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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Peripheral Nerve Disorders After Cardiac Surgery

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: Following cardiac surgery, about 6% of patients will suffer a peripheral nerve injury, mostly due to compression, traction, or nerve ischemia. Proper patient positioning can prevent most of these injuries.

SOURCE: Gavazzi A, et al. Prevalence of peripheral nervous system complications after major heart surgery. *Neurol Sci* 2016;37:205-209.

Following cardiac surgery, up to 30% of patients may experience diaphragmatic paralysis due to phrenic nerve injury, while up to 15% of patients sustain peripheral nerve injury affecting the arm, usually demyelinating in nature and resolving within weeks. What is the complete spectrum of neuropathy following open-heart surgery, what are the risk factors, and what is its prevalence?

Among 374 consecutive patients admitted to the Cardiac Rehabilitation Unit in Multimedica Hospital, Castellanza, Italy, and examined neurologically after coronary artery bypass grafting, cardiac valvular surgery, or ascending aortic aneurysm repair, patients with suspected peripheral nerve complications underwent nerve conduction studies, needle electromyography, or evoked potential studies. Comorbid conditions included renal failure, diabetes, thyroidopathy, peripheral arterial disease, prior history of peripheral nerve dysfunction, and occurrence of sepsis or respiratory failure postoperatively. Critical illness polyneuropathy was diagnosed if a generalized axonal neuropathy was found, as demonstrated by low compound motor action potential amplitudes and fibrillation potentials on needle examination. Compression neuropathy was diagnosed by standard criteria. Statistical analysis comprised student t-test and chi-square test, with $P < 0.05$ considered significant.

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Only 6.1% (n = 23) demonstrated new peripheral nerve complications, with no correlation found between the type of cardiac surgery and occurrence or type of nerve injury. Diabetes was the sole medical risk factor for developing a peripheral nerve adverse event ($P = 0.002$), whereas age, gender, and duration of surgery did not play a role. Critical illness polyneuropathy was seen in five patients (1.3%), while three patients with pre-existing peripheral neuropathy experienced worsening, one with diabetic neuropathy and two with idiopathic polyneuropathy. Mononeuropathies were seen in the remainder, including ulnar neuropathy at the elbow (6), carpal tunnel syndrome (4) or brachial plexopathy (4), peroneal neuropathy at the knee (3), lower cranial neuropathy involving the vagus (2), glossopharyngeal (1) or hypoglossal nerve (1), and median neuropathy at Struthers ligament (2) or meralgia paresthetica (2). Injury to the superior laryngeal branch of the vagus resulted in hoarseness and vocal cord and soft palate paralysis, whereas dysphagia and loss of taste and gag reflex resulted from glossopharyngeal nerve injury. In all cases, symptoms and electrodiagnostic abnormalities continued for at least 1 month following surgery, with persistent symptoms particularly in diabetic patients. Patients with critical illness polyneuropathy fared well. Excluding carpal tunnel syndrome from the mix, due to its high prevalence in the general population, 5.8% experienced peripheral nerve complications following surgery, similar to the known prevalence of central nervous system complications following cardiac surgery, and diabetes remained the sole risk factor.

■ COMMENTARY

Brachial plexus injuries following cardiac surgery last an average of 2-3 months, usually resolve within 1 year, and may be the result of positioning, retractor use and placement, and duration of surgery and cardiopulmonary bypass. Sternal retractors rotate the first rib superiorly, pushing the clavicles posteriorly, compressing the plexus, and typically injuring the medial cord and its major branch, the ulnar nerve. Prolonged cardiopulmonary bypass may result in prolonged nerve ischemia contributing to this injury. Proper patient positioning is central to preventing compression injuries, and padding is essential. Central venous catheter placement may result in hematoma formation, which can also compress the plexus. Radial artery harvesting, in lieu of the saphenous vein, may result in sensory abnormalities in up to 34%, resolving within 3-6 months in almost all, but thumb weakness has been reported in 6%, with decreased grip strength and dexterity. Vasopressor use, particularly dopamine and norepinephrine, may result in digital ischemia, often requiring amputation, but the most common cause of arm ischemia is thromboembolism due to atrial fibrillation, often requiring surgical thrombectomy and anticoagulation.[1] ■

REFERENCE

1. Dineen HA, et al. Upper extremity complications and concerns in patients with cardiac disease. *J Hand Surg Am* 2016;41:470-472. http://dx.doi.org/10.1016/j.jhsa.2015.11.023.

ABSTRACT & COMMENTARY

Thalamic Pain: Who Is Likely to Develop This Disorder?

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: In a careful anatomic and physiologic study of patients with thalamic stroke, the authors demonstrated that the combination of anterior pulvinar nucleus involvement with spinothalamic dysfunction predicts a "thalamic pain syndrome" with > 90% sensitivity.

SOURCE: Vartiainen N, et al. Thalamic pain: Anatomical and physiological indices of prediction. *Brain* 2016;139:708-722.

Approximately 25% of patients with a sensory stroke due to a thalamic lesion will develop central post-stroke pain. Thalamic pain is a severe, treatment-resistant pain syndrome. The pain is often described as burning or constrictive and is frequently accompanied by evoked pain (allodynia/hyperalgesia), paresthesias, or summation hyperpathia. The underlying mechanism that results in post-stroke thalamic pain is uncertain. It is currently impossible to predict which patients will develop this distressing syndrome.

There is agreement that thalamic pain develops following a stroke affecting the territory of the geniculo-thalamic artery, which includes the primary somatosensory thalamic nucleus (ventral posterior lateral [VPL]/ventral posterior medial thalamus [VPM]) and the anterior pulvinar, a major spinothalamic target. Although damage to the VPL initially was thought to be necessary for the development of thalamic pain, not all patients with strokes involving the VPL developed thalamic pain. Studies using atlas-based projection of MRI lesions in humans have suggested that lesions in the border between VPL and the anterior pulvinar were more likely to produce thalamic pain. Central pain is associated with abnormal thermonociception, with damage to the spino-thalamic-cortical system considered necessary for the development of thalamic pain; however, not all spinothalamic lesions lead to the development of thalamic pain.

To further define the localization and mechanism for the development of thalamic pain, the authors combined atlas-based localization of thalamic lesions with quantitative sensory examinations and physiological recordings of spinothalamic evoked potentials (laser-evoked potentials [LEPs]) in a group of 42 patients with thalamic stroke.

All 42 patients had MRI-documented unilateral thalamic stroke. Thirty-one patients had central post-stroke pain and 11 did not. Non-neuropathic causes of pain were specifically addressed and excluded. Sensory examination included testing of light touch, proprioception, graphesthesia, superficial pain, and heat sensation. Pain was considered thalamic central post-stroke pain when it was contralateral to the affected thalamic lesion with a plausible neuroanatomical correlate and an abnormal sensory examination. Spinothalamic function analysis included both negative and positive symptoms and was assessed clinically in 40 patients; pain thresholds were quantified using thermal laser pulses in 35 patients. The affected thalamic nuclei were defined by superimposing MRI data onto the human thalamic atlas.[1]

Abnormal sensory examinations were found in 45% of the thalamic pain patients and in 18% of the non-pain patients, but this was not a significant difference. Increased pain thresholds were seen exclusively in the thalamic pain group. In addition, in the thalamic pain patients, laser-evoked potentials were attenuated on the painful side compared with the normal side; this discrepancy was not seen in the non-pain patients. The development of thalamic pain was significantly associated with signs of abnormal spinothalamic function, either estimated by subjective heat thresholds, pain thresholds, or laser-evoked potentials.

[This study provides a relatively simple way of predicting which patients with thalamic stroke are likely to develop a post-stroke thalamic pain syndrome.]

In patients with thalamic pain, maximal lesion convergence was seen in the anterior pulvinar nucleus. In the pain-free patients, maximal lesion convergence was in the VPL. Both of these thalamic nuclei receive their blood supply via the geniculostriate artery. The only nucleus showing significantly higher incidence of involvement in pain patients than in pain-free patients (87% vs 36%) was the anterior pulvinar nucleus.

■ COMMENTARY

Combining anatomical and functional analyses helped predict which patients with thalamic stroke will develop central post-stroke pain syndrome. Anatomical and functional indexes of spinothalamic involvement were independently and significantly associated with the development of thalamic pain. Involvement of the VPL/VPM nuclei and the presence of lemniscal symptoms were common in all patients with thalamic stroke; however, their incidence was not significantly different in patients with or without thalamic pain. A logistic regression model combining spinothalamic dysfunction and anterior pulvinar nucleus involvement had a 93% sensitivity and 87% positive predictive value for the development of thalamic pain. Injury to the spinothalamic system within the posterior thalamus seems to be the main determinant of the development of thalamic pain syndrome.

This study provides a relatively simple way of predicting which patients with thalamic stroke are likely to develop a post-stroke thalamic pain syndrome. These measures can be used to plan controlled trials of medications and other interventions to reduce the development of this severe pain syndrome. ■

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ABSTRACT & COMMENTARY

Pick Disease: Picking Away at the Pathology

By Joseph E. Safdieh, MD

Vice Chair and Associate Professor, Weill Cornell Medical College

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

SYNOPSIS: The neuropathologic changes of Pick disease may sequentially progress through the brain in specified phases over time and may correlate with the progression of clinical symptoms.

SOURCE: Irwin DJ, et al. Deep clinical and neuropathological phenotyping of Pick disease. *Ann Neurol* 2015;79:272-287.

Pick disease was initially described in the late 19th century in a patient who suffered a progressive neurodegenerative syndrome manifested by behavioral and language changes with gross frontotemporal atrophy noted on pathologic examination. Pick disease is now categorized as pathologic variant of one of the frontotemporal lobar degenerations (FTLD). FTLD pathologic subtypes include FTLD-Tau, FTLD-TDP, and FTLD-FUS. Pick disease is categorized under the FTLD-Tau subtype and is specifically a 3-repeat tauopathy. Pick disease is diagnosed pathologically by the presence of Pick bodies, which are spherical intraneuronal tau inclusions composed predominately of tau isoforms containing three microtubule-binding domain (MTBD) repeats. Some older sources still use the umbrella term of Pick disease to describe the entire family of FTLDs, but this is incorrect. Pick disease is a specific subtype of FTLD-Tau.

The phenotypic presentation of Pick disease typically manifests with behavioral variant frontotemporal dementia, with progressive behavioral and personality changes. Less common phenotypic presentations include primary progressive aphasia or corticobasal syndrome. The clinical phenotype of frontotemporal lobar degeneration syndrome does not easily predict the pathologic subtype of FTLD. Unlike many other forms of FTLD syndromes, Pick disease does not have a clear genetic linkage and is considered sporadic.

In this study, the authors thoroughly investigated the neuropathologic changes, as well as neuroimaging and available clinical histories, of 21 patients with pathologically confirmed Pick disease from a brain bank at the University of Pennsylvania. Tissue samples were immunostained for multiple forms of tau including phospho-tau, 4R tau, 3R tau, tau associated with amyloid as well as ubiquitin, MAP2, and GFAP. Experienced neuropathologists evaluated the specimens for degree of tau inclusions and neuronal loss in multiple brain regions. Clinical histories were derived from chart review by behavioral neurologists. Antemortem MRI imaging was available for five of the 21 cases and was evaluated for gray matter density in various regions as well as white matter diffusivity. After detailed neuropathologic and immunohistochemical analysis of the specimens, the authors hypothesized the presence of four sequential phases of pathologic tau deposition in Pick disease, from mildest (phase I) to most severe (phase IV). Phase I changes involved frontotemporal limbic/paralimbic and neocortical regions. Phase II changes involved subcortical structures, including the basal ganglia, locus ceruleus, and raphe nuclei. Phase III changes involved primary motor cortex and precerebellar nuclei. Phase IV changes involved the visual cortex. Clinically, the mean age of disease onset was 57 years with mean age of death at 65 years. The vast majority of patients (18 of 21) presented with the behavioral variant of FTLD. The other patients presented with either corticobasal syndrome or primary progressive aphasia. All patients eventually manifested behavioral and personality changes. Importantly, pathological tau phases (I through IV) directly correlated with disease duration and inversely correlated with brain weight at autopsy. Imaging changes also correlated with pathologic tau phases. Similar to pathologically defined tau phase I, the authors noted early and severe MRI changes in limbic and paralimbic regions. Regional development of atrophy in follow-up imaging generally correlated with the phases of tau pathology.

■ COMMENTARY

This is an important paper in understanding Pick disease, which is a rare but important form of FTLD. Pick's original description of this disease led to the earliest conceptual understanding of the phenotypic varieties of neurodegenerative illnesses manifesting with cognitive impairment. The concept of progressive, sequential, predictable neuropathologic changes has been well established in other neurodegenerative disorders, especially in Alzheimer's disease and Parkinson's disease. Understanding the pathologic progression of Pick disease may lead to a better understanding of the pathophysiologic underpinnings of this disorder. More work needs to be done to further validate these findings and to build on this work to determine what underlying pathophysiologic etiologies might explain the sequential progression of these pathologic changes. The major unanswered question in all sporadic neurodegenerative diseases is, "What is the cause of the pathologic changes?" Studies like this one help lay the groundwork for future studies that may answer this critical question. ■

ABSTRACT & COMMENTARY

Predicting Seizure Recurrence with Routine EEG after First Unprovoked Seizure

By Kimberly Pargeon, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Pargeon reports no financial relationships relevant to this study.

SYNOPSIS: The authors systematically reviewed prospective and retrospective studies of adults and children undergoing routine electroencephalography (EEG) after a first unprovoked seizure who were followed for at least 1 year. Using positive likelihood ratios, an adult and child with epileptiform discharges on EEG were estimated to have a 77% and 66% probability, respectively, of recurrent seizures.

SOURCE: Bouma HK, et al. The diagnostic accuracy of routine electroencephalography after a first unprovoked seizure. *Eur J Neurol* 2016;23:455-463.

Prior to 2014, the International League Against Epilepsy (ILAE) defined epilepsy as two or more unprovoked seizures separated by more than 24 hours; however, in 2014, the ILAE revised the definition and acknowledged circumstances where a single unprovoked seizure may be diagnosed as epilepsy if the risk of seizure recurrence is ≥ 60% within the next 10 years.[1] One way to assess risk is the routine electroencephalography (EEG), which per the last practice parameter, published in 2007, stated that epileptiform abnormalities after a first unprovoked seizure occur in about 23% of patients and are predictive of future recurrence.[2] The authors of the present study sought to update previous reviews and meta-analyses of the predictive accuracy of routine EEG after a first unprovoked seizure using more rigorous guidelines for conducting and reporting reviews published in 2007 and 2009.

The authors did a systematic search for prospective or retrospective cohort studies looking at patients of any age, presenting with a first unprovoked seizure who underwent a routine EEG, defined as lasting up to 60 minutes, and were followed for recurrence for a minimum of 1 year. A "positive" test was defined as the presence of epileptiform discharges. Other information recorded included seizure type, epilepsy etiology, any treatments with anti-epileptic drugs, timing of EEG relative to the seizure occurrence, and activation procedures. Two authors independently screened all titles and abstracts identified by the initial search (n = 3096), of which 180 full texts which were reviewed, yielding 15 studies.

Despite their systematic process for study selection, there was some heterogeneity between the 15 selected studies, which included 1799 total participants, with some characteristics variably reported. For instance, in nine studies, the participants were primarily pediatric with the remainder of the studies being mostly a mixture of adult and pediatric populations. In seven studies, the duration of the EEG was not defined (described as "routine"). Also, in seven studies, the timing of the EEG relative to the first seizure was not defined, and for the remaining eight studies, there was a range from < 48 hours to several months.

The reported pooled risk of seizure recurrence after a first unprovoked seizure was 44.2%, with the overall pooled sensitivity and specificity for routine EEG of 44.5% and 79.6%, respectively. The pooled sensitivity for routine EEG for adults as compared to children, however, was significantly lower at 17.3% vs 57.8%, whereas the pooled specificity had a trend to be higher in adults (94.7% vs 69.6%). Positive and negative likelihood ratios were calculated for adults and children, which were used with Fagan nomograms (assuming a pretest probability of 50%) to estimate post-test probabilities of epilepsy given a "positive" or "negative" test. They estimated an adult presenting with a first unprovoked seizure has a 77% post-test probability of recurrence if the routine EEG is positive and 47% if it is negative, whereas a child has a 66% post-test probability of recurrence with a positive test and 38% probability with a negative test. They were unable to do any other subgroup analyses given the heterogeneity of the data.

■ COMMENTARY

The 2014 revised ILAE definition of epilepsy, allowing for potential diagnosis after one unprovoked seizure in circumstances where there is at least a 60% chance of recurrence, emphasizes the need to know the diagnostic accuracy of tests, especially EEG. This was the primary goal of this study; however, as with all meta-analyses, it is sometimes difficult to answer specific questions when the source articles are aimed at answering others or are missing key pieces of information. For instance, a few studies included only "genetic" forms of epilepsy, whereas the majority were inclusive of those with either unknown causes or any etiology, which may affect the generalizability of the present results. In addition, for many of the studies, abnormal EEG was one of only

many factors considered for future seizure recurrence, including presence of structural abnormalities, timing of first seizure, treatment with automated external defibrillators, and seizure type. Within a few individual studies, abnormal EEG was not a statistically significant variable related to recurrence. In addition, while a majority of the studies reported either focal or generalized epileptiform discharges, several simply reported "abnormal" EEGs. Finally, the timing of EEG relative to the first seizure either was not reported or was highly variable across the included studies, but early EEG may be more likely to capture epileptiform discharges than a delayed study.[3] ■

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3. King MA, et al. Epileptology of the first-seizure presentation: A clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. *Lancet* 1998;352: 1007-1011.

ABSTRACT & COMMENTARY

Hypoxia-induced Migraine

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: Hypoxia-induced migraine attacks with and without aura, in an experimental paradigm, were accompanied by dilation of cranial arteries in individuals who have migraine with aura, as well as in healthy control subjects.

SOURCE: Arngrim N, et al. Migraine induced by hypoxia: An MRI spectroscopy and angiography study. *Brain* 2016:139;723-737.

The interplay between migraine, alterations in cerebral blood flow, and changes in cerebral oxygen delivery continues to be explored in an effort to explain migraine both with and without aura. Danish investigators tested whether experimental hypoxia could trigger attacks of migraine, as well as metabolic and arterial circumference changes, in patients suffering from migraine with aura. Patients with migraine with aura, who had a typical aura associated with every migraine attack and who also had a minimum of one attack per month, were recruited from the outpatient clinic at the Danish Headache Centre. In a randomized, double-blind, crossover study design, 15 migraine with aura patients were exposed to 180 minutes of normobaric hypoxia (resulting in a capillary oxygen saturation of 70-75%) or to the sham inhalation of atmospheric air on two separate days. Also, 14 healthy controls, recruited via a Danish website for recruitment of volunteers for health research, were exposed to equivalent levels of hypoxia and underwent the same testing. Glutamate and lactate concentrations in the visual cortex were measured by magnetic resonance spectroscopy (MRS). The circumference of standardized extracranial and intracranial cerebral arteries was measured by 3T high-resolution magnetic resonance angiography (MRA). A T1 sequence on MRI ruled out underlying brain pathology.

Eight of 15 migraine patients (53%) experienced migraine-like attacks during hypoxia in comparison to one (7%) during the sham procedure ($P = 0.039$). With hypoxia, three patients reported migraine with aura, and five patients reported migraine without aura. The median time to onset of the migraine-like attacks was 105 minutes, with a median attack duration of 6 hours. One person in the control group of 14 had a migraine-like attack associated with hypoxia. Four out of 15 migraine patients experienced a short period of uncharacteristic visual disturbances, considered to be an atypical aura. For three migraine patients, the visual disturbance occurred during hypoxia, and in one patient it occurred after hypoxia.

Hypoxia did not change glutamate concentration in the visual cortex compared to sham. Hypoxia increased lactate concentration by 61%, as compared to by 7% during sham inhalation. The circumference of the cranial arteries increased with hypoxia. These changes were noted across all experimental groups, as there was no difference in the metabolic or vascular responses to hypoxia between migraine patients and controls. The authors extrapolated from their results that hypoxia may provoke migraine headache and aura symptoms in some patients.

■ COMMENTARY

These investigators found that hypoxia induced migraine-like attacks with and without aura in patients with migraine with aura, without detecting unique cerebral metabolic or vascular changes. Increase in arterial circumference was found due to hypoxia in both experimental groups, not correlating with migraine triggering. In some of the patients, atypical visual auras were also triggered by hypoxia, perhaps mirroring the migraine auras without headache that some migraineurs

experienced. Their work adds to our knowledge of what can cause a migraine attack, and specifically a migraine with aura; but, the mechanisms behind the migraine-inducing effect of hypoxia is still not apparent as no unique correlates were found in those migraineurs with a hypoxia-induced attack. Hypoxia was examined because of the observation that migraine is especially prevalent in areas of higher elevation. However, hypoxia is not a common trigger for most migraine sufferers, and the induced levels of hypoxia were more decreased than in most habitable elevations.

The patients tested all had only migraine with aura, which is unusual as most patients with migraine with aura have auras associated with only a minority of their headaches. The individuals tested seemed to have a particular vulnerability to triggering of attacks that may not be representative of the general migraine population. The probability of inducing a migraine attack appears to be a function of the severity and the duration of the hypoxia, which in this experimental design was profound and prolonged. Another correlate of these hypoxia-induced attacks could be the abruptness of the homeostatic perturbation. Change in weather, sleep, eating habits, and stress can trigger migraine headaches. A revealing experiment would be to gradually decrease oxygen saturation, allowing for adjustment at each decremental level, to mitigate the effect of the abruptness of the change in oxygenation. Acclimatization to high altitude areas of relative hypoxia decreases triggering of headaches.

Despite some knowledge of its pathophysiology, the cause of migraine still remains mysterious, with investigators piecing together information like the three blind men examining different parts of an elephant. One method of investigation is to identify a trigger and then to see if the circumstances of triggering in a vulnerable migraine sufferer can lead to an understanding of why

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Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

A Brief Report of Clinical Trials Results from the 2016 International Stroke Conference

The **FIND A FIB** trial from Switzerland, is a randomized trial of 400 patients with ischemic stroke aged 60 years or older, who were not known to have atrial fibrillation and had normal sinus rhythm at the time of their stroke. One group had standard continuous monitoring of heart rhythm for 24 hours, and the second group had enhanced and prolonged monitoring with three 10-day Holter monitor sessions at the time of the stroke, at 3 months, and at 6 months after the stroke. Atrial fibrillation was found in 13.5% of patients in the group that underwent enhanced and prolonged monitoring and in 4.5% of the control group. Anticoagulation was started when atrial fibrillation was diagnosed; after 1 year, there was a reduced rate of recurrent strokes in the extended monitoring group compared to control (2.5% vs 4.5%).

The **ARUBA** trial is a randomized trial of unruptured brain arteriovenous malformations, and 5-year results were presented. Two hundred twenty-eight patients were enrolled and randomized to medical management of symptoms or to medical management plus invasive management, which included surgery, endovascular embolization, or radiotherapy. Five-year follow-up showed that the death or stroke rate was 40.6% in the intervention group vs 10.8% in the medical group, with a highly significant difference. Stroke rate was 39.6% vs 9.2%. Medical treatment was found to reduce the risk of stroke or death by 78% compared to intervention.

The **CREST** trial, carotid endarterectomy vs stenting for treatment of carotid artery stenosis, presented its long-term results of carotid revascularization endarterectomy (CEA) vs stenting (CAS). In this trial, 2502 patients were randomized and followed at 117 centers, following transient ischemic attack, or mild stroke, or asymptomatic with carotid stenosis. After randomization to either CEA or CAS, they were evaluated every 6 months and followed for a median of 10 years. The primary endpoint, any cause of stroke, myocardial infarction, or death, was not significantly different after 10 years between the two groups. In conclusion, the difference between CEA and CAS was not significant for post-procedural stroke.

The **IRIS** trial was designed to evaluate the effects of pioglitazone, an insulin-sensitizing drug, for secondary stroke prevention in patients with insulin resistance and a recent ischemic stroke or transient ischemic attack. Patients did not have overt diabetes, but had insulin resistance, and were 40 years of age or older. In this trial, 3876 patients were enrolled and the average time for follow-up was 4.8 years. The primary endpoint was fatal or nonfatal stroke or myocardial infarction. Trial results showed that fatal or nonfatal stroke or myocardial infarction occurred in 9% of the pioglitazone-treated patients, and 11.8% of the placebo-controlled group, with a statistically significant difference and *P* value of 0.007. There were more adverse effects in the pioglitazone group, specifically bone fractures, than in the control group. The conclusion was that targeting insulin resistance with pioglitazone resulted in reduction of secondary stroke and myocardial infarction, but there was a greater risk for fractures. ■

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migraine attacks occur under other circumstances. This investigation looked at a relatively unusual trigger for most migraine sufferers. Other similar experimental protocols should be designed around more common triggers, such as sleep deprivation and red wine. ■

CME QUESTIONS

1. **Risk factors for peripheral neuropathic complications following cardiac surgery may include which of the following?**
   a. Patient positioning
   b. Retractor use and placement
   c. Duration of surgery and cardiopulmonary bypass
   d. Use of vasopressors
   e. All the above
2. **Which of the following statements is *false* regarding the development of thalamic pain?**
   a. Involvement of the VPL/VPM is necessary for the development of thalamic pain.
   b. Involvement of the anterior pulvinar is necessary for the development of thalamic pain.
   c. The combination of injury to the spinothalamic system and anatomical involvement of the anterior pulvinar can significantly predict which patients with thalamic stroke will develop thalamic pain syndromes.
   d. Thalamic pain tends to be burning or constrictive.
   e. Abnormalities in lemniscal function do not predict which patients will develop thalamic pain.
3. **Pick disease pathology includes all of the following *except*:**
   a. Pick bodies (intraneuronal tau inclusions).
   b. severe atrophy in limbic and paralimbic areas.
   c. late involvement of the visual cortex.
   d. alpha-synuclein bodies in the cytoplasm.
   e. severe frontotemporal atrophy.
4. **The ILAE updated the definition of epilepsy in 2014 to allow for circumstances where a single unprovoked seizure could lead to a diagnosis of epilepsy where the risk of seizure recurrence is ___% or greater within the next 10 years.**
   a. 80%
   b. 60%
   c. 40%
   d. 20%
5. **Hypoxia-induced increase in cranial arterial circumference occurred in which experimental group or groups?**
   a. Both migraine with aura patients and healthy controls
   b. Both migraine without aura patients and healthy controls
   c. Migraine with aura patients only
   d. Healthy controls only
   e. Neither experimental group
6. **Prolonged cardiac rhythm monitoring increases the rate of finding atrial fibrillation after ischemic stroke.**
   a. True
   b. False
7. **In unruptured arteriovenous malformations of the brain, surgical intervention results in a lower rate of stroke or death than does medical management.**
   a. True
   b. False

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The *Neurology Alert* editors are planning topics for 2016 issues and would like your feedback on topics recently covered. Please help us by answering three questions at the following link: https://www.surveymonkey.com/r/NA0316. Thank you for your help!

[IN FUTURE ISSUES]

Update on Movement Disorders