Anxiety, depression, female gender, and Social Security compensation are independent factors significantly associated with continued psychogenic nonepileptic seizures after correct diagnosis.

Background: It is widely believed that the outcome for patients with psychogenic nonepileptic attacks (pseudoseizures), while variable, is generally poor.

Objective: To describe early outcomes and predictors in patients with psychogenic nonepileptic attacks.

Design: Retrospective cohort study.

Participants: Subjects included 260 consecutive patients diagnosed with pseudoseizures; 75% were women. The mean age was 37.8 years (range, 13 to 87 years), and the mean age at onset of pseudoseizures was 30.8 years (range, 6 to 70 years). The median diagnostic delay was 3.8 years (range, 0.1 to 51.2 years).

Methods: The diagnosis of pseudoseizures was based on video EEG monitoring or ambulatory EEG recording. The only intervention consisted of informing the patients of their correct diagnosis. It is unlikely that patients underwent psychological intervention during the 1-year follow-up because the waiting time for such intervention was about a year.

Results: During the 1-year period after diagnosis, only 72% of these patients attended at least 1 follow-up visit, and only 40% attended 2 follow-up visits. Only 38% of these subjects were spell free at last follow-up, whereas almost 19% of these subjects had a marked increase in spell frequency after diagnosis. Delayed diagnosis had no relationship to outcome. Significant factors that predicted a poor outcome included anxiety or depression (RR, 2.32), receiving Social Security payments at baseline (RR, 2.34), and female gender (RR, 2.46). It is noteworthy that while almost 50% of these patients were using emergency medical services at baseline whenever they had a spell, only 15.5% were using them at follow-up; this was statistically significant and independent of whether the patient became spell free.

Conclusions: A substantial minority of these patients became spell free, with communication of the correct diagnosis being the only intervention, although many patients worsened. Previous psychiatric diagnoses, Social Security payments, and female gender were important predictors of poor outcome. Most patients stopped using emergency services regardless of whether the spells continued.

Reviewer’s Comments: As with psychogenic movement disorders, it appears that the outcome with psychogenic pseudoseizures is quite poor. It would have been interesting to determine whether additional psychiatric intervention would have affected the outcome for these patients. At the risk of being excessively pessimistic, I don't have much enthusiasm that it would. (Reviewer-W. Steven Metzer, MD).
Early- vs Late-Onset Alzheimer's Disease

*Increased Metabolic Vulnerability in Early-Onset Alzheimer's Disease Is Not Related to Amyloid Burden.*

Rabinovici GD, Furst AJ, et al:

Brain 2010; epub ahead of print (February): 512-518

Although early-onset and late-onset AD of similar duration and severity have similar amyloid plaque burden, early-onset disease has greater reduction of cortical metabolism.

**Objective:** To compare the effect of age on amyloid burden and brain glucose metabolism in patients with mild to moderately severe Alzheimer's disease (AD). The hypothesis was positron emission tomographic (PET) uptake of the amyloid-binding tracer Pittsburgh compound B (PIB) would be greater in early-onset disease and would be associated with more severe temporoparietal hypometabolism.

**Participants:** 39 patients meeting standard research criteria for AD were studied; 21 had early-onset disease, and 18 had late-onset disease. These patients were compared to each other and to 30 cognitively normal controls.

**Methods:** PET and MRI were performed. PET data were corrected for atrophy, which could increase plaque density and thereby confound estimation of plaque burden. Early- and late-onset patients were matched for disease duration and functional status. Brain metabolism was measured at PET using [F-18]-labeled fluorodeoxyglucose.

**Results:** Compared to controls, both early- and late-onset patients showed increased PIB uptake in frontal, parietal, and lateral temporal cortices and striatum. There were no significant differences, however, in regional or global PIB binding between early- and late-onset patients. In contrast, early-onset patients had significantly lower glucose metabolism in posterior regions, including precuneus/posterior cingulate, lateral temporoparietal cortex, and occipital cortex.

**Conclusions:** Contrary to the working hypothesis, early-onset AD is associated with an amyloid burden comparable to what is found in late-onset AD of similar duration and severity but with greater posterior cortical hypometabolism. The findings suggest the combination of early beta-amyloid accumulation and increased vulnerability of the brain to beta-amyloid pathology is critical in the pathogenesis of AD in young patients. The nature of the vulnerability is unclear but includes the possibility of increased neurotoxic effects of fibrillar beta-amyloid.

**Reviewer's Comments:** Soluble oligomeric forms of beta-amyloid are more neurotoxic than the fibrillar forms found in amyloid plaques and do not bind PIB. Might early- and late-onset AD have different degrees of oligomeric beta-amyloid burden? Or of hyperphosphorylated tau burden? (Reviewer-John C. Brust, MD).

© 2010, Oakstone Medical Publishing

Keywords: Alzheimer's Disease, Age of Onset, Amyloid-Beta, PIB

Print Tag: Refer to original journal article
Tarenflurbil is metabolized by cytochrome P-2C9.

**Background:** Tarenflurbil (T) is a gamma secretase modulator that decreases the production of the amyloid-beta (Aβ)_{42} amino acid peptide in favor of shorter fragments, which are thought to be less toxic. Tarenflurbil is metabolized by cytochrome P (CYP) 2C9.

**Objective:** To compare the efficacy and safety of tarenflurbil with placebo in patients with Alzheimer's disease (AD).

**Design:** Randomized, double-blind, placebo-controlled study.

**Participants:** 1684 community-dwelling patients with AD who were aged >55 years.

**Methods:** Patients received tarenflurbil 400 or 800 mg twice/day or placebo. Approximately 3 months after inception, the protocol underwent major revisions to include only mild AD and only the 800-mg twice-a-day dose. The changes affected <100 patients. Inclusion criteria were as follows: probable "AD" by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association and DSM-IV criteria; low probability of a vascular dementia; sufficient work/education history to rule out mental retardation; adequate vision and hearing; reliable and involved caregiver; and CT or MRI without focal pathology. Memantine and/or cholinesterase inhibitors were permitted if given at stable doses for several months. In general, other drugs were also allowed. Among many exclusion criteria were closed head injury, epilepsy, major psychiatric disorder (including alcohol/substance abuse), hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs), recent use of NSAIDs other than low-dose aspirin, recent use of cytochrome-P 2C9 substrates or inhibitors, prior immunotherapy for AD, severe cardiac disease, warfarin therapy, history of upper GI bleeding or peptic ulcer disease, cancers (other than prostate and non-melanoma skin), and/or chronic or acute metabolic disorders. Primary outcome measures were Alzheimer Disease Assessment Scale-cognitive Subscale (80-point version) and Alzheimer Disease Cooperative Study activities of daily living (78-point version). Follow-up was 18 months.

**Results:** 51% of subjects were female, and average age was 75 years. Only 18% of patients were not on AD medication, and >50% were on cholinesterase inhibitors plus memantine. The primary efficacy analysis involved 809 patients receiving placebo and 840 receiving 800 mg tarenflurbil twice a day. Unfortunately, no measure of cognition or activities of daily living was significantly different between the 2 groups. Multiple subanalyses also bore no fruit. Adverse reactions led to more discontinuations in the tarenflurbil group than in the placebo group. Tarenflurbil caused transient eosinophilia in one-third of patients and caused persistent elevation of LDL cholesterol.

**Conclusions:** Tarenflurbil, at the dose used, has no effect on the course of mild AD.

**Reviewer's Comments:** The authors presented no evidence that tarenflurbil reduced the production of Aβ_{42}, or increased production of the shorter fragments, which could probably be detected in CSF. The editorialists pointed out that the clinical syndrome of dementia was often the result of convergence of multiple pathologies, including AD, vascular dementia, and other dementias such as Lewy body disease and frontotemporal dementia. In my opinion, we've seen the last of tarenflurbil, but we'll have to wait and see. (Reviewer-James W. Schmidley, MD).

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Keywords: Alzheimer's Disease, Tarenflurbil. Gamma Secretase

Print Tag: Refer to original journal article
The length of post-traumatic amnesia can help determine functional outcome after traumatic brain injury.

**Background:** The Glasgow Outcome Scale (GOS) is the standard to reference prediction and measure global outcome after traumatic brain injury (TBI). The duration of post-traumatic amnesia (PTA) has been found in past studies to be the best predictor of outcome after TBI.

**Objective:** To evaluate the relationship between PTA duration and probability thresholds for GOS levels.

**Methods:** The National Institute on Disability and Rehabilitation Research-funded Traumatic Brain Injury Model Systems (TBIMS) database was used. Inclusion criteria were age ≥16 years, presentation to a designated TBIMS medical center for comprehensive care and rehabilitation within 72 hours of the TBI, PTA duration >24 hours (moderate to severe TBI), end of PTA recorded, and alive after 2 years. The Galveston Orientation and Amnesia Test (GOAT) or Orientation-Log (measures of PTA duration) was prospectively administered 3 times a week. PTA duration was the number of days from the injury until the first 2 consecutive GOAT scores of >75 or Orientation-Log score of >24; in subjects already emerged from PTA, duration was the date of full orientation per chart review. The primary outcome measure, GOS, was evaluated at 12 and 24 months after injury.

**Results:** Of 3129 patients enrolled at TBIMS, 2069 met inclusion criteria; 623 of these were excluded due to incomplete outcome data. The remaining 1332 patients had a mean age of 36.2 years, and 71.2% were male. The mean length of coma was 8.5 days, and mean hospital stay was 43.2 days. Approximately two-thirds of the sample had the same GOS for both years. During the second year, there was more good recovery (44% vs 39%) and less severe disability (19% vs 23%) at year 2 versus year 1. Multinomial logistic regression models confirmed that PTA was a significant predictor of GOS level. It was found that there was good recovery when PTA was ≤18 days, moderate disability when PTA was 29 to 49 days, and severe disability when PTA was >97 days.

**Conclusions:** This study showed PTA to be a good long-term predictor of disability after moderate to severe TBI.

**Reviewer's Comments:** While the results of this study are not unexpected, they do provide guidelines for the likelihood of the recovery expected with the duration of post-traumatic amnesia. (Reviewer-John Schwankhaus, MD).

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Keywords: TBI, Post-Traumatic Amnesia, Outcome Prediction

Print Tag: Refer to original journal article
Amitriptyline vs. Pregabalin in Painful Diabetic Neuropathy: A Randomized Double Blind Clinical Trial.  
Bansal D, Bhansali A, et al:  
Diabet Med 2009; 26 (October): 1019-1026

While there was no significant difference in efficacy between pregabalin and amitriptyline for the treatment of painful diabetic neuropathy, reported adverse events were more commonly associated with amitriptyline (65%) than with pregabalin (35%).

**Background:** One of the oldest treatments for painful diabetic neuropathy is tricyclic antidepressants. Other treatment options include serotonin or norepinephrine reuptake inhibitors, capsaicin, and certain antiepileptic drugs, with the newest one being pregabalin.

**Objective:** To compare amitriptyline and pregabalin for the treatment of painful diabetic neuropathy.

**Design:** Randomized, double-blind, cross-over, active-control clinical trial.

**Participants:** Subjects included 51 men and women with painful diabetic neuropathy (age range, 18 to 75 years). Subjects with significant or unstable medical or psychiatric illness were excluded.

**Methods:** Subjects were randomized to either initial treatment with amitriptyline for 5 weeks (after a 3-week wash-out period) or with pregabalin for 5 weeks (after a 3-week wash-out period). Afterward, subjects underwent another 3-week wash-out period and were then crossed over to the other drug. Amitriptyline was titrated to an optimal dose of 10, 25, or 50 mg at bedtime. Pregabalin was titrated to an optimal dose up to 300 mg twice daily. Subjects and investigators were blind to which drug subjects were receiving. The dependent variable with both treatment modalities was pain reduction, as measured by a visual analog scale, a pain questionnaire, and patient and physician subjective assessments. Adverse events were also recorded.

**Results:** 7 subjects dropped out of the study; data were available for analysis for 44 subjects. Good or moderate pain relief was noted for 61% of subjects treated with pregabalin and 45% of subjects treated with amitriptyline. This trend favoring greater pain control with pregabalin was not statistically significant. Improvement with both treatment modalities was observed by 1 week of treatment with either drug. There was no evidence of depression among the subjects, as tested by the Hamilton rating scale for depression. More subjects (43%) preferred pregabalin, while 34% preferred amitriptyline; this difference was not statistically significant. Fifty-two adverse events related to treatment were reported, with 65% of these adverse events reported with amitriptyline and 35% reported with pregabalin. The most common adverse event with both drugs was drowsiness.

**Conclusions:** There were few differences between the 2 treatments in efficacy, but pregabalin might be preferable because it is associated with fewer adverse effects.

**Reviewer's Comments:** The number of subjects in this study was quite small. Considering that there was a trend in favor of efficacy for pregabalin, this might have been statistically significant if a larger number of subjects have been included in the study. In addition, a majority of the adverse events reported by the subjects occurred while taking amitriptyline rather than pregabalin. I would like to see these 2 drugs compared in a larger study that also has a placebo arm. (Reviewer-W. Steven Metzer, MD).

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**Keywords:** Amitriptyline, Diabetes, Neuropathy, Pain, Pregabalin

**Print Tag:** Refer to original journal article
Both light and dural pain activate thalamocortical “migraine neurons” located in the posterior thalamus.

**Background:** How light aggravates migraine pain is unknown. The pain of migraine is caused by chemical irritation of the dura and mediated by nociceptive afferents of the trigeminal system. Somewhere, the visual and trigeminal pathways converge, but where? A clue comes from the observation that some blind migraineurs suffer photophobia. These individuals have severe damage of rods and cones and cannot see images, but they can still sense light through a surviving subset of retinal ganglion cells that contain the photopigment melanopsin. These individuals exhibit pupillary light reactivity and regular sleep cycles. Can these melanopsin cells be responsible for the sensitization of migraine pain to light? The authors investigated the anatomical overlap of this pathway with dural pain pathways.

**Objective:** To identify the pathway by which retinal signals via the optic nerve could intensify migraine pain.

**Methods:** The authors interviewed 20 blind migraineurs for their medical history, visual history, migraine characteristics, and their sensitivity to light in the presence and absence of a migraine attack. They also conducted neural tract tracing and single-unit recordings in a rat model of migraine to identify neurons and pathways sensitive to both light and noxious dural stimulation. To mimic a migraine attack, Gelfoam, soaked with 1 M potassium chloride (KCl), was applied to the rat dura mater to induce chemical irritation.

**Results:** Among 20 blind migraineurs, 6 had no light perception due to enucleation (4 cases) or severe optic neuropathy (2 cases). Pupillary light reactivity was absent and sleep cycles were fragmented. None were photophobic. The remaining 14 patients had markedly diminished image formation due to dystrophic, degenerated, or severely damaged retinal rods and cones. Though legally blind, they retained pupillary light reactivity, and most had regular sleep cycles. All became photophobic during an attack of migraine. The anatomical tracer studies identified a pathway between the melanopsin retinal ganglion cells and a group of neurons in the posterior thalamus that became active when the dura was irritated with KCl. When microelectrodes were placed in these “migraine neurons,” their electrical activity increased within seconds in response to light. When light was removed, the neuronal discharges continued and showed a very slow rate of decay. These posterior thalamic neurons projected extensively across layers I-V of somatosensory, visual, and associative cortices.

**Conclusions:** A non-image–forming melanopsin retinal pathway modulates the activity of dura-sensitive thalamocortical neurons. The electrophysiological properties of these "migraine neurons" parallel the observation that migraine pain intensifies within seconds of light exposure but requires 20 to 30 minutes to improve in darkness.

**Reviewer’s Comments:** This elegant study offers a road map for future identification of the neurotransmitters responsible for migraine pain and for their pharmacological blockade. (Reviewer-Michael Jacewicz, MD).

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Keywords: Migraine, Photophobia, Posterior Thalamus

Print Tag: Refer to original journal article
Evidence-based medicine would support the use of botulinum toxin type A as an effective and generally safe treatment for localized segmental spasticity.

**Background:** Over 10,000 children born in the United States each year develop cerebral palsy, which is the most common cause of spasticity in children. Treatment of spasticity is often helpful to increase range of motion, function, comfort, and ease of care, as long as it does not cause impairment by decreasing functional strength.

**Objective:** To evaluate the efficacy and safety of various pharmacologic treatments of spasticity in children and adolescents with cerebral palsy based on evidence provided by a comprehensive review of the medical literature.

**Methods:** A systematic review of relevant literature from 1966 to 2008 was performed by a multidisciplinary panel. For inclusion, each study had to be peer-reviewed and performed on human subjects who were age ≤19 years of age and include more than 9 subjects.

**Results:** A total of 218 studies were identified that fulfilled criteria. Based on clinical evidence, botulinum toxin type A injection is established as a generally safe and effective treatment to reduce localized or segmental spasticity in the upper and lower extremities of children with cerebral palsy, but evidence regarding functional improvement is conflicting. It is notable that the Food and Drug Administration is investigating isolated cases of excessive generalized weakness. No studies that utilized phenol, alcohol, or botulinum toxin type B injections for localized or segmental spasticity met the criteria. Diazepam is probably effective in reducing generalized spasticity, but there is not enough data to evaluate the effect on motor function and the associated side-effect profile. Based on 1 study, tizanidine is possibly effective for generalized spasticity produced conflicting results, and side effects of somnolence and hypotonia were common. Oral baclofen is used commonly, however, in clinical practice. Studies of oral dantrolene therapy revealed conflicting and inconclusive effects on spasticity, and dantrolene is not commonly used for this purpose in clinical practice. The evidence was determined to be insignificant concerning intrathecal baclofen therapy because all studies were either Class III or IV, and complications appeared to be common.

**Conclusions:** Evidence-based medicine indicates that botulinum toxin type A is an effective and generally safe treatment for localized or segmental spasticity. Oral diazepam should be considered for short-term therapy for generalized spasticity, and tizanidine might be helpful. Data are insufficient to support or refute the use of phenol, alcohol, or botulinum toxin type B injections for localized or segmental spasticity. For generalized spasticity data on dantrolene, oral and intrathecal baclofen is also insufficient.

**Reviewer's Comments:** Evidence-based medicine is a purists’ approach and has merit, but does not take into account clinical practice and experience. I believe most clinicians would support the clinical use of oral, and especially intrathecal, baclofen. (Reviewer-Gregory B. Sharp, MD).

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Topiramate Is Potentially Useful for Treating Tourette Syndrome

A Randomised, Double-Blind, Placebo-Controlled Study of Topiramate in the Treatment of Tourette Syndrome.

Jankovic J, Jimenez-Shahed J, Brown LW:

J Neurol Neurosurg Psychiatry 2010; 81 (January): 70-73

It may be helpful to try topiramate for Tourette syndrome prior to a dopamine receptor blocker.

**Background:** Drug therapy for Tourette syndrome (TS) employs dopamine receptor blockers and many other medications. Motor tics and behavioral difficulties are often difficult to control. Topiramate enhances gamma-aminobutyric acid subtype A (GABAA) receptors and blocks AMPA/kainate glutamate receptors. It increases cerebral GABA, homocarnosine, and pyrrolidinone and is a weak carbonic anhydrase inhibitor.

**Objective:** To determine the effectiveness of topiramate for TS.

**Methods:** This multicentre, randomized, placebo-controlled, parallel group study looked at the change in severity of tics between topiramate and placebo groups. For inclusion, patients had to have a DSM-IV diagnosis of TS for at least 3 months, be 7 to 65 years of age, and weigh >25 kg. Subjects had to have a Yale Global Tic Severity Scale (YGTSS) rating of ≥19 (moderate to severe), and Clinical Global Impression (CGI) scale severity score ≥4. Those taking >1 agent for tics or >1 agent for behavioral problems were excluded. Prior to randomization, subjects underwent a screening/washout period of up to 30 days (90 days if given botulinum toxin). The study medication (topiramate 25 mg vs placebo) was gradually increased over 6 weeks to 200 mg/day depending on tolerance (but at least to 50 mg/day). The 4-week maintenance phase was followed by a 12-day taper phase. On visits 2 (day 1) and 5 (day 70), subjects underwent the YGTSS, CGI, Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), and the Connors Parent Rating Scale—Revised (CPRS-R:L) (subjects ≤17 years) or the Connors Adult ADHD Rating Scale—Self-Report: Long Version (CAARS-S:L). Some of the scales were administered on visit 3 (day 28) and visit 4 (day 56), and all were followed by phone weekly. The primary efficacy variable was the change in Total Tic Score of the YGTSS at the last visit compared to day 1. Secondary efficacy variables included CGI, premonitory urge CGI, Y-BOCS/CY-BOCS and CPRS-R:L/CAARS-S:L. Adverse events were compared between groups.

**Results:** 29 individuals were included, with the 3 most common comorbidities being attention-deficit disorder, obsessive-compulsive disorder, and migraine headaches; 20 completed the double-blind phase. The TTS improved 14.29 points in the topiramate group and 5.0 in the placebo group. Statistically significant improvements also occurred in the Total Motor Tic Score, Total Phonic Tic Score, and Global Severity Score. The CGI and premonitory urge CGI also improved. There were no clinically significant differences in the secondary measures, frequency of adverse events, or laboratory values between the 2 groups.

**Conclusions:** This study suggests that topiramate may be useful in the treatment of moderately severe TS.

**Reviewer's Comments:** While topiramate may be helpful in treating moderate to severe TS, further studies with larger numbers of patients are needed to confirm these findings. (Reviewer-John Schwankhaus, MD).

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Keywords: Tourette's Syndrome, Topiramate, Tics

Print Tag: Refer to original journal article
Baseline edema and subsequent growth of edema are proportional to the volume of the original ICH.

Background/Objective: Intracerebral hemorrhage (ICH) exerts deleterious effects on the brain initially via the physical effect of the mass. Later, edema, activation of coagulation, release of hemoglobin, and the inflammatory response may play roles.

Design: The Intensive Blood Pressure Reduction In Acute Cerebral Haemorrhage Trial (INTERACT) was a randomized controlled trial of early blood pressure (BP) lowering in acute ICH, involving patients with systolic blood pressures >150 and <220 at presentation. This paper used INTERACT data to examine predictive factors, natural history, and prognostic impact of perihematomal edema (PHE).

Interventions: Intensive therapy (I) (target systolic BP140) or recommended best practice (RBP) (target 180).

Participants: 404 non-comatose patients with CT-confirmed ICH, not secondary to thrombolytic therapy or structural abnormalities (arteriovenous malformation, aneurysm, or tumor), who were able to start treatment within 6 hours.

Methods: Patients were excluded if there was a pre-existing disability, recent ischemic stroke, or planned neurosurgical intervention. CT scans were done at baseline, 24 hours, and 72 hours. Volumes of ICH and PHE were calculated by independent observers using dedicated software. Clinical evaluations were done at baseline, 24, 72 hours, and at 7, 28, and 90 days.

Results: Of the randomized patients, 270 had images of acceptable quality from baseline, 24 hours, and 72 hours. Unanalyzed patients were not significantly different from the analyzed cohort. The mean age was 63 years, and 75% were hypertensive by history. Presenting BP was just over 180/100, median National Institutes of Health Stroke Scale score was 9. Eighty-five percent of the ICHs were basal ganglionic/thalamic; 25% had intraventricular extension. There was a strong statistically significant correlation between the volume of ICH and the volume of PHE at all time points. After multivariate analysis, the only statistically significant predictors of absolute increase in PHE were baseline systolic BP and log baseline ICH volume. Location of ICH, NIH Stroke Scale score, and treatment strategy (I vs RBP) did not predict increase in PHE. After multivariate analysis, accounting for age, sex, treatment strategy and baseline ICH volume, increases in PHE had no effect on outcomes. Treatment strategy also had no effect on PHE growth.

Conclusions: These findings were surprisingly “conservative.” Baseline PHE and subsequent growth of PHE were proportional to the volume of the original ICH (and any growth that might have occurred), but exerted little independent effect on outcome. Thus, they seem to corroborate the primacy of ICH volume in determining outcome.

Reviewer's Comments: Follow-up was only 3 days, and the volume of PHE at later times might have a greater effect on outcome. The authors underplayed the fact that treatment target (140 vs 180 systolic) did not influence PHE growth, despite the fact that this is one of the justifications for aggressive BP lowering in ICH. The ultimate test of this strategy awaits larger randomized trials. (Reviewer-James W. Schmidley, MD).

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Keywords: Intracerebral Hemorrhage, Brain Edema

Print Tag: Refer to original journal article
Psychiatric Comorbidity Common in Children, Adolescents With Demyelinating Disorders

Psychiatric Comorbidity in Pediatric Patients With Demyelinating Disorders.

Weisbrot DM, Ettinger AB, et al:

J Child Neurol 2010; 25 (February): 192-202

Clinicians should routinely screen for and attend to psychiatric symptoms and concerns in pediatric patients with CNS demyelinating disorders.

Background: Psychiatric comorbidities in children and adolescents with demyelinating disorders affecting the central nervous system (CNS) have not been extensively studied. Up to 5% of cases of multiple sclerosis (MS) occur in pediatric patients. Other potential CNS demyelinating disorders include acute disseminated encephalomyelitis (ADEM), a clinically isolated syndrome (CIS) that includes an episode of either focal or multifocal demyelination, neuromyelitis optica, consisting of optic neuritis with transverse myelitis, and recurrent episodes of optic neuritis.

Objective: To investigate the occurrence of psychiatric comorbidities in children and adolescents with CNS demyelinating disorders.

Participants: The 23 subjects ranged in age from 6 to 17 years, with a mean age of 13 years. The mean age at the onset of neurologic symptoms was 11 years. Approximately two-thirds were male. The ethnic distribution was about 70% Caucasian, 20% Hispanic, 10% African American, and 5% other. The established diagnosis was MS in 11, ADEM in 4, CIS in 3, neuromyelitis optica in 2, and recurrent optic neuritis in 3.

Methods: A group of patients <9 years of age who met the established criteria for a CNS demyelinating disorder were retrospectively identified. A semistructured psychiatric interview was then performed with each patient and parent by a single adolescent psychiatrist using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version. Parents and adolescent subjects also completed the Child Symptom Inventory-4 and the Youth's Inventory-4. Close attention was paid to fears and conceptions of their neurological problems. Intelligence was assessed using the Wechsler Intelligence Scale for Children—Revised. Patient disability was rated with the Expanded Disability Status Scale.

Results: Of the 23 subjects, 11 met the criteria for a current psychiatric diagnosis. The diagnosis of a depressive disorder was made in approximately 15%, and an anxiety disorder was identified in 30% of the entire group. Fears were common with at least 1 expressed fear in 75% of patients. Fears and conceptions of the illness tended to be fairly severe and diverse. IQ was in the average to high average range in approximately 90% of subjects, in the superior range in 1 patient, and in borderline range in 2. The mean Expanded Disability Status Score was slightly, but not significantly, higher in the group of patients with a psychiatric diagnosis compared to those without a psychiatric diagnosis.

Reviewer's Comments: Children and adolescents with CNS demyelinating disorders commonly have significant fears and concerns about their illness. Depressive and anxiety disorders are not uncommon. Clinicians should routinely screen for and attend to psychiatric symptoms and concerns in pediatric patients with demyelinating disorders. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Demyelinating Disorders, Psychiatric Comorbidity, Pediatrics

Print Tag: Refer to original journal article
Non-dystrophic myotonias are the result of gene mutations affecting either chloride channels or sodium channels in skeletal muscle.

**Objective:** To review clinical aspects of non-dystrophic myotonias.  
**Methods:** Review article.  
**Results:** Myotonia consists of delayed muscle relaxation following muscle contraction or mechanical stimulation such as percussion. The principal symptom is muscle stiffness, sometimes with pain, weakness, and fatigue. Muscle membrane is hyperexcitable, and this hyperexcitable state is reflected on EMG by repetitive muscle fibre after-discharges. Clinical severity ranges from mild late-onset symptoms to a neonatal life-threatening presentation. Several clinical and genetic subgroups of non-dystrophic myotonia are recognized. Myotonia congenita, the most common, is caused by mutation of the skeletal muscle chloride channel gene (CLCN1) and can be either dominantly or recessively inherited. Both types demonstrate “warm up phenomenon,” with muscle stiffness most pronounced during rapid movements after a period of rest and improvement with repeated activity. Neither type demonstrates cold sensitivity. Recessives often demonstrate transient weakness on initiating an action, and their symptoms, including muscle hypertrophy, tend to be more severe. Paramyotonia congenita is caused by mutation of the skeletal muscle sodium channel gene (SCN4A) and is dominantly inherited. With paramyotonia congenita, cold sensitivity is a prominent feature. Warm up phenomenon is not present, and episodic weakness can last from seconds to days. Eyelid myotonia is common. A second group of myotonias caused by sodium channel mutation is also dominantly inherited and demonstrates variable cold sensitivity and warm up phenomenon as well as eyelid myotonia, but without episodic weakness. Patients with SCN4A mutation may have paradoxical myotonia that worsens with continued exercise. EMG with special technique can provide clues as to which subtype of myotonia is present based on the response of compound muscle action potentials to exercise with or without cooling. Some patients with non-dystrophic myotonia develop myopathy. A puzzling feature of non-dystrophic myotonias is the marked phenotypic heterogeneity. The same mutation can be inherited in a dominant or recessive manner, and kindreds with the same mutation can have marked differences in severity. In myotonia congenita, enhanced excitability of the muscle fibre membrane is the result of reduced sarcolemmal chloride conductance. In paramyotonia congenita and other sodium channel myotonias, excitability is the result of either impaired inactivation or enhanced activation of the muscle sodium channel. The current first-line treatment of choice for non-dystrophic myotonia is the anti-arrhythmic mexiletine. A randomized controlled trial has not been conducted, however, and myotonia is difficult to quantitate. Investigational in vitro strategies include trans-splicing with a ribozyme to restore premature chloride channel degradation and improving defective chloride channel protein transport from endoplasmic reticulum to the Golgi apparatus. (Reviewer-John C. Brust, MD).

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Keywords: Ion Channels, Neuromuscular, Genetics, EMG

Print Tag: Refer to original journal article
Coccidioidal Meningitis -- What You Need to Know

Coccidioidal Meningitis and Brain Abscesses: Analysis of 71 Cases at a Referral Center.
Drake KW, Adam RD:
Neurology 2009; 73 (November 24): 1780-1786

In patients with coccidioidal meningitis, CSF culture and antibody titer are often negative; therefore, diagnosis may depend on positive serum antibody or other evidence of systemic coccidioidomycosis.

**Background:** Coccidioides is the most common cause of chronic meningitis in endemic areas, such as the southwestern United States.

**Objective:** To describe the risk factors, clinical and laboratory features, and prognosis of coccidioidal meningitis.

**Design:** Retrospective study. **Setting:** Referral center in an endemic area.

**Participants:** Patients treated for coccidioidal meningitis from 1996 to 2007.

**Methods:** A diagnosis of coccioidomycosis as the cause was considered confirmed when the presence of the fungus in the central nervous system (CNS) was documented by culture, biopsy, or cerebrospinal fluid (CSF) antibody; it was presumed, when there was evidence of coccidioidomycosis outside the CNS, such as positive serum antibodies, and considered probable when there was no better diagnosis.

**Results:** There were 71 cases of coccidioidal meningitis (37 confirmed, 32 presumptive, and 2 probable). Males accounted for over two-thirds of the cases. Most patients (58%) were immunocompetent. Compromised cell-mediated immunity was present in 30 patients (42%), including 15 with AIDS and 10 receiving corticosteroid treatment. An antecedent illness suggestive of pulmonary coccidioidomycosis was reported in 32 patients (45%). Sixteen patients (22%) already carried a diagnosis of extrapulmonary, non-CNS dissemination. Patients presented with fever (28%), nuchal rigidity (23%), headache (77%), nausea and vomiting (48%), confusion, drowsiness or memory loss (39%), seizure (13%), and unsteady gait (33%). All patients had CSF pleocytosis. As in most chronic meningitides, the cell count was <400/mL (84% of patients), but it was mainly polymorphonuclear in 24% of patients, and 15% had eosinophils. A sizable minority of patients (31%) did not have low CSF glucose, and 13% did not have high protein. Complications developed during the course of meningitis: communicating hydrocephalus (49% of patients), lacunar infarcts (10%), aneurysm of the basilar artery (1 patient), and brain abscess (8% of patients). The vascular complications were ascribed to extension of infection to arteries in the leptomeninges, and the abscesses to extension of infection across the pia mater to the brain. Most patients (90%) were treated with fluconazole, life-long to prevent relapse. Patients recovered neurologic function, and only 2 died.

**Conclusions:** Most patients with coccidioidal meningitis are immunocompetent. CSF culture and antibody titer are often negative; therefore, diagnosis may depend on positive serum antibody or other evidence of systemic coccidioidomycosis. CSF findings may unexpectedly include a predominantly polymorphonuclear leukocytosis, some eosinophils, and a normal protein or glucose level. Communicating hydrocephalus and cerebral infarcts caused by infectious vasculitis are common complications. Treatment with fluconazole is effective but must be life-long to prevent relapse.

**Reviewer’s Comments:** A history of travel to an endemic area is an important aid to diagnosis for those of us who do not practice in an endemic area. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Chronic Meningitis, Fungal Meningitis, Coccidioides

Print Tag: Refer to original journal article
Delayed, post-recovery cerebral infarction appears not to be a direct effect of infection, but a postinfectious reaction possibly related to adjunctive treatment with high-dose corticosteroids.

**Background:** Cerebral infarction is a common, well known, early complication of bacterial meningitis.  
**Objective:** To describe a new complication—delayed cerebral infarction after initial, good recovery from pneumococcal meningitis.  
**Design:** Small case series and literature review.  
**Results:** The authors report on 6 patients, 5 men and 1 woman, aged 30 to 73 years (median, 40 years). All had typical cases of pneumococcal meningitis treated with antibiotics and, for the first 4 days, high-dose corticosteroids (dexamethasone 10 mg IV every 4 hours). The patients had normal brain imaging when treatment began and made a good recovery in the first week. During the second or third week (days 7 to 19; median, day 11), however, they became ill again. They developed headache, fever, seizures, coma, hemiplegia, and brainstem signs. Brain imaging showed acute infarcts, mostly in the thalamus, brainstem, and cerebellum, in the distribution of small, perforating arteries. The CSF showed polymorphonuclear pleocytosis and elevated protein, instead of the expected improvement, but the glucose was higher than it had been in the initial CSF examination, and Gram stain and cultures were negative. Transesophageal echocardiography did not show endocarditis. The patients were treated with antibiotics and high-dose corticosteroids, but their outcome was poor: 4 died and 2 were left with severe neurologic disability. At autopsy, small brain arteries were occluded by thrombus, but neither micro-organisms nor inflammation were seen in their walls. Similar cases were not found in a prospective cohort of 696 cases of community-acquired bacterial meningitis treated before the use of adjunctive corticosteroids had become the norm. In 3 of the 5 similar cases found in the literature, corticosteroids had not been given.  
**Conclusions:** Delayed, post-recovery cerebral infarction is a rare complication of pneumococcal meningitis. It appears not to be a direct effect of infection, but a postinfectious reaction possibly related to adjunctive treatment with high-dose corticosteroids.  
**Reviewer’s Comments:** In an accompanying editorial, Israel Steiner mentions several mechanisms that might underlie the vascular occlusions: immune-mediated thrombotic microangiopathy due to meningitis, hypercoagulable state due to meningitis and dexamethasone, and immune-mediated vasculitis. (Reviewer-Marc D. Winkelman, MD).
Low-dose intravenous immunoglobulin reduces pain intensity in patients with long-standing CRPS.

**Background:** The treatment of complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy, is usually multimodal, but nonetheless, often unsuccessful. Several studies have shown the importance of cytokines, neuronal autoantibodies, and autoimmunity in the maintenance of pain and limb changes in CRPS. Intravenous immunoglobulin (IVIG), used primarily in immunodeficiency states and autoimmune disorders, is thought to interfere with autoantibodies and downregulate proinflammatory cytokines. This study was an attempt to evaluate the efficacy of IVIG in patients with chronic CRPS.

**Design:** Randomized, placebo-controlled, double-blind, cross-over study in a single tertiary center in the United Kingdom.

**Methods:** Patients with confirmed chronic CRPS, with symptoms ranging between 6 and 30 months, were enrolled. Patients with a pain intensity of <5 were rejected (using the numerical pain scale 0 to 10; 0 = no pain and 10 = pain as bad as imaginable). IVIG (a total of 0.5 g/kg) or saline was given over 2 consecutive days. Patients were scheduled for crossover 28 days after the initial infusions. The primary outcome was pain intensity from days 6 to 19 after each infusion period. Secondary outcomes are patients' reports of IVIG effectiveness and CRPS "limb-symptom" scale (including color, swelling, temperature, sweating, and power). Patients self-rated their limbs on a scale of 0 to 5 (0 = complete subsidence of signs, 4 = no change, and 5 = worse).

**Results:** Of 13 eligible patients, 12 completed both arms of the trial and 12 of the 13 had no defined peripheral nerve injury (CRPS type 1). Their mean disease duration was 19 months, and their mean pain score at entry was 7.9. There was an average decrease of 1.55 units (20% to 30%) in the numerical pain scores after IVIG compared with saline (95% CI, 1.29 to 1.82; \( P < 0.001 \)). Five patients (42%) had a 2-point drop in pain score with IVIG compared to saline. When asked which treatment was more effective, 8 of the 12 patients (66%) believed one of the treatments was better than the other and in 7 of these 8 patients, the better treatment was IVIG. Also, 7 of 11 patients reported improvement of limb symptom measurements after IVIG but not after saline (\( P = 0.016 \)).

**Conclusions:** Low-dose IVIG (0.5 g/kg) reduces pain in patients with long-standing CRPS type 1.

**Reviewer's Comments:** This is an interesting study that may ultimately give patients another venue of treatment in addition to what is currently available, such as sympathetic blocks and spinal stimulators. The number of patients studied was small, which increases the possibility of chance influencing the results. Also, the lack of placebo effect in this study is atypical; if present, it may negate the 20% to 30% positive effect of IVIG. As highlighted by the authors, a larger study is needed to confirm these findings and determine the best IVIG dose and frequency of infusions. (Reviewer: Bashar Katirji, MD).

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Keywords: Complex Regional Pain Syndrome, Treatment

Print Tag: Refer to original journal article
Aerosolized Porcine Neural Tissue Triggers a Polyradiculoneuropathy

An Outbreak of Neurological Autoimmunity With Polyradiculoneuropathy in Workers Exposed to Aerosolised Porcine Neural Tissue: A Descriptive Study.

Lachance DH, Lennon VA, et al:

Lancet Neurol 2010; 9 (January): 55-66

Aerosolized porcine neural tissue triggers an autoimmune polyradiculoneuropathy in a swine meat processing plant.

Background/Objective: In 2008, the authors reported an inflammatory neurological disease in workers at a swine meat processing plant in Minnesota and postulated an autoimmune basis for this disorder. This study is a comprehensive study of a group of patients who underwent a thorough neurological evaluation and testing, describing the immunological and pathophysiological characteristics of this syndrome.

Design: Chart review of a cohort of patients in a single tertiary medical center.

Participants/Methods: 24 patients were assessed by one of the authors at a single tertiary center between November 2006 and May 2008 (21 from Minnesota and 3 from Indiana). All worked full time at abattoirs for at least 2 months. Patients underwent comprehensive neurological, serological, electrophysiological, and pathological examinations. Control blood was analyzed from patients and 52 asymptomatic workers who did work at the head tables (where swine brains were extracted and aerosolized) and 38 random workers who worked at various distances from the head tables. These were compared with sera from 178 community controls made up mostly of hospital employees and spouses.

Results: The shortest duration from first exposure to symptom onset was 4 weeks. The onset was subacute in 95% of cases. All patients had a polyradiculoneuropathy. Symptoms consisted of tingling/prickling (100%), pain (96%) and weakness (75%), while sensory loss (79%), impaired deep tendon reflexes (71%), weakness (71%), and impaired nerve stretch signs (59%) were the predominant findings. One patient had transverse myelitis, meningoencephalitis, and aseptic meningitis before developing polyradiculoneuropathy. At least one systemic inflammatory response (elevated erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, or immunoglobulin) was present in 95% of patients. Nerve conduction studies pointed to the most proximal (roots) and distal segments of the nerves with denervation (79%), delayed F waves (64%), and delayed distal motor latencies (67%). Cerebrospinal fluid (CSF) showed high protein in 86% of patients (mean, 134 mg/dL; range, 23 to 450), while pleocytosis was present in only 3%. MRIs (abnormal in 87%) showed dorsal root/ganglia enhancement or T2 hyperintensity. Sera from all patients and 29 (34%) of asymptomatic workers, but none of the community controls, had IgG that bound to several neural elements, while 75% of sera had IgG specific to myelin basic protein. The IgG antibody titers were inversely related to the distance of the worker from the "head table." Immunomodulation was required in 17 patients, and 6 improved spontaneously.

Conclusions: This neurological disorder is related to exposure to aerosolized porcine brain tissue antigens. The disorder is dominated by peripheral nerve and root involvement where the blood-nerve barrier is less secure.

Reviewer's Comments: This very interesting paper reviews this subject and almost confirms the relation between exposure to aerosolized porcine brain and a likely autoimmune neurological disorder. (Reviewer-Bashar Katirji, MD).

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Keywords: Polyradiculopathy, Aerosolized Porcine Neural Tissue

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In febrile children with an initial episode of status epilepticus, the CSF examination is used to provide diagnostic direction, and in afebrile children, MRI of the brain may be most helpful initially.

**Background:** Status epilepticus (SE) in children is a neurologic emergency, and identification of the etiology can sometimes be difficult.

**Objective:** To review unusual causes of SE in children and provide a practical diagnostic approach when the etiology is not apparent.

**Methods:** A search of the PubMed database was performed to identify reports concerning pediatric SE with focused attention on unusual or unsuspected etiologies. Diagnostic flowcharts were designed using this information.

**Results:** 2 flow charts were developed. In the flowchart for febrile children, the cerebral spinal fluid (CSF) examination provides primary direction. With normal CSF, consider severe myoclonic epilepsy of infancy where prolonged seizures commonly occur initially in response to fever. Abnormal CSF usually points to infection. Common bacterial pathogens are typically easily identified by culture. Also consider mycoplasma, Bartonella, Q-fever, chlamydia, and tuberculosis. Viral causes may include herpes virus 6 and 7, influenza, adenovirus, echovirus, rotavirus, respiratory syncytial virus (RSV), parvovirus, West Nile, and Epstein-Barr virus (EBV). Failure to identify a virus does not exclude encephalitis. Parasitic causes include neurocysticercosis, malaria, and paragonimiasis. The child may or may not be febrile and CSF findings may or may not be abnormal in systemic disorders like systemic lupus erythematosus (SLE), Hashimoto thyroiditis, and non-Langerhans cell histiocytosis. In afebrile children, magnetic resonance imaging (MRI) of the brain provides primary direction. The MRI is usually normal with status epilepticus due to: (1) drugs or toxins that may include tricyclic antidepressants, carbon monoxide, isoniazid, bupropion, tramadol, venlafaxine, cocaine, "ectasy," ethanol, carbon monoxide, camfor, or tetramine; (2) underlying epilepsy syndromes or metabolic/genetic causes (including pyridoxine dependency, β-ureidopropionase deficiency, mitochondrial disorders, or polymerase gene mutations [POLG]); (3) an abnormal MRI with white matter/basal ganglia findings that may indicate MELAS, Wilson disease, leukodystrophy or POLG; or (4) cortical abnormalities with or without edema, which may reveal a cortical dysplasia, tumor, ischemic injury, traumatic injury, POLG, MELAS, or neurocysticercosis.

**Reviewer's Comments:** When a child presents with an initial episode of SE and routine diagnostic studies do not reveal an etiology, the above strategy can be used to search for the underlying cause, but should not be considered to include all possibilities. (Reviewer-Gregory B. Sharp, MD.)

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Keywords: Status Epilepticus, Diagnosis, Atypical Causes

Print Tag: Refer to original journal article
Brain MRI Indicated in Children <2 Years Old With New-Onset, Afebrile Seizures

New-Onset Afebrile Seizures in Infants: Role of Neuroimaging.
Hsieh DT, Chang T, et al:

Neurology 2010; 74 (January 12): 150-156

Compared to older patients, infants <2 years of age with new-onset, afebrile seizures appear to have a greater chance of having an abnormality identified with neuroimaging, and MRI has a much greater sensitivity than CT.

Background: Seizures in children have a high incidence of onset in infancy. The recommended evaluation for afebrile seizures includes electroencephalography (EEG) and urgent neuroimaging in all children with a postictal persistent focal neurologic deficit, and nonurgent neuroimaging should be considered with certain circumstances. There has been no large study evaluating the yield of neuroimaging in new onset, afebrile seizures in infants.

Objective: To determine the yield of head computed tomography (CT) and magnetic resonance imaging (MRI) in the evaluation of new onset, afebrile seizures in children <24 months of age.

Design/Methods: A prospective study at a single center included all infants <24 months of age evaluated in the emergency department with new-onset afebrile seizures from 2001 to 2007. Patients were excluded if they had fever, central nervous system (CNS) infection, or a “spell” that was felt to be nonepileptic. All children were admitted to neurology or seen by the neurology consult service. Seizures were classified according to International League Against Epilepsy guidelines.

Results: The 317 infants included in this study mostly represented an urban minority population and ranged in age from 1 to 24 months. Half of the patients had partial onset seizures and the other half had various types including infantile spasms, but primary generalized seizures were uncommon. Two-thirds had experienced >1 seizure at the time of presentation, but most had seizures lasting <5 minutes. Multiple seizures at onset were more likely in younger infants. A head CT was obtained in 95% of patients, and an abnormality was identified in one-third. Half of these abnormalities were incidental findings. The most frequent significant abnormality identified with head CT was cerebral dysgenesis, representing 25% of the abnormal CT results. An abnormality that prompted quick medical intervention was identified in 1 out of every 10 scans. Half of the patients also had brain MRI, with 60% of these studies being abnormal and most frequently revealing cerebral dysgenesis. Half of the patients with a normal head CT later had a brain MRI, and one-third of these were abnormal; however, only 1 scan resulted in a different urgent medical intervention. EEG was abnormal in 75% of the patients who had an abnormal brain MRI.

Conclusions: Neuroimaging in addition to EEG should be performed on all infants <24 months of age who present with new-onset, afebrile seizures. Brain MRI is preferable, but a head CT should be urgently performed in emergency situations as indicated so that medical intervention is not delayed.

Reviewer's Comments: Neuroimaging of the brain should be considered for all children <2 years of age with new-onset, afebrile seizures. MRI is preferable to CT due to increased sensitivity. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Infants, Afebrile Seizures, Neuroimaging

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