When It’s Not ALS!
Pure Motor Syndromes

Richard J. Barohn, MD
Jonathan S. Katz, MD
David S. Saperstein, MD
Vinay Chaudhry, MD
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When It’s Not ALS!
PURE MOTOR SYNDROMES

Faculty

Richard J. Barohn, MD
Chairman and Professor
Department of Neurology
University of Missouri – Kansas City School of Medicine
Kansas City, Kansas

Dr. Barohn is a graduate of the 6-year BA/MD program at the University of Missouri – Kansas City School of Medicine. He completed a medicine internship at Wilford Hall United States Air Force Medical Center at Lackland Air Force (USAF) Base in San Antonio, Texas prior to serving as General Medical Officer for the USAF. He completed a neurology residency there, then performed a neuromuscular fellowship at Ohio State University, and is now Chair of the Department of Neurology at the University of Kansas Medical Center. Dr. Barohn is board-certified by the American Board of Electrodiagnostic Medicine and the American Board of Psychiatry and Neurology with added qualifications in clinical neurophysiology. He is a member of many professional societies, including the American Academy of Neurology, the American Neurological Association, and the AAEM. His present research focuses on myopathies, motor neuron disease, peripheral neuropathies, and myasthenia gravis. In 2000, he was awarded the Alumni Achievement Award for Medicine from the University of Missouri – Kansas City.

David S. Saperstein, MD
Assistant Professor
Department of Neurology
University of Kansas Medical Center
Kansas City, Kansas

Dr. Saperstein earned his medical degree from Boston University School of Medicine, and performed both his internal medicine and neurology residencies at Wilford Hall Medical Center. He is currently an assistant professor in the Department of Neurology, and in the Department of Pathology and Laboratory Medicine at the University of Kansas Medical Center. His academic interests include the clinical aspects of management of neuromuscular disorders with a special interest in the classification and identification of chronic acquired demyelinating polyneuropathies. In addition to membership in the AAEM, Dr. Saperstein is also a member of the Peripheral Nerve Society, the American Academy of Neurology, and the World Muscle Society.

Jonathan S. Katz, MD
Assistant Professor
Department of Neurology
Stanford University School of Medicine
Palo Alto, California

Dr. Katz is currently an assistant professor in the department of neurology and Co-director of the Neuromuscular Disease Clinic at Stanford University and the director of the EMG laboratory at the Palo Alto VA Medical Center. He is certified by the American Board of Psychiatry and Neurology, and also holds added qualifications in clinical neurophysiology. Dr. Katz is active in several organizations, including the American Academy of Neurology, the California State Myasthenia Gravis Association Medical Advisory Board, and the Stanford University Medical School Faculty Senate. He is an ad hoc reviewer for several journals, including Neurology, Muscle & Nerve, and Lancet. He is also a recipient of the Lisia Forno Award for Outstanding Teachers.

Vinay Chaudhry, MD
Professor
Department of Neurology
Johns Hopkins School of Medicine
Baltimore, Maryland

Dr. Chaudhry is currently a professor of neurology and Director of the Neuromuscular Division at the Johns Hopkins University School of Medicine in Baltimore. In addition, he is Co-Director of the Neurology EMG Laboratory and Program Director of the clinical neurophysiology residency there. Dr. Chaudhry received his bachelor of medicine and bachelor of surgery degrees from the All India Institute of Medical Sciences in New Delhi, and went on to study internal medicine in the UK. At the University of Alabama at Birmingham’s School of Medicine, Dr. Chaudhry studied neurology and became Neurology Chief Resident. Dr. Chaudhry is certified by many organizations, including the American Board of Psychiatry and Neurology (Neurology and Neurology with added qualifications), the Royal College of Physicians, and the ABEM. He is a reviewer for several journals and is on the Editorial Board of Neurologist and Muscle & Nerve.

Authors had nothing to disclose.

Course Chair: Richard J. Barohn, MD

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OBJECTIVES
After attending this session, participants will be able to: (1) describe demyelinating acquired motor neuropathy syndromes that can resemble amyotrophic lateral sclerosis (ALS), specifically multifocal motor neuropathy (MMN); (2) discuss the variant multifocal acquired sensorimotor neuropathy and review treatments; (3) describe the phenotype of patients who present with bilateral proximal arm weakness (brachial amyotrophic diplegia) and its relation to ALS; (4) describe motor neuropathies that present with hand weakness, but have only axial neurophysiologic findings – multifocal acquired motor axonopathy and describe this entities relationship to MMN and ALS, and treatment implications; (5) describe pure lower motor neuron syndromes such as progressive muscular dystrophy (and its relationship to ALS), juvenile monomelic amyotrophy in teenagers and young adults, and adult “distal” spinal muscular atrophy (or hereditary motor neuropathy); and (6) describe the pure or predominant upper motor neuron disease primary lateral sclerosis and its relation to ALS.

PREREQUISITE
This course is designed as an educational opportunity for residents, fellows, and practicing clinical EDX consultants at an early point in their career, or for more senior EDX practitioners who are seeking a pragmatic review of basic clinical and EDX principles. It is open only to persons with an MD, DO, DVM, DDS, or foreign equivalent degree.

ACCREDITATION STATEMENT
The AAEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

CME CREDIT
The AAEM designates attendance at this course for a maximum of 3.5 hours in category 1 credit towards the AMA Physician’s Recognition Award. This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he/she actually spent in the activity. The American Medical Association has determined that non-US licensed physicians who participate in this CME activity are eligible for AMA PMR category 1 credit.
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Lois Margaret Nora, MD, JD  
*Rootstown, Ohio*
Primary lateral sclerosis is considered a progressive disorder of either corticospinal or corticobulbar UMN dysfunction for which no etiology is found. There continues to be an ongoing debate regarding the existence of PLS as a separate disease process distinct from ALS or whether it is simply a predominantly UMN manifestation of ALS. Several factors cause difficulties in definitively answering this question. The underlying etiology of ALS and PLS is unknown, and there is no specific diagnostic marker for either. In addition, there are only a handful
of PLS patients who have been autopsied in order to determine if the pathology is indeed restricted to the UMN system. Therefore in practical terms, while the patient is alive, the distinction between these motor neuron disorders is based on phenotype recognition, natural history, and the indirect tests currently employed to implicate involvement of upper and lower motor neurons. As some patients with ALS ultimately are found to have another diagnosis, perhaps PLS should be considered a syndrome composed of heterogeneous diseases, some of which may become apparent over time. On the other hand, the use of PLS as a diagnostic disease category is useful in approaching a patient with a progressive UMN disorder, particularly in regards to determining prognosis.

HISTORY

The earliest reported cases of possible PLS have been attributed to Erb in 1875. In 1902, he reviewed 10 autopsied cases and used the terms “spinal” or “spasmodic” paralysis. However, 4 of the 10 cases were familial and therefore the cases probably fell into the hereditary spastic paraplegia category. Charcot, who described the first cases of ALS, wrote a long discussion regarding Erb’s early cases and described several of his own and preferred the term “spasmodic tabes dorsalis.” He was not prepared to consider PLS a distinct disease entity at that time, pending analysis of further cases. A long excerpt from one of Charcot’s translated lectures is still instructive:

Nevertheless, gentlemen, it is not uncommon clinically to meet with a certain number of cases in which symptoms of spasmodic paralysis ... occur unaccompanied ... by any other symptoms. ... The affection is especially characterized also by its slow evolution, and by a marked tendency to progressive invasions of the upper extremities. To some physicians, of whom I am one, this spasmodic paraplegia seems to be a special variety, so that we are led to think that these are not common cases of transverse myelitis accidentally deprived of their usual features. ... But it is believed that the affection in question is peculiar, autonomous, and probably dependent on a specially localized lesion. Erb was the first to put forward this opinion in 1875. I soon followed him, as my lectures in 1876 testify. This alleged special affection was designated by Erb spasmodic spinal paralysis. ... I proposed the name of spasmodic tabes dorsalis, since the term ‘spasmodic paralysis’ represents only a symptom common to several spinal diseases. The description given by Erb differs, however, in no essential feature from that which I subsequently traced ... I observed that all cases of symmetrical sclerosis without participation of the anterior grey cornua were of old date. ‘It would be necessary,’ I remarked, ‘to revive partly effaced remembrances. We must therefore, before we express an opinion on this matter, await the modifying influence of new observations.’ Up to the present time, gentlemen, as I shall show shortly pathological investigation has not yet furnished any proof, and hence the solution of the problem remains in suspense. Meanwhile the clinical description deserves to exist alone.

Throughout the first half of the 20th century, a number of others attempted to address the PLS issue. Wilson, in his authoritative textbook of neurology, was unconvinced that PLS was a distinct entity. He stated:

Divergent views are still held in regard to so-called primary lateral sclerosis, the ‘spastic spinal paralysis’ of Erb. Some consider it belongs to a separate class from Charcot’s disease, taking presence or absence of muscular atrophy for the criterion; but since ‘pure’ atonic atrophy often co-exists with slight pyramidal lesions only disclosed after death, spasticity without wasting might well represent the opposite extreme of the same condition. Types of Charcot’s disease pass by easy gradations from almost monosymptomatic muscular atrophy to spastic weakness with little sign of the other, notably at an earlier period; to go a step farther in either direction would seem not only allowable but requisite. If this is permitted, ‘primary lateral sclerosis’ becomes a variant of the disease without involvement of lower neurons, and ‘nuclear amyotrophy’ another, with intact corticospinal paths ... for these several reasons the conception of ‘pure’ spastic paralysis caused by progressive decay in corticospinal neurons, of endogenous source alone, and rigidly confined to that system has little to substantiate it. At least some examples are eventually proved to belong to the group of Charcot’s disease, and this may well be true of all.

Rowland and Swash consider the modern era of PLS literature to begin with the paper by Fisher in 1977. Fisher described an autopsied case of presumed PLS and found degeneration of the corticospinal tracts. Since that paper, there has been a heightened interest in the controversial topic of PLS. However, to a large extent, medicine is no closer to solving the dilemma Charcot and Wilson described in the late 19th and early 20th centuries.

EPIDEMIOLOGY AND DEMOGRAPHICS

How Often is Primary Lateral Sclerosis Diagnosed?

Primary lateral sclerosis is an uncommon diagnosis. The best way to get an idea of how often PLS is diagnosed is to look at the larger retrospective series. In the Canadian series by Pringle
and colleagues, of 500 motor neuron disease patients, 8 patients were diagnosed with PLS over a 10-year time span (approximately 1.6%). Le Forestier and colleagues reported 20 PLS patients out of 450 motor neuron disease patients over 5 years (4.4%), and in this author’s Texas series, 13 PLS and 572 ALS patients were diagnosed over 5 years (2%). Therefore, from this small number of series, it appears that between 2% and 4% of patients seen in adult motor neuron disease clinics will be diagnosed with PLS.

Age of Onset

The typical age of onset of PLS is in the late 40s to early 50s, similar to ALS. In this author’s series, mean age of onset was 46.3 years (range 36-73 years). In the Pringle series, mean age of onset was 50.4 years (range 35-66 years). In the Salpetriere Parisian series, mean age of onset was 53.4 years (range 26-64 years). In a large National Institute of Health (NIH) series of 25 patients, mean age of onset was 45.4 years.

Gender

Some series show a male predominance while in others, both genders are equally affected. In the French series, 15 out of 20 cases were male. The Dutch series described 9 males and 1 female. This author’s Texas series of 13 patients had 9 men and 4 women. The Canadian and NIH series both had 50% male to female ratio, while the Marseilles series by Gastaut had 2 males and 3 females.

CLINICAL FEATURES

The two most common presentations in patients diagnosed with PLS are spastic bulbar paralysis, and leg weakness with spasticity. The syndrome of slowly progressive leg weakness and spasticity is more common and accounted for in 56% of the presentations in the NIH series. In the Salpetriere series, 50% (10 out of 20) had bulbar onset. However in the Canadian series of Pringle, only 1 out of 8 had bulbar onset, and in the Dutch series 9 out of 10 had limb onset. This author’s Texas series was similar in that 12 had leg onset, 1 had bulbar onset, and of the limb onset patients, only 1 progressed to bulbar symptoms. The syndrome can progress from bulbar to limb involvement or from limb to bulbar. In the limbs, leg onset is by far more common than arm/hand onset, which, while rare, does occur. Patients can have long periods of plateau in one region with nonprogression to other regions. Rarely patients can present with a progressive hemiparesis (arm and leg) before progressing to the opposite side or to the bulbar region.

In the leg onset syndrome, symptoms usually begin in one leg and then spread to the opposite leg so that patients have a paraplegia for a period of time before further progression. In some patients, simultaneous bilateral leg onset or simultaneous limb and bulbar onset is reported. Spasticity accounts for the most of the limb dysfunction in the early stages, as opposed to weakness; in ALS weakness is usually more prominent than spasticity. Therefore, patients may not complain of weakness, but notice stiffness, clumsiness, or poor coordination and dexterity as the initial limb symptoms. When limb weakness occurs it is usually in a UMN dysfunction pattern, as described later. Some authors have described cases with slow progression from bulbar involvement to leg or from leg to bulbar without mentioning significant arm involvement. However, even in these cases, brisk reflexes and other UMN signs are noted in the arms implicating arm involvement.

Bulbar symptoms consist of dysarthria initially, then dysphagia, and are often associated with emotional lability, and eventually inappropriate laughing or crying, which is labeled “pseudo-bulbar” affect. Because the dysarthria is predominantly UMN and not associated with tongue atrophy or fasciculations, some refer to all of the bulbar symptoms as pseudo-bulbar. The dysarthria can progress to anarthria. Dysphagia can progress in a way that the patient requires a feeding tube even before there is significant limb involvement. In the Salpetriere series, the authors found the dysphagia often remained moderate. It is interesting that some patients who become anarthric can still swallow. However, this is unusual and in this author’s experience most bulbar patients eventually require mechanical feeding.

The recent NIH series provides the most detailed information about the timing of progression. In this series, 14 out of 25 patients presented with spasticity of the legs and they were labeled the “ascending group.” Symptoms spread to the second leg on average within 1.7 years after the first leg (range 1-4 years) and to the hands in 3.6 years later (range 1-6 years) and to the bulbar region 1.5 years (range 0.5-5 years) after arm symptoms.

While most cases of limb onset eventually progress to bulbar and most cases of bulbar onset eventually progress to limb, there are probably cases that remain restricted to these regions for as long as the patient is followed. How often this occurs is unknown.

While cramps, fasciculations, and atrophy are usually believed to be signs of LMN dysfunction and therefore incompatible with pure PLS, some authors report these symptoms and signs in their patients. Le Forestier and colleagues reported 9 out of 20 patients had fasciculations and cramps, supporting their argument that PLS is similar to ALS.

As a result of corticospinal and corticobulbar involvement, patients will demonstrate UMN signs consisting of spasticity, slow movement of limbs and tongue, hyperreflexia with reflex spread (to finger flexors; crossed adductors), brisk jaw reflex, corneal-mandibular reflex, Hoffman’s signs in the fingers, extensor plantar responses, and weakness in a UMN pattern.
Sensory symptoms and signs should prompt a search for another diagnosis. Patients do not complain of visual symptoms, although some authors have reported abnormal visual saccades. Some patients complain of urinary urgency or incontinence, and several report this more frequently—50% (4 out of 8) in the Canadian series, 65% (13 out of 20) in the Salpetriere, and 3 out of 5 in the initial report of the Texas patients. These usually occur a number of years after onset of symptoms. In the Canadian series, bladder symptoms first appeared in four out of eight patients at 5, 8, 9, and 24 years after onset. In most of the early reports, cognition was reported as normal. However, Le Forestier and colleagues reported 16 out of 20 patients had errors on frontal lobe function testing. Others have reported frank frontal lobe dementia syndrome in PLS patients. This is consistent with the recent increasing awareness of frontal lobe dementia in 10-20% of ALS patients.

**DURATION AND PROGNOSIS**

Primary lateral sclerosis patients have a slowly progressive disease which distinguishes them from typical ALS patients. In most of the published cases and series the patients are reported as being alive, and there have been only a small number of autopsied cases. There is no good data to tell physicians what the average life expectancy is for patients with PLS. There is data from numerous papers in the modern era on the duration of symptoms at the time patients were either diagnosed or reported. In the Canadian series, median disease duration at the time of the report was 19 years and the mean was 14.5 years (range 4-34 years). In the Salpetriere series, mean disease duration at first examination was 8.5 years (range 4-14 years). Disease progression as reported as slow with half of the patients experiencing periods of stabilization lasting months. Follow-up on 19 patients showed 5 could walk unaided, 5 used a walker, and 10 needed a wheelchair after 4-6 years duration. In the NIH series, the patients had symptoms present for 7-8 years at the time of diagnosis. Similarly, the 10 patients in the Dutch series had symptoms from 6-35 years. In the Texas series, the average duration of illness was 4.75 years (range 4-15) in 13 patients. All four of Russo’s patients had symptoms more than 5 years with follow up from 25-42 months. The Columbia University group’s three patients who had died had symptoms 1, 6, and 8 years, and their six living patients had symptoms for 2-12 years. The five cases of Gastaut and colleagues had symptoms for 5, 10, 12, and 28 years.

A few cases that were initially diagnosed as PLS eventually had the diagnosis changed to ALS due to progression of the disease. Bryun and colleagues described three patients who had a pure PLS picture until 7.5 years, and 27 years into the disease had fasciculation, atrophy, and a worsening needle electromyography (EMG), at which point ALS was diagnosed.

**LABORATORY FINDINGS**

**Creatine Kinase**

Serum creatine kinase (CK) results are often elevated in ALS (usually less than two times normal), and when this occurs it is probably a reflection of denervation from LMN involvement. Creatine kinase levels are usually not mentioned in published PLS cases. In the Texas series, serum CK was slightly elevated in two out of nine patients. Similarly, in the Dutch series, 4 out of 10 had slightly elevated serum CK levels.

**Electromyography**

Most of the smaller reports in the modern era argued that normal nerve conduction studies and needle EMG proved the patients studied had PLS. However, in most of the larger series, subtle but definite abnormalities on needle EMG are reported. In this author’s series, 7 out of 13 patients had features of mild active denervation in one or more muscles consisting of increased insertional activity (5 out of 7), grade 1+ fibrillations or positive sharp waves in (4 out of 7), or fasciculations (4 out of 7). Decreased recruitment of motor units (fast firing) was seen in three out of seven although motor unit morphology was normal. No patients had sufficient abnormalities on EMG to make a diagnosis of ALS. In the Salpetriere study, 6 out of 20 patients had either denervation activity at rest or denervation potentials with decreased recruitment, but did not meet criteria for definite, probable, or possible ALS. During subsequent examinations, of the 14 who initially had a normal needle EMG, 5 developed denervation or decreased motor unit recruitment. Most patients had multiple needle EMGs and at the time of the last evaluation, three fulfilled electrophysiologic criteria of probable ALS, but without clinical evidence of disease progression. In the Dutch study, 4 out of 10 patients had enlarged motor unit action potentials, but none had spontaneous denervation. All of these authors argued that because of the mild needle EMG abnormalities, there is some evidence of LMN dysfunction and therefore that many cases of PLS are on a spectrum with ALS. In the Columbia Medical Center series, seven cases were excluded because there was evidence of denervation on needle EMG—these cases were referred to as “PLS with EMG denervation.” One of these cases also developed clinical evidence of LMN disease on follow-up and was diagnosed with ALS. In addition, one of their autopsied cases previously had a needle EMG showing fasciculations in multiple muscles in at least two limbs. Interestingly, in the Canadian series where the authors...
argued that PLS is a discrete disorder separate from ALS, two out of eight patients had occasional fibrillations and positive sharp waves which were considered “indicators of a relatively minor degree of denervation ... restricted to a few muscles” that appeared late in the course.42 In the proposed diagnostic criteria by this group, they allow for “occasional fibrillation and increased insertional activity in a few muscles (late and minor).”42 Therefore, if one looks at the existing published literature, the conclusion is that mild needle EMG abnormalities can be found in cases that clinically appear to have a pure slowly progressive PLS syndrome. In rare cases, follow-up needle EMGs can show progression and ultimately change the diagnosis to ALS.8,34,62

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) studies in several large series are typically abnormal.6,33,34,63 Brown and colleagues studied TMS in seven PLS cases and all had central conduction abnormalities. The “ascending” group of Zhai and colleagues showed that motor evoked potentials could not be evoked from hand muscles despite maximal stimulation, and this was interpreted as decreased cortical excitability.63 The Dutch group also had difficulty obtaining responses with TMS, but when they were obtained, the central motor conduction time (CMCT) was significantly prolonged (2-3 times normal). This is in contrast to ALS patients in which CMCT is normal or only slightly delayed.33 The Salpetriere group could not obtain responses in 12 out of 20 patients in either upper and lower limbs, and only in the lower limbs in two patients. In six patients CMCTs were prolonged.34 Of the two patients reported by Swash and colleagues, one had prolonged CMCTs to the lower extremities, and one had borderline findings.52

Somatosensory Evoked Potentials

Somatosensory evoked potentials (SEPs) (visual, brainstem, median, and tibial somatosensory) were performed in six patients in this author's series and were all normal.31 However, in the Salpetriere series, abnormalities in visual (prolonged P100), median (prolonged N20 and N13-20 interval, and tibial (prolonged P40 and P22-40) SEPs were found in over half of their 20 patients.34 The abnormalities were presumably compared to normal control values at their institution. No comparison was made with ALS patients. Their findings are unexpected, particularly since this group argues that PLS frequently has subtle LMN findings and should be considered on spectrum with ALS. In the Dutch series, prolonged latencies were also documented on median and peroneal SEPs in several patients.33

Muscle Biopsy

This author biopsied one patient and found rare angulated fibers suggesting denervation.84 In the Salpetriere series, all 20 patients underwent a deltoid muscle biopsy and signs of denervation or reinnervation was seen in 13 patients; 7 were normal.34 Therefore, muscle biopsy can often be useful in finding evidence of LMN pathology in patients who clinically appear to have a pure UMN syndrome.

Neuroimaging

Routine computerized tomography and magnetic resonance imaging (MRI) brain imaging is typically normal or shows non-specific changes.31,34,52,63 However, atrophy of the precentral gyrus has been reported in some series.33,34,42 A single report of serial MRI scans over a 9-year course showed progressive atrophy of premotor, parietal, and primary sensorimotor cortex, with sparing of the temporal lobe, occipital lobe, and cerebellum.46

Magnetic resonance spectroscopy in some series has shown reduction of N-acetylaspartate/creatinine in the motor cortex,63 a finding that also has been shown in some ALS patients.

Positron emission tomography (PET) has shown a regional decrease in fluorodeoxyglucose uptake.42 In cerebral blood flow (rCBF) a decrease using flumazenil as a marker (an index of synaptic brain function) and regional density of benzodiazepine receptors (BZRs) decrease (a putative index of cortical neuronal density)35 in the precentral gyrus regions. Again, these PET imaging findings may not distinguish PLS from ALS.35,42

More recently, diffusion tensor imaging has demonstrated decreased image intensities reflecting decreased diffusion anisotropy in the posterior limbs of the internal capsules compared to normal control.55 However, that paper also indicates these changes can be seen in ALS patients, and therefore they believe this tool may be useful in distinguishing PLS from other disease states. It remains to be determined if this tool can be a marker for UMN pathology in both PLS and ALS, or if it truly is more specific for these diseases.11

Pathology

There have been surprisingly few autopsy reports of PLS in the modern era since the description by Fisher.2,19,29,42,62 The consistent finding in the six autopsied patients described in these studies is the loss of myelinated fibers in the entire corticospinal system with sparing of the cranial nerve neurons and the
anterior horn cells. Most of these cases also had atrophy of the pre-central gyrus and loss of Betz cells in the motor cortex. In the case by Beal and Richardson, intracytoplasmic eosinophilic inclusion bodies were observed rarely in motor neurons (one in the hypoglossal nuclei and two in spinal cord anterior horn cells), and were suspicious for the Bunina bodies described in ALS.

In rare cases, patients who are diagnosed with a PLS syndrome during life can have changes more typical of ALS at autopsy. In the series of 45 autopsied cases of motor neuron disease by Brownell and colleagues, 3 patients who were diagnosed with PLS in life were found to have anterior horn cells affected at autopsy.

In the recent case by Tan and colleagues, an elderly patient with a 7-year history of progressive bulbar symptoms followed by spasticity and dementia showed typical corticospinal tract involvement seen in PLS as well as marked frontotemporal atrophy with ubiquitin-positive staining neurons in these cortical regions. The cortical pathology was therefore typical of frontotemporal lobar degeneration, in addition to the pyramidal changes of PLS. They also reported Bunina body inclusions in a few LMNs. The patient never developed significant limb weakness or clinical evidence of LMN dysfunction. In this paper, they report that seven previous autopsy cases of a PLS-like syndrome with dementia and ubiquitin immunohistochemistry had been reported, although it appears that most of these were reported only in the Japanese literature.

A patient with a 10-year history and clinical features suggestive of PLS was found at autopsy to have diffuse Lewy body disease, but without ante-mortem clinical features of dementia or Parkinsonism.

**Reports of Concurrent Diseases**

There have been several reports of patients with PLS having a concurrent medical diagnosis, but the relationship is usually uncertain. Five women were reported with breast cancer and PLS, and in three of these cases, ultimately diagnosed with ALS. In addition, two of the patients in the Younger and colleagues series were human immunodeficiency virus (HIV) positive, and one went on to develop acquired immunodeficiency syndrome (AIDS). There has been an autopsied case of multiple myeloma and a PLS syndrome in the absence of cord infiltration by tumor. A patient with PLS of 7 years duration has been reported to have an IgM paraprotein and elevated cerebrospinal fluid (CSF) protein.

**Differential Diagnosis and Work-up**

The differential diagnosis for the progressive corticospinal and corticobulbar syndrome is outlined in Table 1. This is an inclusive table and most of the disorders probably do not need to be seriously considered when evaluating a patient for possible PLS.

While some consider PLS a diagnosis of exclusion, this can be said for most sporadic degenerative conditions for which no diagnostic test is available. In reality, if a patient presents with a pure progressive spastic bulbar and limb syndrome, the differential diagnosis is limited. Most of the conditions listed in Table 1 have either sensory symptoms or evidence of involvement of another neurologic system, such as cerebellar. Also, a number of the disorders in the degenerative group have a hereditary basis and therefore should have a history of other affected family members.

The hereditary spastic paraparesis (HSP) disorders deserve particular consideration. These hereditary conditions have previously been referred to as Strumpell’s disease. In the last several years there has been an explosion in the molecular genetic identification of a number of genes responsible for HSP. Hereditary spastic paraparesis can be autosomal dominant, autosomal recessive, or X-linked. To date, 20 genetic loci (spastic gait loci [SPG]) have been identified. The most common HSP appears to be due to a mutation in the SPG4 gene which produces a protein called spastin. The SPG4 gene mutations account for 40% of autosomal dominant HSP. Other mutations are in genes coding for ataxin, kinesin heavy chain (SPG10), and NIPA1 (SPG6), heat shock protein 60 (SPG13) (all autosomal dominant); paraplegin (SPG7) and spartin (SPG20) (both autosomal recessive); and L1 cell adhesion molecule (SPG1) and proteolipid protein (SPG2) (both X-linked). Genetic testing is currently available for spastin, ataxin, and NIPA1 mutations. Hereditary spastic paraparesis usually presents in the teenage years with symmetrical leg spasticity. While the disorder progresses, arm involvement is uncommon and bulbar involvement is extremely rare. There is some range in the age of onset, and some patients are diagnosed in middle age. Bladder symptoms are common and some patients exhibit mild sensory loss in the feet (vibration and proprioception deficits) suggesting posterior column involvement. Therefore, while it is probable that some patients reported as PLS may have had one of the HSP disorders, the absence of a family history, middle or late life onset, and bulbar involvement make PLS much more likely.

With regard to familial ALS (FALS), these patients have significant UMN and LMN involvement, and therefore usually do not need to be considered in the differential of a possible PLS.
patient. In one family reported by Appelbaum, two first cousins had either a PLS or PMA phenotype. However, in families with the two identified autosomal dominant FALS mutations (SOD1 mutation on chromosome 21 or the 9q34 mutation), PLS phenotypes have not been reported. There are at least two juvenile autosomal recessive forms of ALS. In some of these kindreds, a pure UMN presentation (limb and bulbar) has been described using the term “juvenile PLS.” Recently, a number of these rare cases have been shown to be due to mutations in a gene that codes for a protein called alsin. Many of these children present in the first 1-2 years of life. Not all families have been shown to have the alsin mutation, and since there clearly is an overlap with HSP, this phenotype has also been referred to as infantile ascending hereditary spastic paralysis (IAHSP).

In a sporadic pure UMN syndrome developing in middle age or later, the two main diseases to consider are ALS and PLS. Amyotrophic lateral sclerosis is more common than PLS and therefore is the ultimate diagnosis in patients presenting with this syndrome. However, if there is either minimal or no evidence of LMN pathology, a tentative diagnosis of PLS can be made. In this setting, patients can be told that the prognosis is better compared to ALS and the progression is slow. However, they also need to be informed that they need to be followed closely to determine if their motor neuron disease will evolve into ALS or another diagnosis.

All patients should have standard brain and spinal cord MRI imaging and EMG/nerve conduction studies. Further tests such as evoked potentials and muscle biopsies are determined on a case-by-case basis. Blood work in these patients routinely includes serum CK and human T-lymphotropic virus 1 (HTLV-1) antibodies. This author also obtains serum B12, rapid treponine test and fluorescent antibody test (for syphilis), and serum protein electrophoresis/immunofixation electrophoresis, but without sensory symptoms or signs, the yield on these studies is negligible. If there is absolutely no evidence of a LMN process, CSF studies should be obtained as part of a multiple sclerosis evaluation. If nerve conduction studies indicate an unsuspected sensorimotor neuropathy, this author checks for long-chain fatty acids. Antibodies for HIV are tested in at-risk patients. If there are no bulbar features, one can check for the commercially available genetic mutations for HSP (SPG4, SPG3A, SPG6), but without an autosomal dominant family history, the yield is probably extremely low. This author has not been routinely checking

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Differential diagnosis of the progressive corticospinal and corticobulbar dysfunction syndrome</th>
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<tbody>
<tr>
<td>Sporadic motor neuron disease</td>
<td></td>
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<tr>
<td>Primary lateral sclerosis (PLS)</td>
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<tr>
<td>Amyotrophic lateral sclerosis (ALS)</td>
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<tr>
<td>Structural lesions</td>
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<tr>
<td>Cervical spondylotic myelopathy</td>
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<tr>
<td>Other causes of spinal cord compression</td>
<td></td>
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<tr>
<td>Tumor, arteriovenous malformation, disc</td>
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<tr>
<td>Syringomyelia</td>
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<tr>
<td>Foramen magnum tumor</td>
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<td>Arnold-Chiari malformation</td>
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<td>Hydrocephalus</td>
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<tr>
<td>Degenerative and hereditary diseases</td>
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<tr>
<td>Hereditary spastic paraplegia</td>
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<tr>
<td>Spinocerebellar ataxias</td>
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<tr>
<td>Diffuse Lewy body disease</td>
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<tr>
<td>Leukodystrophies (adrenoleukodystrophy, adrenomyeloneuropathy, metachromate leukodystrophies)</td>
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<tr>
<td>Vitamin E deficiency</td>
<td></td>
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<tr>
<td>Familial ALS (FALS); juvenile FALS</td>
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<tr>
<td>Dysimmune disease</td>
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<tr>
<td>Multiple sclerosis</td>
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<tr>
<td>Infection</td>
<td></td>
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<tr>
<td>*HTLV-1 myelopathy (tropical spastic paraplegia)</td>
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<tr>
<td>**HIV-related vascular myelopathy</td>
<td></td>
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<tr>
<td>Neurosyphilis</td>
<td></td>
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<tr>
<td>Metabolic, nutritional, toxic disorders</td>
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<tr>
<td>Cobalamin (Vitamin B12) deficiency</td>
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<tr>
<td>Vitamin E deficiency</td>
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<td>Copper deficiency</td>
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<td>Lathyrisnm</td>
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<tr>
<td>Vascular</td>
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<tr>
<td>Lacunar state</td>
<td></td>
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<tr>
<td>* HTLV1 – human T-lymphotropic virus 1</td>
<td></td>
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<tr>
<td>** HIV – human immunodeficiency virus</td>
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</tbody>
</table>

When It's Not ALS! Pure Motor Syndromes
molecular genetic mutations for the spinocerebellar ataxia genes unless there is ataxia, family history, or other evidence to suggest involvement outside of the corticospinal/corticobulbar system.

**DIAGNOSTIC CRITERIA**

The most recent proposed diagnostic criteria for PLS have been those of Pringle and colleagues in 1992 and are outlined in Table 2. Interestingly, a pure UMN syndrome in two regions of the body can fulfill the El Escorial research criteria for clinically possible ALS as originally proposed in 1994. If one finds even minimal needle EMG abnormalities in two limbs to the degree that has been reported in some PLS publications, this would meet the revised El Escorial criteria for clinically probable laboratory supported ALS.

**TREATMENT**

Treatment is symptomatic and directed toward the spasticity, usually with baclofen or tizanidine. Rarely dantrolene can be used. However, with the advent of the baclofen pump, this is probably a better alternative than dantrolene in difficult to control patients. Excessive drooling can be treated with a variety of oral anti-cholinergic medications (amitriptyline, hyoscyamine, benzotropine mesylate, glycopyrrolate, or scopolamine patches). The tricyclic antidepressants can also be useful for emotional lability associated with the pseudobulbar condition. There is some preliminary data indicating that botulinum toxin injections into the submandibular glands may decrease saliva production

At this point, there is no data to indicate that riluzole is of benefit in PLS patients as all of the data pertains to typical ALS. This author has treated some PLS patients with riluzole, but the patient needs to be aware that the benefit is unknown in this setting. As with all of this author’s ALS patients, patients are placed on high-dose antioxidant vitamin C, E, and beta-carotene, although no good clinical data is available regarding the benefit of this approach. It is preferable for the patient to be

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### Table 2 Proposed diagnostic criteria by Pringle and colleagues

<table>
<thead>
<tr>
<th>Clinical</th>
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<tbody>
<tr>
<td>1. Insidious onset of spastic paraesis, usually beginning in lower extremities but occasionally bulbar or in an upper extremity</td>
</tr>
<tr>
<td>2. Adult onset, usually fifth decade or later</td>
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<tr>
<td>3. Absence of family history</td>
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<tr>
<td>4. Gradually progressive course (i.e., not step-like)</td>
</tr>
<tr>
<td>5. Duration &gt; 3 years</td>
</tr>
<tr>
<td>6. Clinical findings limited to those usually associated with corticospinal dysfunction</td>
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<tr>
<td>7. Symmetrical distribution, ultimately developing severe spastic spinobulbar paresis</td>
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</table>

<table>
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<tr>
<th>Laboratory (help in exclusion of other diseases)</th>
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</thead>
<tbody>
<tr>
<td>1. Normal serum chemistry including normal vitamin B12 levels</td>
</tr>
<tr>
<td>2. Negative serologic tests for syphilis (in endemic areas, negative Lyme, and HTLV-1 serology)</td>
</tr>
<tr>
<td>3. Normal CSF parameters, including absence of oligoclonal bands</td>
</tr>
<tr>
<td>4. Absent denervation potentials on EMG or at most, occasional fibrillation and increased insertional activity in a few muscles (late and minor)</td>
</tr>
<tr>
<td>5. Absence of high signal lesions on MRI similar to those seen in MS</td>
</tr>
</tbody>
</table>

**Additionally suggestive of PLS**

1. Preserved bladder function
2. Absent or very prolonged latency on cortical motor evoked responses in the presence of normal peripheral stimulus-evoked maximum compound muscle action potentials
3. Focal atrophy of precentral gyrus on MRI
4. Decreased glucose consumption in pericentral region on PET scan

HTLV-1 = human T-lymphotropic virus 1; MRI = magnetic resonance imaging; MS = multiple sclerosis; PET = positron emission tomography; PLS = primary lateral sclerosis.

(Used with permission, Oxford University Press.)

8 Primary Lateral Sclerosis and the Differential of the “Pure” Upper Motor Syndrome AAEM Course
managed in a multi-disciplinary ALS clinic so that their multiple needs can be addressed—equipment, speech, pulmonary, physical, and dietary, as well as having access to social workers, counselors, and occupational therapy professionals.

SUMMARY

Primary lateral sclerosis remains a difficult diagnosis to make. To some extent, some of the same issues that Charcot, Erb, and Wilson faced, are still being struggled with today; particularly regarding whether or not PLS is a distinct entity. Interestingly, there has been a renewed focus on PLS in the neuromuscular disease literature in the last 2 decades, probably because these patients continue to challenge clinicians. While there remain many unanswered questions regarding diagnosis and nosology, it is believed that PLS is a useful concept which carries implications for prognosis that differ from other categories of motor neuron disease.

REFERENCES


57. Wechsler IS, Brody S. The problem of primary lateral sclerosis. JAMA 1946;130:1195-1198.


INTRODUCTION

The goal of this manuscript, other than to describe brachial amyotrophic diplegia (BAD) and multifocal acquired motor axonopathy (MAMA), is to discuss why these definitions need to exist. These terms are used to demonstrate practical problems that clinicians face in the area of diagnosis in pure motor presentations, and it is hoped that some light can be shed on the underlying reasoning process in this domain.

There are three aspects of neuromuscular diseases that, at times, can make practicing in this area particularly daunting. These are:

1. Complexity (making numerous observations about each patient).
2. Lack of exhaustiveness (the nomenclature is too small to account for every presentation).
3. No gold standard tests (physicians are left to rely on their observations for diagnosis).

COMPLEXITY

There are at least nine basic features used to describe any given pure motor presentation (Table 1). Although this may not sound like a lot, consider that this means there are at least $2^9$ possible patterns derived from these observations (actually some features have three or more choices and some have continuous rather than discrete variables, making it even far more complex). This means a minimum of over 500 potential presentations.

Table 1  Nine observations for motor presentations

| 1. Proximal or distal muscles affected |
| 2. Symmetric or asymmetric              |
| 3. Multifocal, generalized, or regional |
| 4. Upper limbs, lower limbs, neck, trunk involved |
| 5. Upper motor neuron signs present or not |
| 6. Acute, subacute, or chronic          |
| 7. Hereditary or sporadic               |
| 8. Axonal or demyelinating              |
| 9. Antibody against nerve is present    |

Since no individual observation can prove or disprove the presence of a disease by itself, physicians must rely on summations of findings, or “the patterns.” For example, amyotrophic lateral sclerosis (ALS) is a pure motor, chronic, asymmetrical disorder with upper motor neuron (UMN) signs. It often presents without antibodies, sometimes with a family history, and with axonal pathophysiology. It is virtually always progressive. Knowledge about these “clusters” of observations is at the root of pattern recognition. The complexity becomes evident because
some ALS patients never develop observable UMN signs. Here, a slightly different pattern has been created, but one which still handles the logic that UMN signs may not be evident.

Now consider two cases; one where the weakness remains largely confined to one region (like the arms for long periods of time) and lacks UMN signs, the other with rapidly progressing weakness, involvement of all four distal limbs at the time of initial presentation, and clear UMN signs. When do these patterns become so different that a physician cannot be confident these are the same condition? Going a step further, when is it useful to think about these presentations as though they are two different disorders? The discussion of BAD will be a practical approach to these questions.

**LACK OF EXHAUSTIVENESS**

Many physicians practice in a way that assumes every disease has actually been named. It should be understood that this assumption might be incorrect. Without a deeper understanding of pathophysiology, it might be assumed that there is more than one way that a motor nerve might die, and differences in presentations may signal different underlying mechanisms.

From a practical standpoint, physicians clearly see presentations that do not fit neatly into a diagnostic “pigeon hole.” These cases can be dealt with by applying the designation variant (ALS variant, etc.). Practicing as though an exhaustive universe exists simplifies the reasoning process. Focusing on a single technology has the same effect. Splitting cases simply by the presence or absence of conduction block (CB), no matter what the phenotype, can cut the number of diseases down to only two.

At the same time, the possibility that atypical patterns could represent an as-yet unnamed disease is often neglected. Table 2 points out one situation where physicians are forced to consider the nonexhaustive universe.

### Table 2

<table>
<thead>
<tr>
<th>Multifocal phenotype</th>
<th>Axonal NCS/EMG</th>
<th>Demyelinating NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse weakness</td>
<td>ALS/PMA</td>
<td>Pure Motor CIDP?</td>
</tr>
<tr>
<td>MMN</td>
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</table>

ALS = amyotrophic lateral sclerosis; CIDP = chronic inflammatory demyelinating polyneuropathy; EMG = electromyography; MMN = multifocal motor neuropathy; NCS = nerve conduction study; PMA = progressive muscular atrophy.

Since ALS presents with diffuse weakness and is axonal, and multifocal motor neuropathy (MMN) is multifocal but demyelinating, it is quickly apparent that one box is unfilled. It is clear that not every case will fit into the rubric of motor neuron disease or motor neuropathy, as they are defined. While cases in the upper right corner are rare, they do exist and they might best be reasoned about as a discrete clinical entity. The situation of exhaustiveness becomes obvious when situations with more than two observations are considered. The only solution is to keep an open mind on how to manage these cases, to think about their pathophysiology, and to move forward with the reasoning process.

**GOLD STANDARDS**

Finally, there are few “gold standards” or simple diagnostic tests to aid physicians in diagnosis. In most cases the existence of a given diagnosis can never absolutely be proven. With no tests, a complex reasoning domain, and the absence of exhaustive naming, physicians are left with pattern recognition as the main diagnostic tool. It is inevitable that they will meet circumstances of real uncertainty. It might be wise to coin the term “nonevidence-based medicine” as the science behind creating rules for managing this area.

**MULTIFOCAL ACQUIRED MOTOR AXONOPATHY**

In the early 1990s after MMN was described and physicians had no experience with its diagnosis, there were several cases carrying the diagnosis of ALS or atypical motor neuron disease making the rounds through this author’s clinic. Before physicians were able to diagnose these cases correctly, they had to overcome a cognitive dilemma. Specifically, they needed to reconsider the role of CB in the diagnosis of MMN since, at that time, the disorder carried the label of “multifocal motor neuropathy with CB.” Through a series of discussions (in Texas at the time) this author’s group began to think of the condition by its phenotype rather than by electrodiagnostic (EDX) testing. Multifocal motor neuropathy became a phenotype marked by the presence of distal, asymmetric, primarily upper limb and stepwise weakness, with absence of retained reflexes.³

This relatively simple change in the way the disease was viewed led to a new set of conclusions about the nature of the condition. It followed that only about 40% of MMN patients diagnosed this way actually fulfilled standard EDX criteria for CB. While a small number of cases had multiple pure CBs, these were the exception and made up approximately 10% of the phenotypic caseload. Instead, the most salient feature was the presence of other evidence of demyelination (temporal dispersion of wave-
forms without changes in area, conduction slowing, and prolonged distal latencies) in virtually all patients. Moreover, in weak nerve distributions, individual nerves often showed axonal manifestations only (low compound muscle action potential [CMAP] amplitude denervation potentials) with no evidence of denervation. Overall, the complete picture of EDX testing in MMN that emerged was a mixture of features, with axonal findings predominating in some affected nerves, obvious CB at other sites, and a combination of other demyelinating findings. It followed that the same underlying pathophysiologic process caused different electrophysiological manifestations.

From here, it was only a short step to the concept of MAMA. Of this author's initial 19 cases, 1 patient had no EDX evidence of demyelination at all. After several more years, eight similar cases were identified with multifocal involvement clinically, a lack of progression, and axonal-appearing EDX testing. It made little sense to diagnose these patients with motor neuron disease based on the EDX testing since this implied progression with time and since motor neuron disease is not supposed to have such clear multifocal involvement. It was further reasoned that if some nerve territories had no evidence of demyelination in MMN, it was plausible that in some patients every affected nerve would lack evidence of demyelination, if not by chance alone. It followed that the same neuropathy would, at times, show up electrodiagnostically as an axonal disorder.

In the initial report of MAMA,1 and in subsequent letters to the editor, it was postulated that several mechanisms for a purely axonal motor neuropathy:4 First, this may simply be a variant of MMN where the nerve lesions may be too proximal. In this scenario, a physician would only be able to find secondary axonal loss since the demyelinating lesions are in a segment where the conduction abnormalities cannot be easily identified (without root stimulation). F waves may also miss a very proximal lesion if there is slowing over only a short segment of nerve or if there is only a partial block of conduction. Second, the lesions might be too distal. Conduction block in the terminal segment of a nerve fiber may be incorrectly interpreted as axonal loss. Third, the injury may actually be directed against the axon. Even using the most common hypotheses—that MMN is an antibody mediated disorder, marked by an immunological attack directed against myelin, myelin/axonal interactions, or ion channels in the axonal membrane—it follows that the same antibodies might actually damage the axon through an inflammatory process without causing much in the way of conduction abnormalities. A related method would be a chronic immune attack against a nerve, where the demyelinating features become “hidden” because there is severe damage of the underlying axon over time. Fourth, if there are few nerves injured or if the injured nerves are difficult to study, or simply not studied on routine testing (anterior interosseous, musculocutaneous, or sciatic) the chances of discovering a demyelinating lesion are reduced simply because the opportunity is lost. Last, others have suggested a dynamic CB, which cannot be discovered with routine testing. Here antibodies are able to cause weakness via CB that occurs only during volleys of nerve action potentials, but not at baseline with a single stimulus, as is the case with standard testing.

It is still unclear whether MAMA and MMN are, if fact, the same disease, or even if MAMA represents a single underlying disorder. Like MMN, these cases have weakness in the distribution of individual peripheral nerves. However, they tend to have proximal involvement more commonly than MMN and onset at a relatively young age in a few cases (around 20). Three of six cases that this author treated responded favorably to therapy, emphasizing the pitfalls in characterizing MAMA as a “motor neuron disease variant” based solely on needle electromyography (EMG) findings. One case of MAMA was prednisone responsive, a finding that differs from MMN, which responds to intravenous immunoglobin (IVIg) but not prednisone. Finally, some of these cases have confluent or overlapping mononeuropathies resulting in a pattern of proximal and distal weakness reminiscent of chronic inflammatory demyelinating polyneuropathy. Thus, it is currently believed that the axonal cases are somehow different.

Multifocal acquired motor axonopathy cases also generally lack GM-1 antibodies, and given that antibodies are present in at least 35% of definite MMN cases, it is hard to understand how no antibodies were found in these first nine cases if this is simply an MMN variant. By pure chance this would amount to a 1% chance if MAMA and MMN were the same disease. (A subsequent case did have anti-GM1 antibodies suggesting at least some of these could be an MMN variant.)

BRACHIAL AMYOTROPHIC DIPLEGIA

Another group of patients examined at this author's clinic had been diagnosed with ALS but were not dying quickly nor were they showing constant progression that is typical of that disease. Most of these cases had a specific phenotype for which the term brachial amyotrophic diplegia (BAD) was used.2 This was marked by the onset of weakness of one arm that spread relatively quickly over periods ranging from 1-2 years to become bilateral, eventually reaching the point where the arms hung limply at the patients' sides. There was a complete absence of weakness outside of the upper limbs, sparing the neck flexors and extensors, breathing, bulbar muscles, and the legs. Thirteen of the first 15 patients had absent reflexes, while 2 others had brisk reflexes in the upper limbs.

Brachial amyotrophic diplegia, by definition, remains localized to the arms for at least 2 years after the first onset of weakness. The rationale was that every case where weakness spread beyond the arms earlier than 2 years, turned out to be clear ALS. While this raises the possibility of a circular argument that those who
do not progress are the ones who do not progress, it turns out that these patients often continue to have focal weakness for up to 5 years. More importantly, it is among this population that there exists a group of patients with no progression at all.

Needle EMG shows denervation in the upper limbs. Some patients had a few positive sharp waves and fibrillation potentials in the legs or paraspinal muscles, a finding suspicious for ALS, but still did not show progression with time. Creatine kinase can be mildly elevated or normal. Magnetic resonance imaging scanning was nonrevealing except for nonspecific spondylosis.

This clinical presentation is important to distinguish from ALS because of the differences in prognosis. It should be clear that within the first 2 years after onset, it is impossible to predict with accuracy exactly how a patient with hanging arms will eventually progress. However, it is clear that some of these cases ultimately turn out to have benign courses (except for the devastating involvement of the arms). This may benefit patients by offering some hope. In fact, 6 of this author’s 15 patients have failed to develop any involvement outside of the arms to date, even after 8 years from onset. The longest duration of static weakness in BAD is now over 30 years. From these observations, it can be concluded that there are “benign” motor presentations.

The underlying pathophysiology of BAD is not known. Among this author’s patients, a specific subset had the onset of weakness mainly in the C5 and C6 muscles, which became bilateral, remained asymmetric, and continued to spare the triceps, wrists, and hands. Some cases with severe involvement of the proximal arms at onset developed only mild to moderate hand involvement and had a benign prognosis. It might be useful to think of some BAD cases as a variant of juvenile monomelic amyotrophy (JMA), but with involvement of the proximal rather than the distal limbs. In contrast to JMA, which tends to affect male teenagers, BAD typically affects men in their late 30s or early 40s. Chronic mechanical impingement of the lower cervical spine, associated with flexing the neck, which develops during a growth phase in teenagers is postulated to be the root cause of JMA. One can only speculate as to whether a similar mechanical factor is at play in BAD.

In contrast, it should be clear that some BAD patients die approximately 5-8 years from onset, with a gradually progressive cause leading to respiratory failure that is typical of ALS. The overall point is that BAD is actually a clinical syndrome comprised of two types of progression. Obviously, the longer the condition remains localized to the arms, the more hope there is that the patient does not have a life-threatening illness.

Under any circumstance, BAD does not appear to be treatable. Several patients were treated when they failed to progress over time, and the initial diagnosis of ALS was questioned. The rationale was that if the patient did not have ALS, they could have a potentially treatable neuropathy. This is not totally unjustified since reports of ill-defined lower motor neuron disorders that respond to IVIg exist. Given that there is no way to know about the response without a trial of therapy, it made sense to give treatment at least a resort.

Bibliography

INTRODUCTION

Diagnosing amyotrophic lateral sclerosis (ALS) is often difficult largely because this disease is uncommon (with a prevalence of approximately 1 per 100,000). However, when both upper and lower motor neuron features are present, diagnosis is usually relatively straightforward. Furthermore, ALS is the most common motor neuron disease (MND). Diagnostic difficulty is more significant when a patient has purely lower motor neuron (LMN) involvement. This manuscript will focus on this situation. The LMN syndromes are heterogeneous and consist of idiopathic conditions similar to ALS, inherited disorders, and—of most interest—immune-mediated disorders. The potentially treatable disorders, multifocal motor neuropathy and its variants, will be discussed elsewhere in this course. Overall, the remaining LMN disorders progress more slowly and tend to have a better prognosis than ALS.

The nomenclature used for these disorders can be confusing. Patients with an idiopathic purely LMN disorder are typically referred to as having progressive muscular atrophy (PMA) or progressive spinal muscular atrophy (PSMA). The term PMA will be used here. It is clear that a significant proportion of PMA patients actually have ALS and lack clinical evidence of upper motor neuron (UMN) involvement. This is supported by autopsy series showing UMN pathology in approximately 50% of PMA patients.1,12,13,19,20 Up to one-third of MND patients lack UMN signs at presentation.21 A significant proportion of PMA patients, if followed over time, will develop UMN examination findings and, therefore, can then be diagnosed with ALS.

In some cases, UMN signs may have been present before the patient was evaluated, but subsequently became undetectable due to progressive LMN loss. During a PMA patient’s lifetime, UMN pathology may be detected with magnetic resonance imaging (MRI) or transcranial magnetic stimulation (TMS).26 Conventional MRI sequences may demonstrate evidence of UMN involvement, but more specialized modalities such as magnetic resonance spectroscopy (MRS) are usually needed.14

Opinions differ on how to refer to patients with an acquired LMN syndrome. For patients presenting with a clinical picture resembling ALS (asymmetrical, progressive weakness), but lacking UMN findings, many clinicians will give a diagnosis of ALS. This is based on the high incidence of UMN features that can be found in these patients on imaging, TMS, or autopsy. Other clinicians tell patients presenting with these symptoms that they do not meet criteria for ALS at the time and are, instead, diagnosed with PMA. Another semantic issue involves the terms PMA and spinal muscular atrophy (SMA). Some physicians use the term SMA synonymously with PMA or PSMA. Many reserve the term SMA for patients with a genetic LMN disorder. It is usually impossible to know with certainty the cause of a particular patient’s LMN syndrome. Although a patient may have a genetic cause for his weakness, if there is no family history and no gene defect identified, the patient may be classified as PMA. However, certain clinical features, such as symmetrical and proximal weakness with legs weaker than arms would favor SMA over PMA, as will be discussed later. The exact classification is not as important; the key is arriving at the best determination of clinical course, prognosis, and management.
Several different LMN syndromes have been described. Although there is overlap, there are distinguishing aspects with regard to age of onset, etiology, site of involvement (regional predilections and restrictions), progression, and mortality (Table 1).

**PROGRESSIVE MUSCULAR ATROPHY**

Progressive muscular atrophy (also referred to as Aran-Duchenne syndrome)\(^2\) comprises approximately 10% of patients with MND.\(^3\) It is slightly more common in men, with an earlier mean age of onset than ALS. Patients receiving the diagnosis of PMA represent a mixed group—some are patients who have ALS but lack clinical features of UMN involvement, while others are patients with a purely LMN disorder. Therefore, it is impossible to know for certain the clinical course and prognosis of PMA. As a group, patients with PMA have a much better prognosis than patients with ALS. In one series, PMA patients showed a 5-year survival of 56%.\(^3\) In contrast, the average 5-year survival for ALS patients is approximately 25%.\(^30\)

Brain MRI using conventional sequences may reveal abnormalities of the corticospinal tract in ALS patients. However, this lacks sensitivity and specificity.\(^14\) Magnetic resonance spectroscopy, which permits assessment of regional brain biochemistry, has shown mixed results in the past for detecting UMN pathology in ALS patients.\(^14,26\) Recently, Kaufmann and colleagues\(^16\) found MRS to be 86% sensitive for identifying UMN pathology in MND patients with and without clinical UMN findings. Autopsies performed in some patients confirmed UMN involvement. Research from German investigators suggests that a new MRI imaging technique called diffusion tensor MRI may be an effective way to detect UMN pathology in MND patients.\(^26\) This modality permits the estimation of the orientation of white matter on the basis of the diffusion characteristics of water. It showed abnormalities in 15 ALS patients, 6 of whom had no UMN findings at the time of testing (but later developed UMN findings and met full diagnostic criteria for ALS).\(^26\) Transcranial magnetic stimulation is another test that may permit the identification of UMN pathology. Studies of the usefulness TMS in ALS have provided mixed results.\(^14,26\)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Features of adult motor neuron disorders</th>
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<tbody>
<tr>
<td><strong>Amyotrophic Lateral Sclerosis</strong></td>
<td><strong>Progressive Muscular Atrophy</strong></td>
</tr>
<tr>
<td><strong>Age of Onset (yrs)</strong></td>
<td>30-60</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Months-years</td>
</tr>
<tr>
<td><strong>Distribution of Weakness</strong></td>
<td>Asymmetrical, Distal</td>
</tr>
<tr>
<td><strong>UMN signs</strong></td>
<td>Present</td>
</tr>
<tr>
<td><strong>LMN signs</strong></td>
<td>Present</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>Sporadic (90%) AD, AR, XR</td>
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<tr>
<td><strong>Distinct Features</strong></td>
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\(^{AD} = \) autosomal dominant; \(^{AR} = \) autosomal recessive; \(^{CAG} = \) cytosine-adenine-quanine nucleotidase; \(^{LMN} = \) lower motor neuron; \(^{UMN} = \) upper motor neuron; \(^{XR} = \) X-linked recessive.
Currently, MRI and TMS are not routinely used in clinical practice. The appropriate roles of these technologies in the diagnosis and management of patients with MND remains to be determined.

There is no data regarding treatment of PMA, therefore, at the present time, these patients are managed the same as those with ALS.

**SPINAL MUSCULAR ATROPHY**

Spinal muscular atrophy is a diverse group of hereditary motor neuron diseases selectively involving LMNs, particularly the anterior horn cells of the spinal cord. Adult-onset SMA, referred to as type IV, has several forms and usually begins over the age of 20. The prevalence is estimated to be 0.32 per 100,000 population and accounts for less than 10% of all SMA cases. Weakness is usually greater in the legs than the arms. The most common inheritance pattern (seen in approximately two-thirds of patients) is autosomal recessive, with a mean age of onset in the fourth decade. The autosomal dominant form accounts for one-third of cases and shares a similar clinical phenotype. The adult-onset disease is slowly progressive with only a small proportion of patients becoming wheelchair-dependent after 20 years. Patients typically present with symmetrical, proximal, or generalized weakness, and fasciculations. Spinal muscular atrophy rarely affects bulbar muscles and respiratory muscles generally remain unaffected. Upper motor neuron signs are absent. Other forms of SMA can involve predominantly distal muscles (so-called “distal SMA”). Distal SMA can also be either autosomal recessive (two-thirds of patients) or autosomal dominant (one-third of patients). Although SMA types I, II, and III are usually caused by deletions in the survival motor neuron gene on chromosome 5, no genes responsible for SMA type IV have been identified.

**SPINOBULBAR MUSCULAR ATROPHY (KENNEDY’S DISEASE)**

Kennedy’s disease is a form of SMA that is associated with bulbar involvement and X-linked recessive inheritance. The disease affects only males, usually beginning in the third or fourth decade of life. The initial symptoms include muscle cramps, a limb-girdle distribution of muscle weakness, and bulbar symptoms. Distinguishing clinical features include facial and perioral fasciculations that are present in more than 90% of patients, hand tremor, and tongue atrophy associated with a longitudinal midline furrow. There is no evidence of UMN involvement. Although sensory examination is typically normal, sensory nerve conduction studies are frequently abnormal. Other systemic manifestations, include gynecomastia in 60-90% of patients due to elevated gonadotropin levels associated with testicular atrophy, feminization, impotence, and infertility. Diabetes mellitus is seen in 10-20% of patients. Genetic testing can be performed to confirm the presence of an abnormal trinucleotide-repeat expansion (CAG) in the androgen receptor gene on the X chromosome. In healthy individuals, the repeats range from 17-26 in this coding area whereas, in Kennedy’s disease, the number of repeats range from 40-65. The number of the enlarged CAG repeat is significantly correlated with the age of onset, but has no correlation with severity of weakness, degree of sensory neuropathy, presence of gynecomastia, or impotence.

**REGIONAL VARIANTS**

Regional variants of MND are disorders that are atypical presentations of generalized MND due to the selected distribution of affected muscles. Several named disorders will be discussed. It is not known whether they constitute distinct pathophysiological entities or if they are a subset of generalized MND (e.g., PMA or ALS). Some entities do appear very distinct. Monomelic amyotrophy, for example, occurs at a young age and remains restricted to specific myotomes.

**Monomelic Amyotrophy (Focal Motor Neuron Disease, Hirayama Disease)**

Monomelic amyotrophy usually refers to an MND originally described as juvenile muscular atrophy of the distal upper extremity by Hirayama in 1959 in which muscle weakness remains limited to several myotomes (usually C5 - T1) within a single extremity. The mean age of onset is typically 20-35 years of age with a male predominance (2:1). Patients demonstrate preferential weakness in the hand and forearm muscles which progresses rapidly over a period of 2-3 years and subsequently remains stable. Approximately 75% of cases involve the upper extremities and the remainder involve the lower extremities. Reflexes in the involved muscles are invariably hypoactive or absent. There are no UMN signs and sensory symptoms are limited to hypesthesia to pin and touch in approximately 20% of patients. In 50% of cases, the weakness remains localized to one limb, and the other 50% of cases show clinical evidence of involvement in the contralateral limb. Electrodiagnostic studies often show evidence of bilateral involvement although weakness may be clinically apparent in only one extremity.

Magnetic resonance imaging may reveal a normal cervical spinal cord, but bilateral or unilateral cord atrophy is often seen. Hirayama and colleagues have suggested that this syndrome may be related to either local compression of the cervical cord or circulatory insufficiency caused by an anterior shift of the posterior dura during neck flexion. Sometimes, abnormalities may be seen on MRI only when images are acquired with the neck in a flexed position (forward displacement of cervical dural sac). Neck flexion may also produce decreased abnormalities on somatosensory evoked potentials. A recent report from Taiwan...
describes a useful finding that can be seen in cervical spine MRI scans taken in a neutral, nonflexed position. These investigators found that an increased separation between the posterior dural sac and adjacent lamina was a highly sensitive and specific finding in Hirayama patients. They endorse a pathogenic theory involving imbalance between the spinal cord and spinal column that results in a “tight dural sac.”

The appropriate management of patients with Hirayama disease is unknown. Uncontrolled data from Japan suggests that wearing a hard cervical collar (to prevent neck flexion) may halt disease progression.

There are MND patients who develop nonprogressive weakness restricted to the lower limb. This entity has been described mostly in India, but has been reported in Westerners as well. This is often described under the term “monomelic amyotrophy,” but most likely represents an entity distinct from the focal upper limb weakness described above.

Flail Arm Syndrome

Flail arm syndrome is an MND regional variant consisting of weakness exclusively confined to the upper extremities. Cases have also been described under the name of “hanging arm syndrome,” and “neurogenic man-in-the-barrel.” These patients have bilateral upper extremity weakness and atrophy that affects predominantly the proximal arms and shoulder girdle. The average age of onset does not differ from that of ALS, but compared with ALS, this syndrome is significantly more common in men. Average survival is approximately 5 years, compared with 3 years for ALS patients. Although, the overall survival is longer than for ALS, some patients presenting with a flail arm phenotype can go on to develop a typical ALS course. A flail arm pattern is seen in approximately 10% of MND patients, although it is much more common in those of African descent. Curiously, these patients do not show the same prolonged survival as Caucasian patients with the flail-arm phenotype.

Within the flail arm clinical phenotype, another significant division can be made. Among patients with this presentation, if weakness remains confined to the arms for at least 18 months, clinically significant progression outside of the upper extremities does not occur and survival is quite prolonged. In the series of Katz and colleagues, after a mean follow-up of 5.5 years, weakness remained restricted to the upper extremities in 7 out of 10 patients. When present, leg involvement was mild. No patient lost the ability to ambulate independently and none developed bulbar or respiratory involvement. One patient had restricted weakness for greater than 10 years. This clinical presentation has been named bibrachial amyotrophic diplegia (BAD). Patients with BAD (showing no progression beyond arms by 18 months) represent approximately 2% of all MND patients.

SUMMARY

Patients with LMN disorders represent a heterogeneous group. Some have ALS whereas others will have conditions with a much more favorable prognosis. Some are hereditary, but the underlying pathophysiology for most of these entities is unknown. Careful use of history, physical examination, electrodiagnosis, MRI, and genetic testing will usually allow for appropriate diagnosis.

REFERENCES


INTRODUCTION

Multifocal motor neuropathy (MMN) is a disorder characterized by slowly progressive asymmetrical weakness predominantly affecting the upper extremities. The lack of sensory involvement and the progressive weakness mimic the presentation of a lower motor neuron (LMN) form of amyotrophic lateral sclerosis (ALS). However, unlike ALS, electrophysiological testing reveals demyelinating findings with partial motor conduction block (PMCB) in multiple motor nerves; approximately half the MMN patients have anti-GM1 antibodies in the serum; and over 80% respond dramatically to treatment with intravenous immunoglobulin (IVIg). Multifocal acquired demyelinating sensory and motor (MADSAM or Lewis-Sumner syndrome) neuropathy on the other hand does not mimic ALS. The presentation can be similar to MMN with asymmetrical involvement of multiple nerves and with PMCB. However, unlike MMN, sensory involvement is as prominent as motor both clinically and electrophysiologically; the disorder is not associated with anti-GM1 antibodies; and the disorder responds to corticosteroid treatment.

Clinical Features

The prevalence of MMN is unknown, but based on the literature and experience at large centers, MMN is a rare disorder. Since its original description approximately 20 years ago, more than 300 patients have been reported with MMN. At this author’s institution, it is estimated that 1 MMN patient is seen for every 20 patients with ALS. One quoted estimate of prevalence is 1-2 per 1,000,000. Cases in the literature indicate the male to female ratio is 3:1, with the age range varying from the second to the eighth decade (mean age 40 years). The duration of the disease ranges from several months to up to 30 years.
### Table 1  Differential diagnosis for multifocal motor neuropathy and Lewis-Sumner syndrome

<table>
<thead>
<tr>
<th>Anatomical</th>
<th>Amyotrophic Lateral Sclerosis</th>
<th>Multifocal motor neuropathy</th>
<th>Lewis-Sumner Syndrome</th>
<th>CIDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Sex)</td>
<td>5th-6th decade (M&gt;F, 2:1)</td>
<td>15-60 yrs (M&gt;F, 3:1)</td>
<td>5th decade (M&gt;F, 2:1)</td>
<td>All ages (M&gt;F, 1.5:1)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Asymmetrical onset; distal &gt; proximal at onset; progresses to all 4 limbs, bulbar, diaphragm muscles; myotome distribution</td>
<td>Asymmetrical distal &gt; proximal upper &gt; lower limbs</td>
<td>Asymmetrical distal &gt; proximal upper &gt; lower</td>
<td>Symmetrical proximal &amp; distal lower &gt; upper</td>
</tr>
<tr>
<td>Progression</td>
<td>Rapidly progressive; fatal in 3-5 yrs</td>
<td>Stepwise/insidious; some functional limitation</td>
<td>Stepwise/insidious; some functional limitation</td>
<td>Progressive &gt;2 months</td>
</tr>
<tr>
<td>Fasciculations/ Cramps</td>
<td>Very common</td>
<td>Common with myokymia</td>
<td>May be present</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Hyperactive</td>
<td>Asymmetrically reduced</td>
<td>Reduced</td>
<td>Areflexia</td>
</tr>
<tr>
<td>SNAP</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Abnormal-symmetric</td>
</tr>
<tr>
<td>CMAP</td>
<td>Reduced</td>
<td>Reduced or normal</td>
<td>Reduced or normal</td>
<td>Reduced</td>
</tr>
<tr>
<td>PMCB</td>
<td>Absent</td>
<td>Present and localizable to small segments</td>
<td>Present and localized to small segments</td>
<td>Present</td>
</tr>
<tr>
<td>CV/DL &amp; F wave</td>
<td>Normal or mildly reduced/nl or mildly prolonged</td>
<td>Reduced segmentally/ may be prolonged</td>
<td>Reduced segmentally/ May be prolonged</td>
<td>Reduced/prolonged or absent</td>
</tr>
<tr>
<td>Fibs/PSW</td>
<td>Widespread ++++</td>
<td>Localized — to +++</td>
<td>Localized — to +++</td>
<td>Length-dependent +</td>
</tr>
<tr>
<td>CSF protein</td>
<td>Usually normal</td>
<td>Usually normal</td>
<td>Usually elevated</td>
<td>Usually elevated</td>
</tr>
<tr>
<td>Anti-GM1 antibodies</td>
<td>Rare</td>
<td>Frequent (50%)</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Sural nerve biopsy</td>
<td>Normal</td>
<td>Minor evidence of demyelination and remyelination</td>
<td>Prominent demyelination, remyelination</td>
<td>Demyelination, remyelination, inflammation</td>
</tr>
<tr>
<td>Treatment response</td>
<td>None; riluzole may slow down the progression</td>
<td>IVIg, cytoxan</td>
<td>Steroids, IVIg</td>
<td>Steroids, PE, IVIg</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Invariably progressive and fatal</td>
<td>Remains focal—slow progression over many years</td>
<td>Remains focal—slow progression over many years</td>
<td>Progressive; relapsing and remitting; monophasic</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Excitotoxic, free radical, oxidative stress, retrovirus; mitochondrial</td>
<td>Immune-mediated</td>
<td>Immune-mediated</td>
<td>Immune-mediated</td>
</tr>
</tbody>
</table>

CIDP = chronic inflammatory demyelinating polyneuropathy; CMAP = compound muscle action potential; CSF = cerebrospinal fluid; CV = conduction velocity; DL = distal latency; fibs = fibrillation potentials; F = female; IVIg = intravenous immunoglobulin; M = male; PE = plasma exchange; PMCB = partial motor conduction block; PSW = positive sharp wave; SNAP = sensory nerve action potential.
The clinical presentation is fairly distinctive with the initial symptom being asymmetrical progressive weakness in the upper limbs, distal greater than proximal. Unilateral wrist drop, finger drop, grip, problems with dexterity, or biceps weakness are often noted at onset. Asymmetrical lower limb weakness, especially foot drop, is less often a presenting symptom. Cranial nerve involvement and respiratory failure are rare, but have been reported. Cramps, twitching of the muscles, fatigue, and cold sensitivity are additional features. By definition, sensory symptoms such as numbness or tingling are absent or minimal.

Physical examination confirms asymmetrical weakness in the distribution of named peripheral nerves without sensory disturbance in the same distribution. Although weakness can occur in the distribution of any nerve, the posterior interosseous branch of the radial nerve, and the median, ulnar, peroneal, and musculocutaneous nerves are most commonly affected. Weakness is often more pronounced than the degree of atrophy would suggest; marked weakness (MRC < 4) is frequently detected in muscles where the bulk is completely preserved. Myokymia and fasciculations are frequently noted. Muscle-stretch reflexes are asymmetrically reduced in the affected limbs and sometimes even in clinically asymptomatic limbs. Occasionally, reflexes are described as “brisk,” but pathological pyramidal signs—clonus, spasticity, extensor plantar responses—do not occur. In spite of the multifocal weakness, most MMN patients retain useful function and continue working for long periods.

Electrophysiological Features

The classic finding in MMN is a well-localized, persistent, segmental, PMCB detected outside the usual sites of entrapment. Conduction block, thought to be the electrophysiological hallmark of focal demyelination, is defined as a reduction in amplitude or area (or both) of the compound muscle action potential (CMAP) obtained by proximal stimulation versus distal stimulation of the motor nerve. Conduction block may go undetected unless several nerves are each tested at multiple sites of stimulation. Forearm segments of the median and ulnar nerves are most frequently affected, followed by the Erb's point-to-axilla segment. In assessing PMCB, the usual sites of entrapment must be excluded, i.e., the across-elbow segment of the ulnar nerve and the across-fibular head segment of the common peroneal nerve. Partial motor conduction block may also be seen in motor nerves not clinically affected. In addition, other electrophysiological features of peripheral nerve demyelination are invariably found: reduced conduction velocity, especially segmentally across sites of partial motor conduction block; absent or prolonged F-wave responses; and prolonged distal motor latencies. These other features of demyelination are, however, not as prominent as one would see in CIDP and often do not meet the proposed demyelinating criteria. The presence of these additional demyelinating findings suggest concomitant, though less intense, diffuse involvement of motor nerves. Remarkably, sensory nerve conductions are normal, even in those mixed nerves where motor fibers are affected (Figure 1).

While some authors have used a reduction in amplitude or area of the proximally evoked response by ≥ 40%, others have used a decrease by greater than 30% with a duration change less than 15%. More commonly, a greater than 50% reduction in the proximally evoked amplitude or negative peak area is used. The American Association of Electrodiagnostic Medicine criteria are shown in Table 2. These criteria require a reduction of proximal versus distal CMAP amplitude in the nerves of upper limbs by greater than 50% and of lower limbs by more than 60% for definite PMCB.

In most patients, when the distal CMAP amplitude is normal in an affected weak muscle, there is seldom any difficulty in detecting PMCB, especially if all proximal stimulation sites are also chosen. The difficulty arises in those cases where the atrophy is significant and the CMAP amplitudes are reduced. In this situation, because of “interphase cancellation” that occurs due to overlap of positive and negative components of different motor units, a conduction block may be misdiagnosed. Thus, extra caution should be used when defining PMCB in situations where CMAP amplitude is less than 50% of the lower limit of normal (LLN). Whenever possible, inching should be performed between those segments with documented conduction block. If the segment where conduction block is detected is between 50 and 100 mm in length, the confidence level for true conduction block is much higher since temporal dispersion and phase cancellation have relatively little effect over this short distance. Technical errors must be minimized by ensuring that supramaximal stimulation is achieved, that anatomical variants such as Martin-Gruber anastomosis are excluded, and ensuring that the spread of stimulus to adjacent nerves does not occur, such as with stimulation distally. It should also be kept in mind that there are other causes of PMCB other than a focal demyelinating process, e., the acute phase of partial nerve injury secondary to trauma or vasculitis, and functional conduction block.

Indirect evidence of a very proximal PMCB can be inferred (1) by finding F-wave responses that are absent, prolonged, or dispersed in a weak muscle with normal distal amplitudes, or (2) by showing that voluntarily evoked muscle action potentials produced by maximal effort (recorded by surface electrodes) are markedly reduced compared to the response evoked by distal electric stimulation (described later). A very distal block may also be inferred if the CMAP amplitudes are reduced in a weak muscle, but then improve rapidly to normal after treatment.
Another indirect sign of distal conduction block is a low amplitude response on distal stimulation, at a time when needle examination provides no evidence of axonal degeneration.

This author and colleagues have used a surface recording technique combined with standard electric stimulation to confirm or detect PMCB in MMN. Distally stimulated electrical (E) response is compared to volitional (V) response obtained by the same recording electrode without electrical stimulation but with maximal voluntary activity. The V/E ratio is markedly reduced in patients with documented conduction block and is significantly different from V/E ratios in healthy subjects or patients with motor neuron disease. The V/E ratio in control subjects varies from 56-58%, similar to that in ALS patients (58-67%). By contrast, in patients with demyelinating neuropathy with conduction block, the V/E ratio was between 12-15%. Patients with upper motor neuron lesions secondary to stroke showed similar findings, with V/E ratios between 11-15% (Figure 2).15

Needle EMG is always abnormal in MMN patients, but the abnormality is restricted to the symptomatic muscles. Unlike ALS, widespread LMN dysfunction is not detected, even in cases where the disease has existed for a long time. Prominent fibrillation potentials and positive sharp waves are rare but fasciculation potentials are common, in 71% of patients.10 Myokymia, although not frequent, is important to note if present since it is not seen in ALS patients. Typically, patients have reduced motor unit recruitment with fast firing units. Giant potentials have been observed only in weak muscles and nerves in normal muscles.
Other Laboratory Features

High titers of IgM antibody directed against GM1 and other gangliosides are reported in 22-84% of patients. Some MMN sera that show anti-GM1 activity also react with other similar glycolipids, including GA1 or GM2 ganglioside. Although high titers of anti-GM1 antibody are supportive of the diagnosis, they are not required to be present for a diagnosis and furthermore are not helpful in predicting response to therapy. The presence of high titers of these antibodies in a patient with multifocal LMN weakness, however, should mandate a careful electrophysiological evaluation. An elevated serum creatine kinase (CK) level is frequently found, probably secondary to the myokymia and cramps in the muscles. Cerebrospinal fluid (CSF) is usually normal or may reveal a slight elevation in total protein content. Serum immunofixation electrophoresis may occasionally reveal the presence of monoclonal gammopathy, mostly of the IgM isotype.

Imaging Studies

Magnetic resonance imaging (MRI) scans of the affected regions may show hypertrophic nerve segments with increased signal intensity in T2-weighted images or in T1-weighted images after gadolinium enhancement. Magnetic resonance neurography is a potential noninvasive technique for identification of focal abnormalities at the level of brachial plexus or along the course of a peripheral nerve. Increased signal intensities on T2-weighted MRI of the brachial plexus were detected in one-third of patients with MMN in one study. Magnetic resonance imaging of the affected regions may show hypertrophic nerve segments with increased signal intensity in T2-weighted images or in T1-weighted images after gadolinium enhancement. Magnetic resonance neurography is a potential noninvasive technique for identification of focal abnormalities at the level of brachial plexus or along the course of a peripheral nerve. Increased signal intensities on T2-weighted MRI of the brachial plexus were detected in one-third of patients with MMN in one study.38,63,91

Pathology

Frequent, albeit mild, morphological abnormalities are seen in sensory fibers in patients with MMN. Increased numbers of large-caliber axons with thinly myelinated fibers, sometimes associated with minor onion bulbs, are reported in sural nerve biopsies. Unlike CIDP, MMN is not marked by epineural and endoneural mononuclear cell infiltrates or endoneurial and subperineurial edema. Two reports of motor or mixed nerve biopsy have showed noninflammatory demyelination with onion bulbs. More recently, Taylor and colleagues performed fascicular nerve biopsies of the motor nerve at the site of conduction block. These authors report reduced density of large myelinated fibers (in a multifocal pattern), regenerating clusters, alterations in size distribution, and low grade axonal degeneration in 7 of 8 nerves studied. The authors did not find evidence to suggest demyelination in paranodal or internodal regions or remyelination in the form of onion bulbs. Based on this pathological study, the authors favor the hypothesis of an antibody-mediated attack directed against components of axolemma at the nodes of Ranvier (resulting in functional conduction block followed by demyelination, and axonal degeneration if the attack is severe) rather than an attack on components of paranodal myelin (with segmental demyelination and axonal degeneration).

Pathogenesis

Multifocal motor neuropathy is now widely accepted to have an immune-mediated pathogenesis. Clinical improvement observed with immunomodulation is the strongest supporting evidence for its immunopathogenesis. Why motor fibers of a mixed nerve are selectively affected is unknown. Possible hypotheses include: (1) the distribution of the demyelination may be determined by fascicular arrangement within the nerve trunk, and demyelinating lesions may be restricted to the “motor fascicles” and, therefore, result in pure motor symptoms; (2) the potential target antigen for this immune disorder may be different for myelin in motor axons than in sensory axons; (3) the underlying
The pathologic process in MMN may affect the sensory and motor fibers equally, but cause conduction failure only in the motor fibers because of a greater safety factor of conduction in the sensory fibers. It has been shown that sensory fibers are less likely to develop activity-dependent conduction block, a feature shown for motor fibers of MMN patients.\textsuperscript{36}

As noted above, under pathological observations, some have suggested that in MMN the immune attack is primarily directed against components of the axon rather than myelin.\textsuperscript{75} Kiernan and colleagues, using excitability testing in patients with MMN, have also shown evidence of membrane hyperpolarization distal to the site of conduction block. They have hypothesized that the conduction block and ectopic discharges are caused primarily by juxtaposed lengths of depolarized and hyperpolarized axonal membrane, and that the block is accompanied by degeneration when the depolarization is severe.\textsuperscript{41}

The pathogenic role of anti-glycolipid antibodies in the serum of MMN patients remains speculative. Some studies correlated clinical improvement with reduction in titers of the antibodies,\textsuperscript{8,65,66} thus suggesting that these antibodies are pathogenic, but this has not been true in other studies.\textsuperscript{16,59} Immunoglobulin deposits have been found at the nodes of Ranvier in biopsied nerve from a patient with MMN\textsuperscript{70} and in rat sciatic nerve treated with anti-GM1 antibody.\textsuperscript{33} Sera from patients with MMN has induced block of conduction when injected into rat sciatic or tibial nerve in vivo\textsuperscript{70,79} or in a mouse phrenic nerve preparation in vitro.\textsuperscript{4,68} These results, however, were not confirmed by Harvey and colleagues\textsuperscript{33} using purified anti-GM1 antibodies. Experimentally, anti-GM1 antisera produced in rabbits immunized with GM1 ganglioside increased K+ current and blocked Na+ channel current in isolated rat myelinated nerve fibers.\textsuperscript{73} This, however, could not by confirmed by Hirota and colleagues.\textsuperscript{34} At this time, anti-GM1 antibodies can at best be considered a marker of the disease.

### Response to Treatment

Since MMN is recognized to be an immune-mediated disorder, several immunomodulatory therapies have been tried, including prednisone, azathioprine, chlorambucil, cyclophosphamide, plasma exchange, and IVIg. High-dose IVIg has been found to be invariably effective in patients reported in the literature.\textsuperscript{6,9,11,14,16,19,24,35,37,40,46,55,59,77,80,81} Four randomized trials of a total of 46 patients have confirmed the benefit of IVIg as well.\textsuperscript{5,28,46,82} Treatment generally begins with IVIg at a dose of 2 g/kg divided over 2-5 days. Beneficial effects begin within days, sometimes hours after the infusion, and peak at an average of 2 weeks. The effect lasts from several weeks to months. Most patients require periodic maintenance doses of IVIg. The dose and frequency of IVIg administration needs to be individualized.
depending on the length of benefit received, which appears to vary between patients, but is relatively constant in an individual patient. After administering the first dose of IVIg, the duration of effectiveness should be determined. Most patients who experience a dramatic benefit have a relapse, which again responds to IVIg treatment. For most, this “yo-yo effect” is unacceptable, and it is prudent to give these patients another dose before the anticipated time of relapse. Patients who experience minimal benefit or patients whose disease is stable may not need a second treatment for years. Occasional patients have a long lasting remission after a single course of IVIg. In cases where more frequent administrations are needed (< 2 months), it is worthwhile to try reducing the dose of IVIg at each administration, and thus to arrive at the minimal dose with maximal effectiveness. Some of the alternative dosing strategies that may work in individual patients are 0.4 g/kg weekly, 0.8 g/kg every 2 weeks, or 1 g/kg every month. In one study, the interval between IVIg infusions could be prolonged with concomitant use of oral cyclophosphamide.

In this author’s experience, and from limited reports of long-term IVIg treatment, no patient has become absolutely refractory to treatment. However, deterioration of muscle strength may occur with long-term IVIg treatment. Increasing the frequency of administration of IVIg may offset any chance of deterioration. Improvement in strength correlates with a reduction in PMCB but no change in anti-GM1 antibody titers. Predictors of a better response include a younger age at onset, a smaller number of affected limb regions, elevated GM1 antibody titers, definite conduction blocks, and higher distal amplitudes. On the other hand, older age at onset, more widespread weakness, and elevated serum CK values are associated with relatively poor response.

Although the high cost of IVIg appears to be the main obstacle to its use, there are some serious, albeit rare, side effects that need to be monitored. Transient headache, chills, myalgia, and nausea are common and can be managed by non-steroidal anti-inflammatory drugs and slowing the infusion rate. Severe headaches or other intolerable allergic side effects can be prevented by pre-administration methylprednisolone (60-100 mg IV) and diphendylamine (25-50 mg IV) 30 minutes prior to IVIg infusion. Moderately severe reactions, including aseptic meningitis and skin rash (urticaria, lichenoid lesions, pruritis, petechiae), occur within days of the infusion and generally require no treatment. More serious reactions are fortunately rare and include anaphylaxis (in patients with severe IgA deficiency, test prior to IVIg administration), renal failure (in patients with preexisting renal disease and volume depletion), thromboembolic episodes, such as stroke, myocardial infarction, pulmonary embolism (in patients with increased risk such as elderly, diabetic, thrombotic, hypergammaglobulinemia), and volume overload (necessitating caution in congestive heart failure patients).

Sometimes a different brand of IVIg may be necessary to avoid side effects. The lot number and name of the commercial preparations of IVIg used in each case should be recorded. Caution should be used in giving IVIg to the elderly and to patients with IgA deficiency, borderline renal dysfunction, or cardiac dysfunction.

The mechanism of IVIg’s immunomodulatory effects are not fully understood. The rapidity of clinical and electrophysiologic improvement after IVIg suggests that improvement is unlikely to be due to structural remyelination of demyelinated axons. Different hypotheses include supply of an anti-idiotypic antibody, interference with antibody binding or accessibility to the antigen, Fc receptor blockade, modulation of cytokine secretion, regulation of B cell and T cell expression or function, neutralization of superantigens, and induction of remyelination.

Prednisone and plasma exchange, two therapies used in the standard treatment of CIDP, have rarely been effective in the treatment of MMN. However, cyclophosphamide is perhaps the only one shown to have consistent efficacy (50-80%) in the treatment of MMN. Although long term maintenance therapy with IVIg has benefited patients in some cases, it is not routinely given because of its toxic side effects, including bone marrow suppression, increased risk of infections, hemorrhagic cystitis, infertility, teratogenicity, alopecia, nausea, vomiting, and an increased risk of hematologic malignancies. Daily oral (100-150 mg/day) or periodic intravenous (1-3 g/m²) regimens have been used for 6 months. A few anecdotal patients have been successfully treated with another alkylating agent, chlorambucil. Interferon-β1 has been successfully used as an alternate treatment of MMN patients. In one study, cyclosporin A was shown to improve MMN in two patients.

Although long-term maintenance therapy with IVIg has beneficial effect on muscle strength and upper limb disability, it does not prevent decrease in strength over time and does not induce remission. It has been suggested that early treatment may prevent future progression of weakness and disability.

**FUTURE DIRECTIONS**

While the immune pathogenesis clearly needs to be defined further, there is a need to find alternative treatment strategies to IVIg. In some patients, the duration of response decreases over time, leading to increased frequency of IVIg administration. The
natural course of the disease is of slow progression over long periods of time, even with treatment. However, despite the progression, the disease rarely, if ever, leads to death or severe disability. Most patients are able to maintain near-normal function. New conduction block and axonal loss has been shown to occur despite treatment as well.

A course of IVIg is expensive and the patient’s disability progresses despite continued treatment. Repeated infusions of IVIg leads to loss of venous access and the frequent need for central venous access. By reducing the B-cell population, rituximab may provide an alternate therapy in MMN. Levin and Pestronk have reported improvement in patients who have motor neuropathy and elevated GM1 antibodies, with four weekly intravenous infusions of rituximab (375 mg/m²). Immunoablative treatment with high-dose cyclophosphamide (50 mg/kg/day IV for 4 days followed by granulocyte colony stimulating factor) does not damage hematopoietic “stem cells,” and permits repopulation of the immune system without bone marrow transplant. Recent evidence indicates that this treatment can induce durable remissions in autoimmune diseases.

**MULTIFOCAL ACQUIRED DEMYELINATING SENSORY AND MOTOR NEUROPATHY**

Lewis and colleagues described five cases of multifocal demyelinating neuropathy with conduction block in 1982. These cases looked like MMN with upper extremity asymmetrical weakness progressing over years and associated with multifocal demyelination and conduction block, but with prominent sensory abnormalities clinically and electrophysiologically. Recently, similar cases have been reported in the literature under different titles including “focal upper limb predominant, multifocal CIDP, and multifocal inflammatory demyelinating neuropathy.”

The term Lewis-Sumner syndrome has been suggested as the preferred term in recognition of its description by Lewis and Sumner, even though Adams and colleagues had described two similar cases of asymmetric pseudohypertrophic inflammatory neuropathy with onion bulb formation in 1965.

**CLINICAL FEATURES**

Approximately 50 patients with MADSAM neuropathy have been reported in the literature. From the reported cases, there appears to be a 2:1 male predominance with mean age of onset in the early 50s (range 14-77 years). Like MMN, the onset is usually insidious with a slowly progressive course. Also like MMN, initial asymmetrical involvement of upper limbs is typical. Both sensory and motor symptoms are present. The presentation is of mononeuropathy multiplex, but with a chronic progressive course. Multifocal weakness and numbness (or pain) conforming to a discrete peripheral nerve distribution rather than a generalized stocking or glove pattern is noted. Cranial nerves, including optic, oculomotor, trigeminal, and facial nerves, can be involved. Decreased or absent muscle stretch reflexes in a multifocal, asymmetric distribution are noted, although complete areflexia can also occur. In patients with the above symptoms, hereditary neuropathy with liability to pressure palsies should also be included in the differential diagnosis.

**Electrophysiological Features**

Like MMN, the electrophysiological features include focal demyelinating features such as conduction block, temporal dispersion, prolonged distal latencies, prolonged F waves, and slow conduction velocities in one or more motor nerves. However, in contrast to MMN, the sensory nerve action potential (SNAP) amplitudes are absent or reduced in amplitude in the affected nerves. Electromyography can reveal fibrillation potentials and positive sharp waves as well as polyphasic, long-duration MUAPs that recruit early.

**Laboratory Features**

In contrast to MMN, CSF protein is elevated in 60-82% of MADSAM neuropathy patients (mean level of around 70 mg/dl). Also in contrast to MMN, most patients do not have IgM anti-GM1 antibodies. However, IgG antibodies gangliosides were reported in patients with multifocal acquired sensory and motor neuropathy with or without demyelinating features.

**Pathology**

Sensory nerve biopsies demonstrate features expected to be seen in CIDP with thinly myelinated large diameter fibers, demyelinated fibers, subperineurial and endoneurial edema, and mild onion bulb formations. Teased fiber preparations revealed demyelinated or remyelinated internodes in 3-88% of the fibers. A smaller percentage of teased fibers show features of axonal degeneration. Fascicle-to-fascicle variability may also be noted.

**Pathogenesis**

The pathogenic basis for MADSAM neuropathy is not known. The clinical, electrophysiological, and treatment response favor an immune basis. If the asymmetry is taken away, the disorder is rather similar to CIDP and is therefore likely to have a similar pathogenesis. In fact, MADSAM neuropathy meets the CIDP criteria formulated by the ad hoc subcommittee of the American Association of Neurology task force.

**Treatment**

The response rate to IVIg appears similar to MMN and CIDP. Retrospective series have demonstrated that 72% of patients...
with MADSAM neuropathy improved with IVIg treatment.\textsuperscript{72} However, in contrast to MMN (but similar to CIDP), 71% of patients with MADSAM neuropathy have also demonstrated improvement with corticosteroid treatment.\textsuperscript{72}

**SUMMARY**

Multifocal motor neuropathy and MADSAM neuropathy are two multifocal demyelinating disorders of the peripheral nerves. Both respond to immunomodulation. Multifocal motor neuropathy may clinically resemble an LMN form of ALS while MADSAM neuropathy is more akin to CIDP (Table 1). Sensory symptoms and signs, both clinical and electrophysiological, and the symmetrical nature of proximal and distal weakness should help in diagnosing CIDP. Pure motor asymmetric disorders may raise the possibility of both MMN and the progressive muscular atrophy variant of ALS. Once peripheral motor nerve demyelinating features have been clearly identified, the diagnosis of MMN is not difficult. The demyelinating features in patients with MMN are recognizable if the correct nerves, including proximal segments, are studied. The diagnosis of ALS is also relatively straightforward in patients without demyelinating features, but clear pyramidal signs at several levels (bulbar, cervical, thoracic, and lumbosacral).\textsuperscript{1} Difficulty may arise in those cases where the patient has a pure LMN syndrome, but no obvious demyelinating physiology. In these cases, careful follow-up at 3-6 month intervals will show the disorder either evolving with diffuse widespread denervation, or developing pyramidal signs confirming ALS. On the other hand, MMN does not change significantly over this time period. High titers of serum IgM anti-GM1 antibodies should also lead the physician to reevaluate the diagnosis of a progressive muscular atrophy variant of ALS.

Several questions regarding the pathogenesis of these rare disorders remain unanswered, including the possible pathogenic role of anti-GM1 antibodies, the reason for the multifocal selective affection being limited to upper limbs, the role of myelin versus axon, motor versus sensory fibers, and the persistence of PMCB over several years.

**REFERENCES**


When It's Not ALS!
Pure Motor Syndromes

CME SELF-ASSESSMENT TEST
Select the ONE best answer for each question.

1. All of the following diseases should be considered in a patient with a progressive upper motor neuron syndrome除外:
   A. Primary lateral sclerosis (PLS).
   B. Amyotrophic lateral sclerosis (ALS).
   C. Progressive muscular atrophy.
   D. Hereditary spastic paraplegia (HSP).
   E. Multiple sclerosis.

2. The first author to report cases that are probably PLS was:
   A. Erb.
   B. Charcot.
   C. Wilson.
   D. Barohn.
   E. Fisher.

3. The duration of symptoms at the time of diagnosis for most PLS patients is approximately:
   A. 3 weeks.
   B. 3 months.
   C. 1 year.
   D. 5 years.
   E. 30 years.

4. HSP patients can be distinguished from PLS patients on the basis of all of the following除外:
   A. Younger age of onset in HSP.
   B. Absence of bulbar symptoms in HSP.
   C. Abnormal needle electromyography in HSP.
   D. Abnormal molecular genetic studies in HSP.
   E. Family history of a similar disorder in HSP.

5. The most common clinical presentations of PLS are:
   A. Tongue and limb atrophy.
   B. Spastic bulbar palsy and leg weakness with spasticity.
   C. Arm and leg fasciculations.
   D. Diplopia and dysphagia.
   E. Paraplegia with a thoracic sensory level.

6. Reasons for missing conduction block in patients with a multifocal motor presentation might include:
   A. Lesions are too proximal.
   B. Lesions may be “burnt out.”
   C. Lesions may actually affect only axons.
   D. Conduction block is dynamic.
   E. All of the above.

7. An exhaustive domain is one:
   A. Where you have to think so hard it makes you tired.
   B. Where the likelihood of all diseases considered adds up to 100%.
   C. Where you need to be on the lookout for patterns that do not fit any of the disorders on the list of possibilities.
   D. That characterizes the field of diagnosis in motor disorders.
   E. None of the above.

8. The reason 2 years is used as the minimal time needed to diagnose brachial amyotrophic diplegia (BAD) is:
   A. It seemed like a good idea.
   B. Amyotrophic lateral sclerosis always becomes clear before 2 years.
   C. All patients who showed spread beyond the arms before 2 years had a poor prognosis.
   D. All cases that remained static for at least 2 years remained focal permanently.
   E. All of the above.

9. Which of the following is more common to multifocal acquired motor axonopathy than multifocal motor neuropathy?
   A. The hands are often affected.
   B. There is an absence of proximal involvement.
   C. Onset is before age 30.
   D. GM-1 antibodies are present.
   E. There is conduction block.
10. Cases of BAD that seemed to remain focal over time:
   A. Tended to begin in the hands.
   B. Tended to affect the shoulders and biceps maximally.
   C. Always remained limited to one or two myotomal distributions over time.
   D. Were usually women.
   E. Responded to immune therapy.

11. Which of the following statements about progressive muscular atrophy (PMA) is FALSE?
   A. Patients with PMA may have undetected upper motor neuron findings.
   B. Overall, the patients with PMA have longer survival compared to those with ALS.
   C. There are reliable clinical means for reliably distinguishing PMA from ALS.
   D. Many patients who appear to have PMA may meet diagnostic criteria for ALS later in their course.
   E. All of the above.

12. Which of the following statements about monomelic amyotrophy is true?
   A. This entity affects predominantly young males.
   B. The proximal upper limbs are preferentially affected.
   C. This entity is treatable with immunosuppressive medications.
   D. Cervical spine magnetic resonance imaging (MRI) does not show any specific diagnostic findings.
   E. None of the above.

13. Which test would be the most useful for the evaluation of a 40-year-old man with symmetrical proximal arm and leg weakness, dysarthria, dysphagia, decreased deep tendon reflexes, and normal sensation?
   A. Genetic testing for a survival motor neuron deletion on chromosome 5.
   B. Genetic testing for expanded trinucleotide-repeat expansion repeats in the androgen receptor gene on chromosome X.
   C. Diffusion tensor MRI imaging.
   D. Cervical spine MRI taken with the neck flexed.
   E. None of the above.

14. A 68-year-old Caucasian man has severe, right greater than left, proximal arm weakness. There are prominent fasciculations and decreased reflexes in the arms. Strength is normal in bulbar and leg muscles. Sensation is normal. His symptoms began 2 years ago. Which of the following statements is most accurate?
   A. The patient will likely die within 1-2 years.
   B. The patient will likely have a prolonged survival.
   C. The patient has Hirayama’s disease.
   D. The patient is likely to have gynecomastia.
   E. The patient is likely to have Stukenlaken’s disease.

15. Each of the following is associated with prolonged survival EXCEPT:
   A. Upper motor neuron signs.
   B. Symmetrical, proximal weakness.
   C. Weakness restricted to the proximal upper arms.
   D. Purely lower motor neuron findings.
   E. None of the above.

16. All of the following diseases should be considered in a patient with a progressive asymmetric weakness EXCEPT:
   A. Lewis-Sumner syndrome.
   B. ALS.
   C. Multifocal motor neuropathy (MMN).
   D. Mononeuroma multiplex.
   E. Chronic inflammatory demyelinating polyneuropathy (CIDP).

17. Conduction block can be seen in all of the following EXCEPT:
   A. ALS.
   B. MMN.
   C. Lewis-Sumner syndrome.
   D. CIDP.
   E. Guillian-Barré syndrome (GBS).

18. Most patients with MMN respond dramatically to:
   A. Steroids.
   B. Intravenous immunoglobulin (IVIg).
   C. Azathioprine.
   D. Plasma exchange.
   E. None of the above.

19. MMN is different from Lewis-Sumner syndrome in the following:
   A. Conduction block.
   B. Asymmetrical distal involvement.
   C. Predominant upper limb involvement.
   D. Absence of sensory findings.
   E. Response to IVIg.

20. MMN is characterized by all of the following EXCEPT:
   A. IVIg response.
   B. Progressive asymmetric involvement.
   C. Myokymia.
   D. Invariably fatal course.
   E. Conduction block.
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Pure Motor Syndromes

EVALUATION

Select ANY of the answers that indicate your opinions.

Your input is needed to critique our courses and to ensure that we use the best faculty instructors and provide the best course options in future years. Please use the computer form to answer the following questions. For the purpose of tabulating evaluations, please enter the last 4 digits of your telephone number in the ID NUMBER box beginning with the left column and fill in the appropriate ovals below each number. Make additional comments or list suggested topics or faculty for future courses on the comment form provided at the end.

21. How would you rate the quality of instruction received during Dr. Barohn’s presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

22. Select any item(s), that, if changed, would have appreciably improved Dr. Barohn’s presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.

23. How would you rate the quality of instruction received during Dr. Katz’s presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

24. Select any item(s), that, if changed, would have appreciably improved Dr. Katz’s presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.

25. How would you rate the quality of instruction received during Dr. Saperstein’s presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

26. Select any item(s), that, if changed, would have appreciably improved Dr. Saperstein’s presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.

27. How would you rate the quality of instruction received during Dr. Chaudhry’s presentation?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.

28. Select any item(s), that, if changed, would have appreciably improved Dr. Chaudhry’s presentation:
   A. Quality of slides.
   B. Quality of handout.
   C. Amount of clinically relevant information in the presentation.
   D. Amount of scientific content in the presentation.
   E. Other: please explain on the comment form at the back of this handout.
29. As a result of your attendance at this course, did you learn anything that will improve the care of your patients?
   A. Yes, substantially.
   B. Yes, somewhat.
   C. Not sure.
   D. Probably not.
   E. This course was not applicable to my patients.

30. Select ALL items where improvement was needed.
   A. The accuracy of advance descriptions of this course.
   B. The specific topics selected for presentation.
   C. The number of speakers in this course.
   D. The amount of time allotted for discussion in this course.
   E. Other: please add other areas and outline specific recommendations for areas needing improvement on the comment form at the back of this handout.

31. Should this topic be presented in the future by a different method of presentation.
   A. No, the topic of presentation should remain as a course.
   B. Yes, the topic should be presented as a dinner seminar.
   C. Yes, the topic should be incorporated into the plenary session.
   D. Yes, the topic should be discussed during a breakfast session.
   E. Yes, the topic should be organized as a special interest group.
FUTURE MEETING RECOMMENDATIONS

Select ANY of the answers that indicate your opinions.

The following questions are included with all dinner seminar, course, and plenary session evaluations. It is only necessary to answer these questions once during the course of the entire meeting.

32. Please indicate below your specialty:
   A. Neurologist.
   B. Physiatrist.
   C. PhD.
   D. Other.

33. How often do you attend AAEM meetings?
   A. Annually.
   B. Every 2-3 years.
   C. Every 4 or more years.
   D. This is the first AAEM meeting I have attended.

34. With regard to this years meeting, which of the smaller group sessions did you attend? (mark all that apply)
   A. Experts' roundtables.
   B. Workshops.
   C. Dinner seminars.
   D. None of the above.

35. If you answered none of the above to the previous question, please answer the following. The reason I did not attend the small group sessions was due to:
   A. The timing of the event.
   B. The cost of the event.
   C. My lack of interest in the topics offered.
   D. The session was full.

36. Did this meeting provide information that will enhance care of your patients?
   A. Extremely.
   B. Somewhat.
   C. Very little.
   D. Not at all.

37. With regard to the social event:
   A. I am signed up to attend the social event.
   B. I did not sign up because of the cost of the event.
   C. I did not sign up because of the day the event was offered.
   D. I did not sign up because I am not interested in attending this type of function.

38. How would you rate this meeting?
   A. Poor.
   B. Fair.
   C. Good.
   D. Very good.
   E. Excellent.

39. Did this meeting meet your expectations?
   A. Not at all.
   B. Somewhat.
   C. As expected.
   D. Exceeded expectations.
   E. Best ever.

40. Was the printed program clear and easy to follow?
   A. Yes.
   B. No.

41. With regard to the meeting hotels:
   A. I stayed at one of the meeting hotels.
   B. I did not stay at one of the meeting hotels.

42. If you answered B to the question above, please explain why you did not stay at one of the meeting hotels (please make your comments under Comments, page 39).

43. How did you first learn about the meeting? (choose the method where you first learned about the meeting)
   A. Preliminary brochure mailing.
   B. Registration brochure mailing.
   C. The internet.
   D. Email message.
   E. From a friend.

44. Did you perceive any commercial bias in any of the educational sessions offered by the AAEM at this meeting?
   A. Yes.
   B. No.

45. Did you attend any of the industry forums provided this year?
   A. Yes.
   B. No.
46. If you answered yes to question 45 and you attended the Pfizer Industry Forum, how would you rate the quality of the session?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.
   On Page 39 under comments, please provide any other comments you have about your attendance at the Pfizer Industry Forum.

47. If you answered yes to question 45 and you attended the Allergan Industry Forum, how would you rate the quality of the session?
   A. Best possible.
   B. Good.
   C. Average.
   D. Fair.
   E. Worst possible.
   On Page 39 under comments, please provide any other comments you have about your attendance at the Allergan Industry Forum.

48. How do you prefer to learn new information?
   A. Lecture only.
   B. Lecture in conjunction with questions and answers.
   C. Small group hands-on.
   D. Small group discussion.

49. I plan to attend the 2005 AAEM meeting in Monterey, California, September 21-24.
   A. Yes, definitely.
   B. No, definitely.
   C. Will wait to see the program content.
   D. Will wait to see if budget allows my attendance.

50. I would be more likely to attend the 2005 AAEM meeting if (please make your comments under Comments, page 39):
COMMENTS

Given time and budget constraints, is there something we could do in terms of altering the format of the meeting that would significantly increase the likelihood of your attendance at future AAEM meetings? Explain:

Write out any additional comments about specific courses or the plenary session (please indicate which), and list suggestions for topics and speakers for future meetings. Leave at the AAEM Registration and Information Center or mail to the AAEM Executive Office at 421 First Avenue SW, Suite 300 East, Rochester, MN 55902.