This double-blind, randomized, placebo-controlled, crossover trial provides good scientific evidence that high-flow oxygen inhalation is an effective abortive therapy for cluster headache attacks.

**Background:** Untreated cluster headache attacks last 15 to 180 minutes, and they occur 1 to 8 times per day. Clusters last weeks to months. Episodic cluster is defined as a bout lasting 7 days to 1 year with a break of ≥1 month between bouts (mean duration, 8 weeks). Chronic cluster lasts >1 year without remission or with remission lasting <1 month. The male-female ratio is 2.5:1, with an estimated prevalence of 0.3% in the general population. Approved treatment for cluster attacks is subcutaneous sumatriptan. Another first choice for treatment of acute cluster headache is inhalation of high-flow oxygen, with efficacy suggested in very small controlled studies.

**Objective:** Placebo-controlled trial of cluster attack treatment with oxygen inhalation.

**Design:** Double-blind, randomized, placebo-controlled, crossover trial.

**Participants:** 334 patients were assessed for eligibility, with 225 excluded for various reasons. Inclusion criteria consisted of a diagnosis of episodic cluster or chronic cluster in adults with 1 attack every other day to 5 attacks per day, with attack duration being 45 to 180 minutes.

**Methods:** 109 subjects were randomly assigned to either treatment with oxygen first or air first, with both gases delivered at high-flow (12 L/minute) for 15 minutes. Four attacks were treated for each subject, and results were recorded in a diary. Subjects not achieving relief within 15 minutes were allowed to use rescue medication. Of 109 randomized subjects, 33 did not receive treatment for a variety of reasons (most common reason: cluster ended), leaving 76 subjects who completed the trial. Subjects using rescue medication after 15 minutes were not included in data analysis. The primary end point was freedom from pain at 15 minutes. Secondary end points included freedom from pain at 30 minutes, reduction in pain up to 60 minutes, need for rescue medication 15 minutes after treatment, overall response to the treatment, and overall functional disability.

**Results:** 57 subjects with episodic cluster and 19 with chronic cluster headache were available for analysis. For the primary end point, the difference between high-flow oxygen (78%) and air (20%) was significant, with no important adverse events. For all secondary end points, oxygen was superior to air.

**Conclusions:** Treatment of patients with cluster headache at symptom onset using inhaled high-flow oxygen compared with placebo was more likely to result in pain freedom at 15 minutes.

**Reviewer’s Comments:** This study provides scientific evidence for efficacy of high-flow inhaled oxygen for treatment of acute cluster attacks. However, the overall efficacy of this therapy for cluster is overestimated by this study, because subjects using rescue therapy after not realizing benefit from 15 minutes of inhalation therapy were not included in analysis. The authors further postulate that episodic and chronic cluster headache might respond differentially to this treatment; this could not be determined from the current study. (Reviewer: W. Steven Metzer, MD).

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Keywords: Cluster Headache, Oxygen Therapy

Print Tag: Refer to original journal article
Memantine Treats L-Dopa-Induced Complications in PD

NMDA Antagonist Memantine Improves Levodopa-Induced Dyskinesias and “On-Off” Phenomena in Parkinson's Disease.
Varanese S, Howard J, Di Rocco A:

Mov Disorders 2009; December 11 (): epub ahead of print

Consider a trial of memantine in patients with Parkinson disease and difficult-to-control motor fluctuations.

Background: Evidence suggests a major role for overactive glutamatergic-striatal circuits in the development of abnormal motor patterns in Parkinson disease (PD). The potent NMDA receptor antagonist, memantine, has been reported to reduce motor fluctuations and Parkinson's symptoms. A double-blind, crossover study failed to confirm this, however.

Methods: Three patients with long-term PD who had motor fluctuations were given memantine.

Results: Patient 1 was a 68-year-old woman with a 13-year history of PD who, after 7 years on levodopa (L-dopa), developed on-off fluctuations and peak-dose dyskinesias. The United Parkinson's Disease Rating Scale (UPDRS) motor score (part III) was 23 before and 18 after starting memantine 30 mg/day. Her complication to therapy score (part IV) was 10 before and 4 after therapy, “on” phase dyskinesia score was 4 before and 1 after, while her fluctuation score was 4 before and 1 after therapy. After 3 years, memantine was discontinued with worsening of motor fluctuations and dyskinesias. This improved with re-instating memantine. Patient 2 was a 52-year-old woman with an 11-year history of PD on L-dopa, entacapone, and amantadine who developed peak-dose dystonia, painful dyskinesia, and on-off fluctuations after 5 years. She had similar improvement with memantine 30 mg/day. The third patient was a 75-year-old man with a 15-year history of PD on L-dopa and entacapone who developed on-off fluctuations and peak-dose dyskinesias after 10 years. Memantine 20 mg/day improved symptoms and UPDRS scores. Memantine was accidentally stopped for 1 month with worsening, which improved with re-introduction of memantine. With time, the motor fluctuations disappeared completely, with UPDRS fluctuation and dyskinesia scores dropping to 0. Memantine improved motor fluctuations in all 3 patients, and no side effects were noted.

Conclusions: Memantine may be an effective drug for the treatment of L-dopa–induced complications in PD.
Reviewer's Comments: The positive benefit to these 3 PD patients with motor fluctuations is encouraging. Further double-blind, placebo-controlled trials are needed to study memantine’s efficacy. (Reviewer-John Schwankhaus, MD).

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Keywords: Parkinson Disease, Dyskinesias, On-Off Phenomenon

Print Tag: Refer to original journal article
Cerebral Ischemia Risk Increased in POEMS

Cerebral Infarction in POEMS Syndrome: Incidence, Risk Factors, and Imaging Characteristics.

Dupont SA, Dispenzieri A, et al:

Neurology 2009; 73 (October 20): 1308-1312

POEMS syndrome is occasionally associated with Castleman disease. Patients with POEMS have an increased risk of cerebral ischemia, but mechanisms are not clear.

Background: POEMS syndrome is a multisystem disorder stemming from a plasma cell dyscrasia. Cardinal features are polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS).

Objective: To systematically examine cerebral ischemia in POEMS syndrome.

Design: Retrospective observational study.

Participants: 208 patients with POEMS seen at a referral institution over 35 years.

Methods: POEMS was diagnosed by standard criteria. Ischemic stroke was classified by the Trial of Org 10172 in Acute Strove Treatment (TOAST) scheme and verified by CT and/or MRI. Only ischemic strokes occurring after onset of the polyneuropathy were considered. Stroke risk factors were noted, and the Framingham Stroke Risk Profile (FSRP) was calculated.

Results: For the entire cohort, 19 of 208 patients had cerebral ischemia. The median patient age was 53 years, and 63% were men. Stroke patients had the usual mix of risk factors, and less than a third received antithrombotic therapy at the time of the cerebral infarct. None had a family history of premature stroke. A subcohort of 90 patients seen during the 21st century, when investigations and care were more standardized and more carefully analyzed. In this smaller group, 9 of 90 patients (about 10%, like the larger cohort) had ischemic strokes, and the mean age was slightly younger (late 40s), but the stroke patients were still predominantly male. Patients with or without stroke were not different with respect to age, gender, length of follow-up or FSRP score. POEMS syndrome may be associated with Castleman disease (angiofollicular lymph node hyperplasia), but the incidence of Castleman disease, other manifestations of POEMS, and levels of interleukin-6 and vascular endothelial growth factor were not different between stroke and non-stroke patients in the more intensively studied cohort. POEMS patients with strokes had higher platelet counts (PLTC) and were more likely to have bone marrow plasmacytosis. The relationship between PLTC and stroke risk showed a graded increase for each tertile of PLTC. Review of the literature reporting cerebrovascular disease in POEMS revealed 11 additional patients with cerebral infarcts, of whom 5 had infarcts in viscera, heart, or limbs, suggesting a widespread process. Two patients had middle cerebral artery stenosis, 2 had internal carotid artery stenosis or occlusion, and 1 had both.

Conclusions: Patients with POEMs have an increased risk of cerebral ischemia, but mechanisms are not clear. Because there is an association between stroke risk and platelet count, antiplatelet therapy seems advisable.

Reviewer's Comments: It is not clear that the patients with stroke were systematically investigated, and it is disappointing that coagulation studies were not done. POEMS and Castleman disease are treated with a variety of approaches, including chemotherapy, monoclonal antibodies, IVIg, plasma exchange, steroids, thalidomide, interferon, antiviral therapy, and even peripheral blood stem cell transplants. Two of these treatments (IVIg and thalidomide) are known causes of stroke. (Reviewer-James W. Schmidley, MD).

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Keywords: POEMS Syndrome, Cerebral Infarction, Castleman Disease

Print Tag: Refer to original journal article
The propofol infusion syndrome can include unexplained metabolic acidosis, refractory bradycardia and cardiac failure, rhabdomyolysis, lactic acidosis, lipemia, hyperkalemia, and renal failure.

**Background:** Refractory status epilepticus (RSE) is defined as status epilepticus that fails to respond to first-line treatment with benzodiazepine and second-line treatment with an antiepileptic drug (AED). It occurs in 9% to 31% of patients with status epilepticus. Propofol, available since 1989 in the United States, has been widely used to treat RSE. The propofol infusion syndrome (PRIS) can include unexplained metabolic acidosis, refractory bradycardia and cardiac failure, rhabdomyolysis, lactic acidosis, lipemia, hyperkalemia, and renal failure. PRIS is believed to be due to the toxic effect of propofol on cellular and mitochondrial function. Only case reports and small series document PRIS in patients with RSE treated with propofol.

**Objective:** To study the frequency of PRIS in patients with RSE treated with propofol.

**Design/Methods:** Retrospective study with outcome assessment.

**Participants:** Subjects included 41 patients with RSE treated at the Mayo Clinic during an 11-year period (1997-2008). Thirty-one of these subjects were treated with propofol, either alone or in combination with other AEDs. The other 10 subjects were treated with drug regimens that did not include propofol. Fewer than half of these patients had a known diagnosis of epilepsy (37%). The median patient age was 51 years, and the group consisted of 24 males. The median hospital length of stay was 12 days (range, 2-145 days), and the median ICU length of stay was 9 days (range, 2-95 days). There were 4 patients in the pediatric age group.

**Results:** 3 of 31 propofol-treated patients (10%) experienced sudden unexpected and unexplained cardiopulmonary arrest, 2 of which were fatal. Eleven additional propofol-treated patients (35%) had non-life-threatening features of PRIS, with metabolic acidosis, bradycardia, and hypotension being most common. No such events were noted in the nonpropofol-treated group. Propofol was used for a median of 63 hours (range, 2-391 hours), with a median cumulative dosage of 12,750 mg and with a median peak infusion rate of 67 µg/kg per minute. Cumulative dose, peak infusion rate, and total infusion time for propofol were significantly higher for patients developing PRIS. Total cumulative dose of propofol was significantly higher for the 3 patients who developed cardiac arrest.

**Conclusions:** Prolonged use of large doses of propofol to treat RSE was associated with significant morbidity and mortality. The authors strongly caution against the use of propofol for RSE.

**Reviewer’s Comments:** This is a very useful article; the conclusion appears to be well-founded. It appears that treatment of RSE with midazolam, lorazepam, or pentobarbital is safer than treatment with propofol. (Reviewer-W. Steven Metzer, MD).

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Keywords: Refractory Status Epilepticus, Propofol Infusion Syndrome

Print Tag: Refer to original journal article
Although ineffective in improving bradykinesia, tremor, or rigidity, deep brain stimulation of the pedunculopontine nucleus seems to reduce the risk of falls in patients with Parkinson disease.

**Objective:** To describe a double-blinded study of pedunculopontine nucleus (PPN) deep brain stimulation in 6 patients with advanced Parkinson disease (PD).

**Methods:** Patients were aged <70 years, did not have dementia, and had severe off-period gait and balance impairment with freezing and falls. The targeted PPN was contralateral to the side of the body with the most marked bradykinesia and rigidity. During the first 2 to 3 months following electrode placement, acute and chronic effects of different amplitudes, frequencies, and pulse widths were assessed, and maximal clinical benefit was sought by keeping the voltage just below what produced side-effects, usually paresthesias. Clinical assessment was based on the motor examination component of the Unified Parkinson Disease Rating Scale (UPDRS), with special attention to a tapping test and a walking test. The activities of daily living component of the UPDRS was used to assess falling and freezing. Another part of the UPDRS was used “on-off” durations. Primary outcome measures were the total scores of UPDRS motor and activities components plus subscores for falling, freezing, gait, and postural stability. Secondary outcome measures were contralateral bradykinesia, rigidity, and tremor, dyskinesia, duration of “off” periods, walking and tapping tests, and dose of dopaminergic therapy.

**Results:** There was no significant difference at 3 and at 12 months in the overall UPDRS motor or activity of daily living scores when “on” stimulation was compared to “off” stimulation. In contrast, patients during “on” stimulation reported significant reduction in falls during both “on” and “off” medication states. **Conclusion:** PPN deep-brain stimulation might be effective in preventing falls in patients with advanced PD. As to the mechanism of action, the PPN receives inhibitory projections from the globus pallidus, suggesting a pallidotomy-like effect. In fact, 1 patient had clear benefit after electrode insertion but before stimulation was begun, perhaps the result of interrupting this pallido-PPN pathway. It is possible that PPN stimulation also produces effects outside the motor system on sleep and alertness.

**Reviewer’s Comments:** The fact that the benefit of pedunculopontine nucleus stimulation affected falls but not motor scores makes these findings tentative, but intriguing. (Reviewer—John C. Brust, MD).

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Keywords: Parkinson Disease, Deep Brain Stimulation, Pedunculopontine Nucleus

Print Tag: Refer to original journal article
Vagus nerve stimulation (VNS) may be effective for patients with tuberous sclerosis complex and intractable epilepsy, but a poor response to VNS does not preclude consideration of epilepsy surgery.

**Objective:** To evaluate the efficacy and safety of vagus nerve stimulation (VNS) in patients with tuberous sclerosis complex (TSC) and refractory epilepsy, and to assess outcomes following subsequent epilepsy surgery in patients with an unsatisfactory response to VNS.

**Methods:** A retrospective review identified 19 patients (11 females, 8 males) with TSC and refractory epilepsy who were treated with VNS. At implantation, these patients ranged in age from 2 to 44 years (mean age, 15 years). At this single center, 12 patients with TSC were implanted for primary VNS therapy, including 1 with generalized epilepsy, 1 with a single seizure focus, 3 with multifocal epilepsy, and 6 with multifocal and generalized epilepsy. This group had failed therapy with 2 to 13 antiepileptic drugs. The ketogenic diet had also failed in 5 patients, and 1 patient had undergone corpus callosotomy. A second group of 7 patients was referred for VNS device removal and epilepsy surgery evaluation. One patient in the primary VNS group was lost to follow-up, thus treatment results were considered for 11 patients.

**Results:** None of these patients experienced permanent complications from VNS. The duration of therapy and follow-up in the primary VNS group ranged from 1 to 10 years (mean follow-up, 5 years). In the 11 patients with primary VNS therapy, the mean reduction in seizure frequency was 72%, and all patients experienced some improvement. Two patients became seizure-free, and 10 of 11 experienced a ≥50% reduction in seizure frequency. In this group, 3 patients underwent subsequent epilepsy surgery. In the second group referred for epilepsy surgery consideration and VNS device removal, 6 had subsequent focal resections and 1 underwent corpus callosotomy. This yielded a total of 10 patients who had epilepsy surgery that followed VNS therapy, and 8 experienced improvement following surgery. Engel Class I status (seizure freedom) was achieved in 2 patients, Engel Class II (>90% reduction in seizure frequency) was achieved in 2, Engel Class III (50%-90% reduction in seizures) was achieved in 3, and Engel Class IV (<50% decrease in seizures) was achieved in 3.

**Reviewer's Comments:** VNS should be considered as a viable therapeutic option for patients with TSC and refractory epilepsy. It appears to be a safe and effective treatment option for these patients. In the primary VNS therapy group, >80% experienced at least a two-thirds reduction in seizure burden. Poor response to VNS therapy in patients with TSC does not predict a poor response to subsequent epilepsy surgery. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Tuberous Sclerosis Complex and Refractory Epilepsy, Vagus Nerve Stimulation

Print Tag: Refer to original journal article
ICA Stenosis Not Directly Related to Postop Stroke

Strokes After Cardiac Surgery and Relationship to Carotid Stenosis.

Li Y, Walicki D, et al:

Arch Neurol 2009; 66 (September): 1091-1096

Carotid stenosis appears to have no direct causal relationship with postoperative stroke in patients undergoing cardiac operations. Most post-cardiac surgery strokes are cardioembolic.

Objectives: To determine whether moderate to severe stenosis of the internal carotid artery (ICA) predicts risk of stroke or ipsilateral cerebral infarction in patients undergoing cardiac surgery and to determine whether preoperative carotid intervention for these stenotic ICAs influences subsequent risk.

Design: Retrospective review of a cohort from a single institution.

Participants: 4335 patients (mean age, 67.5 years) undergoing “non-urgent” coronary artery bypass grafting (CABG, n=3196), aortic valve replacement (VR, n=557), or both (n=582) during a 5.5-year span.

Methods: Patients scheduled for elective cardiac surgery underwent ultrasound imaging of the ICAs. Those with a >70% stenosis, if confirmed by a second modality, were evaluated for carotid endarterectomy (CEA) by a vascular surgeon and a neurologist. Some patients received combined CEA plus cardiac surgery (COMB), others underwent staged procedures (carotid intervention [sten or CEA] then cardiac surgery), and others underwent cardiac surgery alone. Postoperative stroke was defined as a focal or multifocal neurological deficit occurring at any time between cardiac surgery and hospital discharge, lasting >24 hours, and best explained by ischemia. Stroke subtypes were determined by the TOAST criteria.

Results: Of approximately 4000 patients undergoing preoperative carotid studies, 6% (n=239) had >50% ICA stenosis (45 were occluded). Only 5 of these patients were symptomatic. Preoperative ICA stenosis predicted a higher risk of postoperative stroke than did the entire cohort (7.5% vs 1.8%, respectively), but most of the 76 postoperative strokes were cardioembolic, and only 4 were distal to a diseased ICA. Most infarctions visualized on imaging studies were consistent with a cardioembolic source (multiple territories) or were in the vertebobasilar circulation. Looked at another way, of 194 patients who had a preoperative stenosis >50% but did not have an occluded ICA, there were 11 postoperative strokes, but only a single stroke occurred in the territory of a stenotic ICA. Of the 53 patients who underwent COMB (CEA + cardiac surgery at the same anesthetic), 8 (15%) had strokes. Of 21 patients who underwent staged carotid intervention (CEA or stent) followed by cardiac surgery, <5% had an infarct.

Conclusions: ICA stenosis is a predictor of increased risk of postoperative stroke in patients undergoing cardiac surgery, but it can be directly implicated in very few postoperative strokes, most of which are cardioembolic. Combined carotid and cardiac surgery procedures on these patients, done at the same anesthetic, are associated with a high risk of stroke.

Reviewer's Comments: Although not derived from a randomized or protocol-driven study, these data certainly dampen enthusiasm for CEA in combination with cardiac surgery. These results drive home the point that most post-cardiac surgery strokes are not attributable to ICA atherosclerosis. (Reviewer-James W. Schmidley, MD).

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Keywords: Stroke, Cardiac Surgery, Carotid Endarterectomy

Print Tag: Refer to original journal article
Among elderly patients with confusion of unknown origin (CUO), risk factors for nonconvulsive status epilepticus include female gender, lack of response to simple commands, and rapid onset of CUO.

**Background:** Nonconvulsive status epilepticus (NCSE) represents behavioral changes without motor abnormalities associated with continuous or repeated epileptic discharges beyond 30 minutes on electroencephalography (EEG). Clinical and electrical improvements with benzodiazepines help confirm the diagnosis.

**Objective:** To determine the incidence of NCSE as the cause of confusion of unknown origin (CUO) in the elderly.

**Participants:** Prospective patients aged ≥60 years who were sent to the clinical neurophysiology unit for CUO.

**Methods:** Patients were referred by a nonneurologist for CUO. Those with known epilepsy or abnormality on lab or imaging study that could explain CUO were excluded. At the time of EEG, all patients were examined by a neurologist, and the diagnosis of confusion was confirmed using the Confusion Assessment Method. A history was obtained, if possible, from patients and caregivers. Focal neurologic abnormalities, localized or diffuse myoclonia, eyelid myoclonia, lack of response to simple commands, tachycardia, cognitive fluctuation, agitation, and mutism were noted. A video EEG with electrocardiogram (ECG) was recorded for at least 20 minutes and reviewed by 2 clinical neurophysiologists blinded to the patient’s clinical status. Clinical and EEG improvement with benzodiazepines was considered confirmatory. Follow-up data were collected from the medical charts 30 days after the EEG.

**Results:** 54 EEG results for CUO were submitted, of which 10 were excluded (CUO not clearly on request, n=4; lacked confusion, n=4 [2 dementia, 1 transient global amnesia, and 1 psychosis]; age limit, n=1; obvious cause for confusion, n=1). Of the 44 remaining, 7 (15.9%) had EEG tracings compatible with NCSE. Three of these had a history of stroke, and one had a history of dementia. The clinical presentation was variable for these 7 cases. EEG showed typical absence status in 1 and complex partial status in the other 6 (2 with frontal foci). There was no acute medical problem found in 5, and the other 2 were subsequently attributed to benzodiazepine withdrawal and herpes meningoencephalitis. One 97-year-old case died from progression of sepsis, and 1 had cognitive sequelae from limbic encephalitis. Variables that were statistically more frequent in the NCSE group included gender (25% risk female, 0% risk male), rapid onset (<24 hours), and lack of response to simple commands.

**Conclusions:** Approximately 16% of elderly patients with CUO had NCSE, with the highest risk being found in female patients with rapid onset and lack of response to simple commands.

**Reviewer’s Comments:** This study confirms the need to perform EEG recordings in patients with CUO. NCSE should be considered, especially in females with rapid onset and associated acute medical conditions. (Reviewer-John Schwankhaus, MD).

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Keywords: Nonconvulsive Status Epilepticus, Confusion of Unknown Origin

Print Tag: Refer to original journal article
Fluid Intelligence Tests Optimize Frontal Lobe Assessment

Executive Function and Fluid Intelligence After Frontal Lobe Lesions.

Roca M, Parr A, et al:

Brain 2010; 133 (January): 234-247

Some deficits of executive function, both cognitive and social, are only partly explained by impairment in fluid intelligence.

Objective: To assess the contribution of impaired general or “fluid” intelligence to abnormal psychometric test results in patients with frontal lobe lesions.

Methods: 36 patients with chronic focal frontal lesions (mostly cerebrovascular or tumor resection lesions) were compared to healthy controls. MRI scans identified lesions as mainly involving 1 of 4 frontal regions, namely inferior medial, superior medial, left lateral, or right lateral. Tests considered to reflect fluid intelligence included Culture Fair (problem solving with geometric figures), the Wisconsin Card Sorting Test (involving rules that change during testing), and Verbal Fluency (generating as many words as possible beginning with a particular letter). Tests of more specific abilities included motor programming, as reflected in Luria’s “fist, edge, palm” series, motor interference and the go-no go task, backwards digit span, months (backward listing of months), spatial working memory, proverbs (interpreting meaning of various proverbs), the Hayling test of sentence completion, the Hotel task (apportioning limited amounts of time for 5 primary activities), the Iowa gambling task (in which selecting a strategy for smaller wins leads ultimately to larger profits), the Faux Pas test (identifying an unintentional insulting remark), and the Mind-in-the-Eyes test (photographs of eye regions of different faces allow guessing as what the individual was thinking or feeling).

Results: As expected, Culture Fair, Wisconsin Card Sorting Test, and Verbal Fluency deficits correlated with each other, and scatter plots suggested that the deficits were entirely explained by fluid intelligence. There was little difference on these tests between different anatomical subgroups. By contrast, other tests involving both cognitive and social function showed remaining deficits after fluid intelligence was partialled out, and these non-fluid deficits tended to be associated with anterior frontal lesions, especially on the right.

Conclusions: Frontal lobe deficits can be best understood by separating fluid intelligence, which is important in most or all tasks, from more specific impairments and their particular regions of damage.

Reviewer’s Comments: The concept of a general intelligence, reflected in the overall score on IQ tests, has been controversial ever since Spearman published his concept of “g” in 1904. Alternative views have focused on separable intelligences, for example, verbal, mathematical, musical, kinesthetic, and “mentalizing” or theory of mind. With the striking exception of autism, most IQ test results show similarity across subtests. The present study shows, not surprisingly, that there is such a thing as general or fluid intelligence and that it is against such a background that more specific cognitive abilities operate. (Reviewer-John C. Brust, MD).

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Keywords: Frontal Lobe Lesions, Executive Function, Fluid Intelligence

Print Tag: Refer to original journal article
The text states that transcutaneous electric nerve stimulation (TENS) is probably effective for treating painful diabetic polyneuropathy but not for treating chronic low back pain. It also notes that TENS cannot be recommended for treating chronic low back pain. TENS may be useful in the treatment of painful diabetic polyneuropathy. Further research is needed to identify the patient populations and conditions under which TENS may provide pain relief.

**Background:** Transcutaneous electric nerve stimulation (TENS) has been used for chronic pain disorders for >40 years. Its scientific rationale is based on Wall and Melzack's gate control theory of pain. The theory proposes that large nerve fiber activation by TENS will reduce pain sensation by "gating" or blocking central transmission of small nerve fiber activity responsible for mediating pain. Despite the widespread use of TENS, clinical trials evaluating TENS efficacy in pain relief have been few, and the results are conflicting.

**Objective:** To determine if TENS is effective in relieving chronic neuropathic pain.

**Methods:** The authors conducted a systematic literature search of Medline and the Cochrane Library up to April 2009. They classified the quality of the studies according to American Academy of Neurology criteria. These are described in an online data supplement to the article.

**Results:** Among 263 articles reviewed, 11 met inclusion criteria. For chronic low back pain, trials that compared TENS to TENS-sham reported conflicting results. Two Class-II studies showed benefit, but 2 Class-I studies and another Class-II study found no benefit. Because Class-I studies provide stronger evidence, TENS was deemed ineffective for treating chronic low back pain. For painful diabetic polyneuropathy, 2 Class-II studies compared TENS to TENS-sham, and 1 Class-III study compared TENS to high-frequency muscle stimulation for pain relief. A modest reduction in a visual analogue pain scale was observed for TENS versus TENS-sham. However, a larger proportion found benefit for mild pain with the high frequency muscle stimulation compared to TENS. Thus, 2 Class-II studies found TENS to be effective in treating painful diabetic polyneuropathy and 1 Class-III study did not. The former comprised stronger evidence of "probable efficacy."

**Conclusions:** TENS cannot be recommended for treating chronic low back pain. TENS may be useful in the treatment of painful diabetic polyneuropathy. Given the widespread use of TENS, the evidence for its efficacy is meager. Further research is needed to identify the patient populations and conditions under which TENS may provide pain relief.

**Reviewer's Comments:** An accompanying editorial by Binder and Baron observes that absence of proof does not translate into proof of absence regarding TENS efficacy for pain modulation. They state that, "there seems to be considerable empirical evidence that, at least in some patients, TENS is useful." Why not try it if insurance will pay for it? More importantly, there has been little activity to expand the TENS knowledge base. Perhaps the insurance companies will take notice of this article and insist on better evidence for reimbursement purposes. That might be just the prod to get the pain community activated to perform the necessary Class-I trials for TENS use in multiple pain disorders. (Reviewer-Michael Jacewicz, MD).

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Keywords: Chronic Neuropathic Pain, Transcutaneous Electric Nerve Stimulation

Print Tag: Refer to original journal article
IV immunoglobulin is a treatment for some children with intractable epilepsy.

**Background:** IV immunoglobulin (IVIG) has been used successfully to treat intractable epilepsy in some children. Studies reporting a positive response have primarily been open-label and short-term.

**Objective:** To evaluate the long-term efficacy of IVIG in the treatment of intractable epilepsy during childhood, and to identify predictors of a favorable response.

**Methods:** A prospective, uncontrolled, open-label, add-on study was performed during a 5-year study interval at a single center. Participant ages ranged from 2 to 20 years, had intractable epilepsy, had been treated with at least 3 antiepileptic drugs (AEDs), had a minimum of 2 seizures per month, and were not considered as good candidates for epilepsy surgery. An initial IVIG dose of 2 g/kg was given in divided daily doses over 4 days. Repeat doses of 1 g/kg were given over 2 days every month, with a total duration of therapy of 6 months. A positive response was considered as >50% reduction in seizure frequency during the 6 months of therapy. AEDs were not changed, unless a poor response to IVIG occurred and was thus deemed a failure. At that point, IVIG was discontinued and new AEDs were added. Absence seizures and auras were not included in seizure counts. If responders relapsed during the 6 months after the initial course of treatment, IVIG therapy was restarted at 1g/kg per month for 1 year.

**Results:** Of the 37 patients included in the study, the group consisted of approximately 60% males and 40% females, and the mean patient age was 10 years. About 60% had generalized seizure types and 40% had partial-onset seizures. Approximately 25% had infantile spasms or West syndrome, and 45% had Lennox–Gastaut syndrome. About 60% were considered as cryptogenic, and 40% were symptomatic. The mean duration of follow-up was 15 months. Forty-three percent of patients were responders, with a >50% decrease in seizures, including 15% who became seizure-free. Based on epilepsy syndrome, the best response rate was seen with Lennox–Gastaut syndrome (58.8%) compared to partial epilepsy (36.4%) and West syndrome (22.2%). Boys were more likely to respond than girls. The literature review revealed 9 other reports that indicated a positive response to IVIG in the treatment of epilepsy. Only 1 study included statistical analysis, which showed only a trend toward seizure frequency reduction without achieving statistical significance.

**Reviewer’s Comments:** The response to IVIG therapy in children with intractable epilepsy indicates a likely autoimmune role. Obviously, when this mechanism is not present, patients will not likely respond to IVIG. Focused studies using IVIG therapy in children with clinical features such as an abrupt onset of seizures following an infectious illness might reveal higher response rates. Methods are needed to identify factors that would predict a positive response to IVIG. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Intractable Childhood Epilepsy, IV Immunoglobulin

Print Tag: Refer to original journal article
The change in serum IgG level after IVIG infusion correlates positively with the clinical outcome of Guillain-Barré syndrome.

**Background:** IV immunoglobulin (IVIG) is effective in Guillain-Barré syndrome (GBS). Up to 20% of patients do not do well, and significant numbers of patients relapse but may respond to repeated IVIG infusion. The IVIG dose used in the clinical trials and in practice was set arbitrarily at 2 g/kg, which was empirically based on clinical experience in patients with immune deficiencies.

**Objective:** To determine the clinical outcome in GBS patients in relation to their IgG levels after receiving the standard IVIG dose.

**Participants:** Sera from patients who participated in 2 prior clinical trials were analyzed. The first trial compared IVIG to plasma exchange (147 patients), and the second studied the additional effect of methylprednisolone plus IVIG (225 patients). All patients received the same IVIG brand (Gammagard®) and standard dose (total of 2 g/kg). All patients fulfilled clinical criteria for GBS and were unable to walk 10 meters unaided.

**Methods:** Clinical data were collected prospectively during the acute illness and for 6 months afterward. The Medical Research Council (MRC) score (0 to 60) and the GBS disability score (0 to 6) were assessed. IgG levels from blood samples collected prior to IVIG infusion and 2 weeks after start of treatment were obtained. Approximately two-thirds of patients also had IgG levels determined at 3 months and 6 months after the start of treatment. The increase in serum IgG ($\Delta$IgG) at 2 weeks after IVIG infusion was measured, and the patients were divided into quartiles based on $\Delta$IgG.

**Results:** Sera from 174 patients were available for analysis. Pretreatment IgG level correlated well with those at 3 and 6 months ($P<0.001$), indicating a constant baseline IgG level. There was a large variability in $\Delta$IgG at 2 weeks after IVIG treatment (mean, 7.8 g/L; SD, 5.6 g/L). In multivariate analysis, patients with low $\Delta$IgG at 2 weeks had a more severe clinical deficit at nadir as expressed by the MRC and GBS disability scores ($P<0.001$) and a higher chance of disability at 6 months. Of the 27 patients unable to walk unaided at 6 months, 23 (85%) were from the lowest 2 quartiles ($P<0.001$)

**Conclusions:** GBS patients receiving the standard dose of IVIG have a large variation of IgG levels, and those with a smaller increase in IgG level do worse, independent of other prognostic factors.

**Reviewer's Comments:** This useful study will likely trigger other trials that should ultimately help us understand the best therapeutic dose for patients with GBS and whether a second dose is helpful in patients who do not improve or relapse. Patients who show only slight increase in IgG levels may have higher catabolism of IgG, in part related to infections. (Reviewer-Bashar Katirji, MD).

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Keywords: Guillain-Barré Syndrome

Print Tag: Refer to original journal article
Among cases of amyotrophic lateral sclerosis, consider vocal cord dysfunction in patients with dyspnea, stridor, or laryngospasm. It is under-recognized by neurologists, and a referral to otolaryngology is warranted.

**Background:** Amyotrophic lateral sclerosis (ALS) is often associated with bulbar dysfunction, with dysarthria and dysphagia dominating the clinical picture. Vocal cord dysfunction may result in hoarseness or hypophonia and, when more severe, stridor and dyspnea due to glottic narrowing. There is limited literature on this potentially lifethreatening complication.

**Objective:** To describe 4 ALS patients with glottic narrowing due to vocal cord dysfunction and to review the literature.

**Design:** Case series from 2 Dutch tertiary care centers.

**Results:** The case reports of 4 patients (age range, 56 to 69 years) with ALS and acute dyspnea due to vocal cord dysfunction are presented. Three had sporadic ALS and 1 had familial superoxide dismutase 1-negative ALS. All 4 cases had bulbar manifestations with dysarthria and dysphagia. All developed dyspnea and required tracheotomy to maintain the airway. Three developed dyspnea during the course of illness, and 1 had it at diagnosis. The glottic narrowing was due to bilateral vocal cord abduction paresis, and in 1 case, it was due to uncontrolled adduction of the cords. Review of the neurological literature found that vocal cord paresis and laryngospasm occur in 4% of ALS patients, while the otolaryngology literature reported a prevalence of 30%. They conclude that glottic narrowing may result from reduced abductor muscle power or increased adductor muscle activity, or both. These may be mechanistically caused by upper or lower motor neuron mechanisms, or both.

**Conclusions:** Vocal cord dysfunction may occur at any stage of disease in ALS. It is under-reported and under-recognized by neurologists. A referral to otolaryngology is warranted when suspected since severe cases may need tracheotomy to maintain airway.

**Reviewer's Comments:** This paper highlights the importance of recognizing vocal cord dysfunction, which may be life threatening in ALS patients. However, I have several unanswered questions. What is the difference between vocal cord abductor paralysis and laryngospasm? Is laryngospasm due to increased adductor muscle activity? Is vocal cord abductor paralysis a lower motor neuron disorder, and is laryngospasm an upper motor neuron disorder? Also, this paper does not help us understand the true incidence of vocal cord abduction paresis and laryngospasm in ALS patients. (Reviewer-Bashar Katirji, MD).

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Keywords: vocal cord dysfunction; amyotrophic lateral sclerosis

Print Tag: Refer to original journal article
With the low doses of amiodarone currently used, the risk of neurotoxicity is low (2.8%). The most common symptoms are tremor, gait ataxia, peripheral neuropathy, and cognitive impairment.

**Background:** When amiodarone first came into general use in the 1980s, the maintenance dose was high (approximately 600 mg/day), and the frequency of neurologic toxicity was also high (range, 28%-74%). In the 1990s, as the maintenance dose fell to approximately 200 mg/day, the frequency of neurotoxicity also fell, showing that neurotoxicity was dose-related.

**Objective:** To assess the frequency and type of neurotoxic effects associated with amiodarone use.

**Design:** Retrospective study.

**Participants:** The study population consisted of all Olmsted county residents treated with amiodarone from 1996 to 2008 at the Mayo Clinic. Patients from outside Olmsted county were excluded to minimize referral bias and to approximate a population-based study.

**Methods:** Chart review.

**Results:** Of the 707 patients treated with amiodarone, 20 developed neurotoxic effects, yielding a frequency of 2.8%. The mean patient age was 74 years (range, 66-84 years). The mean daily dose of amiodarone was 209 mg (range, 100-400 mg/day). The mean duration of treatment with amiodarone was 3 years (range, 0.04-7 years). The most common neurologic symptom was tremor (not further specified) followed by peripheral neuropathy, gait ataxia, and cognitive impairment. Other previously reported symptoms of amiodarone toxicity, including parkinsonism, myoclonus, various dyskinesias, optic neuropathy, and myopathy, were not encountered. In 8 of the 20 affected patients, amiodarone was stopped, and neurologic symptoms improved in 7. The patients with neurologic toxicity had taken amiodarone significantly longer than those without neurotoxicity (mean, 32 months vs 17 months, respectively), but the 2 groups did not differ in age, gender, indication for amiodarone, or mean daily dose of amiodarone.

**Conclusions:** With the low doses currently used, the risk of neurotoxicity with amiodarone is low. The most common symptoms of neurologic toxicity are tremor, gait ataxia, peripheral neuropathy, and cognitive impairment. Stopping the drug usually leads to recovery.

**Reviewer's Comments:** This study brought out no new knowledge. It is, however, a useful paper because it brings together information scattered through the cardiology and internal medicine literature, with which most of us neurologists do not stay current. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Amiodarone, Neurologic Toxicity, Tremor

Print Tag: Refer to original journal article
Intraneurial perineurioma affects a peripheral nerve or nerve plexus, and it presents with predominantly motor symptoms and signs. Diagnosis requires a multi-disciplinary approach.

**Background:** Perineurioma is a benign tumor of perineurial cells. An intraneural perineurioma (IP) grows as whorls of perineurial cells around fascicles of nerve fibers inside a single nerve and presents as a progressive mononeuropathy.

**Objective:** To describe the clinical features and natural history of IP.

**Design:** Retrospective, cohort study.

**Participants:** All 32 patients with pathologically proven IP seen from 1968 to 2007 at a referral center for peripheral nerve disease.

**Methods:** The diagnosis of perineurioma was made when nerve biopsy showed onion bulb-like formations consisting of perineurial cells (pseudo-onion bulbs), as identified immunocytochemically by epithelial membrane antigen, and not of Schwann cells (genuine onion bulbs), as identified by the S-100 immunocytochemical marker. Long-term follow-up was performed by clinical examination in 12 patients (median, 4 years; range, 1-20 years) and by telephone interview in 23 patients (median, 3 years; range, 0.25-15 years).

**Results:** Neurologic symptoms began at a median age of 14 years (range, 0.5-55 years). The major symptom was focal weakness in 29 patients and focal numbness, tingling, or pain in 3 patients. The sciatic nerve was most often involved (n=15); other involved nerves included the radial, ulnar, median, femoral, and trigeminal nerves and the lumbosacral and brachial plexus. Twenty-seven patients had a mononeuropathy, and 5 had a plexopathy. Only 1 patient had more than a single site of involvement. On examination, all patients had muscle weakness and atrophy; 11 had foot drop and 3 had wrist drop. Most patients (n=23) had sensory loss, which was mild. A standardized disability scale indicated moderate severity for a focal neuropathy. The cerebrospinal fluid protein was normal. Nerve conduction studies indicated axonal loss in 29 patients. MRI showed fusiform enlargement of a long segment of the nerve (median, 8 cm; range, 2.5-32 cm). The tumor was isointense on T1-weighted images and hyperintense on T2-weighted images, and it enhanced avidly with contrast. At follow-up, symptoms, examination, and disability were only mildly worse. No new nerves had become involved, and no tumor had become malignant.

**Conclusions:** IP is a benign tumor found mainly in children and young adults, affects peripheral nerve and nerve plexus, presents with predominantly motor symptoms and signs, and progresses very slowly.

**Reviewer's Comments:** The authors review the differential diagnosis of IP, which includes other benign tumors (neurofibroma, schwannoma, and angiofibroma), injury neuroma, and the focal form of chronic inflammatory demyelinating polyneuropathy. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Intraneural Perineurioma, Features, Natural History

Print Tag: Refer to original journal article
When infants and young children present with poorly explained brain injury, careful exploration of the history, formal fundoscopy, and skeletal survey are warranted.

**Background:** Traumatic brain injury is a relatively common cause for emergency evaluation and hospitalization in children. However, in some circumstances, it can be difficult to determine if the injury is accidental or inflicted. The clinician must be aware of indicators that warrant further investigation and reporting. **Objective:** To identify clinical features that distinguish inflicted from non-inflicted brain injury in children. **Methods:** A systemic review of the literature from 1970 to 2008 was performed that included 320 studies. All studies had 2 independent reviews, with a third if there was disagreement. Brain injury was defined as extra-axial hemorrhage and/or injury to the brain. Inflicted brain injury implied physical abuse, while non-inflicted brain injury was by other mechanisms, such as accidental trauma and medical causes. Only studies that compared the clinical features of inflicted versus non-inflicted brain injury were used. These included studies with a high suspicion of the diagnosis of inflicted brain injury by means such as perpetrator admission, legal decision, or witnessed abuse, along with confirmation of cause in non-inflicted brain injury. Multilevel logistic regression analysis was conducted to determine the positive predictive value (PPV) and odds ratio (OR) for clinical features that included apnea, retinal hemorrhages, rib fractures, long bone fractures, bruising to the head and/or neck, and skull fracture. **Results:** Of the 320 studies, 14 met the inclusion criteria. These studies included data on 1655 children (inflicted brain injury, n=779; non-inflicted brain injury, n=786). Of the above-mentioned features, apnea (PPV 93%), retinal hemorrhages (PPV 71%), and rib fractures (PPV 73%) were strongly associated with inflicted brain injury. Seizures and long bone fractures were more likely present with inflicted injury, but this association was not statistically significant. Skull fractures and bruising to the head and neck were more strongly associated with non-inflicted brain injury than inflicted injury. **Conclusions:** Apnea appears to be the greatest distinguishing feature, with an OR of 17 for inflicted head injury. The OR with retinal hemorrhages was 3.5 for inflicted brain injury, and the high rate of retinal hemorrhages in inflicted brain injury enforces the need for formal fundoscopy on children with unexplained intracranial injury. In addition, any child aged <2 years with unexplained brain injury or in whom abuse is considered should undergo a full skeletal survey. **Reviewer's Comments:** Although it can be difficult to distinguish accidental from inflicted brain injury, certain features are more suspicious of non-accidental trauma as detailed in this review. However, each case must be evaluated individually with many issues considered, including the history, physical examination, imaging, and the exclusion of organic causes. (Reviewer-Gregory B. Sharp, MD).
Pulsatile Dexamethasone for Infantile Epilepsy Syndromes?

Adrenocorticotropic Hormone Versus Pulsatile Dexamethasone in the Treatment of Infantile Epilepsy Syndromes.

Haberlandt E, Weger C, et al:

Pediatr Neurol 2010; 42 (January): 21-27

Background: Adrenocorticotropic hormone (ACTH) has been used in the treatment of drug-resistant infantile epilepsy syndromes for >50 years. Other steroids have also been tried, but there have been no large studies looking at the adverse effects and efficacy of these treatments.

Objective: To compare the efficacy and tolerability of ACTH versus pulsatile dexamethasone in the treatment of drug-resistant infantile epilepsy syndromes.

Methods: A retrospective chart review was performed at the Medical University of Innsbruck and included all patients diagnosed with intractable infantile epilepsy who were treated with either ACTH or pulsatile dexamethasone between 1989 and 2006. All 28 patients identified had failed initial therapy with antiepileptic drugs (AEDs) and were subsequently treated with either ACTH or dexamethasone pulse therapy. The group of 14 children treated with ACTH included 11 with infantile spasms or West syndrome (WS) and 3 with Lennox–Gastaut syndrome (LGS). ACTH was initiated at 15 to 20 IU/day and increased as indicated to a maximum of 120 IU/day. An EEG was performed every 10 to 14 days. Antibiotic prophylaxis was used. The dexamethasone group of 14 patients included 7 with WS, 2 with LGS, and 5 with electrical status epilepticus in slow wave sleep (ESES). These patients received pulse therapy with 20 mg/m2 IV daily for 3 days initially, and then every 4 weeks for at least 5 total treatments. EEG was performed before and after each treatment, and no antibiotic prophylaxis was used. All patients had routine labs and assessment of cardiac function. Improvement in EEG, seizure frequency, and the adverse effects of each treatment were recorded.

Results: A >50% reduction in epileptiform activity on EEG was achieved in 80% of the ACTH group compared to 65% in the dexamethasone group, and normalization was achieved in about 30% and 50%, respectively. Overall, resultant seizure freedom was similar in the ACTH (64%) and dexamethasone (57%) groups, and in WS patients, it occurred in about 80% of those treated with ACTH compared to 60% of those treated with dexamethasone. No patients with LGS became seizure-free with either treatment. Dexamethasone therapy resulted in seizure freedom in 80% of children with ESES. Adverse effects were generally greater in those treated with ACTH, with the most common effects being hypertension, electrolyte disturbances, and elevated liver enzymes. Viral infections and elevated liver enzymes were the most common adverse effects experienced in the dexamethasone group.

Reviewer’s Comments: A regimen of pulsatile dexamethasone can be considered as an alternative therapy for children with infantile epilepsy syndromes that include WS, LGS, and ESES. Results are similar to those achieved with ACTH, and adverse effects appear less severe. Prospective studies are warranted. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Infantile Epilepsy Syndromes, Treatment

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