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Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Migraine with Aura and Systemic Right-to-Left Shunt: Risk for Stroke?

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a consultant for Bayer and Boehringer Ingelheim.

SYNOPSIS: Right-to-left shunts, as detected by transcranial Doppler, are more common in patients with migraine with aura, but are not correlated with increased risk of silent posterior circulation infarcts or white matter lesions on MRI.

SOURCE: Koppen H, Palm-Meinders IH, Mess WH, et al. Systemic right-to-left shunts, ischemic brain lesions, and persistent migraine activity. *Neurology* 2016;86:1668-1675.

Studies of patients in headache clinics have determined that migraine with aura is associated with an increased risk of patent foramen ovale (PFO), with shunting of blood from the right to the left side of the heart. Koppen et al assessed whether migraine patients in the general community, as opposed to those selected from headache clinics, had an increased prevalence of systemic right-to-left shunts (RLS) as compared to a non-migraine population. They also evaluated the association of RLS with ischemic brain lesions on MRI and persistent recurrence of migraine attacks at an older age. The presence of RLS was determined by transcranial Doppler (TCD) with injection of agitated air/saline/autologous blood contrast in 166 migraineurs (mean age: 56 years; 70% women) and 69 controls (mean age: 55 years; 65% women) from the Cerebral Abnormalities in Migraine: An Epidemiological Risk Analysis Study Part 2 (CAMERA-2). In CAMERA-1 in 2000, migraine patients and controls were randomly selected from a community-based study and were assessed for ischemic brain lesions on MRI. The follow-up CAMERA-2 study assessed the prevalence, incidence, and progression of MRI lesions in migraineurs over the nine years from the original study. MRIs were evaluated for "silent infarcts," which were defined as "non-mass parenchymal defects with a vascular distribution, isointense to CSF signal on all sequenc-

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es, and when supratentorial, surrounded by a hyperintense rim on fluid attenuated inversion recovery images." Participants in CAMERA-2 were asked if they had at least one migraine attack in the 12 months prior to the MRI scan, defining active recurrence of migraine attacks.

Valsalva-induced RLS was more frequent in participants with migraine with aura (60%) as compared to controls (42%; $P = 0.02$) and participants with migraine without aura (40%; $P = 0.01$). Participants with migraine with aura also had more frequent spontaneous RLS (35%) than participants with migraine without aura (17%; $P = 0.01$), but not when compared to non-migraine controls (26%; $P = 0.2$). Migraine with aura and spontaneous RLS predicted ongoing recurrence of migraine attacks. Silent posterior circulation infarcts were found in 9% of participants with RLS, not significantly different from 3% of participants without RLS, independent of migraine status. Higher age, but not RLS presence or migraine status, were associated with an increased infarct risk. The presence of RLS on TCD was not associated with an increased risk of deep white matter lesions on MRI. The presence of a spontaneous RLS in a migraineur was associated with ongoing recurrence of migraine attacks. However, the mean attack migraine frequency was not correlated with the presence or absence of spontaneous RLS. The authors concluded that RLS are more prevalent in migraineurs with aura. However, the presence of RLS does not explain the increased prevalence of silent posterior circulation infarcts or white matter lesions found on MRI in migraineurs.

■ COMMENTARY

This study reiterates the known association between migraine with aura and RLS, now shown in a general population of migraine individuals. The study also again demonstrates the lack of correlation between MRI lesions and the presence of RLS. White matter lesions on MRI are frequent incidental findings in migraineurs, both with and without aura. Although these migraine-associated lesions are assumed to be ischemic, the exact neuropathology of these lesions, as localized on MRI but not diagnosed based on tissue sampling, has not been characterized for obvious reasons. Multiple studies have determined conclusively that RLS is more common in individuals whose migraine attacks are presaged by an aura. The hypothesis that microemboli cross unfiltered through the heart to the brain, and thus induce cerebral ischemia with migraine triggering, would be buttressed by a correlation between the presence of an RLS and presumed small vessel ischemic damage as noted on MRI. However, like prior published studies, such as the shunt-associated migraine (SAM) study, this has not shown a correlation between lesions found incidentally on the MRIs of migraineurs and the presence of an RLS.

Koppen et al used TCD with bubble detection to diagnose shunting, stating that TCD cannot distinguish between cardiac and pulmonary shunts. However, TCD is more likely to pick up cardiac, as opposed to less common pulmonary shunting, and other echocardiographic studies have found a PFO and migraine with aura correlation. The reason for the association between a cardiac right-to-left shunt and migraine with aura is unclear, with genetic co-localization, rather than a causative explanation, being the most convincing hypothesis.

This study found that migraine individuals with aura, but not those without aura, more often had ongoing migraine activity over years, if they also had spontaneous RLS. The presence of a shunt may predict more persistent migraines in those with aura, identifying individuals who should be offered early and aggressive preventive therapy. However, there is no evidence that PFO closure in those with migraine with aura has any beneficial effect on migraine frequency and severity, since unconvincing results were found in numerous clinical trials. Therefore, for now, usual migraine acute and preventive therapies should be offered to all patients with migraine, regardless of the presence of systemic shunting. Likewise, the presence of characteristic MRI lesions in a migraineur does not necessitate either further investigation or different therapy beyond that offered to all migraineurs. These findings and correlations, while thought provoking, have not yet changed the way that migraine patients are evaluated or treated. ■

ABSTRACT & COMMENTARY

Eating Behavior in Frontotemporal Dementias

By Makoto Ishii, MD, PhD

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Dr. Ishii reports he is a stockholder in Regeneron.

SYNOPSIS: In a prospective, controlled study of 49 patients with dementia and 25 healthy controls, marked hyperphagia is restricted to behavioral-variant frontotemporal dementia patients that is likely due to differing neural networks, while increased sucrose preference is likely controlled by a similar network in both behavioral-variant frontotemporal dementia and semantic dementia patients.

SOURCE: Ahmed RM, Irish M, Henning E, et al. Assessment of eating behavior disturbance and associated neural networks in frontotemporal dementia. *JAMA Neurol* 2016:73:282-290.

Changes in eating behavior are common in frontotemporal dementia (FTD). Hyperorality (i.e., oral exploration of inedible objects) and dietary changes are criteria for the diagnosis of behavioral-variant frontotemporal dementia (bvFTD), while semantic dementia (SD) patients are reported to have rigid eating behaviors and changes in food preference. However, eating behavior typically is assessed by caregiver questionnaires, which may be biased by subjective interpretation and reporting errors. Furthermore, neuroimaging studies suggest that atrophy in different brain regions contributes to the behavior abnormalities in FTD, but the precise neural networks involved in eating behavior are not known. Therefore, Ahmed et al conducted a prospective controlled study in bvFTD and SD patients to 1) rigorously examine the changes in eating behavior using ecologically valid methods and 2) identify the associated neural networks using voxel-based morphometry analyses of structural brain MRI.

The study was conducted from Nov. 1, 2013, to May 31, 2015. Forty-nine study participants with dementia (19 bvFTD, 15 SD, and 15 Alzheimer's disease [AD]) were recruited in Australia. Twenty-five healthy controls were recruited in Australia and the United Kingdom. Mean age for the four groups ranged from 62 to 66 years. The dementia and control groups were matched for age, sex, and body mass index to remove potential effects on eating behavior. Caloric intake and food preference were assessed by the ad libitum breakfast test meal. Sucrose preference was assessed by measuring the liking ratings of three desserts of varying sucrose content (26%, 39%, and 60%). To identify the neural networks, all participants underwent whole brain 3T MRI on the day of the eating experiments. The MRI data were analyzed with voxel-based morphometry and voxelwise general linear models to identify correlations between performances on the two eating behavior tests and gray matter volume.

In this study, the bvFTD group was more functionally impaired relative to the AD (Frontal Rating Scale; $P = 0.009$) and SD groups ($P < 0.001$). The bvFTD group also had more severe eating disturbances based on caregiver surveys ($P < 0.005$ for all). The two eating behavior tests revealed important similarities and differences between bvFTD and SD groups. All patients with bvFTD had markedly elevated total caloric intake and hyperphagia that was not seen in the other groups ($P < 0.001$). The SD group did not have increased caloric intake, but a number of patients had rigid eating behavior, including refusing to eat, that affected their food preferences. Both bvFTD and SD patients had a strong sweet preference compared with AD and control groups, which was not due to altered sweetness perception, as they were similar among all the groups.

Voxel-based morphometry analyses found complex mechanisms underlying the changes in eating behavior in FTD patients that suggested disturbed functional neural networks involved in reward, visual, autonomic, and neuroendocrine processes, with subtle but important differences between the bvFTD and SD patients. Specifically, in the bvFTD group, increased caloric intake was associated with loss of gray matter intensities in the bilateral cingulate gyri, thalami, bilateral lateral occipital cortex, lingual gyri, and right cerebellum but not in the orbital frontal cortex, suggesting that the altered eating behavior is not due to a loss of inhibitory control. In the SD group, similar brain regions were associated with caloric intake with the addition of bilateral orbitofrontal cortices, nucleus accumbens, and more left-sided structures involved in the semantic networks, suggesting a loss of knowledge concerning foods. Increased sucrose preference correlated with decreased gray matter intensities in bilateral orbitofrontal cortices, right-sided insula-striatal

reward structures, including the nucleus accumbens, amygdala extending into the temporal occipital cortex, lingual gyrus, and cerebellum. This analysis combined both bvFTD and SD groups, as they had similarly increased sucrose preferences.

■ COMMENTARY

This important paper advances our understanding of the eating behavior changes in bvFTD and SD patients and supports the diagnostic value of assessing for hyperphagia in bvFTD. The paper suggests that differences in the behavioral abnormalities of bvFTD and SD patients can be explained by changes with the associated neural networks. Strengths include well-controlled study groups, prospective assessments using ecologically valid methods from obesity research, and detailed voxel-based morphometry analyses to identify for the first time the neural networks that correlate with the changes in eating behavior in FTD. A limitation is the interpretation of behavioral tests and voxel-based morphometry using a relatively small number of subjects. Additionally, caloric intake and sucrose preference correlated with disease severity, making it difficult to determine whether the results are specific to eating behaviors or simply reflect disease severity. Therefore, these results need to be validated by others. Additional studies using functional MRI also would be useful in determining if the brain regions that correlated with these eating behaviors are truly functionally connected and how alterations in these networks are linked to the behavioral changes. Delineating the neural networks involved in the eating behavior changes eventually could lead not only to improved diagnosis and treatment of these changes in FTD patients, but also to an overall better understanding of brain structures that control eating behavior. This would be clearly important in other medical conditions affected by eating behavior such as obesity and anorexia nervosa. ■

ABSTRACT & COMMENTARY

Sleep Disorders Associated with Traumatic Brain Injury

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Patients with traumatic brain injuries need longer sleep times to heal the injured brain, and persistent pleiosomnia at 18 months implies that ongoing abnormalities are producing an increased need for sleep.

SOURCE: Imbach LL, Buchele F, Valko PO, et al. Sleep-wake disorders persist 18 months after traumatic brain injury but remain underrecognized. *Neurology* 2016; Epub April 27, 2016.

Brain injury, no matter the mechanism — traumatic, degenerative, ischemic, or demyelinating — profoundly affects function in the waking state. It is increasingly recognized, however, that sleep, a state in which the brain spends approximately 30% of its time, is also exquisitely sensitive to brain injury. Sleep is driven by the hypothalamus, but its effects are widespread; the hippocampus allows for consolidation of declarative memories, the basal ganglia facilitate muscle relaxation in REM sleep, and the calcarine cortex creates visual imagery while dreaming in REM. Sleep is physiologically necessary, particularly because it promotes the so-called "glymphatic" system within the brain, allowing toxic metabolic waste products accumulated during the waking state to be washed away.

Sleep is a delicate balance between two functions — a homeostatic drive to sleep (Process H), which builds throughout the day and is discharged as we sleep, and a circadian rhythm (Process C), which follows a sinusoidal pattern. Peak circadian alerting influence occurs in the late afternoon (e.g., 4 p.m.) and has its nadir about 12 hours later. Process C allows us to stay awake later in the day, even as Process H builds, and then Process C prevents us from waking up too early, as Process H dissipates. The strength of this intrinsic system may explain why, for example, hunter-gatherer communities, who may or may not have access to electric lights after dark, still have very consistent sleep patterns.

In prior work by these authors, traumatic brain injury (TBI), whether mild, moderate, or severe, was shown to profoundly affect sleep. This was manifested both as an increase in "sleep pressure" (measured by a shortened sleep onset latency) and an increased overall sleep need (known as pleiosomnia). The current study explores the same cohort, initially studied at 6 months, now 18 months post TBI.

Imbach et al initially studied 60 patients with TBI, classified by their initial Glasgow Coma Scale (GCS),

of which 31 were still available for follow up. There were 21 mild patients (GCS 13-15), two moderate patients (GCS 9-12), and eight severe patients (GCS 3-8). Total sleep times (as measured by polysomnography) were significantly greater among TBI patients — over seven hours, compared with 6.5 hours for controls ($P < 0.005$). More extended home monitoring of sleep over a two-week period (as measured by movement sensing actigraphy) showed that TBI patients slept eight hours per night, compared with seven hours for controls ($P < 0.00005$). This was important because it proved that the effects seen during a single polysomnography continued and was validated on an extended nightly basis. TBI patients tended to fall asleep quickly, as measured by a Sleep Onset Latency (SOL) of seven minutes compared with 12 minutes for controls. Thus, TBI patients exceeded the typical cutoff for excessive sleepiness, which is defined as a SOL of less than eight minutes during a Multiple Sleep Latency Test.

Interestingly, all other measurements relating to the quality of sleep were equal. This included time in deep, slow-wave (Stage 3) sleep (measured as "delta power") and time in all other sleep stages, most importantly, REM sleep. A computerized sleep architecture algorithm to define sleep fragmentation was identical between TBI patients and controls. Subjective ratings of daytime sleepiness, such as the Epworth sleepiness scale, were equal. Importantly, these data indicate that the problem was not the quality of sleep in TBI patients, but rather only the quantity.

In the authors' initial study, patients with an underlying intracerebral hemorrhage (ICH) as part of their TBI showed greater sleep demands than patients without ICH. Overall, TBI severity also correlated with sleep need. This effect was lost at 18 months. It is possible that sleep, functioning as an endogenous repair mechanism required by the healing brain, played more of an influence at six months compared to 18 months. Persistent pleiosomnia at 18 months implies that there may be ongoing abnormalities in the brain that are producing an increased need for sleep. Since the 18-month data were comprised primarily of patients with mild TBI, it suggests that abnormalities such as diffuse axonal injury, or perhaps even early amyloid plaque deposition, in these patients may be much more than expected.

■ COMMENTARY

These data are indicative of a phenomenon rarely seen in clinical medicine. That is, a situation in which the patients' subjective complaints actually may underestimate their objectively measurable problems. As the authors noted, TBI patients may have a component of "sleep state misperception" (also known as "paradoxical insomnia"). These patients spend longer periods of time in bed, and may complain that they are awake for much of it. In fact, when studied by objective measures, such as polysomnography or actigraphy, it is found that these patients are sleeping much more than they really think. Mild TBI patients, with post-concussive syndrome — non-specific complaints such as low-grade dizziness or mental fogginess — simply may not be sleeping enough. Given the hazards associated with excessive daytime sleepiness, such misperception may have serious public health consequences. As the authors noted, "normal" scores on subjective indices such as the Epworth (with such questions as "how likely are you to doze off stopped in traffic?") may belie a much more insidious problem. Although there may be confounding factors, there is little doubt that in TBI, longer sleep times are needed, either to heal the injured brain or at least as a consequence of persistent CNS dysfunction. ■

ABSTRACT & COMMENTARY

Mechanisms of Tissue Hypoxia and Cerebral Ischemia in Traumatic Brain Injury

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: Tissue hypoxia after traumatic brain injury occurs in a widespread manner in the brain, including areas that appear structurally normal. Moreover, cerebral tissue hypoxia appears to occur independent of ischemia with areas of no overlap, implying a microvascular etiology.

SOURCE: Veenith TV, Carter EL, Geeraerts T, et al. Pathophysiologic mechanisms of cerebral ischemia and diffusion hypoxia in traumatic brain injury. *JAMA Neurol* 2016; May 1. Doi:10.1001/jamaneurol.2016.0091. Published online March 28, 2016.

This study explores the mechanism of cerebral tissue hypoxia based on earlier studies demonstrating oxygen diffusion gradient. Ten patients with moderate and severe traumatic brain injury (TBI) un-

derwent MRI with a 3-T scanner for structural imaging. Subsequently, they underwent sequential ^{15}O-PET and [^{18}F]-fluoromisonidazole (FMISO) to examine cerebral ischemia and hypoxia, respectively. Data were compared with 10 controls who each underwent ^{15}O-PET and [^{18}F]-FMISO PET. Patients were treated using standard unit-specific ICP-CPP-$PbtO_2$ protocol with thresholds being ICP < 25 mmHg, CPP > 65 mmHg, and $PbtO_2$ > 15 mmHg.

TBI patients had significantly higher ischemic and hypoxic brain volumes than controls. There was no volumetric and spatial correlation between the ischemic and hypoxic brain regions and volumes. Although both ischemic and hypoxic areas were seen in contusion and pericontusional areas, there were also significant areas of hypoxic tissue in brain tissue that appeared normal on structural MRI. Although cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral metabolic rate ($CMRO_2$) were similar in the two areas, oxygen extraction fraction (OEF) was significantly higher in ischemic regions compared to hypoxic regions, which were similar to controls.

This study confirms that regions of hypoxia and ischemia occur in normal-appearing brain tissue following TBI, and that tissue hypoxia does not appear to be a result of macrovascular ischemia but rather a microvascular abnormality and an oxygen diffusion gradient.

■ COMMENTARY

In studies of brain injury following interruption of cerebral blood flow, cerebral ischemia and hypoxia have been demonstrated to co-exist in areas of macrovascular ischemia in stroke and subarachnoid hemorrhage.[1-3] However, previous PET studies have demonstrated areas of diffuse and distant metabolic derangements after TBI as well as reduction in CBF in contusional and pericontusional regions.[4,5] Metabolic crises in the absence of brain ischemia also have been described both by PET and in vivo cerebral microdialysis.[6] Diffusion-limited oxygen delivery also has been described following severe TBI.[7] And variable improvement in $PbtO_2$ and $CMRO_2$ occurs in at-risk tissue with normobaric hyperoxia and augmentation of CPP.[8,9]

In this elegant study, the authors combined measurement and spatial localization of hypoxia and ischemia using respective metabolic PET markers. While cerebral ischemia and hypoxia are seen both in contusional and pericontusional regions, they also occur scattered throughout other normal-appearing brains. In addition, their spatial co-localization is poor, demonstrating areas that are either hypoxic or ischemic in isolation. Ischemic regions increase oxygen extraction to a very high degree prior to becoming hypoxic and may be the reason that hypoxic tissue was not seen within ischemic region, as FMISO is trapped in dying hypoxic cells. In ischemic tissues, in addition to low CBF, very high OEF was seen, which is consistent with tissue in the throes of compensation. However, no ischemia was seen in isolated hypoxic tissue. This may imply that while there is no macrovascular ischemia, the microcirculation is altered due to capillary edema, or collapse from cerebral edema creating an oxygen diffusion barrier/gradient. Due to the absence of oxygen, hypoxic tissue may not be able to increase OEF unlike ischemic regions.

In addition, in patients who had $PbtO_2$ probes in place, no area of hypoxia was seen in the vicinity of the probes. And the lowest $PbtO_2$ was 15 mmHg, which may at least be a threshold at which tissue hypoxia is not seen.

In conclusion, this study demonstrates the presence of cerebral ischemia and hypoxia in normal-appearing tissue and in spatially distinct regions. This generates the discussion that there are two distinct mechanisms for the two processes, which may be macro- and micro-vascular, respectively, or perhaps mediated by more complex mechanisms. ■

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ABSTRACT & COMMENTARY

Demyelinating Neuropathies in Children

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: Electrodiagnostic criteria using nerve conduction velocities are useful to distinguish most hereditary neuropathies from acquired neuropathies in children.

SOURCE: Potulska-Chromik A, Ryniewicz B, Aragon-Gawinska K, et al. Are electrophysiological criteria useful in distinguishing childhood demyelinating neuropathies? *J Peripheral Nervous System* 2016:21:22-26.

Using electrodiagnostic criteria in the pediatric population, is it possible to distinguish chronic inflammatory demyelinating polyneuropathy (CIDP) from hereditary forms of demyelinating neuropathy, including Charcot Marie Tooth 1a (CMT1a), the most common form of CMT, caused by a PMP22 gene duplication, and hereditary neuropathy prone to pressure palsy (HNPP), caused by a PMP22 gene deletion? Lacking biological markers, CIDP diagnosis relies heavily on nerve conduction studies (NCS) and cerebrospinal fluid analysis, both difficult to perform in children, and identifying sensitive and specific NCS parameters would be clinically advantageous.

Retrospective analysis was undertaken of 18 CIDP patients, seven HNPP patients, and 24 CMT1a patients, diagnosed between 2002-2014 at the Pediatric Neuromuscular Unit, Department of Neurology, Medical University of Warsaw, Poland. All had onset of symptoms prior to age 18 years. Nerve conduction studies were performed in the standard fashion and analyzed using at least four sets of diagnostic criteria, including those formulated by the American Academy of Neurology and the European Federation of Neurological Societies/Peripheral Nerve Society.

Among CIDP patients, distal compound muscle action potential (CMAP) duration was longer than 9 ms in at least one nerve in 77% (14 of 17), and motor conduction block of > 30% was found in 88% (16 of 18), mostly (83%) *not* at common entrapment sites. Supportive criteria for acquired neuropathy was present in 50% (9 of 18), comprising: 1) a 10 m/s conduction velocity difference between two corresponding nerves in the arms or legs; 2) an abnormal terminal latency index (TLI), calculated as the distal conduction distance (mm)/(conduction velocity (m/s) x distal motor latency (ms); 3) abnormal median sensory but normal sural sensory response; or 4) the converse, abnormal sural sensory but normal median sensory response.

Among seven HNPP patients, none had a distal CMAP duration > 9 ms, and partial motor conduction block was found in only 28% (2 of 7), all at common sites of entrapment (ulnar nerve at elbow, peroneal nerve at fibular head). Among 24 CMT1a patients, prolonged distal CMAP duration in at least one nerve was seen in 58% (n = 14), and motor conduction block was found in 25% (n = 5). Other than an abnormal TLI in two patients, none had any supportive criteria for acquired neuropathy.

Distal CMAP duration > 9 ms in at least one nerve, abnormal median sensory but normal sural sensory response, and a 10 m/s conduction velocity difference between two corresponding nerves in the arms or legs are strong indicators of pediatric CIDP, differentiating it from HNPP and CMT1a.

■ COMMENTARY

Most childhood neuropathies are genetic in origin. Acquired neuropathies are usually inflammatory, with CIDP representing only 3% of pediatric neuropathies, most of which occur prior to 10 years of age, and 20% of which present as Guillain-Barre syndrome. As in adults, childhood CIDP is more frequent in males, with prevalence of approximately 0.48/100,000 in children compared to 7.7/100,000 in adults. Consequent to the IVIG CIDP Efficacy (ICE) trial, intravenous immunoglobulin (IVIG) has become the treatment of choice for CIDP, although plasma exchange and corticosteroids are equally efficacious.[1] Children respond well to IVIG, as well as to corticosteroids. Azathioprine, in combination with steroids, constitutes a third-line alternative. Approximately 25% obtain long-term remission after discontinuation of immunotherapy, while 45% may require a year or more of regular infusions, given at a dose of 1 g/kg every 3-4 weeks. ■

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CME QUESTIONS

1. **The presence of a spontaneous right-to-left shunt in a migraineur in the general population is associated with an increased risk of which of the following?**
   a. Silent posterior circulation infarcts
   b. White matter lesions
   c. Symptomatic cerebral ischemia
   d. Persistence of migraine attacks over time
   e. Increased mean attack frequency

2. **Which of the following changes in eating behavior are *not* commonly seen in patients with behavioral variant frontotemporal dementia?**
   a. Increased preference for sweet foods
   b. Increased perception of sweetness
   c. Increased caloric intake
   d. Increased oral exploration of inedible objects

3. **After traumatic brain injury, which of the following changes in sleep pattern has been observed?**
   a. Sleep onset latency is prolonged.
   b. Total sleep time is greater than in controls.
   c. Time in REM sleep is less than controls.
   d. Sleep is disrupted and fragmented.

4. **After traumatic brain injury, brain regions that appear normal on imaging may still harbor areas of critical ischemia and/or hypoxia.**
   a. True
   b. False

5. **Useful parameters to differentiate chronic inflammatory demyelinating polyneuropathy from hereditary forms, including Charcot Marie Tooth 1a, and hereditary neuropathy with liability to pressure palsy include which of the following?**
   a. Distal compound muscle action potential duration > 9 ms in at least one nerve
   b. Abnormal median sensory but normal sural sensory response
   c. A 10 m/s conduction velocity difference between two corresponding nerves in the arms or legs
   d. All the above
   e. None of the above

[IN FUTURE ISSUES]

Stroke ALERT Returns!