Certain patients with traumatic brain injuries may demonstrate brain activation on functional MRI, thus reflecting awareness and cognition not detectable with bedside testing.

**Background:** The vegetative state describes patients who emerge from coma with normal wakefulness, but show no awareness of self or surroundings. Meaningful neurological recovery is rare. In 2006, however, Owen and Coleman described a vegetative woman who exhibited volitional brain activity on functional MRI (fMRI). When she was asked to imagine playing tennis, her supplementary motor area (SMA) demonstrated cortical activation similar to controls. When asked to imagine walking through her home, activation occurred in the parahippocampal gyrus, posterior parietal and lateral premotor cortex, indistinguishable from controls. This suggested the vegetative state could be misdiagnosed if based exclusively on clinical criteria. Impaired motor function could prevent an aware individual from responding to commands. This caveat also applies to the minimally conscious state (MCS) where some cognitive behavior is preserved in a severely fragmented form. How often this occurs is unknown.

**Objective:** To determine incidence of undetected awareness in survivors of severe brain injury.

**Methods:** Investigators examined 23 vegetative and 31 MCS patients with fMRI using blood-oxygen-level-dependent (BOLD) responses to the 2 mental-imagery tasks described above. In 1 vegetative patient, the unique cortical activation by the 2 mental tasks allowed a yes-no response to simple autobiographical questions. Imagining playing tennis meant “yes”, moving room-to-room meant “no.”

**Results:** Of 54 patients, 33 had traumatic brain injury (TBI), 16 anoxic brain injury, and 6 stroke or meningitis. Of patients, 5 (4 vegetative, 1 MCS) modulated their brain activity on fMRI when asked to imagine playing tennis or roaming their home. All had suffered head trauma at 1, 2, 6, 30, or 61 months earlier. In 3 of these patients, further bedside testing revealed signs of awareness not previously detected, upgrading the diagnosis to MCS. In the other 2 patients, no voluntary behavior could be detected by clinical testing. One male patient, aged 22 years and in a vegetative state, 5 years after head trauma, used fMRI to answer accurately 5 yes-or-no questions about family members; immediate bedside retesting to establish communication was unsuccessful. fMRI disclosed evidence of cognitive awareness in 2 vegetative (18%) and 3 MCS (14%) TBI patients.

**Conclusions:** fMRI can detect clinically unrecognized cognitive awareness in roughly 15% of vegetative or MCS patients due to TBI. When re-examined clinically, many of these “covertly aware” patients are reclassified to MCS. Similar evidence of awareness is not observed in patients with non-traumatic brain damage.

**Reviewer's Comments:** fMRI was used for "mind-reading" by employing a binary yes-no system linked to mental imagery. This presents a remarkable tool for probing the limits of sentience in the mind of a person who can hear, but is unable to respond motorically. (Reviewer-Michael Jacewicz, MD).

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**Keywords:** Vegetative State, Minimally Conscious State, Functional MRI

**Print Tag:** Refer to original journal article
Check the cornea and skin carefully in suspected cases of Fabry disease.

**Background:** Many reviews of clinical, genetic, and biochemical aspects of inherited metabolic disorders causing stroke are available.  

**Objective:** To review mechanisms and manifestations of cerebrovascular disease in patients with Fabry disease (FD) and mitochondrial encephalomyopathy with lactic acid, strokes and seizures (MELAS).

**Design:** Focused literature review.  

**Discussion:** FD is an X-linked recessive disorder in which a glycosphingolipid accumulates in lysosomes as a result of deficiency of alpha galactosidase. Female heterozygotes sometimes manifest the disease; curiously, they are more likely than males to have a stroke. Key features include skin lesions (red, raised, and classically on the scrotum) and a painful peripheral neuropathy with crises of severe acral pain and paresthesias. Renal failure with proteinuria, congestive failure secondary to premature coronary atherosclerosis, and a variety of ophthalmic manifestations (typically whorled corneal opacities) complete the clinical picture. Diagnosis is by assay of the deficient enzyme in leukocytes or plasma; females may require genetic testing as enzyme levels are not always low. Cerebrovascular disease is caused by accumulation of the abnormal glycosphingolipid in arterial walls with occlusions of smaller, and dilatation of larger, vessels. Ectatic vessels can be a source of artery-to-artery emboli, or even thrombose. Treatment with costly and regular infusions of the deficient enzyme improves many aspects of the disease including pain, but unfortunately effect on stroke is not established. Regarding MELAS, the mitochondrial mutation most often responsible is in a transfer RNA coding for leucine. Mitochondrial disorders are maternally transmitted, but because of heteroplasmia, clinical manifestations may vary as to both severity and organ/tissue affected. In addition to the features contained in the acronym, patients with MELAS frequently have sensorineural hearing loss, migraine headaches, pigmentary retinopathy, and cardiomyopathy. Strokes in MELAS may not be strokes. Typically, focal deficits occur in the setting of headache or seizures. MRIs show cortical diffusion positivity, but not in a "territorial" pattern. A tentative synthesis of studies suggests that the primary event is failure of oxidative phosphorylation, not ischemia. Patients with MELAS have increased lactate and pyruvate in serum and cerebrospinal fluid. Confirmation of diagnosis is by muscle biopsy, showing ragged red fibers. Individual enzymes may be assayed in muscle, or mutation analysis of mitochondrial DNA carried out. Treatment is not standardized, and often hypothetical. Coenzyme Q 10 ± creatine or lipoic acid is most studied, but not proven. A synthetic analogue of Co Q, idebenone, is not available in the United States. The nitric oxide synthetase substrate L-arginine resulted in improvement when infused during episodes and fewer recurrent episodes when administered chronically orally.

**Reviewer's Comments:** Keep these rare but treatable disorders in mind when considering the cause of an ischemic stroke in the patient aged <40 years. Currently FD is more treatable than MELAS. (Reviewer-James W. Schmidley, MD).

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Keywords: MELAS, Fabry Disease

Print Tag: Refer to original journal article
In alcoholics, improvement in cerebral white matter abnormalities following abstinence differs between smokers and non-smokers.

**Objective:** To evaluate cerebral white matter injury and recovery in smoking and non-smoking recently abstinent alcoholics.

**Design:** Longitudinal study.

**Participants:** 16 non-smoking alcoholics, 20 smoking alcoholics, and 22 non-smoking light drinkers.

**Methods:** Alcoholic subjects met Diagnostic and Statistical Manual criteria for physiological dependence. Subjects underwent MRI, magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) within a few days after the last drink and were re-scanned after several weeks. Analyses involving frontal, temporal, parietal, and occipital white matter were adjusted for age, which ranged from 22 to 66 years. Defined outcomes were lobar white matter volumes, diffusion measures (ie, fractional anisotropy [FA] and mean diffusivity), and metabolite concentrations (ie, N-acetyl-aspartate [NAA] and choline).

**Results:** Compared to light drinkers at 1 week of abstinence, smoking alcoholics had higher mean diffusivity only in frontal white matter, whereas non-smoking alcoholics had higher mean diffusivity in frontal, temporal, and parietal white matter. There were no group differences in FA. Smoking alcoholics had lower concentrations of NAA in frontal white matter, whereas non-smoking alcoholics had lower NAA in parietal white matter. These patterns were not accompanied by evidence of white matter atrophy. After several weeks of abstinence, non-smoking alcoholics had an increase in FA and a decrease in mean diffusivity in all lobar regions, whereas no such change was evident in smoking alcoholics. In contrast, frontal and temporal lobe white matter volume increases were observed in smoking alcoholics but not in non-smoking alcoholics. In neither group where there significant changes in NAA or choline concentrations.

**Conclusions:** Cerebral white matter abnormalities in alcoholics do improve with abstinence and the nature of improvement is influenced by tobacco smoking. Inconsistencies in prior reports might be the result of using only a single-imaging modality.

**Reviewer's Comments:** While interesting, the data presented in this study are descriptive rather than explanatory, and the basis of ethanol’s neurotoxicity (glutamate excitotoxicity is a possible mechanism) remains uncertain. (Reviewer-John C. Brust, MD).

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Keywords: White Matter, Diffusion Tensor, Spectroscopy, Cigarette Smoking, Alcohol Dependence

Print Tag: Refer to original journal article
Maternal Family History of Alzheimer Means Greater Risk Than Paternal History

Reduced Gray Matter Volume in Normal Adults With a Maternal Family History of Alzheimer Disease.
Honea RA, Swerdlow RH, et al:

Neurology 2010; 74 (January 12): 113-120

Asymptomatic offspring of mothers with Alzheimer's disease have a higher risk of developing this disorder than if they had had an affected father.

**Background:** Family history of dementia is a risk factor for Alzheimer disease (AD), with maternal transmission being more frequent than paternal transmission. Nondemented offspring of AD-affected mothers have been found to perform less well on cognitive testing than offspring of AD-affected fathers. PET scans have shown AD-like changes in offspring of mothers affected with late onset AD.

**Objective:** To test whether cognitively normal patients with a family history of AD have less gray matter volume (GMV) and whether decreases are different for those with a maternal history of AD.

**Methods:** Recruited subjects underwent standard medical, laboratory, neuropsychological, and MRI examinations. All lacked a history of cognitive or functional decline and scored a 0 on the Clinical Dementia Rating (CDR) indicating no dementia. Those with a non-AD neurological disorder, ischemic heart disease, significant mental illness, diabetes mellitus, or other illness that might interfere with completion of the study were excluded. Patients with a family history of 1 parent with dementia (onset between ages 60 and 80 years) were included but those with both parents dying at age <60 years or both parents with late onset dementia were excluded. Of subjects, 3 groups were compared: (1) maternal family history groups (FHm), (2) paternal family history groups (FHp), and (3) no family history of dementia group (FH-). Each underwent a psychometric battery, mini-mental status exam (MMSE), and 3T MRI, with data analysis measuring total gray matter, white matter, and intracranial volumes which were compared to normalized tissue maps. Specifically, the medial temporal area including the hippocampus, superior, inferior and medial temporal gyri, right insula, left cingulate, bilateral middle frontal, bilateral fusiform gyri, and inferior frontal cortex were evaluated.

**Results:** 67 subjects were included: 43 in the FH-, 8 in the FHp, and 16 in the FHm. As compared with FH-subjects, FH+ subjects had significantly decreased GMV in the precuneus, middle frontal gyrus, inferior frontal gyrus, and superior frontal gyrus. The FHm subjects had significantly smaller right inferior frontal, middle frontal gyrus, and left insula GMV as compared to the FH- group. FHm subjects also had significantly less GMV in the right lingual gyrus, right inferior frontal gyrus, and right middle frontal gyrus compared with FHp subjects. Compared to the FH- group, FHp had decreased GMV in the superior frontal gyrus, precuneus, left middle frontal gyrus and right fusiform gyrus. In apoE4 noncarriers, the FHm group still showed GMV reductions compared to FH-.

**Conclusions:** Maternal family history of Alzheimer disease in cognitively normal individuals is associated with lower GMV in AD-vulnerable brain regions.

**Reviewer's Comments:** It is interesting that the earliest area of involvement in Alzheimer's disease, the hippocampi, showed no volume difference amongst the groups. Long-term follow-up should help determine the significance of the present findings. (Reviewer-John Schwankhaus, MD).

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Keywords: Alzheimer Disease, Maternal Family History, Voxel-Based Morphometry

Print Tag: Refer to original journal article
There is no cure available in the treatment of Niemann-Pick disease type C in children, but miglustat is effective in slowing the progression of symptoms.

**Background:** Niemann-Pick disease type C (NPC) is a rare lysosomal storage disease that is inherited in an autosomal recessive fashion due to mutations in *NPC1* or *NPC2* genes. Severe impairment in intracellular lipid transport results in accumulation of lipid storage materials in neurons and glia. Neurologic symptoms may appear at any time, but are most commonly present during middle to late childhood with clumsiness, progressive ataxia, and cognitive impairment. Vertical eye movements at some point become impaired. Gelastic cataplexy and seizures commonly develop. With progression, dystonia, dysphagia, and dysarthria develop, and the end result is ultimately death. There is currently no cure for this disorder. Miglustat, an inhibitor of glucosylceramide synthase, has been shown to slow progression of this disease in children, adolescents, and adults during 12-month trials.

**Objective:** To evaluate the long-term efficacy and adverse effects of miglustat on children with NPC.

**Design/Methods:** An initial 12-month, open-label noncontrolled trial using miglustat in children aged 3 to 11 years with a confirmed diagnosis of NPC was followed by a 12-month extension study, and a long-term continued extension. Miglustat dose was calculated based on an adult starting dose of 200 mg, 3 times daily and a standard body surface area of 1.8 m2, corrected to the individual child's body. Dose could be decreased as indicated in response to adverse effects. Primary efficacy end point was a quantitative measure of velocity of horizontal saccadic eye movement. Secondary measures included additional assessment of horizontal and vertical saccadic eye movements, neurologic and neuropsychological assessments, and formal assessments of swallowing and ambulation.

**Results:** 12 children were initially enrolled. Vertical supranuclear gaze palsy was present in 100%, ataxia in approximately 80%, and cognitive impairment in two thirds. Of subjects, 2 withdrew prior to completion of the initial 12-month study. Remaining subjects completed 24 months of treatment. Mean age at entrance into the 12-month extension was just >7 years. Daily miglustat dose ranged from 100 to 600 mg/day with a mean dose of 350 mg/day. A dose reduction due to adverse effects was required in 2 patients due to diarrhea in 1 and tremor in 1, which were also the most commonly reported adverse events. Horizontal saccadic eye movement, ambulation, and swallowing were stabilized at 24 months. Overall, disease status remained stable at 24 months in 8 (80%) patients. Deterioration occurred in 2 patients.

**Conclusions:** Miglustat appears to be safe and well-tolerated to stabilize neurologic disease progression in children with NPC.

**Reviewer's Comments:** All patients with NPC should be offered miglustat therapy to potentially slow disease progression. Further assessment is needed to evaluate long-term therapy results. (Reviewer-Gregory B. Sharp, MD).

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**Keywords:** Niemann-Pick Disease Type C, Miglustat, Children

**Print Tag:** Refer to original journal article
Escitalopram May Enhance Cognitive Function After Stroke

Escitalopram and Enhancement of Cognitive Recovery Following Stroke.

Jorge RE, Acion L, et al:

Arch Gen Psychiatry 2010; 67 (February): 187-196

The beneficial effect of escitalopram on cognition after stroke is independent of its effect on depression.

**Background:** Tryptophan deficiency is associated with cognitive dysfunction; studies have reported selective serotonin reuptake inhibitor (SSRI)-enhancement of cognitive functioning among normal healthy subjects. There is evidence that SSRIs produce neuroplastic changes in the hippocampus and cerebral cortex. Researchers previously reported that antidepressant treatment in the subacute phase of stroke can significantly improve activities of daily living and cognitive function among patients suffering from post-stroke depression.

**Objective:** To examine the effect of escitalopram on cognitive outcome following stroke.

**Design:** Randomized controlled study.

**Participants:** 129 patients treated at the University of Iowa Stroke Center.

**Methods:** Inclusion criteria were age 50 to 90 years, along with clinical and imaging findings consistent with cerebral hemisphere, brainstem, or cerebellar ischemic or hemorrhagic stroke. Exclusion criteria included DSM-IV diagnostic criteria for depressive disorder or a Hamilton Scale for Depression score >11, impaired decision making capacity, neurodegenerative disorders, alcohol or substance abuse. Subjects were classified as having a right or left hemisphere, or a brainstem/cerebellar stroke. Subjects were randomly assigned to 1 of 3 treatment modalities within 3 months of the index stroke: (1) treatment with escitalopram, (2) treatment with problem solving therapy (PST), or (3) placebo. Among subjects beginning treatment, 7 dropped out. The only significantly different demographic characteristics between groups were slightly older age for the PST group and slightly less hypertension for the escitalopram group. Duration of the study was 1 year. Subjects were examined every 3 months for depression. Neuropsychological testing was performed at the beginning and end of enrollment, and included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), trail-making tests parts A and B, controlled oral word association, Wechsler Adult Intelligence Scale-III, and the Stroop Test.

**Results:** There was a significant difference among the groups in change in the RBANS total score and the RBANS delayed memory score, with best performance in the escitalopram group, independent of any effect on depression. No other significant findings were noted on other neuropsychological measures.

**Conclusions:** Compared with patients who received placebo or underwent PST, stroke patients who received escitalopram showed significant improvement in global cognitive functioning, specifically in verbal and visual memory functions, independent of its effect on depression and independent of stroke location.

**Reviewer’s Comments:** Investigators speculate that improvement in verbal and visual memory observed in the escitalopram group might be related to increased neurogenesis and remodeling of the hippocampal circuitry. They do note that the stroke patients in this study had mild-to-moderate neurological residual deficit, and these results may not be generalizable to other stroke victims. Although results of this study certainly do not recommend that all stroke victims be treated with an SSRI, findings warrant further investigation, such as comparing cognitive improvement in stroke victims to normal controls with other neurologic diseases, treated with an SSRI. (Reviewer-W. Steven Metzer, MD).

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Keywords: Antidepressant, Cognition, Escitalopram, Recovery, Stroke

Print Tag: Refer to original journal article
For patients with extracranial internal carotid artery stenosis aged <69 years, stenting appears slightly better for the prevention of strokes; older patients appear to fare better with endarterectomy.

**Background:** The status of carotid angioplasty and stenting for patients with extracranial internal carotid artery stenosis is not settled. Recent trials (EVA-SSS and SPACE) have dampened enthusiasm. The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) trial reported 1-year follow-up data for all enrolled patients at the International Stroke Conference in San Antonio. The paper cited in connection with this review provides background on the trial.

**Objective:** To ascertain how carotid angioplasty/stenting compared with carotid endarterectomy for prevention of stroke in patients with extracranial internal carotid artery stenosis.

**Design:** Randomized, controlled clinical trial.

**Participants:** 1326 symptomatic and 1196 asymptomatic patients.

**Methods:** Symptomatic patients had transient ischemic attacks (TIAs; including amaurosis fugax) or nondisabling strokes within 180 days prior to randomization and were required to have >50% ipsilateral ICA stenosis by angiogram, or >70% stenosis by ultrasound, CT, or MR angiography. Asymptomatic patients had to have stenosis >60% by angiogram, 70% by ultrasound, or 80% by CT or MR angiography. Neither group contained patients felt to be "high-risk" for either intervention. Patients were randomized to carotid endarterectomy or angioplasty/stenting with 1 type of stent and using 1 embolic protection system. All patients received antiplatelet treatment and stroke risk factor management. End points included any stroke, myocardial infarction (MI), or death or in the perioperative period (30 days), as well as ipsilateral ischemic stroke from 30 days to end of follow-up. Clinical follow-up was at 1 month, 6 months, and every 6 months thereafter. Patients were also followed for restenosis by ultrasound. Exclusion criteria were those expected in this sort of trial.

**Results:** Patients had a mean age of 69 years, with 35% being women, and <10% minorities. The 30-day data showed that MI was significantly more likely with carotid endarterectomy (2.3% versus 1.1%), but stroke was more likely with angioplasty and stenting (4.1% versus 2.3%); also significant. When the 30-day end points were combined with ipsilateral stroke occurring after 30 days, outcomes were virtually identical: 6.8% in the endarterectomy group and 7.2% in the angioplasty/stent group. Long-term stroke rates after follow-up of about 2.5 years were 2.4% in the endarterectomy group and 2.0% in the angioplasty/stent group. The specialty of the stenter made no difference in outcomes.

**Conclusions:** For patients aged <69 years, stenting was slightly better; those older fared slightly better with endarterectomy. Results were similar in males and females regardless of symptomatic status at entry.

**Reviewer's Comments:** I will wait to see how things turn out in the long run, especially restenosis rates, which have been a problem with stents in previous trials. (Reviewer-James W. Schmidley, MD.)

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**Keywords:** Carotid Endarterectomy, Arterial Stent, Embolic Protection Devices

**Print Tag:** Refer to original journal article
Hypocretin deficiency is associated with rapid eye movement sleep behavior disorder and periodic limb movements independent of cataplexy.

Objective: To explore the association between cataplexy, hypocretin deficiency, rapid eye movement (REM) sleep behavior disorder (RBD), and muscle activations during REM and non-REM sleep in subjects with narcolepsy.

Participants: 48 narcoleptics with cataplexy and 15 without cataplexy.

Methods: Patients received polysomnography, multiple sleep latency testing, human leukocyte antigen (HLA) typing, and determination of cerebrospinal fluid (CSF) hypocretin-1 levels. Symptoms of RBD were identified by interview and included body or limb movements such as kicking, arm flailing, sitting up, or getting out of bed and verbalization such as talking, shouting, swearing, crying or laughing. Polysomnographic recordings included EEG, electro-oculography, EMG of submentalis and anterior tibial muscles, EKG, nasal air flow, thoracic respiratory effort, and oxygen saturation. EMG identified muscle activations as either short (<0.5 second) or long (0.5 to 15 seconds) and then divided long muscle activations into non-periodic limb movements and periodic leg movements.

Results: Patients with narcolepsy and cataplexy had a significantly higher prevalence of HLA-DQB1*0602 positivity and low CSF hypocretin-1 levels compared to patients with narcolepsy but no cataplexy. All patients with narcolepsy without cataplexy who had low CSF hypocretin levels were HLA-DQB1*0602 positive. RBD symptoms were present in 40 patients and tended to be more prevalent in those with cataplexy, but were significantly more prevalent, after multivariate analysis, only in those with low CSF hypocretin levels. Similarly, only low CSF hypocretin levels significantly predicted short and long muscle activity during REM sleep and both non-periodic and periodic leg movements during both REM and non-REM sleep. Patients reporting RBD symptoms had significantly more long muscle activations and periodic leg movements during REM sleep.

Conclusions: REM sleep behavior disorder and periodic leg movements are associated with hypocretin deficiency in narcolepsy, independent of cataplexy. Additional observations from this study are that in contrast to Parkinsonian disorders, RBD did not precede the onset of narcolepsy and RBD symptoms were more disruptive than injurious.

Reviewer’s Comments: The identification of brainstem sleep/wake and REM/non-REM flip-flop switches a decade ago was a major advance in sleep research. Studies such as the present report show how clinical observations can also advance our understanding. (Reviewer-John C. Brust, MD).

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Keywords: Narcolepsy, Cataplexy, Rapid Eye Movement Sleep Behavior Disorder, Periodic Limb Movements, Hypocretin-1
Routine Measurement of QT in Pediatric EEGs May Be Helpful

Assessment of the QT Interval in the Electroencephalography (EEG) of Children With Syncope, Epilepsy, and Attention-Deficit Hyperactivity Disorder (ADHD).

Jha OP, Khurana DS, et al:

J Child Neurol 2010; 25 (March): 284-286

Electroencephalogram can be used as a screening tool for identification of prolonged QT in children if attention is paid to measurement of the QT interval on the electrocardiogram component.

**Background:** Prolonged QT is due to a disorder in myocardial repolarization characterized by prolongation of the QT interval on the electrocardiogram (ECG) and an increased risk of sudden death due to the potential to develop polymorphic ventricular tachycardia. Prolonged QT is associated with syncope and sudden cardiac death and is considered a risk factor for sudden unexplained death. It has also been postulated that prolonged QT may be responsible for at least some cases of sudden unexplained death in epilepsy (SUDEP). It is usually a standard procedure to include one channel of ECG on routine electroencephalogram (EEG) recordings. This allows for correlation and identification of ECG artifact within the EEG recording, and identification of cardiac arrhythmias during the EEG. Specific attention is usually not paid to measurement and interpretation of the QT interval during EEG interpretation.

**Objective:** To identify and compare incidence of prolonged QT via assessment and measurement of the QT interval on the recorded ECG component of the EEG in children being evaluated for seizures, syncope, and attention-deficit hyperactivity disorder (ADHD).

**Design:** Retrospective review of the EEG database at a single pediatric center.

**Participants:** 50 children with a diagnosis of seizure, syncope and ADHD who were most recently referred for EEG.

**Methods:** Children with ADHD were referred for EEG due to inattention and staring spells to rule out the possibility of absence seizures. EEGs were recorded digitally; QT and RR intervals on the ECG channel were measured using digital cursors. Corrected QT intervals were calculated using the standardized Bazett formula. A prolonged QT interval was defined as >460 ms.

**Results:** In review of the ECG component of EEGs obtained in these groups of children, prolonged QT was identified in 2% of those with seizure, 14% of those with syncope, and 4% of those with ADHD.

**Conclusions:** Incidence of prolonged QT as measured on EEG was higher than expected in groups of children with seizure, syncope, and ADHD. The authors proposed that measurement of the QT interval should be routinely considered and performed during interpretation of EEGs in children.

**Reviewer's Comments:** Since prolonged QT is considered a risk factor for sudden death in children with and without seizures, should it be the electroencephalographer's responsibility to formally measure QT intervals on a routine basis? In the event that prolonged QT is identified, referral for 12-lead ECG with interpretation by an experienced cardiologist should be performed. Prospective studies comparing ECG results from EEGs performed on children with formal 12-lead ECG results should be done. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Prolonged QT, EEG, syncope, seizures

Print Tag: Refer to original journal article
Progressive supranuclear palsy-parkinsonism is difficult to distinguish from Parkinson's disease, but less difficult to differentiate from dementia with Lewy bodies, MSA, and vascular parkinsonism.

**Background:** Most patients with progressive supranuclear palsy (PSP) have Richardson's syndrome, with supranuclear gaze palsy, bradykinesia, axial rigidity and retropulsion. However, pathological studies from the UK have shown that a minority of patients with parkinsonism have PSP-parkinsonism (PSP-P), with tau rather than alpha-synuclein pathology.

**Objective:** To investigate whether clinical features might differentiate PSP-P from other parkinsonian syndromes.

**Design:** Retrospective chart analysis of parkinsonian patients diagnosed pathologically.

**Participants:** 726 patients, including 444 with Parkinson's disease (PD), 46 with dementia with Lewy bodies, 127 with PSP, 90 with multi-system atrophy (MSA), 19 with vascular parkinsonism.

**Methods:** Investigators reviewed medical records for subjects, with particular attention to age of onset of disease, duration of disease, falls, cognitive decline, speech disturbance, dysphagia, tremor, hypertonia, supranuclear gaze palsy, other visual symptoms, limb dystonia, pyramidal signs, autonomic dysfunction, dyskinesia, hallucinations and response to levodopa. The proportion of cases with each clinical feature was compared separately for cases with PSP-P and non PSP-P, and individually with Parkinson's disease, MSA, and vascular parkinsonism. A disease feature was considered to be a good discriminator if it had specificity or a positive predictive value (PPV) >0.85.

**Results:** Mean age at disease onset for subjects was 61.6 years, with mean duration of disease being 13.0 years. About 62% of subjects were men. Two thirds of subjects with PSP had Richardson's syndrome, with falls, supranuclear gaze palsy, abnormal vertical saccadic eye movements, and cognitive decline within the first 2 years of their disease. The remaining one third of PSP subjects had PSP-P, with their disease characterized by asymmetric bradykinesia, rigidity, tremor, and positive response to levodopa, with the characteristic features of Richardson's syndrome absent. No clinical features were predictive of PSP-P, although several clinical features had specificity and PPV >0.9 for PSP-P. These clinical features included late drug-induced dyskinesia, late autonomic dysfunction, and any visual hallucinations. Late non-specific eye symptoms and supranuclear gaze palsy were significantly more commonly associated with PSP-P than with MSA. Early autonomic dysfunction and late cerebellar signs occurred in >50% of MSA patients and <10% of PSP-P patients. Response to levodopa did not differentiate between PSP-P and MSA. Presence of pyramidal signs helped differentiate vascular parkinsonism from PSP-P.

**Conclusions:** Within current diagnostic criteria, PSP-P is difficult to distinguish from Parkinson's disease, but less difficult to differentiate from dementia with Lewy bodies, MSA, and vascular parkinsonism.

**Reviewer's Comments:** This study raises awareness of the entity of PSP-P, and confirms the clinical impression of many clinicians that PSP-P is difficult to differentiate from Parkinson's disease on clinical grounds. However, it does appear that this disease can be differentiated from other Parkinson's-plus syndromes clinically with fairly good reliability. (Reviewer-W. Steven Metzer, MD).

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Keywords: Progressive Supranuclear Palsy, Richardson's Disease, Parkinson's Disease, Diagnosis, Parkinsonism

Print Tag: Refer to original journal article
Excessive Hoarding Is Relatively Common With Parkinson’s Disease

Excessive Hoarding in Parkinson Disease.
O’Sullivan SS, Djamshidian A, et al:
Mov Disord 2010; February 3 (): epub ahead of print

Excessive hoarding is part of the impulse control disorders seen in Parkinson disease.

Background: Excessive hoarding entails the pathological acquisition of and failure to discard possessions that are useless to the point of cluttering living spaces and curtailing activities. It can be associated with schizophrenia, depression, and obsessive-compulsive disorder (OCD). Impulse control disorders (ICDs) can occur with dopamine replacement therapy for Parkinson disease (PD).

Objective: To investigate hoarding in Parkinson patients and its relationship to ICDs as well as OCD symptoms, depression, and anxiety.

Methods: Subjects at a Parkinson disease clinic were assessed clinically for ICDs and screened with the Mini-Mental Status Exam with those scoring <26 excluded. Punding was rated by the examiner on a 0 to 3 point scale. Patients were then divided into PD + ICD and PD - ICD groups. Subjects were given questionnaires including the saving inventory-revised (SIR), the obsessive compulsive inventory-revised (OCI-R), the hospital anxiety and depression scale (HADS), the brief self-control scale (BSCS), and the impulse buying (IBT) scale. These scores and other factors including age, gender, duration of PD, daily levodopa equivalent dose (LED) of dopamine agonists and levodopa, clinician punding scale, and presence of documented ICDs were analyzed.

Results: 140 PD patients received questionnaires of which 40 did not consent or fully complete and return. Also included in the study were 50 healthy controls. Of patients, 39 had ≥1 ICD (20 with punding, 14 with binge eating (BE), 11 with pathological gambling (PG), 11 with compulsive shopping (CS), and 11 with dopamine dysregulation syndrome (DDS). About one eighth of PD patients scored >40 on the SIR (excessive hoarders), with the PD + ICD group having more hoarders than the PD - ICD and control groups. About 6.0% of controls and 6.5% of the PD - ICD groups were hoarders. The PD + ICD group had higher levels of CS and had higher OCI-R hoard scores which were not seen in patients with BE, punding, or hypersexuality. Impulse buying tendency scores were much higher amongst hoarders but they did not have any difference in anxiety or depression. A higher percentage of hoarders had hypersexuality, BE, CS, punding, and DDS. In the PD group, SIR scores most strongly correlated with impulse buying levels.

Conclusions: The association of hoarding with other ICDs and low-trait impulse control scores suggests that hoarding is related to the spectrum of impulse behaviors in PD.

Reviewer’s Comments: Hoarding is not uncommon in PD patients on dopamine replacement therapy. Physicians should screen for this and other ICDs as they can have devastating social consequences. (Reviewer-John Schwankhaus, MD).

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Keywords: Parkinson Disease, Impulse Control Disorders, Hoarding, Obsessive Compulsive Disorder

Print Tag: Refer to original journal article
In patients with primary progressive multiple sclerosis, onset with sensory symptoms predicts a slower pace of progression.

Objective: To study the pace of progression of primary progressive multiple sclerosis (PPMS) and to identify clinical factors that affect it.

Design: Retrospective cohort study.

Participants: 5779 patients with multiple sclerosis (MS) of which 552 (10%) had PPMS.

Methods: A longitudinal database including >80% of MS patients in British Columbia was used. Inclusion criteria were a definite diagnosis of MS, enrollment in the database from 1980 to 2003, Extended Disability Status Scale (EDSS) score <6 when enrolled, and a primary progressive course of disease (from onset without relapses). Kaplan-Meier survival analysis and Cox regression models were used to determine the pace of progression of PPMS and to assess influences of gender, age of onset of disease, and type of symptoms at onset. Onset symptoms were classified as sensory, motor, optic neuritis, and cerebellar/ataxic/brainstem. Age of onset was divided into <30 years; 30 to <40 years; 40 to <50 years; and ≥50 years. Outcome measures were time from disease onset to, and age at reaching, an EDSS score of 6 (need for a cane) and “benign MS” (EDSS score of ≤3 after 10 years of disease).

Results: Median time to EDSS 6 was 14 years (95% confidence interval [CI], 11 to 17), and median age at EDSS 6 was 59 years (95% CI, 57 to 60). Disease onset at <30 years of age was associated with a longer time to reach EDSS 6 ($P=0.008$) but also with a younger age when it was reached ($P<0.0005$). Patients with sensory symptoms at onset took longer to reach EDSS 6 ($P=0.008$). Pace of progression varied greatly: 25% of patients reached EDSS 6 quickly, within 8 years of disease onset and by age 49 years, but 25% progressed to it slowly, >27 years and at age 70 years. Of PP patients, 50(9%) fulfilled criteria for benign MS.

Conclusions: Onset with sensory symptoms predicts a slower pace of progression in patients with PPMS. Onset at age <30 years predicts a slower pace of progression but severe disability at a younger age.

Reviewer's Comments: Rate of progression of PPMS was generally slower in this study than in previous ones; many patients lived without severe disability until old age and some even had benign MS. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Primary Progressive Multiple Sclerosis, Prognosis, Natural History

Print Tag: Refer to original journal article
Presence of Serum IgM Antibodies to GD1b May Suggest Likely Treatment

Chronic Ataxic Neuropathies Associated With Anti-GD1b IgM Antibodies: Response To IVIg Therapy.

Attarian S, Boucraut J, et al:

J Neurol Neurosurg Psychiatry 2010; 81 (Jan): 61-64

Patients with idiopathic ataxic polyneuropathy should be tested for serum IgM antibodies to GD1b, because their presence indicates an illness likely to respond to treatment with IVIg.

**Background:** Some cases of idiopathic chronic ataxic polyneuropathy are associated with circulating immunoglobulin M (IgM) antibodies to the glycolipid GD1b, which is located in dorsal root ganglion cells.

**Objective:** To determine whether the presence of antibody predicts a response to intravenous immunoglobulin (IVIg).

**Design:** Retrospective study.

**Methods:** Patients with chronic sensory ataxic polyneuropathy, high serum anti-GD1b IgM antibody level, and follow-up >1 year were included. Sensory ataxia had to be the major clinical feature, but patients were included if they had minor weakness and small-fiber sensory loss as well as abnormal motor nerve conduction studies (NCS). Patients with known causes of ataxic polyneuropathy, such as Sjögren syndrome, cancer, and toxicity of vitamin B6 or cisplatin, were excluded. IVIg 2 gm/kg over 3 to 5 days every 6 weeks or as needed to maintain a clinical response was administered. Outcome measures including a 10-point standardized scale of performing activities of daily living, including dressing, washing, using silverware, handling coins, and walking was applied during follow-up. An improvement of ≥1 point was considered to show a response to treatment.

**Results:** There were 13 patients (7 men and 6 women) aged 36 to 75 years (mean age, 54 years). Mean follow-up time was 4 years (range, 1.5 to 8.0 years). Initial symptom was tingling or numbness in the lower or upper limbs. Ataxia and defects in joint-position and vibratory sense were found in all patients. Loss of pin-prick and temperature sensation was found in all patients. All patients had loss of tendon reflexes. Of patients, 3 had muscle weakness. The course was progressive in all patients, and 4 had superimposed acute relapses. Sensory NCS were abnormal in all patients, but the authors did not say whether the pattern was axonal or demyelinating. Of patients, 4 had abnormal motor NCS, demyelinating in 3 and axonal in 1. Cerebrospinal fluid protein was mildly elevated in 7 patients. Of patients, 9 responded to IVIg, but only 2 improved by ≥1 point on the assessment scale.

**Conclusions:** Patients with idiopathic ataxic polyneuropathy should be tested for IgM antibodies to GD1b, because their presence indicates an illness likely to respond to treatment with IVIg.

**Reviewer's Comments:** Most patients improved only a little, and the lack of a control group makes the claim that improvement was due to IVIg uncertain. Most hospital laboratories cannot measure anti-GD1b, and the difficulty of getting the test sent to a lab that does may be considerable. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Ataxic Neuropathy, Anti-GD1b, Autoantibody, Autoimmune Neuropathy

Print Tag: Refer to original journal article
Myositis, Myocarditis May Occur in Myasthenia Gravis Patients

Autoimmune Targets of Heart and Skeletal Muscles in Myasthenia Gravis.

Suzuki S, Utsugisawa K, et al:

Arch Neurol 2009; 66 (November): 1334-1338

Myositis or myocarditis rarely occur in myasthenia gravis and thymoma patients and is often responsive to treatment.

**Background:** Inflammatory myopathies and/or myocarditis rarely affect patients with myasthenia gravis (MG). Most previously reported patients had also thymoma.

**Objective:** To report on clinical, histological, and immunological characteristics of patients with MG who also developed myositis and/or myocarditis as seen in 4 teaching institutions in Japan.

**Design/Participants:** Retrospective observational study of 8 patients.

**Methods:** Serological testing included antistriational antibodies (against titin, ryanodine receptor, muscular voltage gated potassium channels Kv1.4) and myositis-specific antibodies (including anti-Jo-1). Muscle biopsy was done on 5 patients.

**Results:** 8 (0.9%) study patients were among 924 patients with MG seen at 4 institutions. Of study patients, 7 were women; ages ranged from 43 to 68 years (mean 55.3 years). All had positive acetylcholine receptor antibodies and bulbar muscle weakness (related to MG and responsive to cholinesterase inhibitors). Invasive thymoma was found in 4 (50%). Myositis was found in 6 patients and myocarditis in 3 (1 patient had both). Myositis developed slightly before or at the same time as MG while the myocarditis always occurred after MG presentation (13 to 211 months later). Myositis manifested as limb weakness and myalgia in all 6 patients while one had also a dropped head and paraspinal muscle atrophy. Myocarditis presented with heart failure and arrhythmias. Creatine kinase was elevated in 7 patients (362 to 3193 IU/L). All but 1 patient had ≥1 positive antistriational antibody and all 3 with myocarditis had anti-Kv1.4 antibodies. Muscle biopsy (done on 5 myositis patients) showed inflammatory infiltrates without perifascicular atrophy. One patient died from fulminant myocarditis with autopsy showing widespread inflammatory infiltrates in heart and muscles. The remaining 7 patients responded well to immunomodulatory therapy and had pharmacologic remission or minimal manifestations of MG and myositis.

**Conclusions:** Myositis and/or myocarditis rarely accompany MG and are often associated with a positive antistriational antibody. Myositis occurred before or at the same time as MG while myocarditis occurs later. Invasive thymoma is detected in half of these patients. The prognosis is usually favorable.

**Reviewer's Comments:** This is an interesting and thought provoking paper, despite the rare occurrence of myositis and/or myocarditis in MG patients (<1%). We should consider myositis in MG patients with weakness of trunk, neck, or limbs that resists treatment despite resolution of ocular and bulbar symptoms. Also, we should evaluate cardiac status thoroughly in MG patients with dyspnea or palpitations. The most difficult question that remains unanswered is whether inflammatory cells seen in muscles of MG patients represent naive cells (lymphorrhages) or true inflammatory myositis. (Reviewer-Bashar Katirji, MD).

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**Keywords:** Myasthenia Gravis, Myositis, Myocarditis, Thymoma

**Print Tag:** Refer to original journal article
Pulsed high-dose oral dexamethasone is equivalent to standard oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy.

Background: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), the prototype of immune-mediated chronic polyneuropathies, is responsive to corticosteroids, plasma exchange, and intravenous immunoglobulin (IVIG). Open label studies suggested that pulsed high-dose oral and intravenous corticosteroids are effective with less severe steroid adverse effects.

Objective: To determine whether pulsed high-dose oral dexamethasone induces remission more often and more rapidly, and produces fewer adverse effects than chronic oral prednisolone.

Design: Multicenter, double-blind, randomized controlled trial in 9 centers in the Netherlands and United Kingdom.

Participants: 40 treatment-naïve patients with definite or probable CIDP with moderate or severe sensory or sensorimotor manifestations.

Methods: Patients were randomly assigned to receive pulsed oral dexamethasone (40mg/day for 4 days followed by placebo for 24 days, repeated for 6 cycles) versus oral prednisolone for 32 weeks (starting 60mg/day for 5 weeks then tapering to alternate days and then to 0mg by week 32). Patients were followed from week 32 to 52 (a total of 1 year). All patients also received alendronate to prevent osteoporosis. Primary outcome was percentage of patients who achieved and remained in remission without treatment at 12 months. Remission was defined as sustained significant improvement of ≥3 points on the Rivermead mobility index (0=unable to move and 15=fully mobile) and ≥1 point on the inflammatory neuropathy cause and treatment (INCAT) disability scale (0=healthy to 10=unable to make any purposeful movements). Adverse effects were recorded at each visit (baseline, 8, 16, 24, 33, and 52 weeks).

Results: 24 patients were randomized to dexamethasone and 16 to prednisolone. Median duration of disease was 9 months. Median time to remission was 20 weeks in patients on pulsed dexamethasone and 39 weeks in patients on prednisolone ($P = 0.06$). At 1 year, 16 patients were in remission: 10 in the dexamethasone group and 6 in the prednisolone group (odds ratio 1.2; 95% CI, 0.3 to 4.4). There was no statistically differences between groups for the adverse effects, though more patients in the prednisolone group had severe weight gain (>3 kg) and hypertension than in the dexamethasone group.

Conclusions: Pulsed high-dose oral dexamethasone therapy is equivalent to standard oral prednisolone in patients with CIDP and may be considered as an induction therapy in CIDP.

Reviewer’s Comments: The major drawback of this study is the small number of patients enrolled; this is a common obstacle in recruiting treatment-naïve individuals with CIDP because of the ready availability of IVIG. This study suggests that pulse oral steroids as an alternative treatment may work faster than oral steroids. As admitted by the authors, comparing pulse high-dose steroids to IVIG is warranted. (Reviewer-Bashar Katirji, MD).

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Keywords: Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Dexamethasone, Prednisolone

Print Tag: Refer to original journal article
Topiramate Has Limited Cognitive Effects on Children Treated for Migraine

Cognitive Effects of Topiramate in Migraine Patients Aged 12 Through 17 years.

Pandina GJ, Ness S, et al:

Pediatr Neurol 2010; 42 (March): 187-195

Topiramate at up to 100 mg/day in 2 divided doses for the prevention of migraines in children may have an impact on reaction times, but otherwise will typically have little impact on cognition.

Background: Topiramate is approved by the Food and Drug Administration for the treatment of epilepsy in children and adults and prophylaxis against migraines in adults. A recent randomized, double-blind placebo-controlled trial successfully demonstrated topiramate to be effective in prevention of migraine in children; however, potential cognitive effects have not been defined.

Objective: To evaluate the cognitive effects of topiramate in children treated for migraines with 50 and 100 mg per day given in 2 divided doses.

Design: Randomized, placebo-controlled, double-blind parallel-group study.

Participants: 141 subjects at initial enrollment with 103 entering the double-blind phase.

Methods: Study included a pretreatment phase lasting up to 9 weeks, followed by a double-blind phase lasting 16 weeks, and a taper-exit phase lasting up to 6 weeks. Eligible subjects were aged 12 to 17 years and had a history of migraines for ≥6 months based on International Headache Society diagnostic criteria. Exclusion criteria included a history of significant medical conditions, major psychiatric disorders, or use of anti-psychotic or centrally acting sympathomimetic drugs. Participants were randomized to 3 groups that included 35 assigned to 50 mg/day of topiramate, 35 to receive 100mg/day, and 33 to receive placebo. Demographic and baseline characteristics of groups were similar with a median age of approximately 14 years. About 60% were female and 85% were of European origin. Neurocognitive and mood effects were evaluated using the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Profile of Mood States. Comparisons were made from testing performed prior to and during therapy. Cognitive adverse events and other safety assessments were evaluated at each scheduled visit during the study.

Results: Study completion was achieved by 59 topiramate and 26 placebo-treated subjects. Of the topiramate groups, >90% achieved the target dose. Treatment with topiramate at 100 mg/day resulted in statistically significant slowing compared to placebo in reaction time, pattern recognition memory latency, and rapid visual information processing latency. There was no other significant impact on learning, memory, or visual information processing attributed to topiramate therapy other than a potential improvement in a spatial span accuracy test in the 100 mg/day topiramate group. There were no statistically significant changes in mood in any group. Of topiramate-treated subjects, about three fourths reported at ≥1 treatment-adverse event compared to half of the placebo treated subjects.

Conclusions: Treatment of migraine in children with topiramate resulted in a slight increase in reaction times at a dose of 100 mg/day, but there was no impact on learning, memory, or executive function.

Reviewer's Comments: Migraine prophylaxis with topiramate with a dose of up to 100 mg/day in children appears safe with a limited potential of impaired cognitive functioning. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Cognition, Topiramate, Migraine, Children

Print Tag: Refer to original journal article
Treating Subclinical Seizures in Certain Neonates May Reduce Brain Injury

Effect of Treatment of Subclinical Neonatal Seizures Detected with aEEG: Randomized, Controlled Trial.

van Rooij LGM, Toet MC, et al:

Pediatrics 2010; 125 (February): e358-e366

Detection of subclinical seizures in neonates with hypoxic-ischemic encephalopathy with amplitude-integrated EEG, and treatment of subclinical seizures results in decreased total seizure activity and may positively impact outcome.

Objective: To evaluate term neonates with hypoxic-ischemic encephalopathy (HIE) using amplitude-integrated EEG (aEEG) to determine how often subclinical seizures are missed, and to see if treatment of subclinical seizures may impact outcome.

Design: Multicenter randomized controlled trial.

Participants/Methods: Study was performed in neonatal intensive care units (NICUs) in the Netherlands and Belgium over a 5-year period. Included neonates were ≥37 weeks estimated gestational age, and were admitted to the NICU at age <24 hours with HIE and seizures. They were excluded if they were in status epilepticus at admission, had dysmorphic features, or if they were already treated. Degree of HIE was graded for severity. aEEG using a single channel with 2 parietal electrodes corresponding to P3 and P4 was performed immediately after admission. All clinical seizures were treated. After the first sub-clinical seizure, infants were randomized to 1 of 2 groups: group 1 where both clinical and sub-clinical seizures were treated; and group 2 where only clinical seizures were treated. The aEEG was kept blinded in the second group. aEEGs were later reviewed for total seizure duration and seizure types. Clinical events and times when antiepileptic drugs were given were marked. Brain MRIs were performed at age 4 to 10 days and scored based on injury severity.

Results: One half of the 140 infants who met entry criteria were enrolled; of those, 42 were randomized after having a sub-clinical seizure on aEEG. In group 1, median duration of seizure activity on aEEG was just >3 hours, and in group 2 it was >8 hours. Despite the availability of continuous aEEG to aid in the diagnosis of seizures in group 1, the authors felt that seizure treatment was appropriate in only half of patients. In group 2, one half of patients received treatment for clinical seizures that did not correlate with seizure activity on aEEG. An association was seen between longer seizure duration and higher MRI brain injury scores.

Conclusions: Treatment of sub-clinical seizures detected by aEEG can reduce overall seizure duration in neonates with HIE, and thus may be a potential factor in reducing brain injury severity.

Reviewer's Comments: The findings are limited by the small sample size and the use of aEEG compared to a standard neonatal video EEG. Head cooling and hypothermia as treatment of neonatal HIE may likely decrease sub-clinical and clinical seizures along with brain injury. It is also possible that infants with longer seizure duration have severe injury initially, and thus higher brain injury scores. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Amplitude Integrated EEG, Seizure Detection, Neonates, Hypoxic Ischemic Encephalopathy

Print Tag: Refer to original journal article