis is coma.
   c. Auto-immune encephalitis has a better prognosis than viral encephalitis.
   d. Early intensive care treatment results in a better outcome.

3. **Which of the following treatments for traumatic brain injury have been proven to be effective in randomized clinical trials?**
   a. Corticosteroids
   b. Hypothermia
   c. Hypertonic saline
   d. Progesterone
   e. None of the above

4. **Therapeutic response to intravenous immune globulin in patients with chronic inflammatory demyelinating polyneuropathy may correlate with:**
   a. absence of pain.
   b. equivalent arm and leg weakness.
   c. Neither a nor b
   d. Both a and b.

5. **Statin use has been associated with which of the following neuromuscular side effects?**
   a. Asymptomatic creatine kinase elevation
   b. Myalgias, with or without creatine kinase elevation
   c. Necrotizing autoimmune myopathy
   d. Rhabdomyolysis
   e. All of the above

6. **Intra-arterial clot retrieval using a stent retriever device may improve outcome in patients with ischemic stroke and large vessel arterial occlusion.**
   a. True
   b. False

7. **Intracranial atherosclerotic stenoses are not associated with an increase in ischemic white matter hyperintensities.**
   a. True
   b. False

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