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Critical Discussion and Commentary

Cerebral Edema and Hemorrhages Associated With Abusive Head Trauma in Children

Subarachnoid and extradural hemorrhages are neuroimaging findings more often seen with nonabusive head trauma, whereas subdural and interhemispheric hemorrhages are strongly associated with abusive head trauma in children

By Sarah B. Mulkey, MD

Based on: Kemp AM, Jaspan T, et al. Neuroimaging: What Neuroradiological Features Distinguish Abusive From Non-Abusive Head Trauma? A Systematic Review. *Arch Dis Child* 2011; 96 (December): 1103-1112.

Abusive head trauma is associated with around 30% mortality and significant neurologic morbidity in survivors. The diagnosis may be complicated by the story or surrounding circumstances not being very clear, so it is important to understand the relevant literature regarding neuroimaging findings associated with abusive head trauma compared to nonabusive head trauma in children. The authors sought to perform a thorough review and meta-analysis of the literature describing neuroimaging findings in pediatric abusive head trauma and nonabusive head trauma.

A detailed literature search was performed of multiple databases, websites, textbooks, and conference abstracts covering a 40-year period using multiple synonyms for abusive head trauma including shaken baby syndrome and nonaccidental head injury among others. Included studies had children less than 11 years of age who required hospitalization for head injury and had either abusive head trauma or nonabusive head trauma with neuroimaging in the form of head CT, brain MRI, or both. The studies also had to have a high degree of certainty that the subject's diagnosis was truly abusive head trauma or nonabusive head trauma with clear definitions. A meta-analysis of the studies was performed, odds ratios, and the degree of heterogeneity among the studies was determined. About 2,300 children, 40% with abusive head trauma, and 60% with nonabusive head trauma from 21 studies were included.

> Subdural hemorrhages were strongly associated with abusive head trauma with an odds ratio of 8.2 and low heterogeneity among studies.

Most of those with nonabusive head trauma had a traumatic injury with only 4% having injury from birth or an organic pathology. Most studies were cross-sectional or comparative case series and focused on children less than three years of age. Head CT was most frequently performed either solely or with a brain MRI. In one study, only brain MRI was done. Subarachnoid and extradural hemorrhages were not statistically associated with abusive head trauma. Subdural hemorrhages on the other hand were strongly associated with abusive head trauma with an odds ratio of 8.2 and low heterogeneity among studies. Interhemispheric and posterior fossa hemorrhages were also connected with abusive head trauma with odds ratios of 9.5 and 2.5, respectively. Extraaxial hemorrhages, as per two studies, were found with abusive head trauma with an odds ratio of 6.0. Those with cerebral edema were twice as likely to have abusive head trauma compared to those with nonabusive head trauma. Focal brain injury was not associated with abusive head trauma. In studies evaluating hypoxic brain injury, as in the brain MRI study, injury in those with abusive head trauma tended to be more diffuse and bilateral. Closed head injury likewise was

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Practical Reviews in Critiques Neurology
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also associated with abusive head trauma with an odds ratio of 4.6. Three studies evaluated a combination of neuroimaging findings and found that the combination subdural hemorrhages, low attenuation in subdural fluid, and no skull fracture were strongly associated with abusive head trauma.

The authors concluded that the neuroimaging features strongly associated with abusive head trauma are subdural and interhemispheric hemorrhages, posterior fossa and/or extraaxial hemorrhages, cerebral edema, having a closed head injury with no skull fracture, and a combination of these findings. This study does a good job bringing together the literature showing that certain neuroimaging features are more often seen in abusive head trauma compared to children without abusive head trauma. Neuroimaging, however, is only one part of the detailed evaluation of these children.

Question Gastroenteritis Symptoms in Children Presenting With New-Onset Seizures

In children, mild hyponatremia is associated with longer seizure duration in gastroenteritis-related seizures

By Sarah B. Mulkey, MD
Based on: Zifman E, Alehan F, et al. Clinical Characterization of Gastroenteritis-Related Seizures in Children: Impact of Fever and Serum Sodium Levels. *J Child Neurol* 2011; 26 (November): 1397-1400.

In your practice, have you differentiated children from febrile seizures related to gastroenteritis from other illnesses? Seizures associated with mild gastroenteritis have been reported in the countries of the Far East for some time, but only recently in the Western Hemisphere. Children can have fever, so may be considered as having a febrile seizure and not given thought for this diagnosis. Dr. Zifman and colleagues sought to evaluate gastroenteritis-related seizures in children and the differences in clinical features for those with and without fever.

A retrospective chart review was performed at a hospital in Turkey and one in Israel during a five-year and three-year period, respectively. Data collected included demographics, findings on neurology examination, detailed report of seizure type and duration, EEG results if performed, routine laboratory testing including serum sodium level, stool culture when performed, family history of seizures, and the subjects' personal history of epilepsy or febrile seizures. Follow-up data was also reviewed. Forty-four children, 57% female, with a median age of 25 months, range three months to nine years, with seizures at the time of gastroenteritis symptoms were identified and included.

Half had emesis, but all had diarrhea at presentation. About 60% had fever, temperature greater than 38 C, at presentation.

All subjects had full alertness at admission and normal neurologic examinations. Most seizures were generalized tonic-clonic, about 90%. Most seizures also were very brief, less than three minutes, and 85% of children only had a single seizure on the day of presentation. Interestingly, almost half of children had hyponatremia with a serum sodium level of less than 135 mmol/L, mean in this group of 132 mmol/L. Seventy percent of these children were febrile, whereas the majority of nonfebrile children had normal serum sodium levels. Seizure duration was also significantly longer in children with hyponatremia, about 6.5 minutes compared to those with normal serum sodium levels, about two minutes with a P value of 0.003 regardless of temperature status. Most had negative stool cultures. For many, this was their first seizure. Three patients, however, had a diagnosis of epilepsy, and two had a previous febrile seizure. In those two children, they did have a high fever at presentation. Most of those who had EEGs had normal studies.

During the follow-up period, lasting anywhere from two months to 54 months, only one child who previously was without epilepsy had a nonfebrile seizure. The authors concluded that seizures associated with gastroenteritis in children occur both with and without fever. The presence of hyponatremia is associated with longer seizure duration. Febrile cases should be included in further studies of this condition and not excluded as febrile seizures, in that seizure characteristics and likelihood for recurrence were similar in the two groups. In children presenting with new onset seizures, questions pertaining to gastroenteritis symptoms are important. In those with febrile seizures or epilepsy, it is also valuable to identify those who may have seizures related to gastroenteritis, as this appears to be a separate condition. Further study is needed in the United States.

No Test Can Perfectly Predict Outcomes After Cardiac Arrest

Hypothermia for coma after cardiac arrest has become widespread, yet questions remain as to the reliability of prognostic signs validated on normothermic patients

By James Warne Schmidley, MD
Based on: Bouwes A, Binnekade JM, et al. Prognosis of Coma After Therapeutic Hypothermia: A Prospective Cohort Study. *Ann Neurol* 2011; 70 (September): epub ahead of print.

Even as hypothermia has become widespread as a treatment for patients in coma after cardiac arrest, questions remain as to the reliability and applicability of prognostic signs and lab tests validated on normothermic patients. A Dutch group did a multicenter, prospective, observational study to assess the accuracy of neurologic signs, serum neuron-specific enolase (NSE), and somatosensory-evoked potentials (SEPs) as predictors of poor outcome in patients who were treated with mild hypothermia after resuscitation from cardiac arrest.

Three hundred ninety-one adults in coma after cardiac arrest who were treated with hypothermia to 32 to 34 C were eligible. Those who had severe preexisting disabilities, a life expectancy less than six months, or who needed the CPR for hypovolemic shock were excluded. The baseline data collected included the location of arrest, the initial rhythm, the time from arrest to CPR and to return of spontaneous circulation, and medical history. The duration of hypothermia and use of potentially sedating drugs were also tracked. Reasons for withdrawal of care were also noted if this occurred, but there was no procedure or set of guidelines for withdrawing supportive care. The pupillary light responses, corneal reflexes, and Glasgow Coma Scale motor scores were evaluated at 48 and 72 hours after CPR. NSE was determined in the serum obtained at admission, 12 hours after reaching the hypothermia target, and then 36 and 48 hours after the arrest. Cortical N20 SEPs were done during hypothermia, and they were repeated after rewarming and clearance of sedatives and metabolites if the patient remained in a coma. The primary outcome measure was poor outcome defined as death, vegetative or severe disability after six months, and that would be a 1, 2, or 3 on the Glasgow Outcome Scale. The results of NSE and SEPs done during hypothermia were not disclosed to ICU personnel.

Just over half of the cohort, that is 208 out of 391 patients, had poor outcome at six months with those suffering in-hospital cardiac arrest and asystole or PEA versus V-tach or V-fib, faring significantly worse. The most useful predictive test was the absence of pupillary reactivity to light at 72 hours. This was 99% specific for a poor outcome with confidence intervals of 93% to 100%. There was one good outcome among 22 patients without reactive pupils. Absent corneal reflexes at 72 hours was 96% specific for a poor outcome with confidence intervals 87% to 99% with two good outcomes among 23 patients lacking corneal reflexes. Absent postwarming SEPs had a specificity of 100% with no good outcomes among 42 patients with an absent N20 when they were normothermic. The data for SEPs during cooling was subject to post hoc reanalysis, and therefore I will not present it here. Motor scores at 72 hours and NSE levels, particularly the latter, were less specific.

The authors concluded that the best predictors of poor outcome after cardiac arrest and hypothermia are brainstem reflexes at 72 hours after arrest and absent SEPs measured after rewarming. As a clinician, I have always been inherently suspicious of SEPs and NSE used for the task of helping predict outcome after global cerebral hypoxia ischemia. This paper found very poor performance of the latter, at least at the cutoff values used. Better specificity can be obtained with a cutoff value that is much higher than the 33 mcg/L used in this trial. It also seems to me that generalizing the results of SEP studies done in dedicated centers to the larger world is also perilous, a problem that the authors acknowledge. It is interesting that EEG was not done or at least was not reported. The findings on the reliability of absent pupillary light reflexes and corneal reflexes and doubts regarding motor responses generally mirror other smaller studies on this issue.

Effect of OnabotulinumtoxinA on Chronic Migraines Is Likely Multifactorial

There will not likely be one mechanism for the effect of botulinum toxin on chronic migraines

By John Schwankhaus, MD
Based on: Durham PL, Cady R. Insights Into the Mechanism of OnabotulinumtoxinA in Chronic Migraine. *Headache* 2011; 51 (November/December): 1573-1577.

Chronic migraine headaches are generally defined as migraine headaches occurring at least four hours a day on at least 15 days a month. They are one of the most challenging disorders for treatment and are often associated with comorbid medication overuse, psychiatric dysfunction, and substance abuse. Botulinum toxin injections have been attempted for this entity and until recently showed promise in open-label studies, but not well-designed placebo controlled trials. Recently two large, phase III, randomized, placebo-controlled, parallel clinical trials entitled Phase II Research Evaluating Migraine Prophylaxis Therapy (PREEMPT 1 and 2) lead to the approval of onabotulinumtoxinA for the treatment of chronic migraine. Positive results have only been shown for chronic migraines and not episodic migraines. The authors of the present review suggest that chronic migraine is not just an extension of episodic migraine and likely has a different pathophysiology and etiology with different diagnostic criteria and response to treatments. Unlike acute pain, chronic pain is not felt to provide a protective function, but instead leads to neuroplastic changes in the nervous system that have a negative impact on health. OnabotulinumtoxinA is not recommended at this time for prophylactic treatment of episodic migraines or tension-type headaches, only the chronic form of migraines.

The following review attempts to explain the mechanism by which this medication provides relief for chronic migraine. It is well known that onabotulinumtoxinA prevents the release of excitatory mediators by preventing the fusion of intracellular vesicles containing neurotransmitters to the cell membrane thereby preventing their release. This is accomplished by disrupting the soluble N-ethylmaleimide sensitive factor attachment protein (SNARE) complex that facilitates vesicle fusion and release. Specifically it binds and cleaves a 25 kDa synaptosomal-associated protein (SNAP-25) that is anchored to the cell membrane and responsible for binding the vesicle-associated membrane protein or VAMP/synaptobrevin. In motor neurons, this blocks the release of acetylcholine. Muscle pain in the neck and shoulders is common in migraines. Sustained signals from the tonic contractions of craniofacial muscles are theorized to be enough to induce prolonged sensitization of nociceptive fibers. Suppressing myogenic trigger points may therefore decrease persistent nociceptive stimulation that helps maintain central sensitization of pain pathways. Internalization of the neurotoxin and sensory neurons that innervate the skin and muscles is postulated to inhibit the release of the proinflammatory mediators (substance P and calcitonin gene-related peptide [CRGP]) at several sites within the sensory neuron. Blocking the release of CRGP and glutamate from nociceptive fibers terminating in the spinal cord could block the maintenance of central sensitization and pain. There may also be an effect on trigeminal neurons by blocking the release of CRGP, glutamate, and substance P and thus inhibiting activation of second order neurons within this system.

The effect of onabotulinumtoxinA on chronic migraines is likely multifactorial, possibly involving several sites within the nervous system, both peripherally and centrally. The exact mechanism of action is unknown at this point. The fact that it does not work for all chronic migraineurs may be due to varying cellular mechanisms for chronic migraine headaches in different individuals. It has been a puzzle to me how botulinum toxin could act to suppress chronic migraine headaches and why the present amount and method of injection of this toxin in the PREEMPT studies is the only one which has shown statistical significance in a well-designed study. Chronic migraines may result from sensitization of peripheral and central pathways. The authors of this review article suggest the onabotulinumtoxinA has direct analgesic effects in addition to its muscle relaxation effects. They postulate that it inhibits overactivity of motor neurons and hyperexcitability of sensory neurons, thus suppressing peripheral and central sensitization of pain pathways. At this time, however, the mechanism of action of botulinum toxin in treating chronic pain is still unknown. Personally I am still in the process of trying this new method of injecting onabotulinumtoxinA in chronic migraineurs to convince myself that it actually works. More studies in both animals and humans will be needed to show the actual mechanism involved in pain relief.

CSF Biomarkers May Help Predict Future AD in Cognitively Normal Subjects

Higher education and greater whole-brain volume are associated with increased neuronal/cognitive reserves that attenuate the development of dementia in subjects harboring Alzheimer pathology

By Michael Jacewicz, MD
Based on: Roe CM, Fagan AM, et al. Cerebrospinal Fluid Biomarkers, Education, Brain Volume, and Future Cognition. *Arch Neurol* 2011; 68 (September): 1145-1151.

Smaller-sized brains and low educational achievement have been considered risk factors for developing Alzheimer disease. Brain size reflects the number of neurons. A smaller, atrophic brain implies a smaller neuronal reserve to cope with evolving brain disease. Higher educational attainment provides a proxy measure of cognitive reserve. Neuronal networks are presumably more efficient and more flexible so that alternative cognitive strategies can be deployed when one strategy fails to complete a task or solve a problem. Thus, both brain size and education have been hypothesized to attenuate and delay the appearance of cognitive impairment in the presence of Alzheimer pathology. This hypothesis of cognitive/brain reserve has received indirect support from multiple clinical observations, but until recently, it has not been possible to test it directly.

That has changed with the advent of CSF biomarkers for Alzheimer pathology. In a recent article, Roe and colleagues examine how CSF β-amyloid, tau, and phosphorylated-tau interact with education and brain volume to predict dementia in cognitively normal subjects.

The primary constituent in amyloid plaques, β-amyloid, is decreased in the CSF of Alzheimer patients, whereas tau and phosphorylated-tau, the primary components of neurofibrillary tangles, are increased. Accumulating evidence indicates that these CSF biomarkers can predict future cognitive impairment in cognitively normal individuals. However, they do not predict when this will happen. It is conceivable that in some individuals these biomarkers may reach abnormal levels in the CSF a decade or more before dementia becomes clinically evident. That poses a problem if one wants to use one of the disease-modifying drugs currently being developed for Alzheimer disease and avoid exposing healthy individuals to their potential adverse effects and expense of treatment many years before treatment is needed. It thus becomes highly desirable to identify the factors that influence the time course of Alzheimer dementia in patients identified as being at risk for its development.

The authors recruited 197 individuals, all with normal cognition, 50 years and older, from participants in longitudinal studies of dementia at a university-based Alzheimer Research Center. They called their cohort a "convenience sample" implying that they could not exclude some sampling selection bias. CSF was tested for β-amyloid, tau, and phosphorylated-tau. Brain volume was measured by MRI. Subjects were evaluated annually for a decline in their Clinical Dementia Rating. This was a composite rating that the investigators had previously validated for memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Brain volume and education were analyzed for their interaction with CSF biomarkers and the time to cognitive impairment.

The subjects had an average age of 69, and 65% were women. The years spent in education totaled a mean 16 years plus or minus a standard deviation of three years. In other words, the average study subject had a college education. The Mini-Mental State Examination (MMSE) averaged 29 out of 30. During an average 3.3 years follow-up, 26 patients developed cognitive impairment. Of these 26 patients, eight satisfied criteria for Alzheimer disease. In 17 the dementia type was still uncertain. One was diagnosed with vascular dementia.

The following refers to the 26 patients who developed cognitive impairment over the course of the study. In subjects who were found to have low CSF tau values and therefore were not considered at risk for Alzheimer dementia, brain volume but not education correlated with time to cognitive impairment. About 10 to 20% with smaller brain volumes started to show cognitive impairment at three years. In other words, small brain size was a risk factor for earlier cognitive decline unrelated to Alzheimer pathology, and education provided no protection. In subjects with low CSF phosphorylated-tau and also considered a low risk for Alzheimer disease, neither education nor brain volume influenced the time of cognitive impairment. For individuals harboring high CSF levels of tau and/or phosphorylated-tau, considered high risk for Alzheimer disease, education interacted with brain volume to moderate early versus late cognitive impairment. Kaplan-Meier curves showed 40 to 50% of these high-risk individuals exhibited cognitive impairment by three years when brain volume and educational levels were both low.

In contrast, less than 10% of the high-risk individuals showed cognitive impairment at three years if brain volume was normal and education levels were higher. If brain volume was normal but education low, cognitive fall off started to appear at four years in these high-risk individuals. Surprisingly, no such interaction between brain volume and education was found for individuals with low CSF β-amyloid. Other variables that independently predicted time to impaired cognition included minority race and male sex. Oddly enough, age did not influence time to cognitive impairment. This was explained by the fact that brain volume and age are so tightly associated, that adding age as a variable into the statistical analysis provided no additional predictive power.

The authors conclude that cognitively intact individuals, who have higher levels of CSF tau and phosphorylated-tau and therefore are at risk for Alzheimer pathology, develop cognitive impairment earlier if brain volume is smaller and educational attainment is low. In contrast, similarly high-risk individuals who exhibit normal brain volume and greater educational achievement develop dementia later. The results support the cognitive/brain reserve hypothesis.

Why the authors found a modifying effect of education and brain volume on incident cognitive impairment for tau-based but not amyloid-based Alzheimer pathology is not clear. They suggest that the latter may require a higher sample size and/or longer follow-up than that realized in this study. Alternatively, tau-based pathology might turn out to be more important than amyloid in governing the timing of dementia onset.

Seizure Risk Within First Seven Days Post-Stroke Greatest With Primary Intracerebral Hemorrhage

Cortical lesions increase the risk of seizures within the first seven days after stroke

By Brian Silver, MD
Based on: Beghi E, D'Alessandro R, et al. Incidence and Predictors of Acute Symptomatic Seizures After Stroke. *Neurology* 2011; 77 (November 15): 1785-1793.

Stroke is the leading cause of seizures in older patients. However, the reported incidence of early seizures has varied significantly across studies possibly due to population studied (general population versus referred patients), study design (prospective versus retrospective), diagnostic criteria (first or recurrent stroke), timing of seizures, length of follow-up, and use of anti-epileptics. More precise knowledge of incidence and predictors of seizures might lay the groundwork for future trials of primary seizure prevention after stroke.

Beghi and colleagues sought to determine the incidence and predictors of "early" seizures after first stroke in a large prospective cohort. Patients with first-ever stroke who were hospitalized at one of 31 Italian hospitals from November 1, 2007 onward were included in the study. Although the Institutional Review Board at each hospital approved the study, signed informed consent was not required from each patient. According to Italian law, the information obtained was an integral part of the diagnostic workup, and anonymous data were collected. Therefore, researchers were able to track all patients rather than just those who agreed to have their data used as part of the study. The diagnosis of stroke required confirmation on neuroimaging. Seizures were classified as "early" if they occurred within the first seven days of stroke and "unprovoked" if they occurred after that time. Epilepsy was defined as repeated unprovoked seizures. Patients with recurrent stroke, a prior history of seizures, onset of symptoms more than 24 hours after admission, and subarachnoid hemorrhage were excluded. Possible seizure predictors that were investigated included age, gender, family history, patient risk factors for stroke, stroke subtype, lesion size, lesion location, arterial territory, stroke etiology according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, stroke severity on the NIH stroke scale, and functional disability on the modified Rankin scale. The diagnosis of seizure was based on direct observation by medical staff or by history according to a reliable witness such as a close family member or ambulance personnel. A brief episode of loss of consciousness or mental confusion was not considered sufficient for the diagnosis of seizure. An EEG was performed only when it was thought to be indicated by the attending physician.

Seven hundred fourteen patients with first-ever stroke were enrolled. Fifty-six percent were male, and the mean age was 71.2 years; 14.7% of patients had a primary intracerebral hemorrhage, and the remainder had ischemic stroke. Of ischemic stroke patients, 4.5% had hemorrhagic transformation. Nineteen point seven percent (19.7%) of patients had a large lesion, and 41.5% had a cortical lesion. Most commonly, multiple lobes were involved. Only 1.7% of patients reported a family history of seizures. "Early" seizures occurred in 6.3% of all patients. Nearly three-fourths of all "early" seizures occurred within the first 24 hours. Partial seizures was the most common type and accounted for 68% of the entire group. By stroke subgroup, 16.2% of patients with intracerebral hemorrhage, 12.5% of patients with ischemic stroke with hemorrhagic transformation, and 4.2% of patients with ischemic stroke had an "early" seizure. The paper has additional details according to gender, age, family history, lesion site, lesion size, arterial territory, cerebral location, modified Rankin score, and NIH stroke scale score. In multivariate analysis, independent predictors of seizures were intracerebral hemorrhage which predicted a seven-fold increase and cortical location which predicted a three-fold increase. Hyperlipidemia predicted a five-fold lower risk of seizures in patients with intracerebral hemorrhage. Thirty-day mortality was 12.5% in patients with seizures versus 6.3% in patients without seizures.

The authors concluded the incidence of "early" seizures in their series was the highest reported in patients with first-ever stroke. Previous series have shown rates ranging from 1.8 to 5.5%. They also concluded that intracerebral hemorrhage and cortical location were independent predictors of seizures in all patients with stroke while hyperlipidemia was protective in those with intracerebral hemorrhage.

This is a very good study because of the large sample size, careful classification of stroke etiology, and excellent recruitment and retention. These studies may form the basis for future studies of intervention with AEDs in high-risk subgroups. Long-term follow-up is already planned in this study.

reviews

Literature Reviews

Subjective Muscle Symptoms Are Common With Statin Use

Acquired Muscular Disorders

Take Home Pearl:

Among subjects taking a statin, 24.5% of diabetic patients have subjective muscle symptoms of myalgia or weakness.

Background: Statins are 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) inhibitors that reduce serum cholesterol levels and provide significant reductions in atherosclerosis and vascular complications. Major adverse reactions occur in liver and muscle. Elevated hepatic transaminase enzymes occur in 0.5% to 2.0% of patients. Clinical trials designed to test statin efficacy, case reports, and case series have suggested that 1% to 7% of patients taking a statin will report myalgia, with myopathy occurring in 0.1% to 0.2% of patients. A retrospective cohort analysis suggested that a person taking a statin is 7.6 times as likely to develop a myopathy than a member of the general population. A variety of concomitant risk factors have been suggested.

Objective: To investigate the prevalence and risk factors of muscle complications secondary to statins.

Design: Prospective, comparative study.

Participants: 345 subjects receiving a statin (M/F, 207/138; age, 59 ± 8 years) were included and compared to an age-matched and gender-matched control group of 85 subjects (M/F, 54/31; age, 57 ± 11 years). There were no significant differences between the two groups for age, gender, body mass index (BMI), and history of stroke or diabetes, although there was a trend for the control group to have less prevalent stroke or diabetes. The total duration of statin use was 1 to 180 months (mean, 21 ± 28 months).

Methods: Subjects were followed for 12 months. Any subject with muscle

complaints (myalgia or weakness) was examined and serum CPK was checked.

Results: Adverse reactions were reported by 21% of patients and 5.9% of controls (*P* =0.0013). Objective weakness was found on examination in 15% of patients who reported muscle symptoms (3.2% of the cohort), but not in controls. Older age, longer duration of statin use, diabetes, stroke, and lower BMI were associated with increased risk of developing these symptoms. Only 2 subjects had modest CPK elevations; both had objective weakness on examination. Muscle symptoms were significantly associated with older age, duration of statin use, lower BMI, and history of stroke or diabetes; 24.5% of diabetic subjects had subjective muscle symptoms.

Conclusions: Adverse reactions to statins may be more common than previously reported, although usually mild, and may be affected by specific patient and disease characteristics. Older age, longer duration of statin use, diabetes, stroke, and lower BMI may increase the odds of developing these complications.

Reviewer's Comments: Statin use is ubiquitous. Sometimes patients report that they can tolerate one statin, but not several others. Muscle symptoms may be more common than previously reported, although necrotizing myopathy appears to be uncommon. The major strength of this study is that it was prospective and controlled. It could have been better with larger groups and longer follow-up.

Reviewer: W. Steven Metzer, MD
Article Reviewed: El-Salem K, Ababneh B, et al. Prevalence and Risk Factors of Muscle Complications Secondary to Statins. *Muscle Nerve* 2011; 44 (December): 877-881.

SpA Remains Gold Standard for Diagnosis of Spinal Vascular Malformations

Imaging

Take Home Pearl:
Spinal angiography is safe and remains the gold standard for diagnosis of spinal vascular malformation because of low routine MRI sensitivity.

Background: Spinal angiography (SpA) is the diagnostic modality of choice for visualization of vascular anomalies of the spinal cord. Historically, and based mostly on case reports, there is an unproven assumption that spA carries a high risk of iatrogenic adverse events including neurological complications.

Objective: To evaluate the rates and risk factors for complications of spinal digital subtraction angiography (SpDSA) and to assess the diagnostic value of SpA.

Design: Retrospective review of all SpAs done in one tertiary center in the U.S. over a 10-year period.

Methods: Most studies were performed by neuroradiology fellows supervised closely by an experienced neuroradiologist. Intraoperative spAs and SpAs done as part of a therapeutic intervention were excluded. The primary outcome was the incidence of neurologic, non-neurologic, and local complications during or immediately after the procedure. The secondary outcome was assessment of the diagnostic utility of SpA.

Results: 302 diagnostic spinal angiograms, performed in 288 patients were selected and analyzed. Of those, 286 were complete (ie, investigated all intersegmental arteries). Vertebral artery injections were performed in 202 patients (67%). The artery of Adamkiewicz was successfully identified in 294 patients (97%). There were no intraprocedural or postprocedural neurologic or thromboembolic complications recorded (0.0%; 95% CI, 0.0% to 1.2%). Local groin hematomas occurred in 3 patients (1.0%; 95% CI, 0.2% to 2.9%). One patient developed pulmonary edema and one other had back spasms. The indication for SpA was vascular malformation in 236 procedures (78%) and a vascular malformation (mostly dural arteriovenous fistulas) was detected in 65 cases (21%). In 45 patients with prior diagnosis of transverse myelitis, 14 (31%) had vascular malformations. Of 61 patients with vascular malformation, MRI was positive (flow voids or abnormally enlarged and enhancing vessels) in 31, while in 175 patients with no malformation, negative MRI was seen in 141 (51% sensitivity, 83% specificity).

Conclusions: SpA is a safe procedure with low systemic and neurologic complications. It remains the gold standard for the diagnosis of spinal vascular malformations.

Reviewer's Comments: Complete spinal angiography is labor intensive and requires expert neuroangiographers. This study is very useful since it negates the myth that spinal angiography is risky even when performed in tertiary centers. This study also shows that routine MRI is not sensitive enough to exclude spinal vascular malformations. Unfortunately, it did not evaluate an emerging and promising new technology, contrasted spinal MR angiography, which is likely more sensitive in visualizing spinal arteriovenous malformations than routine MRI.

Reviewer: Bashar Katirji, MD, FACP
Article Reviewed: Chen J, Gailloud P. Safety of Spinal Angiography: Complication Rate Analysis in 302 Diagnostic Angiograms. *Neurology* 2011; 77 (September 27): 1235-1240.

Does Thrombolytic Treatment Affect Favorable Outcomes Post-Ischemic Stroke?

Ischemia

Take Home Pearl:

The rate of intracranial bleeding after thrombolysis is no higher among ischemic strokes caused by arterial dissection than among those caused by other arterial diseases.

Objective: To determine the risks and benefits of thrombolytic treatment of ischemic stroke caused by arterial dissection.

Design: Retrospective study.

Methods: The National Inpatient Sample, a large administrative database derived from inpatient stays in 1000 U.S. hospitals, was the source of information. Available data included diagnoses, procedures, demographic information, and hospital discharge status. The latter was used as a surrogate for clinical outcome. Odds ratios (ORs) of outcomes were adjusted by multivariate analysis for many confounding variables, including age, sex, hypertension, and diabetes.

Results: Among 47,899 patients treated by thrombolysis for ischemic stroke from 2005 to 2008, 488 (1%) had arterial dissection, but location (extracranial or intracranial, anterior or posterior circulation) and NIH Stroke Scale scores were unknown. Most patients were treated with intravenous thrombolysis, but more than 3 times as many with dissection (32%) were treated with intra-arterial thrombolysis as those without dissection (9%). The rate of subarachnoid and cerebral bleeding after thrombolysis was no higher in patients with dissection (6.9%) than in those without dissection (6.4%). The rate of moderate to severe disability upon hospital discharge (poor outcome) was higher among the patients with dissection than those without it (OR, 2.8; 95% CI, 1.7 to 4.6; P <0.001). The same was true, however, among the 3 million stroke patients with and without dissection who were not treated with thrombolysis.

Conclusions: The rate of intracranial bleeding after thrombolysis is no higher among ischemic strokes caused by arterial dissection than among those caused by other arterial diseases. The functional outcome of stroke caused by arterial dissection is worse than that of stroke caused by other diseases, whether treated by thrombolysis or not.

Reviewer's Comments: The risk of subarachnoid hemorrhage in intracranial vertebral-artery dissection is thought to be higher than that in intracranial carotid dissection, but this study lacks the data to determine whether thrombolysis increases the relative risk. It also lacks the data to determine whether there is any benefit of thrombolysis in stroke due to arterial dissection.

Reviewer: Marc David Winkelman, MD
Article Reviewed: Qureshi AI, Chaudhry SA, et al. Thrombolytic Treatment of Patients With Acute Ischemic Stroke Related to Underlying Arterial Dissection in the United States. *Arch Neurol* 2011; 68 (December): 1536-1542.

$CHADS_2$ Score Helps Predict Stroke, Bleeding, Death in Treated AF Patients

Imaging

Take Home Pearl:

Both doses of dabigatran in the Randomized Evaluation of Long-Term Anticoagulation Therapy trial (150 mg and 110 mg twice daily) are associated with lower risk of intracranial bleeding compared with warfarin.

Background: $CHADS_2$ score is validated for predicting stroke risk in atrial fibrillation (AF) patients untreated with anticoagulants. Patients are assigned 1 point each for congestive heart failure, hypertension, age ≥75 years and diabetes, and 2 points for a history of stroke/transient ischemic attack. There are few data on survival and bleeding rates related to this score, especially during anticoagulant treatment. The threshold at which oral anticoagulant benefit for stroke prevention in AF exceeds risk for bleeding is unclear.

Objective: To evaluate the prognostic importance of $CHADS_2$ score in AF patients receiving oral anticoagulants and to assess study treatment interactions by $CHADS_2$ risk groups.

Design: The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial compared the direct thrombin inhibitor, dabigatran, with warfarin for stroke prevention in AF patients. This is a subgroup-analysis evaluating the prognostic importance of $CHADS_2$ risk score in AF patients receiving oral anticoagulants and assessing study treatment interactions by $CHADS_2$ risk groups.

Participants: 18,112 patients with AF receiving oral anticoagulants, including 5775 subjects with $CHADS_2$ of 0 to 1, 6455 with $CHADS_2$ of 2, and 5882 with $CHADS_2$ of 3 to 6 were part of this study.

Methods: This trial compared 2 blinded doses of dabigatran (150 mg and 110 mg twice daily) with open-label warfarin, in AF patients.

Results: Rates of stroke/systemic embolism, major/intracranial bleeding, and vascular/total mortality each increased in the warfarin and dabigatran groups as $CHADS_2$ score increased. Annual stroke/systemic embolism rates among all treated participants were 0.93% with a $CHADS_2$ of 0 to 1, 1.22% with a $CHADS_2$ of 2, and 2.24% with a $CHADS_2$ of 3 to 6. Major bleeding occurred in these groups for 2.26%, 3.11%, and 4.42% of subjects, respectively. Intracranial bleeding occurred in these groups for 0.31%, 0.40%, and 0.61% of subjects, respectively. Vascular mortality occurred in these groups for 1.35%, 2.39%, and 3.68%, respectively. All of these comparisons were statistically significant (P <0.001). An almost linear increase in the annual rate of major bleeding for each 1-point increase in $CHADS_2$ score occurred in the overall cohort, from 1.6% to 5.4% per year (P <0.001). Intracranial bleeding rates were related to $CHADS_2$, with rates from 0.11% per year with a $CHADS_2$ score of 0, to 1.1% with a $CHADS_2$ score of 5 (P <0.001). Intracranial bleeding was lower in both dabigatran groups compared to the warfarin group.

Conclusions: Higher $CHADS_2$ scores were associated with increased risk for stroke/systemic embolism, bleeding, and death in AF patients receiving oral anticoagulants. Both dabigatran doses were associated with a reduction in intracranial bleeding compared with warfarin.

Reviewer's Comments: $CHADS_2$ score can help predict the risk for stroke, bleeding, and death for treated AF patients. However, bleeding rates are significantly lower with dabigatran. It appears that the utility of warfarin for the prevention of stroke in AF patients may be coming to an end.

Reviewer: W. Steven Metzer, MD
Article Reviewed: Oldgren J, Alings M, et al. Risks for Stroke, Bleeding, and Death in Patients With Atrial Fibrillation Receiving Dabigatran or Warfarin in Relation to the $CHADS_2$ Score: A Subgroup Analysis of the RE-LY Trial. *Ann Intern Med* 2011; 155 (November 15): 660-667.

What Dose of Dihydroergotamine Provides Better Headache Relief?

Migraine

Take Home Pearl:

A dose of dihydroergotamine of 11.25 mg given over 5 days leads to a better response of refractory headache than the customary dose of 3 to 9 mg given over 2 to 3 days.

Background: Giving repeated IV doses of dihydroergotamine (DHE) in the hospital for 2 to 3 days is an effective way to treat migraine and cluster headache refractory to oral medicines.

Objective: To test 2 hypotheses: (1) a higher total dose of IV DHE, given over a longer period of time, will be even more effective; and (2) poorly controlled nausea during treatment leads to a poor response of headache.

Design: Contemporaneous "audit" of treatment of a cohort of patients.

Participants: This cohort consisted of 163 patients treated for refractory headache with IV DHE. Most (n=114) had migraine, with an average duration of chronic daily headache (>14 days per month) of 21 years and an average attack frequency of 4 days/week before treatment. There were 34 patients with chronic cluster headache and 4 with episodic cluster; they had an average of 27 attacks per week before treatment. Eleven patients had new daily persistent headache (NDPH).

Methods: Statistical methods were used to see whether control of nausea or the dose of DHE correlated with a response of "pain free" at the end of treatment. DHE was given IV every 8 hours. The first dose was 0.5 mg, the second was 0.75 mg, and the next 10 were 1 mg each. Each dose was given in 250 mL of normal saline over 1 hour. The total dose of DHE ranged from 8.25 to 11.25 mg and depended on side effects, response of headache, and logistics of admission. To prevent nausea, ondansetron 4 to 8 mg IV was given 30 minutes before each dose of DHE.

Results: Among the migraine patients, 67% achieved freedom from headache during treatment and 75% reported headache freedom within the next month. The effect lasted an average of 28 days. Among the patients with cluster headache, 84% became headache-free during treatment. The mean time to return of headaches was 17 days. Only 18% of patients with NDPH had even a slight response to DHE, and the others had none. A higher dose of DHE correlated directly, and more severe nausea, inversely, with freedom from headache immediately after treatment.

Conclusions: A total dose of DHE of 11.25 mg given over 5 days leads to a better response of refractory headache than the customary dose of 3 to 9 mg given over 2 to 3 days. Effective control of nausea also leads to a better response. Patients with migraine may not become pain-free until after leaving the hospital.

Reviewer's Comments: Some patients with refractory migraine do not become pain-free after the customary 3-day protocol of IV DHE. This study shows that they may become so if given an extra day or 2 of treatment. It does not, however, show that they stay headache-free longer.

Reviewer: Marc David Winkelman, MD
Article Reviewed: Nagy AJ, Gandhi S, et al. Intravenous Dihydroergotamine for Inpatient Management of Refractory Primary Headaches. *Neurology* 2011; 77 (November 15): 1827-1832.

Is Immunomodulation a Sensible Approach to Treat PPMS?

Multiple Sclerosis

Take Home Pearl:

Treatment of primary progressive multiple sclerosis with interferon beta-1b produces modest gains in some clinical and MRI measures that persist 5 years later but has not been shown to produce a clinically meaningful reduction in long-term disability.

Background: No treatment of primary progressive multiple sclerosis (PPMS) is known to retard the accumulation of disability, but in a recent clinical trial, patients given interferon beta-1b (Iβ-1b) developed fewer active lesions on MRI and performed better on parts of the Multiple Sclerosis Functional Composite (MSFC; a battery of tests of neurologic and cognitive function) than patients given placebo (*Multiple Sclerosis*. 2009; 15: 1195-1205).

Objective: To determine whether the treated patients had maintained their gains, without treatment, 5 years later.

Design: Patients who took part in the 2-year, double-blind, placebo-controlled trial were reassessed 5 years after it had ended.

Participants: 63 patients with PPMS: 32 from the Iβ-1b group and 31 from the placebo group.

Methods: Patients were assessed with the Expanded Disability Status Scale (EDSS), the MSFC, the Brief Repeatable Battery of Neuropsychological Tests (BRBNT), and with MRI of the head.

Results: Patients from the Iβ-1b group had significantly better scores on the 9-hole peg test, a test of upper-limb function from the MSFC, and on the word-list generation test, a test of semantic fluency from the BRBNT, than patients from the placebo group. The treated patients did not do better on the EDSS or the many other tests in the MSFC or BRBNT. Patients from the placebo group had significantly more brain atrophy on MRI than those from the Iβ-1b group, but the 2 groups did not differ in the burden of MS lesions on T1-weighted or T2-weighted MRI or in the number of active lesions.

Conclusions: Treatment of PPMS with Iβ-1b produces modest gains in some clinical and MRI measures that persist 5 years later; therefore, according to the authors, "immunomodulation is a sensible approach to treat PPMS".

Reviewer's Comments: I do not think clinicians will use immunomodulatory drugs to treat PPMS until the drugs have been shown to produce a clinically meaningful reduction in long-term disability, not just a statistically significant one.

Reviewer: Marc David Winkelman, MD
Article Reviewed: Tur C, Montalban X, et al. Interferon Beta-1b for the Treatment of Primary Progressive Multiple Sclerosis: Five-Year Clinical Trial Follow-Up. *Arch Neurol* 2011; 68 (November): 1421-1427.

Written Protocols for Screening Augment Care in Stroke Units

Other

Take Home Pearl:
In this study, dysphagia screening improved from 7% to 46% in the first 24 hours when a written protocol was introduced.

Background: Up to 50% of stroke patients have temperatures >37.5°C, up to 50% become hyperglycemic, and up to 78% have dysphagia.

Objective: To assess the effect of multidisciplinary teams and standardized education programs to implement evidence-based treatment protocols for the management of fever, hyperglycemia, and dysphagia on 90-day outcomes after stroke.

Design: Cluster randomized trial.

Participants/Methods: Hospitals included those in New South Wales, Australia with patients aged ≥18 years presenting within 48 hours of an ischemic or hemorrhagic stroke. Prior to randomization, a baseline sample of patients admitted to all stroke units from July 30, 2005, to October 30, 2007, was recruited. Afterwards, randomization of acute stroke units to an abridged version of existing guidelines versus detailed protocols occurred between May 15, 2007, and August 25, 2010. The intervention consisted of a prescribed protocol to treat fever, elevated blood sugar, and deranged swallowing abbreviated by the acronym FeSS. Primary outcomes were modified Rankin scores, Barthel indices, and SF-36 scores at 90 days.

Results: Of 19 stroke units randomly assigned, 10 received detailed protocols as previously described, and 9 received the abridged version of existing guidelines. Nearly 1700 patients were included in the study of which 687 were pre-intervention and 1009 were post-intervention. Baseline data from patients in the pre- and post-randomization period were similar in both the intervention and control stroke units. After adjustment for baseline variables, patients in the stroke units receiving detailed protocols were less likely to be dead or dependent at 90 days and had a better physical component score on the SF-36 survey. The number needed to treat to reduce death and disability (Rankin ≥2) was 6.4. No differences were observed in 90-day mortality, functional dependency, and mental health scores on the SF-36 survey. Patients in the stroke units with detailed protocols had statistically lower mean temperatures in the first 72 hours (36.5°C vs 36.6°C), had lower mean blood sugar levels in the first 72 hours (122 vs 126 mg/dL), and more likely received a swallowing screen in the first 24 hours (46% vs 7%).

Conclusions: Evidence-based protocols for the management of fever, hyperglycemia, and dysphagia improve patient outcome and further augment stroke unit care.

Reviewer's Comments: The strength of this study is the large group of patients studied and the demonstration of improved outcomes in randomized trials with organized systems of care. What is less clear from this study is which intervention specifically led to the improved outcomes. The changes in patient temperatures and blood sugars were rather small, while changes in dysphagia screening were rather large. Further studies are needed to precisely define which interventions provide the most significant clinical benefit.

Reviewer: Brian Silver, MD
Article Reviewed: Middleton S, McElduff P, et al. Implementation of Evidence-Based Treatment Protocols to Manage Fever, Hyperglycaemia, and Swallowing Dysfunction in Acute Stroke (QASC): A Cluster Randomised Controlled Trial. *Lancet* 2011; 378 (November 12): 1699-1706.

What Clues Help Distinguish ICAD From VAD?

Other

Take Home Pearl:
Cervical pain is more common with vertebral artery dissection, and headaches are more common with internal carotid artery dissection.

Background: Cervical artery dissections (CEADs) affecting both the internal carotid artery dissection (ICAD) and the vertebral artery dissection (VAD) are a common cause of stroke in young adults.

Objective: To identify distinguishing characteristics of ICAD and VAD.

Participants: Consecutive patients with CEAD who had been enrolled in the Cervical Artery Dissection and Ischemic

Stroke Patients (CADISP) study were included.

Methods: The CADISP study was a genetic association study to identify genetic risk factors for the development of CEAD. CADISP included 983 patients with CEAD plus 658 age- and gender-matched controls with a diagnosis of non-CEAD ischemic strokes. Patients with CEAD had to present a mural hematoma, aneurysmal dilatation, long tapering stenosis, intimal flap, double lumen, or occlusion >2 cm above the carotid bifurcation revealing an aneurysmal dilatation or a long tapering stenosis after recanalization in a cervical artery. A single patient with a dissection of the common carotid and subclavian was excluded as were 36 patients who had both ICAD and VAD. The prevalence of factors previously known to be associated with increased risk was examined, including hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications), cervical trauma (severe if sought medical advice, otherwise minor), recent infection, and migraine. Also, those associated with a decreased risk were evaluated, including elevated body mass index and hypercholesterolemia (fasting total cholesterol ≥6.20 mmol/L or fasting low-density cholesterol ≥4.1 mmol/L). The presence of cerebral or retinal ischemia, cervical pain, or headache was recorded. Radiological parameters recorded included arterial occlusion, stenosis, aneurysmal dilatation, mural hematoma, and multiple dissections. The short-term outcome was rated by the modified Rankin scale. Statistical analysis was performed.

Results: ICAD patients were significantly older. VAD occurred equally among males and females, while ICAD was more frequent in males. An infection in the preceding week was more common in ICAD, whereas minor cervical trauma was more common in patients with VAD. Cervical pain was twice as common in VAD, while headache on admission was slightly more common in the ICAD group. Cerebral ischemia, and specifically ischemic stroke (IS), was significantly more frequent with VAD. In those with IS, the NIH Stroke Scale score was higher in the ICAD group. Three-month follow-up information was available in 300 patients; all survived. The 3-month functional outcome was favorable in 74.7% of patients with ICAD and 92.5% with VAD; 19 had recurrent ICAD at 3 months.

Conclusions: There were significant differences between VAD and ICAD in terms of risk factors, baseline features, and functional outcome.

Reviewer's Comments: This study provides clues that can help distinguish ICAD from VAD. A favorable outcome is usually seen in both types of dissections.

Reviewer: John Schwankhaus, MD
Article Reviewed: Debette S, Grond-Ginsbach C, et al. Differential Features of Carotid and Vertebral Artery Dissections: The CADISP Study. *Neurology* 2011; 77 (September 20): 1174-1181.

Antiglycine Receptor Antibodies May Be Present in Stiff-Person Syndrome

Other

Take Home Pearl:

Antiglycine receptor antibodies should be added to antiglutamic acid decarboxylase and amphiphysin antibodies in the evaluation of patients presenting with stiff-person–like syndromes.

Background: Glycine, a simple amino acid, is a major neurotransmitter of inhibitory neurons in the spinal cord and brainstem, and often coexists with gamma-aminobutyric acid (GABA). Well-recognized, life-threatening motor hyperexcitability disorders result from intoxications that result in the loss of glycine inhibition, such as with tetanus toxin, which impairs glycine presynaptic release, or strychnine, which blocks glycine postsynaptic receptors. More recent advances have shown that excessive synaptic levels of glycine may explain the manifestations of nonketotic hyperglycinemia, an autosomal recessive disorder caused by mutations that causes deficiency in the glycine cleavage system. In contrast, mutations of the glycine presynaptic transporter or postsynaptic glycine receptor lead to glycine loss-of-function and are the basis of the syndromes of familial hyperekplexia. Patients with progressive, and sometimes fatal, syndromes with encephalopathy, myoclonus, cerebellar ataxia, and limb rigidity have been classified progressive encephalomyelitis with rigidity and myoclonus (PERM) or stiff-person syndrome plus (SPS-Plus). This syndrome has recently been reported to be associated with autoantibodies against components of the glycine receptor complex.

Objective: To report the clinical manifestations of 3 patients with elevated antiglycine receptor antibodies.

Methods: All patients had normal routine hematological, biochemical, and cerebrospinal fluid (CSF) analysis, normal brain and spine MRI and whole-body CT, as well negative CSF oligoclonal bands, glutamic acid decarboxylase (GAD) antibodies, and paraneoplastic antibodies (including anti-Hu, Yo, Ri, CV2, Ma2, and amphiphysin). Serum from all 3 patients and CSF from 2 patients were positive for glycine receptor antibody with scores of 3 to 3.5 on a scale of 0 to 4.

Results: One patient had a typical subacute presentation of PERM with encephalopathy, brainstem findings, rigidity, and stimulus-sensitive myoclonus. He also had additional seizures, severe dysautonomia, and poor outcome. The other 2 patients developed less aggressive disorders, but had also personality changes, rigidity, dysphagia, and involuntary jerks. One of them had trismus and opisthotonus. Both responded to treatment with IV immunoglobulins and corticosteroids in addition to diazepam, baclofen, and gabapentin.

Conclusions: Patients with progressive encephalomyelitis with rigidity and myoclonus (PERM) or SPS-Plus may have elevated antiglycine receptor antibodies and respond to immunomodulation therapy.

Reviewer's Comments: Autoimmunity is increasingly recognized as an important cause of subacute onset motor hyperactivity syndromes as

seen in the SPS (with or without additional neuraxis involvements). Although anti-GAD antibodies are still the most common, amphiphysin antibodies should be considered in older women and alert for an occult breast cancer. Now, antiglycine receptor antibodies should also be added, and this syndrome may also respond to immunomodulation.

Reviewer: Bashar Katirji, MD, FACP
Article Reviewed: Mas N, Saiz A, et al. Antiglycine-Receptor Encephalomyelitis With Rigidity. *J Neurol Neurosurg Psychiatry* 2011; 82 (December): 1399-1401.

How Does Neurologic Disease Associated With PCA-1 Present?

Remote Effects/Paraneoplastic

Take Home Pearl:
Although most women with neurologic disease associated with Purkinje-cell cytoplasmic antibody type 1 present with cerebellar ataxia and have gynecologic cancers, some have other neurologic presentations, some never develop ataxia, and some have other cancers.

Background: For almost 30 years, paraneoplastic cerebellar degeneration in women with breast or ovarian cancer has been known to be associated with a circulating autoantibody, Purkinje-cell cytoplasmic antibody type 1 (PCA-1, also known as anti-Yo).

Objective: To report a wider variety of cancers and neurologic findings associated with PCA-1.

Design: Retrospective study.

Participants: All Mayo Clinic patients whose serum was tested for the presence of paraneoplastic autoantibodies from 1987 to 2007.

Methods: All patients, regardless of what neurologic findings they had, were tested with the same comprehensive panel of paraneoplastic autoantibodies. This strategy allowed the full spectrum of clinical associations with PCA-1 to appear.

Results: Of the 133,138 patients tested, 83 (all women) were seropositive for PCA-1. The onset of neurologic symptoms was subacute (not defined). Cerebellar ataxia was the initial symptom in 77% of patients. The other 23% presented with polyneuropathy, myelopathy, or brainstem abnormalities. Only 89% of patients eventually developed cerebellar ataxia. Most patients (60%) also had extracerebellar findings. These reflected involvement of the CNS (corticospinal-tract signs, gaze palsies, ocular palsies, eyelid ptosis, ocular bobbing, facial and trigeminal nerve lesions, dystonia, rest tremor), peripheral nervous system (polyradiculoneuropathy, sensory and sensorimotor polyneuropathy, lower motor neuronopathy), and autonomic nervous system (bowel pseudo-obstruction, gastroparesis). Confirming the widespread distribution of the disease, the autopsy of 2 patients showed perivascular inflammation, loss of neurons, and gliosis in the cerebellum, brainstem, spinal cord, and dorsal-root ganglia but not the cerebrum. Cancer was found in 88% of patients. Most (95%) had adenocarcinoma of the breast, ovary, or fallopian tube; the others had lymphoma or adenocarcinoma of other tissues. Cancer chemotherapy and immunotherapy (IVIG, plasmapheresis, or corticosteroids) led to sustained neurologic improvement in only 15%.

Conclusions: Although most women with neurologic disease associated with PCA-1 present with cerebellar ataxia and have gynecologic cancers, some have other neurologic presentations; some never develop ataxia, and some have other cancers.

Reviewer's Comments: Paraneoplastic autoantibodies are more specifically associated with the type of cancer than with the site of neurologic disease. Most paraneoplastic neurologic diseases have a subacute onset and progressive course. Thus, it is more rational to test patients whose illness has such a tempo for a comprehensive panel of paraneoplastic autoantibodies than for any single one. This study shows that even PCA-1, which is more homogeneous in its neurologic and oncologic accompaniments than most paraneoplastic autoantibodies, has enough heterogeneity to consider it as a diagnosis in women whose symptom is not ataxia and to look for nongynecological cancers in women who have PCA-1.

Reviewer: Marc David Winkelman, MD
Article Reviewed: McKeon A, Tracy JA, et al. Purkinje Cell Cytoplasmic Autoantibody Type 1 Accompaniments: The Cerebellum and Beyond. *Arch Neurol* 2011; 68 (October): 1282-1289.

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1. Subarachnoid hemorrhages are strongly associated with abusive head trauma (compared to nonabusive head trauma) in children with brain injury.

   Practice: T F ***Answer Submitted:*** **T F**

2. Cognitively intact individuals with high levels of cerebrospinal fluid tau and phosphorylated tau are at risk for Alzheimer disease, but the development of dementia is attenuated by higher education and greater brain volume.

   Practice: T F ***Answer Submitted:*** **T F**

3. Lower body mass index appears to be a risk factor for developing muscle symptoms when taking a statin.

   Practice: T F ***Answer Submitted:*** **T F**

4. Detailed protocols for the management of fever, blood sugars, and swallowing in stroke units results in physical function (as measured by the SF-36 survey) improving but not mental function.

   Practice: T F ***Answer Submitted:*** **T F**

5. Neuron-specific enolase is extremely specific for predicting poor outcome from coma after cardiac arrest.

   Practice: T F ***Answer Submitted:*** **T F**

6. Mechanisms for the effect of onabotulinumtoxinA on chronic migraine likely involve action on both sensory and motor neurons.

   Practice: T F ***Answer Submitted:*** **T F**

7. The $CHADS_2$ score can help predict risk for stroke, bleeding, and death for atrial fibrillation patients treated with oral anticoagulants.

   Practice: T F ***Answer Submitted:*** **T F**

8. There are no differences found in risk factors, baseline features, and functional outcomes between internal carotid artery dissection and vertebral artery dissection.

   Practice: T F ***Answer Submitted:*** **T F**

9. Seizures associated with gastroenteritis in children tend to be brief and have a single occurrence.

   Practice: T F ***Answer Submitted:*** **T F**

10. Within the first 7 days after stroke, ischemic stroke carries a greater risk for seizure than primary intracerebral hemorrhage.

    Practice: T F ***Answer Submitted:*** **T F**

11. Although most women with neurologic disease associated with Purkinje-cell cytoplasmic antibody type 1 present with cerebellar ataxia and have gynecologic cancers, some have other neurologic presentations, some never develop ataxia, and some have other cancers.

    Practice: T F ***Answer Submitted:*** **T F**

12. A total dose of dihydroergotamine of 11.25 mg given over 5 days leads to a better response of refractory headache than the customary dose of 3 to 9 mg given over 2 to 3 days.

    Practice: T F ***Answer Submitted:*** **T F**

13. Patients with elevated antiglycine receptor antibodies do not respond to immunomodulation therapy.

    Practice: T F ***Answer Submitted:*** **T F**

14. Spinal angiography for the diagnosis of spinal vascular malformation has a high rate of systemic and neurologic complications.

    Practice: T F ***Answer Submitted:*** **T F**

15. Treatment of primary progressive multiple sclerosis with interferon beta-1b produces modest gains in some clinical and MRI measures that persist 5 years later.

    Practice: T F ***Answer Submitted:*** **T F**

16. The rate of intracranial bleeding after thrombolysis is no higher among ischemic strokes caused by arterial dissection than among those caused by other arterial diseases.

    Practice: T F ***Answer Submitted:*** **T F**

1. F A recent study found that patients had a better outcome with withdrawal of statin medications early in stroke hospitalization.

2. F Cerebrospinal fluid opening pressures are lowest in infants compared to older children.

3. T The most common side effects associated with teriflunomide are diarrhea, nausea, and hair thinning.

4. T Despite technical success, an extracranial-intracranial bypass procedure did not provide any benefit in a selected group of patients known to be at high risk for stroke.

5. T Immunotherapy is superior to treatment with antiepileptic drugs for seizure control in most patients with pathogenic autoantibodies to the central nervous system.

6. F Cefepime causes continuous epileptiform discharges only in those with impaired renal function.

7. T Recent data on levetiracetam and 3,4-diaminopyridine suggest that these agents do not reduce limb tremor and are not useful in treating essential tremor.

8. T Nonmotor symptoms in Parkinson disease are greater in women, are age independent, and correlate with severity of motor symptoms.

9. T For patients with severe intraventricular hemorrhage, repeated intraventricular injections of recombinant tissue-type plasminogen activator accelerate lysis of intraventricular clot.

10. F A recent study found that neonates with cerebral sinovenous thrombosis treated with low-molecular-weight heparin had the same short-term outcomes as neonates treated only with hydration and supportive care.

11. T Patients with cavernous malformations have a high risk of epilepsy, but achieve seizure freedom as often as arteriovenous malformation patients.

12. F In a recent study, Parkinson patients on 400 mg caffeine had decreased daytime somnolence, but worse nighttime sleep quality.

13. T About half of selected patients who undergo epilepsy surgery will be seizure free or have only simple partial seizures 10 years after surgery.

14. T The incidence of normal-pressure hydrocephalus treated with ventriculoperitoneal shunt is low, equal to that of progressive supranuclear palsy.

15. T The volume of tissue involved in central pontine myelinolysis and the degree of hyponatremia do not correlate with long-term clinical outcome and should not be used in formulating a prognosis when the patient is acutely ill.

16. F Meralgia paresthetica is frequently associated with obesity, young age, and diabetes mellitus.

17. F Muscle ultrasound of the tongue is inferior to electromyography in detecting fasciculations.

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