Possible Length-Dependent Conduction Slowing in IgM Neuropathy

In autoimmune demyelinating neuropathies (such as chronic immune demyelinating polyneuropathy and multifocal motor neuropathy), demyelinating lesions are generally random and conduction slowing is not length-dependent (Neurology 1991; 41:617). These authors aimed to determine whether IgM-associated neuropathy—an acquired, autoimmune, demyelinating neuropathy—instead involves nonrandom, length-dependent conduction slowing. They compared neurophysiologic findings in 22 patients with IgM neuropathy (16 of whom had anti-MAG antibodies), 20 fairly well-matched patients with CIDP, and 36 healthy controls.

Using a technique of short-segment stimulation and conduction studies in the arm and leg, they found significant differences between the IgM and CIDP patients in proximal and distal nerve conduction. There was evidence for greater delay than proximal slowing of conduction and axonal loss in the IgM patients than in the CIDP patients (measurements were normalized using average values of control measurements). These findings suggest a different pathologic mechanism in IgM neuropathy than in another autoimmune demyelinating neuropathies and raise questions about a possible primary axonopathy with secondary demyelination.

Comment:

These authors and others have noted that IgM neuropathies have disproportionately long distal latencies, suggesting possible length-dependent pathologic changes (Brain 1994; 117:941, Muscle Nerve 1998; 21:55, and Muscle Nerve 2000; 23:164). If true, this length dependency would require a different pathologic mechanism for this acquired demyelinating neuropathy, such as axonal degeneration with secondary demyelination (Ann Neurol 1981; 9:575). Generally, the disproportionate slowing in the most distal nerve segments has been explained by compression at pressure sites. Compression occurs most commonly in the distal parts of nerves, causing a defective blood-nerve barrier, which presumably would allow increased access of the pathogenic anti-IgM antibodies to the endoneurium (Kimura J. Peripheral Nerve Diseases: Handbook of Clinical Neuropathology, Vol. 7: Elsevier B.V.; [in press]:749).

This argument is bolstered by nerve conduction studies in these patients, which generally show that the median nerve has the longest distal latency. The current findings show that the compression explanation may not be the only one to account for the neurophysiologic changes. There appears to be a real gradient not only in conduction slowing (an electrophysiological surrogate for demyelination), but also in axonal damage. This opens the door for new pathologic theories of nerve damage in acquired chronic neuropathies, because most display random demyelinating lesions with secondary axonal loss and equal degrees of proximal and distal slowing (Neurology 1991; 41:617). Aside from the pathology considerations, further study and better understanding of the mechanisms of nerve damage may lead to better treatments, as the current treatments for anti-MAG and IgM neuropathies are far from ideal (Nosworthy JL. Neurologic Therapeutics: Principles and Practice. Martin Dunitz; 2003:1361).

—John J. Kelly, MD


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What Is the Diagnosis? Arm Weakness After T5 Paraplegia

A 38-year-old-old man with a 10-year history of T5 paraplegia due to a motor vehicle accident complained of acute painless swelling and limited range of motion of the right shoulder. He noted that his hands were numb to hot water and that phlebotomy was not painful. Physical examination revealed loss of sensation for all modalities to the T4 level, with decreased sensation of pain and temperature extending to the T2 level and also proximally in the right arm. Right-shoulder x-ray demonstrated significant destruction of the humeral head with heterotopic ossification (see image).

What is the diagnosis? Send your ideas to jwnc$ero@mms.org. The final diagnosis will appear in the next issue.

— Sasbank Prasad, MD, and Grant T. Liu, MD

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But the relevance of these studies to clinical practice, where the goal is long-term freedom from seizures and adverse drug effects, is questionable. This non-systematic review of several newer AEDs focuses on retention rate — the percentage of patients still taking the drug after a specified period — as a reasonable measure combining efficacy and tolerability.

The author cites one study showing that at 3 years, 29% of participants remained on lamotrigine, 30% on topiramate, and <10% on gabapentin. By contrast, for levetiracetam, a study by the author demonstrated a 3-year retention rate of 37%, and a newer one that has since been published (J Neurol Neurosurg Psychiatry 2006; 77:101) yielded an "estimated" 3-year retention rate of 58%.

**Comment:**
The author makes a convincing case that retention rate is a reasonable measure of real-world clinical efficacy and appropriately qualifies this conclusion by advocating individualization of therapy based on comorbid conditions and pharmacokinetic properties, including drug interactions. It is not clear, however, that the use of retention rate across different study populations allows reliable comparisons among the drugs discussed. Specifically, insufficient information is given to justify the statement that retention rate is higher for levetiracetam, the drug manufactured by the article sponsor, than for lamotrigine or topiramate. The dilemma remains that the more rigorously controlled a study is, the less likely it is to reflect real-world practice.

— Edward B. Bronfman, MD

Dr. Bronfman has received honoraria and research support from UCB Pharma, manufacturer of levetiracetam; GlaxoSmithKline, manufacturer of lamotrigine; and Pfizer, manufacturer of gabapentin.


Real-World Performance of New Antiepileptic Drugs

In carefully controlled, short-term clinical trials, all newly approved antiepileptic drugs (AEDs) are superior to placebo in reducing seizures in adults with medically refractory focal epilepsy.
Case Diagnosis:  
Arm Weakness  
After T5 Paraplegia

In the patient with arm weakness after T5 paraplegia (see JW Neurology June 2006, p. 7), spine MRI revealed a large syrinx from C1 (image 1) to T10 (image 2), and significant kyphosis. This classic example of a Charcot neuropathic shoulder associated with post-traumatic syringomyelia likely resulted from repetitive trauma in an insensate joint as well as from dysregulated sympathetic outflow with vasmotor changes in the limb. If less severe, neurosurgical decompression of the syrinx might have been beneficial.  — Sasbank Prasad, MD, and Grant T. Liu, MD

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Image 1 (above): Spine MRI revealed a large syrinx that extended from C1 (arrow).  
Image 2 (right): The syrinx extended to T10 (arrow).

cause was identified in 66% of cases: enterovirus (26%), herpes simplex virus 2 (HSV-2; 17%), varicella-zoster virus (VZV; 8%), and tick-borne encephalitis virus (TBEV; 6%); other viruses, bacteria, parasites, or medication caused the rest. PCR testing identified the causative agent in 43% of the cases — a much higher diagnostic yield than culture (12%) or CSF antibody testing (4%). Most patients with HSV-2 meningitis were women.

Most of the 42 encephalitis patients (median age, 53) presented with altered mental status. A cause was identified in 36% of cases: VZV (12%), HSV-1 (9%), and TBEV (9%) were the primary causes; mumps, Mycoplasma pneumoniae, and Chlamydia pneumoniae accounted for the remaining cases with identified causative agents. PCR testing established the diagnosis in 17% of the 42 cases.

COMMENT:
These findings confirm prior work that identified enteroviruses as the leading cause of aseptic meningitis and more recent PCR-based studies that indicated that HSV-2 is also an important etiology in adults. TBEV, endemic in parts of Europe, was a common cause of aseptic meningitis and encephalitis in this Finnish study, as was VZV, which occurred in several patients without skin lesions. In earlier studies, most encephalitis cases could not be traced to a specific pathogen despite comprehensive evaluation. Whether this low diagnostic yield reflected the influence of as-yet unidentified pathogens or limitations in current tests remains to be determined. — Cheryl A. Jay, MD


Risk, Recognition, and Prevention of Kernicterus

Kernicterus (neonatal bilirubin encephalopathy) is a serious and disabling disease that may be increasingly common in industrialized nations. In this retrospective chart review from one Canadian hospital, the authors identified 12 infants admitted between 1990 and 2000 with elevated unconjugated bilirubin levels (>23.4 mg/dL) and with the pattern of brainstem and basal-ganglia injury suggestive of kernicterus. Three fourths were boys, and 11 were full term. All but one had been discharged home 1 day after birth and returned at 3 to 5 days of life to the hospital with lethargy and toxic bilirubin levels. Seven had glucose-6-phosphate dehydrogenase (G6PD) deficiency, three were dehydrated, one was septic, and one had galactosemia and hemolysis. Of the children tested, three of nine had abnormal visual evoked potentials, seven of 10 had abnormal brainstem auditory evoked potentials, and five of five had abnormal EEGs. MRI suggested kernicterus in two of four, as did CT in one of five. It is not clear at what age these tests were performed. On follow-up in 10 of 12 patients (the timing and nature of which is difficult to judge), four had hypertonia, five hypotonia, three ataxia, and only two had vertical-gaze paresis.

COMMENT:
It is difficult to place the somewhat uneven data collected in this study within the context of previous studies of kernicterus. Only five children are represented in the outcome table, and their findings are not correlated with test results that are reported elsewhere in the article. It is unclear how many actually had kernicterus (only two manifested vertical-gaze palsy, and only two had consistent MRI results, and it is unclear whether these were the same two patients). With so many patients lost to follow-up, with an uneven application of tests, and with uncertainty as to which clinician followed up with which patient, and when, it appears misleading to express outcome variables with a denominator of 12. The conjunction of hyper- and hypotonia is perplexing — were some infants actually hypertonic and weak? The authors do join other researchers who have recently drawn attention to (1) the possibly increasing danger of kernicterus in neonates with early hospital discharges and inadequate early follow-up and (2) the important fact that jaundice due to G6PD deficiency may be late-presenting. Otherwise, the usefulness of this article in advanc-