Acute neuromuscular weakness in the intensive care unit

Bobby Varkey Maramattom, MD, DM; Eelco F. M. Wijdicks, MD

Introduction: **Patients in the intensive care unit develop generalized weakness due to a number of factors. Neuromuscular weakness is a common cause of failure to wean from the ventilator and decreased limb movements. A rational approach to evaluation of weakness will help to identify most of the common causes of neuromuscular weakness in the intensive care unit.**

Aims: **This review provides an analysis of neuromuscular weakness and a practical algorithm to assist in diagnostic evaluation.**

Conclusions: **The most common acquired causes of weakness in the critically ill patient in the intensive care unit are critical illness polyneuropathy and critical illness myopathy. In the intensive care unit setting, electrophysiological studies, biopsies, and imaging studies are often necessary to complement the clinical impression. (Crit Care Med 2006; 34:2835–2841)**

KEY WORDS: diagnosis; intensive care unit; outcome sepsis; treatment; weakness

Sick patients can be weak, but only a proportion of these individuals develop a neurologic disorder causing muscle weakness. However, critically ill patients are exposed to multiple stressors, fluid and electrolyte changes, catabolic stresses, nutritional deficiencies, and medications that act in combination to produce damage to the motor unit. Thus, critically ill patients have a higher likelihood of acquiring neuromuscular weakness in the intensive care unit (ICU). In addition to prolonging hospital stay and increasing morbidity and mortality, these disorders also inflate hospital costs by of thousands of dollars (1).

The spectrum of neuromuscular disease that is encountered in today's ICU has evolved over the last few decades. Nowadays, weakness acquired in the ICU due to critical illness myopathy (CIM) or polyneuropathy (CIP) is two to three times more common than primary neuromuscular disorders such as Guillain-Barré syndrome (GBS), myopathies, or motor neuron diseases (2).

From the Department of Neurology, Lourdes Hospital, Kochi, Kerala, India (BVM); and Division of Critical Care Neurology, Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN (EFMW).

There are no financial disclosures.

Address requests for reprints to: Eelco F. M. Wijdicks, MD, Mayo Clinic College of Medicine, Division of Critical Care Neurology, Department of Neurology, W8B, 200 First Street SW, Rochester, MN 55905. E-mail: wijde@mayo.edu.

DOI: 10.1097/01.CCM.0000239436.63452.81

Patients in the ICU can develop a variety of mononeuropathies or plexopathies related to ischemia, pressure palsies, prolonged recumbency, compartment syndromes, hematomas, or other causes. They can also develop weakness due to intracranial processes such as ischemic stroke or other diseases. The discussion of these focal or central causes of weakness in ICU patients is also outside the scope of this review. Nevertheless, a brief mention will be made of some of these conditions because a review of weakness in the ICU will be incomplete if these entities are omitted.

To be fair to the title, this review will, however, focus on patients with generalized neuromuscular weakness in the ICU. Two clinical presentations are encountered among this group. One group is those patients who are admitted to the ICU with a nonneurologic illness and subsequently are detected to have generalized weakness in the ICU. The other group of patients is those in whom catastrophic weakness and respiratory failure necessitate emergent admission to the ICU. In these cases, diagnostic tests are usually postponed until the patient is stabilized.

Although a good history and examination help in identifying and localizing the weakness, there are a number of confounding factors. Patients in the ICU are often confused, sedated, or intubated and may find it difficult to communicate with the clinician. Weakness is often detected incidentally or during attempts to wean, and the exact onset of weakness is often unclear. Examination is also hampered by indwelling intravascular catheters, restraints, and sedatives. Nevertheless, important clues can be obtained from the history, examination, scrutiny of medication charts, and investigation reports. Particular attention should be paid to the use of neuromuscular blockers, steroids, antiretroviral agents (3), statins (4, 5), and fibrates (6) (Table 1). The cumulative drug dosage; adjustment for renal, hepatic, and organ failure; and drug interactions should be analyzed. The identification of the level of pathology will help guide further investigations.

EVALUATION OF THE ICU PATIENT WITH NEUROMUSCULAR WEAKNESS

Important components of history are outlined in Table 2. Clinical examination also provides invaluable clues. Specific findings that should be elicited include muscle wasting or swelling, muscle tenderness, fasciculations or myokymia, myotonia, presence of tendon reflexes, and skin lesions. Fasciculations are random single muscle fiber twitches visible in superficial muscles, especially over the limbs. The phenomenon of myokymia refers to an undulating rippling movement of muscle fibers beneath the skin that mimics a wriggling worm (7). Myotonia is a delayed relaxation of muscle after voluntary contraction (action myotonia) or mechanical stimulation (percussion myotonia) (8). Facilitation of sluggish reflexes after repetitive tendon taps or brief isometric exercise is a clue to the Lambert-Eaton syndrome. Important skin lesions such as the heliotrope rash of dermatomyositis, purpura, telangi-

Table 1. Drugs and their effects on the neuromuscular system

Common Drugs Affecting Neuromuscular Function	Mechanism of Action	Clinical Manifestation
D-penicillamine	Impairment of neuromuscular transmission	Myasthenia-like syndrome
Interferon alpha		
Antibiotics		
Aminoglycosides, quinolones, polymyxin antibiotics, erythromycin, imipenem		
Neuromuscular blockers		
Pancuronium, vecuronium, atracurium, succinylcholine		
Antiarrhythmics		
Quinidine, procainamide		
Calcium channel blockers		
Verapamil, Diltiazem		
Beta blockers		
Magnesium containing laxatives, antacids		
Phenytoin		
Corticosteroids		
Chloroquine		
Lithium		
Statins	Interaction with cytochrome P-450 system	Necrotizing myopathy
Fibrates	Unclear	Rhabdomyolysis
D-penicillamine	Unclear	Inflammatory myopathy
Zidovudine, stavudine, lamivudine	Impairment of mitochondrial metabolism	Myopathy

Table 2. Clues toward specific disorders producing neuromuscular weakness

Critical illness, sepsis, multiple organ dysfunction syndrome	Critical illness myopathy
Skin rash	Dermatomyositis, vasculitis
Fluctuating weakness, ptosis, coexistent autoimmune conditions	Myasthenia gravis
Aminoglycoside use	Antibiotic induced myasthenia
Family history, episodic crises, infantile onset	Congenital myasthenic syndromes
Antecedent infections, vaccinations, diarrhea, upper respiratory tract infections, sensory-motor symptoms	Guillain-Barré syndrome, CIDP
Episodic abdominal crises, psychiatric illness, dysautonomia, seizures, encephalopathy	Porphyria
Trauma, crush injuries, renal failure	Rhabdomyolysis, phrenic nerve injuries
History of mosquito bites, fever, asymmetric flaccid weakness, encephalopathy	West Nile virus infection
Family history, retinitis pigmentosa, mental retardation, seizures, deafness, progressive myoclonic epilepsy	Mitochondrial myopathy

CIDP, chronic inflammatory demyelinating polyneuropathy.

Table 3. Mnemonic for differential diagnosis of generalized weakness in the intensive care unit

M	Medications: steroids, neuromuscular blockers (pancuronium, vecuronium), zidovudine, amiodarone
U	Undiagnosed neuromuscular disorder: myasthenia, LEMS, inflammatory myopathies, mitochondrial myopathy, acid maltase deficiency.
S	Spinal cord disease (ischemia, compression, trauma, vasculitis, demyelination)
C	Critical illness myopathy, polyneuropathy
L	Loss of muscle mass (cachectic myopathy, rhabdomyolysis)
E	Electrolyte disorders (hypokalemia, hypophosphatemia, hypermagnesemia)
S	Systemic illness (porphyria, AIDS, vasculitis, paraneoplastic, toxic)

LEMS, Lambert-Eaton myasthenic syndrome; AIDS, acquired immunodeficiency syndrome.

ectasias, digital ulcers, splinter hemorrhages, or the palmoplantar hyperkeratosis and raindrop lesions of arsenic poisoning should be scrupulously looked for. A "train of four" stimulation may demonstrate a train of four fade or a posttetanic response, which might indicate a persistent neuromuscular (NM) blockade. In that case, it is worthwhile waiting for the NM blockade to wear off before reexamining the patient.

A simple mnemonic MUSCLES is helpful in remembering some of the most common causes of generalized weakness in the ICU (Table 3).

A practical algorithm is also helpful in guiding the clinical approach to these patients (Fig. 1). Biopsy of nerve or muscle and ancillary investigations (Table 4) can be invaluable in typing and subclassifying the neuromuscular pathology and can guide prognostication to some extent. Magnetic resonance imaging (MRI) of the brain and spine need to be ordered in selected cases when there is a suspicion of upper motor neuron involvement. Although clinical examination can be difficult in the ICU patient, findings such as an encephalopathy, cranial nerve involvement, hyperreflexia, spasticity, extensor plantar responses, sensory levels, or multifocal neurologic signs should prompt a request for MRI. Other indications include patients with polytrauma, coagulopathies, systemic malignancies, or infective causes of neuromuscular weakness such as West Nile virus or paralytic rabies.

Patients in a "locked-in state" sometimes pose a diagnostic conundrum. Such patients are often fully conscious but anarthric, quadriplegic, and able to communicate only through eye blinks or vertical eye movements. This state is classically described with a ventral pontine infarction, although it can be seen after midbrain infarction, hematomas, central pontine myelinolysis, trauma, and central nervous system infections (9–12). It can also rarely occur in GBS, amyotrophic lateral sclerosis, myasthenia gravis, critical illness polyneuropathy, or critical illness myopathy (Fig. 2). These patients can appear comatose. Unless the clinician is vigilant, uses a structured neurologic examination, and specifically looks for this state or uses a coma scale specifically adapted to ICU patients that is capable of separating diverse states of consciousness (such as the FOUR [Full Outline of UnResponsiveness] score), this entity may go unrecognized (13). Detection of the

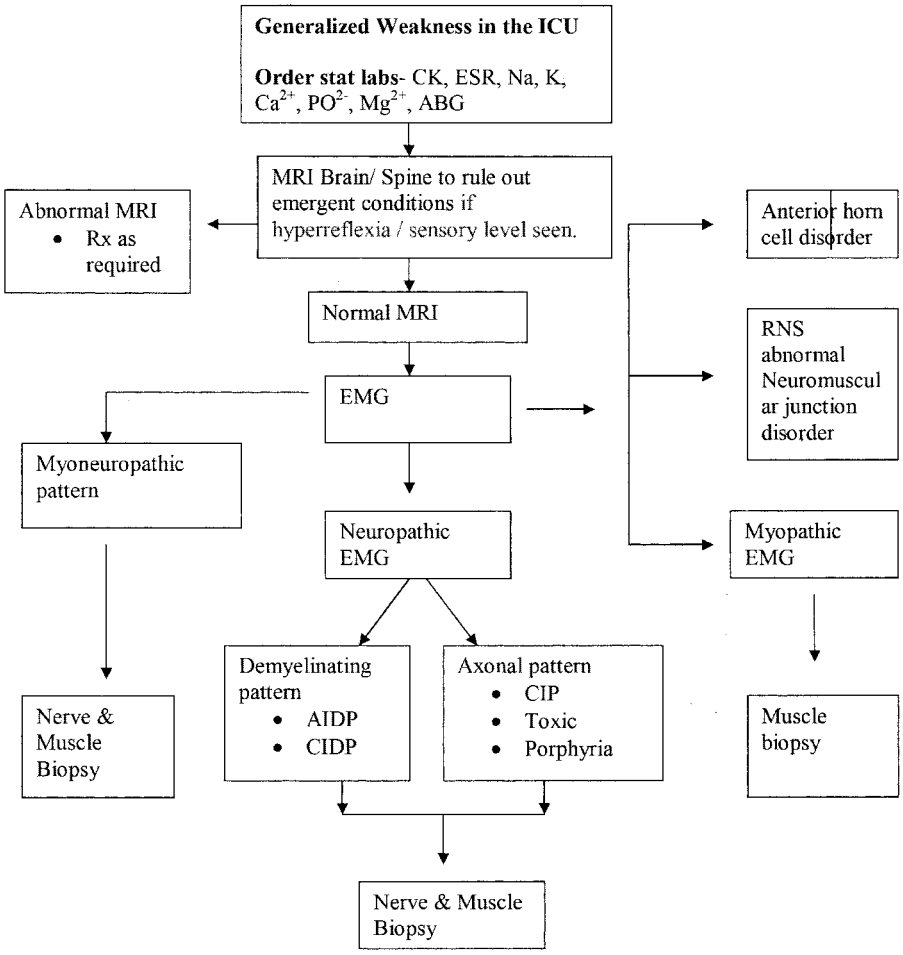

Figure 1. Algorithm for evaluation of generalized weakness in the intensive care unit (*ICU*). *CK*, creatine kinase; *ESR*, erythrocyte sedimentation rate; *ABG*, arterial blood gas; *MRI*, magnetic resonance imaging; *Rx*, prescription; *EMG*, electromyograph; *AIDP*, acute inflammatory demyelinating polyneuropathy; *CIDP*, chronic inflammatory demyelinating polyneuropathy; *CIP*, critical illness polyneuropathy; *RNS*, repetitive nerve stimulation.

Table 4. Relevant lab investigations in the diagnosis of neuromuscular weakness

Hemogram
Erythrocyte sedimentation rate
Electrolytes: sodium, potassium, calcium, phosphorus, magnesium
Muscle enzymes
Creatine kinase
Serum lactate levels
Autoantibody panel
Anti-Jo1 antibodies, antibodies to the PM-Scl nucleolar antigen complex, acetylcholine receptor antibodies, anti-MuSK antibodies, anti-voltage gated calcium channel antibodies
Electrophysiological studies
Nerve conduction study including phrenic nerve study, electromyography including respiratory, diaphragmatic muscles, repetitive nerve stimulation, single fiber EMG
CSF examination
To look for albuminocytological dissociation, pleocytosis, malignant cells or cultures
MRI imaging of brain and spine with gadolinium
Muscle and nerve biopsy, with overlying skin.
Chest radiograph/CT chest to look for contributory parenchymal lung diseases as well as thymoma, other neoplastic conditions

PM-Scl, polymyositis/scleroderma; MuSK, muscle-specific receptor tyrosine kinase; EMG, electromyogram; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; CT, computed tomography.

locked-in state will direct the further line of investigations. Computed tomography scans or MRI will identify most of the central nervous system lesions responsible for this state.

Spinal Cord Disorders. The most common noncompressive myelopathy causing quadriparesis is transverse myelitis or myelopathy. Transverse myelitis or myelopathy is most often idiopathic or postinfectious but can also be due to infectious myelitis caused by viruses such as Coxsackievirus, herpes, or cytomegalovirus or bacteria including *Mycoplasma* or *Legionella* as well as multiple sclerosis, Devic's disease, collagen vascular diseases, or spinal cord infarction (14).

Spinal cord infarction is a known complication of aortic dissection, acute aorto-iliac occlusion, and thoracoabdominal aortic surgeries. Spinal cord infarction can also occur after cardiac arrest and global hypotension. In such cases there is a predilection for the lumbosacral cord to be involved (15). Such patients can potentially suffer a "double hit" with cortical watershed infarctions producing brachial paresis and spinal cord infarction resulting in paraplegia. Unexplained hypotension or bradycardia in an unconscious trauma patient should prompt evaluation of spinal cord injury with a whole-spine MRI if possible. MRI adequately delineates most myelopathies that produce generalized weakness.

Patients present with acute flaccid areflexic weakness that mimics GBS during the stage of spinal shock. Clinical clues such as early bowel or bladder dysfunction, a sensory level, neck pain, or impalpable lower limb pulses should alert the clinician to a myelopathy and the need for a spinal MRI. Transverse myelitis may respond to high-dose intravenous methylprednisolone and should be identified early (16). Spinal cord infarction has no specific therapy and patients usually receive only supportive care. Infectious myelitis is treated with the appropriate antiviral or antibiotic regimen.

Anterior Horn Cell Disorders. Although acute poliomyelitis due to polio virus has nearly been eradicated, there are a number of viral mimics of acute poliomyelitis (17). Notable among this is the West Nile virus (WNV), which is known to produce a meningo-encephalitis with an acute flaccid paralysis (18). Severe WNV infection can also mimic GBS but is differentiated by fever; encephalopathy; predominantly proximal, asymmetric weakness; axonal pathology

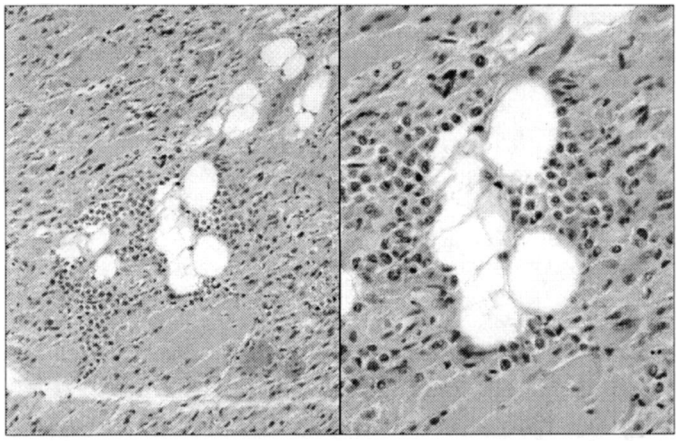

Figure 2. Hematoxylin and eosin (*HE*) staining showing inflammatory cell infiltrate into muscle in critical illness myopathy.

on nerve conduction studies (19); and cerebrospinal fluid variables. The cerebrospinal fluid typically shows lymphocytic pleocytosis with elevated proteins. Enzyme-linked immunosorbent assay for immunoglobulin (Ig)M antibody to WNV is highly sensitive and should be considered. As IgM antibodies can persist for up to a year after primary infection, serial IgM titers or IgG avidity studies can help to differentiate primary infection from past infection (20). MRI may show enhancement of the cauda equina, spinal cord signal changes, and cerebral parenchymal or leptomeningeal signal changes (21). Treatment is mainly supportive, and no antiviral medications have any proven benefit in the management of WNV.

Of the other anterior horn cell disorders, amyotrophic lateral sclerosis is well known to present with respiratory failure due to primary involvement of the phrenic motor neurons (22). The diagnosis is usually clear-cut on electrophysiological studies, and widespread denervation is seen on electromyogram. Although paraneoplastic motor neuron disorders can present with rapidly evolving respiratory weakness, they are uncommon (23).

Polyneuropathies. The most common variety of polyneuropathy encountered in the ICU nowadays is CIP (24) followed by CIM.

Sepsis, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome are important in the development of these syndromes although additional factors such as use of NM blocking agents, corticosteroids, cytotoxic drugs, and status asthmaticus have also been identified in the development of CIP/CIM (25–29). Together, these disorders are encountered in about 30–60% of ICU patients (30–32). CIM may be the more common of the two disorders in ICU patients. CIP may occur as early as 2–5 days in the presence of sepsis or SIRS, but most often it takes ≥1 wk of mechanical ventilation before these syndromes develop (30, 32). One of the reasons for the delay is that most patients with SIRS or sepsis either have an underlying encephalopathy ("septic encephalopathy") or are administered neuromuscular blocking agents or sedatives around the clock to facilitate mechanical ventilation.

The first neurologic consultation is requested when the critical care team finds it difficult to wean the patient from the ventilator and lung, chest wall, or cardiac causes of failure to wean have been excluded. The typical CIM/CIP patient has a flaccid quadriparesis and is often areflexic or hyporeflexic. Cranial nerves are often spared. Sensory examination is often difficult in these patients, and the differentiation between CIP and CIM often rests on electrophysiology. Compound muscle action potential amplitudes are reduced in both conditions; however, sensory nerve action potentials amplitudes are normal in CIM and reduced or absent in CIP. Phrenic nerve studies and needle electromyogram of the respiratory muscles can also establish CIM/CIP as the cause of failure to wean from the ventilator.

A number of terminologies such as acute quadriplegic myopathy, critical care myopathy, acute necrotizing myopathy of intensive care, thick filament myopathy, acute corticosteroid myopathy, acute myopathy in severe asthma, and acute pancuronium-associated myopathy have been used to allude to CIM. "Lumpers" prefer to term them all "CIM" and "splitters" prefer to subclassify CIM. Histopathologically, four subtypes of CIM have been identified on muscle biopsy—the necrotizing, cachectic, acute rhabdomyolysis, and the thick filament (myosin) loss type (30, 33–35). Histopathologic subtyping greatly influences the prognostic outcome of CIM as muscle recovery is poor in the necrotizing variant and relatively better in the other subtypes.

Muscle biopsies demonstrate characteristic features of muscle necrosis or selective loss of thick (myosin) myofilaments with preservation of thin (actin) myofilaments and Z discs without muscle necrosis in the thick filament loss type of CIM (35). Creatine kinase levels are elevated in about 50% of patients with CIM if estimated early in the illness. Treatment of these syndromes is mainly supportive and rests on aggressive management of the underlying sepsis/SIRS. Fluid resuscitation, antibiotic therapy, surgical drainage of abscesses, and physiotherapy all have a role. Intravenous immunoglobulin has thus far not been promising in patients with CIP (36). The long-term outcome following CIP/CIM ultimately depends on the underlying illness. If these are surmountable (the median hospital stay in patients with CIP is around 3 months), recovery from CIP can be surprisingly good; however, the outcome following CIM can be poor particularly in the necrotizing variants (37, 38).

Patients with GBS present with an ascending paralysis with respiratory and cranial nerve involvement and diffuse areflexia or hyporeflexia. Most patients show features of demyelination on nerve conduction studies and show a good response to intravenous immunoglobulin (IgIV) or plasma exchange. A proportion of patients develop regional variants of GBS or an axonal form of GBS, which may have a poorer prognosis (the acute motor axonal neuropathy or acute motor sensory axonal neuropathy variants). The clinical features of GBS are quite distinct from CIM/CIP and include weakness developing before ICU admission, history of a preceding upper respiratory or diarrheal illness, conspicuous cranial nerve involvement, albumino-cytological dissociation on cerebrospinal fluid examination, and demyelinating features on nerve conduction studies (24). Some patients have a documented prior infection with certain serotypes of *Campylobacter jejuni* that evoke antiganglioside antibodies against the nodes of Ranvier (39). Moreover, CIP occurs on the background of

sepsis and SIRS in a patient who is being mechanically ventilating rather than developing *de novo*. A peculiar situation arises when patients with demyelinating variants of GBS develop sepsis or SIRS and resultant worsening of their neuropathy. Repeat electrophysiologic studies may show axonal degeneration. In such a situation, superadded CIP may be a more likely cause of worsening than axonal GBS (30). In this case, treatment and management of sepsis and SIRS should take precedence over repeat IgIV or plasma exchange.

Other hospital-acquired polyneuropathies are rare but include acute vasculitic neuropathies, acute porphyria, drug-induced neuropathies, and the AIDS-associated cytomegalovirus polyradiculoneuropathy (Table 5).

Neuromuscular Junction Disorders. Common myasthenic syndromes encountered in the ICU include myasthenia gravis, Lambert-Eaton myasthenic syndrome, prolonged neuromuscular blockade, and antibiotic-induced myasthenia. Oculobulbar involvement should raise the suspicion of myasthenia gravis and prompt a request for repetitive nerve stimulation studies and assessment of acetyl choline receptor antibody titers. Patients with myasthenia gravis can present in a crises with profound worsening of respiratory or other muscles. Common precipitants of crises include intercurrent infections, administration of drugs that impair neuromuscular junction transmission (Table 1), myasthenic crises (undermedication), or cholinergic crises (overmedication). Although it is often difficult to distinguish between myasthenic and cholinergic crises, fasciculations, miosis, hypersalivation, lacrimation, diarrhea, and emesis are more suggestive of overmedication (cholinergic crises). To complicate matters, a poor response or even a "hypersensitivity" to anticholinesterase agents is observed in some "seronegative" myasthenic patients who are positive for antibodies to muscle-specific receptor tyrosine kinase (40). Hypersensitivity is manifested by severe muscle fasciculations in the facial muscles, blurring of vision, sialorrhea, and abdominal cramping mimicking a cholinergic crises (41). These patients may respond only to plasma exchange during their episodes of crises (42).

IgIV and plasma exchange are often used as rescue therapies in myasthenic patients with crises (43). Steroids, immunosuppressive medications, and thymectomy are alternative options in the long-term management of myasthenia gravis.

Table 5. Common neuromuscular conditions presenting with generalized weakness in the intensive care unit

Muscle diseases
• Critical illness myopathy
• Inflammatory myopathies: polymyositis, dermatomyositis
• Hypokalemic myopathy
• Rhabdomyolysis
• Muscular dystrophies
• Myotonic dystrophy
• Mitochondrial myopathies
• Acid maltase deficiency
Neuromuscular junction disorders
• Myasthenia gravis
• Neuromuscular blocking agent induced weakness
• Antibiotic induced myasthenia
• Organophosphorus poisoning
• Snake bite
• Insect/marine toxins
• Lambert-Eaton myasthenic syndrome
• Congenital myasthenic syndromes
• Hypermagnesemia
• Botulism
• Tick paralysis
Peripheral neuropathies
• Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy)
• Chronic idiopathic demyelinating polyneuropathy
• Critical illness polyneuropathy
• Phrenic neuropathies
• Toxic neuropathy
• Vasculitic neuropathy
• Porphyric neuropathy
• Diphtheria
• Lymphoma
• Cytomegalovirus-related polyradiculoneuropathy
Anterior horn cell disorders
• Amyotrophic lateral sclerosis
• Paraneoplastic motor neuron disease
• West Nile virus infection
• Acute poliomyelitis
• Spinal muscular atrophy
Spinal cord disorders
• Trauma
• Hematoma
• Spinal cord infarction
• Epidural abscess
• Demyelination: multiple sclerosis, Devic's disease, acute disseminated encephalomyelitis, transverse myelitis
• Infective myelitis: Coxsackievirus A, B, cytomegalovirus, *Mycoplasma*, *Legionella*, herpes
• Paralytic rabies ("dumb rabies")

High-rate repetitive nerve stimulation studies and assessment of antivoltage gated calcium channel antibodies should be ordered if Lambert-Eaton myasthenic syndrome is suspected. Lambert-Eaton myasthenic syndrome responds variably to 3,4-diaminopyridine or IgIV (44).

Competitive nondepolarizing neuromuscular blockers (NMB) are used in ICU patients to facilitate mechanical ventilation. All of these NMBs, including older amino steroids (pancuronium and vecuronium) and the newer benzylisoquinolinium NMBs such as atracurium (45), cisatracurium (46), and doxacurium, can induce prolonged NM blockade in ICU patients. NM blockade is also prolonged by metabolic acidosis and dyselectrolemia such as hypokalemia. NMBs also act synergistically with sepsis and SIRS in the pathogenesis of CIP and CIM.

Uncommon neuromuscular junction disorders seen in the ICU include botulism, tick paralysis, and hypermagnesemia. Botulism involves autonomic functions in addition to producing flaccid paralysis and areflexia. Hence patients often have internal and external ophthalmoplegia, dry mouth, and a paralytic ileus. Repetitive nerve stimulation studies may show features of presynaptic blockade. *Clostridium botulinum* or its toxin can be detected in stool, serum, wound cultures, or food samples by cultures or mouse bioassays. However, these are cumbersome procedures and not widely

available. Although the mainstay of treatment is mechanical ventilation, it is imperative that the disease be diagnosed early to ensure that trivalent antitoxin is administered before the toxin binds to presynaptic nerve terminals. If administered early enough, the antitoxin reduces the mortality, morbidity, and length of hospital stay associated with botulism (47). Tick paralysis is found mostly in North America and Australia. It mimics GBS with an ascending motor paralysis, preserved sensations, and areflexia. Complete ophthalmoplegia provides a clue toward tick paralysis. Careful search and removal of the tick, which may be embedded in scalp hair, can result in rapid resolution of the paralysis. Hypermagnesemia mimics Lambert-Eaton myasthenic syndrome with respiratory failure, generalized weakness, and diminished reflexes (48). It is seen more often in patients with renal failure who consume magnesium-containing laxatives or antacids or eclamptic patients who are administered magnesium sulfate.

Myopathies. Among myopathies, the most common variety to be encountered in the ICU is probably CIM. Among other acquired myopathies, inflammatory myopathies deserve a special mention, of which two types are encountered frequently in the ICU: dermatomyositis and polymyositis. Dermatomyositis has a more malignant course than polymyositis and is easier to recognize by virtue of its characteristic skin rash. The rash is often erythematous, periorbital, and purplish (heliotrope) and may spread into the neck and back in a "shawl" sign. It can be hyperpigmented or "salt and pepper" as in dark-skinned people. Rashes over the knuckles (Gottron's sign) or subcutaneous calcifications may also be seen. Muscle enzymes (creatine kinase) are elevated in the majority of cases, and electromyogram and muscle biopsy should establish the diagnosis. Autoantibodies such as anti-Jo-1 antibodies and antibodies to the polymyositis/scleroderma nucleolar antigen complex are of limited clinical relevance. Nevertheless, they are often ordered along with autoantibody panels to exclude other conditions as well as to increase the level of diagnostic certainty.

Corticosteroids are the cornerstone of therapy. Patients with respiratory failure may require pulse therapy with intravenous methyl prednisolone with subsequent conversion to oral prednisolone (49). Addition of steroid sparing agents such as methotrexate or azathioprine should be considered at the outset itself (50, 51). IgIV is used as a second-line agent in dermatomyositis especially when drug resistance is encountered or disease remains active (52, 53).

Among the electrolyte disorders, potassium disturbances are the most common disturbances that produce weakness. Hypokalemic periodic paralysis due to familial periodic paralysis or thyrotoxic periodic paralysis presents with recurrent weakness. Rarely, patients with hypokalemic periodic paralysis can progress to respiratory failure (54). Acquired hypokalemia from causes such as gastroenteritis can also result in weakness and respiratory failure (55). Serum K^+ levels are often <3.5 mEq/L, and these patients respond well to oral or intravenous potassium loading. Potassium should be coadministered only with normal saline as glucose infusions worsen hypokalemia. Other, more rare, electrolyte disturbances include severe hypophosphatemia (56).

Rhabdomyolysis can be precipitated by ischemic arterial occlusion, compartment syndromes, or trauma and presents with swollen, tender muscles, focal weakness, and extreme elevations of creatine kinase levels (>10,000 IU). Rhabdomyolysis may also coexist with generalized weakness in one of the subtypes of CIM. It is important to check whether the patient is receiving any of the drugs that predispose to muscle necrosis such as statins, fibrates, colchicine, or zidovudine.

CONCLUSIONS

The differential diagnosis of generalized weakness depends on the situation in which the patient is encountered. In general, patients seen after cardiothoracic procedures (especially extensive aortic repairs) tend to have ischemic myelopathies; patients in medical ICUs with critical illness, sepsis, or SIRS and on mechanical ventilation tend to have CIM, CIP, or prolonged NM blockade. Consideration of the common causes of neuromuscular weakness and adequate electrophysiological work-up will help to identify a large proportion of these patients with neurologic weakness. Nerve-muscle biopsies play an important role in subclassification of the underlying syndrome and in prognostication. Although the predominant determinant of outcome is the underlying illness, supportive care is of paramount importance and a multidisciplinary approach to patient care is necessary to ensure a speedy and satisfactory functional recovery.

REFERENCES

1. Rudis MI, Guslits BJ, Peterson EL, et al: Economic impact of prolonged motor weakness complicating neuromuscular blockade in the intensive care unit. *Crit Care Med* 1996; 24:1749–1756
2. Lacomis D, Petrella JT, Giuliani MJ: Causes of neuromuscular weakness in the intensive care unit: A study of ninety-two patients. *Muscle Nerve* 1998; 21:610–617
3. Dalakas MC: Peripheral neuropathy and antiretroviral drugs. *J Peripher Nerv Syst* 2001; 6:14–20
4. Bae J, Jarcho JA, Denton MD, et al: Statin specific toxicity in organ transplant recipients: Case report and review of the literature. *J Nephrol* 2002; 15:317–319
5. Ravnan SL, Locke C, Yee WP, et al: Cerivastatin-induced rhabdomyolysis: 11 case reports. *Pharmacotherapy* 2002; 22:533–537
6. Bannwarth B: Drug-induced myopathies. *Expert Opin Drug Saf* 2002; 1:65–70
7. Gutmann L: Myokymia and neuromyotonia 2004. *J Neurol* 2004; 251:138–142
8. Ptacek LJ, Johnson KJ, Griggs RC: Genetics and physiology of the myotonic muscle disorders. *N Engl J Med* 1993; 328:482–489
9. Dollfus P, Milos PL, Chapuis A, et al: The locked-in syndrome: A review and presentation of two chronic cases. *Paraplegia* 1990; 28:5–16
10. Pirzada NA, Ali II: Central pontine myelinolysis. *Mayo Clin Proc* 2001; 76:559–562
11. Thadani VM, Rimm DL, Urquhart L, et al: "Locked-in syndrome" for 27 years following a viral illness: Clinical and pathologic findings. *Neurology* 1991; 41:498–500
12. Chia LG: Locked-in syndrome with bilateral ventral midbrain infarcts. *Neurology* 1991; 41:445–446
13. Wijdicks EF, Bamlet WR, Maramattom BV, et al: Validation of a new coma scale: The FOUR score. *Ann Neurol* 2005; 58:585–593
14. de Seze J, Stojkovic T, Breteau G, et al: Acute myelopathies: Clinical, laboratory and outcome profiles in 79 cases. *Brain* 2001, 124: 1509–1521
15. Duggal N, Lach B: Selective vulnerability of the lumbosacral spinal cord after cardiac arrest and hypotension. *Stroke* 2002; 33:116–121
16. Sebire G, Hollenberg H, Meyer L, et al: High dose methylprednisolone in severe acute transverse myelopathy. *Arch Dis Child* 1997; 76:167–168
17. Bouffard JP, Riudavets MA, Holman R, et al: Neuropathology of the brain and spinal cord in human West Nile virus infection. *Clin Neuropathol* 2004; 23:59–61
18. Sejvar JJ, Leis AA, Stokic DS, et al: Acute flaccid paralysis and West Nile virus infection. *Emerg Infect Dis* 2003; 9:788–793
19. Flaherty ML, Wijdicks EF, Stevens JC, et al: Clinical and electrophysiologic patterns of

flaccid paralysis due to West Nile virus. *Mayo Clin Proc* 2003; 78:1245–1248
20. Fox JL, Hazell SL, Tobler LH, et al: Immunoglobulin G avidity in differentiation between early and late antibody responses to West Nile virus. *Clin Vaccine Immunol* 2006; 13:33–36
21. Jeha LE, Sila CA, Lederman RJ, et al: West Nile virus infection: A new acute paralytic illness. *Neurology* 2003; 61:55–59
22. Chen R, Grand'Maison F, Strong MJ, et al: Motor neuron disease presenting as acute respiratory failure: A clinical and pathological study. *J Neurol Neurosurg Psychiatry* 1996; 60:455–458
23. Forman D, Rae-Grant AD, Matchett SC, et al: A reversible cause of hypercapnic respiratory failure: Lower motor neuronopathy associated with renal cell carcinoma. *Chest* 1999; 115:899–901
24. Bolton CF, Laverty DA, Brown JD, et al: Critically ill polyneuropathy: Electrophysiological studies and differentiation from Guillain-Barre syndrome. *J Neurol Neurosurg Psychiatry* 1986; 49:563–573
25. Perea M, Picon M, Miro O, et al: Acute quadriplegic myopathy with loss of thick (myosin) filaments following heart transplantation. *J Heart Lung Transplant* 2001; 20:1136–1141
26. Wijdicks EF, Litchy WJ, Wiesner RH, et al: Neuromuscular complications associated with liver transplantation. *Muscle Nerve* 1996; 19: 696–700
27. Ghaus N, Bohlega S, Rezeig M: Neurological complications in liver transplantation. *J Neurol* 2001; 248:1042–1048
28. Miro O, Salmeron JM, Masanes F, et al: Acute quadriplegic myopathy with myosin-deficient muscle fibres after liver transplantation: Defining the clinical picture and delimiting the risk factors. *Transplantation* 1999; 67:1144–1151
29. Cassidy JV, Bolton DT, Haynes SR, et al: Acute rhabdomyolysis after cardiac transplantation: A diagnostic conundrum. *Paediatr Anaesth* 2002; 12:729–732
30. Bolton CF: Neuromuscular manifestations of critical illness. *Muscle Nerve* 2005; 32:140–163
31. Leijten FS, Harinck-de Weerd JE, Poortvliet DC, et al: The role of polyneuropathy in motor convalescence after prolonged mechanical ventilation. *JAMA* 1995; 274:1221–1225
32. Tennila A, Salmi T, Pettila V, et al: Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. *Intensive Care Med* 2000; 26:1360–1363
33. Bolton CF: Sepsis and the systemic inflammatory response syndrome: Neuromuscular manifestations. *Crit Care Med* 1996; 24: 1408–1416
34. Hund E: Neurological complications of sepsis: Critical illness polyneuropathy and myopathy. *J Neurol* 2001; 248:929–934
35. Sander HW, Golden M, Danon MJ: Quadriplegic areflexic ICU illness: Selective thick filament loss and normal nerve histology. *Muscle Nerve* 2002; 26:499–505
36. Wijdicks EF, Fulgham JR: Failure of high dose intravenous immunoglobulins to alter the clinical course of critical illness polyneuropathy. *Muscle Nerve* 1994; 17:1494–1495
37. Fletcher SN, Kennedy DD, Ghosh IR, et al: Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. *Crit Care Med* 2003; 31:1012–1016
38. Hund EF, Fogel W, Krieger D, et al: Critical illness polyneuropathy: Clinical findings and outcomes of a frequent cause of neuromuscular weaning failure. *Crit Care Med* 1996; 24:1328–1333
39. Moran AP, Annuk H, Prendergast MM: Antibodies induced by ganglioside-mimicking Campylobacter jejuni lipooligosaccharides recognise epitopes at the nodes of Ranvier. *J Neuroimmunol* 2005; 165:179–185
40. Liyanage Y, Hoch W, Beeson D, et al: The agrin/muscle-specific kinase pathway: New targets for autoimmune and genetic disorders at the neuromuscular junction. *Muscle Nerve* 2002; 25:4–16
41. Lavrnic D, Losen M, Vujic A, et al: The features of myasthenia gravis with autoantibodies to MuSK. *J Neurol Neurosurg Psychiatry* 2005; 76:1099–1102
42. Sanders DB, El-Salem K, Massey JM, et al: Clinical aspects of MuSK antibody positive seronegative MG. *Neurology* 2003; 60: 1978–1980
43. Gronseth GS, Barohn RJ: Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000; 55:7–15
44. Maddison P, Newsom-Davis J: Treatment for Lambert-Eaton myasthenic syndrome. *Cochrane Database Syst Rev* 2005; (2):CD003279
45. Hoey LL, Joslin SM, Nahum A, et al: Prolonged neuromuscular blockade in two critically ill patients treated with atracurium. *Pharmacotherapy* 1995; 15:254–259
46. Davis NA, Rodgers JE, Gonzalez ER, et al: Prolonged weakness after cisatracurium infusion: A case report. *Crit Care Med* 1998; 26:1290–1292
47. Tacket CO, Shandera WX, Mann JM, et al: Equine antitoxin use and other factors that predict outcome in type A foodborne botulism. *Am J Med* 1984; 76:794–798
48. Krendel DA: Hypermagnesemia and neuromuscular transmission. *Semin Neurol* 1990; 10:42–45
49. Matsubara S, Sawa Y, Takamori M, et al: Pulsed intravenous methylprednisolone combined with oral steroids as the initial treatment of inflammatory myopathies. *J Neurol Neurosurg Psychiatry* 1994; 57:1008
50. Mastaglia F, Phillips B, Zilko P, et al: Relapses in idiopathic inflammatory myopathies. *Muscle Nerve* 1999; 22:1160–1161
51. Miro O, Laguna M, Grau JM: Relapses in idiopathic inflammatory myopathies. *Muscle Nerve* 1999; 22:1159–1160
52. Dalakas MC, Illa I, Dambrosia JM, et al: A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993; 329: 1993–2000
53. Dalakas MC: Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA* 2004; 291:2367–2375
54. Liu YC, Tsai WS, Chau T, et al: Acute hypercapnic respiratory failure due to thyrotoxic periodic paralysis. *Am J Med Sci* 2004; 327: 264–267
55. Chhabra A, Patwari AK, Aneja S, et al: Neuromuscular manifestations of diarrhea related hypokalemia. *Indian Pediatr* 1995; 32:409–415
56. Varsano S, Shapiro M, Taragan R, et al: Hypophosphatemia as a reversible cause of refractory ventilatory failure. *Crit Care Med* 1983; 11:908–909