NM Update I: MND Pathophysiology and Genetics Rehab Aspects of Treatment, CIDP, and Related Disorders

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NM Update I: MND Pathophysiology and Genetics Rehab Aspects of Treatment, CIDP, and Related Disorders

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Chair: Dianna Quan, MD

The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
Objectives

Objectives - Participants will acquire skills to (1) utilize a pattern recognition approach elucidated through clinical vignettes in the diagnosis and management of patients with MNDs, (2) recognize clinical and electrophysiological features of CIDP and related disorders and become familiar with treatment options, and (3) practice the vignette-based format used for many questions on the NM medicine board examination.

Target Audience:
- Neurologists, physical medicine and rehabilitation and other physicians interested in neuromuscular and electrodiagnostic medicine
- Health care professionals involved in the management of patients with neuromuscular diseases
- Researchers who are actively involved in the neuromuscular and/or electrodiagnostic research

Accreditation Statement - The AANEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

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**NM Update I: MND Pathophysiology and Genetics Rehab Aspects of Treatment, CIDP, and Related Disorders**

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Dr. Bromberg received a doctorate in neurophysiology at the University of Vermont and was on the faculty at the University of Michigan, where he then attended medical school and completed his neurology residency and a neuromuscular-EMG fellowship. He now is a professor in the Department of Neurology at the University of Utah and serves as the director of the MDA Clinics there. Dr. Bromberg’s clinical interests focus on nerve and muscle disorders, in particular ALS. His research interests are in ALS clinical trials and quality of life assessments. He also is interested in new EMG techniques to facilitate the diagnosis of ALS and in following the course of the disease.

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Dr. Joyce is an assistant professor in the Department of Physical Medicine and Rehabilitation at the University of California, Davis (UC-Davis) School of Medicine. She is board certified in both physical medicine and rehabilitation and neuromuscular medicine. She completed her medical degree at Touro University College of Osteopathic Medicine, her PMR residency at Michigan State University, and her fellowships at UC Davis. Dr. Joyce has authored or co-authored 12 publications. Her research focuses on developing stem cell therapies for treatment of ALS, for which she is supported by a K12 early career development award through the Association of Academic Physiatrist and the National Institutes of Health.

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Dr. Lewis is professor and associate chair of neurology at Wayne State University, moving soon to a position at Cedars-Sinai Medical Center in Los Angeles. He received his neurology training at the University of Pennsylvania. Dr. Lewis’ interests are in the clinical and electrophysiologic consequences of peripheral nerve demyelination as it relates to inflammatory and inherited neuropathies. Multifocal sensorimotor demyelinating neuropathy with persistent conduction block now is known as the Lewis-Sumner Syndrome, due to his paper on this topic written with Drs. Austin Sumner, Mark Brown, and Arthur Asbury. Dr. Lewis has been involved in multiple investigations of CIDP, multifocal motor neuropathy, and other immune-mediated neuromuscular disorders and was the principal investigator on the first multicenter North American trial in CMT-1A.

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Motor Neuron Disease Pathophysiology and Genetics Update: Rehabilitative Aspects of Treatment

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This is a two-part update on amyotrophic lateral sclerosis, with the first part a review of recent information on genetic and pathophysiologic aspects by Mark Bromberg and the second part focusing on rehabilitative aspects by Nanette Joyce.

PART I: MOTOR NEURON DISEASE PATHOPHYSIOLOGY AND GENETICS UPDATE

Amyotrophic lateral sclerosis (ALS) has long been known to have a familial component (fALS) with transmission, for the most part, following an autosomal dominant pattern and with high penetrance. This suggests that a single gene mutation can be causative in these families. In 1993, a linkage was discovered between fALS and superoxide dismutase 1 (SOD1) gene mutations, and in the intervening years over 150 mutations have been found in the SOD1 gene. Some mutations are common, some show ethnic differences due to founder effects (D90A common in Scandinavia and A4V common in North America), but others are rare, and clinically some mutations have a slow course while others have a rapid rate of progression. While most families follow an autosomal dominant pattern, in Scandinavia there is a modifying factor and the fALS patients with the D90A mutation have a recessive pattern.

Since the discovery of the SOD1 gene, other genes have been linked to autosomal dominant adult or classic fALS, one to X-linked ALS, and several to rare autosomal recessive juvenile ALS (Table). A useful and up-to-date resource can be found at http://alsod.iop.kcl.ac.uk. It is believed that fALS represents, by family history, ~5% of classic ALS cases, but the current list of mutations can only be linked to about ~50-60% of the families, with other genes to be discovered.

This raises the question of the utility of testing in an ALS patient with a negative family history, as a negative gene test at this time will be inconclusive.

The clinical complexities and evolving testing for fALS will be illustrated with a case. This will be followed by a discussion of new genes and their implications for postmortem pathologic findings and pathophysiology.

Table. Genes and proteins for amyotrophic lateral sclerosis and frontotemporal dementia

<table>
<thead>
<tr>
<th>ALS type</th>
<th>Onset</th>
<th>Mode</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS1</td>
<td>Adult</td>
<td>AD</td>
<td>SOD1</td>
<td>Cu/Zn superoxide dismutase</td>
</tr>
<tr>
<td>ALS2</td>
<td>Juvenile</td>
<td>AR</td>
<td>SOD2</td>
<td>Alas</td>
</tr>
<tr>
<td>ALS3</td>
<td>Adult</td>
<td>AD</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>ALS4</td>
<td>Juvenile</td>
<td>AR</td>
<td>SEZ1</td>
<td>Serotonin</td>
</tr>
<tr>
<td>ALS5</td>
<td>Juvenile</td>
<td>AD</td>
<td>TDP43</td>
<td>TAR DNA binding protein</td>
</tr>
<tr>
<td>ALS6</td>
<td>Adult</td>
<td>AD</td>
<td>FTSP</td>
<td>Fused in sarcoma</td>
</tr>
<tr>
<td>ALS7</td>
<td>Adult</td>
<td>AD</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>ALS8</td>
<td>Adult</td>
<td>AD</td>
<td>FAPB</td>
<td>VAMP-associated protein B</td>
</tr>
<tr>
<td>ALS9</td>
<td>Adult</td>
<td>AD</td>
<td>LING</td>
<td>Lingusin</td>
</tr>
<tr>
<td>ALS10</td>
<td>Adult</td>
<td>AD</td>
<td>TARDBP</td>
<td>TAR DNA binding protein</td>
</tr>
<tr>
<td>ALS11</td>
<td>Adult</td>
<td>AR</td>
<td>FUS</td>
<td>Fused in sarcoma</td>
</tr>
<tr>
<td>ALS12</td>
<td>Adult</td>
<td>AD</td>
<td>OPTN</td>
<td>Optineurin</td>
</tr>
<tr>
<td>ALS13</td>
<td>Adult</td>
<td>AD</td>
<td>ATXN2</td>
<td>Ataxin 2</td>
</tr>
<tr>
<td>ALS14</td>
<td>Adult</td>
<td>AD</td>
<td>VCP</td>
<td>VCP-associated protein</td>
</tr>
<tr>
<td>ALS15</td>
<td>Adult</td>
<td>AD</td>
<td>UBQLN2</td>
<td>Ubiquilin 2</td>
</tr>
<tr>
<td>ALS16</td>
<td>Adult</td>
<td>AD</td>
<td>SIGMAR1</td>
<td>Sigma nonopiod intracellular receptor 1</td>
</tr>
<tr>
<td>ALS-FTD1</td>
<td>Adult</td>
<td>AD</td>
<td>C9orf72</td>
<td></td>
</tr>
<tr>
<td>ALS-FTD2</td>
<td>Adult</td>
<td>AD</td>
<td>C9orf72</td>
<td></td>
</tr>
<tr>
<td>ALS-FTD3</td>
<td>Adult</td>
<td>AD</td>
<td>C10orf2B</td>
<td>Chromatin modifying protein 2B</td>
</tr>
</tbody>
</table>

From: http://alsod.iop.kcl.ac.uk
CASE REPORT

A 69-year-old woman was referred for right hand weakness beginning in the summer of 2003. Weakness had progressed within the right arm, marked limiting in use. She noted new onset cramps in her legs. Examination was remarkable for atrophic weakness in distal muscles as well as weakness of more proximal muscles and pathologic reflexes in the right arm. The electrodiagnostic (EDX) study was remarkable for active and chronic neurogenic denervation in four limbs and thoracic paraspinal muscles. After questioning the patient for a family history of ALS a diagnosis of sporadic ALS (sALS) was made. Weakness progressed to include all limbs as well as the diaphragm, and she passed away in the summer of 2006.

In the summer of 2008, her 50-year-old son was referred for progressive distal left arm weakness. He was very active physically (competitive trail running and cycling), but over time weakness progressed and EDX evaluations supported initial focal and later diffuse active and chronic neurogenic denervation in all limbs. Tendon reflexes were pathologically brisk. The patient was briefly intubated in the setting of a respiratory crisis, and he passed away in January 2012.

With the diagnosis in the son the family history was reviewed several more times, and eventually it was determined that a paternal uncle of his mother had passed away from progressive bulbar weakness and had a diagnosis of progressive bulbar palsy (Figure 1). The family came from Germany, and the mother’s father, who would be a suspected carrier, died in World War II at a young age.

The son enrolled in a study of fALS and was negative for known gene mutations until the hexanucleotide repeat expansion (C9ORF72) mutation was described in mid-2011, and he was positive for the expansion. No other family members have requested testing.

POINT 1: FAMILY HISTORIES

The case above is an example of an initially false-negative family history despite detailed questioning of the index patient. There is no consistent definition in the literature of how many members of a family must be involved for fALS, but usually at least two members of an extended family are required. In this case, one family member was one generation remote from the mother, and her father died at an early age, obscuring a possible obvious family history. While spontaneous mutations occur, difficulties with ascertainment include an inaccurate diagnosis of ALS in other family members and death at an early age (there are reported cases of symptom onset in obligate carriers in the seventh and eighth decades). It is of clinical interest that sALS and fALS cannot be distinguished by neurologic examination, and although some steps in the pathophysiological cascade likely differ between sALS and fALS, there is also likely a common final pathway resulting in death of a similar set of neurons.

POINT 2: AMYOTROPHIC LATERAL SCLEROSIS AND DEMENTIA

It has become clear over the past decade that up to 40% of ALS patients have a degree of frontotemporal lobe dysfunction, and a percentage of patients who present to a dementia clinic and are found to have frontotemporal lobe dementia (FTLD) also have evidence for concurrent ALS. Further, there are examples of familial FTLD (fFTLD) and the combination of fALS+fFTLD. There is no link between ALS and Alzheimer’s dementia. When a family history from a patient with ALS includes members with dementia, the type of dementia (Alzheimer’s versus FTLD) may not be clearly distinguished, and inquires into a possible family history in the setting of ALS needs to include details of the familial dementia.

Patients with ALS who have features of frontotemporal lobe dysfunction or syndrome may not fulfill formal criteria for FTLD. A consensus recognizes traditional subtypes of frontotemporal lobe dysfunction or syndrome in ALS: behavioral variant with altered social conduct, impaired regulation of interpersonal conduct, emotional blunting and loss of insight; and semantic variant characterized by fluent speech with impaired understanding of word meaning or object identity. However, the consensus emphasized that dysfunction can be subtle, and elements of dysfunction include word finding difficulties, executive decision making, poor retrieval, apathy, impatience, and rigidity. Word finding difficulties are readily assessed by asking a patient to give as many animal names in 60 s: normal is > 26 distributed over the minute, while patients with frontotemporal lobe dysfunction will offer a few names at the onset and none for most of the rest of the minute. Family members will frequently relate that the patient has difficulty making common decisions. There is frequently a withdrawal from usual activities. Patients may carry out the same activities on a set schedule. Patients, as they become weaker, may request help with an activity with little flexibility as to when the help can be given. Retention of memory, on the other hand, is usually preserved in FTLD.

POINT 3: PROTEIN AGGREGATES

Intracellular inclusions have long been observed in the cytoplasm of neurons involved in ALS, both sALS and fALS. These include Bunina bodies, and, more recently with immunohistochemical staining, ubiquinated proteins in various patterns (fibrils, skein-like, dense, or compact bodies). Ubiquination is one of two cellular processes to dispose of degraded proteins (the other is autophagia). Ubiquitin molecules are attached to proteins which are then transported to proteasomes where they are further degraded to peptides. Aggregates of ubiquinated proteins represent an abnormal protein disposal process.

A number of other proteins have recently been identified in aggregates in motor neurons, including trans-activation-responsive region (TAR) DNA binding protein-43 (TDP-43), fused in sarcoma...
(FUS), and Ubiquilin 2. These proteins have also been identified in frontotemporal lobe structures in FTLD and ALS-FTLD. Some of these proteins (TDP-43, FUS) are primarily nuclear proteins, but the aggregates are found prominently in the cytoplasm. Of note, there are ubiquinated inclusions in patients with SOD1 mutations but they do not also include TDP-43 inclusions.

These findings support abnormal protein disposal as an element in the pathophysiology of ALS and FTLD. However, it is not clear where the aggregates fit in the pathophysiology of ALS. Possibilities include direct cytotoxic effects of the aggregates, an upstream process that alters the proteins and hence interferes with protein degradation and where the aggregates are simply a nonspecific marker, or a combination.

While SOD1 is a well-known enzyme that reduces toxic free radicals produced by normal cellular metabolism, not all SOD1 mutations result in a deficiency of enzyme activity, and thus a “toxic gain of function” is postulated, but it remains to be elucidated. Mutations in genes coding for TDP-43 and FUS are found in fALS, supporting a pathophysiologic role of aggregated TDP-43 and FUS proteins in both sALS and fALS. Aggregates of TDP-43 and FUS may also possess a toxic gain of function. It is not known why only certain neurons degenerate. Of note, age appears to be a factor as the incidence of ALS increases with age. TDP-43 and FUS are involved in RNA trafficking, as they have RNA binding motifs and specific targets, and they are likely involved in transcriptional regulation, messenger RNA processing, and micro RNA biogenesis, and thus abnormalities of RNA processing may be a fundamental process in many examples of ALS.

**POINT 4: IDENTIFIED GENES**

There are now ~19 genes identified in families with ALS (Table). A number code for protein products is found in protein aggregates, strengthening a pathologic role of that mutation in fALS. To summarize, some genes appear to occur rarely, and others may be common in a population due to founder effects, and at this time perhaps 40% of fALS has no identified underlying gene. Note is made that there remain other modifying factors in the penetration of ALS, as exemplified by the recessive pattern of D90A mutations in Scandinavia and more complex gene patterns may apply.

**POINT 5: PROPAGATION OF WEAKNESS**

The clinical symptoms of ALS start focally and progress within the initial region and to other regions. Recent postmortem examinations support a simultaneous locus of upper and lower motor neuron pathology with spread of involved neurons to match clinical spread. The mechanism of spread of degeneration within the central nervous system is not known, but there is evidence for spread of “toxic” elements from cell to cell. Protein aggregate inclusions are found in most neurodegenerative diseases (amyloid in Alzheimer’s disease, tau in Parkinson’s disease) and this may represent a common mechanism or propagation for neurodegenerative diseases. One hypothesis is that there may be a “seeding” of a misfolded protein, possibly in the setting of cell stress and via stress granules or mutant proteins (Figure 2). There are analogies with propagated misfolding of prion proteins in prion diseases, and to differentiate such processes in ALS from prion disease, the terms “prionoid or prion-like” mechanisms have been put forward. Normal proteins (SOD1, TDP-43, FUS) may be brought into misfolding. The mechanisms of spread among cells is not clear but could be by neurosecretory granules into the extracellular matrix with uptake by neighboring cells, via neurotransmission between cells, or through glial cells.

**Figure 2.** Cartoon of two neurons. Hypothesis: Normal or mutant SOD1, TDP-43 or FUS protein can be induced to misfold and aggregate. There may be “seeding” of misfolding that could be linked to mutant protein forms or related to cell stress and the normal formation of stress granules. The aggregated proteins recruit and misfold more proteins. Through a variety of mechanisms (synaptic, exocytosis-endocytosis) the aggregated protein can move to the next neuron, thus propagating misfolded and aggregated proteins. It is further hypothesized that the abnormal protein aggregates represent a “toxic gain” of cellular function leading to cell death.

FUS = fused in sarcoma, SOD1 = superoxide dismutase 1, TDP-43 = trans-activation-responsive region (TAR) DNA binding protein-43

**SUMMARY**

Many points are coming into better focus in the pathophysiology of ALS that includes the clinical similarities of sALS and fALS and the pattern of progression. Protein aggregates, including mutant and normal proteins, appear to be key features. Protein aggregates also link frontotemporal lobe pathology to motor neuron pathology. Another feature is cellular stress, and an abnormal response that gets out of control. There are now data from Alzheimer’s disease of cell-to-cell propagation of aggregated protein which could apply to ALS. Overall, there are emerging similarities among neurodegenerative diseases and new opportunities for therapeutic targets.
REFERENCES

Motor Neuron Disease Pathophysiology and Genetics Update: Rehabilitative Aspects of Treatment

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“This is a disease of daily discovery . . . I wake up each morning and wonder, what can’t I do today that I was able to do yesterday?”

—68-year-old ALS patient

PART II:

The typical clinical course for the patient diagnosed with motor neuron disease (MND) is one of steady progressive functional decline and loss of independence. The effects of the disease become easily identifiable as patients commonly lose the ability to speak, swallow, move volitionally, and breathe independently. Although, MND is presently incurable, it is not untreatable. When caring for the patient with amyotrophic lateral sclerosis (ALS), the goal of rehabilitation is to maintain quality of life by providing treatment focused on maximizing the patient’s functional capacity, prolonging independent mobility, decreasing pain and deformity, providing resources to sustain community integration, and developing a care plan to meet the patient’s and caregiver’s needs as the patient progresses to dependence and end-of-life.¹

The comprehensive rehabilitative management of the patient with ALS is complex due to the disease’s phenotypic heterogeneity and wide variety of associated clinical symptoms. For this reason, a referral to a multidisciplinary ALS clinic should be considered for ALS patients, as evidence supports increased survival and improved quality of life for those receiving their care in this setting where access to the cumulative expertise of the multidisciplinary clinic team is provided.² A multidisciplinary team often includes a neuromuscular disease specialist (neurologist and/or physiatrist), physical therapist, occupational therapist, speech therapist, respiratory therapist, nutritionist, medical social worker, psychologist, and representatives from ALS patient support/advocacy groups. The best teams have dedicated staff, who become expert in knowing the many faces of motor neuron disease and its related symptoms, and are able to anticipate and provide timely recommendations thereby meeting the rehabilitation needs of their patients.

DISEASE PHENOTYPE PROVIDES CLUES TO PATIENT’S FUTURE NEEDS

The patient’s MND phenotype offers predictive information regarding their likely pattern of functional decline, providing clues to the timing of rehabilitation and durable medical equipment needs. Chio and colleagues prospectively studied 1,332 patients diagnosed with MND and stratified this large cohort into eight phenotypes with distinguishable clinical and prognostic characteristics (Table 1).³ These clinical phenotypes provide the rehabilitation specialist with a framework for predicting functional decline and can enable the timely acquisition of durable medical equipment prior to the complete loss of function, thus avoiding a situation where a patient is rendered helpless while waiting for the arrival of a necessary assistive device. For example, a patient who presents with the classic phenotype and lower limb weakness will likely lose ambulation and require a power wheelchair (PWC) for mobility. The process of acquiring a PWC often takes months. If the PWC order is placed late—once the patient has reached insurance criteria to qualify for a PWC—the more rapidly progressing patient may become immobile before equipment delivery, unnecessarily losing their independence.
Table 1: Motor neuron disease phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Site of onset</th>
<th>Presence of FTD</th>
<th>Incidence across sex</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>Upper or lower limb onset and mild pyramidal signs</td>
<td>4%</td>
<td>M &gt; W; Most common pattern in men</td>
<td>2.6 years</td>
</tr>
<tr>
<td>Bulbar</td>
<td>Bulbar muscles</td>
<td>9%</td>
<td>M = W</td>
<td>2 years</td>
</tr>
<tr>
<td>Flail arm</td>
<td>Proximal upper limb atrophy</td>
<td>1.40%</td>
<td>M &gt; W; Rare</td>
<td>4 years</td>
</tr>
<tr>
<td>Flail leg</td>
<td>Distal lower limb atrophy</td>
<td>4%</td>
<td>M = W</td>
<td>3 years</td>
</tr>
<tr>
<td>Pyramidal</td>
<td>Spastic para/tetraparesis</td>
<td>2.50%</td>
<td>M = W</td>
<td>6.3 years</td>
</tr>
<tr>
<td></td>
<td>One or more abnormal reflex and/or pseudobulbar affect with LMN signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure lower motor neuron</td>
<td>Upper or lower limbs</td>
<td>_</td>
<td>2M:W</td>
<td>7.3 years</td>
</tr>
<tr>
<td>Pure upper motor neuron</td>
<td>Upper or lower limbs</td>
<td>3.80%</td>
<td>M = W</td>
<td>10 years in 71.1%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Muscles of respiration</td>
<td>_</td>
<td>6M:W; Most rare phenotype</td>
<td>1.4 years</td>
</tr>
</tbody>
</table>

FTD = frontotemporal dementia, LMN = lower motor neuron, M = men, W = women
Adapted from Chio and colleagues. 3

both in the home and the community. Compared to the patient who presents with lower limb weakness due to a pure lower motor neuron phenotype, the patient with the classic phenotype will likely require a PWC earlier after diagnosis due to the more rapid progression of this phenotype.

Another example is illustrated by the patient who presents with bulbar predominant weakness. Bulbar patients are likely to have early respiratory deficits and may succumb from respiratory failure prior to having sufficient lower limb weakness to require a power mobility device. Instead, the ALS patient with a bulbar phenotype may derive the greatest benefits in survival or quality of life from the prudent initiation of noninvasive ventilation, voice banking, and the use of an augmentative communication device.

Because MND is rapidly progressive, the patient with ALS may transition through a stage when an assistive device would provide maximal benefit to one where the device becomes useless over a relatively short period of time. Therefore, it is beneficial to the patient to anticipate functional decline. For example, a patient with foot drop and mild knee extensor weakness may be prescribed an ankle foot orthosis to prevent tripping falls and improve ambulation, but by the time the orthosis is measured, molded, and delivered, the patient is no longer ambulatory due to rapid deterioration of knee extensor strength. Early initiation for an assistive device—in this case when dorsiflexion weakness is first detected—can provide the time required to receive the equipment so it is available when needed by the patient.

However, not all patients will need every assistive device or will accept every piece of equipment when it is first recommended, if at all (see Table 2 for a list of commonly prescribed adaptive equip-
Patients with ALS will often benefit initially from exclusive use of bimodal positive airway pressure (BIPAP) at night while sleeping. It can be used with low inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) settings that initially improve patient tolerability, but should be monitored periodically for efficacy by nocturnal pulse oximetry and increased as needed. The lowest settings used for this purpose are an IPAP of 8 cmH2O and EPAP of 4 cmH2O. There are many available mask interface options and a BIPAP prescription should specify mask selection by patient tolerability. The use of BIPAP can be increased to include daytime use as symptoms of dyspnea worsen, and the patient’s PWC can be modified to accommodate the equipment.

Average volume-assured pressure support (AVAPS) is a newer noninvasive ventilation technology that automatically adjusts its settings to ensure delivery of a consistent tidal volume for patients who have changing respiratory needs. Although studies have yet to be completed assessing the longterm tolerability and efficacy of AVAPS compared to BIPAP in the ALS patient population, anecdotal evidence has been positive and the author’s clinic patients have been successfully managed using this technology to meet their extended respiratory needs.

In 2011, the United States Food and Drug Administration approved a phrenic nerve diaphragm pacing (DP) system for patients with ALS under a humanitarian device exemption. The device was initially developed and approved for use in patients with high level spinal cord injuries in 2008 but, while there is convincing data that supports the use of DP in spinal cord injured patients, there is lack of evidence to confirm both efficacy and longterm safety in patients with ALS.

Diaphragm pacing requires surgical implantation of electrodes that target the motor point of each hemidiaphragm. Patient selection requires confirmation of a positive stimulation effect of the phrenic nerve by demonstration of bilateral diaphragm movement during a fluoroscopic sniff test or with needle needle electromyography (EMG) recordings and nerve conduction times. Thus far, the literature indicates con-

### Table 2. Commonly prescribed adaptive equipment for patients with amyotrophic lateral sclerosis

<table>
<thead>
<tr>
<th>Assistive device</th>
<th>Symptom</th>
<th>Special recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck collar</td>
<td>Head drop</td>
<td>Foam collar: Often too warm. Headmaster: lightweight support Miami J or Philadelphia collars: Full support</td>
</tr>
<tr>
<td>Writing board</td>
<td>Dysarthria</td>
<td>Many options from pencil and paper, white erase board to computerized boogie boards</td>
</tr>
<tr>
<td>Assistive Augmentative Communication device</td>
<td>Dysarthria</td>
<td>Voice banking prior to loss of speech. Options include eye gaze, forehead, and brain interface systems</td>
</tr>
<tr>
<td>Splints:</td>
<td>Finger flexion contractures</td>
<td>Contracture may provide a functional benefit</td>
</tr>
<tr>
<td>Neutral hand splints</td>
<td>Foot Drop</td>
<td>AFO Should be lightweight to avoid fatiguing proximal muscles</td>
</tr>
<tr>
<td>Ankle foot orthosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tools for activities of daily living</td>
<td>Hand weakness</td>
<td>Button hook, Velcro shirt, pant and shoe fasteners, Elastic waist pants, Sock aide, Long-handed shoe horn, gripper and bath tools, Adaptive eating utensils</td>
</tr>
<tr>
<td>Single point cane</td>
<td>Hip flexion or knee extensor weakness</td>
<td>Must have good strength in at least one upper extremity that will hold the cane</td>
</tr>
<tr>
<td>Four-wheeled walker</td>
<td>Hip flexion or knee extensor weakness</td>
<td>Must have hand strength to use the breaks</td>
</tr>
<tr>
<td>Manual Wheelchair</td>
<td>Less than functional strength in the lower limbs. Fall prevention</td>
<td>Most appropriate for patients with FTD. If it will be the only mobility device order tilt and recline, and a quality cushion to avoid skin breakdown. If transport chair it should be light-weight and foldable.</td>
</tr>
<tr>
<td>Power mobility device</td>
<td>Loss of independent ambulation and Fall prevention</td>
<td>Avoid prescribing a scooter. PWC should have both recline and tilt functions for pressure relief and skin protection</td>
</tr>
<tr>
<td>Hoyer lift or lift system</td>
<td>Total assist transfers</td>
<td>Often not able to fit in bathrooms</td>
</tr>
<tr>
<td>Bed rails, Foam wedge cushions, Pressure relief mattress</td>
<td>Poor bed mobility</td>
<td>Used for bed positioning to avoid pressure wounds.</td>
</tr>
<tr>
<td>Hospital Bed</td>
<td>Poor bed mobility</td>
<td>Order fully automatic with hand controls. Increases ease of care giving, improves pulmonary function, and helps prevent pressure wounds.</td>
</tr>
<tr>
<td>Shower or bath chair system</td>
<td>Loss of independent grooming</td>
<td>Needs back support and option for seatbelt. Should meet transfer needs for ease and safety of use.</td>
</tr>
<tr>
<td>Bedside commode and/or Raised toilet seat</td>
<td>Toileting safety</td>
<td>3-in-1 commode can often slide over the toilet seat taking the place of a separate device to increase the height of the toilet</td>
</tr>
<tr>
<td>Suction device and/or Suction toothbrush</td>
<td>Bulbar weakness Sialorrhea</td>
<td>Patient/caregiver will require training.</td>
</tr>
<tr>
<td>Insufflation-exsufflation device</td>
<td>Inadequate cough</td>
<td>Patient/caregivers will require training. Prescribe with a suction device.</td>
</tr>
<tr>
<td>Positive pressure ventilators, e.g. BIPAP, AVAP, or IVAP</td>
<td>Restrictive lung disease. FVC less than 50% predicted</td>
<td>Many different interfaces. For better compliance encourage patients to try masks and chose the most comfortable.</td>
</tr>
<tr>
<td>Ramp</td>
<td>Unable to climb stairs</td>
<td>Needed for safety to rapidly exit the home in an emergency</td>
</tr>
</tbody>
</table>

AVAPS = average volume-assured pressure support, BIPAP = bimodal positive airway pressure, FTD = fronto-temporal dementia, PEP = positive expiratory pressure, PWC = power wheelchair
continued progression of respiratory dysfunction after implantation, and its advantages over noninvasive ventilation have not been adequately investigated. Reported survival benefits from data of treated patients compared to historical control subjects have not been confirmed by randomized clinical trial. Further studies are needed before evidence-based recommendations can be made.

There are various methods of improving respiratory hygiene that may also help the patient with ALS, including manual assisted cough techniques and devices that artificially augment cough. Mechanical insufflation/exsufflation devices improve secretion management and may be considered for use when PECF rate drops below 270 L/min. While mechanical insufflation/exsufflation may significantly increase cough flow rates, patients with bulbar dysfunction may not benefit due to upper airway collapse during the exsufflation phase.

In most centers, only a small percent of patients elect to have a tracheostomy with invasive mechanical ventilation. Early after diagnosis the patient should be provided with unbiased information regarding the benefits and care requirements associated with mechanical ventilation, as well as information outlining expected disease progression despite invasive ventilator support. End-of-life discussions and defining circumstances for discontinuation of ventilator support should occur before invasive mechanical ventilation is initiated.

**NUTRITIONAL TREATMENT OPTIONS MAY EXTEND LIFE**

Malnutrition is common in the ALS population and is a negative predictor of survival. Enteral feeding by gastrostomy tube stabilizes weight loss and improves nutritional deficits.

Malnutrition is very common in ALS, and is reported to occur in 16-55% of ALS patients. Dysphagia and an underlying hypermetabolic state, the cause of which is not fully understood, are blamed for the nutritional disorder. Body mass index (BMI) has been identified as an independent predictor of survival; those patients whose BMI is between 30-35 kg/m2 have the longest survival, and a BMI of lower than 18.5 kg/m2 negatively predicts survival. Endoscopic gastrostomy (PEG) tube circumvents the problems of dysphagia and has inconsistently been shown to prolong survival. Although evidence is lacking to support the optimal timing of intervention, when an ALS patient loses more than 10% of his or her baseline body weight or is taking longer than 1 hour to eat a meal PEG or radiographically-inserted gastrostomy tube should be considered. It is safest to place the gastrostomy tube before the patient’s FVC drops to less than 50% of the predicted value. Patients should be reassured that they will still be able to eat food orally for enjoyment.

**CONCLUSION**

Patients with MND present with a wide variety of clinical symptoms due to the phenotypic heterogeneity of the disease. Symptomatic treatments including noninvasive ventilation and enteral nutrition by gastrostomy tube have the potential to prolong survival. Due to the unique aspects of MND with its rapid steady progression, the prescient rehabilitation specialist will anticipate their patient’s needs and provide them with the tools necessary to extend independence, improve quality of life and prolong survival.

**REFERENCES**

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Neurological Institute
New York, New York

CASE PRESENTATION

History

A 62-year-old man developed 4 months of progressive weakness, which he initially attributed to exhaustion. He was unable to climb stairs and had numbness and tingling in the hands and feet. Later he had hand weakness and was unable to stand. He has no family history of neuropathy, neuromuscular disease, or other neurological illnesses.

Physical Examination Findings

Motor testing revealed Medical Research Council scale 5 in the neck flexors, extensors, deltoids, biceps, triceps, and wrist extensors; 4 in the wrist flexors; and 3 in the interossei and abductor pollicis brevis. He had 4− in the hip flexors and hamstrings, 5 in the quadriceps, 1/5 in the tibialis anterior, and 3/5 in the plantar flexors. He had preserved reflexes in the arms and absent reflexes in the knees and ankles. His toes are downgoing. He had absent vibration and impaired position sense in the toes. He had diminished pin sensation distally in the legs.

Differential Diagnosis

The sensory symptoms and signs would not be seen in a motor neuron disease, neuromuscular disorder, or myopathy. Most peripheral neuropathies have distal weakness. The proximal weakness in this patient suggests the presence of a demyelinating neuropathy. The time course with progression for 4 months is too long for Guillain-Barré syndrome (GBS) or the rare subacute inflammatory demyelinating polyneuropathy. Patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have progression for over 2 months. Other demyelinating neuropathies include POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, rare cases of hypothyroidism, anti–myelin-associated glycoprotein (MAG) neuropathy, multifocal motor neuropathy, and rare toxic neuropathies. He was not exposed to bortezomab or amiodarone, two drugs that can cause toxic neuropathies that can be demyelinating.

Other neuropathies that can be severe are vasculitis, amyloidosis, and sarcoidosis. The symmetrical proximal weakness would be unusual in all of these. Amyloidosis usually has autonomic dysfunction.

Patients who were ultimately diagnosed with CIDP have initially been misdiagnosed with idiopathic neuropathy or Charcot-Marie-Tooth disease, without genetic confirmation. Patients with the following diagnoses, have been mistakenly diagnosed initially with CIDP: POEMS syndrome, transthyretin familial amyloidosis, mitochondrial neurogastrointestinal encephalopathy (MNGIE), inclusion body myositis with a mild neuropathy associated with impaired glucose tolerance, amyotrophic lateral sclerosis, multifocal motor neuropathy, and anti-MAG neuropathy. A serum protein...
electrophoresis (SPEP) and an immunofixation electrophoresis (IFE) are important to obtain. A lambda monoclonal protein should be seen with POEMS syndrome and an immunoglobulin M (IgM) monoclonal protein should be seen in anti-MAG neuropathy.

**Diagnostic Test Results**

**Nerve Conduction Studies and Needle Electromyography**

Motor nerve conduction study (NCS) of the left peroneal and tibial nerves showed prolonged distal motor latency, low response amplitude with markedly increased duration (at 15 ms and 19 ms) at the distal compound muscle action potential (CMAP) and slow conduction velocity (CV) (< 70% LLN). The left median nerve shows increased distal motor latency, low response amplitude, and slow CV. The left ulnar nerve shows increased distal motor latency, low response amplitude with increased CMAP duration (> 9 ms), and slow CV in the forearm and even slower conduction velocity across the elbow. The right median nerve shows increased distal motor latency, low response amplitude, and slow CV.

F-wave responses are absent in the left peroneal and tibial nerves, and the F-wave minimal latency is severely prolonged in the left median and mildly prolonged in the left ulnar nerves.

No evoked responses were seen in the left superficial peroneal, sural, median, and ulnar nerves. The left radial and right median nerves shows low response amplitude and slow CV.

Needle electromyography (EMG) examination of selected muscles in the left leg and the lumbosacral paraspinal muscles show fibrillation potentials in the distal muscles. The motor unit potentials in the leg show long duration and recruitment of the distal leg muscles is discrete with maximal effort.

**Conclusions**

There was electrophysiologic evidence of a severe chronic multifocal demyelinating sensorimotor polyneuropathy.

**Laboratory Test Results**

Cerebrospinal fluid (CSF) revealed 1 white blood cell count, 1 red blood cell count, and a protein of 252 mg/dl.

Negative or normal results include: SPEP, IFE, thyroid-stimulating hormone, antinuclear antibody, myeloperoxidase antibodies, proteinase 3 antibody, C reactive protein (negative), Sjögren’s syndrome antigens (SSA and SSB), J01 antibodies, SCL-70, ribonucleoprotein antibodies, total IgA, anti-Hu antibody, sulfatide antibody, anti-Ri antibody, rheumatoid factor, serum lyme antibodies, hepatitis B surface antigen, hemoglobin A1C (4.1%), vascular endothelial growth factor (normal at 43), GM1 antibody, erythrocyte sedimentation rate (9), urine arsenic, urine mercury, urine cadmium, urine cobalt, urine thallium, GQ1b antibody, serum IgM, and vitamin B12 (571 pg/mL).

**DISCUSSION**

The classical features of CIDP include progressive symmetrical proximal and distal weakness, large fiber sensory loss, and areflexia. Demyelination can be demonstrated by NCSs and nerve biopsy. There is cytoalbuminergic disassociation and improvement with immunotherapy. It is a commonly encountered treatable neuropathy and accounts for approximately 20% of patients with initially undiagnosed peripheral neuropathies in peripheral neuropathy or neuromuscular clinics.

The classical pattern in CIDP of symmetrical proximal and distal weakness is seen in approximately one-half of patients. There are regional variants, including patients with multifocal or asymmetric involvement, as well as patients with predominantly distal or sensory involvement. By definition, CIDP has a progression of symptoms for more than 2 months. There can be a relapsing and remitting course or a progressive course.

**Epidemiology**

The prevalence of CIDP has been estimated as 1/100,000 using the American Academy of Neurology research criteria as a case definition. Other studies, using broader diagnostic criteria have found a prevalence of 9/100,000. The incidence is similar to GBS. There is a peak occurrence in women in their 20s. The disease is more common in men over the age of 60.

**Diagnosis**

Currently, there is no universally present diagnostic test or biomarker to identify patients with CIDP. The diagnosis is based on clinical features, electrodiagnostic (EDX) findings, spinal fluid analysis, and, if necessary, nerve biopsy. More than 15 sets of diagnostic criteria have been published. Symmetrical proximal and distal weakness seen in patients with CIDP is unusual for most other types of neuropathy. However 8-9% of patients present with multifocal involvement and 6-31% present with a sensory or distal pattern.

An elevated CSF protein with a normal white blood cell count is seen in 85-95% of patients.

Electrodiagnostic findings are particularly helpful. Published EDX criteria require nerve conduction velocity slowing beyond that seen with axonal or neuronal disorders. Because CIDP is a multifocal disorder, without uniform involvement that is typical of inherited demyelinating neuropathies, EDX abnormalities in distal segments (prolonged distal motor latencies) and proximal segments (prolonged or absent F-wave responses with preserved distal responses) are also used. Temporal dispersion or conduction block are also findings used to arrive at a conclusion of demyelination.

Nerve biopsy is usually reserved for atypical presentations and should be performed in neuropathology laboratories with appropriate expertise. A nerve biopsy can show demyelination demonstrated as thinly myelinated or demyelinated fibers on epoxy resin semithin sections. Onion bulbs may be seen. Inflammation may be demonstrated. Demyelination can also be demonstrated on teased fiber preparations or electron microscopy. Because CIDP is an
inflammatory multifocal disease, a nerve biopsy may not always be abnormal if a biopsy specimen is taken from an area unaffected by the disease.

**Treatment**

The patient was treated with plasmapheresis (PE) because he had renal insufficiency. There was no improvement so he received intravenous immunoglobulin (IVIg) immediately followed by PE. There was still no improvement so he began IV solumedrol, with continued progression. He then received IVIg 2 gm/kg. His strength improved but after a few weeks worsened again. He was then given prednisone 60 mg daily. He then became depressed and had psychotic thoughts. He was then restarted on IVIg with a maintenance dose of 0.5 gm/kg every 2 weeks. After 1 month he was able to stand. His prednisone was tapered. After 4 months he could walk with a walker. He was able to discontinue prednisone. He was able to walk without a walker. He has normal proximal strength but still has some distal weakness. His IVIg treatment was reduced to 0.5 gm/kg every 3 weeks without a return of symptoms.

In randomized placebo controlled studies, IVIg, PE, and prednisone have all been demonstrated to be effective treatment for CIDP. Chronic inflammatory demyelinating polyradiculoneuropathy is a chronic disorder and IVIg has been shown to be an effective maintenance treatment in a randomized, double blind, placebo controlled study. In small 6-week studies, IVIg compared to PE and IVIg compared to prednisone showed similar efficacy.

The initial dose of IVIg is usually 2 mg/kg in divided doses. The maintenance dose varies, typically from 0.4-2.0 gm/kg every 1-4 weeks. It is generally well tolerated. Rare serious adverse events include thromboembolic events, including stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolus. Another serious adverse event is renal failure in patients with preexisting renal disease, particularly with preparations that include sucrose as a stabilizing agent.

The onset of benefit of high doses of prednisone (60 mg/day) averages 2 months, but it can occur in days or take up to 5 months. Side effects are common with the use of prednisone or other corticosteroids and because of this most clinicians limit their use. Associated side effects include facial swelling, weight gain, diabetes mellitus, hypertension, immunosuppression, osteoporosis, fractures, aseptic necrosis of the hip, psychosis, gastritis, and gastrointestinal bleeding.

A typical course of four to six PEs can remove 90% of circulating IgG and therefore remove pathogenic antibodies. Plasmapheresis has been beneficial in several randomized, placebo-controlled, double blind, clinical trials for CIDP. Adverse events include hypotension, bleeding, allergic reactions from infusion of plasma substitutes, and complications from the central catheters that are frequently required.

Other agents have been used in select patients with CIDP, including mycophenolate mofetil, cyclophosphamide, alemtuzumab, and rituximab. A recently completed randomized, placebo-controlled, double blind study of methotrexate in CIDP showed it was ineffective.

**REFERENCES**

CASE ONE

History

A 31-year-old woman presented with dysesthetic numbness in the left 4th and 5th digits with weakness in hand strength for 10 weeks. She subsequently noticed numbness in the dorsum of the right foot and lateral calf and a foot drop. In the past week she noticed similar symptoms in the right arm with numbness affecting the dorsum of the thumb and index finger and difficulty with finger extension.

There was no trauma, no family history of neurologic or immune disorders, and no other medical problems. She did not drink, smoke, or use illicit drugs.

Examination

Her general physical examination was normal. In particular, there were no skin lesions or rash. Neurologically, cranial nerves were normal. There was weakness of right finger extension but wrist extension was normal. Left ulnar intrinsic hand muscles were weak but median-innervated muscles were normal. The right anterior tibialis, extensor hallucis longus, and extensor digitorum brevis were weak, as was eversion. Strength was otherwise normal. The only mild atrophy was of the left first dorsal interosseus. Deep tendon reflexes were all present. Sensory examination revealed abnormalities to pin and touch in the right superficial radial, left ulnar, and peroneal distribution. Vibration sense was mildly reduced in the toes. Tapping over the right median nerve in the forearm and left ulnar nerve 6-8 cm below the elbow caused paresthesias.

Differential Diagnosis

The patient presented with a mononeuropathy multiplex. The differential diagnosis includes:

- Vasculitic disorders
- Those related to collagen vascular disorders such as systemic lupus erythematosus and rheumatoid arthritis
- Primary systemic vasculitides such as polyarteritis nodosa and Churg-Strauss syndrome
- Isolated neuropathic vasculitis
- Infiltrating disorders of nerve
  - Lymphoma
  - Leukemia
  - Other malignancies
  - Granulomatous disorders including sarcoid
- Hereditary neuropathy with predisposition to pressure palsies (HNPP)
- Multifocal immune and inflammatory neuropathies
• Lewis-Sumner syndrome (L-SS)
• Multifocal motor neuropathy (MMN)

**Investigations**

Laboratory studies did not reveal any systemic abnormality. Spinal fluid protein was slightly elevated at 50 mg% with no other abnormality. No antiganglioside antibodies were found.

Electrodiagnostic studies revealed partial motor conduction blocks of > 50% amplitude and area reductions in the left ulnar nerve in the forearm, right median nerve in the forearm, and radial nerve in the upper arm. The extensor digitorum brevis and anterior tibial amplitudes were reduced on right peroneal nerve stimulation. Sensory amplitudes were reduced and there was excessive reduction of amplitude on proximal stimulation. Left median distal latency and right ulnar conduction across the elbow were normal.

**Diagnostic Considerations After Investigations**

There was no evidence of a systemic disease. Nonsystemic vasculitis remained a consideration but the multifocal conduction blocks made the highly unlikely. The sensory symptoms, signs, and sensory changes on needle electromyography (EMG) were inconsistent with MMN. The conduction blocks were not at sites of compression and the other conduction did not fit the pattern of HNPP (Li and colleagues).

Thus, this patient has a multifocal sensorimotor demyelinating neuropathy with conduction block as seen in L-SS.

**Clinical Course**

Intravenous immunoglobulin (IVIg) was initially used at 500 mg/kg for 4 days, then 1 gm/kg every 3 weeks for two treatments. After the last treatment she developed profound weakness of her right deltoid and infraspinatus. Plasma exchange was initiated and during the treatment she developed weakness of her right tongue. Prednisone 60 mg/day was started and in 6 weeks she reported improvement in her tongue and shoulder and over 4 months all deficits had resolved. Prednisone was tapered and she remained stable for over 5 years (Chronic Inflammatory Demyelinating Polyradiculoneuropathy [CIDP] Disease Activity Status level 1) (Gorson and colleagues).

**CASE TWO**

**History**

A 54-year-old man first developed a painless left wrist drop 18 months prior to visiting the author. He then developed right shoulder weakness. He was evaluated at a center near his home and was diagnosed with bilateral brachial neuropathies and he was treated with prednisone. He developed multiple other nerve lesions and none of the previous ones improved. He then sought another opinion.

He has a history of hypertension and no family history of neurologic or immunologic disorders.

**Examination**

There was weakness of the right deltoid and infraspinatus, left wrist and finger extension, and triceps but no weakness of the deltoid. There was also weakness of the ulnar intrinsics bilaterally and weakness of the right quadriceps and iliopectos but normal adduction and bilateral foot dorsiflexion weakness with the left planter flexion also being weak. Fasciculations were seen in a number of involved muscles. Despite this profound motor involvement, sensory examination was normal except for mild vibration sense reduction in the toes. Deep tendon reflexes were very brisk but plantar responses were downgoing.

**Differential Diagnosis**

Similar to Case One. The major difference here is the lack of sensory involvement.

**Investigations**

No systemic disorders were identified. Anti-GM1 antibodies were not detected.

Conduction block lesions were found in the left radial nerve on Erb’s point stimulation and the left ulnar nerve in the forearm. Compound muscle action potential (CMAP) amplitudes on distal stimulation of the ulnar, peroneal, and left radial nerves were reduced and needle EMG revealed fibrillations, positive sharp waves, and large polyphasic units in all weak muscles.

Magnetic resonance imaging scans of the brachial plexus revealed hyperintense, swollen, and glutamate decarboxylase-enhancing nerves changes.

**Diagnostic Considerations After Investigations**

The pure motor mononeuropathy multiplex with persistent conduction blocks, fasciculations, and lack of sensory involvement in the distribution of the motor lesions strongly points to MMN.

**Clinical Course**

The patient was taken off corticosteroids and begun on IVIg 2 gm/kg initially, then 1 gm/kg every 3 weeks. After the second treatment he noticed improvement in his quadriceps and foot drops and over the next 6 months there was partial improvement of all regions. However, recovery was not complete and over the next 3-4 years some mild increase in weakness was noted in previously involved muscles but no new nerve lesions developed.

**DISCUSSION**

**Multifocal Demyelinating Neuropathies**

There are two disorders that can present as mononeuropathy multiplex and are due to abnormalities in myelin: HNPP and L-SS. Notice that MMN is not included in this grouping. Hereditary neuropathy with predisposition to pressure palsies is usually due to a deletion of one transcript of peripheral myelin protein 22. There is a characteristic pattern of conduction abnormalities that strongly
points to that disorder. Most germaine to the current discussion is that the conduction block (CB) lesions, when they occur, are at sites of compression. Lewis-Sumner syndrome may have CB at sites of compression but also will have CB at noncompression sites. Some other conduction abnormalities pointing to segmental demyelination may occur but these may not be prominent or seen at all. No specific laboratory abnormality is noted and no patient with clear cut L-SS has had high titers to GM1 or other ganglioside. Nerve biopsy has usually shown evidence of segmental demyelination and inflammatory cells similar to that seen in CIDP. Treatment responses for L-SS mirror that seen in the symmetric proximal-distal (“classic”) form of CIDP. Because L-SS has physiologic, pathologic, and treatment parallels to CIDP, L-SS is considered in the European Federation of Neurological Societies/Peripheral Nerve Society classification as a “variant” of CIDP.

On the other hand, MMN has a number of features that make it different than CIDP. Conduction abnormalities outside the regions of the CB are not usually detected (there is some controversy on this point). Elevated serum IgM antibodies against GM1 are seen in a large minority of patients and recent studies suggest that the percent may be much higher if GM1 is complexed with other gangliosides. Sural nerve biopsies are almost always normal and fascicular biopsies of the site of the CB have not found inflammatory cells or evidence of segmental demyelination. There is a well recognized worsening of disease when corticosteroids are used (as seen in Case Two) and the only recognized benefit has been with IVIg. Most clinicians treating patients with MMN have not found benefit from plasma exchange or other immunosuppressants other than cyclophosphamide, and even that is mostly anecdotal. Thus, because there are clinical, laboratory, pathologic, and treatment differences with CIDP, MMN is not considered a variant of CIDP, but a separate disorder. In addition to the pathologic evidence, there is increasing physiologic evidence from axonal excitability studies that the CB in MMN is likely to be due to a disorder of the Node of Ranvier. MMN may therefore not be a demyelinating neuropathy but an immune disorder of the node. As such, MMN may be considered the chronic, multifocal, restricted form of acute motor axonal neuropathy (AMAN). Both have CB as a major feature, are pure motor, have antibodies to similar gangliosides (AMAN has IgG and MMN has IgM antibodies), and are disorders of the node of Ranvier.

**DIAGNOSIS OF LEWIS-SUMNER SYNDROME AND MULTIFOCAL MOTOR NEUROPATHY: PEARLS AND PITFALLS**

**Lewis-Sumner Syndrome**

The diagnosis of L-SS is dependent on finding a true sensorimotor mononeuropathy multiplex pattern. Some clinicians will diagnose L-SS in a CIDP patient with mild asymmetries. Unless the history points to previous involvement of individual nerves, it is probably a stretch to call minor asymmetries L-SS. While there is little clinical consequence in doing this, as treatment approaches are similar, understanding of these disorders will be hampered with blurring the boundaries of the variants with the “classic” disorder. Pain is seen in a number of patients and is usually paresthetic and relates to the prominent Tinel’s sign that is sometimes encountered.

The CB lesions should be at sites that are not typically prone to compression. If, as in the author’s most embarrassing case, the CB is only at sites of compression, strongly consider HNPP. Although there are reports of CB in vasculitic neuropathies, these are usually transient or of a minor extent. It is extremely rare to see persistent CB in vasculitis.

**Multifocal Motor Neuropathy**

The concerning differential diagnosis in many cases of MMN is amyotrophic lateral sclerosis (ALS). Although ALS is much more common than MMN, it is still wise to consider MMN when the diagnosis of ALS does not meet strict criteria. The two most common situations in which this occurs is when a patient has very brisk reflexes but no clear pathologic reflexes and the upper motor neuron aspect of ALS cannot be confirmed. The other instance is the purely lower motor neuron patient with more symmetric disease and no CB. What should one do in these instances? One approach is to consider an empiric trial of IVIg for 2-3 months. If this is done, then it is important that the patient and clinician have mutually understood goals and outcome measures that will determine whether further treatment is appropriate. Clearly, continued progression of the disease points to lack of efficacy. Increased energy, less fatigue, and general feeling of well being are probably not due to any affects of the treatment on the disease but more likely a more general effect of therapy on nonspecific systemic factors. On the opposite side, expectations of improvement in muscles that have severe axonal loss are unrealistic and lack of improvement in these muscles should not be considered treatment failures.

**Some Issues Related to Conduction Block**

The hallmark of both L-SS and MMN is persistent CB. It is impressive that these disorders have been both over- and under-diagnosed due to misinterpretation of the conduction studies.

Inability to detect CB can occur due to severe axonal loss and the inability to stimulate below the lesion if very distal or above the lesion if very proximal. Over interpretation of CB can occur due to under stimulation at the proximal stimulation site or overstimulation distally. The latter is a particular issue for the median nerve. Supramaximal stimulation may volume conduct to the neighboring ulnar nerve, recruiting motor units from ulnar-innervated thenar muscles, causing an excessively large distal CMAP. A pure median response on proximal stimulation will factitiously suggest CB. Ulnar CB in the forearm can be mimicked by median-ulnar anastomosis (Martin-Gruber anastomosis) in which the distal stimulation includes all nerve fibers, but the elbow stimulation does not include fibers that are coursing with the median nerve at the elbow.

The other aspect of CB that is confusing is what criteria is optimal to make the determination. There have been multiple attempts to set criteria but no consensus has been reached. It is fairly clear that the best balance of sensitivity and specificity remains with amplitude and area reductions of > 50%. Lesser percents may be appropriate over short distances such that a 20% amplitude reduction over 6 cm may be abnormal but not if the distance is 30 cm. It is also critical for the electrodiagnostic physician and the clinician to correlate the physiologic findings with the clinical picture. An 80% motor block on needle EMG in a patient who is clinically
strong suggests a physiologic-clinical mismatch most likely due to a misinterpretation of the nerve conduction study.

**Therapy and Rehabilitation**

The treatment of L-SS mirrors that of CIDP. However, the decision of when to treat, what agents to use, and the expectations and outcome measures may be different. For MMN, the only treatment that has been shown to be effective is IVIg but, even here, dosing and length of treatment must be individualized. If disease progression occurs despite IVIg, the choice of alternative therapy is difficult with very limited information to assist the clinician. Cyclophosphamide may be the best option in severe situations. Rituximab has not been as clearly beneficial as had been anticipated.

The rehabilitative therapy of these patients may be as important as pharmacologic treatment. Appropriate use of orthotics, exercise therapy, and adaptive aides and judicious use of injections to reduce pain and discomfort is crucial for optimal quality of life for these patients.

**CONCLUSION**

The clinical, physiologic, and pathologic features suggest that L-SS is a multifocal demyelinating neuropathy, a variant of CIDP. On the other hand, MMN is most likely a disorder of the node of Ranvier and is a related but most likely unique disorder. It may be considered a relative of AMAN. The diagnosis and treatment of these disorders requires a sophisticated approach that recognizes potential confounding factors and pitfalls. Many patients with L-SS do very well with treatment and can have long periods of remission. Often, MMN can be controlled but progressive axonal loss tends to occur over years.

**BIBLIOGRAPHY**

Neuromuscular Vignettes

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VIGNETTE ONE

In November, a 57-year-old woman presents in Las Vegas, Nevada, with 5 days of fever, malaise, fatigue, and weakness. Complete flaccid paralysis and profound encephalopathy develop within 5 days. Electrodiagnostic (EDX) studies reveal severely reduced compound motor action potential amplitudes in the right arm, with milder reductions in the legs. Sensory nerve action potential (SNAP) amplitudes are mildly reduced with normal conduction velocities. Concentric needle electromyography (EMG) records no spontaneous activity or voluntary motor unit potentials. Her medical history is significant for prior lung transplant for alpha-1 antitrypsin deficiency and treatment with prednisone, tacrolimus, cytoxan and rituximab.

Questions

1A. The history and findings BEST fit a syndrome of which of the following?

A. Severe sensorimotor polyneuropathy.
B. Severe myopathy.
C. Severe neuromuscular junction defect.
D. Severe motor neuron disorder.

Lumbar puncture shows a white blood cell count of 8 with 48% lymphocytes, 45% monocytes, 3% polymorphonuclear leukocytes, and 4% bands; protein 125 mg/dl; and glucose 125 mg/dl. Stains show no organisms and routine cultures are negative. Serum West Nile virus immunoglobulin M (IgM) and G (IgG) antibodies are negative. Additional blood and cerebrospinal fluid (CSF) are collected to perform more studies.

1B. After this a reasonable next step would be to:

A. Give solumedrol.
B. Lower the doses of her immunosuppression.
C. Perform plasma exchange (PE).
D. Biopsy the weak quadriceps muscle.
E. Give oseltamivir.

The patient dies and postmortem analysis of the spinal cord shows the following pathology:

![Pathology Image]
NEUROMUSCULAR VIGNETTES

1C. Which diagnosis BEST fits this case?
   A. Guillain-Barré syndrome.
   B. Vasculitis.
   C. Critical illness myopathy.
   D. West Nile virus infection.

VIGNETTE TWO

A previously healthy 34-year-old man presents with bilateral arm numbness, weakness, and paresthesias. Symptoms began 8 weeks before presentation and were preceded by strenuous yard work over a few days. He developed severe right upper arm pain which was followed 4-5 days later by weakness and numbness in the right arm. A week and a half later, the left arm became similarly involved. The legs have been unaffected.

Questions

2A. Which of the following is the MOST LIKELY diagnosis?
   A. Cervical stenosis.
   B. Lewis-Sumner syndrome.
   C. Neuralgic amyotrophy.
   D. Lyme disease.

Clinical examination shows a pattern of muscle weakness as follows (grading on the Medical Research Council scale):

<table>
<thead>
<tr>
<th>Side</th>
<th>Arm abduction</th>
<th>Elbow flexion</th>
<th>Elbow extension</th>
<th>Finger abduction</th>
<th>Thumb abduction</th>
<th>Finger flexion</th>
<th>Finger extension</th>
<th>Supination</th>
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<tr>
<td>Left</td>
<td>5</td>
<td>2</td>
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<td>3- to 4+</td>
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</tbody>
</table>

2B. Which nerve distributions are MOST LIKELY affected?

   A. Left posterior interosseus, left musculocutaneous, right radial, and right median.
   B. Bilateral radial, left musculocutaneous, and right ulnar.
   C. Right median, right radial, right anterior interosseus, and left musculocutaneous.
   D. Left musculocutaneous, right radial, and left anterior interosseus.

2C. Which genetic test would be MOST appropriate?
   A. GDAP1 mutation.
   B. SEPT9 mutation.
   C. Mitofusin-2 mutation.
   D. PMP22 deletion.
   E. Lamin A/C mutation.

2D. Which of the following associated features can be seen in this condition?
   A. Calf hypertrophy.
   B. Paget’s disease.
   C. Cardiomyopathy.
   D. Hypertelorism.
   E. Retinopathy.

VIGNETTE THREE

A 39-year-old previously healthy man presents for 2 days of tingling and numbness in the feet and legs and frequent tripping. He
reports no bowel or bladder symptoms. Examination demonstrates inability to walk on heels or toes. He is unable to arise from an office chair without assistance. The upper extremities are strong. Reflexes are 1+ in the arms and at the knees and absent at the ankles. Pin and vibratory sensation are reduced below the hips.

Questions

3A. Which of the following treatments is MOST appropriate?
   A. Intravenous immunoglobulin (IVIg).
   B. Intravenous steroids.
   C. Pyridostigmine.
   D. Diazepam.

3B. In the third week of his illness, the patient is not improved and is no longer able to walk. The MOST appropriate course of action is to:
   A. Give an additional round of a different brand of IVIg.
   B. Give PE.
   C. Start an oral immunosuppressant.
   D. Reassure the patient but offer no other disease modifying medication.

The patient improves with the correct management but relapses 10 weeks later. He again loses the ability to walk unassisted. He has no intercurrent illness to explain the worsening. A needle EMG confirms your clinical suspicion.

3C. The MOST appropriate course of action is to:
   A. Do nothing. This is the cyclical nature of the disease.
   B. Give PE.
   C. Start prednisone.
   D. Start azathioprine.

VIGNETTE FOUR

A 60-year-old man presents with progressive respiratory difficulty over 6 months. He is also dysarthric. Your examination demonstrates the following:

Questions

4A. Which of the following is the MOST LIKELY diagnosis?
   A. Amyloid light-chain amyloidosis.
   B. Amyotrophic lateral sclerosis.
   C. Tangier disease.
   D. Muscle-specific tyrosine kinase-antibodies–positive myasthenia gravis.

4B. Respiratory difficulty is also a common finding in which of the following disorders in adults?
   A. Acid maltase deficiency.
   B. Type 2D limb girdle muscular dystrophy.
   C. Dermatomyositis.
   D. DCTN1 (protein dynactin) gene mutation motor neuropathy.

The following phrenic nerve conduction studies (NCSs) were recorded in a previously healthy 45-year-old man who developed shortness of breath over the course of a day. He noted antecedent transient pain at the base of his neck radiating into the right shoulder.

4C. Which of the following is the MOST LIKELY diagnosis?
   A. Spontaneous pneumothorax.
   B. Myasthenia gravis.
   C. Phrenic neuritis.
   D. Anxiety.
VIGNETTE FIVE

A 66-year-old man presents with a 1-year history of head drop. He denies any sensory symptoms, neck pain, or weakness in ocular, bulbar, or limb muscles. His past medical history is significant for remote Hodgkin’s lymphoma treated with mantle field radiation 23 years ago, hypothyroidism, coronary artery disease status post coronary artery bypass grafting, and aortic valve replacement. Examination demonstrates mild neck flexion weakness (4+) and severe neck extension weakness (2). Examination of cranial nerves, reflexes, sensation, and limb strength is normal.

Questions

5A. What is the LIKELY etiology of his dropped head syndrome?

A. Motor neuron disease.
B. Facioscapulohumeral muscular dystrophy.
C. Dermatomyositis.
D. Anxiety.
E. Radiation fibrosis syndrome.

5B. What features would not be expected on EDX testing?

A. Short duration, small amplitude motor unit action potentials (MUAPs).
B. Long duration, large amplitude MUAPs.
C. Decreased recruitment.
D. Motor unit instability.
E. All of the above.

5C. What treatments may be considered for dropped head syndrome?

A. Cervical collar.
B. Baseball cap orthosis.
C. Surgical fixation.
D. All of the above.
E. None of the above.

VIGNETTE SIX

A 72-year-old man presents with progressive weakness and sensory loss. Physical examination demonstrates distal sensory loss, mild proximal and distal lower limb weakness, and reduced muscle stretch reflexes.

Questions

6A. The patient is admitted for evaluation of possible chronic inflammatory demyelinating polyradiculoneuropathy. Which of the following is LEAST consistent with this diagnosis?

A. Reduced conduction velocities on NCSs.
B. Elevated CSF protein.
C. Respiratory failure and cranial nerve involvement.
D. Proximal and distal limb weakness.
E. Duration of greater than 8 weeks.

During the course of his inpatient admission the patient develops worsening weakness, congestive heart failure, lactic acidosis, confusion, and respiratory failure. Examination demonstrates severe generalized weakness and extraocular ophthalmoplegia. The patient’s brain magnetic resonance imaging (MRI) scan is shown.

6B. Which test is MOST LIKELY to confirm the diagnosis?

A. CSF analysis.
B. Muscle biopsy.
C. Nerve biopsy.
D. Thiamine level.
E. GQ1b antibodies.

6C. Which of the following is associated with external ophthalmoplegia?

A. Miller Fisher syndrome.
B. Trinucleotide repeat at the 5’ end of the coding region of the PABPN1 gene.
C. GQ1b antibodies.
D. Kearns-Sayre syndrome.
E. All of the above.
**VIGNETTE SEVEN**

A 41-year-old woman presents with progressive limb weakness. One year ago she noticed weakness in her proximal right upper limb. This weakness subsequently spread to the contralateral limb and distally into her hands. The patient denies lower limb weakness, diplopia, dysphagia, dysarthria, respiratory symptoms, pain, numbness, or tingling. Manual muscle testing demonstrates the following: shoulder abduction 0/0, elbow flexion 1/1, elbow extension 2/2, wrist extension 3−/3−, wrist flexion 4/4, finger flexion 4+/4+, and finger abduction 4/4. Reflexes are reduced in the upper limbs. Lower limb reflexes, sensation, and cranial nerves are normal. A previous EDX study demonstrated diffuse active and chronic denervation localized to the upper limbs. Other than mildly reduced motor amplitudes the sensory and motor conduction studies are normal.

Questions

7A. The patient is diagnosed with a motor neuron disorder. What specific disorder fits BEST with the patient’s clinical presentation?

A. Progressive muscular atrophy.
B. Brachial amyotrophy diplegia.
C. Spinal muscular atrophy.
D. Kennedy’s disease.
E. Amyotrophy lateral sclerosis (ALS).

7B. Which of the following is TRUE about the patient’s condition?

A. Average life expectancy is between 2 and 5 years.
B. Prognosis is worse than that typical for ALS.
C. Prognosis is better than that expected in ALS.
D. Lifespan is not shortened.
E. None of the above.

The patient subsequently develops distal lower limb weakness limiting her gait. She reports difficulties with falls related to her knees buckling. Examination demonstrates weakness in ankle dorsiflexion (grade 2), ankle plantar flexion (grade 3−), and knee extension (grade 4−).

7C. Of the following devices, which should be considered?

A. Rigid ankle foot orthosis.
B. Hinged ankle foot orthosis.
C. Posterior leaf spring ankle foot orthosis.
D. Floor reaction (ground reaction) ankle foot orthosis.
E. Patellar tendon weightbearing ankle foot orthosis.

**VIGNETTE EIGHT**

A 22-year-old woman presents with progressive proximal weakness in all four limbs following pregnancy. She denies bulbar or ocular weakness. She has a history of remote poliomyelitis at age 2 requiring treatment with in an iron lung, but she denies any residual deficits. Examination demonstrates severe proximal limb weakness and head drop. Examination of sensation, cranial nerves, and reflexes is normal. (A video showing needle electrode examination findings will be presented during the live course.)

Questions

8A. On the basis of the patient’s clinical presentation and the needle electrode examination findings, which of the following testing should be considered?

A. Creatine kinase.
B. Nerve biopsy.
C. Repetitive nerve stimulation.
D. Targeted mutation analysis for deletion of SMN1 exon 7-8.
E. Both A and C.

8B. You performed the following test (results of testing will be presented during the live course). What is the basis of the needle electrode examination findings?

A. Muscle fiber necrosis.
B. Axonal loss.
C. Jitter.
D. Blocked muscle fiber action potentials.
E. Muscle sarcolemmal inexcitability.

8C. The patient is treated with aggressive immunomodulatory treatment without any significant benefit. What is the LIKELY diagnosis?

A. Dermatomyositis.
B. Hereditary neuropathy.
C. Limb girdle muscular dystrophy.
D. Congenital myasthenic syndrome.
E. Myasthenia gravis.
VIGNETTE NINE

A 31-year old woman presents with difficulty walking and bilateral lower extremity tingling and burning. There is a family history of lupus and rheumatoid arthritis. She complains of difficulty focusing on new information and some vague memory loss. Her mental status, higher cortical functions, and cranial nerve examination appear normal. Motor examination reveals bilateral foot drop and otherwise no weakness or atrophy noted but increased tone at the knees (slight “catch”) with the patient tested supine. Muscle stretch reflexes are absent at the ankles and pathologically increased at the knees with spread to contralateral adductors, and they are brisk at the biceps and triceps. Cutaneous and plantar responses are absent. Jaw jerk and Hoffmann sign are present. Sensory examination reveals patchy reduced sensation to light touch and patchy increased sensation pinprick in the lower extremities below the knees. There is no sensory level on the trunk. Using a graduated Rydel-Seiffer tuning fork, her pallesthesia is absent at the toes, ankles, and knees but normal in the upper extremities. Joint position sense is absent at the toes, impaired at the ankles, and normal at the fingers. Beevor sign is absent. Coordination examination is normal. Stance is normal, Romberg test is negative, and gait is mildly ataxic, with difficulty walking on toes, bilateral foot drop slapping on attempted walking on heels; and she cannot perform tandem gait.

Questions

9A. What is the clinical pattern of her symptoms and signs?
A. Small fiber sensory neuropathy.
B. Mixed lower and upper motor neuron syndrome.
C. Sensorimotor polyneuropathy.
D. Kearns-Sayre syndrome.
E. Myelopathy.

9B. What other information would be helpful?
A. History of anemia.
B. Bariatric surgery.
C. History of myasthenia gravis.
D. All of the above.

9C. What other studies would be MOST useful?
A. Methylmalonic acid level.
B. Ceruloplasmin level.
C. MRI of the cervical spine.
D. All of the above.

VIGNETTE TEN

A 44-year old man presents with a 1-year history of gradual onset of left hand grip weakness over 2 months, followed 3 months later by gradual onset contralateral wrist extension weakness over 5 weeks. He denies any sensory loss in the upper or lower extremities. He was referred to the EMG Laboratory for evaluation. On examination there is left hand weakness particularly affecting the first dorsal interosseus and abductor digitii minimi muscles, without atrophy. He has mild finger and wrist extension weakness but can easily move against gravity and mild resistance. Sensory examination is normal to all modalities. Finger extensor and wrist extensor muscle stretch reflexes are absent on the right, and finger flexor reflex is absent on the left. Bilateral triceps and biceps reflexes are normal.

Questions

10A. What is the pattern of his weakness?
A. Left ulnar and right posterior interosseus neuropathy.
B. Left ulnar and right anterior interosseus neuropathy.
C. Left C8/T1 and right C7 radiculopathy.
D. Left lateral cord and right posterior cord plexopathy.

Routine NCSs showed demyelinating findings as noted on the tables below. Needle EMG of both arms are normal.

<table>
<thead>
<tr>
<th>Nerve and site</th>
<th>Lat (ms)</th>
<th>Amp (mV)</th>
<th>Dur (ms)</th>
<th>Area (mVms)</th>
<th>Temp (°C)</th>
<th>Lat diff (ms)</th>
<th>Dist (mm)</th>
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<tbody>
<tr>
<td>Median L to abductor pollicis brevis R</td>
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<tr>
<td>Wrist</td>
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<td>6</td>
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F Wave Studies

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L = left, Lat = latency

Sensory NCSs

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<td>1.7</td>
<td>2.3</td>
<td>28</td>
<td>33.9</td>
<td>1.7</td>
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<tr>
<td>Lateral antebrachial cutaneous R to forearm R</td>
<td>2.2</td>
<td>2.8</td>
<td>16</td>
<td>33.8</td>
<td>2.2</td>
<td>120</td>
<td>59</td>
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<tr>
<td>Medial antebrachial cutaneous R to forearm R</td>
<td>2.3</td>
<td>2.8</td>
<td>13</td>
<td>33.8</td>
<td>2.3</td>
<td>120</td>
<td>57</td>
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<tr>
<td>Lateral antebrachial cutaneous L to forearm L</td>
<td>2.3</td>
<td>2.8</td>
<td>15</td>
<td>33.3</td>
<td>2.3</td>
<td>120</td>
<td>57</td>
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<tr>
<td>Medial antebrachial cutaneous L to forearm L</td>
<td>2.5</td>
<td>2.9</td>
<td>14</td>
<td>33.3</td>
<td>2.5</td>
<td>120</td>
<td>52</td>
</tr>
</tbody>
</table>

Amp = amplitude, CV = conduction velocity, Dist = distance, L = left, Lat = latency, Lat diff = latency difference, R = right, Temp = temperature

Needle EMG Examination

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Insertion activity</th>
<th>Spontaneous activity</th>
<th>Volitional MUPs</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amp/PSWs</td>
<td>Fasc</td>
<td>Other</td>
<td>Amp</td>
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<tr>
<td>Deltoid R</td>
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<td>None</td>
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<td>Biceps brachii R</td>
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<td>None</td>
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<tr>
<td>Triceps brachii R</td>
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<td>Flexor carpi radialis R</td>
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<tr>
<td>Flexor carpi ulnaris R</td>
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<tr>
<td>Extensor communis R</td>
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<td>First dorsal interosseus R</td>
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<td>Abductor pollicis brevis R</td>
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<td>Sternocleidomastoid R</td>
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<tr>
<td>Infraspinatus R</td>
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<td>C6 paraspinal R</td>
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<tr>
<td>C7 paraspinal R</td>
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<tr>
<td>T1 paraspinal R</td>
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<td>None</td>
<td>None</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Amp = amplitude, Dur = duration, Fasc = fasciculations, Fibs = fibrillations, L = left, MUP = motor unit potential, Poly = polyphasic potentials, PSWs = positive sharp waves, R = right, Recruit = recruitment

10B. What is the BEST EDX correlate of weakness on clinical examination?

A. Abnormal temporal dispersion.
B. Partial conduction block.
C. Severe conduction velocity slowing.
D. Severely prolonged F-wave minimal latency.

Elevated titers of anti-ganglioside antibodies were noted on the patients serum.

10C. What is the MOST LIKELY diagnosis?

A. Chronic inflammatory demyelinating polyneuropathy (CIDP).
B. Anti-myelin associated glycoprotein (anti-MAG) neuropathy.
C. Vasculitic multiple mononeuropathies (mononeuritis multiplex).
D. Multifocal motor neuropathy with conduction block.
VIGNETTE ELEVEN

A 32-year-old woman comes in for third opinion regarding her bilateral foot numbness and burning, which started on the left foot around the toes 1 year ago, and the numbness has gradually progressed to the other foot and gradually evolved to a sock pattern above her ankles up to her mid-calves. Her numbness is more noticeable when she lies down at night, or when sitting still. She reports difficulty walking because of the foot pain. There is no significant drinking or travel history. On examination she has normal mental status and higher cortical functions, normal cranial nerve testing; motor examination (including extensor digitorum brevis bulk) and sensory examination reveals increased sensation to pinprick at the toes compared to the ankles, but normal sensation to light touch, cool temperature, vibration, and joint position sense. Muscle stretch reflexes are all reduced at the ankles and normal at the knees, biceps, triceps, and brachioradialis. Plantar responses are flexor. Coordination, stance, and gait are normal.

Questions

11A. What is the clinical pattern of his symptoms and signs?
   A. Small fiber polyneuropathy.
   B. Small and large fiber polyneuropathy.
   C. Sensory ganglionopathy (sensory neuronopathy).
   D. Plantar fasciitis.

11B. What would you expect to find on NCSs?
   A. Prolonged tibial distal motor latencies.
   B. Absent sural SNAPs.
   C. Increased distal compound muscle action potential durations of the tibial nerves.
   D. Normal study.

The patient’s EDX studies are normal. Laboratory studies show unremarkable hemoglobin A1c, hepatitis C virus antibody, thyroid-stimulating hormone, antinuclear antibody, Sjogren antibodies (SSA/Ro and SSB/La), and serum immunofixation.

11C. What other test could be helpful?
   A. Autonomic tests.
   B. Nerve biopsy.
   C. Muscle biopsy.
   D. All of the above.

Skin biopsy showed significantly reduced intraepidermal nerve fiber density at the distal leg more so than on the proximal.