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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Prediction of Survival After Cardiac Arrest Using Pupillometry

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: Automated infrared pupillometry holds promise as a quantitative, reproducible measure that aids in determining neurological prognosis after cardiac arrest and coma.

SOURCE: Solari D, Rossetti AO, Carteron L, et al. Early prediction of coma recovery after cardiac arrest with blinded pupillometry. *Ann Neurol* 2017;81:804-810.

The current standard of prediction of outcome after cardiac arrest uses neurological examination, neurophysiological tests, blood biomarkers, and neuroimaging.[1] This process remains limited to defining only patients with grossly poor outcomes. Solari et al examined the additional utility of objective pupillary light reactivity in prediction of recovery of coma after cardiac arrest.[2]

The study was performed at the intensive care unit of Lausanne University Hospital in Switzerland. Patients were enrolled prospectively if they were alive and remained comatose 48 hours after cardiac arrest. Automated infrared pupillometry was performed using the handheld NeuroLight-Algiscan device, which measures pupillary size and pupillary light reactivity up to 0.05 mm. All measurements were blinded and not used for any clinical decision-making, including withdrawal of care. Most patients underwent therapeutic hypothermia and received sedation-analgesia and pharmacological paralysis. Daily neurological exams were performed in addition to video electroencephalogram (EEG) during hypothermia (day 1) on sedation, and post hypothermia (day 3) off sedation-analgesia. Somatosensory Evoked Potentials (SSEP) and serum neuron-specific

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Neurology [ALERT]

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enolase (NSE) testing were performed. Outcomes were measured as one-year Cerebral Performance Categories (CPC) score.

Of 103 enrolled patients, 53 died (CPC5). Of survivors, 32 had a good recovery (CPC1), 16 had moderate disability (CPC2), two had severe disability (CPC3), and none was in a vegetative state. At 48 hours, all survivors had ≥ 13% pupillary reactivity (median 20%). Of these, nine had lower reactivity at 24 hours, but this increased to ≥ 13% by 48 hours. Pupil size and sedation/analgesia dose were identical in both groups. This threshold of 13% reactivity had a 100% positive predictive value for survival, with a specificity of 100% and sensitivity of 61%.

Pupillometry reactivity threshold of < 13% was comparable to EEG non-reactivity and absent SSEP N20 in positive predictive value of poor outcome, but was superior to neurological examination. Low pupillary reactivity was strongly correlated with high NSE.

■ COMMENTARY

This study demonstrated the utility of quantitative measurement of pupillary light reactivity in predicting poor prognosis after cardiac arrest in comatose patients. It was performed prospectively with blinding of study data such that it did not influence clinical decision-making or affect outcomes, most importantly decisions regarding withdrawal of care. Pupillary light reactivity was ≥ 13% at 48 hours in all survivors, and the lower threshold, which occurred in two patients, was not visible on standard neurological examination.

The determination of an objective threshold of reactivity is a useful tool in prognostication and was equal in predictive value to EEG and SSEPs and superior to a neurological examination. Apart from absent SSEP and elevated NSE levels, all other measures of outcome are subjective and can be prejudiced by clinical judgment. No exact criteria are specified for EEG reactivity. In addition, EEG, SSEP, and NSE testing may not always be available and can be expensive. The ability to use a bedside objective measure of brainstem injury that does not require specialized training to perform and correlates with clinical outcomes is of immense importance.

However, there are some limitations to the study. This is a single-center study, and while the pupillometry findings were not used to prognosticate, EEG and NSE levels were. In addition, U.S. guidelines for prediction of recovery after cardiac arrest recommend prognostication at 72 hours. The current study performed pupillometry at 48 hours, and it is unknown if these results would be reproducible at 72 hours. Last, pupillometry only predicted survival and not degree of recovery.

[The ability to use a bedside objective measure of brainstem injury that does not require specialized training to perform and that correlates with clinical outcomes is of immense importance.]

In conclusion, this study does provide strong proof-of-concept and pilot data on the use of bedside pupillometry as a strong correlate of brainstem injury and clinical outcome after cardiac arrest, and warrants further investigation in a larger study. ■

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2. Solari D, Rossetti AO, Carteron L, et al. Early prediction of coma recovery after cardiac arrest with blinded pupillometry. *Ann Neurol* 2017;81:804-810.

ABSTRACT & COMMENTARY

Tacrolimus for Treatment of Myasthenia Gravis

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: A large observational study performed in Korea suggests that tacrolimus is an effective immunomodulating, steroid-sparing medication for the treatment of myasthenia gravis.

SOURCE: Ahn SW, Joo IS, Kim BJ, et al. A multicenter prospective observational study on the safety and efficacy of tacrolimus in patients with myasthenia gravis. *J Neurol Sci* 2016; doi:10.1016/j.jns.2017.05.060. [Epub ahead of print].

Immunomodulating agents useful in the treatment of myasthenia gravis (MG) include glucocorticoids, azathioprine, mycophenolate mofetil, and cyclosporine. Patients with generalized MG who are refractory to these agents may benefit from monthly intravenous immunoglobulin, or the administration of rituximab, methotrexate, etanercept, cyclophosphamide, or tacrolimus. Recent evidence suggests that tacrolimus may serve as an effective immunosuppressant, even as an initial therapeutic agent in patients with MG.

In this prospective, observational study involving 15 Korean medical centers, 150 consecutive patients with corticosteroid-treated MG were followed for 24 months, comprising a 12-month enrollment period followed by a 12-month observational period after the initial administration of tacrolimus, 3 mg/day orally, with follow-up adjustment of dosage based on clinical judgment. Inclusion criteria encompassed age > 19 years, diagnosis of MG based on typical clinical features with positive serum autoantibodies to AchR or MuSK, decrement on repetitive nerve stimulation studies, or improvement on administration of anticholinesterase inhibitors, and MG refractory to standard corticosteroid and anticholinesterase therapy. Primary study endpoints were tolerability and safety of tacrolimus, whereas secondary endpoints were efficacy of tacrolimus based on improvement of MG Composite Scales (MGCS) and reduction of corticosteroid dosage. Patient evaluations occurred at baseline and at three-month intervals thereafter for 12 months following tacrolimus administration. Statistical analysis used the general linear model repeated measure analysis of variance (ANOVA) and Mauchly's test of sphericity, with P values < 0.05 considered statistically significant.

Among 150 patients enrolled at baseline, two withdrew with no explanation, allowing safety to be evaluated in 148 patients, and 14 were discontinued after initiation of tacrolimus because of an adverse event or drug reaction, permitting efficacy to be evaluated among the remaining 134 patients, including 90 women and 44 men of mean age 56.2 years. Overall, 21.6% (n = 32) experienced an adverse drug reaction, usually minor, including gastrointestinal disturbances (10%), increased liver enzymes (2.7%), hyperglycemia or upper respiratory infection (2% each), or headache (1.6%). These resolved spontaneously or with dose reduction. Serious adverse reactions affected seven patients, three each with either herpes zoster or nephrotoxicity, and one with leukopenia, all of whom were removed from the study. An additional five patients were removed after consultation with their attending physician for gastrointestinal symptoms (n = 2) or chest discomfort, alopecia, and elevated liver enzymes/hyperglycemia (n = 1 each). Among the 134 patients who completed the study, mean corticosteroid dosage decreased significantly compared to baseline, both among generalized (n = 79) and ocular (n = 55) MG patients, and regardless of prior thymectomy (n = 50). MGCS significantly improved after 12 months in the generalized MG group but not in the ocular group compared to baseline. In this study, tacrolimus was an effective immunosuppressant with an acceptable safety profile for treatment of MG.

■ COMMENTARY

Tacrolimus, at an oral dose of 3 mg/day, reduces steroid requirements in MG and improves clinical symptoms. What is its optimal serum concentration for MG? In a Japanese study, where it is approved for treatment of MG, trough concentrations of tacrolimus were measured using a chemiluminescent enzyme immunoassay in 51 MG patients who were receiving 3 mg/day for more than a year. Median trough concentration, which correlated with minimal manifestation of disease

or better, was 5.4 ng/mL (range 2.9-7.6), and, using a receiver operating characteristic curve, a minimal concentration of 4.8 ng/mL or higher was associated with better reduction of AchR antibody titers, greater improvement of activities in daily life scores, and achievement of minimal manifestation or better status. Improved MG prognosis requires an adequate tacrolimus blood concentration.[1] ■

REFERENCE

1. Kanai T, Uzawa A, Kawaquchi N, et al. Adequate tacrolimus concentration for myasthenia gravis treatment. *Eur J Neurol* 2017:24:270-275.

ABSTRACT & COMMENTARY

Plasma α-Synuclein Is a Leading Candidate Biomarker in Parkinson's Disease

By Claire Henchcliffe, MD, PhD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is a consultant and on the speakers bureau for Acadia, Impax, and Allergan, and is a consultant for US WorldMeds and Gerson Lehrman Group.

SYNOPSIS: In this cross-sectional study, plasma alpha-synuclein levels were higher in individuals with Parkinson's disease than controls, and correlated with cognitive decline.

SOURCE: Lin CH, Yang SY, Horng HE, et al. Plasma alpha-synuclein predicts cognitive decline in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2017; May 26. doi:10.1136/jnnp-2016-314857. [Epub ahead of print].

Neuroimaging biomarkers, including single positron emission computerized tomography (SPECT) and positron emission tomography (PET) scans, are already in sporadic use to aid in diagnosis of Parkinson's disease (PD), but the search is on for a fluid-based biomarker that would be simpler, cheaper, and more broadly accessible than sophisticated neuroimaging. In this study, plasma was collected at a tertiary referral center from 80 participants with PD and 34 controls for analysis of α-synuclein levels. The groups were well matched for gender and education level, but those with PD were significantly older than controls (mean age, 69.6 ± 12.3 years vs. 61.9 ± 9.5 years, respectively; $P < 0.01$). The immunoassay used by these investigators is highly innovative, making use of magnetic nanoparticles that have anti-α-synuclein monoclonal antibodies bound to them. Binding to plasma α-synuclein then is measured by a reduction in magnetic susceptibility, termed the immune-magnetic reduction (IMR) signal. Using this assay, α-synuclein plasma concentration was markedly higher in PD than control subjects at 1.96 pg/mL (95% confidence interval [CI], 1.02-1.98 pg/mL) compared with 0.02 pg/mL (95% CI, 0.01-0.03 pg/mL), respectively ($P < 0.0001$). No correlation with age was determined in control subjects, leading to the suggestion that the difference between PD and control groups was due to disease state and not the difference in age. PD participants were then divided by Hoehn and Yahr stage (range 1-4), in which higher stage denotes worse function. Although those with higher Hoehn and Yahr stages had increased α-synuclein plasma concentration, this association did not hold when using a multivariate linear regression model that included age, gender, and disease duration. However, higher α-synuclein plasma concentrations were found to be associated with more profound cognitive dysfunction, as assessed by the Mini-Mental Status Examination (MMSE). Median α-synuclein plasma concentration increased between groups from 0.42 pg/mL (95% CI, 0.25-0.93 pg/mL) for PD, to 1.29 pg/mL (95% CI, 0.76-1.93 pg/mL) for PD with mild cognitive impairment, to 4.09 (95% CI, 1.99-6.19) pg/mL for PD with dementia.

■ COMMENTARY

Although α-synuclein already is a leading candidate as a fluid-based PD biomarker, several issues remain to be addressed. The first is what samples would be best to test. The most robust results to date have measured α-synuclein in cerebrospinal fluid (CSF), finding a decrease in CSF α-synuclein in PD, as opposed to the increase in plasma α-synuclein determined in this study. Obtaining CSF from patients for analysis generally is straightforward, but a blood-, urine-, or saliva-based marker would be preferable given the relative speed and simplicity of collection of these biofluids compared with CSF. A second issue concerns the debate over what technique is best for measurement. A major problem is that α-synuclein is present at low concentration in plasma and is

abundant in red blood cells. Therefore, difficulties associated with measuring low concentration of this specific protein are compounded by even a small degree of red blood cell contamination of the sample. This has led to varying results from previous studies, despite encouraging findings in CSF. However, Lin and colleagues presented robust data based on a novel detection technology, making use of antibodies immobilized onto magnetic nanoparticles, which they have used previously to investigate Alzheimer's disease biomarkers. This has enabled them to measure in a range of 0.3 fg/mL to 310 pg/mL, according to their previous study. The major finding of this study is the association of increased plasma α-synuclein concentration with degree of cognitive decline, suggesting that this assay could be a predictive marker of cognitive decline. If this association holds, it could serve as a biomarker to detect effects of a clinical trial intervention. The findings need to be replicated in an independent cohort that includes more detailed cognitive testing, and, eventually, a longitudinal study will have to be undertaken. Nonetheless, this is an encouraging finding, and this study highlights a novel technology that could well be applied in other disorders. ■

ABSTRACT & COMMENTARY

Severe Olfactory Impairment Is Associated With Preclinical Alzheimer's Disease

By Makoto Ishii, MD, PhD

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

SYNOPSIS: In this cross-sectional, population-based, cohort study of 829 cognitively normal participants, abnormal neuroimaging biomarkers known to be associated with Alzheimer's disease were associated with severe olfactory impairment.

SOURCE: Vassilaki M, Christianson TJ, Mielke MM, et al. Neuroimaging biomarkers and impaired olfaction in cognitively normal individuals. *Ann Neurol* 2017;81:871-882.

Since the pathological abnormalities that eventually lead to Alzheimer's disease (AD) begin decades prior to the cognitive decline during the preclinical stage of AD, identifying cognitively normal individuals with the highest risk for developing AD is essential for the success of AD prevention trials. Currently, biomarkers used to identify those individuals are too expensive, invasive, or not widely available. Therefore, there is a need for an inexpensive, noninvasive test to screen and identify older healthy individuals potentially at risk for AD. Recent studies have found an association between olfactory impairment and cognitive decline, including mild cognitive impairment and dementia from AD. Importantly, in cognitively normal older individuals, worse odor identification has been associated with AD markers of brain pathology, suggesting that olfactory impairment could be a symptom of preclinical AD. In this study, the investigators tested the hypothesis that in vivo neuroimaging biomarkers of AD pathology are associated with olfactory impairment among cognitively normal older individuals.

Participants of this cross-sectional study were from the Mayo Clinic Study of Aging, an ongoing population-based study initiated on Oct. 1, 2004. Between 2004 and 2010, 829 cognitively normal participants were recruited and completed an in-person evaluation and the Brief Smell Identification Test (B-SIT) for assessment of olfactory impairment, and underwent magnetic resonance imaging (MRI) to evaluate AD signature cortical thickness (i.e., averaging cortical thickness for entorhinal, inferior temporal, middle temporal, and fusiform cortices) and hippocampal volumes. Of these participants, 306 had ^{11}C-Pittsburgh compound B (^{11}C-PiB) positron emission tomography (PET) scans for evaluation of brain amyloid load, and 305 had ^{18}fluorodeoxyglucose (^{18}F-FDG) PET scans for evaluation of brain glucose metabolism.

Of the 829 participants (mean age = 79.2 years, 51.5% men), anosmia was identified in 78 (9.4%) participants, hyposmia was identified in 503 (60.7%) participants, and the rest (248, 29.9%) had normal olfactory sensation (normosmia). Abnormal cortical thickness was found in 249 (30%) participants and abnormal hippocampal volume in 128 (15.5%) participants. For those participants who underwent PET scans, 119 (38.9%) participants had abnormal ^{11}C-PiB PET scans, and 90

(29.5%) participants had abnormal ^{18}F-FDG PET scans. In addition, 51 (16.9%) participants were positive for both amyloid-beta and neurodegeneration biomarkers. Abnormalities in brain amyloid accumulation, cortical thickness, and hippocampal volumes increased in frequency among those participants with olfactory impairment compared to those without olfactory impairment.

After adjusting for age, sex, and education, individuals with abnormal ^{11}C-PiB PET scans, abnormal cortical thickness, and abnormal hippocampal volumes had significantly increased odds of having anosmia compared to normosmia (odds ratio [OR] = 2.74, 95% confidence interval [CI] = 1.12-6.66; OR = 2.20, 95% CI = 1.25-3.86; OR = 2.45, 95% CI = 1.21-4.94, respectively). None of the biomarkers were associated significantly with hyposmia. Abnormal cortical thickness and abnormal hippocampal volumes were significantly associated with lower B-SIT score (slope = -0.43, 95% CI = -0.76 to -0.09, P = 0.01; slope = 0.72, 95% CI = -1.15 to -0.28, P < 0.01, respectively). When participants were separated between those who had abnormal ^{11}C-PiB or amyloid abnormalities and those who did not, abnormal hippocampal volume was associated with B-SIT score only in those with abnormal ^{11}C-PiB PET scans. Furthermore, having both amyloid and neurodegeneration abnormalities was associated with a 3.84-fold increased odds of having anosmia (OR, 3.84; 95% CI, 1.14-12.97; P = 0.03) and significantly lower B-SIT score (slope, -0.99; 95% CI, -1.71 to -0.27) compared to those negative for both markers.

Finally, MRI and ^{18}F-FDG PET ROI measurements representing areas of primary olfactory cortex and secondary olfactory regions were significantly associated with B-SIT score. There were no statistically significant associations between any of the ^{11}C-PiB PET ROIs and B-SIT score.

■ COMMENTARY

These study results are intriguing and add to our expanding knowledge of the non-cognitive manifestations of AD, particularly in the preclinical stage. Although this study has significant strengths, including a relatively large sample size obtained from a well-characterized study population and the use of well-established multimodal neuroimaging markers of AD, there are notable limitations to this study, including a lack of ethnic and racial diversity in the study population and the cross-sectional study design, which precludes the ability to assess causality. If the results from this study can be verified in other populations and, importantly, in longitudinal studies, olfactory function could be used potentially as a noninvasive and inexpensive screen to identify those individuals at risk for AD. Because of the high number of older individuals with olfactory impairment, it is unlikely that screening olfactory function alone would be sufficient to identify accurately all those at risk. However, combining an initial inexpensive and noninvasive screen (e.g., olfactory function) followed by selectively screening with more sensitive and specific AD biomarkers (e.g., neuroimaging) potentially could increase the ability to identify individuals who have the highest risk of developing AD. ■

ABSTRACT & COMMENTARY

Direct DNA Sequencing of Dominant Cerebellar Ataxias

By M. Elizabeth Ross, MD, PhD

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

SYNOPSIS: Current genetic testing techniques with DNA sequencing can diagnose the molecular-genetic causes for the majority of dominantly inherited cerebellar ataxias.

SOURCE: Coutelier M, Coarelli G, Monin ML, et al.; for the SPATAX Network. A panel study on patients with dominant cerebellar ataxia highlights the frequency of channelopathies. *Brain* 2017;140:1579-1594.

Dominant, monogenic cerebellar ataxias have been associated with mutations in at least 34 genes to date. Trinucleotide, CAG repeat expansions were among the first mutations to be found in connection with this condition and include *ATXN1*, *ATXN2*, *ATXN3*, *ATXN6 (CACNA1A)*, *ATXN7*, and *TBP*. A common diagnostic strategy is to test for repeat expansion mutations when an ataxia patient is newly encountered in clinic. However, this approach leaves some 40% of

dominant ataxia cases unresolved. Coutelier et al tested the efficiency of a panel approach of direct sequencing known ataxia-causing genes. Investigators examined 412 cases of dominantly inherited cerebellar ataxia for which CAG/polyglutamine repeat mutations had been excluded. The investigators pursued direct sequencing of the protein-coding regions of 65 known ataxia genes and candidates.

Several significant insights were obtained. Relevant genetic variants were found in 59 patients, representing 14.3% of the study cohort, or 7.2% in the entire group that included those with CAG repeat mutations. Thus, the investigation of conventional sequence mutations is productive. Interestingly, conventional mutations were found most frequently in channel genes, namely *CACNA1A*, *KCND3*, *KCNC3*, and *KCNA1*. In addition, *SPG7* and *POLG* were implicated as possible risk factors for cerebellar ataxia. Examination of clinical phenotypes revealed that channelopathies tended toward earlier age at onset (average 24.6 years at onset) and longer duration (20.5 years) in contrast to the CAG repeat mutations (average 40.9 years at onset, 9.3 years duration) and *SPG7*-associated ataxia (average 37.8 years at onset, 13.7 years duration). Especially interesting was that a particular channel, *CACNA1A*, caused cerebellar ataxia associated with either a CAG repeat or a conventional point mutation. Further genotype-phenotype analyses revealed that channelopathy mutations more often were accompanied by early intellectual deficiency (23% contrasting with 0% polyglutamine expansion or *SPG7*-related cases), while the prevalence of late-onset cognitive impairment was no different among CAG repeat, channelopathy, or *SPG7* genotypes.

■ COMMENTARY

The study is important in that it cautions the diagnostician not to be satisfied with only trinucleotide repeat expansion testing. Together with repeat testing, direct DNA sequencing could achieve a positive diagnosis in 75% of dominantly inherited cerebellar ataxia cases. It would be of further interest to compare the diagnostic success rate of whole exome sequencing (WES) compared to a direct sequencing panel of 65 genes, since WES could identify additional potential candidate mutations as more patients are tested. ■

STROKE ALERT

Treatment of Intracerebral Hemorrhage Guided by the 'Spot Sign'

By Santosh Murthy, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Although the "spot sign" is a predictor of early hematoma expansion, selective treatment of this group with aggressive antihypertensive therapy did not alter hematoma size or neurological outcome.

SOURCE: Morotti A, Brouwers HB, Romero JM, et al.; for the Antihypertensive Treatment of Acute Cerebral Hemorrhage II and Neurological Emergencies Treatment Trials Investigators. Intensive blood pressure reduction and spot sign in intracerebral hemorrhage: A secondary analysis of a randomized clinical trial. *JAMA Neurol* 2017; June 19. doi:10.1001/jamaneurol.2017.1014. [Epub ahead of print].

Hematoma expansion is a significant predictor of poor outcome in patients with intracerebral hemorrhage (ICH). Therefore, over the past decade, clinical research in ICH has focused on primary injury and hematoma expansion, particularly on early diagnosis and prevention. The "spot sign" present on computed tomographic angiography (CTA) is considered a radiological marker for hematoma expansion, with relatively high predictive accuracy. From the prevention standpoint, intensive blood pressure control has been a long-standing physiological target of interest. However, recent randomized, clinical trials have shown no clinical benefit of aggressive blood pressure reduction in the acute phase of ICH. These results imply that while the early diagnosis of impending hematoma expansion is reasonably accurate, no effective therapeutic intervention exists.

In this study, Morotti et al combined the two approaches mentioned above. They reported the results of a prospective observational study, SCORE-IT (Spot Sign Score in Restricting ICH Growth), which was nested in the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-II) randomized, clinical trial. The objective of the study was two-fold: first, to evaluate the utility of the spot sign in predicting hematoma

expansion across different centers, and second, to assess the role of intensive blood pressure reduction in the presence of a CTA-confirmed spot sign. Of the 133 patients with ICH, 53 (39.8%) had a CTA spot sign. Although the spot sign significantly predicted ICH expansion, there was no association between intensive blood pressure control and reduction of hematoma expansion in patients with the spot sign.

■ COMMENTARY

In light of the acute-phase treatment trials in ICH failing to show a clear clinical benefit, recent studies have used the CTA spot sign to aid the selection of patients who are high-risk for hematoma expansion. For instance, two parallel studies, SPOTLIGHT from Canada and STOP-IT from the United States, explored the role of hemostatic treatment with recombinant factor VII in patients with the spot sign. The pooled analysis validated the predictive ability of the spot sign, but there was no significant association between hemostatic therapy and reduction in hematoma growth or improvement in functional outcomes. A notable limitation of all studies using the CTA spot sign is low statistical power. Although the data consistently affirm the prognostic accuracy of the spot sign, larger studies targeting different physiological mechanisms, such as surgical intervention, may yield success in combating hematoma expansion and improving outcomes of this devastating disease. ■

CME QUESTIONS

1. **After cardiac arrest and resuscitation, recovery from coma may be predicted using which of the following diagnostic tests?**
   a. EEG reactivity
   b. Somatosensory-evoked potentials
   c. Neurological examination
   d. None of the above

2. **Which of the following statements is true regarding tacrolimus in myasthenia gravis (MG)?**
   a. It is contraindicated in MG.
   b. Drug levels for maximal efficacy in MG must be ≥ 1.5 ng/mL.
   c. It decreases antibody levels but does not improve clinical symptoms in MG.
   d. None of the above

3. **α-synuclein in the plasma or CSF is a potential biomarker for Parkinson's disease (PD). Which statement is correct based on studies to date?**
   a. α-synuclein is present at high concentrations in plasma, making it preferential to test in plasma rather than CSF.
   b. α-synuclein may be useful as a diagnostic biomarker of PD caused by α-synuclein gene mutations, but not in other genetic or idiopathic cases.
   c. Lower α-synuclein concentration in plasma is associated with greater cognitive decline.
   d. Higher α-synuclein concentration in plasma is associated with greater cognitive decline.

4. **In the Mayo Clinic Study of Aging that examined cognitively normal individuals, which of the following neuroimaging markers was not significantly associated with Brief Smell Identification Test score?**
   a. Abnormal cortical volumes
   b. Abnormal hippocampal volumes
   c. Abnormal ^{11C}-Pittsburgh B Compound PET ROI measurements of primary olfactory cortex
   d. Abnormal ^{18}fluorodeoxyglucose PET ROI measurements of primary olfactory cortex

5. **Dominant cerebellar ataxias may be caused by which of the following?**
   a. Trinucleotide CAG repeat expansions
   b. Channelopathies
   c. Both a and b
   d. Neither a nor b

6. **Which of the following statements regarding the CTA spot sign is correct?**
   a. The CTA spot sign is a significant predictor of hematoma expansion, although the predictive accuracy is variable across studies.
   b. Systolic blood pressure reduction to < 140 mmHg is not associated with improved outcomes even in the presence of the spot sign.
   c. The consensus definition of the spot sign is a focus of contrast extravasation in the hematoma with density >100 Hounsfield units.
   d. Both a and b

[IN FUTURE ISSUES]

Sleep Disorders