A meta-analysis of PFO and prior cryptogenic stroke treated medically found the pooled absolute rate of recurrent ischemic stroke to be 1.6 events per 100 person-years.

**Background:** In patients with a patent foramen ovale (PFO) and a previous cryptogenic ischemic stroke or transient ischemic attack (TIA), the absolute and relative risk of recurrent ischemic events is not known.

**Objective:** To estimate the absolute rate of recurrent cerebral ischemic events in patients with a PFO treated medically, and to determine the relative risk (RR) for event recurrence compared to patients without a PFO.

**Design/Methods:** The medical literature was systematically reviewed for studies that reported original data on recurrent cerebral ischemic events in patients with cryptogenic stroke or TIA found to have a PFO. Clinical studies meeting predetermined quality criteria were subjected to a meta-analysis.

**Results:** 15 studies met criteria for inclusion. Four studies included a non-PFO comparison group. The pooled absolute rate of recurrent events in the 15 studies was 4.0 events (95% CI, 3.0 to 5.1) per 100 person-years for stroke or TIA and 1.6 events (95% CI, 1.1 to 2.1) per 100 person-years for ischemic stroke. In the 4 studies with non-PFO groups, the pooled relative risk (RR) for recurrent ischemic stroke or TIA in patients with PFO versus without PFO was 1.1 (95% CI, 0.8 to 1.5), and for ischemic stroke alone, the pooled RR was 0.8 (95% CI, 0.5 to 1.3).

**Conclusions:** Medically treated PFO patients with prior cryptogenic stroke have a low pooled absolute rate of recurrent ischemic events. The risk for recurrence of TIA or stroke is not significantly different from patients without PFO. These results do not support a need for PFO closure, and invasive procedures to close the PFO cannot be routinely recommended until the results of ongoing clinical trials are known.

**Reviewer's Comments:** An accompanying editorial by Tamayo and Harrer reviews the problems raised by the heterogeneous and contradictory data reported for PFO and risk for ischemic stroke. Conclusions from the meta-analysis should be interpreted cautiously, since conflicting data may reflect patient selection bias, confounding factors, or other flaws in study design. Despite the limitations, the current meta-analysis provides a long-needed overview of PFO and stroke. It suggests restraint in PFO closures, and supports the American Academy of Neurology Practice parameters for PFO treatment that recommend antiplatelet agents for cryptogenic stroke patients with PFO but without an atrial septal aneurysm (ASA). There is insufficient evidence to guide treatment of patients with both PFO and ASA. Patient management, however, may need to be individualized. The presence of a hypercoagulable state, strong history for paradoxical embolism, a large PFO, and/or an ASA may warrant anticoagulation or PFO closure. The completion of several large randomized trials should provide better guidance regarding the benefit of PFO closure versus medical management, and whether anticoagulation is superior to antiplatelet therapy. (Reviewer-Michael Jacewicz, MD).

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Keywords: Patent Foramen Ovale, Cryptogenic Stroke, Recurrent Cerebral Ischemic Events
Background: Misuse of common tools is felt to result from damage of the dominant parietal lobe, but this has been questioned.

Objective: To determine the location of lesions associated with defects of functional knowledge, mechanical problem solving, and use of common tools.

Methods: Consecutive, right handed patients who had suffered a left hemispheric stroke at least 3 weeks before and had no MRI evidence of diffuse or bilateral lesions were included. Patients with bleeding were included when blood was completely or partially resolved and there was no edema on imaging studies. To test functional associations, patients viewed a photograph of a tool above 4 photographs of other objects. Patients were asked to select the appropriate recipient for the tool and then to select an alternative tool that could be used for the same purpose. Each subtest had a maximum score of 16. The novel tool test consisted of 6 cylinders and 6 tools. Each cylinder had a part to which one of the tools fit. Patients were asked to select the suitable tool for each cylinder. Scoring considered selection and use of the correct tool. If unable to select the correct tool, it was supplied and points awarded for correct use. The test probed the use of 5 common tools: hammer, scissors, screwdriver, key, and spanner. A rack with a nail, thread, screw, padlock, and bolt were presented for manipulation by the correct tool. Scoring was similar to that for novel tools. Normal controls performed each of the tests. Lesions on MRI and CT were analyzed using MRICro software. Voxel-wise statistics were also obtained.

Results: 38 patients were included with brain damage from ischemia (23) and bleeding (15). All were aphasic, 17 did testing with their left hand due to hemiparesis, and 9 had a hemianopia. Two anatomical regions influenced success of the experimental tests: (1) from the central region rostrally and ventrally through the middle frontal cortex to the inferior frontal gyrus, and (2) from the supramarginal gyrus dorsally and caudally through the inferior to the superior parietal lobule. The frontal lesions had influence on all experimental tests, while the parietal lobe affected novel and common tools.

Conclusions: The left parietal lobe is felt to control general principles of tool use rather than knowledge of prototypical use of common tools, and the comprehension of mechanical interactions of the tool with other tools rather than selection of grip formation and manual movements.

Reviewer’s Comments: This study did not show an effect of left temporal lesions on tool use. The left parietal lobe is felt to provide information regarding external objects, which is necessary for motor planning, but does not contain the motor representation specifying particular grips or movements. (Reviewer-John Schwankhaus, MD).

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Keywords: Apraxia, Tool Use, Aphasia, Frontal, Parietal

Print Tag: Refer to original journal article
Amnestic MCI patients with depression may represent a specific subgroup of MCI patients who respond better to treatment with cholinesterase inhibitors for protective therapy.

**Background:** Amnestic mild cognitive impairment (MCI) is defined as subjective concern and clinical determination of memory deficit in the absence of significant global cognitive and functional impairment, with the annual progression rate from MCI to dementia ranging from 5% to 32%. Thus far, cholinesterase inhibitors have proven to be of no or minimal benefit in delaying the progression of MCI to Alzheimer's disease (AD).

**Objective:** To investigate whether depressive symptoms are a risk factor for progression of MCI to AD, and if this can be mitigated by donepezil.

**Design:** Multicenter double-blind placebo-controlled drug trial.

**Participants:** 756 subjects with MCI who failed to meet accepted diagnostic criteria for AD were evaluated. Exclusion criteria included significant clinical symptoms of depression, cerebrovascular disease, and focal neuroimaging lesions. Subjects taking stable doses of antidepressants were not excluded. All subjects took the Beck Depression Inventory (BDI) at baseline, and 208 scored >9. The remaining 548 scored within the normal range and were classified as nondepressed. There were no significant differences between these 2 groups with respect to demographic data and cognitive testing.

**Methods:** All subjects were randomized to treatment with donepezil, vitamin E, or placebo. The vitamin E and placebo subjects were grouped together for analysis (no effect of vitamin E had been noted). Primary end point for the study was time to diagnosis of possible or probable AD using accepted criteria.

**Results:** After 3 years of follow-up, age, APOE genotype, and BDI score were independently significantly associated with progression from MCI to AD. Each 1 point higher score on the BDI was associated with a 3% higher hazard of progression to AD. Comparing the depressed MCI subjects to the nondepressed MCI subjects, progression to AD was significantly delayed by donepezil at 1.7 years and 2.2 years, and was marginally lower at 2.7 years.

**Conclusions:** Depressive symptoms as measured by the BDI may be associated with increased risk of progression of MCI to AD, and this progression may be delayed by donepezil.

**Reviewer's Comments:** The authors postulate that depressed patients with MCI may constitute a distinct subpopulation of MCI patients that progress more rapidly to AD and respond better to treatment with cholinesterase inhibitors than nondepressed MCI patients. An important limitation of this study is that subjects with clinically significant depressive symptoms were specifically excluded from this study. If they had been included, it may very well have altered the outcome of this study. (Reviewer-W. Steven Metzer, MD).

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Keywords: Mild Cognitive Impairment, Alzheimer's disease, Depression, Donepezil

Print Tag: Refer to original journal article
Memantine is a simple, safe treatment consideration for Lewy body dementias, but further studies are needed to determine its efficacy.

**Background:** Modest clinical benefits have been found with the cholinesterase inhibitor, rivastigmine for Lewy body dementias. While there are alterations of glutamatergic function in these dementias, memantine has shown mixed results.

**Objective:** To test the efficacy of memantine versus placebo for symptoms of both Parkinson's disease dementia (PDD) and diffuse Lewy body disease (DLB).

**Methods:** Patients with mild-to-moderate PDD or DLB with Mini-Mental State Examination score (MMSE) of ≥12 were enrolled. Diagnoses were based on standardized criteria for both disorders. Exclusion criteria included other brain disease, recent major changes in health status, major depression, moderate-to-severe disease of the heart, lungs, liver, or kidneys, or clinically relevant abnormalities of laboratory tests. Patients were randomly assigned to memantine (gradually increased to 10 mg orally twice daily over 4 weeks) or placebo. All underwent a full history and medical, neurological, and psychiatric examinations. Electrocardiogram and laboratory tests were done as well as a brain CT scan or MRI within 1 year. Stable treatment with cholinesterase inhibitors for 6 months was allowed as well as anti-Parkinsonian medications (dose adjustment allowed), antidepressants, anxiolytics, and antipsychotics begun at least 4 weeks before trial. Anticonvulsant drugs and other NMDA receptor antagonists (amantadine) were not allowed. The primary outcome was the Clinical Global Impression of Change (CGIC) including cognition, attention, psychiatric symptoms, motor symptoms, and daily functioning. Secondary outcomes included 24-week scores on MMSE, a global test of cognition, a quick test of cognitive speed, a structured clinical interview of the caregiver, and the disability assessment for dementia. On statistical analysis, an improvement of 0.6 points on the CGIC was deemed clinically significant.

**Results:** 75 patients were randomly assigned, and 72 started study medication (40 with PDD and 32 with DLB); 34 received memantine and 38 placebo. Sixteen withdrew from the study due to adverse events, but the proportion was similar in the 2 groups. There were no significant differences in demographic or clinical variables between the groups. At week 24, the patients in the memantine group had better CGIC scores than those taking placebo (mean difference, 0.7). With the exception of improved speed on attentional tasks in the memantine group, there were no significant differences between the groups in secondary outcome measures.

**Conclusions:** Patients with PDD or DLB might benefit from memantine treatment.

**Reviewer's Comments:** This is the first prospective randomized placebo-controlled study of memantine for PDD and DLB. While there are potential problems (small patient numbers, high attrition rate, use of cholinesterase inhibitors, and allowing of change in dose of anti-parkinsonian and psychiatric medications), a significant difference between the 2 groups was found. Confirmation of these results from further studies is needed. (Reviewer-John Schwankhaus, MD).

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Keywords: Parkinson's disease Dementia, Diffuse Lewy Body Disease, Memantine

Print Tag: Refer to original journal article
Think Twice Before Giving Prophylactic AEDs in ICH

Prophylactic Antiepileptic Drug Use is Associated with Poor Outcome Following ICH.
Messé SR, Sansing LH, et al:
Neurocrit Care 2009; 11 (August): 38-44

In this study, early use of pAED after acute nontraumatic ICH was associated with poor outcome, independent of other factors known to influence outcome in ICH.

Background: Prophylactic antiepileptic drug (pAED) use in intracerebral hemorrhage (ICH) is variable; there is no consensus concerning the proper approach.

Objective: To ascertain whether the administration of pAEDs affects outcome in nontraumatic ICH.

Design: CHANT (Cerebral Hemorrhage and NXY-059 Trial) was a randomized trial comparing a neuroprotective (NXY-059) with placebo in patients with ICH. The current study addressed CHANT patients given placebo.

Methods: CHANT enrolled patients within 6 hours following nontraumatic ICH. Key exclusion criteria included significant extra-axial hemorrhage (subdural, epidural, subarachnoid), hemorrhage secondary to tumor or encephalitis, planned surgery on the ICH, alcohol/drug abuse, and unconsciousness or a clinical impression that the patient was unlikely to survive the first 72 hours. Insertion of intracranial pressure monitors and external ventricular drains, osmotic agents, and glucocorticoid use were allowed. Patients already taking AEDs were excluded. All treatments, other than study drug, were left to local investigators. The usual clinical, demographic, and outcome data were collected, including the occurrence of seizures following enrollment and drugs administered. Benzodiazepines were not considered to be AEDs. The primary outcome measure was the modified Rankin scale, with scores of 6 and 5 (death and severe disability, respectively) considered poor outcomes and higher scores considered good. The data were analyzed using multivariate analysis, looking for an effect of pAED use on outcome. Further analyses were performed to examine confounding factors. Details of the statistical analysis are well explained in the paper.

Results: 295 patients participated, mean age was 67.5 years, 65% were male, and mean ICH volume was about 23 mL. Five patients had clinical seizures following enrollment, all on day 2 or 3, and none were on pAEDs. All patients with clinical seizures had cortical or subcortical hemorrhage. In total, 23 patients received pAED (ie, no seizures were present before treatment with AED was begun). Nearly all patients received phenytoin, and 4 received valproate. pAED use was more frequent at U.S. sites. None of the patients receiving pAED had seizures out to 90 days. At the end of extensive multivariate analysis, pAED use remained strongly associated with poor outcome (odds ratio, 6.8), as did age, hematoma volume, presence of intraventricular hemorrhage, lower Glasgow coma score, and prior warfarin use.

Conclusions: In this cohort, early use of pAED after acute nontraumatic ICH was associated with poor outcome, independent of other factors known to influence outcome in ICH.

Reviewer's Comments: While this retrospective cohort review suffers from all the drawbacks associated with that type of research, and in particular, very few patients received pAEDs, the data certainly justify continuing skepticism regarding the blanket/automatic use of pAEDs in non-traumatic ICH patients. It also provides useful insights into the incidence of clinical seizures in the hours and days following non-traumatic ICH - these were rare, occurring in less than 2% of patients. (Reviewer-James W. Schmidley, MD).

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Keywords: Intracerebral Hemorrhage, Seizures, Antiepileptic Drugs

Print Tag: Refer to original journal article
In young children with headache and no additional concerning history or abnormality on neurologic examination, a head CT is very unlikely to reveal a significant finding and is typically not warranted.

**Objective:** To determine if computed tomography (CT) scans of the head are helpful and improve acute care for young children who present to the emergency department (ED) with a complaint of headache.

**Design/Methods:** A retrospective review of the medical records was performed on 364 children between the ages of 2 and 5 years who presented to a large urban ED over a 3-year period with a chief complaint of headache. An initial identification of patients with secondary headache was performed and included those with a known preexisting pathologic condition that might cause headache such as a ventriculoperitoneal shunt or brain tumor, an acute illness such as viral syndrome, probable meningitis or fever, or trauma. The records of remaining patients were reviewed with attention to headache history, previous evaluations, family and social history, and findings on physical examination with special attention to neurologic abnormalities. Potential "red flags" were identified that included a chronic progressive pattern of symptoms, acute onset of the worst headache of the patient's life, focal neurologic symptoms, or headache or emesis on awakening. Results of laboratory tests and CT scans, when performed, were reviewed. The final diagnostic impression and disposition were then noted.

**Results:** The majority of children - almost 85% - were considered to have secondary headaches. Almost three fourths of children with secondary headaches had an acute febrile illness or viral respiratory infection. A head CT was performed in approximately 20% of children with secondary headache, and 8 of 16 were abnormal. The main focus was on children with primary headache, where there was no recognized central nervous system or systemic disease. CT scans were performed on 28% of these 58 children. Only one of these scans revealed an abnormal finding with identification of a brainstem glioma. The patient was a 5-year-old boy with "red flags" of escalating headache over the prior 5 days, and pain upon awakening at times associated with emesis. The ordering physician noted concern for possible increased intracranial pressure. The neurologic examination was also abnormal, with vertical nystagmus noted by the neurosurgeon (but not by the ED physician.)

**Conclusions:** For young children presenting to the ED with headache but normal neurologic examination findings and non-worrying history, CT scans seldom lead to diagnosis or contribute to immediate management.

**Reviewer's Comments:** A head CT is typically warranted in young children seen with headache in the ED with a history of trauma, ventriculoperitoneal shunt, or brain tumor. A head CT should be performed prior to lumbar puncture in children with signs or symptoms of possible meningitis. When the primary complaint is headache, there is no prior history of pathological significance, the history is devoid of pathological "red flags," and the neurologic exam is normal, a head CT is very unlikely to reveal a significant finding and is usually not warranted. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Head CT, Childhood Headache, Emergency Care
Mirror visual feedback therapy is beneficial in some patients with phantom limb pain and hemiparesis following stroke.

Objective: To review mirror visual feedback and offer explanations for how it might work. Discussion: “Phantom limb” refers to a vivid sense that an amputated arm or leg is still present, often with intractable pain. Cortical plasticity is evident in subjects with phantom limbs - for example, touching the face might produce sensation in the amputated hand - and cortical remapping can be shown with magnetoencephalography. Some patients can move their phantoms; in those who cannot, the limb is often perceived as paralyzed in a painful position. Mirror therapy consists of putting a patient in a rectangular box with a mirror propped vertically and sagittally. A patient with left arm amputation would place his phantom on the non-reflecting side of the mirror and his normal right arm on the reflecting side so that its reflection seems visually superimposed on the felt location of the phantom. The effect is an illusion that the phantom has been restored, and when the patient is told to move both his normal right hand and his immobile painful left hand, he gets the visual impression that his phantom hand is "obeying" his command. This procedure often immediately produces relief of pain and the feeling that the phantom is moving. Mirror therapy has also been tried in patients with hemiparesis following stroke. Those who observed in the mirror the apparently normal movement of their paretic limbs achieved statistically significant improvement in strength compared to those who did not. Mirror therapy has also benefited patients with complex regional pain syndrome whose limbs are immobilized as a result of pain. Attempting to explain these observations, the authors suggest that visual stimuli produced by mirror therapy override tactile and proprioceptive stimuli. Moreover, imaging studies suggest that mirror therapy actually reverses the maladaptive reorganization of somatosensory pathways that follow limb amputation. The authors speculate that the benefit of mirror therapy in stroke rehabilitation might involve "mirror neurons," a subset of motor control neurons in the frontal and parietal cortex that fire not only when an act is performed, but also when a subject sees someone else performing the same act. The visual stimulus of mirror therapy might stimulate mirror neurons that survive a stroke but are functionally "dormant."

Conclusions: The authors conclude that their observations support the view that the brain does not consist of hierarchical modules that are hardwired and autonomous; rather, its modules are in "a state of dynamic equilibrium with each other and with the environment (including the body), with connections being constantly formed and re-formed in response to changing environmental needs."

Reviewer’s Comments: While such speculation exceeds the data at hand, one must acknowledge that the effects of mirror therapy as described are indeed provocative. (Reviewer-John C. Brust, MD).

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Keywords: Mirror Visual Feedback, Phantom Pain, Hemiparesis, Complex Regional Pain Syndrome

Print Tag: Refer to original journal article
Elevated CSF Levels of NfH May Predict Poor Px in Acute Guillain-Barré Syndrome

CSF Protein Biomarkers for Proximal Axonal Damage Improve Prognostic Accuracy in the Acute Phase of Guillain-Barre Syndrome.

Petzold A, Brettschneider J, et al:

Muscle Nerve 2009; 40 (July): 42-49

Age, need for ventilatory support, and elevated CSF NfH protein all predict poor outcome in GBS.

Background: About 20% of patients with Guillain-Barré Syndrome (GBS) lose their long-term ability to walk independently, and this tends to correlate with axonal loss in GBS. Identification of many of these patients using electrodiagnostic testing can take 2 to 3 weeks. It is important to identify these individuals as early as possible to treat early with IVIg or plasmapheresis. A biomarker to identify these patients early would be useful.

Objective: To investigate whether cerebrospinal fluid (CSF) protein biomarkers of axonal damage predict poor outcome for GBS patients.

Design: Prospective multicenter cohort study.

Participants: 132 patients (38 with GBS, 38 with a variety of neurological symptoms, 42 with headaches, and 14 with chronic inflammatory neuropathy).

Methods: All patients had lumbar puncture. GBS patients underwent lumbar puncture a median of 6 days after onset and nerve conduction studies a median of 7 days after onset of symptoms, with GBS diagnosed using accepted criteria. Two CSF markers for axonal damage were quantified for all subjects: neurofilament heavy chain levels (NfH) and CSF tau levels. Two CSF biomarkers for demyelination were quantified for all subjects: S100B and glial fibrillary acidic protein (GFAP). The time of follow-up is not clear in the publication. General functioning was assessed at follow-up using a functional grading scale. Poor outcome designated patients who were not able to walk independently at follow-up.

Results: Significantly higher CSF S100B and GFAP levels were found in GBS patients compared with controls; these did not correlate with outcome. There was no correlation of CSF total protein concentration with CSF NfH, tau, GFAP, or S100B concentrations. Among the patients with GBS, 8 patients were lost to follow-up. There were 20 GBS patients with a good outcome and 10 with a poor outcome. High CSF tau levels on admission did not predict poor outcome, but high CSF NfH levels on admission predicted poor outcome (odds ratio, 7.3), with a very wide confidence interval.

Conclusions: Pathological levels of the axonal protein biomarker NfH measured in CSF at onset of GBS predicted poor outcome with inability to walk independently.

Reviewer’s Comments: This study had several limitations, including loss of 21% of the GBS patients to follow-up, poor definition of the time of follow-up, and an extremely wide confidence interval of CSF axonal protein concentrations among the patients with poor outcome. CSF NfH concentration may prove to be a useful biomarker for poor outcome in early GBS, although a more scientifically rigorous study appears to be needed. (Reviewer-W. Steven Metzer, MD).

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Keywords: Guillain-Barré Syndrome, Axonal Damage, Prognosis, Biomarkers, CSF

Print Tag: Refer to original journal article
Depending on the percent stenosis and gender, delaying CEA for as little as 2 weeks after symptoms may reduce or eliminate the benefit of this procedure for symptomatic stenosis of 50% to 99%.

**Background:** The benefits of carotid endarterectomy (CEA) for patients with symptomatic internal carotid artery (ICA) stenosis are time sensitive. Depending on percent stenosis and gender, delays as brief as 2 weeks between symptoms and CEA reduce or eliminate the benefit of this procedure for symptomatic stenosis of 50% to 99%.

**Objective:** To ascertain the length of delays between symptoms and performance of CEA following transient ischemic attack (TIA) or stroke, and to examine trends over time.

**Design:** Retrospective population-based cohort study utilizing the Registry of the Canadian Stroke Network, which tracks strokes at 12 designated stroke centers in Ontario.

**Participants:** 105 patients who had CEA for unilateral 50% to 99% stenosis within 6 months of presenting with a non-disabling cerebral infarct or TIA. Patients with transient monocular blindness, posterior circulation events, and in-hospital events were excluded.

**Methods:** Patients were identified in the course of the ongoing prospective registry, which collected extensive clinical, demographic, imaging, and outcome data. The duration of delay between symptoms of internal carotid artery stenosis and CEA was calculated and analyzed in light of possible influencing factors including age, gender, percent stenosis, and clinical presentation (TIA vs stroke).

**Results:** Of approximately 1100 patients found to have unilateral, symptomatic ICA stenosis of 50% to 99% during initial hospitalization for the index event, 105 underwent carotid endarterectomy within 6 months. The key result was that the median time to carotid endarterectomy at these dedicated stroke centers was 30 days. About one third (38 of 105) received the operation within 2 weeks, and about half (53 of 105) within 1 month. One quarter of the patients (26 of 105) were not operated on until after 3 months. Thus, only one third were operated on within the optimal time frame, and one fourth were operated on unacceptably late. In the multivariate analysis, the only predictor of surgery <2 weeks following the index event was that the event was a TIA as opposed to a stroke. Time to CEA varied widely across institutions (median, 2 to 129 days). The reasons for the delays were not explored. Over the 3 years of the study, the median time to endarterectomy decreased from 74 days in 2003 to 21 in 2006 ($P=0.022$). The fraction of patients who had endarterectomy within 2 weeks also improved significantly - 18% in 2003, 25% in 2004, and about 45% in 2005 and 2006 ($P=0.036$).

**Conclusions:** Ontario patients, even at stroke centers, do not always receive a proven stroke preventive therapy within a time frame that allows for optimal benefit.

**Reviewer's Comments:** Such delays are not unique to Canada - they have also been seen in 2 EU nations. It should be remembered that this study addressed only inpatients who had carotid imaging. The EXPRESS and SOS-TIA studies demonstrate that with concentrated effort, the percentage of patients receiving early CEA can be increased. (Reviewer-James W. Schmidley, MD).

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**Keywords:** Carotid Endarterectomy, Secondary Stroke Prevention

**Print Tag:** Refer to original journal article
Much of the reading impairment in pure alexia occurs independently of any coexisting homonymous hemianopia.

**Objective:** To define the role of right homonymous hemianopia in the reading disability of pure alexia ("alexia without agraphia").

**Participants/Methods:** 6 patients with pure alexia and varying degrees of right homonymous hemianopia were studied. All had extremely slow reading that was worse with longer words ("word length effect"), but they could correctly identify letters. They were compared to 6 patients with hemianopic dyslexia (slow reading as a consequence of right homonymous hemianopia and inefficient eye movement strategies) and 6 healthy adults. Testing included single word reading, with recorded timing for each correct word identification; MRI analysis of brain lesions; and eye movement analysis during reading short articles from a local newspaper.

**Results:** On single word reading, pure alexics showed marked word length effect; hemianopic alexics did not. On MRI, 5 of 6 pure alexics had lesions involving the "word form area" of the left fusiform gyrus and posterior occipitotemporal cortex; none of the hemianopic dyslexics had lesions involving this region. On text reading, eye movement analysis of the pure alexics revealed increased fixation frequency, prolonged fixation durations, shortened amplitudes of rightward saccades, higher percentages of leftward corrective saccades, and pronounced effects of word length on fixation frequency and viewing time. Hemianopic dyslexics had only 3 of these defects - increased fixation frequency, prolonged fixation duration, and shortened amplitudes of rightward saccades.

**Conclusions:** Visual field defects contribute to only some of the visuo-motor impairments seen in pure alexics, who, when their visual field defects are of sufficient severity, can be said to have a combination of pure alexia and hemianopic dyslexia.

**Reviewer's Comments:** It appears that pure alexia reflects damage to posterior parts of the fusiform gyrus and occipitotemporal cortex rather than a callosal disconnection syndrome. (Reviewer-John C. Brust, MD).

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Keywords: Reading, Eye Movements, Visual Field Defect, Pure Alexia, Hemianopic Dyslexia

Print Tag: Refer to original journal article
Increased Cortical Excitability Correlates With Morning Seizures in IGE

*Why Do Seizures in Generalized Epilepsy Often Occur in the Morning?*

Badawy RAB, Macdonell RAL, et al:

Neurology 2009; 73 (July 21): 218-222

Patients with idiopathic generalized epilepsy and, particularly, juvenile myoclonic epilepsy have a tendency for early morning seizures, which is likely due to increased cortical excitability.

**Background:** It is a well-recognized phenomenon that seizures in patients with idiopathic generalized epilepsy (IGE) commonly occur in the morning, often at the time of, or shortly after, awakening. This is especially true for patients with juvenile myoclonic epilepsy (JME), who often have early morning myoclonus, and a tendency for generalized tonic-clonic (GTC) seizures also occur at this time.

**Objective:** To evaluate diurnal variations of cortical excitability in patients with epilepsy using transcranial magnetic stimulation (TMS).

**Participants:** A group of 30 drug-naive patients with a newly confirmed diagnosis of epilepsy were enrolled in this study. There were 20 patients with IGE who ranged in age from 17 to 49 years (12 women and 8 men). A diagnosis of JME was made in 10 of these patients, 9 had GTC seizures only, and 1 had juvenile absence epilepsy. All patients with IGE had experienced at least 1 GTC seizure. A focal epilepsy group of 10 patients ranged in age from 21 to 47 years (6 women and 4 men). All of these patients had lateralizing findings on EEG, normal MRI of the brain, and normal neurologic examination. A diagnosis of temporal lobe epilepsy was made in 8 and frontal lobe epilepsy in 2. A group of 10 healthy control subjects who did not have epilepsy ranged in age from 21 to 46 years.

**Methods:** All TMS studies were performed prior to initiation of antiepileptic drug therapy. Testing was performed on all patients on 2 separate days, 1 to 4 weeks apart. Testing was performed in the early morning within 1 hour of awakening and in the late afternoon. The transcranial stimulation protocol is somewhat complex and can be reviewed in the original article. The primary assessment of increased cortical excitability was based on determination of decreased short and long intracortical inhibition. In other words, a decrease in the post-stimulus period of intracortical inhibition is compatible with increased cortical excitability.

**Results:** In patients with JME, cortical excitability was increased in the morning compared to the afternoon as indicated by a decrease in both short and long intracortical inhibition. A decrease in only long intracortical inhibition was observed in the other patients with IGE. There was no observed effect in patients with focal epilepsy or the control group.

**Reviewer's Comments:** This study, using TMS, confirms that patients with IGE, particularly those with JME, have increased cortical excitability in the early morning compared to late afternoon. The underlying responsible mechanism is not understood, but this does provide objective evidence that correlates with the tendency for early morning seizures in patients with IGE and especially JME. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Idiopathic Generalized Epilepsy, Transcranial Magnetic Stimulation

Print Tag: Refer to original journal article
Natalizumab is effective in reducing relapse rate and progressive disability in relapsing multiple sclerosis, especially when the disease is highly active.

**Background:** The AFFIRM and SENTINEL studies showed the efficacy of natalizumab in relapsing multiple sclerosis (MS), both as monotherapy and in combination with interferon beta (IFNbeta)-1a. Disease activity and severity vary significantly in MS patients. Factors predicting poor prognosis in relapsing MS include age of onset >40.0 years, motor involvement at onset, >4.0 T2-weighted lesions suggestive of MS, <2.5 years between the first 2 relapses, >2.0 relapses in the first year of disease, and poor recovery from the initial 2 relapses.

**Objective:** To analyze responsiveness to natalizumab in patient subgroups in AFFIRM and SENTINEL populations, especially in reference to pre-study disease activity and demographic attributes.

**Methods:** Patients were recruited into the AFFIRM and SENTINEL studies according to previously published criteria. Data from these 2 studies were analyzed according to number of relapses during the year prior to enrollment, Expanded Disability Status Scale score, number of T2 lesions, presence of gadolinium-enhancing (Gd+) lesions, age, and gender. Highly active MS was defined as >2 relapses in the year prior to study entry and >1 Gd+ lesion at study entry.

**Results:** Of 942 patients enrolled in AFFIRM, 315 received placebo, and 627 received natalizumab. In SENTINEL, 582 patients received IFNbeta-1a alone and 589 received IFNbeta-1a plus natalizumab. In AFFIRM and SENTINEL, natalizumab reduced the relapse rate frequency by 68% and 55%, respectively, and this reduction was statistically significant across all subgroups. In the overall AFFIRM population, the probability of 12-week sustained disability progression at 2 years was 17% in the natalizumab group and 29% in the placebo group: in the SENTINEL population, the numbers were 23% in the IFNbeta-1a plus natalizumab group and 29% in the IFNbeta-1a alone group, respectively. Benefits were particularly seen in subgroups with >9 T2 lesions, >1 Gd+ lesions, women, and patients aged <40 years. In the AFFIRM study, highly active disease was present in 148 natalizumab and 61 placebo patients. In the SENTINEL study, highly active disease was present in 74 combination therapy patients and 95 IFNbeta-1a patients. In this group, natalizumab reduced the risk of relapse by 81% and disability progression by 64% in treatment-naive patients, and by 58% and 76%, respectively, in those on IFNbeta-1a.

**Conclusions:** Natalizumab is successful in significantly reducing the risk of relapses and progressive disability in patients with relapsing MS, and it is particularly beneficial in patients with highly active disease, women, and younger patients.

**Reviewer's Comments:** Based on these data, younger patients with highly active disease and patients relapsing on other immunomodulating agents should be considered for natalizumab therapy. The TOUCH program has been designed to closely monitor the safety of natalizumab, especially development of progressive multifocal leukoencephalopathy. (Reviewer-Chitharanjan Rao, MD).

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Keywords: Multiple Sclerosis, Natalizumab, Interferon, Relapse, Disability
A short-lived reduction in headache frequency is seen with botulinum toxin A injections in patients with chronic tension-type headache associated with myofascial trigger points.

**Background:** Tension-type headache (TTH) is the most prevalent of all headache disorders. Referred pain from the cervical myofascial trigger points (MTPs) has been implicated in chronic TTH (CTTH). Botulinum toxin A (BT-A) has been considered as one of the options in the treatment of MTPs. Treatment of CTTH with BT-A has yielded mixed results. However, there are no studies of use of BT-A in patients with CTTH associated with specific cervical MTPs.

**Objective:** To study the effectiveness of BT-A in patients with CTTH associated with cervical MTPs.

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

**Participants/Methods:** Patients aged >18 years who had CTTH with cervical MTPs with referred head pain matching their typical headache pattern were studied. Exclusion criteria were pregnancy, breastfeeding, daily opioid therapy, prior BT-A treatment, and contraindications to BT-A. Outcome measures were trigger point pressure algometry, range of motion assessment, pain and psychological questionnaires, daily headache diaries, and pill counts. After a follow-up period of 3 months, patients were offered participation in an open-label extension study.

**Results:** 23 patients completed the study; 12 received BT-A and 11 received placebo (isotonic saline) injections. The BT-A group reported a greater reduction in headache frequency in the initial weeks (1 to 8 weeks) by about 5 days/month, but the frequency was comparable between groups by 10 to 12 weeks ($P = 0.013$). While a positive trend was seen toward reduction in headache intensity, it was not statistically significant. However, there was no significant difference in any of the remaining measures.

**Conclusions:** BT-A treatment in CTTH with cervical MTPs shows some promise in this pilot study.

**Reviewer's Comments:** BT-A treatment in CTTH has shown mixed benefits in various studies, although none of the previous studies focused on patients with specific cervical MTPs. Another study using BT-A in patients with cervicothoracic myofascial pain showed no positive outcome. It may be worth replicating this pilot study in a larger patient population and to study any benefits of repeated BT-A treatments. (Reviewer-Chitharanjan Rao, MD).

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Keywords: Tension-Type Headache, Myofascial Trigger Points, Botulinum Toxin A

Print Tag: Refer to original journal article
Several Effective Options Available for Fighting AAG

**Efficacy of Immunotherapy in Seropositive and Seronegative Putative Autoimmune Autonomic Ganglionopathy.**

Iodice V, Kimpinski K, et al:

Neurology 2009; 72 (June 9): 2002-2008

Autoimmune autonomic ganglionopathy may be responsive to IV immunoglobulin, plasma exchange, or immunosuppressive therapy.

**Background:** Autoimmune autonomic ganglionopathy (AAG) is increasingly being recognized as a cause of primary autonomic failure. Up to 50% of patients with AAG have elevated ganglionic (alpha3-type) acetylcholine receptor autoantibody.

**Objective:** To describe the response of several patients with AAG to IV immunoglobulin (IVlg), plasma exchange, and immunosuppressive agents alone or in combination.

**Design:** Case series of patients seen at single tertiary center.

**Participants/Methods:** 6 women with AAG resulting in dysautonomia were assessed at baseline and after each course of IVlg or plasma exchange, or during immunosuppressive therapy. Patients were treated in a sequential protocol depending on clinical response, with IVlg as a first line of treatment in 5 patients. Four patients were evaluated prospectively, while 2 were assessed retrospectively. A 10-point composite autonomic severity score (CASS) was used, based on comprehensive autonomic testing that included cardiac responses to deep breathing and Valsalva maneuver, head-up tilt, and quantitative sudomotor axon reflex testing (QSART). Patients were classified based on CASS into mild (1 to 3), moderate (4 to 6), or severe (7 to 10) autonomic failure. Thermoregulatory sweat test quantitated the extent of anhidrosis. A subjective CASS (COMPASS) was completed by patients using a validated questionnaire of a wide spectrum of autonomic symptom profiles.

**Results:** 4 patients were seropositive; 2 were seronegative and had associated somatic polyneuropathy. Mean age was 49.3 ± 10.6 years. Four patients had gradual onset (>3 months), while 2 had a subacute onset (<3 months). Five patients had moderate or severe autonomic failure (CASS score, 4 to 10); and 5 had orthostatic hypotension. CASS improved by 1 to 3 points in 5 patients. Surface body anhidrosis and QSARTs improved in 4 of 6 and 4 of 5 patients, respectively. COMPASS change score improved in all 4 prospectively treated patients.

**Conclusions:** IVlg, plasma exchange, and immunosuppressive drugs alone or in combination are effective in patients with pure autonomic failure due to AAG.

**Reviewer's Comments:** Our ability to diagnose and treat patients with autonomic failure continues to improve. Therapy had been mostly symptomatic, aimed at treating orthostatic intolerance and hypotension. This report suggests that immunomodulating therapy is useful in patients with AAG, with or without positive ganglionic acetylcholine receptor antibodies. This is analogous to responses to immunomodulation in patients with seropositive and seronegative myasthenia gravis or Lambert-Eaton syndrome. Obviously, a larger, and preferably controlled, study is necessary to confirm this positive response. (Reviewer-Bashar Katirji, MD).

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Keywords: Autoimmune Autonomic Ganglionopathy, Immunotherapy

Print Tag: Refer to original journal article
Cervical traction expands, while Spurling's maneuver constricts, the intervertebral foramina.

**Background:** In 1944, Spurling described a bedside test to diagnose cervical root compression. During this maneuver, the head is first slightly extended, rotated, and laterally flexed and then compressed downward. A positive sign (reproducible radicular pain) is diagnostic of cervical radiculopathy. Cervical traction has been used for years to treat radicular pain triggered by cervical root compression. These maneuvers theoretically lead to narrowing or enlarging the intervertebral foramina.

**Objective:** To evaluate the dimensions of the intervertebral foramina in healthy subjects in the neutral position and during the above-mentioned maneuvers.

**Participants:** 23 healthy subjects (12 men) with an age range of 19 to 34 years (mean, 24.5 years).

**Methods:** Kinematic MRI was performed to measure the foraminal cross-sectional area (FCSA) of the right C4-5, C5-6, C6-7, and C7-T1 intervertebral foramina during 4 head positions: neutral, axial compression in neutral position (using 7 kg), Spurling test (extension [12.79°], rotation [63.36°], lateral flexion [28.49°] with compression using 7 kg compression), and traction (using 12 kg). FCSA was measured in all 4 head positions while subjects were lying in the MRI equipment. In addition, the foramen shape was assessed by comparing anteroposterior dimensions during neutral position and other maneuvers.

**Results:** With the Spurling test, the FCSA significantly decreased to approximately 70% of control (neutral position) at all cervical levels tested ($P < 0.001$ to $P < 0.01$). With cervical traction, the FCSA significantly increased to approximately 120% of control at C4-5, C5-6, and C6-7 level ($P < 0.001$ to $P < 0.05$) but did not change at the C7-T1 level. Axial compression in neutral position had no significant effect on FCSA at all levels. In addition, there were significant differences in the foramen shape, as measured by the anteroposterior dimensions, between cervical traction and Spurling test at C4-5 and C5-6 levels ($P < 0.05$) but not at C6-7 and C7-T1.

**Conclusions:** Cervical traction and Spurling test produce significant enlargement and reduction, respectively, of the surface area and shape of the cervical intervertebral foramina, particularly at the mid-cervical spine.

**Reviewer's Comments:** We have used Spurling's test (to diagnose) and cervical traction (to treat) for cervical radiculopathy for decades without strong evidence for anatomical changes that support these maneuvers. This study supplies us now with good proof that these procedures do actually change (enlarge or narrow) the intervertebral cervical foramina in healthy individuals. Although MRI underestimates the size of the intervertebral foramen, and these findings may not apply to the diseased or aging cervical spine, this study will remain a valuable reference. (Reviewer-Bashar Katirji, MD).

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**Keywords:** Cervical Spine Anatomy, Clinical Tests, Traction, Compression, Spurling Test

**Print Tag:** Refer to original journal article
Background: Ullrich congenital muscular dystrophy (UCMD) was first described in 1930. Clinical features include contractures of proximal and hyperlaxity of distal joints, proximal weakness, torticollis, scoliosis, respiratory failure, and normal intelligence. UCMD was first believed to be quite rare, but mutation analysis now reveals that it is one of the most common forms of congenital muscular dystrophy, with variable clinical features and course. A variable deficiency in most, or a rare complete absence, of collagen VI at the basal lamina with preserved expression in the interstitial connective tissue is present. Mutation analysis has now revealed recessive and dominant mutations of COL6A1, COL6A2, and COL6A3 genes, thus accounting for the variable expressivity. Collagen VI deficiency appears to result in mitochondrial permeability transition pore dysfunction and increased muscle apoptosis.

Objective: To describe the clinical course, complications, and prognosis of UCMD with attention to significant life-changing events such as loss of ambulation, respiratory insufficiency, and death.

Methods: Records of 13 patients with UCMD who had reached the age of at least 15 years were reviewed. Attention was paid to age at symptom onset, presenting symptoms, mobility, contractures, scoliosis, respiratory function, and feeding difficulties.

Results: Mean age at onset of symptoms was 12 months, with a range from birth to 3 years. About half the patients were symptomatic at birth. Delayed motor milestones were the most common presenting symptom. Torticollis was present in only 2 patients. A pattern of proximal to distal weakness was present in all patients, contractures developed in all but 1 patient, and scoliosis developed in all but 1 patient. Independent ambulation was achieved by 8 patients at a mean age of 20 months, and 5 learned to walk with support. Constant wheelchair use was required at a mean age of 11 years in 9 patients. Four individuals had maintained at least some ability to ambulate independently. Forced vital capacity was abnormal in all patients by age 6 years, and declined at a mean rate of about 3% per year. Assisted nocturnal ventilation was required in about three fourths of patients (9 of 13) at a mean age of 14 years. Development of feeding difficulty was common, and 3 patients required gastrostomy. Two patients had died due to respiratory insufficiency at 10 and 15 years, respectively. Five patients were aged ≥20 years, and 1 was alive at age 30 years.

Conclusions: The decline in motor and respiratory function was most rapid during the first decade. The rate and degree of deterioration did not always correlate with the severity of presenting symptoms.

Reviewer’s Comments: UCMD is a more common and variable condition than once thought. Symptoms are present at birth in about half of all patients. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Ullrich Congenital Muscular Dystrophy, Natural History, Clinical Course

Print Tag: Refer to original journal article
Screen for Auditory Neuropathy in At-Risk Newborn Infants

**Auditory Neuropathy: Unexpectedly Common in a Screened Newborn Population.**

Dowley AC, Whitehouse WP, et al:

Dev Med Child Neurol 2009; 51 (August): 642-646

Perform auditory brainstem response testing in infants with risk factors that include gentamycin exposure, sepsis, meningitis, and hyperbilirubinemia.

**Background:** Auditory neuropathy is detected by performing auditory brainstem response testing, which will reveal an abnormal or absent response in patients who have intact otoacoustic emissions or cochlear microphonic. In other words, cochlear function is intact, but there is a defect in transmission from the cochlea to the brainstem via the auditory nerve. As a result, there is impaired hearing, absence of acoustic reflexes, and poor speech perception. The incidence of auditory neuropathy in people with profound hearing loss is about 10%. Since newborn hearing screening has become standard in some areas, a diagnosis of auditory neuropathy has been documented in children at risk with a prevalence of 0.23%.

**Objective:** To identify infants with auditory neuropathy via a local newborn hearing screening program in the UK, and to identify associated risk factors.

**Design/Participants:** Prospective newborn hearing screening program evaluating 45,050 infants from 2002 to 2007. In addition to standard otoacoustic emission testing, auditory brainstem response testing was also performed.

**Methods:** Medical records were reviewed to identify risk factors in infants who were identified as having severe to profound hearing impairment. Hearing testing, including auditory brainstem response testing, was repeated on this group of patients at age 3, 9, and 12 months to determine if there was improvement over time.

**Results:** A total of 30 infants were identified with suspected severe to profound hearing loss (16 boys and 14 girls). Auditory neuropathy was identified in 12. The annual incidence of severe to profound hearing loss was 0.67/1000 births, and 0.27/1000 for auditory neuropathy. The most significant risk factors associated with auditory neuropathy are hyperbilirubinemia, sepsis, and exposure to gentamycin. Of those with auditory neuropathy, one third had experienced hyperbilirubinemia, half had sepsis, and three fourths had received gentamycin. Hearing maturation or improvement occurred in 2 of 12 children with auditory neuropathy and in 1 of 18 with hearing loss not due to auditory neuropathy.

**Reviewer's Comments:** Auditory neuropathy appears to be present in a distinct subgroup of infants who are found to have severe to profound hearing loss. Important risk factors include gentamycin exposure, sepsis, meningitis, and hyperbilirubinemia. This report documents the importance of performing auditory brainstem response testing in infants with these risk factors. Some infants with auditory neuropathy may improve with time. (Reviewer-Gregory B. Sharp, MD).

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Keywords: Auditory Neuropathy, Brainstem Response Testing, Newborns

Print Tag: Refer to original journal article
Presence of circulating nicotinic ganglionic acetylcholine receptor antibodies is associated with a wide variety of cancers and autoimmune neurologic syndromes.

**Background:** Presence of circulating, nicotinic, ganglionic, acetylcholine-receptor autoantibodies (ngAChRAb) is known to be associated with thymoma and small-cell carcinoma of the lung, as well as subacute or chronic dysautonomia.

**Objective:** To report further oncologic and neurologic associations.

**Design:** Case-control study.

**Participants:** Of 15,000 patients whose Mayo Clinic physicians ordered tests for neurologic paraneoplastic autoantibodies from 2005 to 2007, 155 (1%) who were seropositive for ngAChRAb were studied. Serum samples from age- and sex-matched healthy people (n=173) and neurologically healthy patients with lung cancer (n=245) and Sjögren's syndrome or systemic lupus erythematosus (n=39) served as controls.

**Results:** Median age of seropositive patients, when neurologic symptoms began, was 65 years (range, 17 to 103 years), and 55% were men. Cancer was found in 24 (30%) of 78 seropositive patients evaluated for it, but in 15 of these, cancer was known to have been present before the ngAChRAb. There was no correlation between the antibody titer and presence of cancer. The most common tumor type was adenocarcinoma (breast, prostate, lung, etc). The onset of neurologic symptoms was subacute in 46% of seropositive patients and insidious in 54%. The likelihood of an autoimmune cause of a patient's neurologic symptoms depended on the antibody titer: 92% of patients with a high titer (≥1 nmol/L) and 82% with a medium titer (0.1 to 0.99 nmol/L), but only 54% with a low titer (<0.1 nmol/L), had an autoimmune neurologic syndrome. Peripheral neuropathy was the most common neurologic accompaniment of seropositivity (28%); 21% of seropositive patients had dysautonomia, and 17% had cerebral symptoms. Peripheral neuropathy took the form of sensorimotor and sensory polyneuropathy, polyradiculopathy, and cranial neuropathy; dysautonomia of pandysautonomia and limited syndromes; and cerebral symptoms of dementia, psychosis, and parkinsonism. Twelve of 16 seropositive patients treated with immunotherapy improved, but follow-up lasted only a few months. Of control patients, 8.0% with lung cancer, but <0.5% of those in the other 2 groups, were seropositive.

**Conclusions:** Presence of ngAChRAb is associated with a wide variety of cancers and autoimmune neurologic syndromes.

**Reviewer's Comments:** This study provides another illustration of the principle that neural autoantibodies are associated with, not a single neurologic syndrome, but with several. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Paraneoplastic, Autoantibody, Nicotinic Ganglionic Acetylcholine Receptor

Print Tag: Refer to original journal article
In patients with idiopathic, adult-onset lower motor neuron disease of >4 years’ duration, extent of weakness determines prognosis. Those with only segmental weakness have a good prognosis, but those with generalized weakness have a poor one.

**Objective:** To learn what determines prognosis in indolent, sporadic, adult-onset lower motor neuron disease (LMND).

**Design:** Inception cohort.

**Participants:** Inclusion criteria were age at disease onset of >18 years, lower motor neuron signs, and signs of muscle denervation on EMG. Exclusion criteria were disease duration of <4 years; respiratory failure at study entry (to avoid including patients with aggressive disease); family history of motor neuron disease; molecular-genetic diagnosis of Kennedy's disease or spinal muscular atrophy; past history of poliomyelitis, spinal radiculopathy, diabetic amyotrophy, thyrotoxicosis, and hyperparathyroidism; upper motor neuron signs (to exclude amyotrophic lateral sclerosis [ALS]); clinical sensory signs; and motor conduction block on EMG.

**Methods:** Patients were followed for 6 years. Disease classification was based on extent of clinical findings of LMND: progressive muscular atrophy (PMA) was diagnosed when weakness was generalized (3 or 4 limbs involved); and segmental muscular atrophy (SegMA) when only muscles of the arms or legs were involved.

**Main Outcome Measures:** Severity and extent of muscle weakness, assessed clinically; respiratory function, assessed by vital capacity; and functional impairment, assessed by the ALS Functional Rating Scale.

**Results:** The study enrolled 32 patients: 10 with PMA and 22 with SegMA. The arms were involved at onset in 19 of 21 patients with SegMA. At baseline, weakness was asymmetric in all but 4 patients, and weakness and functional impairment were worse in PMA than in SegMA. During follow-up, 3 patients (2 with PMA and 1 with SegMA) developed ALS; their mean age at disease onset (59 years) was higher and their median disease duration (8 years) was shorter than those of other patients with PMA (37 and 17 years, respectively). All 10 patients who entered the study with PMA and the patient whose SegMA turned into ALS developed widespread, severe weakness and severe functional impairment as time passed; 5 acquired bulbar signs; 6 developed respiratory failure; and 5 died. Although muscle weakness spread to adjacent myotomes in some patients with SegMA, none developed severe weakness or functional impairment, bulbar signs, or respiratory failure, and none died. The extent of denervation of muscle on EMG did not differ between groups.

**Conclusions:** In patients with idiopathic, indolent, adult-onset LMND, the extent of weakness 4 years after onset determines prognosis. Those with only segmental weakness have a good prognosis, but those with generalized weakness have a poor one.

**Reviewer's Comments:** Sporadic, adult-onset, indolent LMND is a common clinical problem in neuromuscular disease. Once multifocal motor neuropathy with conduction block has been ruled out, these results will be useful in determining a patient's prognosis. It is important to remember that involvement is considered generalized or segmental by the extent of clinical findings, not EMG findings. (Reviewer-Marc D. Winkelman, MD).

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Keywords: Lower Motor Neuron Syndromes, Adult Onset, Prognosis

Print Tag: Refer to original journal article