Neuromuscular Update I
Toxin Induced Neuromuscular Diseases, Neuromuscular Junction Disorders, and Neuromuscular Vignettes

Neuromuscular Update II
ICU Related Neuromuscular Complications, Alternative and Rehab Approaches to Managing NMD, and Neuromuscular Vignettes

Photo by Michael D. Stubblefield, MD
ICU Related Neuromuscular Complications, Alternative and Rehab Approaches to Managing NMD, and Neuromuscular Vignettes (Neuromuscular Update II)

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ICU Related Neuromuscular Complications, Alternative and Rehab Approaches to Managing NMD, and Neuromuscular Vignettes (Neuromuscular Update II)

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Dr. Quan held Pfizer stock and is a consultant for and does clinical trials for Genzyme. All conflicts of interest have been resolved according to ACCME standards. All other authors/faculty have nothing to disclose.

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 - This two-part NM update course (labeled CC and CF) will present participants with clinical cases in NMDs. This course is an excellent review of NM medicine. Update II covers ICU related NMCcomplications, alternative and rehabilitative approaches to managing NMD, and a vignette session that will include both neuropathic and myopathic disorders. Participants will acquire skills to (1) utilize a pattern recognition approach elucidated through clinical vignettes in the diagnosis and management of patients with ICU related NM complications, (2) discuss alternative and rehabilitative approaches to managing NMdisorders (3) practice the vignette-based format used for many questions on the NMmedicine 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

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ICU Related Neuromuscular Complications, Alternative and Rehab Approaches to Managing NMD, and Neuromuscular Vignettes (Neuromuscular Update II)

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Dr. Bakri Elsheikh is currently assistant professor of neurology at The Ohio State University, where he serves as the director of the EMG laboratory. He received his medical degree in 1991 from the University of Khartoum, Sudan. He completed his internship and general medicine training in Khartoum Teaching Hospital. He obtained a postgraduate internal medicine degree form the Royal College of Physicians in the United Kingdom (MRCP). He did neurology training and worked as a consultant neurologist in Saudi Arabia. He also completed a neurology residency and neurophysiology/neuromuscular fellowship at OSU Medical Center. He is board certified in neurology, clinical neurophysiology, electrophysiology, and neuromuscular medicine. His research interests include spinal muscular atrophy, muscular dystrophy, myasthenia gravis and other neuromuscular diseases. Dr. Elsheikh received The David Kotlarek Award for Excellence in Compassionate Patient Care and he was awarded by medical students and residents multiple excellence in teaching awards. He is a member of the American Association of Neuromuscular & Electrodiagnostic Medicine, fellow of the Royal College of Physicians of Edinburgh (FRCP Edin), and an active member of the American Academy of Neurology.

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C\_ase \_Presentation \_One

**History**

A 56-year-old woman with a past medical history of chronic obstructive pulmonary disease was admitted to the intensive care unit (ICU) with a fever to 36.5°C and bilateral lobar pneumonia. Despite intravenous (IV) fluids and broad-spectrum antibiotics, she developed progressive respiratory failure requiring mechanical ventilation. Neurologic examination upon admission was normal. Escherichia coli was cultured from the urine and Enterobacter from the blood. Within the first week she had persistent fever and tachycardia, hypotension requiring vasopressor support, acute renal insufficiency, leukocytosis (13,500 to 15,200), and hypoxia. She was markedly obtunded with no response to pain and no voluntary movement. A lumbar puncture and a head computed tomography scan were normal. By hospital day 15, her fever, leukocytosis, and renal insufficiency had resolved. She no longer required vasopressor support and blood and urine cultures were negative. At day 17, she was noted to be more alert and would grimace to painful stimuli. However, she remained profoundly weak in her limbs and could not be weaned from mechanical ventilation despite improvement in her respiratory status.

**Examination**

The patient was intubated and on mechanical ventilation. She appeared alert and could follow commands to open and close her eyes, as well as to look at the examiner. She grimaced appropriately to painful stimuli. Mental status testing was otherwise limited. Examination of the cranial nerves was unremarkable. There was no ptosis and eye movements were intact. There was no facial weakness. There was moderate neck flexor weakness. There was no muscle atrophy or fasciculations in the limbs. Tone was normal. She appeared to grimace to painful stimuli over the proximal arm and chest, but much less so to painful stimuli applied to the distal limbs.

**Initial Differential Diagnosis**

As with most patients who are septic and critically ill, she had a profound encephalopathy with unresponsiveness. Those patients with severe encephalopathy in the setting of sepsis often have profound limb weakness as well. However, as the critical illness improved her encephalopathy largely resolved. Despite that, she remained profoundly weak in her limbs. This profound limb and
respiratory muscle weakness was unlikely to be on a central basis given her apparent normal mental status, normal brain and spine imaging studies, and the lack of any upper motor neuron signs on her examination. A neuromuscular cause of her weakness was suspected.

The list of neuromuscular disorders that may produce weakness in the setting of critical illness is extensive (Table 1). However, a useful way to organize the differential diagnosis of neuromuscular weakness in the ICU is to separate pre-existing neuromuscular conditions that produce weakness themselves severe enough to necessitate ICU care from those who develop it as a consequence of critical illness itself. Guillain-Barré syndrome (GBS) and myasthenia gravis (MG) are examples of the former. In this particular case, the patient had no neurologic complaints prior to hospitalization and her neurologic examination upon admission was entirely normal. Therefore, her quadriparesis and respiratory muscle weakness are best explained by a neuromuscular disorder that resulted as a consequence of critical illness.

The neuromuscular complications of critical illness include critical illness polyneuropathy (CIP), critical illness myopathy (CIM), and pharmacologically prolonged neuromuscular junction blockade (PNJB). She did not receive neuromuscular blocking agents, so that is not a consideration. The distally-predominant weakness is suggestive of a polyneuropathy, rather than myopathy. However, this pattern of weakness and reflex loss may be seen in both disorders and frequently they coexist as discussed below.

**Tests and Procedures**

The serum creatine kinase (CK) was normal at 180 IU/L (normal <210). The other blood work was normal and included: electrolytes, calcium, magnesium, glucose, blood urea nitrogen and creatinine, hepatic function studies, complete blood count (CBC), thyroid stimulating hormone (TSH), sedimentation rate, rheumatoid factor, serum protein electrophoresis, lactate, aldolase, and acetylcholine receptor antibodies. An MRI of the brain and cervical spine was normal. An EEG showed only mild generalized slowing.

**Electrodiagnostic Studies**

On day 20, an electrodiagnostic (EDX) study was performed. The sensory nerve conduction studies (NCSs) demonstrated absent bilateral sural, right median and right ulnar sensory responses. The radial sensory nerve action potentials (SNAPs) were reduced at 6.2 µV on the right and 4.0 µV on the left (normal >15 µV) with a normal velocity of 55 m/s and 57 m/s, respectively (normal >50 m/s). The motor NCSs were notable for absent or reduced compound motor action potential (CMAP) amplitudes with normal distal latencies and conduction velocities (Table 2). This included absent phrenic CMAPs bilaterally. There was no conduction block or abnormal temporal dispersion. F-wave responses were absent from the legs but were normal from the median and ulnar nerves. Repetitive nerve stimulation studies at 2 Hz in the right median and spinal accessory nerves were normal. The needle electromyography (EMG) examination was notable

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Amplitude (mV)</th>
<th>Distal latency (ms)</th>
<th>Conduction velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.9/1.7 (nl &gt;4.0)</td>
<td>3.8 (nl &lt;4.4)</td>
<td>47 (nl &gt;50)</td>
</tr>
<tr>
<td>Ulnar</td>
<td>1.1/0.9 (nl &gt;6.0)</td>
<td>2.4 (nl &lt;3.3)</td>
<td>50 (nl &gt;50)</td>
</tr>
<tr>
<td>Peroneal</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tibial</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Phrenic</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = no response, nl = normal
for a sparse amount of abnormal spontaneous activity in the form of fibrillation potentials. With voluntary effort, the motor unit potential (MUP) morphology was normal but recruitment was markedly reduced, more so distally (Table 3). This EDX study was characteristic of an acute, axonal sensory–motor neuropathy.

Discussion

Critical Illness Polyneuropathy

An axonal sensory–motor polyneuropathy commonly develops in the ICU setting. This was first described by Bolton and colleagues who named it “critical illness polyneuropathy.” During a period of critical illness, characterized by sepsis and multiorgan failure, their five patients developed a severe sensory–motor polyneuropathy. CIP was convincingly shown to be a distal sensory and motor axonal neuropathy, differing from GBS on electrophysiologic and morphologic studies. The clinical, electrophysiologic, and pathologic features have subsequently been detailed and, in the setting of critical illness, these characteristics define a distinctive form of acute polyneuropathy. The clinical features of CIP are similar to other length-dependent neuropathies, with distally-predominant limb weakness and reduced reflexes. Failure to wean from artificial respiration is common and may be the first recognized manifestation. Muscle atrophy is present, but it is a late finding not seen until the second or third month of illness. Sensory loss can be present, but it is usually difficult to demonstrate in patients unable to cooperate with the examination due to coexistent encephalopathy, an even more common complication of critical illness. If there is reduced limb movement after painful stimulation of the distal limb and facial grimacing, limb weakness should be suspected. Cranial nerve involvement is rare and should suggest the possibility of another neuromuscular disorder.

One early, illustrative prospective study detailed 43 ICU patients who had sepsis and multiple organ failure. The patients were in the ICU for a mean of 28 days (range: 5-89) when evaluated and all had evidence of encephalopathy. Thirty-five percent had clinical findings consistent with neuropathy, defined as distal weakness and hyporeflexia or inability to wean from the respirator. Twice as many (70%) had electrophysiologic evidence of an axonal polyneuropathy. The severity of the neuropathy correlated with the total time spent in the ICU and with those who survived the period of critical illness (only half), recovery was as expected from an acute axonal neuropathy. Those patients who had mild-to-moderate axonal loss recovered fully over months, as a result of collateral sprouting from remaining motor neurons. Those with severe neuropathy, requiring axonal regeneration for recovery, either had no recovery or had a significant persistent deficit.

Electrophysiologic studies of CIP are those of an axonal neuropathy. NCSs are characterized by reduced motor and sensory response amplitudes. There are no features that suggest demyelination. In general, conduction velocities and distal motor latencies are not significantly affected. Repetitive nerve stimulation studies of neuromuscular transmission are unremarkable, unless there is persistent pharmacologic neuromuscular blockade. Needle EMG examination of a limb muscle often is notable for spontaneous activity (fibrillation potentials and positive sharp waves) with the muscle at rest. With voluntary muscle activation, there may be an excess of polyphasic MUPs. In significantly weak muscles, these MUPs are recruited with an increased recruitment ratio. These features on needle EMG examination are consistent with acute denervation. Phrenic NCSs often are absent in those with severe neuropathy and needle EMG examination of the diaphragm can demonstrate denervation.

Sural nerve biopsy, as well as postmortem autopsy, studies in patients with CIP show features of an acute, axonal sensory–motor neuropathy. The pathology is that of axononal degeneration of both sensory and motor fibers without evidence of significant inflammation or of primary demyelination. DeLetter and colleagues prospectively performed muscle biopsies on 30 patients whom they characterized as having CIPNM (critical illness polyneuropathy and myopathy). In these biopsy specimens, neuropathic changes were seen in 37%, myopathic changes in 40%, and both in 23%, emphasizing the frequent coexistence of both CIP and CIM.

The pathogenesis of CIP is uncertain. As noted above, pathological specimens reveal acute primary axonal degeneration

Table 3. Needle electromyography studies

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Fibrillation potentials</th>
<th>MUAP duration</th>
<th>MUAP amplitude</th>
<th>MUAP polyphasia</th>
<th>MUAP recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deltoid</td>
<td>0</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>Biceps</td>
<td>0</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>Triceps</td>
<td>0</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>EDC</td>
<td>0</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>FDIO</td>
<td>1+</td>
<td></td>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>VM/VL</td>
<td>0</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>TA</td>
<td>0</td>
<td></td>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>PL</td>
<td>1+</td>
<td></td>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>MG</td>
<td>2+</td>
<td></td>
<td></td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

EDC = extensor digitorum communis, FDIO = first dorsal interosseous, MG = medial gastrocnemius, MUAP = motor unit action potential, NL = normal, None = no voluntary motor unit potential recruitment, PL = peroneus longus, TA = tibialis anterior, VM/VL = vastus medialis and lateralis, ↓ ↓ = reduced
of sensory and motor nerve fibers, without inflammation. Prospective studies have not supported a causative role of drugs (particularly corticosteroids), neuromuscular blocking agents, or aminoglycoside antibiotics.\textsuperscript{1,2,4,13,15} No specific toxin, infectious agents or nutritional deficiencies have been identified in this disorder. The current view is that cytokines and free radicals associated with systemic inflammatory response syndrome (SIRS) adversely affect the microcirculation, producing endoneurial hypoxia and ultimately distal axonal degeneration.\textsuperscript{16} This view appears to be supported by the finding that critically-ill patients with a high Acute Physiology and Chronic Health Evaluation (APACHE) III score and SIRS are most prone to the development of CIP.\textsuperscript{15}

Sepsis activates humoral and cellular responses.\textsuperscript{16} Humoral responses occur locally in tissues as antigen-presenting cells produce proinflammatory cytokines such as tumor necrosis factor, interleukin 1, and free radicals. These humoral factors, together with local cellular responses, interact with adhesion molecules on platelets and endothelial cells producing platelet-fibrin aggregates that may reduce capillary flow. Cytokines released in sepsis have histamine-like effects that may increase microvascular permeability, produce endoneurial edema, and then endoneurial hypoxia. An increase in local tissue nitric oxide, or endothelial relaxing factor, may cause arteriolar dilatation further reducing capillary flow. The microvascular structures of peripheral nerve lack autoregulation which may make nerve particularly vulnerable to these effects.\textsuperscript{16}

Treatment and prognosis. There is no specific pharmacologic treatment for CIP.\textsuperscript{17,18} Nevertheless, the first step—recognizing the presence of one of these disorders—often improves management. Prevention of CIP is feasible in part by avoiding risk factors and aggressive medical management of critically-ill patients. Intensive insulin therapy in ICU patients appears to reduce the likelihood of developing CIP and/or CIM. Future treatments of sepsis may further reduce the incidence of these neuromuscular consequences of critical illness.

The principles of recovery after CIP are the same as those related to axonal loss and recovery from GBS. In muscles where there is incomplete denervation, recovery of strength occurs with collateral sprouting from the remaining motor axons over a 3 to 6 month period. More severely affected muscles may require axonal regeneration and reinnervation for recovery. This may take up to 2 years to occur, if ever. As with GBS, the more severe the axonal loss the more likely there will be residual disability. The few longterm followup studies on these patients show that many have persistent neurologic deficits.\textsuperscript{19}

Incidence and Risk Factors. In general, the incidence of CIP and/or CIM appears to be about 50% in those patients who are critically ill in the ICU for more than a week.\textsuperscript{5,20-24} This has been demonstrated in small, but well-designed, single-site prospective studies, as well as in larger multicenter ones. Khan and colleagues recently conducted a prospective cohort study of patients with severe sepsis in the ICU.\textsuperscript{25} Twenty patients survived the analysis period and half (50%) of those developed CIP, CIM, or features of both, most by day 14 of illness. They also found that, of those affected, 10% had CIP, 10% had CIM, but 80% had both.

Stevens and colleagues performed a systematic review of 24 studies (19 prospective) of critically-ill patients who developed CIP and/or CIM.\textsuperscript{24} Most of these studies avoided the problem of distinguishing between CIP and CIM (see below) by combining them in some fashion as an endpoint. Of the total 1,421 patients in these studies, 655 (46%) developed one or both of these disorders.

Three large (61-95 patients each) prospective studies have examined risk factors in critically-ill patients for the development of neuromuscular weakness.\textsuperscript{20,21,26} All agree that measures of illness severity (APACHE III score, presence of SIRS, or organ failure assessment scores) correlate with the development of CIP/CIM. The likelihood of developing CIP and/or CIM is strongly influenced by the severity of illness. For those with a high APACHE III score (>85) and the presence of sepsis at the time of study entry (day 4 of mechanical ventilation), the probability of developing CIP/CIM by 30 days was 72%. This compares to only 8% in patients with low APACHE III scores (<70) and no sepsis.\textsuperscript{27} This is almost a tenfold higher risk in severely-ill patients.

The causative association between high-dose corticosteroids, nondepolarizing neuromuscular blocking agents (NMBAs), and sedative drugs like propofol with acquired-ICU weakness, particularly for CIM, is likely but not established. The first reports of CIM were in patients with status asthmaticus treated with high-dose corticosteroids and NMBAs. Many of the early reports of critically-ill patients with severe CIM emphasized the prodromal use of corticosteroids and NMBAs.\textsuperscript{17,18} However, the results from prospective trials have been inconsistent. Of the reports that detailed this information, there was no significant univariate association with corticosteroids, NMBAs, midazolam, or aminoglycosides.\textsuperscript{24} Multivariable analysis identified a relationship between corticosteroids and CIP/CIM in one of the two studies that addressed this. In this study, the use of corticosteroids was a significant risk factor (odds ratio=14.9).\textsuperscript{28} Similarly, one of three studies that performed a multivariable analysis showed an association of CIP/CIM with NMBAs (odds ratio=16.32).\textsuperscript{22} One limitation of the studies that did not show an association was the inclusion of a relatively small number of patients who had received substantial doses of corticosteroids and/or NMBAs.

**Differentiating Critical Illness Polyneuropathy and Critical Illness Myopathy**

There is a large cohort of patients in the ICU who have clinical and EDX features common to both CIP and CIM. However, these patients are not easily classified as purely CIP or CIM.\textsuperscript{17,18} The clinical presentation of both disorders is dominated by limb weakness that develops in the ICU, usually accompanied by a delay in weaning the patient from mechanical ventilation.

On electrophysiologic examination, one typically finds features common to both disorders. This includes reduced CMAP amplitudes on NCSs and the presence of fibrillation potentials on needle EMG examination. Sensory NCSs often are hampered by technical factors (limb edema and electrical noise from the ICU equipment), or the sensory responses may be low amplitude due to pre-existing neuropathy. Furthermore, the assessment of motor unit action potential morphology and recruitment is
often limited by the patient’s encephalopathy or sedation. Direct muscle stimulation and measures of the CMAP duration may help identify CIM (see below), but specific diagnostic criteria for these techniques have not been formally established. Of course, establishing the presence of CIM by direct muscles stimulation or prolonged CMAP amplitudes does not address the presence or absence of CIP. Despite the limitations in differentiating CIM from CIP, suggested criteria for each have been proposed (Tables 4 and 5).

In addition to the technical considerations that may limit these studies, the risk factors for both disorders overlap (see above) and many patients have a variable combination of both disorders. Nonetheless, is helpful for the ICU staff to recognize that the cause of acquired limb weakness and failure to wean in the ICU is due to CIP, CIM, or a combination of both.

**CASE PRESENTATION TWO**

**History**

A 46-year-old Caucasian female with history of bronchial asthma and chronic obstructive pulmonary disease was hospitalized for respiratory failure due to status asthmaticus, requiring intubations, mechanical ventilation, and transfer to ICU. She was paralyzed with vecuronium, and received IV aminophylline and methylprednisolone 500 mg/day. A few days after admission her blood gases deteriorated, and she was encephalopathic. Chest x-ray showed left lung pneumonia, and she was treated with antibiotics (penicillin and tobramycin). Ten days after admission the patient’s medical and neurological condition started to improve. Vecuronium and methylprednisolone were discontinued, but she continued to receive oral prednisone. She was noted to have severe weakness in all limbs and could not be totally weaned off mechanical ventilator. A neurological consultation was requested.

**Examination**

The patient was afebrile and her blood pressure was normal. She was alert and appeared to understand all verbal commands. Cranial nerves showed mild facial paresis but were otherwise normal, including extraocular muscles movements. She was noted to have severe weakness of neck flexors, decreased muscle tone, and severe weakness and mild muscle atrophy of all limbs, more prominent proximally. Tendon reflexes were depressed throughout, and she demonstrated normal sensory perception.

Initial laboratory tests showed elevated serum creatine kinase (CK) at 846 IU/L (normal <220). Normal CBC, except for a white blood cell count of 9,680 and hematocrit of 33.2%. Serum chemistry profile showed mild hyponatremia and mildly elevated liver enzymes, otherwise normal. Her erythrocyte sedimentation rate was 62 mm/h and her TSH was normal.

<table>
<thead>
<tr>
<th>Table 4. Suggested diagnostic criteria for critical illness polyneuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The patient is critically ill (sepsis and multiorgan failure, systemic inflammatory response syndrome).</td>
</tr>
<tr>
<td>2. There is difficulty weaning the patient from mechanical ventilator support after nonneuromuscular causes (i.e., cardiac and pulmonary disease) have been excluded.</td>
</tr>
<tr>
<td>3. There is possible limb weakness.</td>
</tr>
<tr>
<td>4. There is electrophysiologic evidence of an axonal sensory and motor neuropathy.</td>
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<td>5. Under the appropriate clinical circumstances, other causes of acute neuropathy should be excluded (i.e., porphyria, acute massive intoxications from arsenic or thallium, fulminant vasculitis, etc.).</td>
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Adapted from Lacomis.²

<table>
<thead>
<tr>
<th>Table 5. Suggested diagnostic criteria for critical illness myopathy*</th>
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<tr>
<td>1. The patient has had a variable combination of nondepolarizing neuromuscular blocking agents, high-dose corticosteroids, and sepsis.</td>
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<tr>
<td>2. The patient has the following Clinical features (one or both):</td>
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<tr>
<td>A. Limb weakness.</td>
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<td>B. Difficulty weaning from mechanical ventilator support, and cardiac and pulmonary causes have been excluded.</td>
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<tr>
<td>3. Electrophysiologic studies of the patient show the following:</td>
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<tr>
<td>A. Reduced motor responses (CMAP amplitudes &lt;80% of the lower limit of normal in two or more nerve without conduction block).</td>
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<tr>
<td>B. Normal repetitive nerve stimulation studies.</td>
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<tr>
<td>C. Needle EMG with short-duration, low-amplitude MUPs with early, full, or normal recruitment, with or without fibrillation potentials.</td>
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<tr>
<td>D. Demonstration of muscle inexcitability with direct muscle stimulation techniques.</td>
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<tr>
<td>E. Prolonged CMAP durations (&gt;9.0 ms).</td>
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CMAP = compound muscle action potential, EMG = electromyography, MUP = motor unit potential

*For the clinical diagnosis of critical illness myopathy, patients should have features 1, 2, 3A, 3B, and one of the following three: 3C, 3D, 3E, or 4.

Adapted from Bird.²⁸
Initial Differential Diagnosis

The causes of newly acquired neuromuscular weakness in the ICU, noted upon improvement of the underlying critical non-neurological illness, are multiple. Thus the differential diagnosis is wide including:

- Patient’s primary disease;
- Brain disorders, such as brainstem stroke or encephalopathy;
- ICU treatment complications, such as paralyzing agents and high-dose corticosteroids;
- Acute spinal cord or anterior horn cell disorders;
- Acutely evolving peripheral neuropathy, such as GBS or CIP;
- Acute myopathy such as toxic, infectious, rhabdomyolysis, CIM, and a few others; and
- Neuromuscular junction disorders, such as exacerbation of MG or PNJB.

In this case, the patient’s primary critical illness clearly improved and no significant metabolic abnormalities were identified. She was not encephalopathic and did not have cranial nerve deficits, long tract signs, or other brainstem findings. Although tendon reflexes were depressed, her normal sensory perception did not support the diagnosis of acutely evolving peripheral neuropathy such as GBS or CIP, and there was no history of exposure to neurotoxic agents. She received vecuronium; however, there were no weaknesses of the extraocular muscles, which are key features seen in PNJB. The patient had no prior history of MG, although this may not be totally excluded. Given that she had flaccid muscle weakness (more prominent proximally), muscle atrophy, and a normal sensory perception, acute myopathy was a primary consideration. Because she was treated for status asthmaticus with high-dose IV methylprednisolone and neuromuscular blocking agents, known risk factors for CIM, this was the most likely diagnosis. Rhabdomyolysis usually is associated with much higher serum CK level than in this case, and often with muscle aches and pain.

Electrodiagnostic Evaluation

A motor NCS showed normal latencies, conduction velocities (CVs), F waves, and low-amplitude CMAPs. A sensory NCS showed normal latencies, CVs, and SNAPs of the examined nerves. Needle EMG of multiple muscles in various limbs showed diffuse fibrillations potentials and positive waves, along with numerous polyphasic MUPs of low amplitude and short duration. A repetitive motor nerve stimulation test of the median and musculocutaneous nerves showed no clinically-significant CMAP decrement or increment.

Muscle Biopsy

Muscle biopsy of the left biceps muscle showed myofiber atrophy (especially type II fibers), variation in muscle fibers size, few necrotic and regenerating fibers. Myofibrillar adenosine triphosphatase (ATPase) stain showed extensive central pale areas in most muscle fibers of both histochemical types. Nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR) stain showed many fibers with myofibrillary network disruption. Acid phosphatase and periodic acid-Schiff were normal. Electron microscopy showed many fibers with extensive loss of myosin thick filaments, with preservation of thin filaments and Z-bands.

Discussion

Critical Illness Myopathy

CIM is a rapidly evolving myopathy that affects critically ill patients and may occur independently or in association with CIP. Various names to describe this entity have been used, including acute quadriplegic myopathy, critical care myopathy, necrotizing myopathy of intensive care, thick filament myopathy, among others. However, the term “critical illness myopathy” is now widely accepted.

CIM usually afflicts patients exposed to high-dose IV corticosteroids, often in combination with nondepolarizing neuromuscular junction blocking agents. It often occurs in at least one-third of status asthmaticus ICU patients treated with high-dose IV corticosteroids and in 7% of organ transplant patients. Likewise, CIM also has been associated with propofol administration, with MG patients who received high-dose IV corticosteroids, and, rarely, with patients with sepsis and multiorgan failure who were not exposed to corticosteroids.

The primary clinical feature is diffuse flaccid muscle weakness that should have started after the onset of critical illness. The weakness usually is symmetric and proximal more than distal, although in some patients it is more prominent distally. In most patients all limb muscles, neck flexors, facial muscles, and the diaphragm are involved. Respiratory failure is common with subsequent difficulty to wean from mechanical ventilator. Tendon reflexes are often depressed, but they can be preserved or increased in some patients with concurrent encephalopathy. Variable muscle atrophy is common. Sensory perception usually is normal in cooperative patients. Extraocular muscle weakness rarely is seen in CIM, and it usually suggests PNJB.

The pathogenesis of CIM is uncertain, although a number of triggering factors are known. Exposure to both corticosteroids and neuromuscular-blocking agents suggest a potential pathogenic role, however CIM also is reported in patients who were not exposed to both or either of these agents. It appears that high-dose IV corticosteroids in conjunction with neuromuscular blocking agents, critical illness, protracted immobility, high stress catabolic state, and calpain over-expression together trigger apoptosis and a proteolytic mechanism that leads to myofiber atrophy (especially type II fibers), intermyofibrillar network disruption, and varying degrees of myofiber necrosis and regeneration.

Electrophysiologic studies in CIM demonstrate muscle membrane inexcitability to direct electrical stimulus, whereas denervated muscle maintains normal excitability. Animal models showed abnormalities in ion channels and inexcitability of myofibers due to increased sodium channels inactivation at their resting potential.

Muscle biopsy rarely is needed for diagnosis of CIM, and it shows myofiber atrophy (especially type II fibers), varied degrees of...
myofiber necrosis, degeneration, and regeneration. Selective loss in thick filaments of myosin is a characteristic finding in CIM, manifesting as a disrupted or patchy loss of myofiber staining with ATPase (Fig. 1), and best confirmed by immunohistochemical stains.\(^\text{37,41}\) Widespread myofiber necrosis is seen in a more severe entity, known as “acute necrotizing myopathy of intensive care.”\(^\text{42}\) Electron microscopy shows many fibers with myosin thick filaments loss (Fig. 2). Selective loss of thick filaments in human muscle is not specific to CIM. It has been reported in other disorders, such as dermatomyositis, thrombocytopenic purpura, cases of congenital myopathy, and myopathy associated with human immunodeficiency virus infection.\(^\text{31,43,44}\)

Laboratory studies in CIM show elevation of serum CK during the first 2 weeks, which can be missed if neuromuscular evaluation is delayed once medial complications obscure the weakness.\(^\text{45}\) EDX studies often show reduced CMAP amplitudes, normal NCSs, and the absence of CMAP amplitude changes on repetitive nerve stimulation. SNAPs usually are normal, but at times they show mild abnormalities suggestive of concurrent neuropathy. Needle EMG examination reveals spontaneous activity, which indicates underlying muscle fiber necrosis and membrane irritability. Myopathic MUPs are sparse initially but prominent later in the course of the disease.\(^\text{29,46}\)

Treatment and prognosis. There is no specific treatment for CIM available. Treating underlying illness, infections, and associated metabolic disorders should be initiated vigorously, along with adequate nutrition. Muscle biopsy rarely is needed. Prophylaxis to prevent deep venous thrombosis with subcutaneous heparin or enoxaparin (Lovenox®) and pneumatic stockings are warranted. Physical therapy and nursing care of paralyzed patients are necessary to prevent decubitus, ulcers, and joint contractures or superimposed disuse muscle atrophy. Monitoring respiratory functions, mechanical ventilation, and early tracheotomy are indicated in patients with respiratory failure. Instituting a rehabilitation program as patients improve is highly recommended. Avoidance of high-dose IV corticosteroids and cautious use of neuromuscular blocking agents (or limiting the duration of their use) reduce the risk of CIM occurrence. Serial CK measurements during high-doses IV corticosteroids and paralytic agents in the ICU may provide an early diagnosis of CIM and lower its incidence.

Patients with an established or suspected CIM diagnosis should be tapered of corticosteroids and paralytic agents. In patients with rhabdomyolysis, IV hydration with alkaline diuresis is recommended.

In general, most patients with CIM who survive their critical illness recover fully within 2-3 months; however, CIM prolongs the ICU hospitalization and is associated with high medical cost.\(^\text{47}\) Patients with more severe muscle necrosis may have a poor prognosis. Mortality secondary to associated critical illness is high, in the range of 30-50%.

**Prolonged Neuromuscular Junction Blockade**

Neuromuscular blocking agents used to facilitate mechanical ventilation may cause a transient prolonged weakness. It usually is seen in patients with renal or liver failure treated with high doses of pancuronium or vecuronium.\(^\text{48,49}\)

Neuromuscular blocking agents are metabolized by the liver and cleared by the kidney; the effect of these agents may last for a number of days, or up to a week or two, after their use has been discontinued. Concurrent use of corticosteroids and aminoglycosides may contribute to neuromuscular junction failure. Female gender, acidosis, and hypermagnesemia are risk factors for PNJB.\(^\text{50,51}\) Like other ICU neuromuscular weakness syndromes, patients with PNJB have generalized flaccid muscle weakness. However, facial and extraocular muscles weakness and areflexia are characteristic of PNJB. Some patients may have associated CIM, especially those who received concomitant high-dose corticosteroids.\(^\text{48}\) Sensory disturbances usually are absent or minimal. Electrophysiological studies demonstrate a change in the CMAP amplitude and area with repetitive nerve stimulation.\(^\text{52}\) Both presynaptic and postsynaptic defects in neuromuscular transmission have been suggested, thus abnormal responses to low or high stimulation rates have been described. Spontaneous activity and myopathic MUPs may be seen on needle EMG examination in severe cases.\(^\text{48}\) Motor and sensory nerve CV and SNAP amplitude are normal.

Prevention of PNJB by minimizing the use (or bolus instead of continuous administration) of paralytic agents is recommended.
Administration of neostigmine may transiently improve the weakness. Hemodialysis is not an effective therapy and only partially reduces the paralytic agents metabolites. Hyperglycemia has a detrimental effect on nerve and muscle function, and glycemic control is warranted. In general, PNJB is self-limited syndrome, usually persisting for days or a week until the paralytic agent metabolites are excreted. PNJB cases with persistent weakness lasting for more than 2 to 3 weeks are more likely to have coexisting CIM or CIP.

ACKNOWLEDGMENT


REFERENCES


INTRODUCTION

Alternative health therapies may include herbal and folk medicines, homeopathy, dietary manipulation, naturopathy, chiropractic, and many forms of mind body medicine, including meditation, hypnotherapy, music therapy, and many other approaches (as this is not meant to be an exhaustive list). Alternative therapies are employed as an alternative to conventional medicine in the hope that they exert some healing process on the underlying disease. Moreover, what was considered alternative care 20 years ago may now be considered mainstream medicine. Many alternative health therapies and nonpharmacological modalities now are being used routinely in western medicine. Mainstream medical treatment and alternative or complementary therapy today are considered part of the same spectrum of integrated medicine. There are now some very strong scientifically valid studies verifying the safety and efficacy of alternative therapies. Indeed, nontraditional and nonpharmaceutical based approaches may have some distinct advantages over conventional medicine. Recent studies showed that approximately 72 million adults in the United States used complementary and alternative therapies, spending an out-of-pocket amount of over a billion dollars annually.1,3 In most neuromuscular diseases (NMDs), where there is a lack of effective treatment, it is necessary to explore and evaluate such therapies.4,5

The Western practitioner may need to change his or her expected patient outcomes from what is commonly anticipated in Western medicine. Alternative therapies may help improve the quality of life (QOL) in NMD, helping the patient feel better, enjoy an improved overall QOL, and provide the patient with a sense of control. Alternative therapies may help via reducing anxiety, stress, depression, sleeplessness, and tension. This may help to reduce feelings of pain, breathlessness, constipation, diarrhea, tiredness, and lack of appetite as well as help to moderate some of the effects of NMD, including muscle cramping or spasms.

It is important that the patient is aware that these treatments are not an alternative to traditional, orthodox medical approaches. Rather, they should be viewed as complementary therapies that provide emotional, spiritual, and physical well being, in conjunction with what may be otherwise used by the clinician. For patients with NMDs, therapies that have been tried include aromatherapy, acupuncture, homeopathy, massage, hypnotherapy, herbal therapy, reiki, meditation, and reflexology. It is critical that physicians consider that their NMD patients may be availing themselves of alternative therapies and it is critical to double check that any additional alternative treatment will not adversely affect any current treatment program.

This two-part discussion will focus on the emerging role of herbal cannabis therapeutics in the management of NMD as well as review the role of exercise in helping maintain and improve QOL for this patient population.
MEDICAL MARIJUANA (CANNABIS) AND NEUROMUSCULAR DISEASE

A Brief Overview of Cannabinoid Pharmacology

The use of marijuana (heretofore referred to as cannabis) as medicine continues to grow in the United States as more healthcare providers become educated about the physiologic importance of the endogenous cannabinoid system and about the wide safety margins and broad clinical efficacies of cannabinoids, the active ingredients in cannabis. Cannabinoid medicines are available in both purely botanical (natural) and purely chemical varieties. Prior to the last decade there was little known about the specific pharmacological and molecular effects of cannabis. However, important advances have taken place recently that have greatly increased the understanding of the receptors and ligands composing the endogenous cannabinoid system.6-18 Research has shown that two major cannabinoid receptor subtypes exist, including the cannabinoid receptor type 1 (CB1) subtype, which is predominantly expressed in the brain and nervous system, and the cannabinoid receptor type 2 (CB2) subtype, which is primarily found on the cells of the immune system.19-21 A variety of ligands for these receptors based on the cannabinoid structure have been synthesized and studied. Experiments performed with several types of neural cells that endogenously express the CB1 receptor suggest that the activation of protein kinases may be responsible for some of the cellular responses elicited by the CB1 cannabinoid receptor.22

The discovery of the endocannabinoids (i.e., endogenous metabolites capable of activating the cannabinoid receptors) and the understanding of the molecular mechanisms leading to their biosynthesis, release, and inactivation have created a new area in research on the pharmaceutical applications of cannabinoid-based medicines.23 The characterization of endocannabinoids such as anandamide and the detection of widespread cannabinoid receptors in the brain and peripheral tissues suggest that the cannabinoid system represents a previously unrecognized ubiquitous network in the nervous system.

Cannabinoid receptors are G protein-coupled, seven-segment transmembrane proteins similar to the receptors of other neurotransmitters such as dopamine, serotonin, and norepinephrine.22,23 Dense receptor concentrations are found in the cerebellum, basal ganglia, and hippocampus, likely accounting for the effect of exogenously administered cannabinoids on motor tone and coordination as well as mood state.24,25 Low concentrations are found in the brainstem, accounting for the low potential for lethal overdose with cannabinoid-based medicines.26-30 A growing number of strategies are emerging for separating sought after therapeutic effects of cannabinoid receptor agonists from the unwanted consequences of CB1 receptor activation. Recently, ligands have been developed that are potent and selective agonists for CB1 and CB2 receptors, as well as potent CB1 selective antagonists and inhibitors of endocannabinoid uptake or metabolism.31 In addition, varieties of cannabis are known to contain a mix of partial cannabinoid agonists and antagonists, which can be rationally utilized. This knowledge may lead to the design of synthetic cannabinoid agonists and antagonists as well as cannabis strains with high therapeutic potential.

The fact that both CB1 and CB2 receptors have been found on immune cells suggests that cannabinoids play an important role in the regulation of the immune system. Recent studies show that cannabinoids downregulate cytokine and chemokine production, both mechanisms that suppress inflammatory responses.32-35 Manipulation of endocannabinoids (i.e., via use of exogenous cannabis) has great potential treatment viability against inflammatory disorders, including the inflammation seen in the central nervous system (CNS) of patients with amyotrophic lateral sclerosis (ALS). The potential use of cannabinoids as a novel class of anti-inflammatory agents may become one the predominant indications, as it addresses not only neuromodulation but pain as well.36,37 Indeed, any number of inflammatory processes that are at least partially triggered by activated T cells or other cellular immune components could be treated with cannabis and other cannabinoid-based medicines.

Tamoxifen, a Food and Drug Administration-approved drug used to treat breast cancer, is a terpene, the same chemical classification as the cannabinoids.38-40 Terpenes are organic, lipid soluble compounds which, like petrochemicals, readily penetrate the highly lipophilic CNS.39 This affinity for nervous tissue may explain the potential implication of prior petrochemical exposure as a risk factor for ALS. The chemical similarity between cannabinoids and tamoxifen points to a possible shared mechanism of action for nerve protection.40 Phase II clinical trials of tamoxifen in ALS demonstrated preliminary efficacy and safety.40 Results from a Phase IIIb study demonstrated an increase in survival by the end of 2 years in the groups taking the higher doses of tamoxifen, although two lower dose groups had no increase in survival.40 The three higher dose groups experienced a 4 to 6 month prolongation of survival over a 24-month trial, with no significant side effects observed.40 Interestingly, glutamate uptake in cultured retinal cells is inhibited by tamoxifen, thus this mechanism may be part of a possible beneficial effect in ALS.40

The Cannabis Plant

Cannabis is a remarkably complex plant. There are several existing phenotypes, with each containing over 400 distinct chemical moieties. Approximately 85 are chemically unique and classified as plant cannabinoids or phytocannabinoids.41-44 The cannabinoids are 21 carbonmonoterpenoids, biosynthesized predominantly via a recently discovered deoxyxylulose phosphate pathway.45 The cannabinoids are lipophilic. Delta-9 tetrahydrocannabinol (THC) and delta-8 THC appear to produce the majority of the psychoactive effects of cannabis.44-46 Delta-9 THC, the active ingredient in dronabinol (Marinol), is the most abundant cannabinoid in the plant and this has led researchers to hypothesize that it is the main source of the drug’s impact.

However, other major plant cannabinoids, including cannabidiol (CBD) and cannabiol (CBN), may modify the pharmacology of THC and have distinct effects of their own. CBD is the second most prevalent of cannabis’s active ingredients and may produce most of its effects at moderate, midrange doses. Up to 40% of the cannabis resin in some strains is CBD.41 The amount varies according to plant. Some varieties of Cannabis sativa have been found to have no CBD.41 CBD appears to modulate and reduce any untoward effects of THC.41 It has significant anticonvulsant, sedative, and other pharmacological activities likely to interact
with the effects of THC. CBD may induce sleep and may provide some protection against seizures for epileptics. Both THC and CBD are derived from a common precursor known as cannabigerol. THC over time breaks down into CBN, which has fewer therapeutic properties.

**How Might Cannabis Help in Neuromuscular Disease: A Look at Amyotrophic Lateral Sclerosis**

It is now known that during active neurodegeneration from disease or trauma in the CNS, the concentration of tumor necrosis factor alpha (TNF-α) rises well above normal levels during the inflammatory response. Addition of exogenous TNF-α, both in vitro and in vivo, to neurons has been shown to significantly potentiate glutamatergic excitotoxicity. Thus the discovery of drug targets reducing excess TNF-α expression may help protect neurons after injury. Zhao and colleagues investigated the neuroprotective role of the CB1 receptor after TNF-α exposure in the presence or absence of CB1 agonists. They demonstrated that CB1 activation blocks the TNF-α-induced increase in inflammation, thus protecting the neurons from damage. Thus, neuroprotective strategies which increase CB1 activity may help to reduce damage to motor neurons in ALS that are mediated by CNS inflammation.

Additionally, CB2 receptors are dramatically upregulated in inflamed neural tissues associated with CNS disorders, including ALS. In mutant mice expressing the glycine to alanine substitution of cytosolic Cu, Zn-superoxide dismutase (G93A-SOD1), endogenous cannabinoids are elevated in the spinal cords of symptomatic mice. Furthermore, treatment with nonselective cannabinoid partial agonists prior to, or upon, symptom appearance minimally delays disease onset and prolongs survival through undefined mechanisms. Shoemaker and colleagues demonstrated that messenger RNA levels, receptor binding, and function of CB2, but not CB1, receptors are dramatically and selectively upregulated in spinal cords of G93A-SOD1 mice in a temporal pattern paralleling disease progression. Daily injections of the selective CB2 agonist AM-1241, initiated at symptom onset, increased the survival interval after disease onset by 56%.

The primary murine model for human ALS is the G93A-SOD1 mutant mouse, which is genetically engineered to replicate familial ALS. There is strong evidence in this model that the endocannabinoid system is involved, both directly and indirectly, in the pathophysiology of the disease. Several recent studies have highlighted this. Rossi and colleagues investigated both excitatory and inhibitory synaptic transmission in the striatum of symptomatic G93A-SOD1 mice, along with the sensitivity of these synapses to CB1 receptor stimulation. They reported a reduced frequency of glutamate-mediated spontaneous excitatory postsynaptic currents and increased frequency of gamma-aminobutyric acid (GABA)-mediated spontaneous inhibitory postsynaptic currents in recordings from striatal neurons in ALS mice. This likely is due to some presynaptic defects in transmitter release. The sensitivity of CB1 receptors in controlling both glutamate and GABA transmission was potentiated in ALS mice. This provides good evidence that adaptations of the endocannabinoid system might be involved in the pathophysiology of ALS. This is consistent with current theories on pathophysiological mechanisms of ALS.

Bilsland and colleagues showed that treatment of postsymptomatic, 90-day-old G93A-SOD1 mice with a synthetic cannabinoid (WIN55,212-2) significantly delayed disease progression. Furthermore, genetic ablation of the fatty acid amide hydrolase (FAAH) enzyme, which results in raised levels of the endocannabinoid anandamide by preventing its breakdown, prevented the appearance of disease signs in 90-day-old G93A-SOD1 mice. Surprisingly, elevation of cannabinoid levels with either WIN55, 212-2 or FAAH ablation had no effect on life span. Ablation of the CB1 receptor, in contrast, had no effect on disease onset in G93A-SOD1 mice but significantly extended life span. Together these results indicate that cannabinoids have significant neuroprotective and disease-modifying effects in this model of ALS and suggest that these beneficial effects may be mediated by non-CB1 receptor-based mechanisms.

**The Role of the Endocannabinoid System**

The endocannabinoid anandamide demonstrates dopamine-blocking and anti-inflammatory effects and is also tonically active in the periaqueductal gray matter. Endocannabinoids also modulate glutamatergic neurotransmission indirectly via NMDA (N-methyl D-aspartate) receptors, and these pathways can be modulated to produce a clinical effect, such as reduction in motor tone, increase in seizure threshold, protection from neuronal injury, decrease in perception of pain, and elevation in mood state. These clinical, biochemical, and pathophysiological patterns could reflect an underlying abnormality in the endocannabinoid system in ALS that potentially could be treated with exogenous cannabinoids (i.e., via clinical use of cannabis or some derivative thereof).

**Using Cannabis to Manage Clinical Symptoms of Neuromuscular Disease**

In addition to the neuroprotective effect, patients report that cannabis helps in treating symptoms of the disease, including alleviating pain and muscle spasms, improving appetite, diminishing depression, and helping to manage sialorrhea (excessive drooling) by drying up saliva in the mouth. Indeed, in a large survey it was noted that ALS patients who were able to obtain cannabis found it preferable to prescription medication in managing their symptoms. However, this study also noted that the biggest reason ALS patients were not using cannabis was their inability to obtain it, either due to legal or financial reasons or lack of safe access.

There are many other clinical problems faced by NMD patients that could be helped by cannabis. The majority of NMD patients experience significant pain. The pain largely is due to immobility, which can cause adhesive capsulitis, mechanical back pain, pressure areas on the skin, and, more rarely, neuropathic pain. Pain in NMD is a frequent symptom especially in the later stages of disease and can have a pronounced influence on QOL and suffering. Treatment of pain therefore should be recognized as an important aspect of palliative care in NMD. Despite the major pain problems encountered by patients with NMD, there are no clear guidelines and few randomized clinical trials that address how to manage pain in this population. However, as noted previously, the cannabinoids have been shown to produce...
an anti-inflammatory effect by inhibiting the production and action of TNF-α and other acute phase cytokines. Additionally, cannabis may reduce pain sensation, likely through a brainstem circuit that also contributes to the pain suppressing effects of morphine. Cannabinoids produce analgesia by modulating rostral ventromedial medulla neuronal activity in a manner similar to, but pharmacologically distinct from, that of morphine. This analgesic effect is also exerted by some endogenous cannabinoids (anandamide) and synthetic cannabinoids (methanandamide) and may be prevented by the use of selective antagonists. Thus cannabinoids are centrally and peripherally acting analgesics with a different mechanism of action than opioids, although the analgesia produced by cannabinoids and opioids may involve similar and synergistic pathways at the brainstem level. A recent systematic review and meta-analysis of double-blind randomized controlled trials that compared any cannabis preparation to placebo among subjects with chronic pain showed a total of 18 completed trials. The studies indicate that that cannabis is moderately efficacious for treatment of chronic pain. In the setting of advanced NMD, the medications should be titrated to the point of comfort. Concomitant use of narcotics may be needed if pain is severe. However, cannabis may lower the amount of opiates needed, and because cannabinoids do not cause respiratory depression or constipation, this may be very advantageous. The anti-emetic effect of cannabis may help with the nausea sometimes associated with narcotics.

In addition to pain, spasticity is also a major problem for some NMD patients, particularly those with ALS. Spasticity is induced both at the motor cortex and at the spinal cord level through the loss of motor neuron inhibition. Cannabis has an inhibitory effect via augmentation of GABA pathways in the CNS. This produces motor neuron inhibition at spinal levels in mice. Several past studies have suggested that cannabinoid therapy provide at least a subjective reduction of spasticity, although virtually all of the studies have been done in patients with multiple sclerosis (MS). One survey study has shown that ALS patients do subjectively report that cannabis helps alleviate symptoms of spasticity. As mentioned previously, cannabis is also a potent antispasmodic compound and ALS patients have reported benefit in controlling saliva when using it. Although this remains to be studied, other potential uses of cannabis in managing NMD symptoms include, improving appetite, mood state, and sleep patterns.

How Would an Neuromuscular Disease Patient Safely Use Cannabis as Medicine?

Cannabinoids are volatile and will vaporize at temperatures in the range of 200°F, much lower than actual combustion. Heated air can be drawn through cannabis and the active compounds will vaporize, which can then be inhaled. This delivers the cannabinoids in a rapid manner that can be easily titrated to desired effect. Additionally, cannabis can be ingested orally or through a feeding tube using extracts prepared in lipophilic or alcohol-based media, although absorption is much slower, making dose titration more difficult.

For patients with severe dysphagia, inhalation offers obvious advantages. Dosing for symptom management would be “titrate to desired effect” and an individual, patient-controlled, dosing model may be used. Dosing paradigms for clinical effects in terms of pain have been previously described in the literature. A patient-determined, self-titrated dosing model is acceptable given the low toxicity of cannabis and the multiple variables involved here. However, based on the available studies, a typical pulmonary administration dosing range would likely be 1-2 g/day of cannabis with an average THC content of 20% by weight.

NONPHARMACOLOGICAL/REHABILITATION STRATEGIES TO IMPROVE HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH NEUROMUSCULAR DISEASE

There is incredible diversity in the spectrum of disease burden incurred by individuals with NMD. However, skeletal muscle weakness is the ultimate cause of the majority of clinical problems in NMDs. There have been a number of well-controlled studies documenting the effect of exercise as a means to gain strength in NMDs, although much remains to be learned. In slowly progressive NMDs, a 12-week moderate resistance (30% of maximum isometric force) exercise program resulted in strength gains ranging from 4-20% without any notable deleterious effects. However, in the same population, a 12-week high-resistance (training at the maximum weight a subject could lift 12 times) exercise program showed no further added beneficial effect compared with the moderate resistance program, and there was evidence of overwork weakness in some of the subjects, particularly following eccentric contractions.

In a study comparing patients with Charcot-Marie-Tooth (CMT) disease and to patients with myotonic muscular dystrophy (MMD), only the CMT patients appeared to benefit significantly from a strengthening program. This clearly points out that the most effective exercise regimens for neuropathies and myopathies most likely are going to be different, although further investigation is needed. In rapidly progressive disorders like Duchenne muscular dystrophy (DMD) and ALS, there is active ongoing muscle degeneration and the risk for overwork weakness and exercise-induced muscle injury is much greater. In this population exercise should be prescribed with caution and a common sense approach. It is advisable that all NMD patients be advised not to exercise to exhaustion, due to the risk of exercised-induced muscle damage. NMD patients in an exercise program should be monitored for signs of overwork weakness. This includes excessive delayed onset muscle soreness. This usually occurs 24-48 hours following exercise. Other warning signs include severe muscle cramping, heaviness in the extremities, and prolonged dyspnea.

Submaximal, low-impact aerobic exercise (walking, swimming, stationary bicycling) will improve symptoms of fatigue via enhancement of cardiovascular performance and increase muscle oxygen and substrate utilization. This is important because fatigue is a significant limiting factor in physical performance in patients with NMDs. Fatigue in this setting likely is multifactorial, due to deconditioning and impaired muscular activation. Improving cardiopulmonary performance through aerobic exercise will improve not only physical functioning but also improve mood state and help fight depression and osteoporosis, which in turn reduces fracture risk. Patients with...
Orthotics

Joint contractures and scoliosis are a major clinical problem in NMDs, particularly DMD and spinal muscular atrophy type II patients. Routine examination of the spine and major joints in NMD patients should be performed at each clinic visit. Contractures appear to be related to prolonged static limb positioning and frequently develop shortly after the patient becomes wheelchair dependent. In ambulatory patients, upper extremity contractures may occur and be complicated by joint subluxation, particularly in the shoulder girdle. Slings may provide support but will not prevent contracture formation. Again, stretching and positional splinting may slow the progression of contractures, although the actual efficacy of this has not been well studied or documented in the literature. Surgical release of contractures in the lower extremities may allow a patient to be functionally braced. This may prolong ambulation although a number of studies have shown that weakness, not contractures, contribute most to the loss of functional ambulation.

For the extremities, bracing should be used with the goal of improving function and joint stability. Long-leg bracing to prolong ambulation time in DMD has been one of the best-studied uses in NMDs. A number of studies have shown that ambulatory ability may be prolonged up to 2 years with long-leg braces and appropriate contracture release. However, it is not clear if this represents a subset of patients with a slower disease progression and relatively less weakness. Further, there does not appear to be any clear association between prolonging ambulation with long-leg bracing and delaying or decreasing scoliosis in DMD. If bracing is used, a “long-leg brace” or knee-ankle-foot orthosis (KAFO) generally is needed due to the amount of weakness in hip and knee extension as well as ankle plantar flexion and dorsiflexion.

Most CMT patients require “short-leg braces” or ankle-foot orthoses (AFOs). It is best if these are custom-made with a lightweight polymer (polypropylene or carbon fiber). They should fit intimately to avoid skin problems and provide good stability. If a pressure sores occur, the patient should be taken out of the brace until they heal. Double metal upright AFOs may be built into the shoe but are usually too heavy and may limit ambulation for those patients with proximal muscle weakness. If there is significant ankle instability noted, the braces should be high profile (come around in front of the malleoli). Pes cavus and hammertoe deformities can be accommodated with built-up arches and metatarsal bars. CMT and other sensory neuropathy patients are at very high risk for skin ulcers and neuropathic arthritis (Charcot joint). Thus, skin integrity and joint stability should be checked at every clinic visit.

Patients with NMD weakness may benefit from bracing, depending on the distribution of weakness, gait problems, and joint instability. The decision to brace should include the risk of added weight of the brace and the willingness of the patient to use the brace. NMD patients should be referred for a course of physical therapy after being fitted with braces to help them learn to use the devices effectively.

Equipment

Proper equipment can significantly improve quality of life for an NMD patient. Common examples include hospital beds, commode chairs, wheelchairs and wheelchair ramps, hand-held showers, bathtub benches, grab bars, and raised toilet seats. An occupational therapist is best qualified to determine if any of these devices would be useful for the NMD patient.

Wheelchairs are a critical component of mobility in those with severe NMD. Wheelchairs need to be fitted appropriately with the right frame size, type of seat, lumbar support and cushioning to avoid pressure ulcers. Other mechanical devices, such as the Tilt-N-Space (Postural Seating Materials, Inc., Lawrence, Kansas) allow the patient to independently tilt the wheelchair seat, providing improved comfort and better pressure relief for the skin. These devices often can be retrofitted on to existing chairs. The patient should be evaluated by a physical or occupational therapist to ensure proper wheelchair prescription. Simply giving the patient a prescription for a wheelchair frequently results in a chair that does not fit properly or has improper components. Power wheelchairs are indicated in most NMD patients who can no longer ambulate and do not have enough upper extremity strength to independently propel a manual chair. Although expensive, power wheelchairs can be justified to third-party payers on the basis that they help prolong independent mobility, thus decreasing medical and psychological comorbidity.

For patients who can still ambulate, walkers or quad (four-point) canes help reduce fall risk. Pressure-relieving mattresses, with foam wedges for proper positioning, help prevent pressure skin ulcers. In some NMD patients, particularly those with ALS, severe weakness in neck musculature may produce neck pain and muscle spasms. A cervical collar, particularly the Freeman or Headmaster type (a wire-frame collar with padding over the pressure points) may be very helpful. In patients with dysarthria, typically ALS patients, augmentative communicative aids, including an alphabet board, word board, or computer-based speech synthesizer, can maintain functional communication. A speech language pathologist is best qualified to determine which, if any, of these devices would work best.

DEDICATION

Dedicated with loving respect to the memory of Drs. David D. Kilmer and Lisa S. Krivickas. Their pioneering work in this area is cited frequently herein.

REFERENCES


Neuromuscular Vignettes

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VIGNETTE ONE

A 55-year-old man presents with an insidious onset of painless and symmetric weakness affecting all four extremities. He is unable to get up from a low chair. He notices that his feet slap when he walks and sometimes his leg will just give out suddenly and he falls. You examine him and find diffuse weakness, with prominent weakness of the finger flexors (3/5) bilaterally. He also has quadriceps atrophy weakness of 2/5 bilaterally. Ankle dorsiflexion is 3/5 bilaterally. He has diminished reflexes. Review of laboratory studies reveals a serum creatine kinase (CK) level of 484 IU/L. He has been taking simvastatin for several years.

Questions

1A. What is the MOST LIKELY diagnosis?
   A. Amyotrophic lateral sclerosis (ALS).
   B. Inclusion body myositis.
   C. Polymyositis.
   D. Toxic myopathy.

1B. What is the MOST appropriate prescription for his lower extremity symptoms?
   A. Ankle foot orthosis (AFO) with an articulating joint.
   B. Posterior leaf spring (PLS) orthosis.
   C. Solid ankle AFO with floor reaction.
   D. Long-leg brace with locking knee and articulating ankle joint.

1C. What is the MOST appropriate prescription for his upper extremity symptoms?
   A. Built-up eating utensils.
   B. Dynamic hand splint.
   C. Myoelectric hand orthosis.
   D. Weight training.

VIGNETTE TWO

A 63-year-old Amish woman presents with a 2-year history of progressive weakness and fatigue affecting the lower extremities. The right lower extremity is primarily affected. She has a history of polio at age 14 resulting in her being bedridden for several weeks. She was given a brace but she never really liked it and threw it away. She never was able to run very well but otherwise denies disability until about 2 years ago when her current symptoms began.

Examination reveals motor function to be without clear deficit in the upper extremities. Motor function in the right lower extremity is 3/5 at the hip and knee and 2/5 at the ankle. Motor function in the left lower extremity is 4/5 throughout. Sensation is intact throughout the upper and lower extremities and DTRs are diffusely diminished.

Nerve conduction studies (NCSs) show CMAPs of reduced amplitude but were otherwise unremarkable. Needle electromyography (EMG) showed very large motor unit potentials throughout the right lower extremity and in the left vastus lateralis,
vastus medialis, and biceps femoris. The left tibialis anterior, gastrocnemius, and peroneus longus are spared.

Questions

2A. What is the MOST LIKELY diagnosis?
A. ALS.
B. Glutaric aciduria.
C. Radiculoplexus neuropathy.
D. Postpolio syndrome.

2B. Which of the following is MOST correct regarding bracing for this patient?
A. A carbon fiber low-profile AFO is indicated.
B. A long-leg brace is indicated.
C. A myoelectric prosthosis is indicated.
D. Do not try a brace with her because she will not accept one.

2C. Regarding exercise for this patient:
A. Functional electrical stimulation has been shown to be the most effective type of exercise for this condition.
B. Progressive resistive exercises (PREs) are indicated for only the weak muscles.
C. PREs are indicated for all of the muscles.
D. Needle EMG results should be used as a guide to customize the patient’s exercise routine.

VIGNETTE THREE

A 28-year-old man presents with complaint of pain and weakness affecting the left upper extremity. He awoke 8 weeks ago with severe left sided chest and shoulder pain. After a few days he noticed weakness. He was seen in the emergency room and his cardiac workup was unremarkable. He has since had an magnetic resonance imaging (MRI) scan of the neck and shoulder and a computed tomography scan of the chest, both of which were unremarkable. His pain has improved over the past week and is now down to 4/10.

Examination reveals 2/5 left finger extension and 2/5 left wrist extension. Left side intrinsics are difficult to evaluate, but there is resistance obtained with the fingers flat on a table. Left shoulder abduction is 2/5 and left elbow extension is 3/5. Left supination is 3/5. All other motor function tested in the upper extremities is at least 4+/5. Sensation is decreased to pinprick in a patchy distribution in the left upper extremity and intact on the right.

NCSs reveal moderately reduced amplitude of the left radial motor response with stimulating in the forearm and arm; no response is elicited with stimulating at the axilla. The left axillary motor response was absent. The left radial sensory response also was of reduced amplitude. The lateral antebrachial cutaneous response was absent on the left and easily obtainable on the right. All other NCSs were within normal limits.

Needle EMG showed spontaneous activity and reduced recruitment in the biceps, extensor digitorum communis, triceps, and deltoid. Needle EMG was normal in the flexor carpi radialis, first dorsal interosseous, and abductor pollicis brevis.

Questions

3A. The patient MOST LIKELY has which of the following?
A. Acute brachial neuritis.
B. ALS.
C. Cervical radiculopathy.
D. Pancoast tumor.

3B. Which of the following would be the BEST treatment?
A. Intravenous immunoglobulin (IVIg).
B. PREs.
C. Steroids.
D. Watchful waiting.

3C. Recovery of hand function is LIKELY to be which of the following?
A. A prolonged process.
B. Minimal.
C. Rapid.
D. Indeterminate.

3D. Which of the following would be the BEST bracing option?
A. Balanced forearm orthosis.
B. Dynamic hand splint.
C. Thumb spica hand splint.
D. Bracing is not indicated.

VIGNETTE FOUR

A 60-year-old woman presents with muscle stiffness and pain since the age of 7. She recalls winters in elementary school when she was unable to unzip her coat without the teacher’s help. In addition to cold weather, her stiffness is worse with any form of repeated activity or exercise. She tells you, “I learned to live with it, but lately I feel worse.” She reports difficulty pulling weeds from the garden or even slicing a loaf of bread. Her past medical history includes hypothyroidism and hypertension for which she takes levothyroxine and atenolol. She is a retired flight attendant. She has no siblings. She reports no similar history in the family, including her son and her two grandchildren. Examination reveals normal strength, 2+ symmetric deep tendon reflexes (DTRs), and normal pinprick and vibratory sensation. Her records indicate a normal complete blood count, electrolytes, and thyroid stimulating hormone (TSH) and a serum CK of 75 IU/L. Needle EMG demonstrates diffuse myotonic discharges. (A video showing dynamic findings on examination will be presented during the live course.)

Questions

4A. What is the MOST LIKELY diagnosis?
A. Proximal myotonic myopathy.
B. Dominant myotonia congenita (Thomsen’s disease).
C. Recessive myotonia congenita (Becker’s disease).
D. Paramyotonia congenita.
4B. The responsible disorder is LIKELY associated with which of the following?
   A. Chloride channel gene mutation.
   B. Potassium channel gene mutation.
   C. Sodium channel gene mutation.
   D. Calcium channel gene mutation.

4C. If you performed a short exercise test, which of the following patterns would be MOST characteristic of this condition?
   A. No significant change in the compound muscle action potential (CMAP).
   B. An initial fall in the CMAP that is less prominent with repeated trials.
   C. An initial increase in the CMAP that is more prominent with repeated trials.
   D. An initial fall in the CMAP that is more prominent with repeated trials.

4D. This condition can be distinguished from potassium aggravated myotonia by the presence of which of the following?
   A. Sodium channel gene mutation.
   B. Extreme cold sensitivity.
   C. Myotonic potentials on needle EMG.
   D. Age at onset of symptoms.

VIGNETTE FIVE

A 38-year-old man presents with attacks of weakness since the age of 12. His initial symptoms were weakness of one limb or another provoked by exertion. He had an episode in high school where he could not stand up from his desk. He was taken to the hospital and was found to have low potassium of 2.5. He was given the diagnosis of hypokalemic periodic paralysis (HypoPP). His treatment regimen includes acetazolamide and potassium supplements. Despite the absence of discrete attacks of weakness, he reports that in the last couple of years he is more aware of difficulty going up steps or getting up from the floor. His examination is unremarkable except for mild proximal limb weakness.

Questions

5A. Which of the following is LEAST LIKELY to trigger an attack of weakness in his condition?
   A. A long car ride.
   B. Rest after exercise.
   C. Fasting.
   D. A large carbohydrate meal.

5B. HypoPP is associated with which of the following?
   A. Chloride channel gene mutation.
   B. Calcium channel gene mutation.
   C. Sodium channel gene mutation.
   D. Both B and C.

5C. Which of the following electrophysiological findings is expected in HypoPP?
   A. Postexercise myotonic potentials.
   B. Short exercise test positive for 50% initial CMAP decline followed by gradual recovery in 20-40 s.
   C. Long exercise test positive for 50% CMAP decline at 40 min.
   D. During paralytic attack, CMAP amplitudes are twice the baseline size.

5D. Other treatment options for HypoPP include all the following EXCEPT:
   A. Dichlorphenamide.
   B. Trimaterene.
   C. High-dose steroids.
   D. Spironolactone.

VIGNETTE SIX

A 58-year-old female presents with 3 years of progressive weakness, numbness, and gait and balance difficulty. She became wheelchair dependent in the last year. She also reports bladder control difficulty and constipation. Examination reveals mild proximal arm weakness and proximal and distal leg weakness. Her DTRs are brisk with sustained ankle clonus and positive Hoffman’s and Babinski’s reflexes. She has decreased vibration to the knees and position sense at the ankles. She has decreased pinprick sensation in a stocking and glove distribution to the mid thigh and midforearm, respectively. There is no definite sensory level in the trunk. Her previous records indicate a concern about multiple sclerosis however MRI of the brain and cervical cord are reported as unremarkable. Her cerebrospinal fluid analysis revealed the following: protein 27 mg/dl, glucose 75 mg/dl, 0 white blood cells/mm3. Tests venereal disease, acetylcholinesterase, and oligoclonal bands were negative.

Other tests performed were all normal: vitamin B12 (688 pg/ml), methylmalonic acid, homocysteine, vitamin E, thyroid function test, rapid plasma reagin, fluorescent treponemal antibody, antinuclear antibody (ANA), extractable nuclear antigen antibodies, human immunodeficiency virus, human T-lymphotropic virus type I, and Lyme and neuromyelitis optica serology. A needle EMG showed an axonal sensory motor neuropathy.

Questions

6A. Review of the cervical spine MRI reveals a C3-5 posterior cord signal on T2-weighted images. Which of the following tests will LIKELY help with the diagnosis?
   A. Flexion and extension cervical spine MRI.
   B. Spinal cord angiography.
   C. Serum copper and zinc levels.
   D. Measurement of serum very long chain fatty acids.

6B. Which of the following facts is relevant to her diagnosis?
   A. History of L4-5 laminectomy and fusion.
   B. History of vegetarian diet for the last 10 years.
   C. History of daily use of denture cream for the last 20 years.
   D. History of head trauma as a child.
6C. Which of the following statements is FALSE regarding the etiology of her condition?
A. Bariatric surgery is an established cause.
B. Anemia and neutropenia may occur.
C. Vitamin B12 deficiency may coexist.
D. Response to chelation.

6D. Which of the following is the MOST APPROPRIATE treatment for this patient?
A. IVIg.
B. High-dose oral steroids.
C. Oral copper gluconate.
D. Cytoxan.

**VIGNETTE SEVEN**

A 23-year-old woman presents for evaluation of weakness. As a child, she could walk but not run. She eventually was given long-leg braces to wear because of leg weakness. On examination, she had poorly developed musculature, moderate upper and lower facial weakness, moderately severe limb weakness proximally, and well-preserved limb strength distally. Reflexes were decreased or absent. Sensation was normal. She was able to arise from a chair only with assistance, and walked with long-leg braces and an exaggerated lumbar lordosis. Normal or negative blood tests included sedimentation rate, ANA, thyroxine (T4), TSH, vitamin B12, serum CK. NCSs were normal. Needle EMG revealed no abnormal spontaneous activity. Motor unit action potentials (MUAPs) in proximal upper and lower extremity muscles were of low amplitude and short duration and demonstrated rapid recruitment. Needle examination of distal muscles was normal. A muscle biopsy from the biceps muscle was interpreted as demonstrating mild myopathic changes, with increased variation in fiber size and a mild increase in the number of internalized nuclei.

**Questions**

7A. Which of the following is the BEST next diagnostic procedure to perform in the evaluation of this patient?
A. Biochemical testing of muscle for disorders of glycogen or lipid metabolism.
B. Biochemical or genetic assessment for mitochondrial diseases.
C. Genetic testing for limb-girdle muscular dystrophies.
D. Repetitive stimulation studies of one or more nerves.

7B. Repetitive nerve stimulation studies of the accessory nerve were performed at 3 Hz at (from left to right) pre-exercise, immediately after 30 s of isometric exercise, and 2 min postexercise. Such a finding can be found in all of the following disorders EXCEPT:

A. Acquired, autoimmune myasthenia gravis.
B. Centronuclear myopathy.
C. A congenital myasthenic syndrome.
D. Lambert-Eaton myasthenic syndrome.

7C. The patient was found to have a mutation in the gene DOK-7. Which of the following treatments are likely to produce the BEST response?
A. Ephedrine and albuterol.
B. 3,4-diaminopyridine.
C. Pyridostigmine (Mestinon®).
D. Prednisone and IVIg.

**VIGNETTE EIGHT**

A 58-year-old woman presents with a 6-month history of cramping in the muscles of the upper and lower extremities. She also noted a stiffness in her muscles which improved with use and some generalized decrease in muscle strength. She had a history of a thymoma resected 4 years earlier which was found during an evaluation for a persistent cough and was not associated with any muscle weakness at that time. Examination revealed mild weakness of the neck flexors and of the distal upper extremity muscles. Reflexes were absent. Sensation was normal. She could arise from a squatting position only by pushing with her arms. The ANA was 1:640. Anti-SSA and SSB antibody titers were normal. T4 and TSH were normal. Acetylcholine receptor binding antibodies were elevated to 0.17 nmol/L (normal <0.01) at the time of discovery of her thymoma, but they declined to normal after thymoma resection. Sensory and motor NCSs were normal. Needle examination revealed abnormal spontaneous activity in the form of very high frequency (150-250 Hz) discharges in several muscles which waned in amplitude and frequency. Repetitive nerve stimulation studies of the ulnar and accessory nerves performed at 3 Hz revealed no change in the CMAP amplitude from the first to the fourth stimulus pre- or post-exercise.

**Questions**

8A. This disorder is LIKELY to be associated with which of the following?
A. Voltage-gated potassium channel antibodies.
B. Abnormally high number of CTG trinucleotide repeats.
C. Voltage-gated calcium channel antibodies.
D. Low levels of acid alpha glucosidase (acid maltase) activity.
8B. Which of the following is the source generator for the abnormal discharges seen on the needle EMG examination?
A. Muscle fiber.
B. Neuromuscular junction.
C. Motor unit (motor neuron/axon).
D. Cortical motor neuron.

8C. Appropriate treatments for this condition include each of the following EXCEPT:
A. Carbamazepine.
B. Amitriptyline.
C. Prednisone.
D. Phenytoin.

VIGNETTE NINE

A 51-year-old man presents with a 2-year history of lower extremity weakness, beginning with difficulty climbing stairs. This persisted and worsened. His maternal grandfather and the grandfather’s brother both experienced progressive leg weakness as they became older, without a specific diagnosis. Examination revealed mild tongue atrophy, with tongue and chin fasciculations. There was mild weakness of the spinati and of the hip flexors. Reflexes were absent. There was mild distal sensory loss in the feet. Gait was normal, but he arose from a squatting position by pushing with his arms. Laboratory studies were remarkable for serum CK levels of 1,259 and 1,372 IU/L. Normal or negative studies included sedimentation rate, ANA, T4, and TSH. NCSs are shown below.

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<th>Sensory nerve (all left)</th>
<th>Amplitude (µV)</th>
<th>Peak latency (ms)</th>
<th>Distance (mm)</th>
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Needle examination revealed fibrillation potentials and positive sharp waves in muscles of the right upper and lower extremities. MUAPs in virtually all muscles tested, proximally and distally, were of large size and demonstrated decreased recruitment.
Questions

9A. This patient is LIKELY to have which of the following conditions?
   A. Cardiomyopathy.
   B. Retinal pigmentary degeneration.
   C. Gynecomastia.
   D. Cataracts.

9B. Inheritance of this disease is which of the following?
   A. Autosomal recessive.
   B. Via mitochondrial DNA.
   C. Autosomal dominant with incomplete penetrance.
   D. X-linked.

9C. The underlying genetic basis for this condition is which of the following?
   A. CTC trinucleotide repeat expansion on the DMPK gene.
   B. CAG trinucleotide repeat expansion on the androgen receptor gene.
   C. CAG trinucleotide repeat expansion on the HTT (Huntington’s disease) gene.
   D. CCTG repeat expansion on the CNBP (zinc finger protein 9) gene.

VIGNETTE TEN

A 17-year-old girl presents for evaluation of a 4-year history of progressive, proximal muscle weakness, characterized by difficulty climbing stairs even when pulling on the railing, and a need to push with her arms when arising from a chair. Her leg weakness had resulted in several falls. Family history was negative for any disorder producing muscle weakness. Examination revealed a very thin young woman with normal mental status and normal cranial nerve examinations. She demonstrated full strength in the upper extremities. Lower extremities were characterized by moderately severe hip flexor weakness and mild-to-moderate distal weakness. Reflexes were absent. Sensation was normal. She arose from a chair by pushing with her arms on her knees. Gait was characterized by an exaggerated lumbar lordosis and a swaying of the hips. Laboratory studies demonstrated a serum CK level of 1,158 IU/L. Sedimentation rate and thyroid function tests were normal. Sensory and motor NCSs of an upper and lower extremity were normal. Needle EMG examination revealed fibrillation potentials, positive sharp waves, and myotonic discharges in several muscles, more prominent in the lower than the upper extremities, more prominent proximally than distally. MUAPs were of short duration, small amplitude, and demonstrated early recruitment.

Questions

10A. The predominant finding in a muscle biopsy from this patient is MOST LIKELY to be which of the following?
   A. CTC trinucleotide repeat expansion on the DMPK gene.
   B. CAG trinucleotide repeat expansion on the androgen receptor gene.
   C. CAG trinucleotide repeat expansion on the HTT (Huntington’s disease) gene.
   D. CCTG repeat expansion on the CNBP (zinc finger protein 9) gene.

10B. A muscle biopsy revealed a vacuolar myopathy with increased variation in fiber size and an increased number of internalized nuclei. Areas of positive staining with periodic acid-Schiff were noted. Electron microscopy demonstrated glycogen both within the vacuoles and freely in the cytoplasm. The etiology of this patient’s condition MOST LIKELY is due to an abnormality in which of the following?
   A. The DMPK gene.
   B. The GNE gene.
   C. Mitochondrial DNA.
   D. The GAA gene.

10C. Biochemical analysis of the muscle revealed a markedly reduced level of acid maltase activity of 0.38 mmol/min/g tissue (normal 1.74-9.98). In view of this finding, which of the following is MOST LIKELY to occur?
   A. Cardiomyopathy and heart failure.
   B. Hepatomegaly and liver failure.
   C. Respiratory muscle weakness and respiratory failure.
   D. Retinal degeneration and blindness.
1. A combination of steroids and neuromuscular blocking agents in the intensive care unit has been associated with:
   A. Nemaline rod myopathy.
   B. Cachectic (disuse) myopathy.
   C. Polymyositis.
   D. Critical illness myopathy.
   E. Critical illness neuropathy.

2. A characteristic muscle biopsy finding in critical illness myopathy is:
   A. Inflammatory cellular infiltrate.
   B. Extensive muscle fibers necrosis.
   C. Thick filaments (myosin) loss.
   D. Grouped muscle fibers atrophy.
   E. Variation in muscle fibers size and shape.

3. Which of the following electrophysiological findings is NOT associated with critical illness myopathy?
   A. Low compound muscle action potential (CMAP) amplitude.
   B. Short duration, small amplitude polyphasic motor unit potential.
   C. Irritative changes (fibrillations and positive waves).
   D. Occasional mild sensory abnormalities.
   E. CMAP amplitude changes on repetitive nerve stimulation.

4. Which of the following features is most characteristic of prolonged neuromuscular junction block?
   A. Flaccid weakness of all limbs (tetraplegia).
   B. Depressed or absent tendon reflexes (areflexia).
   C. Facial and extraocular muscles weakness.
   D. Sepsis and multi-organ failure.
   E. Failure to wean from mechanical ventilator.

5. Risk factors for acquired neuromuscular weakness in the ICU include all the following EXCEPT:
   A. High doses of pancuronium or vecuronium.
   B. High doses of IV corticosteroids.
   C. Systemic inflammatory response syndrome.
   D. Known history of asthma or organ transplant.
   E. Known history of diabetic polyneuropathy.

6. A 27-year-old male presents with numbness and weakness in the lower extremities. He has a family history of Charcot-Marie-Tooth disease. On examination, he demonstrates significant 4/5 strength in most major muscle groups, except dorsiflexion where he is 3/5 bilaterally. After walking for several minutes, he does start to drag his feet. Which type of bracing modality is most likely to improve his gait?
   A. Custom fit shoe orthotics with metatarsal pads.
   B. Bilateral universal foot orthotics.
   C. Bilateral long leg double metal upright knee-ankle-foot orthotics.
   D. Bilateral double metal upright ankle-foot orthotics (AFOs).
   E. Light weight, low profile, AFOs with dorsiflexion assist.

7. Which type of exercise is most likely to damage muscle and potentially contribute to loss of strength in a patient with limb girdle muscular dystrophy?
   A. Progressive endurance training in a pool.
   B. Submaximal weight training in muscles with greater than 3/5 strength on manual muscle testing.
   C. Eccentric resistance training to failure in muscles with less than 3/5 strength on manual muscle testing.
   D. Maximal isometric contractions in pelvic girdle musculature.
   E. None of the above.

8. Which gait characteristic is LEAST likely to be helped by orthotics in a patient with Becker muscular dystrophy?
   A. Toe walking.
   B. Pes cavus with equino varus.
   C. Gluteus medius gait.
   D. Foot drop with a steppage gait.
   E. None of the above.
CME QUESTIONS

9. Regarding the use of medicinal cannabis in managing amyotrophic lateral sclerosis (ALS), which statement is the most appropriate and correct?
   A. Cannabis would not be helpful for a patient with ALS.
   B. ALS patients have self-reported that cannabis is helpful to control pain, muscle spasms, drooling, loss of appetite, and diminished mood state.
   C. Pre-clinical studies have shown no effect of cannabinoids in a mouse model of ALS (SOD1 mouse).
   D. ALS patients cannot use cannabis because smoking is contraindicated.
   E. There is no way any ALS patient in the United States can use medical cannabis because it is classified as a schedule I drug by the Drug Enforcement Agency.

10. Cannabinoids, the active ingredients in medicinal cannabis, have been shown to have all of the following properties EXCEPT?
    A. Neuroprotection.
    B. Anti-inflammatory, both centrally and peripherally.
    C. Retrograde transmission in the central nervous system.
    D. Strong binding to respiratory centers in the brainstem.
    E. Analgesia via a mechanism that is synergistic but distinct from opiates.