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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Serum and CSF Biomarkers of Brain Injury After Sports-related Concussion

By Nitin K. Sethi, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Sethi reports no financial disclosures relevant to this field of study.

SYNOPSIS: The search for serum and CSF biomarkers for mild traumatic brain injury is an active field of investigation, but so far, none of the currently measured biomarkers has sufficient sensitivity or specificity to be clinically useful.

SOURCE: Papa L, et al. Systematic review of clinical studies examining biomarkers of brain injury in athletes after sports-related concussion. *J Neurotrauma* 2015;32:661-673.

Concussion (mild traumatic brain injury) is a clinical syndrome characterized by immediate and transient alteration in brain function, including alteration of mental status and level of consciousness, resulting from mechanical force or trauma. Concussion is a common injury in athletes, especially those involved in contact sports, such as boxing, American football, and mixed martial arts. There is growing concern that repetitive concussive and subconcussive brain trauma leads to chronic traumatic encephalopathy (CTE), and the search for biofluid and neuroimaging biomarkers of concussion has accelerated. An ideal biomarker would help to accurately diagnose a concussion in a timely fashion and provide useful prognostic information.

The authors of this study performed a systematic review of clinical studies from 1966 to 2013 that examined a variety of biofluid biomarkers of concussion — S100ß, glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE), tau, neurofilament light protein (NFL), amyloid beta, brain-derived neurotrophic factor, creatine kinase (CK) and heart-type fatty acid binding protein, prolactin, cortisol, and albumin — in different sports, such as boxing, soccer, running, hockey, basketball, cycling, and swimming. They found that some had potential to provide useful diagnostic, prognostic, and monitoring information. Thirteen

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prospective clinical studies examining biofluid biomarkers of concussion in athletes across different sports were identified, all published since the year 2000. Three studies evaluated biomarkers in cerebrospinal fluid (CSF), one in both serum and CSF, and 10 exclusively in serum. Eleven distinct biomarkers were measured in 13 studies with S100ß most frequently assessed. Some studies assessed biomarkers both before and after play or exercise.

Overall, the results were mixed. In one study, S100ß levels rose after running, but no significant differences were found in the levels between jogging, running a 25 km race, and boxing. Another study found elevation in S100ß level after swimming, independent of any head trauma. Yet another study found elevation and correlation in serum S100ß and CK levels after a marathon race. Tau protein level in plasma was found to be increased after a bout of Olympic boxing and decreased after a rest period. CSF tau levels were also found to be elevated in boxers, but no correlation was found between plasma and CSF tau. NSE levels were found to show a prolonged decay, and elevation of CSF levels of NFL, GFAP, T-tau, and S100ß were documented in boxers, including those who had not suffered a concussion. In professional ice hockey players, tau and S100ß levels peaked within the first hour after concussion compared with preseason, while NSE levels remained unchanged. T-tau levels remained elevated in players with post-concussion syndrome (PCS) lasting more than 6 days, as compared to those with PCS of shorter duration. Measurement of GFAP also yielded conflicting results.

■ COMMENTARY

Physicians who evaluate and treat athletes, especially those involved in contact sports, are faced with a number of diagnostic and prognostic questions. Did the athlete with no reported loss of consciousness suffer a concussion? Was the reported event severe enough to warrant removal from play? How long should the athlete be rested, and when can he or she be cleared to return back to play safely? An ideal concussion biomarker, whether biofluid or imaging, should be able to answer the above questions in a timely fashion and also be reliable and reproducible. Various biomarkers have been studied in serum and CSF with studies yielding mixed and, at times, inconsistent results. At present, biofluid biomarkers of concussion lack sensitivity and specificity. Future studies should be designed to assess the level of these biomarkers at different points of time, both before and after athletic contact, and correlated with well-defined clinical measures. New candidate biomarkers planned for future studies include copeptin, galectin 3, matrix metalloproteinase 9, and occludin.[1,2,3] ■

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ABSTRACT & COMMENTARY

Cerebrospinal Fluid Biomarkers of Neuronal Injury in Mild AD

By Alon Seifan, MD, MS

Assistant Professor of Neurology, Memory Disorders Program, Weill Cornell Medical College

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

SYNOPSIS: Cerebrospinal fluid (CSF) visinin-like protein 1 is a useful marker, along with CSF tau and phospho-tau measurements, to predict brain atrophy and neurodegeneration in patients who carry a clinical diagnosis of Alzheimer's disease.

SOURCE: Tarawneh R, et al. Cerebrospinal fluid markers of neurodegeneration and rates of brain atrophy in early Alzheimer's disease. *JAMA Neurology* 2015;72:656-665. doi:10.1001/jamaneurol.2015.0202.

Currently accepted frameworks for biomarker progression in preclinical Alzheimer's disease (AD) postulate that markers of amyloidosis are the first to become abnormal, followed by markers of neuronal injury, and ultimately measures of impaired cognition, function, and quality of life. In fact, biomarkers of amyloidosis and neuronal injury can stage individuals along the continuum from healthy (Stage 0) to asymptomatic amyloidosis (Stage 1) to neurodegeneration (Stage 2 and 3), even prior to overt clinical symptoms.[1] At present, biomarkers available to detect neuronal injury include cerebrospinal fluid (CSF) tau and phosphorylated tau, as well as hypometabolism or atrophy on functional or structural neuroimaging. However, a significant percentage of persons can show evidence of neuronal injury prior to amyloidosis. In these individuals (up to 25% in some cohorts), cognitive impairment may be explained by pathologies unrelated to AD (such as other tauopathies), or by the possibility that some individuals (perhaps related to genetics) manifest a different sequence of biomarker abnormalities in preclinical AD.[2] Complicating matters further, the underlying pathologies causing dementia are often mixed in older individuals and often heterogeneous in individuals at risk for atypical neurodegenerative diseases such as primary progressive aphasia. In the context of such uncertainty, the identification of biomarkers of neuronal injury specific to AD is particularly important. To this end, Tarawneh et al recently investigated the usefulness of CSF visinin-like protein I (VILIP-1), as compared to traditional markers of neuronal injury (tau and phosphorylated-tau), in predicting rates of whole brain and hippocampal atrophy in individuals prior to moderate stages of dementia due to AD. VILIP-1 is a neuronal calcium sensor protein that becomes elevated in CSF in the presence of neuronal injury due to AD. This biomarker may be particularly useful because it may reflect AD-specific neuropathology. The investigators compared CSF and neuroimaging data of healthy, community-dwelling volunteers (n = 64) and individuals with mild AD (n = 20) who were being longitudinally followed at the Charles F. and Joanne Knight Alzheimer's Disease Research Center at Washington University School of Medicine in St Louis. At each assessment over a mean duration of follow-up of 2.7 years, diagnoses were made using standard criteria, and dementia severity was rated using the Clinical Dementia Rating scale. CSF samples were analyzed from all participants.

At baseline, biomarker differences were present between the AD and control groups that were consistent with the known pathophysiological changes in AD. Specifically, the AD group included a higher proportion of amyloid-positive individuals and also higher baseline levels of CSF tau, lower Aß42 levels, and more global and regional atrophy in areas associated with AD. Longitudinally, rates of atrophy were different, as to be expected. In the AD group, rates of atrophy were 0.9% per year for whole brain and 4.3% per year for entorhinal cortex and hippocampus, compared to 0.4% and 1.3% per year in the control group. The AD group had higher levels of VILIP-1 at baseline. Baseline VILIP-1, tau, or phosphorylated-tau levels in the highest tertile (but not amyloid levels) predicted greater whole brain and regional atrophy, after adjusting for age, sex, imaging system type, and APOE epsilon 4 genotype. The findings suggest that CSF tau and VILIP-1 levels are closely associated with disease intensity and with rates of subsequent brain atrophy in early symptomatic AD.

[The findings suggest that CSF tau and VILIP-1 levels are closely associated with disease intensity and subsequent brain atrophy in early symptomatic AD.]

■ COMMENTARY

Important limitations of this study include small sample size and short duration of follow-up. An important strength of the study includes the fact that the center has a 92% postmortem confirmation rate of AD clinical diagnoses made in individuals who are followed longitudinally. Despite the limitations, the study by Tarawneh et al suggests that VILIP-1 could represent a useful measure to predict hippocampal or whole brain atrophy, at least in the short-term in individuals at risk for AD.

Identification of biomarkers specific to underlying pathology in the prodromal stages of neurodegenerative disease is especially important, not only for a better understanding of AD pathophysiology, but also for promoting more accurate characterization of individuals for AD prevention trials and better measurement of treatment response during neurodegenerative stages of disease due to AD. Future studies are required to determine whether VILIP-1 can provide additional value over existing, less-invasively obtained biomarkers, and, specifically, whether it can distinguish impending AD-related neurodegeneration from neurodegeneration due to other dementias, including synucleinopathies, other tauopathies, and vascular causes of cognitive decline. ■

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ABSTRACT & COMMENTARY

Prevalence of Rest Tremor in Essential Tremor

By Alexander Shtilbans, MD, PhD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Rest tremor is seen in patients with more advanced essential tremor, yet its prevalence varies significantly between patient groups.

SOURCE: Louis ED, et al. Prevalence and correlates of rest tremor in essential tremor: Cross-sectional survey of 831 patients across four distinct cohorts. *Europ J Neurol* 2015, 22:927-932.

Essential tremor (ET) is a common neurological disorder affecting approximately 4% of people age 40 years and older. It manifests as kinetic and postural tremor, but occasionally resting tremor is seen as well, contributing to diagnostic confusion with Parkinson's disease (PD). Few studies have looked at the prevalence of rest tremor in patients with ET, and the authors of this study aimed to estimate the prevalence of rest tremor in patients with ET and to assess the clinical correlations of that tremor. They used four different patient groups: a population-based study in northern Manhattan, a genetics study of movement disorders, a study of the environmental epidemiology of essential tremor, and a brain repository group of patients who were examined and signed consent for postmortem evaluation of their brains. The authors hypothesized that the prevalence of rest tremor could be related to the severity of the disease (ET). In total, 831 patients were analyzed from all four patient groups. Experienced movement disorder neurologists performed examinations, which included assessments of postural and kinetic tremors in the arms, as well as head, voice, and jaw tremors. Rest tremor was evaluated in seated and standing positions and while walking.

The results showed that the severity of arm tremor, duration of tremor, and the prevalence of head tremor were lowest in the population-based study and highest in the brain repository group. Rest tremor occurred in 1.9% of the population-based study, 9.6% of the family study group, 14.7% of the study of the environmental epidemiology of essential tremor, and 46.4% of patients in the brain repository group. No patient had tremor in the legs or feet. The patients with rest tremor were found to be significantly older than those without and they had their tremor for a longer period of time. Interestingly, patients with rest tremor also were more likely to have voice or head tremor. Rest tremor appeared to be asymmetric in approximately half of the patients who had it, and in those patients, action and postural tremor also were more pronounced in the same arm. The authors concluded that the prevalence of the rest tremor in ET patients varied greatly among the examined groups, ranging from 1.9% in the population-based setting to 50% in a brain repository group.

■ COMMENTARY

The authors of this study evaluated the prevalence of resting tremor in patients with essential tremor in four different patient groups and attempted to find clinical correlates of that tremor. The study was well-designed and the patients had similar demographic characteristics, except for the ET brain repository group, in which the patients were considerably older. It was astutely observed that the rest tremor was only noted in the arms, not the legs, which was a fundamental difference from what we see in PD, where leg tremor at rest can be common. The other observation was that the rest tremor emerged as the ET progressed later in life, and is consistent with what is usually seen in movement disorder clinics. The mechanisms underlying the resting tremor in ET remains unclear, but the authors suggest cerebellar pathology as the potential cause based on the animal models with cerebellar lesions.

The results of this study were logically interpreted, but the certainty of the diagnosis is based on the clinical examination. It is well-known that patients with ET are at five-fold increased risk for developing PD later in life. In fact, it is quite common to see people with both conditions. The authors stated that none of the patients with ET had any parkinsonian features except for the rest tremor. It is possible, however, that some of the patients with longstanding ET developed Lewy body pathology in the brain, which did not yet result in any rigidity, bradykinesia, or reduced rapid alternating movements, suggestive of PD. DaT scans were not performed in this study to rule out dopamine deficiency, so we cannot exclude some patients with very early-stage PD who developed parkinsonian tremor superimposed on the existing action and postural tremor, except for some deceased patients from the brain repository group whose brains were examined pathologically. More prospective studies would be needed to follow the progression of rest tremor and find anatomical correlations that can help understand the pathophysiology of the disease and lead to more effective treatment. ■

ABSTRACT & COMMENTARY

Diagnosing POLG-related Diseases

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: Mutations of the polymerase-gamma (POLG) subunit in mitochondrial DNA is a common cause of adult mitochondrial syndromes, such as myopathies, encephalopathies, epilepsy, and ataxias.

SOURCE: Tchikviladzé M, et al. A diagnostic flow chart for POLG-related diseases based on signs, sensitivity and specificity. *J Neurol Neurosurg Psychiatry* 2015;86:646-654.

Mutation of polymerase motif B, the catalytic subunit of the mitochondrial DNA (mtDNA) polymerase γ (POLG), which maps to 15q25, was first associated with progressive external ophthalmoplegia with multiple mtDNA deletions in 2001. Since then, many diverse syndromes have been associated with these mutations, responsible for up to 25% of adult mitochondrial disease, including mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS); mitochondrial recessive ataxia syndrome; myoclonus, epilepsy, myopathy, sensory ataxia; and sensory ataxic neuropathy with dysarthria and ophthalmoplegia. What is the sensitivity and specificity of signs that would be indicative of POLG-related diseases?

Among 311 patients who underwent sequencing of the POLG gene in the Department of Metabolic Biochemistry of La Salpêtrière Hospital, Paris, between 2003-2012, follow-up data were available on 154 patients, representing diverse neurological conditions for "plausible" POLG mutations. Of these, 122 were followed at the National Reference Center for Neuromuscular and/or Rare Neurogenetic Diseases at La Salpêtrière Hospital, and 32 in various neurology departments of other Paris hospitals. Data collected included clinical information, brain magnetic resonance imaging (MRI), nerve conduction studies, electromyography, and muscle histochemistry and enzymatic assays, including respiratory chain assays, and search for multiple deletions. Statistical analysis encompassed the Fisher exact or $\chi 2$ test with the Yates correction, and the Mann–Whitney analysis of variance.

Among the 154 patients, 34 demonstrated deleterious mutations on both POLG alleles, and 10 demonstrated deleterious mutations on only one POLG allele, of which only two recognized dominant mutations were known to be pathogenic, and thus this group was omitted from comparison. One hundred ten patients had a normal POLG sequence. All groups had similar gender, age of onset, and disease duration. Comparing those with mutations on both alleles to those with normal alleles, peripheral neuropathy, ptosis, ophthalmoplegia, dysphagia, axial or limb muscle weakness, or both, psychiatric symptoms were significantly more frequent in the former. Sensory neuronopathy associated with either ophthalmoplegia, dysphagia, and axial or limb weakness was the only highly specific and sensitive association for POLG mutation. No patient had a demyelinating neuropathy, although all patients with mutations on both alleles had abnormal nerve conduction studies, compared to 55% without mutations. Solitary findings, such as weakness, cerebellar or movement disorders, or sensory neuropathy, were sensitive but not specific, unless associated with seizures, psychiatric issues, or cognitive impairment. Neither brain MRI nor mitochondrial studies, including muscle histology, lactate measurement, respiratory chain complex activity, or multiple mtDNA deletions in muscle, allowed for specific diagnosis.

[Mutations of the polymerase-gamma (POLG) subunit in mitochondrial DNA is a common cause of adult mitochondrial syndromes.]

■ COMMENTARY

With an estimated prevalence of more than 1 in 5000, mitochondrial diseases result from more than 200 different mtDNA mutations and 100 nuclear mutations, the most frequent gene affected being POLG, with more than 80 mutations described. Leber hereditary optic neuropathy is the most common mitochondrial disease due to mtDNA mutations, followed by MELAS. Resting serum lactate and pyruvate, frequently increased, are the most important laboratory measurements, with creatine kinase often normal or mildly elevated, and electromyography studies spanning the spectrum from normal to neurogenic, myopathic, or nonspecific. Ragged red fibers, usually without cytochrome C oxidase (COX) activity, are always found on muscle biopsy. ■

ABSTRACT & COMMENTARY

Can Dietary Intervention Delay the Onset of Alzheimer's Disease?

By Richard S. Isaacson, MD

Associate Professor of Neurology (Education), Weill Cornell Medical College

Dr. Isaacson reports he is a consultant for Accera.

SYNOPSIS: In a prospective study of an elderly population, moderate adherence to the MIND diet was associated with a 53% reduction in the development of Alzheimer's disease.

SOURCE: Morris MC, et al. MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement* 2015; Feb 11. Online at http://dx.doi.org/10.1016/j.jalz.2014.11.009. [Epub ahead of print].

There has been an explosion of recent evidence supporting the potential effect of nutrition on the development of cognitive decline and Alzheimer's disease (AD). Many recent studies have looked into the effect of nutrition on a variety of conditions, such as mild cognitive impairment due to AD and AD dementia, age-related cognitive decline, and vascular cognitive impairment. This research has demonstrated that therapeutic effects of nutrition are not just limited to cognitive function, with improvements across the spectrum of cardiovascular risk reduction, weight loss, and insulin resistance, among many others. Nutritional interventions include two main types of categories: 1) dietary patterns and 2) single or multi-nutrients. A dietary pattern is a specific style of eating, commonly referred to most simply as a diet. The best example of this category is the Mediterranean-style diet, which has the largest volume of dietary pattern research for AD. Other studies have focused instead on an individual nutrient (e.g., the omega-3 fatty acid DHA) or multiple nutrients (e.g., vitamins B12, B6, and folic acid) in combination.

The Mediterranean diet (MeDi) includes plentiful amounts of plant-derived foods and fresh fruit (as the primary source of carbohydrates), olive oil (primary source of fat), fish and lean poultry (primary source of protein, in low to moderate amounts), red meat (in low amounts), low-fat yogurt and milk (in moderate amounts), and wine (in low to moderate amounts). Regular physical activity is also a part of this diet, which is representative of cultural patterns of eating in countries like Italy, Greece, Spain, and Morocco.

In part, because it has been shown to reduce inflammation, oxidative stress, and insulin levels, MeDi has long been known to help reduce the risk of heart disease, and has been associated with a decreased risk of AD as well. By one estimate, MeDi can decrease AD risk by as much as 40% in older patients. The more strictly the patients adhered to the diet, the more dramatically their risk was reduced. Another dietary pattern, called Dietary Approaches to Stop Hypertension (DASH), was shown to improve cognitive function in a group of hypertensive, overweight subjects when combined with exercise. Based on these data, Morris and colleagues from Rush University Medical Center devised the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), which was initially shown to be more predictive of slower cognitive decline than MeDi or DASH. In the current study, Morris and colleagues aimed to shed more light on the effect of MIND adherence, more specifically on the development of AD rather than cognitive decline alone. The MIND diet is characterized by whole grains (> 28/week), green leafy vegetables (7+/week), berries (½ cup/day), regular cheese (≤ 1/day), butter (< 1 T/day), beans (3+/week), nuts (1/8 cup/day), lean red meats (< 4/week), fish (1+/week), poultry (2+/week), olive oil (> 1 T/d), and alcohol/wine (> 1/day). Key differentiating factors from MeDi and DASH include fewer grains/week, an emphasis on whole grains and berries, more red meat (but lean), less olive oil than MeDi, and unlike DASH, no specific percentage of total fat/saturated fat.

This study prospectively followed more than 900 people aged 58-98 years over 4.5 years and asked them to track their food patterns via food frequency questionnaires. Morris and colleagues found that moderate adherence to the MIND diet was associated with a 53% reduced risk of AD for those in the highest tertile of adherence (compared to a 35% risk reduction in the middle tertile). This effect was independent of other lifestyle conditions and cardiovascular-related conditions. When compared to adherence to MeDi and DASH, only those with the highest adherence to these dietary patterns showed an association with AD prevention.

■ COMMENTARY

To reinforce these associations, two recent randomized, controlled trials (RCTs) have found additional support for the importance of nutritional interventions for AD. The Finnish Geriatric Intervention Study to Prevent

Cognitive Impairment and Disability (FINGER) study[1] was the first longitudinal RCT to prove that multimodal lifestyle intervention (nutrition, exercise, cognitive training) reduces the risk of cognitive decline. The second RCT by Ros and colleagues[2] randomized subjects to three groups. Two of the groups followed the MeDi, also adding either 5 tablespoons of extra virgin olive oil each day or a handful of mixed nuts (30 grams of almonds, walnuts, or hazelnuts) each day. The third group followed a low-fat diet. Compared to the low-fat diet group, cognitive function in the areas of attention and executive function were higher in the MeDi plus olive oil group, and memory function was higher in the MeDi plus nuts group. Although further RCTs are warranted, from a practical clinical perspective, targeted nutritional interventions are an evidence-based and safe means of reducing the risk of AD and cognitive decline. ■

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2. Ros E, et al. Mediterranean diet and age-related cognitive decline: A randomized clinical trial. *JAMA Intern Med* 2015; May 11 doi: 10.1001/jamainternmed.2015.1668. [Epub ahead of print].

Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

Consequences of Intracerebral Hemorrhage in Young Adults

SOURCE: Koivunen RJ, et al. Intracerebral hemorrhage at young age: Long-term prognosis. *Eur J Neurol* 2015;22:1029-1037.

Intracerebral hemorrhage (ICH) accounts for 10-20% of all strokes in North America and Europe, with an overall incidence of 25 cases per 100,000 population annually. It occurs most commonly in the elderly, has a high early mortality, and a high proportion of survivors are left with serious functional impairments. There is no specific treatment, and in the acute phase, treatment is supportive. In a recent meta-analysis, the 5-year mortality in a general population of all ages was reported as 71% (*J Neurol Neurosurg Psychiatry*; 2014;85:660-667), and only 22% of patients were independent at 12 months. In this study, the authors evaluated the long-term survival and recovery of 268 1-month survivors ages 16-49 years to assess the prognosis of ICH in the younger group.

One-year survival was 98.1% in those who survived the first month, five-year survival was 93.2%, and 10-year survival was 88.8%. Increased mortality was associated with age, intraventricular hematoma extension, male sex, and diabetes. Poor functional outcome was present in 49% of the entire group, and was associated with a high initial stroke severity scale (NIHSS) and the presence of intraventricular hemorrhage. The etiology of the hemorrhage did not play a significant role in either mortality or long-term impairments. Of note, in 131 patients who could be followed long-term, 84% were living in their homes without requiring assistance outside of their immediate family. Post-ICH epilepsy occurred in 22.9% of patients. There was no association between the development of post-ICH epilepsy and surgical evacuation of the hematoma. Overall, young adults with ICH have a better long-term prognosis then the elderly, but they continue to have a high rate of serious neurological impairment, approximating 50%. ■

Convexal Subarachnoid Hemorrhage and Amyloid Angiopathy

SOURCE: Beitzke M, et al. Contribution of convexal subarachnoid hemorrhage to disease progression in cerebral amyloid angiopathy. *Stroke* 2015;46:1533-1540.

Cerebral amyloid angiopathy is emerging as a major cause of spontaneous intracerebral hemorrhage in the elderly. The risk of intracerebral hemorrhage in these patients seems to be related to the number of factors — lobar microbleeds, previous clinical episodes of hemorrhage, and the extent of leukoaraiosis. It has also been postulated that cortical superficial siderosis may be an indicator of increased risk for future intracerebral hemorrhage in this elderly population. The authors of this study undertook a careful review of all of the patients in their database over a 9-year period who had spontaneous convexal subarachnoid hemorrhage, and they performed a careful longitudinal analysis of clinical and neuroimaging data.

Of 38 cases with convexal subarachnoid hemorrhage (mean age, 77 years), 29 (76%) had imaging features of cerebral amyloid angiopathy on baseline imaging, and 26 (68%) had convexal superficial siderosis. Sixteen subjects who underwent post-contrast MRI had extravasation of gadolinium at the site of the acute subarachnoid hemorrhage. After a mean follow-up of 24 months, 39% of the patients had experienced recurrent convexal subarachnoid hemorrhage events, and 37% suffered lobar intracerebral hemorrhage. Of the new intracerebral hemorrhage events, most occurred at sites of previous convexal subarachnoid hemorrhage. In one autopsy case, leakage was demonstrated in meningeal vessels on pathologic examination. The authors concluded that in cerebral amyloid angiopathy, leakage of meningeal vessels is a major cause for recurrent bleeding, which may lead to propagation and frank intracerebral lobar hemorrhage. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **Which of the following statements regarding biofluid biomarkers of concussion is correct?**
   a. S100ß in cerebrospinal fluid is the ideal biofluid biomarker of concussion.
   b. At present, biofluid biomarkers of concussion lack sensitivity and specificity.
   c. Neuron-specific enolase is the ideal biomarker of concussion.
   d. Cerebrospinal fluid tau is the ideal biomarker of concussion.

2. **CSF measurements of tau, phospho-tau, and visinin-like protein 1 can help predict progressive neurodegeneration in patients diagnosed with early AD.**
   a. True
   b. False

3. **Rest tremor associated with essential tremor has which of the following characteristics?**
   a. Rest tremor is accompanied by rigidity and bradykinesia.
   b. Rest tremor occurs during sleep.
   c. Rest tremor in the arm may be accompanied by tremor in the leg.
   d. Rest tremor is often accompanied by head and voice tremor.
   e. Rest tremor only occurs with Parkinson's disease.

4. **Which of the following statements is true regarding POLG-related disease?**
   a. Sensory neuronopathy associated with ophthalmoplegia is a highly specific and sensitive association for POLG mutation.
   b. Sensory neuronopathy associated with dysphagia is a highly specific and sensitive association for POLG mutation.
   c. Sensory neuronopathy associated with axial or limb weakness is a highly specific and sensitive association for POLG mutation.
   d. All of the above

5. **Which of the following dietary patterns has not been associated with delay of cognitive and/or Alzheimer's disease?**
   a. Dietary Approaches to Stop Hypertension (DASH)
   b. Mediterranean diet (MeDi)
   c. Vegan diet
   d. Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)

6. **Young adults with intracerebral hemorrhage caused by an arteriovenous malformation have a worse prognosis than those caused by hypertension.**
   a. True
   b. False

7. **Intracerebral hemorrhage associated with amyloid angiopathy is caused by leakage of blood from fragile meningeal blood vessels.**
   a. True
   b. False

CME OBJECTIVES

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

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

[IN FUTURE ISSUES]

Update on Epilepsy