CHAPTER 106 Neuromuscular Disorders

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PERSPECTIVE

Disorders of the neuromuscular unit can result in clinical presentations that range from subtle symptoms to acute respiratory failure. Morbidity and mortality are often related to failure of the muscles that maintain airway integrity and drive respiration. In most cases, the pathophysiology of these disorders is well understood and permits an organization and understanding that is based on the level of the nervous system affected. This facilitates an approach that is based on signs and symptoms, the findings of which direct the urgency of diagnostic testing and treatment.

Processes involving the brainstem and brain can usually be differentiated from those in the spinal cord and in the peripheral nervous system on the basis of historical and physical findings. In general, lesions at the level of the brainstem or above produce unilateral weakness; bilateral weakness caused by lesions above the spinal cord is generally associated with a change in mental status or cranial nerve involvement. Lesions of the central nervous system result in upper motor neuron signs that include spasticity, hyperreflexia, and extensor plantar reflexes. As a corollary, when bilateral upper motor neuron signs are found in conjunction with normal mental status, diagnostic testing including neuroimaging should focus on looking for a lesion in the spinal cord.

PRINCIPLES OF DISEASE

The neuromuscular unit has four components: the anterior horn cells of the spinal cord, the peripheral nerve, the neuromuscular junction, and the muscle being innervated. The level of the pathology determines associated signs and symptoms (Table 106-1). *Myelopathies* involve the spinal cord; *radiculopathies* involve the nerve roots as they leave the spinal cord; *neuropathies* involve the peripheral nerves; and *myopathies* involve the muscle. The use of physical signs to differentiate these disorders is discussed in Chapter 11.

Neuropathies involve the axon itself or the myelin sheath (or the Schwann cells that make the myelin sheath) of the nerve. Nerve conduction studies can differentiate the locations of involvement. As the conduction along the axon is disrupted, the subsequent delay in transmission first causes symptoms in the muscles controlled by longer nerve axons, resulting in a history of weakness beginning in the distal extremities. As the myelin destruction or axonal degeneration progresses, patients usually note a slowly progressive course of symptoms.

The motor nerve branches into multiple terminals as it approaches the muscle. The neuromuscular junction is composed of the presynaptic membrane, the postsynaptic membrane, and the synaptic cleft. The neurotransmitter is acetylcholine (ACh). The motor synapse is a nicotinic receptor, whereas muscarinic synapses link the central nervous system with the autonomic nervous system. Disorders of the postsynaptic nicotinic receptors produce weakness. Postsynaptic ACh receptors are continually turned over at a rate that is related to the amount of stimulation. A disorder of transmission often leads to increased production of ACh receptors. Myasthenia gravis (MG) is the prototype of neuromuscular junction diseases.

CLINICAL FINDINGS

History

The history of patients with complaints of weakness focuses on the acuity and progression of onset and the potential for airway compromise. Any complaint of difficulty breathing or swallowing raises suspicion of bulbar involvement and concern for life-threatening deterioration. The history must elicit whether the weakness is muscular or nonspecific generalized fatigue. Weakness implies the inability to exert normal force, whereas fatigue implies a decrease in force with repetitive use. When muscular weakness exists, the clinician should determine whether it is focal or generalized, proximal or distal. The history of present illness must include the duration of symptoms, exacerbating and mitigating factors, and presence of associated symptoms such as fever, weight loss, and bowel or bladder changes.

Historical elements might explain the presenting complaint: a preexisting neuromuscular disorder that could lead to deterioration; prior episodes or a family history of weakness suggesting periodic paralysis; a recent respiratory or diarrhea illness suggesting a postinfectious, autoimmune process such as transverse myelitis or Guillain-Barré syndrome (GBS); a cancer history suggesting a metastatic tumor as the cause of a compressive myelopathy; a food or travel history suggesting botulism or tick exposure.

Physical Examination

The physical examination should first assess the patient's airway and ventilation and then proceed to localize the level

Table 106-1 Clinical Characteristics of Neuromuscular Diseases

DISEASE	HISTORY	STRENGTH	DEEP TENDON REFLEX	SENSATION	WASTING
Myelopathy	Trauma, infection, cancer	Normal to decreased	Increased	Normal to decreased	No
Motor neuron disease (ALS)	Progressive difficulty swallowing, speaking, walking	Decreased	Increased	Normal	Yes
Neuropathy	Recent infection Ascending weakness	Normal or decreased Distal > proximal	Decreased	Decreased	Yes
Neuromuscular junction disease	Food (canned goods) Tick exposure Easy fatigability	Normal to fatigue	Normal	Normal	No
Myopathy	Thyroid disease Previous similar episodes	Decreased Proximal > distal	Normal	Normal	Yes

ALS, amyotrophic lateral sclerosis.

BOX 106-1 GRADING SCORE FOR MOTOR STRENGTH

5 = Normal strength
4 = Weak but able to resist examiner
3 = Moves against gravity but unable to resist examiner
2 = Moves but unable to resist gravity
1 = Flicker but no movement
0 = No movement

of the lesion. The presence of swallowing and a strong cough suggests that the patient has sufficient protective and ventilatory reserve. The muscles used to lift the head off the bed may weaken before those of respiration and should be assessed. A patient who is not yet intubated but is complaining of shortness of breath or difficulty breathing should have frequent vital capacity measurements. Normally, these values range from 60 to 70 mL/kg. When the forced vital capacity reaches 15 mL/kg, intubation is necessary. If vital capacity cannot be measured, a maximal negative inspiratory force (NIF) is easily determined. An NIF less than 15 mm Hg suggests the need for endotracheal intubation. A bedside assessment used to follow ventilatory status is to have the patient count numbers with one breath.[1] With sequential performance of this test, a decline in respiratory function is detected as the patient fails to count as high as before. Arterial blood gas is not necessarily helpful because functional reserve can be severely diminished by the time a patient develops either hypercarbia or hypoxia.

The assessment of vital signs is important because some causes of weakness may result in dysregulation of the autonomic system. A systematic neurologic examination should assess the patient's mental status, cranial nerves, motor function, sensory function, deep tendon reflexes, and coordination, including cerebellar function. The motor examination begins by determining whether the weakness is unilateral or bilateral and which muscle groups are involved. Key components of the examination include motor strength, muscle bulk, and presence of fasciculations. Box 106-1 provides the grading system used in motor strength assessment. Table 106-2 provides the findings used to distinguish upper motor neuron from lower motor neuron processes.

Differential Considerations

Myelopathies

A patient with myelopathy shows signs of upper motor neuron dysfunction. Without upper motor neuron function, muscle weakness is present with increased spinal reflexes, including an extensor plantar reflex (Babinski's response). Muscle tone initially ranges from normal to slightly increased, eventually leading to spasticity as a late finding. The same reflex arcs eventually create spasticity in the affected muscles. The weakness is ascending in nature, and there is often bladder and bowel involvement. When sensory findings are present, they often define the level of the lesion. The presence of bowel or bladder dysfunction, or diminished sensation, localizes the lesion to the spinal cord. The presence of pain often connotes a compressive lesion such as a herniated intravertebral disk, epidural hematoma, abscess, or tumor. Acute, painless spinal cord lesions include transverse myelitis and spinal cord infarction.

Motor Neuron Disease

Amyotrophic lateral sclerosis is the prototypical disease process resulting from a degeneration of the motor neuron without sensory involvement. These patients may complain of dysarthria or dysphagia; however, the characteristic findings are those of combined upper and lower motor neuron dysfunction. Consequently, findings include hyperreflexia, muscle wasting, and fasciculation. Pain is not a component of the clinical picture.

Poliomyelitis affects the anterior horn cells and results in lower motor neuron disease without sensory involvement. The

Table 106-2 Distinguishing Upper Motor Neuron (UMN) from Lower Motor Neuron (LMN) Involvement

MOTOR NEURON	DEEP TENDON REFLEX	MUSCLE TONE	ATROPHY	FASCICULATIONS	BABINSKI
UMN	Increased	Increased	No*	No	Present
LMN	Decreased	Decreased	Yes	Yes	Absent

*Not significant but can occur.

weakness can be symmetrical or more often asymmetrical. Patients initially have a clinical picture similar to that of viral meningitis, with fever and neck stiffness. Currently, most cases follow exposure of an immunocompromised host to the oral polio vaccine, and this should be sought in the history. The cerebrospinal fluid analysis resembles that of viral meningitis.

Neuropathies

Weakness from a neuropathy is often noted first in distal muscles and then ascends. Decreased grip strength or footdrop may be noted first. Muscle tone ranges from slightly diminished to flaccid. As all outflow from the spinal cord is affected, deep tendon reflexes are diminished or absent. Patients exhibit varying degrees of altered sensation, muscle wasting, and fasciculation depending on the duration of the symptoms. Disorders that should be considered include GBS, toxic neuropathies, diabetic neuropathy, and tick paralysis (which is caused by inhibition of both nerve conduction and function of the neuromuscular junction).

Diseases of the Neuromuscular Junction

Disorders of the neuromuscular junction cause progressive motor fatigability. The initial depolarization of the muscle causes stimulation of a maximum number of receptors, producing a normal, or nearly normal, strength response. Repeated stimulation leads to diminishing motor strength, which is caused by the blockage of the receptors (as in MG) or by a decrease in the amount of ACh released (as in botulism) or by inactivating Ach by irreversibly binding with it (as in organophosphate poisoning). A decrease in the release of ACh may produce a combination of nicotinic and muscarinic effects leading to anticholinergic findings such as decreased visual acuity, confusion, urinary retention, tachycardia, low-grade fever, and dry, flushed skin. In the case of Lambert-Eaton myasthenic syndrome, weakness is more pronounced at the beginning of muscle use and improves with repeated use as more ACh builds up in the synaptic cleft with each stimulation. Diseases of the neuromuscular junction should be considered in patients who present with generalized weakness in association with an acute cranial nerve deficit. Muscle tone is generally diminished and sensation is preserved.

Myopathies

Myopathies produce generalized, symmetrical weakness. Reflexes are present but diminished, muscle tone is usually diminished, but sensation is preserved. Myopathies caused by inflammatory disorders (polymyositis, dermatomyositis, polymyalgia rheumatica, and viral myositis) cause muscle pain and tenderness. Metabolic disorders affecting muscle strength (e.g., electrolyte and endocrine disorders) are painless in nature.

DIAGNOSTIC STRATEGIES

Laboratory Studies

Serum potassium, calcium, and phosphorus should be assessed in patients with acute weakness. Thyroid function tests are recommended in cases of suspected myopathies. A creatine kinase (CK) level assesses for muscular inflammation; a urinalysis should be performed for the presence of myoglobinuria and possible rhabdomyolysis.

Special Studies

Magnetic resonance imaging (MRI) is the preferred test for suspected cases of acute myelopathy. Computed tomography of the spinal cord with myelography can help to differentiate compressive (herniation, abscess, tumor) from noncompressive causes when MRI is not available. Cerebrospinal fluid analysis is indicated when GBS or transverse myelitis is suspected.

SPECIFIC DISORDERS

Disorders of the Neuromuscular Junction

Myasthenia Gravis

Perspective. It is rare for the emergency physician to diagnose a new case of MG; more commonly, patients with established disease present with exacerbations of their disease that must be recognized and addressed. In addition, the emergency physician must be aware of medication interactions in patients with MG.

Principles of Disease. MG is a rare disorder that affects approximately 60,000 Americans.[2] Age of onset is bimodal, with the first peak among women 20 to 40 years of age and a second peak among men 50 to 70 years old.

MG results from autoantibodies directed against the nicotinic acetylcholine receptor (AChR) at the neuromuscular junction. This leads to complement-mediated destruction of AChRs with a decrease in the total number of available receptors. The autoantibodies further compete with ACh for binding at remaining receptors. Thus, with repeated stimulation of the same muscle, fewer and fewer sites are available and fatigue develops.

Fatigability and muscular weakness are the hallmarks of MG. Considering the slow clinical progression of MG and the low likelihood of short-term complications from its progression, the importance of suspecting the diagnosis is to facilitate proper referral for further evaluation.

Clinical Features. Ocular symptoms are often the first manifestation of MG. The typical symptoms are ptosis, diplopia, or blurred vision. Ocular muscle weakness is the first sign in up to 40% of patients, although 85% of patients with MG eventually have ocular involvement. When present, ptosis is often worse toward the end of the day. Respiratory failure is rarely the initial symptom of MG. Even so, up to 17% of patients may have weakness of the muscles of respiration.[3] Bulbar muscles may be involved, producing dysarthria or dysphagia.

Lambert-Eaton myasthenic syndrome is a rare disorder in which almost 50% of cases are associated with small cell carcinoma of the lung. Autoantibodies cause inadequate release of ACh from nerve terminals, affecting both nicotinic and muscarinic receptors. With repeated stimulation, the amount of ACh in the synaptic cleft increases, leading to an increase in strength, the opposite of that seen with MG. The classic syndrome includes weakness that improves with use of muscles, particularly proximal hip and shoulder muscles; hyporeflexia; and autonomic dysfunction, most commonly seen as dry mouth.[4] Management primarily focuses on treating the underlying neoplastic disorder, although IVIG has been reported to be useful.[5]

Diagnostic Strategies

New-Onset Myasthenia Gravis. The diagnosis of MG is based on clinical findings and a combination of serologic testing, electromyographic testing, and the bedside edrophonium or ice bag tests. Serum testing for AChR antibodies is positive in 80 to 90% of patients with MG, but not available in the emergency department setting.

The edrophonium test and ice bag tests are similar to perform and the results are based on their effect on the ptosis seen in patients with suspected MG. The production of edrophonium was discontinued in early 2008 and it will no longer be available once current stores are depleted. Edrophonium is a short-acting acetylcholinesterase (AChE)-blocking agent that produces an increase of ACh in the synaptic cleft and a reduction in ptosis after intravenous administration. With the ice bag test, cooling decreases symptoms in MG while heat exacerbates symptoms. In both tests, the change in the amount of ptosis is measured before and after the application of edrophonium or an ice bag. The distance from the upper to the lower eyelid in the most severely affected eye is measured first. If edrophonium is given, an intravenous test dose of 1 to 2 mg is given first as some patients have a severe reaction. If no adverse reaction is found and the patient does not dramatically improve in 30 to 90 seconds, a second dose of 3 mg is given. If there is still no response, a final dose of 5 mg is given for a total maximum dose of 10 mg.[6] Atropine should be available at the bedside during the test. Because of the potential for cholinergic-induced increased airway secretions, this test should be used with caution in asthmatics and patients with chronic obstructive pulmonary disease. If an ice pack is used, it is applied to the affected eye for approximately 2 minutes, and the distance between the lids is measured again. A prospective evaluation of the ice bag approach found the test result to be positive (an improvement in distance of at least 2 mm) in 80% of patients with MG and in no patients without MG.[7]

Myasthenic Crisis. Myasthenic crisis is defined as respiratory failure leading to mechanical ventilation. It occurs in 15 to 20% of patients with MG,[8] usually within the first 2 years of disease onset. Although it is potentially life-threatening, the mortality from this complication of MG has declined dramatically with better and more aggressive ICU care and the use of plasmapheresis (PE) and/or immunodulatory therapy with high-dose intravenous immunoglobulin (IVIG) and corticosteroids.

Underlying infection, aspiration, and medication changes—stopping anticholinergic medications or taking a new medication that precipitates weakness—most often set off crisis, but the precipitant may not be found in up to 30% of cases.[9] Other precipitants can be surgery and pregnancy (Box 106-2).

BOX 106-2 DRUGS THAT MAY EXACERBATE MYASTHENIA GRAVIS

Cardiovascular
- Beta-blockers
- Calcium channel blockers
- Quinidine
- Lidocaine
- Procainamide

Antibiotics
- Aminoglycosides
- Tetracyclines
- Clindamycin
- Lincomycin
- Polymyxin B
- Colistin

Other
- Phenytoin
- Neuromuscular blockers
- Corticosteroids
- Thyroid replacement

The initial step in managing the patient in crisis is stabilization of the airway. In less severe cases in which intubation is not imminent, it is imperative to monitor ventilatory status pending intensive care unit admission through forced vital capacity or NIF measurement. Noninvasive ventilation with biphasic positive airway pressure may be effective in managing patients who need ventilatory support.[10]

Signs of myasthenic crisis should be sought in all patients with MG, even when they do not complain of weakness. Many commonly used drugs can adversely affect patients with MG (see Box 106-2). A patient with stable MG who has an acute medical or surgical condition requires a full neurologic examination. The decision to admit or discharge a patient with MG from the emergency department should take into account the potential for neurologic deterioration.

Management

Cholinesterase Inhibitors. Pyridostigmine (60–120 mg every 4–6 hours) and neostigmine (15–30 mg every 4–6 hours) prolong the presence and activity of ACh in the synaptic cleft. They are the backbone of chronic outpatient therapy and provide symptomatic improvement. The most common side effects are those of excessive cholinergic stimulation, such as increased airway secretions and increased bowel motility. At extremes there may be bradycardia or even worsening of weakness, simulating a myasthenic crisis. These drugs are often used as adjunctive therapy to control symptoms while other therapy is being instituted, after which they are often discontinued.[11] The use of intravenous pyridostigmine in the setting of acute exacerbation is controversial and not recommended because PE or IVIG is recommended. Cholinergic drug therapy is not recommended for the treatment of MG in the emergency department.

Immunosuppressant Drugs. Immunosuppressant drugs are often used for the chronic control of MG. Although they have no role in the acute management of a myasthenic crisis, they may be started before extubation of a patient recovering from crisis. Cochrane Database reviews in 2005 and 2007 found support for the use of corticosteroids but only limited evidence that cyclosporine and cyclophosphamide and azathioprine improve MG.[12,13] Of note, the initiation of corticosteroids in patients with moderate to severe weakness may actually precipitate a worsening of weakness or even myasthenic crisis.

Thymectomy. While the association between thymoma and MG is not fully elaborated, it is well known that thymectomy for patients with thymoma can lead to remission of MG or enable a reduction in other medications. Thymectomy for patients with MG but without thymoma has been shown to have similar benefits and is recommended for patients younger than 60 with remission or improvement in up to 50% of cases and is supported by a clinical policy of the American Academy of Neurology.[14] The onset of improvement after thymectomy is often delayed for 2 to 5 years.

Immunomodulatory Therapy. PE and IVIG can be used for patients with exacerbations of MG or preoperatively in patients with stable MG.

PE removes the AChR antibodies and other immune complexes from the blood. The fall in AChR levels is associated with improvement in symptoms of MG. There is a risk of complications from hypotension or anticoagulation. Because of safety concerns, clinical trials have not been done in children. Although there are no randomized controlled studies, a review yielded many case series with short-term benefit, especially in myasthenic crisis, and it is recommended by the American Academy of Neurology.[15]

A review of IVIG trials found one randomized controlled trial of IVIG versus placebo that demonstrated the benefit from IVIG. Another trial failed to show a difference between

IVIG and PE.[16] The decision to institute either therapy is based on the input of the consulting neurologist and the resources available at the admitting hospital. If PE is not readily available for a patient with myasthenic crisis, IVIG should begin with 1 g/kg.

Botulism

Principles of Disease. Botulism is a toxin-mediated illness that can cause acute weakness leading to respiratory insufficiency. The Centers for Disease Control and Prevention (CDC) reports that an average of 145 cases are reported each year: 15% are foodborne, 65% are infant botulism, and 20% are wound related.[17] *Clostridium botulinum* is an anaerobic, spore-forming bacterium. Three of eight known toxins produced by *C. botulinum* (types A, B, and E) cause human disease. There has been an increase in the incidence of botulism from wound infections. In a 4-day period in 2003 in Washington State, four people contracted wound botulism from black tar heroin.[18] Botulism is also thought to be a potential agent for bioterrorism. The botulinum toxin works by binding irreversibly to the presynaptic membrane of peripheral and cranial nerves, inhibiting the release of ACh at the peripheral nerve synapse. As new receptors are generated, the patient improves.

Clinical Features. The toxin blocks both voluntary motor and autonomic functions. Because the disorder is at the neuromuscular junction, there is no sensory deficit and no sense of pain. The onset of symptoms is 6 to 48 hours after the ingestion of tainted food. There may or may not be accompanying signs and symptoms of gastroenteritis, with nausea, vomiting, abdominal cramps, diarrhea, or constipation. The classic feature of botulism is a descending, symmetrical, flaccid paralysis. The muscles often affected first are the cranial nerves and bulbar muscles, and the patient presents with diplopia, dysarthria, and dysphagia, followed later by generalized weakness. There may be associated blurring of vision. Because the toxin decreases cholinergic output, anticholinergic signs may be seen in the form of constipation, urinary retention, dry skin and eyes, and increased temperature. Pupils are often dilated and not reactive to light. This can be a point of differentiation from MG. Deep tendon reflexes are normal or diminished.

Infantile botulism results from the ingestion of *C. botulinum* spores that are able to germinate and produce toxin in the high pH of the gastrointestinal tract of infants. The same spores are not active in the gut of adults because of the lower pH. The CDC reports approximately 100 cases per year.[19] It occurs in infants between the ages of 1 week and 11 months and has been implicated as a cause of sudden infant death syndrome. Because spores can survive in honey, it is recommended that honey not be fed to infants. The clinical presentation includes constipation, poor feeding, lethargy, and weak cry; consequently, this diagnosis must be in the differential diagnosis of the floppy infant.

Diagnostic Strategies. The diagnosis is made by both clinical findings and exclusion of other processes. The toxin can be identified in serum and stool, but the assay is not commonly available in most hospitals and requires a prolonged turnaround time. If the suspected food source is available, it should also be tested for the toxin.

Management. The treatment is initially focused on stabilizing the airway and supportive measures. There is an equine antitoxin that can shorten the disease course, although it is not clear that the antitoxin decreases ventilator dependence and there is a risk of anaphylaxis and serum sickness. Nevertheless, the antitoxin should be administered as soon as possible. The toxin is available through the CDC by calling (404) 329-2888. An intravenous human botulism immune globulin (BIG-IV) has been developed for treatment of infantile botulism[20] and is available through the California Department of Health Services Infant Botulism Treatment and Prevention Program on-call physician at (510) 231-7600.

Tick Paralysis

Principles of Disease. The pathogenesis of tick paralysis, also known as *tick toxicosis*, is not fully understood. It is known that a toxin is injected while the tick feeds, and it is referred to as an *ixovotoxin*. The toxin appears to diminish the release of ACh at the neuromuscular junction and also reduces nerve conduction velocity. It may also have effects at autonomic ganglia, leading to pupillary signs. According to the CDC, the state of Colorado reports on average one case per year, though in 2006 four cases were reported during one week.[21]

Clinical Features. Tick paralysis is an acute, ascending, flaccid motor paralysis that can be confused with GBS, botulism, and MG. It typically begins with the development of an unsteady gait, followed by ascending, symmetrical, flaccid paralysis. Although symptoms usually begin 1 to 2 days after the female tick has attached and begun to feed, delays of up to 6 days have been reported.[22] There may be associated ocular signs, such as fixed and dilated pupils, that can help distinguish it from GBS.

Management. The management is supportive care and tick removal. A tick can be removed using forceps to grasp it as closely as possible to the point of attachment. Care must be taken not to leave mouth parts in the patient's tissue. Although symptoms may resolve rapidly after removal of the tick, supportive measures such as intubation should not be withheld pending resolution of symptoms.

Disorders of the Muscles

Perspective

Newly acquired weakness originating at the muscular level can be divided into two types: inflammatory and toxic-metabolic. Inflammatory disorders usually produce pain and tenderness, but metabolic disorders do not.

Inflammatory Disorders

Principles of Disease. The most common inflammatory myopathies are polymyositis (PM) and dermatomyositis (DM). PM may be idiopathic in nature, occur secondary to infections (viral or bacterial), or be seen in conjunction with other disorders such as sarcoidosis or hypereosinophilic syndromes. Inflammatory myopathies cause weakness, pain, and tenderness of the muscles involved. They must be distinguished from simple myalgias related to a fever or cramping that may suggest myotonia (inability to relax the muscle).

Clinical Features. DM and PM can occur at any adult age, although DM may also affect children. There is a slightly increased incidence in women. An associated increased risk of malignancy, especially breast, ovary, lung, gastrointestinal, and lymphoproliferative disorders, has been noted after the diagnosis of DM or PM, although the reported rate of malignancy varies widely. Proximal muscle weakness predominates and leads to complaints of difficulty rising from a seated position or climbing stairs and weakness in lifting the arms over the head. There is often pain and tenderness in these proximal muscles as well. There is a decrease in reflexes as the weakened muscles fail to contract. Thus, the decrease in reflexes is in proportion to the decrease in strength. Fasciculations are not seen, and atrophy is a very late finding.

DM is similar to PM, but it is also associated with classic skin findings. These are more prominent in childhood but are also found in adults. They include a periorbital heliotrope and erythema and swelling of the extensor surfaces of joints. The facial rash is usually photosensitive and may also involve the exposed areas of the chest and neck.

Diagnostic Strategies Electrolyte abnormalities must be ruled out and the serum CK checked. If possible, the skeletal muscle isoform (MM) should be distinguished from the cardiac muscle isoform (MB). The CK must be interpreted in light of the entire clinical picture. The presence of an elevated CK does not establish the cause of weakness as a myopathy because some neuropathies can also produce an elevated CK. Similarly, a normal CK does not rule out a myopathy as the cause of weakness. Electromyography and muscle biopsy are used to confirm the diagnosis.[23]

Management. PM and DM are usually managed with oral prednisone in a dose of 1 to 2 mg/kg/day. When steroids prove ineffective and during acute exacerbations, cytotoxic drugs such as azathioprine or methotrexate are added. Fortunately, the degree of rhabdomyolysis seen with the inflammatory myopathies is not sufficient to cause renal impairment.

Metabolic Disorders

Perspective. Acute, generalized muscle weakness can be seen with severe electrolyte abnormalities of any cause: hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypophosphatemia. Acute painless myopathies can also be seen with endocrine disorders involving the thyroid, parathyroid, or adrenal glands.

Of particular interest are several disorders referred to collectively as the *periodic paralyses*. This group of entities includes familial periodic paralysis (FPP) of the hyperkalemic and hypokalemic forms and thyrotoxic periodic paralysis (TPP), which is similar to hypokalemic FPP except that it is associated with hyperthyroidism.

Periodic Paralysis

Principles of Disease. These are autosomal-dominant disorders of ion channels resulting in intermittent attacks of flaccid extremity weakness associated with either hyperkalemia or hypokalemia, although the latter is more common. It is most often associated with an inherited genetic mutation. Patients usually report a personal and family history of similar episodes.[24]

Clinical Features and Diagnostic Strategies. Patients may suffer either isolated or recurrent episodes of flaccid paralysis. The lower limbs are involved more often than the upper, although both can be affected. Bulbar, ocular, and respiratory muscles are usually not involved. Onset is rapid; a prodrome of myalgias and muscle cramps may occur but is uncommon; mental status and sensory function are typically preserved, but reports of sensory nerve involvement have been documented.[25] Males are more often affected than females, and there is a higher incidence in Asians, particularly Japanese, although it occurs in other ethnic groups.

Attacks may be induced by the injection of insulin, epinephrine, or glucose. The onset of symptoms often follows a high carbohydrate intake (with subsequent insulin rise) and a period of rest. A typical complaint is the acute onset of weakness noted on waking in the morning after a large meal the preceding evening. An electrocardiogram, which should be done immediately in all patients suffering from acute paralysis, demonstrates signs of hyperkalemia or hypokalemia. An immediate potassium level should be ordered; in the hypokalemic form, the potassium level during an attack falls to values below 3.0 mEq/L.

Management. Many cases resolve spontaneously with supportive care alone. The mainstay of management is the treatment of the underlying electrolyte imbalance. In the hypokalemic state the total body potassium is not depleted but has shifted intracellularly. Thus, in the repletion of potassium, caution is necessary to prevent overtreatment. For this reason, intravenous potassium should be used sparingly; one or two 10-mEq doses of potassium chloride (KCl), each administered over 1 hour, should be the maximum given intravenously. This can be done in parallel with 40 mEq oral potassium repletion and retesting of serum potassium levels. Intravenous hydration helps to redistribute the body's potassium stores.

Thyrotoxic Periodic Paralysis. The clinical picture of TPP is almost identical to that of hypokalemic FPP, and indeed a small number of patients with hypokalemic FPP have hyperthyroidism. In TPP, symptoms related to hyperthyroidism are often present at the same time the patient develops weakness. The relation of the hyperthyroidism to hypokalemia is probably due to increased sodium-potassium adenosine triphosphatase activity, which causes a rapid shift of potassium from the extracellular into the intracellular compartment. Treatment of the hyperthyroid symptoms, such as tachycardia, may help the treatment of the paralysis as well. There are case reports of TPP in which the patient's weakness did not respond to potassium replacement until propranolol was given to treat tachycardia.[26,27] There is probably a genetic feature underlying this disorder because there is a higher incidence of repeated attacks of hypokalemic periodic paralysis among Japanese and Chinese patients with hyperthyroidism. It is important that all patients have thyroid function testing done after a first episode of hypokalemic paralysis.

KEY CONCEPTS

- The approach to evaluating patients with acute neuromuscular weakness is facilitated by first determining the location of the lesion (spinal cord, nerve, neuromuscular junction or muscle) and then considering the most common disorders that affect the area in question.
- In patients with bilateral upper motor neuron signs and a normal mental status, neuroimaging of the spinal cord should be strongly considered.
- In patients presenting with acute neuromuscular weakness, complaints of difficulty in breathing or swallowing should heighten suspicion of bulbar involvement with possible airway compromise. In such patients, a forced vital capacity less than 15 mL/kg or a maximal NIF less than 15 mm Hg are potential indications for mechanical ventilation.
- Botulism usually arises as a painless descending paralysis, often first affecting the cranial nerves and bulbar muscles, without sensory deficits or significant alteration of consciousness. The treatment is airway management and administration of antitoxin.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.