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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Measurement of Brain Vital Signs in Concussed Athletes

By Karishma Parikh, MD, and Barry Kosofsky, MD, PhD

Dr. Parikh is Fellow in Pediatric Neurology, Weill Cornell Medical College. Dr. Kosofsky is Professor of Pediatrics and Neurology, and Chief, Division of Pediatric Neurology, Weill Cornell Medical College and New York Presbyterian Hospital.

Dr. Parikh reports no financial relationships relevant to this field of study. Dr. Kosofsky reports he is the founder and president of ANSwers Neuroscience.

SYNOPSIS: These investigators prospectively studied auditory event-related potentials (ERPs) in junior competitive male ice hockey players and identified a pattern of ERPs that distinguishes acutely concussed from non-concussed players, establishing this noninvasive, easy-to-administer test as a biomarker to assist trainers, coaches, and clinicians with making the diagnosis of concussion.

SOURCE: Fickling SD, Smith AM, Pawlowski G, et al. Brain vital signs detect concussion-related neurophysiological impairments in ice hockey. *Brain* 2019;142:255-262.

Concussion from sports continues to be an ongoing growing public health concern, particularly as it relates to the cumulative effects on cognition and long-term brain health. Recently, the emphasis has focused on augmenting the clinical diagnosis of concussion based on self-report, with objective biomarkers reflective of functional brain injury. Such physiologic metrics can be followed over time and enable objective recommendations informing decisions regarding return to learn, as well as return to play.

One such potential biomarker is auditory event-related potentials (ERPs). ERPs are derived from EEGs and represent the brain's evoked neural response to auditory input as reflected by the amplitude and latency of three easily identified and well-studied waveforms, which can be collected using a portable device requiring five minutes of testing. Specifically, the N100, the P300, and the N400 waves induced by auditory stimulation are known to be reflective of auditory sensation, basic attention, and cognitive processing, respectively.

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In prior work, Ghosh Hajra et al established an analytic framework, normative values, and graphic depiction for the amplitude and latency of each of these waveforms, which they refer to as six unique "brain vital signs."

In the study by Fickling et al, 47 tier III junior-A competitive male ice hockey players were recruited over two seasons, more than half of whom had one to five prior concussions. Forty-three players participated in baseline testing. Twelve players sustained concussions following baseline testing and then completed assessments within 24 hours of injury, as well as when they passed the protocol for return to play. Twenty-three players were not diagnosed with a concussion during the season and completed both baseline and post-season testing.

The ERP for each player was generated with a task that involved a five-minute auditory stimulus sequence with interlaced tones and spoken word pair primes. The auditory tones were randomized to produced specific frequency-related ERPs, and the word primes were created to be both semantically congruent or incongruent. The results were generated on radar plots that showed group mean changes across test points and on plots that compared individual brain vital signs components test points for each participant.

There was a statistically significant difference between baseline and concussion in all six brain vital signs. This included increased amplitude and increased latency in all three waveforms when analyzed acutely in concussed athletes compared with their individual baselines, which then normalized. Of note, the amplitude of the P300 wave remained increased from its baseline at the time of return to play in concussed athletes, suggesting there were measurable physiological effects still persistent even though each athlete's symptoms had resolved.

Additionally, the authors also looked at the hockey players pre- and post-season who did not sustain a concussion to see if there were changes in their baseline (i.e., suggestive of subconcussive effects). This study showed a significant increase in the latency of the P300 wave, which is hypothesized to reflect impaired cognitive processing. This suggests that subconcussive impacts may result in cumulative effects, which, although clinically silent, may be reflective of significant changes in brain function.

■ COMMENTARY

The novelty of this study rests on the claim that this simple, rapid, and objective test can be used as a sensitive biomarker for concussion. In addition, Fickling et al proposed that this test also is sensitive to functional brain injury resulting from subconcussive brain injury. As the authors noted, the study was small and needs to be replicated in larger populations with the addition of relevant control groups.

[Although this approach appears to help clinicians discern within-group differences between baseline and acutely concussed subjects, the test is unable to identify such differences in individual subjects consistently.]

Although this approach appears to help clinicians discern within-group differences between baseline and acutely concussed subjects, as well as between pre- and post-season for non-concussed subjects, the test is unable to identify such differences in individual subjects consistently. As such, more sensitive metrics will be required to enable athletes to be diagnosed definitively with functional deficits following concussive or subconcussive blows sustained during the hockey season.

When used in combination with other non-invasive biomarkers of brain function, such as eye tracking, balance, and autonomic function, there may be an opportunity to develop an integrated suite of objective tests that will assist coaches, trainers, and physicians in making decisions regarding when athletes should be removed from play following concussion, when they are ready to return to play following concussion, and when they should cease play as a result of

cumulative subconcussive brain injury. Such tools are urgently needed to inform the return-to-play protocols now required for athletes participating in collision and helmet sports. ■

REFERENCE

1. Ghosh Hajra S, Liu CC, Song X, et al. Developing brain vital signs: Initial framework for monitoring brain function changes over time. *Front Neurosci* 2016;10:211.

ABSTRACT & COMMENTARY

Lacosamide for Painful Small Fiber Neuropathy Due to Voltage-Gated Sodium Channel Mutations

By Jennifer Langsdorf, MD

Assistant Professor of Neurology, Peripheral Neuropathy Center, Weill Cornell Medical College

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

SYNOPSIS: The results of this randomized trial showed significant neuropathic pain score reduction with the use of lacosamide in patients with Nav1.7 mutations.

SOURCE: de Greef BTA, Hoeijmakers JGJ, Geerts M, et al. Lacosamide in patients with Nav1.7 mutations-related small fibre neuropathy: A randomized controlled trial. *Brain* 2019;142:263-275.

Small fiber neuropathy can be associated with intense itching and burning pain and skin sensitivity that can affect physical functioning, sleep, and quality of life. Current medications for small fiber neuropathy pain provide some relief. However, pain control often can be difficult to obtain and may require trials of multiple different medications. New approaches to treatment of neuropathic pain are needed.

Some patients with small fiber neuropathy have been found to have mutations in voltage-gated sodium channels, particularly in SCN9A, which encodes for Nav1.7. These sodium channels are found in dorsal root ganglion neurons and peripheral sensory neurons and have an essential role in the sensation of pain through effects on neuronal excitability. Variant Nav1.7 sodium channels have been identified that can produce either gain of function or loss of function and thereby cause either pain hypersensitivity or congenital indifference to pain. Gain-of-function mutations in voltage-gated sodium channels are associated with small fiber neuropathy. Lacosamide is a modified amino acid that acts on Nav1.3, Nav1.7, and Nav1.8 voltage-gated sodium channels. It is FDA approved for treatment of partial seizures. Trials also have been done showing some effect on neuropathic pain in diabetic small fiber neuropathy. Lacosamide is thought to preferentially bind to Nav channels in the inactivated state. de Greef et al evaluated the potential effectiveness of lacosamide for treatment of neuropathic pain in patients with genetically confirmed mutations in SCN9A, which encodes for Nav1.7.

In this study, 24 subjects with Nav1.7 mutation-related small fiber neuropathy entered a randomized, placebo-controlled, crossover design study. Patients with pure small fiber neuropathy in combination with SCN9A variant were eligible. Pure small fiber neuropathy was diagnosed based on typical clinical symptoms in combination with diminished epidermal nerve fiber density in skin biopsy and/or abnormal temperature threshold testing. The primary endpoint was a one-point average pain score reduction compared to baseline. The pain scores were recorded using the Pain Intensity Numerical Rating Scale (PI-NRS). The PI-NRS is an 11-point scale ranging from zero to 10, with zero meaning no pain and 10 correlating to the worst pain possible.

The patients were randomized to start with either lacosamide or placebo. An initial titration period of three weeks was followed by an eight-week treatment period and ended with a two-week tapering period. After a washout period of at least two weeks, the same eight-week study periods took place with the different treatment during the crossover phase. The dose of lacosamide during the treatment period was 200 mg twice daily. The starting dose was 50 mg twice daily for one week, followed by an increase to 100 mg twice daily the second week and 150 mg twice daily the third week. An electrocardiogram was performed at the study onset.

Pain scores were recorded twice each day in the morning and evening at fixed time points using the PI-NRS. For each subject, a baseline mean on-treatment pain score was calculated. The primary endpoint was at least a one-point improvement (score reduction) on the average PI-NRS compared to baseline. Secondary outcomes included the proportion of patients having an average pain improvement on the PI-NRS of two

points or more, the daily sleep interference scale (DSIS), Neuropathy Pain Scale (NPS), Patient Global Impression of Change (PGIC), Small-Fiber Neuropathy Symptoms Inventory Questionnaire, and the 36-item Short Form Health Survey.

At study completion, 24 patients had received lacosamide and 23 patients received placebo. One patient dropped out during the washout period. Results showed that in 58.3% of patients receiving lacosamide, the mean average pain score on the PI-NRS decreased by at least one point compared to 21.7% in the placebo group (odds ratio, 5.65).

The PGIC reflects the patient's belief in the efficacy of treatment. The PGIC showed significant differences between the two groups. In the lacosamide group, 33.3% reported their general condition improved vs. 4.3% in the placebo group ($P = 0.0156$). Additionally, a significant decrease in daily sleep interference was demonstrated by improvements in DSIS scores on lacosamide ($P = 0.0484$). The NPS showed significant improvement with lacosamide on surface pain intensity, one item in the NPS scale ($P = 0.004$).

Generally, lacosamide was well tolerated. Two serious adverse events occurred on lacosamide: one patient reported diplopia and one patient reported vomiting. Other minor adverse events included dizziness, nausea, and headache.

■ COMMENTARY

In this study, lacosamide improved neuropathic pain in small fiber neuropathy associated with SCN9A mutations with a response rate of about 50% to 60%. This is comparable to the response rates to currently available medications for neuropathic pain. Positive effects on sleep quality and general well-being also were reported. For patients with SCN9A voltage-gated sodium channel mutations, lacosamide may be a useful treatment option for neuropathic pain. Its use in other small-fiber neuropathies remains to be investigated. ■

ABSTRACT & COMMENTARY

Cholecystokinin as a Biomarker Linking Metabolic Function to Alzheimer's Disease

By Makoto Ishii, MD, PhD

Assistant Professor of Neuroscience and Neurology, Feil Family Brain and Mind Research Institute, Department of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In a study cohort from the Alzheimer's Disease Neuroimaging Initiative, cerebrospinal fluid levels of cholecystokinin were associated with better outcomes that may reflect compensatory protection as Alzheimer's disease pathology progresses. However, because of significant study limitations, these findings need to be validated in additional studies.

SOURCE: Plagman A, Hoscheidt S, McLimans KE, et al. Cholecystokinin and Alzheimer's disease: A biomarker of metabolic function, neural integrity, and cognitive performance. *Neurobiol Aging* 2019;76:201-207.

Weight loss is a common clinical manifestation of Alzheimer's disease (AD), but the underlying mechanisms have not been entirely elucidated. Cholecystokinin (CCK) is a gut hormone that can suppress appetite. CCK also is an abundant neuropeptide with putative roles in regulating hippocampal and memory function. Thus, CCK is well positioned to be involved in AD pathogenesis; however, little is known about the role of CCK in AD. Therefore, Plagman et al set out to determine whether cerebrospinal fluid (CSF) levels of CCK were associated with the onset and severity of AD and if CSF CCK levels were related to changes in cognition, neuroimaging, and AD biomarkers such as amyloid-beta and tau.

This study was a retrospective analysis of cross-sectional data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Baseline CSF data were available from 287 subjects: 86 cognitively normal, 135 with mild cognitive impairment (MCI), and 66 with AD. MCI and AD were classified based on clinical criteria. The levels of various proteins were measured in the CSF by a proteomics approach using Multiple Reaction Monitoring Mass Spectrometry, which targeted quantitation of 567 peptides representing 221 proteins in a single run. For this study, the CSF proteomics panel referring to the peptide AHLGALLAR was chosen to represent CCK levels.

In the study population, there was no significant difference among the three groups in years of education, APOE E4 carrier percentage, or age. As expected, cognitive function was significantly worse for the MCI and AD groups compared to the cognitively normal group. CSF CCK levels were significantly lower in the AD group compared to the MCI or cognitively normal groups, but there was substantial overlap among all

groups. A logistic regression analysis found that higher CSF CCK expression levels predicted a decreased likelihood of MCI or AD with a per ng/mL increase in CSF CCK corresponding to roughly 65% less likelihood of being diagnosed with AD compared to cognitively normal or MCI. However, there was no relation between CSF CCK levels and increased risk when comparing cognitively normal vs. MCI, cognitively normal vs. AD, or MCI vs. AD individually. Among the MCI subjects, a per ng/mL increase in CCK was related to a 61.7% less likelihood of progressing to AD.

Regarding AD CSF biomarkers, CSF CCK levels were not associated with CSF amyloid-beta42 levels, but higher CSF CCK levels were associated with higher CSF total tau ($\beta \pm SE = 37.857 \pm 4.799$; $F = 62.237$; $P < 0.001$) and CSF p-tau-181 levels ($\beta \pm SE = 10.046 \pm 1.630$; $F = 37.992$; $P < 0.001$). Higher CSF CCK levels were also related to better global cognition score, memory function factor scores, and executive function factor scores. Furthermore, CSF tau and p-tau-181 mediated associations with CSF CCK for several of these cognitive scores. Finally, using a voxelwise analysis of T1-weighted MRI data, higher CSF CCK was significantly associated with greater grey matter volume in several large clusters, including the cingulate cortex and parahippocampal gyrus. However, there was no significant association between CSF CCK levels and FDG-PET glucose uptake.

■ COMMENTARY

Based on these findings, the authors proposed CSF CCK as a biomarker that is associated with metabolic function, neural integrity, and cognitive performance in AD. However, there are significant limitations that need to be addressed. First, the methods used to measure CCK levels needs to be rigorously validated. Plagman et al relied on the measurement of a small peptide fragment by mass spectrometry and assumed this is equivalent to measuring the full-length CCK protein. Based on the data provided, there is no way to distinguish if degraded protein fragments or biologically active full-length proteins are measured. Even if the measurement of CCK in the CSF was accurate, it is not known if CSF levels reflect physiological levels of CCK in the brain parenchyma. Second, this study provides no direct evidence to support the role of CCK in regulating metabolic function in AD. If CSF CCK reflected CCK's role as a satiety hormone, there should be a significant association of CSF levels of CCK with body weight, eating behavior, or other measures of metabolic function. Third, the study presents intriguing data that higher CSF levels of CCK are associated with better outcomes, suggesting a protective effect for CCK. However, there is a discrepancy between this possible protective role of CCK and the association of higher CSF CCK levels with higher CSF tau and p-tau181 levels, which may reflect an association between higher CSF CCK levels and increasing neuronal injury. The authors postulated that as AD progresses, CCK actually is increased to protect the brain from any further injury, which is mitigated by progressive neurodegeneration. Although this is plausible, additional evidence is needed to support this claim, such as by conducting longitudinal studies measuring CCK levels as AD progresses or mechanistic studies in model systems. Regardless of the exact role of CCK in AD, this study does provide evidence to support the use of CSF CCK as a potential biomarker of cognitive impairment and volumetric loss. However, because of the significant limitations and concerns from this study, additional well-designed studies are clearly needed to validate these findings. ■

ABSTRACT & COMMENTARY

Witness Observations in Diagnosing Transient Loss of Consciousness

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: These investigators found that adding witness-reported observations to patient demographics and patient-reported symptoms improved the diagnostic accuracy between epilepsy, syncope, and psychogenic nonepileptic seizures.

SOURCE: Chen M, Jamnadas-Khoda J, Broadhurst M, et al. Value of witness observations in the differential diagnosis of transient loss of consciousness. *Neurology* 2019;92:e895-e904.

The differential diagnosis of transient loss of consciousness (TLOC) includes epilepsy, syncope, and psychogenic nonepileptic seizures (PNES). The gold standard for confirming the diagnosis is the simultaneous recording of clinical events and physiological measures. In practice, this standard is rarely reached, and the diagnosis is made based on the patient's history and witnessed descriptions. Misdiagnosis rates of 25%

have been reported. Chen et al performed a retrospective study evaluating the contribution of additional witness observations in determining the etiology of transient loss of consciousness. Previously, the authors demonstrated that self-reportable associated symptoms collected using the Paroxysmal Event Profile (PEP), an 86-item symptom questionnaire, made an important diagnostic contribution in distinguishing between epilepsy, syncope, and PNES in laboratory-proven cases. When PEP data were added to basic patient information, 66% of patients with epilepsy, 91% with syncope, and 78% with PNES were classified correctly. The authors investigated to what extent a 31-item profile (Paroxysmal Event Observer [PEO]) of observer-reportable event manifestations improved the diagnostic differential.

The authors reviewed 249 patients from a total sample of 300 patients from three British medical centers who had completed both the PEP and PEO questionnaires (86 with epilepsy, 84 with syncope, and 79 with PNES). All diagnoses were confirmed by recordings of typical events with video electroencephalogram (EEG), ambulatory EEG, or tilt-table. Of 31 items collected, 24 differed significantly between the three groups. These factors were combined into four broader categories: unconsciousness, reduced self-control, excessive movement, and skin/face/recovery.

Observer-reported factors differentiated syncope and epilepsy better than patient-reported factors (accuracy: 96% vs. 85%; C-index $P = 0.0004$). When the analysis of the patient information was combined with that from observers, this distinction rose to from 90% to 100% (C-index $P = 0.005$). In the differentiation of PNES and epilepsy, additional observer-reported factors improved the predictive accuracy from 76% to 83% (C-index $P = 0.006$) and from 93% to 95% (C-index $P = 0.098$) in PNES and syncope. When analyzed in isolation, more patients were classified correctly by the observer-derived data than by the patient-provided symptoms.

In this study, witness questionnaire responses correctly classified patients with a sensitivity of 84.4% and a specificity of 84.2%. The answers to the PEO factor "reduced self-control" distinguished most clearly among the three diagnostic groups, with low levels of TLOC-associated self-control more frequently observed in epilepsy than in syncope or PNES. Other distinguishing factors included that, unlike syncope and PNES, epileptic seizures "never" looked like normal sleep, and pale skin and limp collapse were more commonly seen in syncope than in epilepsy. PNES observers more commonly replied that they could "never" do something to make the attack pass more quickly. This study provides confirmatory data that witness-provided information contributes to the correct differentiation between epilepsy, syncope, and PNES. The witness-provided data were most useful in correctly distinguishing epilepsy from syncope or PNES. The differentiation of syncope from PNES was highly accurate without the addition of observation data. The poorest differentiation was between epilepsy and PNES. Although observer-provided data improved diagnostic accuracy, additional data, such as video EEG monitoring, likely will be required to optimize this differential.

■ COMMENTARY

This study provides support for the importance of witness observations in distinguishing common causes of transient loss of consciousness. By adding witness-reported observations to patient demographics and patient-reported symptoms, the diagnostic accuracy between epilepsy, syncope, and PNES is improved. Although differentiating between epilepsy and PNES still may require additional data, such as a spell captured on video EEG, observer-reported data can improve the diagnostic accuracy of syncope and epilepsy significantly. Structured witness interviews that include observations of reduced self-control, sleep-like appearance, skin pallor, and/or limp limbs provide the most important distinguishing factors. ■

ABSTRACT & COMMENTARY

Vasculitic Neuropathy: Improving Diagnostic Accuracy

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: Vasculitic neuropathy is characterized by stepwise progression of sensorimotor neuropathy, usually with axonal features on electrodiagnostic studies, and often the presence of antimyeloperoxidase and rheumatoid factor antibodies and cryoglobulins. However, peripheral nerve biopsy is necessary for a definitive diagnosis.

SOURCE: Nathani D, Barnett MH, Spies J, et al. Vasculitic neuropathy: Comparison of clinical predictors with histopathological outcome. *Muscle Nerve* 2019; Jan 31. doi: 10.1002/mus.26431. [Epub ahead of print].

Vasculitis may affect any organ or tissue. However, when it affects the vasa nervorum, vasculitic neuropathy is the result, often as one component of a systemic vasculitis typically affecting skin, lungs, and kidneys. Most commonly, systemic vasculitis involving either small- or medium-sized arteries is implicated in vasculitic neuropathy. In 10% to 30%, the peripheral nervous system is the sole organ involved, which is termed nonsystemic vasculitic neuropathy or isolated peripheral nervous system vasculitis. The mode of presentation in either scenario is variable, making diagnosis challenging. What features might improve diagnostic accuracy, perhaps precluding the need for nerve biopsy and its attendant complications?

Nathani et al performed a retrospective analysis of clinical, serologic, electrophysiologic, and biopsy data for all patients referred for nerve biopsy over a 21-month period at the Brain and Mind Centre, University of Sydney, and Royal Prince Alfred Hospital, Sydney, Australia. Stepwise progression was defined by a history of acute, multifocal attacks separated by time. Symptoms were categorized as acute (less than one month), subacute (one to three months), or chronic (more than three months). C-reactive protein (CRP) and antinuclear antibody (ANA) titer were defined as clinically relevant when values were > 10 mg/L and 1:160 or above, respectively. When a premorbid erythrocyte sedimentation rate (ESR) was available for comparison, an increase of at least 25% was considered clinically relevant. Otherwise, an ESR greater than age/2 for males or (age plus 10)/2 for females was considered significant. Based on electrodiagnostic studies, neuropathy was determined to be primarily axonal, primarily demyelinating, or mixed. Nerve biopsy, including teased fiber analysis, was reported as normal, axonal, demyelinating, or mixed. A statistical analysis encompassed the t-test and either the $\chi 2$ or Fisher's exact test, using SPSS Statistics for Windows Version 24.0.

Among 202 patients referred for nerve biopsy, 78 (38.6%) were suspected to have vasculitis and served as the study group. Biopsy of the sural nerve was performed in 75 (96.2%), with the superficial radial or superficial peroneal nerve in the remainder, and muscle biopsy was concomitantly done in 17 (21.8%), usually the vastus lateralis (55.6%). Based on histopathology, vasculitis was diagnosed as definite in eight (10.3%), probable in 15 (19.2%), possible in nine (11.5%), and absent in 46 (59%).

Patients with confirmed vasculitis reported stepwise progression of sensorimotor symptoms and signs more frequently, with 18.2% of those with purely sensory symptoms and signs and 14.2% of those with purely motor symptoms and signs showing vasculitis. Among those with purely sensory symptoms and signs, 50% had motor involvement on nerve conduction studies, and among those with purely motor symptoms and signs, all had sensory abnormalities on nerve conduction studies. Pure axonal neuropathy was seen in 76.2% of confirmed vasculitis cases, asymmetric was seen in 66.7%, and demyelination seen in 10.8% of the study group, 87.5% of whom had pathologically unlikely vasculitis. Arm-dominant symptoms were seen in only three patients, and neither pain nor length-dependent symptoms distinguished the presence of vasculitis. Among patients presenting with a chronic, symmetric neuropathy, only 14.8% had biopsy-confirmed vasculitis. Vasculitis was confirmed in 85.7% of myeloperoxidase (MPO)-positive patients, 72.7% of rheumatoid factor (RF)-positive patients, and 80% of cryoglobulin-positive patients. Neither positive ANA titer, raised inflammatory markers, the presence of a paraprotein, cerebrospinal fluid findings, nor pattern of electrodiagnostic abnormalities correlated with biopsy-proven vasculitis. Stepwise progression, anti-MPO antibody and RF seropositivity, and the presence of cryoglobulins best differentiated pathologically confirmed vasculitis. Vasculitis is unlikely in patients with arm-predominant symptoms, clinically and electrodiagnostically pure motor presentations, and electrodiagnostic studies with normal findings or demyelinating features.

■ COMMENTARY

Immunosuppression of any identifiable systemic vasculitis or connective tissue disease associated with vasculitic neuropathy remains the mainstay of therapy. Medications include glucocorticoids for mild vasculitic neuropathy, without, or combined with, cyclophosphamide. Rituximab may be substituted for cyclophosphamide, and, in antineutrophil cytoplasmic antibody-associated

vasculitis, mycophenolate mofetil appears noninferior to cyclophosphamide to induce remission, although with a higher relapse rate. No satisfactory controlled trials for the treatment of nonsystemic vasculitic neuropathy are available and, hence, treatment must be based on experience.[1] ■

REFERENCE

1. Jones RB, Hiemstra TF, Ballarin J, et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: A randomised, non-inferiority trial. *Ann Rheum Dis* 2019;78:399-405.

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CME QUESTIONS

1. **The measurement of auditory event-related potentials in athletes after suspected concussion may reveal which of the following abnormalities?**
   a. Abnormal eye movements
   b. Abnormal limb movements
   c. Abnormal evoked potentials
   d. Abnormal memory testing

2. **What was the result in patients who took lacosamide at a dose of 200 mg twice daily for treatment of painful small-fiber neuropathy?**
   a. No significant benefit
   b. Intolerable due to unacceptable side effects
   c. Interrupted and poor sleep
   d. Reduced pain in most of the treated patients

3. **Based on the recent study examining the cerebrospinal fluid (CSF) levels of cholecystokinin (CCK) in the Alzheimer's Disease Neuroimaging Initiative cohort, which of the following association was found with higher CSF levels of CCK?**
   a. Higher CSF levels of CCK are associated with higher CSF levels of amyloid-beta42
   b. Higher CSF levels of CCK are associated with higher CSF levels of tau
   c. Higher CSF levels of CCK are associated with worse cognitive outcomes
   d. Higher CSF levels of CCK are associated with decreased grey matter volumes

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]

Update on Headaches