Late recovery from a vegetative state is more likely to occur in traumatic brain injury and in young individuals.

**Background:** Recovery of cognitive awareness is believed to be rare after a patient with traumatic brain injury (TBI) survives 1 year in a vegetative state (VS). Recovery is also unlikely after 3 months in VS due to a nontraumatic brain injury (eg, hypoxia). How reliable these time points are for prognostication, however, has been questioned, since most studies addressing a VS outcome have not systematically examined the course of VS patients beyond 1 year.

**Objective:** To follow prospectively VS patients surviving beyond 6 months and to quantify the frequency and extent of late cognitive recovery. **Design/Participants:** Prospective study of 50 consecutive patients who had been hospitalized for at least 6 months in a unit specifically designed for them in the Institute for Rehabilitation in Telese, Italy.

**Methods:** Exclusion criteria included the presence of any response, even if ambiguous or inconsistent, to environmental stimuli found on periodic testing over time. Thus, patients with a minimally conscious state (MCS) were deliberately excluded. The level of responsiveness and functional disability were evaluated by means of validated scales (Coma Recovery Scale-Revised and Disability Rating Scale).

**Results:** Causes of brain injury resulting in VS included TBI (36%), hemorrhage (36%), and anoxia (28%). Patients were followed for a mean 26 months after injury, including 5 patients who were followed for >4 years. Twenty-one patients (42%) died, and 17 (34%) remained in VS. Two patients with TBI (4%) recovered responsiveness within 12 months of trauma. Ten patients (20%), 6 with TBI, 1 with hemorrhage, and 3 with anoxia, emerged from VS to MCS; 5 TBI and 1 anoxia patient (12%) progressed to conscious awareness. Late recovery was associated with younger age (mean of 32 years vs 54 years in those without recovery) and was more frequent in TBI (33%) versus anoxia (21%). Emerging from a MCS to awareness behavior occurred in 5 of 18 TBI patients (28%) and in 2 of 14 anoxia patients (14%). Functionally, however, all patients remained severely impaired and totally dependent in their activities of daily living.

**Conclusions:** Late recovery of responsiveness and conscious awareness can occur in a minority of patients with traumatic and nontraumatic VS, but disability remains severe. This improvement is more common in younger patients and in TBI.

**Reviewer’s Comments:** In contrast, a companion article by Luaute et al, found that VS patients followed over a 5-year observation period showed no late improvement; they died or remained in VS. However, one-third of the patients with MCS improved after >1 year had elapsed. The majority that improved had suffered TBI. Despite the differences in VS outcome, both studies support the notion that late neurological recovery is more likely to occur after severe brain injury when the etiology is trauma and when patients are younger in age.

(Reviewer-Michael Jacewicz, MD).

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Keywords: Vegetative State, Consciousness, Awareness, Responsiveness

Print Tag: Refer to original journal article
Use It or Lose It -- Intellectual Enrichment Protects Cognition in MS

Intellectual Enrichment Lessens the Effect of Brain Atrophy on Learning and Memory in Multiple Sclerosis.

Sumowski JF, Wylie GR, et al:

Neurology 2010; 74 (June 15): 1942-1945

Lifetime intellectual enrichment appears to protect patients with multiple sclerosis from cognitive decline due to brain atrophy.

**Background:** The cognitive reserve hypothesis (CRH) posits that intellectual pursuits in education, vocation, and other cognitively challenging activities (lifetime intellectual enrichment) lessen the detrimental effects of neurological disease on cognition. Most studies on the CRH have been done in the setting of Alzheimer’s disease. There is little data on other neurological diseases, such as multiple sclerosis (MS), even though pathology from MS can lead to brain atrophy and deficits in learning and memory.

**Objective:** To test the CRH in a cohort of patients with MS.

**Participants/Methods:** 44 subjects with long-standing MS were included. Subjects with recent exacerbations, recent corticosteroid use, serious psychiatric illness, illicit drug use, and learning disability were excluded. Subjects were assessed on measures of verbal learning and verbal memory. Lifetime intellectual enrichment was measured using the Wechsler Abbreviated Scale of Intelligence, which evaluates the subjects’ vocabulary knowledge. The width of the third ventricle on 3-T MRI imaging was used as a measure of brain atrophy.

Hierarchical regression models were created to evaluate how brain atrophy and intellectual enrichment affect performance on learning and memory tasks, specifically examining how the interaction between brain atrophy and intellectual enrichment may affect performance.

**Results:** Age, gender, and disease duration did not affect performance on learning and memory tasks. There was a relationship between brain atrophy and poorer performance on learning and memory tasks. In contrast, intellectual enrichment was associated with better performance on the learning task but not on memory tasks. Most importantly, intellectual enrichment moderated the effect of brain atrophy on cognition. That is, for those with a high level of intellectual enrichment, there was a similar level of performance on the verbal learning and verbal memory tasks across the spectrum of brain atrophy, whereas in those with low levels of intellectual enrichment, there was a sharp decline in performance on these cognitive tasks with worsening brain atrophy.

**Conclusions:** Lifetime intellectual enrichment appears to protect cognitive function in persons with MS.

**Reviewer’s Comments:** This study adds to the growing literature that suggests that challenging mental activities throughout life can help protect individuals from cognitive decline due to brain disease. From the Alzheimer’s literature, intellectual enrichment seems to exert a protective effect on cognition, perhaps by creating greater synaptic connectivity throughout the brain. In this study, enhanced intellectual enhancement did not necessarily lead to better performance on cognitive tasks. However, as the degree of brain atrophy increased, those with a high level of intellectual enrichment maintained better performance on these cognitive tasks than those who were on the low end of intellectual enrichment. Thus, this study supports the cognitive reserve hypothesis and suggests that when it comes to maintaining cognition, the old adage, “Use it or lose it,” applies. (Reviewer-Aninda B. Acharya, MD, MSPH).

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**Keywords:** Learning, Memory, Cognition, Brain Atrophy

**Print Tag:** Refer to original journal article
Criteria for hemicrania continua should be broadened to include patients with side-shifting pain, headache of either moderate or worse severity, and a wider range of autonomic features than currently listed.

**Objective:** To describe 39 patients with unilateral head pain responding to indometacin.

**Results:** Of the 39 patients, 33 fulfilled International Headache Society criteria for hemicrania continua. Among the 6 patients who did not fulfill the criteria, 3 had side-alternating pain, 2 did not have cranial autonomic features with exacerbations, and 1 had moderate rather than severe pain with exacerbations. Thirty-eight patients had daily continuous pain for over 3 months, and 1 patient had daily pain initially for 3 months, followed by pain 5 days per week and then either no pain or pain for 2 days per month. Most patients rated the severity of pain exacerbations between 6.5 and 10 out of 10. Two rated the severity of background pain as 10 out of 10. Cranial autonomic features were more extensive than those listed by the International Headache Society. In order of frequency, they included lacrimation, nasal congestion, conjunctival injection, ptosis, forehead or facial flushing, rhinorrhea, forehead or facial sweating, itching eye, eyelid edema, aural fullness or swelling, miosis, mydriasis, and facial swelling. Twenty four patients were female and 15 were male; the mean age at onset was 39 years (range, 10 to 67 years). Sites of pain included temporal, orbital, frontal, retro-orbital, occipital, parietal, vertex, neck, maxilla, and ear. Exacerbations of pain were daily in half the patients and between 1 and 5 times per week in one-third of patients. One patient had 1 to 3 exacerbations per day and 1 had exacerbations every few months. Exacerbations could last between hours and days or between 30 and 60 minutes. Pain was most often described as throbbing, sharp, continuous, pressure, or dull. Two-thirds of patients had a personal or family history of migraine or headache. Nine patients had headache onset in close temporal relation to head injury. All patients had a positive intramuscular or oral indometacin test. For abortive treatment, 11 patients had tried oxygen and 9 had tried sumatriptan, with no response in either group. Of the 34 patients who tried a nonsteroidal anti-inflammatory drug other than indometacin, 5 had a good response and 29 did not.

**Conclusions:** Criteria for hemicrania continua should be broadened to include patients with side-shifting pain, headache of either moderate or worse severity, and a wider range of autonomic features than currently listed. Because 2 patients did not have cranial autonomic features and because hemicrania can be difficult to distinguish from other trigeminal autonomic cephalgias, especially paroxysmal hemicrania with interictal pain, an indometacin test should be considered for any patient with unilateral head pain.

**Reviewer's Comments:** These observations might support the view that hemicrania continua and paroxysmal hemicrania are on a spectrum. Whether or not they represent a single disorder, it remains a mystery why indometacin is so specifically effective. (Reviewer-John C. Brust, MD).

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Keywords: Hemicrania Continua, Primary Headache, Indometacin

Print Tag: Refer to original journal article
There are major problems with this disappointing study, and it should not be interpreted as indicating that patients with all types of tremor might not benefit from stereotactic gamma knife thalamotomy.

**Background:** Treatment of tremor associated with Parkinson's disease (PD) and essential tremor (ET) with thalamotomy has been utilized for over 50 years. More recently, thalamotomy has been eclipsed by deep brain stimulation. Gamma knife thalamotomy (GKT) is a less invasive procedure for treatment of tremor.

**Objective:** To prospectively evaluate clinical outcomes after GKT for disabling tremor due to ET and PD.

**Design:** Prospective, uncontrolled study with blinded independent neurologic evaluations.

**Participants:** Subjects included 18 consecutive patients (15 with ET; 3 with PD) considered to have disabling tremor and unsuitable to undergo thalamotomy or deep brain stimulation surgery.

**Methods:** Subjects underwent unilateral GKT for tremor. Pre-GKT and post-GKT data were collected for severity of tremor up to 24 months post-GKT. Videos for 14 of these 18 subjects (ET, 11 and PD, 3) were available for blinded tremor analysis (mean age, 75 years; 12 males, 2 females; mean symptom duration, 21 years; follow up, 19.2 ± 7.3 months). Upper limb and head tremor were graded by an independent movement disorders neurologist using the Fahn-Tolosa-Marin Tremor Rating Scale. For the 3 subjects with PD, the activities of daily living (ADL) were analyzed using the Unified Parkinson's Disease Rating Scale (UPDRS).

**Results:** There was significant improvement in the Fahn-Tolosa-Marin Tremor Rating Scale ADL scores for the GKT-treated subjects. However, there was no significant improvement in other tremor rating scale items for resting tremor, postural tremor, action tremor, drawing, pouring water, or head tremor. Three subjects developed late neurologic adverse events, with 1 of these being serious. A few individual subjects were noted to have significant improvement in tremor after GKT (ET, 2 and PD, 1).

**Conclusions:** The investigators conclude that GKT provided only modest anti-tremor efficacy. Of the 2 subjects with ET who experienced marked improvement in tremor, 1 subsequently experienced a serious adverse event.

**Reviewer's Comments:** The results of this uncontrolled study are disappointing. There are 3 major problems. First, the study included a small number of subjects. Second, it included a heterogeneous group of tremor subjects (ET and PD patients). Third, all subjects (ET and PD) were rated using the Fahn-Tolosa-Marin scale, although this scale was developed for assessment of tremor with ET, not PD. Of greater importance, the thalamic lesion produced in the subjects at this single center may not have been adequate to attenuate tremor in these patients. This study should not be interpreted as indicating that patients with all types of tremor might not benefit from stereotactic GKT. What is needed is a multicenter, randomized, controlled, blinded investigation of the effect of GKT on a homogeneous group of tremor patients. (Reviewer-W. Steven Metzer, MD).

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Keywords: Essential Tremor, Gamma Knife, Parkinson's Disease, Treatment, Tremor

Print Tag: Refer to original journal article
The presence of epilepsy has no effect on the incidence of cognitive impairment.

**Background:** The International Subarachnoid Aneurysm Trial (ISAT) showed that patients with ruptured, predominantly anterior circulation aneurysms and good clinical grades at presentation randomized to coiling had fewer unfavorable outcomes at 1 year than those clipped neurosurgically, but outcome was only judged using the relatively insensitive modified Rankin Scale (mRS).

**Objective:** To report the results of a substudy of ISAT that examined neuropsychological impairments in patients who survived with no major physical disability (mRS, 0 to 2) to 1 year.

**Methods:** Patients were assessed with a battery of tests covering all major areas of cognition. Cognitive impairment was considered to be present in patients who had at least 2 impaired test scores in >2 of 6 cognitive “domains:” verbal memory; general verbal skills; processing speed; nonverbal skills; spatial working memory; and executive skills.

**Participants:** 836 patients treated in ISAT at 8 centers in the United Kingdom.

**Results:** After patients with 1-year mRS scores >2 had been excluded, 328 patients randomized to coiling and 284 randomized to clipping remained. Between 20% and 25% of the patients did not attend testing sessions, leaving 262 coil and 212 clip patients who were completely evaluated. Baseline characteristics in the coil and clip cohorts were nearly identical (age, sex, clinical grade at presentation, aneurysm size, and number of aneurysms). There were only 8 crossovers. Among the 262 coil patients evaluated, 70 met the study’s definition of cognitive impairment; the proportion in the clip group was 82 of 212 (OR favored coil, 0.58; 95% CI, 0.38 to 0.87; \( P =0.0055 \)). The clip group was significantly more likely to be impaired in a greater number of cognitive domains than the coiled patients. Fewer than 5% of the cohort had epilepsy following the procedure, but the presence of epilepsy did not influence the incidence of cognitive impairment. The frequency of cognitive impairment was higher in patients with higher mRS scores (approximately 25% in those with an mRS of 0 and closer to 40% with an mRS of 2). Within each mRS stratum, more clip patients had cognitive deficits than coil patients. If a perfect outcome is judged to be an mRS of 0 and no cognitive impairment, then 69 coil patients (26% of the coil cohort) and 33 clip patients (16% of the clip cohort) achieved this.

**Conclusions:** Cognitive impairment is a common sequel of aneurysm intervention, but is more frequent in the neurosurgical clipping group.

**Reviewer’s Comments:** This study would have been better had it included measures of depression and taken this and concomitant medications into account. The rate of nonparticipation was not optimal, but certainly not unacceptable. Were the nonparticipating patients too busy back living their lives to bother or too impaired to even think about participating? (Reviewer-James W. Schmidley, MD).

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Keywords: Endovascular Coiling, Neurosurgical Clipping, Saccular Aneurysms, Subarachnoid Hemorrhage

Print Tag: Refer to original journal article
**What Is Clinical Course of NMDA Receptor Antibody Encephalitis?**

*N-Methyl-D-Aspartate Antibody Encephalitis: Temporal Progression of Clinical and Paraclinical Observations in a Predominantly Non-Paraneoplastic Disorder of Both Sexes.*

Irani SR, Bera L, et al:

Brain 2010; 133 (June): 1655-1657

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N-methyl-D-aspartate receptor antibody encephalitis is a biphasic illness.

**Objective:** To describe the clinical features in 44 patients with *N*-methyl-D-aspartate receptor (NMDAR) antibody encephalitis.

**Methods:** NMDAR antibodies were measured in sera and cerebrospinal fluid (CSF), and the degree of binding was quantitated.

**Results:** Intrathecal synthesis of antibodies was identified, but the absolute level of antibodies was higher in serum than in CSF. Among 44 patients, 31 were females aged 2 to 49 years; only 8 (aged 20 to 35 years) had ovarian teratomas. The 13 males were 4 to 59 years of age. One had a recurrent Hodgkin lymphoma. One-quarter of the patients had an infectious episode within 21 days prior to neurological disease. Early neurological features included cognitive dysfunction (confusion, behavioral change, amnesia, and aphasia), psychiatric symptoms (hallucinations, psychosis, agitation, depression), and seizures (both generalized and partial). Later features, appearing 10 to 20 days after neurological onset, included most prominently abnormal movements (choreoathetosis, parkinsonism, myoclonus, oculogyric crisis, and opisthotonus). Other late features included decreased level of consciousness and dysautonomia (tachy/brady-cardia, hyperhidrosis, fever, hypoventilation, labile or high blood pressure, hypersalivation, pseudoobstruction, and cardiac asystole). CSF pleocytosis was present in two-thirds of patients early in the course, clearing within 35 days. By contrast, CSF oligoclonal bands were increasingly present as the disease progressed. Electroencephalography (EEG) showed epileptiform discharges in half the patients, usually early; later, 80% of patients showed generalized slowing. MRI was initially normal in 89% of patients and remained normal in 77%. Abnormalities consisted of hippocampal or white matter signals on fluid-attenuated inversion-recovery imaging, and subcortical abnormalities that tended to accompany the later-appearing movement disorders and brainstem features. Severity of illness correlated with level of serum NMDAR antibodies. Early tumor removal or early immune therapy appeared to improve outcome. High persistent antibody levels were present in the 3 patients who died, and antibody levels declined in those who improved. Nine of 10 patients who relapsed had received less intensive immunotherapy than those who did not.

**Conclusions:** NMDAR antibody encephalitis is a biphasic disorder, with early neuropsychiatric features and seizures sometimes accompanied by CSF pleocytosis, epileptiform discharges on EEG, and abnormal MRI signals in the hippocampus. Later appearing features include abnormal movements, dysautonomia, and reduced level of consciousness, sometimes accompanied by CSF oligoclonal bands, EEG slowing, and subcortical MRI signals. It is possible that antigenic stimulation begins in the periphery and that central nervous system antibodies initially target the temporal lobe and later the basal ganglia and brainstem.

**Reviewer’s Comments:** The most important message of this paper is that treatment, whether teratoma removal or immunosuppression, must be given early and that immunotherapy must be intensive and probably prolonged. (Reviewer-John C. Brust, MD).

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Keywords: NMDA Antibody Encephalitis, Autoimmunity, Non-Paraneoplastic

Print Tag: Refer to original journal article
Define Underlying Etiology to Treat Acute Movement Disorders in Children

A Prospective Study of Acute Movement Disorders in Children.

Dale RC, Singh H, et al:

Dev Med Child Neurol 2010; 52 (August): 739-748

The management of acute movement disorders in children is foremost dependent on identification of the underlying cause followed by diagnosis-directed therapy.

Objective: To prospectively evaluate children who present with acute movement disorders.

Participants/Methods: 52 children (31 girls and 21 boys; age range, 2 months to 15 years) who presented to a single tertiary pediatric hospital over a 40-month period with acute-onset movement disorders were included, except those with tic disorders. A thorough evaluation for etiology was performed in all cases.

Results: The presenting movement abnormalities were chorea in 20 children, dystonia in 17, tremor in 12, myoclonus in 10, and parkinsonism in 10. There were 22 children with inflammatory or autoimmune disorders, 18 with noninflammatory conditions, and 12 with a psychogenic etiology. Inflammatory or autoimmune disorders included a diagnosis of N-methyl-D-aspartate receptor (NMDAR) encephalitis in 5 children, opsoclonus-myoclonus syndrome (OMS) in 4, Sydenham chorea in 3, systemic lupus erythematosus/antiphospholipid antibody syndrome (SLE/APS) in 3, acute necrotizing encephalopathy (ANE) in 3, and other types of encephalitis (EO) in 4. Noninflammatory disorders included drug-induced movement disorder in 6 children, post-pump chorea in 5 children following cardiac bypass surgery, metabolic etiology in 3 (including 2 with glutaric academia and 1 with Leigh syndrome), and vascular disease in 2 with stroke. All patients with psychogenic movement disorders were >10 years of age and were more likely to be female (10/12). Causes of chorea included post-pump chorea (5), NMDAR encephalitis (3), Sydenham (3), vascular (2), ANE (2), drug-induced (2), metabolic (1), SLE/APS (1), and EO (1). Causes of dystonia included NMDAR encephalitis (4), drug-induced (3), ANE (3), psychogenic (3), metabolic (2), and EO (2). Acute onset tremor was most commonly psychogenic (10 of 12 patients), 1 case was caused by SLE/APS, and the etiology was unknown in the other. Acute onset myoclonus was psychogenic in 50% of cases, due to OMS in 40%, and drug induced in 1 case. Parkinsonism was due to NMDAR encephalitis (3), encephalitis/acute disseminated encephalomyelitis (3), SLE/APS (1), drug induced (1), metabolic (1), and psychiatric with catatonia (1). Inflammatory or autoimmune disorders were primarily treated with steroids and/or intravenous immunoglobulin. Drug-induced movement disorders tended to resolve with discontinuation or modification of the causative agent, and cases of post-pump chorea tended to resolve without therapy. Psychogenic-induced movement disorders tended to resolve in response to identification of underlying psychological stressors and appropriate intervention and therapy, but 3 children developed intractable psychiatric movement disorder. In general, outcomes were variable and ranged from complete recovery to severe morbidity and death, but were primarily related to the underlying etiology.

Reviewer’s Comments: Management of acute movement disorders in children is foremost dependent on identification of the underlying cause followed by diagnosis-directed therapy. Psychogenic cases should not be dismissed, because they are equally disabling and require psychiatric intervention. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Children, Acute Movement Disorders, Etiology

Print Tag: Refer to original journal article
Background: For the diagnosis of Parkinson's disease (PD), rest tremor is one of the 4 major diagnostic criteria. The typical tremor is unilateral, occurs at rest, and has a frequency of 4 to 6 Hz. While the tremor may involve various body parts, it most typically involves the arms. A lower limb tremor as the initial manifestation of this disease is unusual.

Objective: To determine the diagnosis in patients presenting with an isolated lower extremity rest tremor.

Participants/Methods: All patients seen at a movement disorders clinic over an 8-year period were included in the study. The study group included those initially presenting with an isolated lower extremity rest tremor. A response to levodopa was considered positive if the patient developed motor fluctuations or had sustained improvement on the United Parkinson's Disease Rating Scale. Cerebellar signs included gait ataxia, limb ataxia, dysarthria, and horizontal nystagmus occurring without evidence of lower motor neuron or vestibular dysfunction. All patients underwent either CT or MRI brain scans. Those who fulfilled the clinical criteria of the United Kingdom PD Society Brain Bank were diagnosed with PD. Those with pyramidal, autonomic, and cerebellar signs that fulfilled the consensus statement criteria were diagnosed with possible multiple systems atrophy (MSA). Patients with an unclear diagnosis between PD and MSA underwent a cardiac MIBG SPECT.

Results: 16 patients with lower limb rest tremor (average age, 58 ± 16 years) were identified and included in the study. Five of these had an excellent response to levodopa and were diagnosed with PD. Three fulfilled criteria for the diagnosis of MSA. Four patients had a poor response to levodopa or symmetrical symptoms but no significant pyramidal, cerebellar, or autonomic signs. Cardiac MIBG scans done in these 4 patients showed abnormal uptake in 3, strongly suggestive of PD. The other patient had a negative scan indicating possible MSA. Of the 4 remaining patients, 2 had a fluctuating tremor that disappeared and was felt to be psychogenic. The other 2 had tremor that started after being on a dopamine receptor blocking agent and were considered drug induced. Their tremors subsided when the medication was withdrawn. Over the 8 years, 445 PD patients were identified, 8 of which presented with lower limb tremor; 48 patients with probable MSA were diagnosed, 4 presenting with lower limb tremor.

Conclusions: While lower extremity tremor is unusual and most commonly seen with PD, one should also consider MSA and other neurodegenerative disorders.

Reviewer's Comments: This article emphasizes the difficulty in the diagnosing of idiopathic PD at times, especially in the early phases. Repeat examinations over time are important. (Reviewer-John Schwankhaus, MD).

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Keywords: Unilateral Lower Extremity Tremor, Parkinson's Disease, Multiple Systems Atrophy

Print Tag: Refer to original journal article
This study suggests no role for the adjunctive use of entacapone in early Parkinson's disease.

**Background:** Parkinson's disease (PD) treatment becomes associated with fluctuations and dyskinesia in approximately 50% of patients within 5 years after starting levodopa. Pulsatile stimulation of dopamine receptors may contribute to this. A commonly accepted theory is that continuous dopamine stimulation (CDS) may help prevent these complications. A study of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys found that levodopa/carbidopa/entacapone (LCE) at regular intervals helped prevent dyskinesia.

**Objective:** To determine if the addition of entacapone to carbidopa/levodopa could delay or reduce dyskinesia in PD, presumably through prolonging levodopa action with more CDS.

**Design:** Multicenter, double-blind study.

**Participants:** 747 men and women with PD for <5 years, taking stable doses of a dopamine agonist or other anti-parkinsonian medications (but not amantadine) without exposure to levodopa or a catechol-O-methyltransferase (COMT) inhibitor.

**Methods:** Subjects were randomized to treatment with levodopa/carbidopa (LC) (mean age, 59.8 years; 59.7% men; mean PD duration, 2.0 years), or LCE (mean age, 60.6 years; 65.7% men; mean PD duration, 2.0 years) at 3.5-hour intervals 4 times daily. There were no significant demographic differences between groups; 58.3% of both groups were taking a dopamine agonist. Subjects on dopamine agonists in both groups were significantly younger, had significantly longer disease duration, and were almost 5 years younger at disease onset than those not receiving dopamine agonists. The primary end point was time to onset of dyskinesia. Secondary end points included frequency of dyskinesia, change from baseline total UPDRS, and time to wearing-off episodes. Study duration was 134 weeks.

**Results:** 541 subjects (72.6%) completed the study as planned (71% to 74% of both groups). Compared to LC subjects, LCE subjects had a significantly shorter time to onset of dyskinesia and a significantly increased frequency in week 134 of dyskinesia (LC, 32% vs LCE, 42%). These effects were most pronounced in subjects receiving baseline dopamine agonists. An unanticipated finding was increased incidence of prostate cancer and myocardial infarction in the LCE group, although this was slight.

**Conclusions:** Initiating levodopa therapy with LCE failed to delay the time of onset or reduce the frequency of dyskinesia compared to LC. In fact, LCE was associated with a shorter time to onset and increased frequency of dyskinesia compared to LC, which is a very unexpected finding.

**Reviewer's Comments:** The surprising results of this study are discussed in an informative editorial. The outcome probably does not indicate that the theory that pulsatile stimulation leads to complications of therapy is wrong. The treatment paradigm may not have resulted in true continuous dopamine stimulation. Also, the increased risk of dyskinesia with LCE was restricted to subjects probably with more severe disease, requiring more frequent treatment with dopamine agonists. This study suggests no role for the adjunctive use of entacapone in early PD; entacapone is still very useful for the management of motor fluctuations when they occur in levodopa-treated PD. (Reviewer-W. Steven Metzer, MD).
**Acyclovir Resistance May Occur in Herpes Simplex Encephalitis**

**Acyclovir Resistance in Herpes Simplex Encephalitis.**

Schulte EC, Sauerbrei A, et al:

Ann Neurol 2010; 67 (June): 830-833

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HSV-I resistance to acyclovir is mediated by mutations in the thymidine kinase gene.

**Background:** Herpes simplex type I virus (HSV-I) encephalitis has a 70% mortality if untreated. Intravenous (IV) acyclovir reduces this rate to 20%. Resistance to the drug is uncommon, especially in immunocompetent hosts.

**Objective:** To present a case of acyclovir-resistant HSV-I encephalitis in an immunocompetent woman who had never received acyclovir or similar treatment.

**Results:** This 27-year-old Romanian woman was working on a cruise ship traveling through Germany when she developed a right-sided headache, fever, personality change, and mild left hemiparesis. She had a history of only migraines, with no immunocompromise, prior herpes virus infections, or previous treatment with acyclovir. Exam showed a fever of 39°C, encephalopathy, and mild left hemiparesis. CSF showed 292 white cells/μL and protein of 1.32 g/L, with normal glucose. She was started on acyclovir 750 mg IV every 8 hours, ceftriaxone 2 g IV every day, and ampicillin 1.5 mg IV every 8 hours. MRI of the brain showed a T2 hyperintense lesion in the right temporal, insular, and thalamic areas. There was a positive polymerase chain reaction for HSV-I in the CSF (411,000 HSV-I genome equivalents/mL). Treatment with ceftriaxone and ampicillin was discontinued. Over the next couple of days, her alertness further deteriorated. Electroencephalogram showed asymmetric slowing with intermittent sharp waves. A lumbar puncture was performed on day 6 after the patient developed a supranuclear oculomotor palsy. There were 338 white cells/μL, total protein was 2.59 g/L, and there was increased synthesis of IgM and IgA. HSV-I had increased to 1,420,000 genome equivalents/mL. Foscarnet was added at 40 mg/kg body weight every 8 hours. The patient dramatically improved except for the oculomotor changes. On day 4 of foscarnet, CSF pleocytosis decreased to 76 cells/μL, and HSV DNA was no longer detected. The patient completed 14 days of foscarnet and 19 days of acyclovir with good result. White blood counts, CD4+, CD8+, serum IgA, IgG, and IgM, and C3 and C4 were within the normal range. Levels of acyclovir were within the expected margins. The thymidine kinase gene of the HSV-I detected in the CSF on days 1 and 6 showed 5 nonsynonymous mutations.

**Conclusions:** Continued deterioration of the patient after 6 days of acyclovir and mutations in the thymidine kinase gene are consistent with acyclovir resistance.

**Reviewer's Comments:** Continued clinical deterioration of a patient with herpes simplex encephalitis type I on IV acyclovir should make the physician entertain the possibility of drug resistance, even if the host is immunocompetent, and foscarnet should be added. (Reviewer-John Schwankhaus, MD).

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Keywords: Herpes Simplex, Encephalitis, Acyclovir Resistance

Print Tag: Refer to original journal article
How Common Is Recurrence After First CSVT?

Long-Term Evaluation of the Risk of Recurrence After Cerebral Sinus-Venous Thrombosis.

Martinelli I, Bucciarelli P, et al:

Circulation 2010; 121 (June 29): 2740-2746

Although cerebral sinus-venous thrombosis occurs most often in women of reproductive age, recurrences are probably more common in men because risk factors specific to females are easily modified.

**Objective:** To establish the long-term rate of recurrent cerebral sinus-venous thrombosis (CSVT) or other venous thromboses after a first episode of CSVT, and to evaluate factors affecting recurrence rate.

**Design:** Prospective observational study.

**Participants:** This study evaluated patients with a first episode of CSVT who were referred for thrombophilia testing to one center over a 17.5-year span.

**Methods:** The diagnosis of CSVT had to be confirmed by imaging. Data gathered included the location of CSVT, presenting symptoms, and medical history, including known risk factors for CSVT—cancer, infection, trauma, oral contraceptive (OC) use, and/or pregnancy. Follow-up started only when anticoagulant therapy for the index CSVT was discontinued. All patients were, by definition, tested for thrombophilia disorders (TPD)—activated protein C resistance (factor V Leiden), G20210A prothrombin gene mutation, fibrinogen, antithrombin III, protein S and C levels, lupus anticoagulant, and anti-phospholipid antibodies. A severe TPD was diagnosed when antithrombin III, protein S or C deficiencies, lupus anticoagulant, and/or anti-phospholipid antibodies were found, or if there was >1 abnormal test. Patients with activated protein C resistance, prothrombin gene mutation, or abnormal fibrinogen were considered to have a mild TPD. The final cohort was comprised of 132 patients. Outcome events were recurrent CSVT, venous thrombotic events (VTE) elsewhere, or pulmonary embolism. Mean follow-up was 6 years.

**Results:** About three-fourths of the patients were female, almost all of whom had a CSVT when pregnant, during the postpartum period, or when taking OCs. Laboratory evidence of a severe TPD was found in 9% of the cohort, with mild TPD in 27%. There were 15 total recurrent VTEs, but 10 were non-CNS. The recurrence rate was 0.5% per 100 patient-years for CSVT and 1% for non-CNS. The risk of recurrence was highest in the first year off anticoagulants, and was definitely higher in males. By Kaplan-Meier analysis, mild TPDs did not increase the risk of a recurrent VTE, but the severe TPDs did. No woman used OC in follow-up. There were 44 pregnancies during follow-up, and almost all women (37 of 44) were treated with low-molecular-weight heparin (LMWH) during pregnancy. Numbers were small, but it appeared that women who received LMWH had better obstetrical outcomes.

**Conclusions:** The recurrence rate of CSVT and other VTEs is low after anticoagulation for a first episode of CSVT has been discontinued. The results argue against long-term anticoagulation of patients with a CSVT unless they have a high risk (severe) TPD.

**Reviewer’s Comments:** This study differed from others on the same question because the follow-up was much longer and it was started only after anticoagulation was stopped. Although the first CSVT tends to occur much more often in women of reproductive age, recurrences are probably more frequent in men, because risk factors specific to females are easily avoided (OC) or modified (LMWH during subsequent pregnancies).

(Reviewer-James W. Schmidley, MD).

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Keywords: Cerebral Sinus-Venous Thrombosis, Thrombophilia Disorders

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Idiopathic intracranial hypertension occurs only rarely in older and non-overweight patients. It is more likely to be medication induced in non-overweight than in overweight patients. Both older and non-overweight patients have a relatively good visual prognosis.

**Background:** Most patients with idiopathic intracranial hypertension (IIH) are young, obese women.
**Objective:** To describe 2 groups of atypical patients: those age ≥50 years and those who are not overweight.
**Design:** Retrospective study involving 3 neuro-ophthalmology referral centers.
**Participants:** From 1989 to 2007, 721 patients with IIH were treated; the mean age was 29 years (standard deviation, 11 years). The subjects consisted of all patients with IIH whose age was ≥2 standard deviations above the mean, (ie, age, ≥50 years; body-mass index [BM], ≤25). The control group consisted of all other adult patients (at least 18 years old).
**Methods:** The diagnosis of IIH was based on the modified Dandy criteria: signs and symptoms of increased intracranial pressure, no localizing signs except abducens palsy, CSF opening pressure ≥25 cm, normal CSF composition, and normal imaging of brain and dural venous sinuses. Medications considered capable of causing IIH were vitamin A, cyclosporine, minocycline, tetracycline, doxycycline, and recent withdrawal of corticosteroids. Severe visual loss was defined as legal blindness (best-corrected visual acuity 20/200 or worse) or a total central visual field <20 degrees.
**Results:** There were 407 adults with IIH, 18 of whom (4%) had a BMI ≤25 (not overweight); 341 patients (84%) had a BMI ≥30 (obese). Medication-induced IIH was more frequent in the non-overweight subjects than in the controls (28% vs 7%; \P =0.008). The normal-weight subjects were more likely to be men than were the controls (22% vs 7%; \P =0.048). No normal-weight subject, but 17% of controls, suffered severe visual loss. Nineteen of 721 patients (5%) were at least 50 years old (range, 50 to 67 years) at the time of diagnosis of IIH. The older subjects were more likely to present with visual symptoms than were controls (42% vs 21%; \P = 0.03) and were less likely to present with headache (36% vs 76%; \P <0.001). The older subjects were more likely to have chronic persistent papilledema, but their visual outcome was no worse than that of controls.
**Conclusions:** IIH occurs only rarely in older and normal BMI patients. It is more likely to be medication induced, and the visual outcome is likely to be better in normal-weight than overweight patients. Older patients with IIH are more likely to present with visual symptoms than headache, but their visual prognosis is no worse than that of young patients.

**Reviewer’s Comments:** The authors recently described a third group of atypical patients: men with IIH (*Neurology* 2009; 72: 304-309). Their visual outcome is worse, on the whole, than that of women. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Pseudotumor Cerebri, Benign Intracranial Hypertension, Idiopathic Intracranial Hypertension, Atypical

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Consider Methylprednisolone Pulse Therapy for Infantile Spasms

Outcomes in Treatment of Infantile Spasms With Pulse Methylprednisolone.
Mytinger JR, Quigg M, et al:

J Child Neurol 2010; 25 (August): 948-953

This treatment regimen for infantile spasms includes IV methylprednisolone pulse therapy at a dose of 20 mg/kg per day for 3 days, followed by oral prednisone at 4 mg/kg per day with a tapering dose over 8 weeks.

Background: Adrenocorticotropin hormone (ACTH) therapy has become extremely expensive, prompting many to re-explore the use of corticosteroid therapy to treat infantile spasms (IS).

Objective: To evaluate the efficacy of intravenous (IV) methylprednisolone followed by an oral prednisone taper in a series of patients with IS.

Methods: Families of infants with IS were offered an option of therapy with ACTH, an oral corticosteroid regimen, or pulse methylprednisolone for 3 days followed by a prednisone taper. Ten consecutive infants with IS were treated with IV methylprednisolone at a dose of 20 mg/kg per day for 3 days, followed by oral prednisone starting at 4 mg/kg per day and tapered over 8 weeks. The primary outcome measure was cessation of IS within 2 weeks. The secondary outcome measure was resolution of the hypsarrhythmia pattern on follow-up EEG.

Results: The mean age at onset of IS was 4 months with a median age at initiation of treatment of 5 months. Antiepileptic drug therapy had been started before steroids in 70% of patients. One-half of these infants experienced cessation of IS within 1 week after starting the steroid protocol. When the treatment protocol was initiated within 1 month of spasm onset, 5 of 6 infants experienced cessation of spasms within the first week. Resolution of hypsarrhythmia occurred in one-half of patients at the time of follow-up EEG, at an average of 3 weeks after initiation of steroid therapy. Interestingly, one patient with cessation of IS had persistence of hypsarrhythmia on EEG, and one patient with continued IS had resolution of hypsarrhythmia. Recurrence of spasms occurred in 4 of 5 of the primary responders, but all experienced subsequent resolution of spasms. Ultimately, 70% had experienced resolution of IS at the time of last follow-up at least 1 year after onset of spasms. The only reported adverse effects were hypertension and adrenal insufficiency during prednisone taper, each in one child. No significant adverse effects were noted in 80% of these infants.

Conclusions: This regimen of pulse methylprednisolone for 3 days followed by an oral prednisone taper appeared to be reasonably efficacious, especially when started soon after the onset of spasms. Adverse effects were minimal. The estimated medication cost for this regimen was about $200 compared to $70,000 for a typical course of ACTH.

Reviewer's Comments: ACTH therapy has always been associated with a high incidence of adverse effects and has become extraordinarily expensive. Studies need to further investigate the comparative results of ACTH therapy with various corticosteroid regimens and synthetic ACTH compounds such as cosyntropin. It is also recognized that vigabatrin is now available for the treatment of IS in the United States. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Infantile Spasms, Methylprednisolone Pulse Therapy

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Leptomeningeal Metastasis -- the Prognosis Has Not Improved

Leptomeningeal Metastases in the MRI Era.

Clarke JL, Perez R, et al:

Neurology 2010; 74 (May 4): 1449-1454

Although MRI has simplified the diagnosis of leptomeningeal metastases, the prognosis remains poor. Patients with hematologic malignancies outlive those with solid tumors.

**Background:** MRI became the initial and often sole diagnostic test for leptomeningeal metastases (LM) in the 1990s.

**Objective:** To determine whether this has affected the diagnosis or outcome of LM.

**Design:** Retrospective study from a referral cancer hospital.

**Participants:** All adults with LM diagnosed from 2002 to 2004 were included. Primary CNS tumors were excluded.

**Methods:** The Karnofsky performance status (KPS) was used to measure patients’ functional status.

**Results:** There were 187 patients aged 19 to 87 years (median, 56 years). More patients had solid tumors (80%) than hematologic malignancies (20%). Most patients (73%) were women, because breast cancer was the most common primary tumor (35%). The next most common types were lung (25%), lymphoma (11%), leukemia (8%), gastrointestinal (6%), and melanoma (5%). At the time of diagnosis of LM, 81% of patients with solid tumors had known metastatic disease; 70% of these had brain metastases; and 81% of these with hematologic tumors had active disease. Twenty-five percent of patients had symptoms or signs of involvement of the cerebral hemispheres, posterior fossa, and spinal roots; 39% had clinical involvement of 2 of those areas, and 34% had involvement of only 1 area. The diagnosis of LM was established by MRI in 53% of patients, by CSF cytology in 23%, and by both techniques in 24%. MRI was diagnostic in 88% of solid-tumor patients but in only 48% of hematologic-tumor patients tested, presumably because cells of solid tumors form large nodules in the leptomeninges. CSF cytology was positive in a high proportion of patients with solid (85%) and hematopoietic (89%) tumors. Sensitivity and specificity for MRI and CSF cytology could not be calculated, because all patients had a positive result from one or the other. The CSF white blood cell count was elevated in 64% of patients; the protein was elevated in 59%; the glucose was low in 31%; and the opening pressure was elevated in 50%. Only 3% of patients had normal CSF. Patients were treated with radiotherapy alone (36%), chemotherapy (intrathecal or systemic) alone (25%), both (19%), or palliative measures alone (15%). Median survival was 2.3 months (95% CI, 1.7 to 2.6) for patients with solid tumors and 4.7 months (95% CI, 2.7 to 6.8) for those with hematopoietic tumors. Multivariate analysis showed that a poorer KPS, increased intracranial pressure, and solid tumor type were significantly associated with shorter survival. The effect of treatment could not be determined because of patient selection for treatment and palliative care.

**Conclusions:** Although MRI has simplified the diagnosis of LM, the prognosis remains poor. Patients with hematologic malignancies outlive those with solid tumors.

**Reviewer's Comments:** Leptomeningeal metastasis continues to be a feature of late, widespread malignant disease, and its prognosis has not improved in many decades. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Leptomeningeal Metastases, Meningeal Carcinomatosis, Meningeal Lymphoma, Meningeal Leukemia

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People with ≥2 first-degree relatives with a history of subarachnoid hemorrhage (SAH) should be screened for intracranial saccular aneurysms with MRA, in order to prevent SAH. Doing so every 7 years from age 20 to 80 years is cost-effective.

**Background:** The risk of subarachnoid hemorrhage (SAH) in people with ≥2 affected first-degree relatives is much higher than in the general population. Screening for intracranial saccular aneurysms in these subjects, in order to prevent SAH, has been recommended but must be done repeatedly because aneurysms develop throughout life.

**Objective:** To determine the most cost-effective way to screen such individuals for aneurysms.

**Design:** Simulated prospective cohort study involving one million imaginary people with ≥2 first-degree relatives who had SAH.

**Methods:** The authors used a mathematical model to follow the subjects throughout their lives without screening, as a simulation of natural history, and then with screening at different time intervals and different ages when screening was started and stopped. Screening was done with MRA, and positive tests were confirmed with digital subtraction angiography (DSA). Aneurysms were treated with coiling or clipping. The risk of aneurysm development, enlargement, and rupture and the risk of death or disability after SAH, preventive clipping or coiling, and DSA were taken from the literature. Quality-adjusted life-years (QALY) were used to measure health benefits. (A QALY is rated 1 for good health but <1 for poor health; for example, a QALY for a disabled person in a nursing home is rated 0.31). Cost-effectiveness was expressed as cost per QALY. A cost of $29,900 per QALY was considered the highest acceptable price (a common figure in the cost-effectiveness literature).

**Results:** Compared to no screening, any screening reduced the frequency of SAH. Furthermore, even the most aggressive program (MRA every 2 years from age 20 to 80 years), which yielded the highest gains in QALY, turned out to be cost-effective ($20,008 per QALY). However, the most cost-effective schedule was screening every 7 years from age 20 to 80 years ($9331 per QALY).

**Conclusions:** People with ≥2 first-degree relatives with a history of SAH should be screened for intracranial saccular aneurysms with MRA in order to prevent SAH. Doing so every 7 years from age 20 to 80 years is cost-effective.

**Reviewer’s Comments:** The problem with thought experiments such as this is that the validity of the conclusion depends on that of the data used. The authors admit that only limited data on the rate of aneurysm development and the time interval between development and rupture are available. These data being so key and integral to their model limits the validity of its conclusions. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Subarachnoid Hemorrhage, Aneurysm, Screening

Print Tag: Refer to original journal article
Ephedrine is effective in patients with the Dok-7 subtype of congenital myasthenic syndrome.

**Background:** Congenital myasthenic syndromes (CMS) are a group of inherited neuromuscular junction disorders with defects in presynaptic, synaptic, or postsynaptic proteins. CMS due to a defect in Dok-7 is a recently described subtype characterized by early childhood onset of limb girdle muscle weakness, no weakness of extraocular muscles, and lack of response to cholinesterase inhibitors. Dok-7 is an adaptor protein that is a key component of the muscle-specific tyrosine kinase at the postsynaptic membrane. Ephedrine enhances neuromuscular transmission through an unknown mechanism and was used to treat myasthenia gravis in the past. Anecdotal reports suggested that ephedrine is useful in patients with CMS.

**Design:** Prospective single French tertiary center study performed between June 2005 and October 2008.

**Methods:** 10 patients with Dok-7 CMS were treated with ephedrine and assessed using the quantitative myasthenia gravis (QMG) score. The QMG score is a validated scoring system in adults with myasthenia gravis but has not been well validated for children. It is made up of 13 components, each scoring 0 (normal) to 3 (severe weakness), with total scores ranging from 0 (normal) to 39 (severe generalized weakness). Patients received a dose of 0.5 to 1 mg/kg per day depending on tolerability.

**Results:** The patients' age at symptom onset varied from birth to 21 years, whereas the age that ephedrine was started ranged from 5 to 46 years. QMG scores improved significantly from a mean score of 17 of 39 at baseline to a score of 10 of 39 at 6 to 8 months ($P = 0.009$). The component of the QMG score that assessed arm raise, leg raise, head lift, forced vital capacity, and hand grip improved significantly at 6 to 8 months, ranging from 163% to 11%, respectively. Mobility scores also improved ($P = 0.0006$), and activities of daily living were enhanced. The drug was well tolerated; one child had insomnia, and one adult had hypertension.

**Conclusions:** Ephedrine significantly improves muscle strength in patients with Dok7-CMS and is well tolerated.

**Reviewer's Comments:** This study brings an old drug to the forefront of the available drugs for patients with CMS. It is recommended that salbutamol (Albuterol) may substitute for ephedrine in countries where ephedrine is not available. (Reviewer-Bashar Katirji, MD).

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Keywords: Congenital Myasthenic Syndromes

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Miyoshi Myopathy and LGMD2B Are Similar

Redefining Dysferlinopathy Phenotypes Based on Clinical Findings and Muscle Imaging Studies.

Paradas C, Llauger J, et al:
Neurology 2010; 75 (July 27): 316-323

Miyoshi myopathy and limb-girdle muscular dystrophy 2B have a similar progression rate, MRI images, and prognosis.

Background: Clinically, dysferlin deficiency presents either as a distal myopathy that affects the calf muscles preferentially (Miyoshi myopathy [MM]) or as a non-distinct proximal weakness (limb-girdle muscular dystrophy 2B [LGMD2B]). It is not known why mutations in the dysferlin gene result in different phenotypes, sometimes in the same family.

Objective: To identify clinical or MRI markers that may help differentiate the 2 phenotypes of dysferlin myopathies.

Methods: Patients with reduced or absent dysferlin expression in muscle and mutation in the dysferlin gene were included. All patients had period neuromuscular assessment including a composite manual muscle testing score (CMMT) and MRIs of the thigh and lower leg during the study period. These patients were followed up for 6.4 ± 5.7 years. A total of 57 MRI studies (1 to 6 per patient) were done over the study period.

Results: Of 29 patients included, 14 had MM and 12 LGMD2B. Mean age at symptom onset was 23 ± 8.5 years, with a duration of disease at 9.2 ±10.3 years. The mean creatine kinase value was 9279 ± 6087 IU/L with a tendency to decline with time. Although the initial muscle weaknesses were dissimilar (distal leg vs proximal girdle), these early differences in clinical weakness disappeared as the disease progressed. They were no differences in the functional status and time to require wheelchair use between groups. Similarly, MRI changes showed no relation to the phenotype: medial gastrocnemius and adductor magnus were the first muscles to show abnormal T2-weighted signal, followed by the soleus, semitendinosus, and vastus lateralis, while the biceps femoris, rectus femoris, and tibialis posterior remained relatively spared.

Conclusions: The 2 phenotypes of dysferlin myopathies (MM and LGMD2B) show clinical and MRI convergence as the diseases progress with time.

Reviewer’s Comments: It has been intriguing why specific protein deficiencies in inherited myopathies may manifest in distinctive phenotypic presentations with a wide variety of muscle weakness distribution. This study suggests that we should be lumping rather than splitting the muscular dystrophies. (Reviewer-Bashar Katirji, MD).

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Keywords: Dysferlin Myopathy

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