Mirror therapy may provide relief in complex regional pain syndrome type 1, which is often refractory to conventional therapy.

**Background:** Complex regional pain syndrome (CRPS) is a debilitating condition often refractory to treatment. In the affected limb, the patient may experience burning, allodynia, hyperalgesia, weakness, tremor, muscle spasm, edema, and changes in temperature and vascular tone. Why this happens is unclear. One hypothesis suggests a mismatch between proprioceptive feedback and motor action causes CNS sensory distortion and pain. If true, the misperception of continued pain might correct itself if the offending proprioception could be suppressed. Visual feedback can substitute for impaired proprioception if patients watch their feet when they walk. Similarly, a sensory denervated, pseudoathetotic limb can be controlled with visual guidance. In 2007, Chan reported remarkable improvement in phantom limb pain when the patient experienced the illusion of limb movement through use of a mirror.

**Objective:** To determine if mirror therapy can reduce pain and improve motor function in stroke patients with CRPS type 1 (no identifiable peripheral nerve injury).

**Participants:** 11 men and 13 women (median age, 62 years) who developed CRPS in the paretic arm at 7 to 21 months after stroke.

**Methods:** 8 patients were randomly assigned to mirror therapy and tried to move their painful arm while viewing the reflected image of the normal arm attempting the same movement. Controls either did the same but with the mirror covered (n=8) or imagined the same movements with their eyes closed (n=8). All performed the assigned task for 30 minutes daily. After 4 weeks, pain severity was measured using a visual analogue scale (VAS scores ranged from 0 to 100 mm). The 2 control groups then crossed over to mirror therapy for 4 weeks while the group originally assigned to mirror therapy continued as before. Outcome evaluators were blinded to group assignments.

**Results:** All 3 groups had comparable baseline pain (VAS median score, 63 mm). After 4 weeks, pain intensity increased to 80 for both control groups but dropped to 8 in the mirror therapy group. Seven mirror therapy patients reported reduced pain versus 1 for sham mirror and 2 for mental imagery. Reduced pain was demonstrated in 93% of control patients who crossed over to mirror therapy. Motor function, brush-induced allodynia, and edema also improved with mirror therapy.

**Conclusions:** Mirror therapy reduces pain and enhances motor function in the paretic arm of stroke patients with chronic CRPS type 1.

**Reviewer's Comments:** There must be a fascinating principle at work here regarding the dubious ways in which the brain processes sensory information. One has to wonder how often the brain plays similar tricks on itself in both health and disease. (Reviewer-Michael Jacewicz, MD).

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Keywords: Complex Regional Pain Syndrome, Mirror Therapy

Print Tag: Refer to original journal article
Corticosteroid treatment of Bell palsy reduces the risk of unsatisfactory recovery. Antiviral agents administered in conjunction with a steroid may be associated with additional benefit.

**Background:** Bell palsy is extremely common, with an annual incidence of 20 to 30 per 100,000 population. Seven of 10 untreated patients recover completely, and 84% have complete or near normal recovery. Poor outcome can be due to incomplete recovery, autonomic dysfunction, and synkinesis. Recent evidence indicates that Bell palsy may be best managed with a corticosteroid and that antiviral agents are of no benefit.

**Objective:** To investigate the efficacy of treating Bell palsy with corticosteroid and antiviral therapy.

**Design:** Systematic review and meta-analysis.

**Methods:** Of the 854 studies of Bell palsy treatment identified, 18 were eligible for inclusion because they were randomized controlled trials comparing treatment with steroid and/or antiviral agents with a control, and they measured outcomes and adverse events. These 18 trials included 2786 patients with Bell palsy.

**Results:** Steroid treatment alone was associated with a significantly reduced risk of unsatisfactory recovery (RR, 0.69) and a significantly reduced risk of synkinesis and autonomic dysfunction (RR, 0.48). Antiviral agents alone were not associated with a reduced risk of unsatisfactory recovery. When combined with a steroid, antiviral agents were associated with significantly greater risk reduction of poor outcome compared with steroid treatment alone (RR, 0.75). Steroid treatment was not associated with an increased risk of adverse events.

**Conclusions:** Corticosteroid treatment of Bell palsy is associated with a reduced risk of unsatisfactory recovery and antiviral agents administered in conjunction with a steroid may be associated with additional benefit with an acceptable risk profile.

**Reviewer's Comments:** One question that remains unanswered is the importance of the time interval between onset of Bell palsy and treatment. In this meta-analysis, these investigators found no difference in the effect of steroid therapy on unsatisfactory recovery when patients were treated within 72 hours versus later treatment. However, the authors note that this subgroup analysis is statistically weak. At this time, there is now good evidence that a good outcome from Bell palsy can be promoted with steroid therapy and that antiviral therapy may augment this effect. (Reviewer-W. Steven Metzer, MD).

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Keywords: Bell Palsy, Treatment

Print Tag: Refer to original journal article
Water Test Results -- Swallowing Problems Common in PD

Swallowing Problems in Parkinson Disease: Frequency and Clinical Correlates.

Miller N, Alcock L, et al:

J Neurol Neurosurg Psychiatry 2009; 80 (September): 1047-1049

Among patients with Parkinson disease, self-reports about swallowing ability are not indicative of their true abilities in this matter.

**Background:** Objective testing shows that nearly all patients with Parkinson disease (PD) have swallowing problems, but most are unaware of problems until later in the disease course.

**Objective:** To determine the prevalence of symptomatic swallowing problems and to relate performance to other disease variables.

**Methods:** Participants had to meet the UK Parkinson's Disease Society Brain Bank Criteria for the diagnosis of PD. Patients were excluded if they had dysphagia prior to symptoms of PD, comorbidity associated with swallowing, or refused to be studied. After fasting overnight, they underwent a timed swallowing test using 150 mL of water. Before the test, they underwent the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr rating, Geriatric Depression Scale (GDS), and Mini Mental Status Exam (MMSE). Patients were classified as tremor dominant (TD), postural instability/gait disorder (PIGD), or indeterminate.

**Results:** Of 140 consenting patients who were eating and drinking, 3 could not reliably complete swallowing assessment. For the others, there was no correlation between the rate or amount of drinking and UPDRS facial and upper limb tremor. In the timed swallowing test, 106 drank the full 150 mL of water, 31 (23%) started but could not finish, 29 stopped because they desired to do so, 2 stopped because of severe coughing, and 3 coughed mildly but were not stopped. For rate of swallowing, 115 patients (84%) were >1 standard deviation below the mean control values for speed, and 21 (all males) were >2 standard deviations below the mean. Overall, 44 patients (32%) had significant swallowing difficulties. Those unable to complete 150 mL of water had a significantly slower swallow rate, a worse Hoehn and Yahr stage, significantly different UPDRS part II and III scores, greater depression, and longer disease duration. Age and MMSE were not significantly different between the 2 groups. There were moderate correlations between swallowing speed and UPDRS parts II and III scores, Hoehn and Yahr stage, GDS score, and MMSE score, but not with disease duration. Differences were significant between the PIGD and TD groups and between the TD and indeterminate groups. Five variables affecting swallowing speed were age, gender, GDS score, disease phenotype, and UPDRS part III score. Of the patients who did not feel they had swallowing problems, 60 (78%) were found to have significant problems.

**Conclusions:** Swallowing problems are common in PD. A self-report of denying difficulties is not a reliable indicator of one’s swallowing ability.

**Reviewer's Comments:** It is unreliable to count on self-reports of dysphagia in PD patients. Periodic bedside swallow tests should be considered. (Reviewer-John Schwankhaus, MD).

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Keywords: Parkinson Disease, Swallowing

Print Tag: Refer to original journal article
stroke prevention in AF -- lAA closure attractive alternative


holmes dr, reddy vy, et al:

lancet 2009; 374 (august 15): 534-542

the left atrial appendage (lAA) was completely occluded in only about 75% of patients with atrial fibrillation who were assigned undergo percutaneous lAA occlusion using the watchman® device.

objective: to compare the outcomes of occlusion of the left atrial appendage (lAA) versus warfarin (W) for the prevention of stroke in patients with atrial fibrillation (AF).

Design: prospective, multicenter, randomized clinical trial.

Participants: adults with nonvalvular AF were included if they had at least one of the following: previous stroke or transient ischemic attack, congestive heart failure, diabetes, hypertension, or were ≥75 years of age.

Methods: baseline assessments were done by neurologists, and CT or MRI was performed when there was a history of stroke. Patients also had transesophageal echocardiography (TEE). the intervention group had percutaneous lAA occlusion using the watchman® device. the control group received W to a standard INR of 2 to 3. the intervention group took W for 45 days after insertion, then clopidogrel and aspirin for 6 months, then aspirin alone. If occlusion of the lAA was incomplete, W was continued. composite efficacy end point (EE) was any stroke, systemic embolization, and sudden or cardiovascular death. the composite safety end point was serious bleeding plus procedure-related complications.

Results: the device was successfully implanted in 88% of patients. the lAA was completely occluded in only 349 of the 463 patients in the intervention group, and these patients were able to stop W at 45 days. the W-therapy group had therapeutic INRs 66% of the time. the EE rate was 3/100 patient-years (p-y) in the intervention group and 4.9/100 p-y in the W group. ischemic stroke rates were 2.2/100 p-y in the intervention group and 1.6/100 p-y in the W group. these ischemia rates were counterbalanced by intracranial hemorrhage rates of 0.1/100 p-y in the intervention group and 1.6/100 p-y in the W group. all strokes occurred at a rate of 2.3/100 p-y in the intervention group and 3.2/100 p-y in the W group. criteria for noninferiority were met for the lAA occlusion device. in the intervention group, pericardial effusions developed in 5% (usually required drainage) and ischemic strokes occurred in 1%.

Conclusions: lAA closure via a percutaneously inserted device was not inferior to treatment with W. this approach presents an attractive alternative to W for stroke prevention in AF.

Reviewer's Comments: the initial complication rate is discouraging, but long-term outcomes may be significantly better than for W. if thrombin inhibitors replace W as standard medical treatment for stroke prevention in AF patients, this device will need to be proven against these drugs as well. (Reviewer-James W. Schmidley, MD).

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Keywords: Atrial Fibrillation, Stroke Prevention

Print Tag: Refer to original journal article
Dabigatran Versus Warfarin in Patients With Atrial Fibrillation.

Connolly SJ, Ezekowitz MD, et al:


Background: In recent years, ximelagatran proved equal to warfarin (W) for stroke prevention in atrial fibrillation (AF) patients, but was withdrawn because of hepatotoxicity.

Objective: To compare the effectiveness of dabigatran (D), a direct thrombin inhibitor, versus W for the prevention of stroke in AF.

Design: Randomized, partly blinded, controlled clinical trial comparing 2 doses of D with standard W treatment.

Participants: >18,000 patients with AF and at least one of the following: prior stroke/TIA, left ventricular ejection fraction <40%, congestive heart failure, age ≥75 years, or the combination of age 65 to 74 years plus diabetes, hypertension, or coronary atherosclerosis. Patients were excluded if they had severe valvular heart disease, a severe or recent stroke, chronic renal insufficiency, liver disease, pregnancy, or any other conditions known to increase the risk of hemorrhage.

Methods: Patients were randomly assigned to D 110 mg twice daily, D150 mg twice daily, or W (target INR 2 to 3). W treatment was unblinded, but patients receiving D were blinded to dose. Follow-up was clinical, with regular testing of liver functions. The primary outcome measure was stroke plus systemic embolism, and the primary safety outcome was major hemorrhage. Secondary outcome included the combination of stroke plus systemic embolism plus death. Statistical analysis was oriented toward noninferiority of either dose of D compared to W.

Results: Both doses of D were noninferior to W. D 150 mg twice daily was superior to D 110 mg twice daily for the primary end point, for all stroke, and for ischemic stroke. Both doses of D were superior to W for intracranial hemorrhage, but only the 110-mg dose of D was superior to W for all major bleeding. The assessment of "net clinical benefit" (rates of all stroke, systemic embolism, pulmonary embolus, MI, death, and major hemorrhage) was about 7% per year with both doses of D versus about 7.6% per year with W. There was no difference in the incidence of abnormal liver chemistries in any arm of the trial.

Conclusions: D appears to be an attractive alternative to W for stroke prevention in AF. Both doses of D were not inferior to W. D at 150 twice daily was superior to W in preventing emboli, but 110 mg of D twice daily was superior to W with respect to bleeding.

Reviewer’s Comments: D or a similar drug may eventually replace W as the mainstay of anti-thrombotic therapy for stroke prevention in AF. The direct thrombin inhibitors, unlike warfarin, do not require monitoring of any hematological variable. (Reviewer-James W. Schmidley, MD).

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Keywords: Atrial Fibrillation, Stroke Prevention

Print Tag: Refer to original journal article
**Objective:** To determine whether functional MRI (fMRI) performed on vegetative or minimally conscious subjects might be useful either diagnostically or prognostically.

**Methods:** 28 men and 13 women (age range, 17 to 68 years) were studied. Of these subjects, 22 met criteria for vegetative state and 19 for minimally conscious state. Diagnoses included cardiac arrest, brain trauma, and midbrain stroke. fMRI was performed with a 3T system measuring hemodynamic responses. A speech processing paradigm, previously validated in normal subjects, consisted of 4 conditions: (1) high ambiguity spoken sentences requiring semantic processing; (2) low ambiguity spoken sentences requiring recognition of the sounds as speech; (3) nonspeech sounds; and (4) silence. Nonspeech sounds normally activate primary auditory regions. Low ambiguity sentences normally activate the superior temporal sulcus bilaterally and the left inferior frontal gyrus. High ambiguity sentences, for example using homonyms, normally activate the left posterior inferior temporal lobe and the left inferior frontal gyrus.

**Results:** 16 patients showed no significant auditory response, and 6 showed significant responses to only nonspeech sound. Nineteen patients showed significant responses to both sound and speech, and of these, four gave evidence of intact semantic processing. The level of auditory processing revealed by fMRI did not correlate with each patient's clinical assessment at the time of the scan. For example, 2 of the 4 patients with intact semantic processing were assessed as having a minimally conscious state, and 2 were assessed as vegetative. Notably, at 6 months follow-up, 8 vegetative patients had emerged to a minimally conscious state, and 7 of these had demonstrated either midlevel or high-level speech processing 6 months earlier. There were no false-positive results; no patient who demonstrated midlevel or high-level speech processing at fMRI failed to improve into minimally conscious state.

**Conclusions:** fMRI has diagnostic and prognostic potential and might influence the timing of rehabilitation interventions, although only positive findings had prognostic value.

**Reviewer’s Comments:** One must consider the possibility that even high-level speech processing demonstrated at fMRI can occur in the absence of conscious awareness. One is reminded of phenomena, such as blindsight, in which volitional responses are made to visual stimuli seemingly outside a subject's conscious awareness. (Reviewer-John C. Brust, MD).

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Keywords: Disorders of Consciousness, Brain Imaging

Print Tag: Refer to original journal article
Objective: To evaluate the clinical importance of CSF phosphorylated tau (p-tau) for the diagnosis of Alzheimer's disease (AD) and the prognosis of mild cognitive impairment (MCI).

Design: A systematic search, critical appraisal, and meta-analysis of CSF p-tau for the diagnosis of AD as well as the diagnosis and prognosis of MCI.

Methods: Studies were evaluated using the Standards for Reporting of Diagnostic Accuracy criteria and the review guidelines for diagnostic tests from Evidence Based Medicine. A meta-analysis was then performed comparing AD patients to healthy individuals, AD patients to non-AD dementia patients, MCI patients with healthy individuals, and MCI patients who did and did not progress to dementia. AD vs Healthy Controls: Of 2300 individuals analyzed, 1329 were diagnosed with probable AD and the remainder were healthy controls. The overall pooled weighted sensitivity of p-tau was 77.6%, and the overall specificity was 87.9%. Use of p-tau would facilitate 81.8 correct diagnoses for every 100 individuals tested. The clinical utility of the test was rated as good. AD vs Other Dementias: Of 1892 individuals analysed, 1304 had AD and 588 had other dementias. The overall pooled weighted sensitivity of p-tau was 71.6%, and the overall specificity of p-tau was 77.8%. P-tau would facilitate 73.7 correct diagnoses for every 100 individuals tested. MCI vs Healthy Controls: Of 447 individuals analysed, 247 had MCI and 200 were healthy controls. The overall pooled weighted sensitivity of p-tau was 79.6%, and the overall specificity was 83.9%. Thus, p-tau would be expected to facilitate 77.4 correct diagnoses for every 100 individuals tested. MCI Progressive vs MCI Stable: Of 338 individuals analysed, 163 had progressive MCI that converted to dementia, and 175 had stable MCI. The overall pooled weighted sensitivity of p-tau was 81.1%, and the overall specificity was 65.3%. The positive predictive value was 62.9% and negative predictive value was 82.7%, which suggests that p-tau may be better predicting those who would not progress to dementia.

Conclusions: P-tau is a good diagnostic biomarker for probable AD, but it is not as good for MCI or for determining which MCI patients will progress to dementia. It is not good at differentiating AD from other dementias.

Reviewer's Comments: P-tau alone will not help in the diagnosis of early AD or in determining which MCI patient will progress to dementia. (Reviewer-John Schwankhaus, MD.)

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Keywords: Alzheimer's Disease vs Mild Cognitive Impairment, CSF p-Tau

Print Tag: Refer to original journal article
MRI of the brain should be performed in children with a new diagnosis of epilepsy when there is evidence to support localization-related epilepsy, symptomatic epilepsy, or when epilepsy classification is uncertain.

Objective: To establish practical guidelines for obtaining neuroimaging studies in children with a new diagnosis of epilepsy.

Methods: The International League Against Epilepsy Subcommittee for Pediatric Neuroimaging evaluated the usefulness of CT and MRI and the indications for obtaining neuroimaging studies in the evaluation of children with a new diagnosis of epilepsy. They reviewed 18 retrospective and prospective studies published during the last 20 years. Each study included ≥30 children with a new diagnosis of epilepsy who were evaluated with either CT or MRI of the brain.

Results: In children with newly diagnosed localization-related epilepsy, a neuroimaging abnormality was identified in almost 50%, and useful information concerning the etiology or seizure focus was present in 15% to 20%. Findings were identified that affected immediate medical management in 2% to 4%. Imaging studies were rarely helpful in the absence of an abnormal neurologic examination, focal finding on EEG, or other findings to indicate localization-related epilepsy. Imaging studies were not helpful in children with a diagnosis of childhood or juvenile absence epilepsy, juvenile myoclonic epilepsy, or benign epilepsy of childhood with centrotemporal spikes.

Conclusions: Imaging of the brain should be performed when a child presents with new-onset epilepsy and when the description of the seizure, EEG findings, or the neurologic examination supports the possibility of focal-onset epilepsy. Imaging should also be performed whenever a symptomatic etiology is suspected with generalized epilepsy syndromes, such as infantile spasms or Lennox-Gastaut syndrome. A neuroimaging study should also be performed when epilepsy classification is uncertain. MRI is the preferred method over CT due to superior resolution and sensitivity. Some abnormalities (cortical dysplasia, low-grade tumors, mesial temporal sclerosis, and vascular malformations) can be missed with CT and are better detected with MRI. Another advantage of MRI is the absence of radiation exposure. As epilepsy progresses, seizures worsen or become uncontrolled, or seizure characteristics change, neuroimaging is indicated if not previously performed. Signs of increased intracranial pressure, status epilepticus, new abnormalities on neurological examination, or persistent alteration of consciousness or encephalopathic findings indicate a need for emergent neuroimaging. CT is often more readily available and appropriate in emergent settings.

Reviewer's Comments: Obtaining a neuroimaging study in children with a new diagnosis of epilepsy should not be an automatic decision. Appropriate consideration should be applied, and the guidelines outlined here are rational. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Pediatric Epilepsy, Neuroimaging

Print Tag: Refer to original journal article
Maintenance Heroin -- A Practical Therapy for Heroin Addiction?

_Diacetylmorphine Versus Methadone for the Treatment of Opioid Addiction._

Oviedo-Joekes E, Brissette S, et al:


Diacetylmorphine therapy can benefit some heroin addicts who have failed other treatments including methadone maintenance.

**Objective:** To compare injectable diacetylmorphine (the active ingredient in heroin) with oral methadone in the treatment of long-term heroin addicts.

**Participants:** Subjects had injected opioids daily for at least 5 years, had experienced tolerance or withdrawal symptoms, and were ≥25 years of age. They had undergone at least 2 previous treatments for opioid dependence, including at least 1 attempt at methadone maintenance therapy (≥60 mg daily for at least 30 days). No patient had received methadone maintenance therapy within the previous 6 months.

**Methods:** Patients were randomly assigned to receive oral methadone (n=115) or injectable diacetylmorphine (up to 3 times daily with a maximum daily dose of 1000 mg [n=115]). An additional 25 patients received injectable hydromorphone, and these subjects were double-blinded with the diacetylmorphine patients.

**Results:** The average daily dose was 392 mg for diacetylmorphine and 96 mg for methadone. At 12 months, 88% of diacetylmorphine subjects were still receiving treatment compared to 54% of methadone subjects. Also at 12 months, a reduction in illicit drug use or other illegal activities was seen in 67% of diacetylmorphine subjects and in 48% of methadone subjects. Among the hydromorphone subjects, retention and response rates were similar to those of the diacetylmorphine subjects. None of the methadone subjects experienced serious adverse events related to the study drug. But, 18 diacetylmorphine subjects had overdose, seizure, or both. Of the 11 subjects with overdose, 7 had used benzodiazepines or cocaine at the time of overdose. Of the 7 with seizure, 2 were epileptic seizures and 5 had used cocaine or benzodiazepines before the seizure. To gauge compliance during the study, random urine checks for heroin were made on the 25 hydromorphone subjects, and none tested positive for diacetylmorphine or morphine.

**Conclusions:** Consistent with studies from Europe, maintenance treatment with injectable diacetylmorphine can be more effective than oral methadone in selected patients who have failed all other approaches. Noting the frequency of overdose and seizures among those receiving diacetylmorphine, the authors recommend that therapy be delivered in a setting where prompt medical response is possible.

**Reviewer’s Comments:** As with similar observations from Europe, the findings of this study will be viewed skeptically by those ideologically opposed to such an approach. Indeed, the study could not have been conducted in the United States. One might question, moreover, the practicality of a treatment that requires injections daily in a medical setting. Of course, such a dosage schedule is what an otherwise untreated heroin addict would adopt on his own, with the added inconvenience of dangerous adulterants, infection (including HIV), and unavoidable criminal behavior. (Reviewer-John C. Brust, MD).

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Keywords: Heroin Addiction, Treatment

Print Tag: Refer to original journal article
Evidence Links RLS to Increased Dopamine Production in Brain

*Altered Dopaminergic Profile in the Putamen and Substantia Nigra in Restless Leg Syndrome.*

Connor JR, Wang XS, et al:

*Brain* 2009; 132 (September): 2403-2412

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Neuronal regulation of dopamine metabolism in restless leg syndrome matches that seen in cell culture and animal models of iron deficiency.

**Background:** Restless leg syndrome (RLS) can be caused by iron deficiency, with low serum ferritin and decreased brain levels of iron seen. There is clinical evidence that the dopaminergic system is altered in RLS, although thus far there have been no consistent findings documenting an abnormality of dopamine (DA) metabolism in RLS brain tissue.

**Objective:** To investigate DA metabolism and the relationship between DA metabolism and iron deficiency in RLS.

**Methods:** This study involved examination of the substantia nigra and putamen after autopsy from the brains of 8 patients with RLS (age of onset, 22.9 ±17.4 years; age at death, 75.5 ±10.7 years). Of these RLS patients, 5 had been treated with a DA agonist or L-DOPA. The RLS brains were compared to the brains of 15 women with no neurologic disease. There were no significant differences between these groups in ages of death or post-mortem interval to examination. D1 and D2 receptor density was measured in the putamen. Tyrosine hydroxylase (TH) and phosphorylated TH levels were measured in the substantia nigra. Also, TH levels in rat brain from a group of iron deficient rats were compared to levels from a group of control rats. Further, a pheochromocytoma cell line was established to determine the impact of iron deficiency on TH, with cultured cells exposed to increasing concentrations of an iron chelator.

**Results:** RLS brains had significantly lower levels of dopamine 2 receptors in the putamen, but not dopamine 1 receptors, compared to control brains. They also had significantly higher levels of TH concentration in the substantia nigra. Findings were not different for patients who were or were not treated with L-DOPA/DA agonists. These results were interpreted as being consistent with an overly activated dopaminergic system as part of RLS pathology. Significant increases in TH were also seen in both the animal and cell models of iron deficiency, similar to that from the RLS autopsy data.

**Conclusions:** For the first time, a clear indication of dopamine pathology in RLS has been reported. The results suggest cellular regulation of dopamine production in RLS closely matches the data from cellular and animal iron deficiency models.

**Reviewer's Comments:** This elegant research provides significant information linking iron deficiency and dopamine metabolism in RLS. It would have been helpful if the investigators had directly measured dopamine concentrations in the putamen of RLS patients compared to controls. A question that begs to be answered is why people with RLS respond positively to treatment with direct DA agonists, considering this evidence that the dopaminergic system is overly active in RLS. (Reviewer-W. Steven Metzer, MD).

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Keywords: Restless Leg Syndrome, Iron Deficiency, Dopamine Metabolism

Print Tag: Refer to original journal article
In children with mild head injury, a CT is not warranted in the absence of severe injury mechanism, altered mental status, loss of consciousness, vomiting, scalp hematoma, signs of palpable or basilar skull fracture, and severe headache.

Background: Traumatic brain injury (TBI) is a leading cause of death and disability in children. In the United States, head trauma (HT) in children younger than 19 years of age results in about 600,000 emergency department (ED) visits, 60,000 hospital admissions, and 7400 deaths per year. A CT scan is performed in about 50% of these children and is the standard test performed to identify brain injury and the need for neurosurgical intervention.

Objective: To identify children with HT who are at very low risk for clinically important TBI (ci-TBI) for whom head CT is not indicated.

Methods: A prospective study at 25 EDs in North America enrolled children younger than 18 years of age who presented within 24 hours of HT with a Glasgow Coma Scale (GCS) score of 14 to 15. CT scans were obtained at the discretion of the ED physician. Determination of ci-TBI was based on hospitalization for >1 night, intubation for >24 hours, neurosurgery, or death from TBI. Age-specific prediction rules for ci-TBI were derived and validated.

Results: >43,000 enrolled children with HT were evaluable. Only about 1% had ci-TBI, and 0.1% underwent neurosurgery. Approximately 2% presented with GCS of 3 to 13. More than 42,000 children had mild HT with a presenting GCS of 14 to 15 and constituted the target group. The mean age was 7 years, and 25% were younger than 2 years of age. The GCS was 15 in 97%. A head CT was obtained in 35%, and TBI was identified with CT in 5% of those studied. In children under age 2 years, a prediction rule that had a negative predictive value and sensitivity of 100% for ci-TBI included these factors: normal mental status, no scalp hematoma (except frontal), no loss of consciousness or loss of consciousness for <5 seconds, nonsevere injury mechanism, no palpable skull fracture, and acting normally according to parents. For children older than age 2 years, the prediction rule that had a negative predictive value of 99.95% and a sensitivity of 96.8% for ci-TBI included these factors: normal mental status, no loss of consciousness, no vomiting, nonsevere injury mechanism, no signs of basilar skull fracture, and no severe headache.

Reviewer's Comments: The decision to obtain a head CT in children with mild HT is commonly driven by medicolegal concerns. In addition to attention to cost-effectiveness, it is prudent to also avoid radiation exposure from unnecessary CT scans. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Traumatic Head Injury, Head CT Guidelines

Print Tag: Refer to original journal article
A mild form of ataxia-telangiectasia (AT) known as "variant AT" presents not with ataxia but with extrapyramidal signs and may never produce ocular or cutaneous telangiectasia.

**Background:** Ataxia-telangiectasia (AT) is an autosomal recessive, multisystem disease. The responsible A-T mutated (ATM) gene encodes the ATM protein, which helps repair damaged DNA. "Classic AT" is lethal at an early age. A less common and less known form is "variant AT," which is milder and has a longer course.

**Objective:** To describe variant AT by comparing it to classic AT.

**Participants:** 6 adult patients with classic AT and 13 with variant AT.

**Results:** The age range of symptom onset was 1 to 5 years in classic AT (median age, 1.5 years) and 0.5 to 34 years in variant AT (median age, 16 years). All classic-AT patients were wheelchair bound by ages 8 to 11 years (median age, 10 years), but only 5 variant-AT patients became so by ages 15 to 43 years (median age, 21 years). The classic-AT patients died at ages 21 to 27 years, but 11 of the variant-AT patients survived to ages 32 to 51 years. The initial neurologic sign was cerebellar ataxia in classic AT and was choreoathetosis or resting tremor in variant AT. Likewise, ocular and cutaneous telangiectasia appeared early in classic AT but not in variant AT. Ataxia eventually appeared in variant AT, but late in the course, and it was mild and only slowly progressive. Only 50% of variant-AT patients developed telangiectasia. All classic-AT patients had oculomotor apraxia and nystagmus, atrophy of the cerebellar vermis on MRI, polyneuropathy, short stature, undeveloped secondary sexual characteristics, sterility, diabetes mellitus, immunoglobulin deficiency, and restrictive lung disease, but most variant-AT patients did not. Shared characteristics included dysarthria, dystonia, elevated serum level of α-fetoprotein, rearrangements in chromosomes 7 and 14, and proclivity to cancer and the ill effects of ionizing radiation. Among variant-AT patients, those with more severe disease had lower tissue levels of ATM protein and kinase activity, and they had splicing mutations of the ATM gene. Less severe variant-AT cases had higher levels of ATM protein and kinase activity, and they had missense mutations of the gene.

**Conclusions:** Variant AT should be in the differential diagnosis of unexplained extrapyramidal signs. Although the disease is untreatable, diagnosis is important because patients are prone to cancer and the ill effects of its treatment with radiation. Measurement of serum α-fetoprotein level and routine karyotyping can aid diagnosis, which can be confirmed with ATM protein studies and gene mutation analysis. There is a genotype-phenotype relation in variant AT: the clinical severity depends on the quantity and activity of the ATM protein, which depends on the genotype.

**Reviewer's Comments:** Variant AT does not present as ataxia and may never cause telangiectasia. Therefore, its very name makes it hard to diagnose. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Variant Ataxia-Telangiectasia, Description

Print Tag: Refer to original journal article
Many drugs can cause toxic myopathy by a variety of mechanisms. Some of these drugs include statins, steroids, certain anti-AIDS medications, cocaine and heroin, and antipsychotic drugs.

Objective: To review drug-induced myopathies in the literature.

Results: Statin myopathy occurs, in descending order of frequency, with simvastatin, lovastatin, pravastatin, atorvastatin, and fluvastatin. The drugs injure the mitochondria and reduce intracellular ubiquinone, a coenzyme Q10 (CoQ10). Asymptomatic hyperCKemia occurs in 5% of statin patients. The CK level is usually <5 to 6 times the upper limit of normal (ULN) but can reach 10 times the ULN. Muscle biopsy is normal or shows ragged red or necrotic fibers. The author does not recommend discontinuing the statin. Myalgia occurs in 9% to 25% of statin patients. Switching statins is the author's recommendation. Muscle weakness with elevated serum CK is usually mild, subacute, and temporally related to starting statin therapy, and it resolves after stopping the drug. Statin-related cases of polymyositis and dermatomyositis have been reported. The incidence of rhabdomyolysis is low (<1 per 100,000 statin prescriptions), but it rises (1) in the presence of drugs that inhibit the cytochrome P-450 3A4 system, such as amiodarone, gemfibrozil, cyclosporin, tacrolimus, and macrolide antibiotics; (2) with hepatic insufficiency, hypothyroidism, and diabetes; and (3) with heterozygosity for phosphorylase, acid maltase, myoadenylate deaminase, and carnitine palmitoyltransferase deficiencies. The author recommends treatment with CoQ10, 600 to 800 mg/day. D-penicillamine and interferon-α rarely cause polymyositis and myasthenia gravis. Chloroquine and hydroxychloroquine cause a myopathy with weakness of proximal limb and respiratory muscles, normal serum CK, and, on muscle biopsy, vacuoles containing acid phosphatase-positive material. A peripheral neuropathy may be present, as well, similar to the myopathy of colchicine, which consists of proximal limb weakness, elevated serum CK, and vacuoles inside muscle fibers. Steroid myopathy occurs with long-term administration of prednisone >20 mg/day or dexamethasone >186 mg administered for 15 days. Weakness is mild, serum CK and EMG are normal, and muscle biopsy shows atrophy of type-II fibers. Acute quadriplegic myopathy, with loss of thick filaments from muscle fibers, occurs in patients treated with depolarizing neuromuscular blocking agents and high doses of glucocorticoids. High doses of glucocorticoids can transiently worsen myasthenia gravis. The anti-AIDS nucleoside analogue reverse transcriptase inhibitors zidovudine, stavudine, and fialuridine deplete muscle mitochondrial DNA and, after 6 to 12 months of treatment, cause a myopathy with proximal muscle weakness, myalgia, elevated serum CK, myopathic changes on EMG, and a histologic picture similar to that of mitochondrial myopathy. Cocaine, heroin, amphetamine, PCP, and alcohol cause rhabdomyolysis. The antipsychotic drugs clozapine, risperidone, olanzapine, loxapine, and haloperidol cause asymptomatic elevation of serum CK in 10% of patients.

Reviewer's Comments: Many drugs can cause myopathy by a variety of mechanisms. This is a comprehensive and thoughtful review of the subject. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Drug-Induced Myopathy, Characteristics

Print Tag: Refer to original journal article
Corticosteroid treatment is beneficial in the acute phase of neuralgic amyotrophy. These benefits appear to include earlier recovery from paresis, decreased duration of initial pain, and earlier functional recovery.

**Background:** Neuralgic amyotrophy (NA) presents with acute onset, severe neuropathic pain in the shoulder and arm, followed by patchy weakness. NA exists in 2 forms: idiopathic (INA) and autosomal dominant hereditary variant (HNA) with relapsing and remitting course. Both INA and HNA are self-limiting conditions and usually show moderate to good recovery. However, even at 3 years, 75% of patients report some residual pain and weakness.

**Objective:** To report the effects of oral prednisolone on NA.

**Participants:** 50 patients with NA were seen at the authors' national referral center for NA during a 7-year study interval. All patients an attack of acute severe shoulder and arm pain followed by weakness.

**Methods:** All patients underwent EMG. All patients were treated with steroids within 31 days. The standard regimen consisted of 13-day oral prednisolone (60 mg/day for 7 days, tapered by 10 mg/day for the next 5 days, and ending with 5 mg/day on day 13). The clinical benefits were compared with the control group of 203 untreated NA patients.

**Results:** The baseline characteristics were similar between the 2 groups. Of the 50 patients evaluated, 76% had INA, and 52% had recurrent attacks. The median time to pain relief was 12.5 days with prednisolone versus 20.5 days in the control group. Within the first month of treatment, strength improvement was seen in 18% of the study group versus 6.3% of controls. Full recovery within 1 year was seen in 12% of the study group and by 10.7% of controls. The patients with antecedent infection recovered earlier. Recovery was more delayed and less complete in patients with recurrent attacks than in those with first attacks. All 6 patients who had full recovery received steroids within 10 days of symptom onset, significantly earlier than those who reported partial recovery. Neuropathic pain recurred in 22% when steroids were discontinued, and 20% reported progression of weakness during the treatment.

**Conclusions:** The results provide evidence that corticosteroid treatment improves the outcome in patients with NA. Steroid treatment is recommended in the acute phase of NA, pending a prospective study confirming these results.

**Reviewer's Comments:** This is a very useful observational study supporting the use of corticosteroids in NA. The retrospective, nonblinding nature of the study is a limiting factor. It is also likely that steroid treatment may have been suboptimal, as possibly suggested by recurrence of pain on stopping steroids or progression of weakness during steroid treatment. (Reviewer-Chitharanjan Rao, MD).

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Keywords: Neuropathic Amyotrophy, Steroid Treatment

Print Tag: Refer to original journal article
Lewis Scheme Provides Useful Framework for Subclassifying PD

A Clinico-Pathological Study of Subtypes in Parkinson’s Disease.

Selikhova M, Williams DR, et al:

Brain 2009; September 16 (epub ahead of print):

The new clinical classification scheme of Parkinson disease based on early symptoms is validated by analysis of clinical data from a large group of pathologically confirmed cases of Parkinson disease.

Background: A number of attempts have been made to classify Parkinson disease (PD) patients based on their clinical manifestations. The tremor dominant form is said to be a benign form of PD. Early postural and gait problems are thought to be associated with a worse prognosis. However, a surprising number of these patients have progressive supranuclear palsy (PSP) or multiple system atrophy (MSA) at autopsy. Recently, cluster analysis of symptoms (without predetermined notions) was used to classify PD patients. The most recent attempt by Lewis and colleagues (J Neurol Neurosurg Psychiatry. 2005;76:343-348) used early clinical findings to classify the patients into 4 groups.

Objective: To verify the subgroup classifications (proposed by Lewis) in pathologically confirmed cases of PD.

Methods: Clinical records of pathologically verified cases of PD available at the Queen Square Brain Bank were reviewed. The cases were subclassified into: (1) earlier onset of disease (EDO) at age <55 years; (2) tremor dominant (TD); (3) nontremor dominant (NTD); and (4) rapid disease progression without dementia (RDP), defined as death from PD within 10 years of symptom onset regardless of age.

Results: 242 cases were studied. The mean age of onset was 61.0 years (age range, 29 to 85 years), and the mean disease duration was 15.6 years (range, 3 to 41 years). The subtype frequencies were 25% for EDO, 31% for TD, 36% for NTD, and 8% for RPD. The EDO group had the longest disease course (mean duration, 22.5 years) and the greatest delay to onset of falls and cognitive decline. A strong correlation was seen between NTD and cognitive decline. There was no difference between the TD and NTD patients in terms of life span and mean time to onset of falls and hallucinations. Rapid disease progression was associated with old age, early depression, and early midline motor symptoms (dysarthria, dysphagia, gait and balance problems). Pathologically, NTD patients had higher mean cortical Lewy bodies than all other groups and more cortical amyloid-β plaque load and cerebral amyloid angiopathy than EDO and TD groups. A strong link exists between bradykinetic onset, cognitive decline, and Lewy body deposition in the neocortex.

Conclusions: The Lewis classification scheme is supported by analysis of clinical data from a large cohort of pathologically confirmed cases with PD.

Reviewer’s Comments: This is an excellent study confirming the validity of a Parkinson disease subtype classification scheme using clinical characteristics. Interestingly the findings refute the long-held notion that prominent tremors indicate a longer and slowly progressive disease course. It is quite instructive that end-stage Lewy body pathology was able to predict certain clinical features. (Reviewer-Chitharanjan Rao, MD).

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Keywords: Parkinson Disease, Subtypes

Print Tag: Refer to original journal article
Deficit Risks Increase After First Unprovoked Seizure in Children


Fastenau PS, Johnson CS, et al:

Neurology 2009; 73 (August 18): 526-534

The risk of neuropsychological deficits and potential for a negative impact on future academic achievement increase in children after a first unprovoked seizure. The clinician should be in tune with these possibilities.

Background: Referral for neuropsychological evaluation for children with epilepsy is most commonly made when academic problems have been recognized, and testing is usually performed remote from seizure onset. Objective: To assess neuropsychological status, academic performance, and risk factors for cognitive deficits in children soon after an initial recognized seizure. Design: A prospective, community-based study. Participants: A cohort of 282 children who experienced a first recognized unprovoked seizure (first-seizure group) with a mean age of about 10 years (range, 6 to 14 years) were compared with 147 healthy siblings with a mean age of about 11 years. Children were excluded if they had an IQ <70, provoked seizures, or an underlying chronic condition that impacted daily activities. Methods: A neuropsychological assessment was performed within 3 months following the seizure and included a battery of standardized neuropsychological and academic achievement tests. Testing was likewise performed on a group of identified siblings. Results: Neuropsychological deficits were identified in 27% of the first-seizure group and in 18% of the sibling controls. Compared to siblings, deficits were most significant and about twice as likely to be present in the seizure cohort in the areas of attention/executive/construction, verbal memory and learning, and language. The significant risk factors identified in the seizure group included recurrent seizures, treatment with antiepileptic drugs, symptomatic or cryptogenic etiology, and epileptiform activity on EEG. A neuropsychological deficit was identified in 40% of children when at least one of these risk factors was present. Each risk factor was associated with an increased odds ratio of about 2. Children with all 4 risk factors were 3 times more likely than healthy siblings to have neuropsychological deficits. Absence epilepsy was associated with an increased odds ratio of 2 for neuropsychological impairment. Academic performance was not significantly different in the seizure cohort compared to sibling controls. Reviewer's Comments: Children who experience a first seizure have a slightly increased risk of neuropsychological deficits. Recurrent seizures, treatment with antiepileptic drugs, symptomatic etiology, epileptiform activity on EEG, and absence seizures appear to be associated with an increased risk for deficits. Academic achievement is likely to be unaffected early but may eventually become negatively impacted. The authors suggest that children with a first seizure should be referred for neuropsychological assessment as soon as possible after seizure onset to identify deficits and direct intervention. This is an admirable goal but may not be easy to accomplish from a practical perspective. Referral for testing should be appropriately considered when available. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Pediatric First Seizure, Cognitive Deficit Risks

Print Tag: Refer to original journal article
The clinician should be aware of the potential for a negative impact on health-related quality of life in children following a single seizure or a new diagnosis of epilepsy, and the clinician should be ready to address problems as they arise.

**Background:** Health-related quality of life (HRQOL) is commonly affected in children with epilepsy, as documented by several prior studies. The impact of a single seizure on HRQOL in children has not been previously addressed.

**Objective:** To compare normative data with parent-rated HRQOL in children (1) following a single seizure or (2) with untreated newly diagnosed epilepsy.

**Design:** Retrospective medical chart review.

**Participants:** A cohort of consecutive children who were evaluated for seizures at a New-Onset Seizure Disorder Clinic during a 1-year study interval. Of 109 children identified, 53 were diagnosed as having a single seizure and 56 were given a diagnosis of epilepsy that had not been previously treated. The mean age was just over 8 years for both groups.

**Methods:** Demographic data, information concerning seizures and comorbidities, and results from a parent-rated Pediatric Quality of Life Inventory (PedsQL) were collected and evaluated. An EEG was performed on all patients. The PedsQL has been previously validated as a measure of HRQOL in children with chronic illnesses.

**Results:** In the 56 children with newly diagnosed and untreated epilepsy, 43% had partial onset seizures, 45% had generalized onset seizures, and 12% could not be classified. Both children with a single seizure and those with a new diagnosis of untreated epilepsy had significant impairments in HRQOL according to parents' assessment (based on the PedsQL results) in comparison to normative data. All HRQOL domains that included physical, emotional, social, school, psychosocial, and total functioning were negatively affected in both groups. There were no significant differences identified in HRQOL between the single seizure and the untreated epilepsy groups, and there were no significant differences between the groups with partial onset seizures and generalized onset seizures. There were no identified demographic or comorbidity differences between the single seizure and epilepsy groups.

**Reviewer's Comments:** There is an apparent immediate potential for a negative impact on HRQOL in children following a single seizure or a new diagnosis of epilepsy. Formal evaluation of HRQOL can be very helpful to identify children at risk and to promote timely psychosocial interventions as indicated. At the very least, the clinician should be aware of the potential for a negative impact on HRQOL following a single seizure or a new diagnosis of epilepsy and should be ready to identify and address problems as they arise. (Reviewer-Gregory B. Sharp, MD).

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**Keywords:** Pediatric First Seizure, Quality of Life

**Print Tag:** Refer to original journal article
High serum aldolase without creatine kinase elevation is associated with myopathies that harbor mostly perimysial pathology and that are part of a systemic immune disorder.

**Background:** Serum aldolase and creatine kinase (CK) are often elevated in patients with myopathies. However, the utility of elevated serum aldolase in the evaluation of myopathies has not been assessed, mostly because of lack of specificity.

**Objective:** To assess the clinical and pathological findings in patients with elevated aldolase but normal CK levels.

**Methods:** Patients with elevated aldolase and normal CK levels seen at a single neuromuscular center during a 10-year span were reviewed. Muscle biopsies were reviewed independent of the knowledge of aldolase and CK values. Muscle biopsies were compared to 75 biopsies of patients with immune or inflammatory myopathies and 14 patients with myopathies associated with anti-Jo-1 antibodies (antisynthetase syndrome).

**Results:** 6 men and 6 women (mean age, 41 years) had elevated aldolase levels (9–21 U/L) and normal CK levels at presentation (n=9) or during exacerbation (n=3) of muscular symptoms. Myalgia and/or cramps were the most common symptoms (92%), followed by arthralgia (75%), skin disorders (75%), and pulmonary involvement (50%). Eosinophilia was present in 25% of patients. In 5 patients tested, anti-Jo-1 antibody was not found. Needle EMG showed myopathic changes without fibrillation potentials in 45%, myopathic changes with fibrillation potentials in 18%, and normal findings in 36% (n=4). Most patients had systemic immune disorders (graft-versus-host reaction, dermatomyositis, rheumatoid arthritis, vasculitis, and myasthenia gravis). Muscle biopsies showed perimysial pathology in all patients, including acid phosphatase positive cellularity (83%) and fragmentation of connective tissue (75%). Both findings were statistically significant when compared to immune and inflammatory myopathies, but not with Jo-1-antibody-associated myopathies. Perivascular mononuclear infiltrate was present in 50%. Muscle fiber pathology was subtle with perifascicular atrophy or MHC class I upregulation.

**Conclusions:** Aldolase elevation in serum without CK rise is associated with myopathies that harbor mostly perimysial pathology and are part of a systemic immune disorder. This clinical syndrome is similar to the myopathies associated with anti-Jo-1 antibodies (antisynthetase syndrome).

**Reviewer's Comments:** Many physicians have abandoned requesting aldolase in the evaluation of myopathy since serum aldolase is nonspecific and may increase with malignancy, liver disease, and anemia. Personally, this study has rekindled the relevance of assessing serum aldolase in patients with possible myopathies, particularly those with muscle pain and systemic symptoms (joint pain, skin lesions, or pulmonary disease). Since only 4 of 12 patients had anti-Jo-1 antibody tested, this study could not determine whether aldolase is also elevated without CK rise in myopathies associated with anti-Jo-1 antibodies (antisynthetase syndrome).

(Reviewer-Bashir Katirji, MD)

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**Keywords:** Aldolase Elevation, Perimysial Pathology

**Print Tag:** Refer to original journal article
Immunosuppression therapy using oral prednisolone combined with azathioprine reduces the recurrence of myasthenic crisis, especially after treatment for >6 months.

**Background:** Myasthenic crisis (MC), defined as worsening myasthenia gravis (MG) symptoms requiring mechanical ventilation, affects up to 25% of patients. Older and MuSK-seropositive patients and those with bulbar weakness and thymoma are at higher risk for MC. Oral prednisolone combined with azathioprine (PR-AZA) was shown to be effective in improving MG symptoms in a double-blind placebo-controlled study (Neurology 1998;50:1778-1783).

**Objective:** To evaluate the effect of PR-AZA in reducing the frequency of MC.

**Design:** Case-control study in a single European institution.

**Participants:** Patients with an index episode of MC were assessed for recurrence of MC. Charts of 27 patients treated with PR only without immunosuppression (Non-IM group) between 1990 and 1996 were compared to 42 patients treated with the PR-AZA combination (IM group) between 1997 and 2004.

**Methods:** All patients received plasma exchange during the index MC. The non-IM group was treated with high doses of steroids (64-1000 mg), which were then tapered during their hospital stay without further immunosuppressive therapy. The IM group was treated with PR-AZA (PR, 1.0-1.5 mg/kg; AZA, 2.0-2.5 mg/kg), and PR was slowly tapered after 3 months of remission until withdrawal or lowest effective dose, while the AZA dose remained constant for the entire follow-up. The primary end point was the difference in the frequency of MC recurrence during the follow-up period of >5 years.

**Results:** There were no statistically significant differences between groups regarding age, gender, thymoma, thymectomy, pyridostigmine dose, or ocular, bulbar or respiratory manifestation at initial MG presentation. There was a marked overall reduction in recurrent MC in the IM group compared to the non-IM group (19% vs 59%, respectively). Although the trend started in the first 6 months of IM treatment (17% vs 30%, respectively), this became statistically significant only after 6 months (2% vs 44% respectively), supporting the expected delayed effect of AZA. During MC recurrence, the length of ICU stay and mechanical ventilation days were not different.

**Conclusions:** Immunosuppressive therapy with PR-AZA is effective in preventing the recurrence of MC. This effect is more evident with long-term use (>6 months).

**Reviewer's Comments:** Although this is a retrospective study, it is unique since the 2 groups of MG patients were treated distinctly, making the comparison easy. It reinforces the utility of this type of immunosuppressive treatment (PR-AZA) in preventing MC and improving the natural history of MG. The authors do not specify the timing of thymectomy, which was frequently done (70% in the non-IM group and 57% in the IM group) and may have had an effect of MC recurrence. (Reviewer-Bashar Katirji, MD).