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Neuromuscular Junction Disorders and Peripheral Neuropathies

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Most of us dread the chief complaint of weakness. This nonspecific symptom engenders a differential that ranges from malingering to fatal, from psychiatric to cancer. The finding of demonstrable muscle weakness helps, but then leads to a confusing set of relatively rare diagnoses.

This issue of Primary Care Reports *discusses some of the most important disorders that present with muscle weakness. Most of these are "cannot miss" disorders that can lead to rapid deterioration of the patient, such as botulism and Guillain Barré. The authors present these disorders in a logical manner, separating out the sensory and motor findings and giving readers a rapid reference point to help differentiate these disorders.*

—Sandra M. Schneider, MD, FACEP, Editor

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Introduction

Neurological complaints and muscular weakness are seen in forms that vary from life threatening to minor. This article reviews the evaluation and management of the life-threatening and more common but benign neuromuscular junction disorders and peripheral neuropathies. This review breaks down each disorder with a focus on strength, sensation, reflexes, and autonomic dysfunction in a way that will help the clinician to better differentiate these patients when they present. As with most things in medicine, there is rarely one finding or historical feature that solidifies the diagnosis when evaluating the patient with a complaint of weakness or numbness. This review is written to give the physician a way to focus the history and neurologic examination to best determine the diagnosis for those patients who present with peripheral neurological complaints. While it may be trite to state that the clinician must have a high index of suspicion for the life-threatening peripheral neuropathies and neuromuscular disorders, it is nevertheless true as patients may present early in their disease process and easily can be missed without a focused evaluation.

Trying to differentiate a central neuropathy from a peripheral neuropathy or neuromuscular junction disorder can be difficult because these disorders have overlapping historical and physical examination features. The best approach is to inquire about the historical features discussed in each section and to break down the neurologic examination with a focus on the following areas: sensory, motor, reflexes, and upper motor neuron signs. In general, there is no one specific finding that will clinch the diagnosis, rather it is the combination of historical and examination findings that will lead the physician to the presumed diagnosis. In most cases, the patient with a neuromuscular disorder or peripheral neuropathy will require further diagnostic testing to confirm the diagnosis. However, it is well within the expertise of the physician to make the initial diagnosis and to begin the appropriate treatment for all of these disorders.

On the sensory examination, peripheral lesions are generally restricted to a single dermatome with a sharp border of demarcation. With central lesions, especially spinal lesions, sensory symptoms more commonly involve multiple dermatomes and may be bilateral. One area that commonly is overlooked on the sensory examination is the trunk. More specifically, patients with a thoracic spine lesion may appear to have sensation that is symmetric and present over the legs. However, when compared to the trunk, sensation may be diminished. The classic stocking-glove distribution of sensory deficit is a peripheral neuropathy that is most commonly seen in diabetes and chronic alcohol use.

With the motor examination, peripheral lesions usually cause unilateral weakness and are limited to the muscle group that is innervated by the involved nerve. The major exception to this finding is Guillain-Barré syndrome as it is a polyneuropathy that affects the peripheral nerves. With central findings, there is weakness or paralysis distal to the site of the lesion. These central lesions are most commonly bilateral and may have associated upper motor neuron signs such as spasticity, hyperreflexia, and clonus. There are instances when the patient will complain of leg weakness but have no demonstrable weakness on the initial examination. One maneuver that may demonstrate weakness is to have the patient squat down and rise to the standing position without any assistance from their arms. Normally, most patients without weakness are able to rise with only minor difficulty. If patients are unable to rise or cannot rise without assistance, then they have weakness. A second maneuver to differentiate weakness in the calf muscles is to have the patient perform a unilateral heel raise while standing flat footed on one foot only. The patient may balance with a hand, but most of the weight should be on one foot. Then have the patient switch feet and perform the same test with the opposite foot. In general, most physicians cannot use their arms to bring out calf weakness. However, this maneuver uses the patient's body weight and is very good for bringing out more subtle weakness.

Reflexes that involve a specific nerve involved in a peripheral neuropathy are diminished or absent. Otherwise, reflexes are normal. For central lesions, the patient may have hyporeflexia to areflexia, although the patient also may be hyperreflexic and demonstrate clonus.

Other important areas to evaluate are urinary and fecal incontinence, and impotence. Urinary and fecal incontinence are almost always seen with a central lesion, although there has been urinary incontinence associated with variant of Guillain-Barré syndrome. Impotence and priapism also indicate a central lesion.

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Urgent Neuromuscular Disorders and Peripheral Neuropathies

Guillain-Barré Syndrome. *Epidemiology.* Guillain-Barré syndrome (GBS) occurs equally in males and females in all age groups at a rate of 1-3 per 100,000 persons annually.[1,2] It is classically preceded a prodromal event 1–4 weeks before the onset on symptoms, with the most commonly identified event being gastroenteritis due to *Campylobacter jejuni*.[1,3,4] It is also associated with nonspecific viral upper respiratory infections, surgery, vaccination, herpes infection, mycoplasma infection, and HIV infection.[1,5,6] Frequently, no clear etiology is present.

Pathophysiology. GBS is the most common acute motor neuropathy.[1,2,7] GBS is not one specific disease, but rather it is a term that encompasses a heterogeneous group of immune mediated peripheral neuropathies that do not have another clearly discerned etiology.[1,2] A more descriptive term for GBS is acute inflammatory demyelinating polyradiculoneuropathy. GBS is an immune mediated inflammation of the peripheral nerves that results in the disruption or stripping of myelin from the peripheral nerve axons.[2,4,6,8] Although GBS is classically described as affecting only the peripheral nerves, it seems to have a predilection for the spinal nerve roots and, in rare cases, it can involve the central nervous system to a minor degree.[2] The net result is that there is a loss of innervation of the muscles as well as some sensory deficits in most cases.

Diagnosis. The physician must have a high index of suspicion for GBS to diagnose cases that present early in the disease process. Patients are afebrile and have a normal mental status. Usually, the patient complains of gradually worsening symptoms for several days before presenting for medical care unless he or she has a more aggressive form of the disease. The onset of GBS is heralded by paresthesias in the toes or fingertips, which is then followed within days by leg weakness.[1,2,6] In addition to the paresthesias, more than half of patients complain of pain in their back, buttocks, or legs. The pain is described as a deep aching pain that is worse with movement and is commonly described as a "charley horse."[1,2,6]

Motor. The classic presentation is that of an ascending motor weakness that is symmetric and associated with areflexia.[1,2,6] However, the presenting complaint may not be one of distal leg weakness, rather it may be one of difficulty walking up stairs or performing activities such as prolonged walking. This is due to the fact that the weakness of the proximal muscles is more significant to the patient than the distal muscles due to their size and strength. In almost all cases, the legs will be affected before the arms. The physical examination will demonstrate symmetric weakness that initially affects the legs more than the arms.[1,2,6] With progression of the disease process, the arms will become involved, then the cranial nerves along with respiratory distress and arrest.[1,2,6]

Sensory. Sensory findings and complaints occur in more than half of patients. In addition to the initial paresthesias, the patients may have diminished light touch and vibratory sensation that is minimal in comparison to the motor findings.[1,2,6]

Reflexes. The Achilles' and patellar reflexes are either diminished or, more commonly, absent, especially after the first few days of symptom onset.[1,2,6] As the upper extremities are affected, they will develop hyporeflexia to areflexia.

Autonomic Dysfunction. Autonomic dysfunction is seen in approximately half of all patients during their hospital course. This most commonly involves fluctuations in blood pressure and heart rate, but acute urinary retention may occur as well.[6,9] Autonomic dysfunction is less commonly seen in the initial presentation but is more prevalent during the hospital admission.

Diagnostic Evaluation. Initially, GBS is a clinical diagnosis. One can use cerebrospinal fluid (CSF) evaluation to help rule in the diagnosis of GBS. In the more severe or prolonged cases, the CSF will show an elevated protein in the presence of few or no cells, which is called albuminocytologic dissociation. This finding suggests the diagnosis; however, one cannot use a normal CSF to rule out GBS as the CSF may be normal early in the disease process.[2,10]

Clinical Management. Once there is a strong suspicion for GBS, the patient requires hospital admission for further monitoring and management. The patient should have a neurology consultation as soon as possible. These patients may progress rapidly and decompensate. In the hospital, the patient will be evaluated further with electrodiagnostic studies such as an electromyelogram or nerve conduction velocity. If available, measure a forced vital capacity (FVC) to help determine the degree of respiratory muscle involvement. A normal FVC is approximately 65 mL/kg.[2] If the FVC is less than half of the predicted FVC, then the patient should be admitted to the ICU and may require endotracheal intubation and mechanical ventilation.[11] Other predictors of the potential need for endotracheal intubation and mechanical ventilation include the following: time from GBS onset to hospital admission of less than seven days; inability to lift the elbows or head above the bed; inability to stand; ineffective coughing; increased liver enzymes.[1] In the hospital the patient will be treated with either intravenous immunoglobulin (IVIG) or plasmapheresis, but not both together. There is no proven benefit to treatment with steroids.[1,2,7]

The clinical course of the patient progresses over two to four weeks, with most patients reaching the nadir of their weakness by two to three weeks.[1,2,6] Of all patients with GBS, 25-30% will require ventilatory support and 3-8% will die.[1,2,6,11] Common etiologies for death are cardiac arrest (most likely due to dysautonomia), sepsis, acute respiratory distress syndrome, and pulmonary embolism.[1,2] Unfortunately, 3% of patients may have a recurrence of their disease.[1]

Variants of GBS. Because GBS is not a specific disease, there are several variants that the physician must be aware of. The following are those variants and their distinctive qualities:[1,2,4-7,9,12]

Miller-Fisher Variant: Symptoms include ophthalmoplegia, areflexia, and ataxia.

Descending Motor Weakness: Motor weakness that involves the cranial nerves first and then descends to involve the arms, then the legs. This may occur in up to 14% of cases.

Pure Sensory GBS: An ascending sensory loss with dimin-

ished or absent reflexes but without any motor loss.

Pure Pandysautonomia: Autonomic dysfunction and areflexia without motor or sensory loss. This is uncommon and unlikely to be diagnosed in the primary care setting.

Myasthenia Gravis. *Epidemiology.* Myasthenia gravis (MG), which is twice as common in women as men, has a bimodal peak of incidence. It peaks in women in their 30s and later it peaks in men in their 50s to 60s. In more than 75% of patients, it is associated with abnormalities of the thymus gland, particularly thymoma and thymus hyperplasia.[13]

Pathophysiology. Myasthenia gravis is not a peripheral neuropathy. It is the most common disease of the neuromuscular junction.[13] It is an autoimmune disorder with antibodies directed against the acetylcholine receptors post-synaptically in the neuromuscular junction. This results in a diminished number of acetylcholine receptors as well as widening of the postsynaptic clefts, which results in impaired neuromuscular transmission.[13] Clinically, the patient presents with weakness and fatigue.

Diagnosis. The clinical hallmarks of myasthenia gravis are muscular weakness and fatigability. These symptoms fluctuate throughout the day but are usually worse at the end of the day. In most cases, the patient will have symptoms over a period of weeks to months before seeking medical care. Initial symptoms most commonly involve the ocular muscles and include ptosis, diplopia, and blurred vision.[13,14] The ptosis is usually worst at the end of the day. Patients may also present with dysarthria, dysphagia, and less commonly with difficulty walking up stairs.

Motor. The patient presents with weakness or fatigability that fluctuates throughout the day. The progression of weakness usually occurs in a craniocaudal direction.[13] On examination, the patient may have ptosis, ocular palsy, or generalized muscular weakness. Occasionally patients will have a normal ocular examination and complain of weakness but have no demonstrable weakness. In these patients, the examiner can elicit weakness by stressing the ocular muscles by having the patient look upward for a period of three to four minutes with a goal of causing ptosis or extraocular muscle weakness. If the patient presents with ptosis, placing an ice pack over the eye may help with the diagnosis. Patients with myasthenia gravis will have resolution of the ptosis.[13,15] At times a patient will present with ptosis, and MG will be in the differential. Ptosis in MG will often resolve if ice is applied to the affected eye for a few minutes. Additionally, repeated abduction of the deltoids or flexing of the hip flexors (iliopsoas) will bring out weakness or fatigability in these patients.

Sensory. There are no objective sensory deficits.

Reflexes. Reflexes are generally intact.

Autonomic Dysfunction. There are no autonomic changes.

Diagnostic Evaluation. There is no specific test to confirm a suspicion of MG. Tests that are available are acetylcholine receptor antibody and muscle specific kinase antibody (MuSK Ab) levels. Acetylcholine receptor antibody testing will be positive in approximately 80-90% of patients with MG.[13,14] While it is very specific to MG, titer levels do not correlate with the disease severity.[14] The MuSK Ab test is a newer assay that is specific to the muscle specific kinase antibody. This test is only positive in one-third of cases, but more commonly is present in younger females.[13] One test that the physician can perform is the Tensilon test. Tensilon (edrophonium) is a short-acting carbamate that reversibly inhibits acetylcholinesterase, thus increasing the amount of acetylcholine present in the neuromuscular junction. Tensilon is administered to evaluate for a reversal of ptosis by at least 2 mm. However, due to the time it takes to perform the test and the side-effects including muscle fasciculations, respiratory depression, bradycardia, AV block, and increased salivation, it is generally not performed by the primary care physician.[13,16] As it is an uncommon procedure to be performed in the primary care setting, this article will not outline the whole process. However, if one elects to perform this test, atropine should be ready at the bedside to reverse the effects if they become too severe or life-threatening.[13,16]

Clinical Management. There are two areas in managing the patient with MG. First is the recognition and management of myasthenic crisis and the second is prevention of worsening of the MG through cautious use of medications prescribed when treating other medical problems. Myasthenic crisis is the major complication of MG that needs to be recognized and managed.[13] It is defined as acute respiratory distress in the myasthenic patient and may lead to the need for mechanical ventilation. It occurs in 15-20% of patients with MG, usually within the first 2 years of disease onset.[13] It may occur due to several etiologies: infection, change in medications, aspiration pneumonitis, pregnancy, surgery, and unknown. It is important to differentiate myasthenic crisis from cholinergic crisis. Cholinergic crisis is weakness due to excess anticholinesterase medication, which may also lead to weakness and respiratory failure. Cholinergic crisis presents with miosis, diarrhea, increased salivation, excessive sweating, abdominal cramps, and bradycardia. However, in the patient with acute respiratory distress, it is sometimes difficult to differentiate cholinergic from myasthenic crisis. Do not attempt to use edrophonium to help differentiate the process, as it can cause acute deterioration and is unreliable in truly differentiating the cause. In managing myasthenic crisis the primary step is airway stabilization. If necessary, intubate the patient to maintain control of the airway. If the patient is not acutely decompensating, then measure the FVC as a guide to monitor. These patients require hospital admission. Stop all myasthenic agents, including steroids, and arrange for plasmapheresis. Steroids must be avoided acutely as their use may exacerbate the weakness and respiratory difficulty.

MG can be exacerbated with numerous medications that are commonly prescribed either in the primary care setting or to patients when they are discharged from an ED visit. Use caution when treating the patient with MG for other medical problems. Specifically, there are numerous medications that can exacerbate the weakness of MG. (*See Table 1.*)

Table 1. Medications that Can Exacerbate Myasthenia Gravis

CARDIOVASCULAR
• Beta-blockers
• Calcium channel blockers
• Lidocaine
• Quinidine
• Procainamide
ANTIBIOTICS
• Aminoglycosides
• Tetracyclines
• Erythromycin
• Clindamycin
• Chloroquine
PHENYTOIN
CORTICOSTEROIDS
THYROID REPLACEMENT
BOTULINUM TOXIN
Commercial use as a beauty aid

Lambert-Eaton Myasthenic Syndrome. *Epidemiology.* Lambert-Eaton Myasthenic Syndrome (LEMS) is a rare disorder that is associated with malignancy, most commonly small cell lung carcinoma, in more than half of cases.[17] Interestingly, LEMS was diagnosed in 35% of patients before the diagnosis of lung cancer was made.[17] In those patients without cancer, LEMS is an autoimmune disease that is associated with other autoimmune phenomena.[18] In those patients who present with LEMS without a clear etiology, a rigorous evaluation is undertaken looking for cancer.

Pathophysiology. LEMS is caused by an antibody mediated decrease in the number of acetylcholine release sites on the presynaptic membranes of the neuromuscular junction. This results in an inadequate release of acetylcholine at the neuromuscular junction and clinical weakness.[19] This weakness is improved with repeated stimulation due to an increased amount of acetylcholine in the neuromuscular junction.[14,20] Although its name includes myasthenic syndrome, it presents clinically as the opposite of myasthenia gravis and may initially appear to be similar to GBS. It is not a form of MG.

Diagnosis. Motor. The patient will have muscular weakness that improves with repeated use of those muscles. This syndrome involves the lower extremities primarily, but can involve the upper extremities and other skeletal muscles. Ocular muscle involvement can occur, but it is less common.[14,18,21] Respiratory involvement is rare.[20,21]

Myotonic dystrophy is a rare genetic disorder that generally presents in adulthood similar to Lambert Eaton syndrome. On close questioning, however, patients will give a history of muscle contraction such as being unable to release a door knob. Many patients will also have diabetes.

Sensory. There are no sensory deficits.

Reflexes. Hyporeflexia to areflexia of the muscle groups involved with the weakness.[18,21]

Autonomic Dysfunction. Thirst due to decreased salivation (xerostomia) and impotence.[18,22]

Diagnostic Evaluation. There is no specific diagnostic test to make this diagnosis. One should consider other abnormalities such as electrolyte disorders in the cancer patient. Electrodiagnostic testing is the method of making the definitive diagnosis, although this is not necessary in the primary care setting.

Clinical Management. The most important aspect is recognition of this disorder. Once it is recognized, then the clinical management revolves around management of the cancer and the possible use of steroids, immunosuppressants (azathioprine), and plasmapheresis. There is no specific treatment in the primary care setting.

Botulism. *Epidemiology.* Botulism is a relatively rare disorder, with approximately 110 cases reported annually to the Centers for Disease Control and Prevention.[23] Because it is so rare, it is frequently confused with other neurologic conditions on the initial presentation. There are three distinct varieties of botulism: food-borne, wound, and infantile. All have similar clinical manifestations, but the mechanism of each is unique.

Pathophysiology. Clostridium botulinum is an anaerobic, spore-forming bacterium. The toxin is taken up presynaptically in the cholinergic nerve endings by endocytosis and prevents the fusion of the synaptic vesicles with the nerve terminus. This prevents the release of acetylcholine presynaptically, which disrupts neurotransmission.[24,25]

Food-borne Botulism. This condition is caused by the ingestion of preformed toxin and is responsible for approximately 20% of cases. Reports are clustered in the western states, particularly Alaska, where improper canning techniques or failure to prepare home-canned food properly are blamed. In the summer of 2007, four cases of food-borne botulism were reported. Each of those four cases presented to different emergency departments. All of the cases were connected to the ingestion of Castleberry's Hot Dog Chili Sauce.[26]

Wound Botulism. This is the rarest of the three entities.[23] It is the result of a wound that is contaminated with *Clostridia botulinum* spores, which then allows the Clostridia to germinate and produce toxin that is systemically absorbed.[25] Typically, these wounds do not appear to be grossly infected as one would expect. Most cases in the United States are associated with injection drug use, more specifically the use of black tar heroin.[27]

Infantile Botulism. This is the most common form of botulism.[23,25] It is caused by the ingestion of botulism spores, which then germinate, proliferate, and produce toxin in the infant's colon.[28] While classically associated with honey, only 15% of cases are directly attributed to this.[23] The source of the remaining cases has not been identified, but the ingestion of environmental agents such as contaminated soil and vacuum cleaner dust are thought to be likely culprits.[25,29] This disease is unique to infants because their gastrointestinal tract has yet to be colonized by the

Table 2. Diagnosis and Common Findings

DIAGNOSIS	MOTOR	SENSORY	REFLEXES	AUTONOMIC DYSFUNCTION
Guillain Barré syndrome	Ascending symmetric weakness	Only seen in ½ of patients Paresthesias Diminished sensation	Hyporeflexia to areflexia	Seen in ½ of patients Fluctuations in blood pressure and heart rate
Myasthenia Gravis	Weakness and fatigability	None	Generally intact	None
Lambert Eaton	Ascending symmetric weakness that improves with repeated use	None	Hyporeflexia to areflexia	Increased thirst and impotence
Botulism	Descending weakness Cranial nerves involved initially	None	Hyporeflexia as the arms become involved	Dry mouth, dilated pupils, postural hypotension
Tick paralysis	Ascending symmetric weakness	Paresthesias but no deficits	Hyporeflexia to areflexia	None

competitive flora that protect adults and older children.[29]

Food-borne and wound botulism have indistinguishable symptomatology. The incubation period for food-borne botulism is 12-72 hours.[23] Distinguishing a precise incubation period for wound botulism is problematic, if not impossible.

Diagnosis. Motor. Cranial nerve deficits are the most common initial presentation. Common findings are diplopia, facial weakness, ptosis, dysphagia, and speech changes. The paresis and subsequent paralysis then descends to involve the upper extremities, then the lower extremities. Respiratory muscle paralysis ensues as the process descends.

Sensory. There are no specific sensory deficits with botulism.

Reflexes. As the upper extremities become involved hyporeflexia is seen.

Autonomic Dysfunction. The autonomic nervous system is affected, which results in dry mouth, postural hypotension, paralytic ileus, and pupillary abnormalities.

Diagnostic Evaluation. In all three varieties of botulism, the diagnosis is clinical. Stool and blood should be obtained for culture and toxin identification. Wounds may be cultured. However these are of no help in the primary care diagnosis and management of the condition. Routine diagnostic studies are only helpful to rule-out other conditions.

In one emergency department case series of 29 patients with food-borne botulism, all patients had at least three of the following: weakness, dry mouth, double vision, and difficulty speaking.[30] In a larger study of 705 patients with botulism, 68% of the patients had at least three of the following symptoms on admission: nausea and vomiting, dysphagia, diplopia, dry mouth, and fixed and dilated pupils.[25]

Infant Botulism. Infant botulism presents after hours to days (mean of 4.2 days) of symptoms before it is recognized.[29] Constipation is often the initial symptom and it may precede the neurologic symptoms by days.[25] Cranial nerves are affected first, resulting in loss of facial expressions, poor feeding, and decreased suck and cry. These symptoms are initially very subtle. Symptoms progress to poor head control and diffuse hypotonia ("floppy baby").[28] As in adults, respiratory paralysis is responsible for botulism mortality. Infantile botulism is thought to be an occasional etiology for Sudden Infant Death Syndrome (SIDS).[29]

Clinical Management. All suspected cases of botulism should be admitted to the ICU for observation and supportive care. If the patient's respiratory function is in peril, he or she should be immediately intubated and maintained on mechanical ventilation until the toxin's effects have abated, which can take weeks. Because the toxin binds irreversibly, patients will recover as they regenerate neuromuscular connections at their synapses.

Food-borne. In addition to supportive care, all patients should be treated with botulism antitoxin.[29] Because this is derived from horse serum, all patients should have skin testing done before IV administration to evaluate for hypersensitivity. The antitoxin has been shown to decrease mortality and reduce hospitalization. It prevents progression of the process but does not reverse the paralysis. The antitoxin can be obtained through state and local health departments and the CDC.[23]

Wound. These patients should also receive the equine derived antitoxin and should be treated supportively. The wound should be debrided. Antibiotics should be given for coexisting infection,

but no studies have shown that their administration hastens recovery from the paralysis.

Infantile. Supportive care is the primary treatment from the primary care perspective. However, Human Botulism Immune Globulin (HBIG) has been shown to decrease the length of the ICU stay, ventilation requirements, and mortality.[31] This is different from the equine-derived antitoxin and is only FDA approved for use in infants. Like the antitoxin, it can be obtained by calling the Infant Botulism Treatment and Prevention Program at 510-231-7600 to obtain HBIG. Antibiotics are ineffective.[29]

Tick Paralysis. *Epidemiology.* Tick paralysis is a rare toxin-induced condition characterized by an ascending paralysis that looks similar to Guillain-Barré syndrome. Because it is not reportable in all 50 states, it is difficult to ascertain its incidence. The condition occurs most frequently in the western United States and Canada, although it has been reported worldwide. From 1988-2000, 6 cases were reported in the state of Washington.[32] An estimated one case per year occurs in Colorado; however 4 cases were reported there in May of 2006.[33] Tick paralysis usually occurs during the spring months, as this is when the female tick is feeding just prior to laying her eggs. Children are classically the only victims of tick paralysis as the toxin is thought to be diluted in an adult's larger blood volume.[34,35] However, in the cluster of cases reported in Colorado in 2006, 3 of the 4 patients were adults.[33]

Pathophysiology. Tick paralysis occurs when an adult female tick attaches to its victim. The tick passes the toxin on to the victim through its saliva while feeding. In the United States, *Dermacentor variabilis* (American Dog Tick) and *D. andersoni* (Rocky Mountain Wood Tick) are the most commonly blamed species.[33] In Australia, *Ixodes holocyclus* releases a particularly virulent toxin.[34] The mechanism of action of the toxin is not definitively established, but the leading theory is that it reduces sodium flux across axon membranes at the nodes of Ranvier, which results in diminished nerve conduction amplitude and velocity.[34]

Diagnosis. Symptoms develop within 4-7 days after the tick attaches. Paraesthesias and ataxia are usually noted first. Then, weakness starts with the legs and spreads cranially. Loss of deep tendon reflexes and respiratory drive eventually occur. Patients are usually alert, although they may appear lethargic because of their muscular weakness. Fever is uncommon.

Motor. A progressive ascending weakness that appears similar to GBS is noted. One difference with tick paralysis is that there is commonly an associated ataxia that is not seen with GBS.

Sensory. Patients will complain of paresthesias but generally will not have sensory deficits on examination.

Reflexes. Hyporeflexia to areflexia will occur in the similar distribution as the ascending motor weakness.

Autonomic Dysfunction. There are no specific autonomic findings.

Diagnostic Evaluation. The primary diagnostic evaluation is a thorough physical examination, especially looking in the hair for the tick. No child should be diagnosed with GBS without thoroughly examining him or her for ticks (generally in the scalp, axillae, and perineum).[34]

Clinical Management. Removal of the tick results in rapid recovery. To remove the tick, grasp as close to the patient's skin as possible with a forceps and pull firmly.[32] Patients usually completely regain their strength within 48 hours. In Australia, the *I. Holocyclus* anti-toxin should be given prior to removal of the tick, as symptoms often worsen initially.[34]

Non-urgent Peripheral Neuropathies

Carpal Tunnel Syndrome. *Epidemiology.* Carpal tunnel syndrome (CTS) is the most common of the entrapment neuropathies. Approximately 3% of the American population has been affected by this condition.[36] Women are three times more likely than men to have symptoms. While most cases of CTS are idiopathic, up to one-third of cases are associated with coexisting states such as pregnancy, hypothyroidism, diabetes, renal failure, acromegaly, and steroid use.[37] Occupations such as typing, logging, and construction work have also been associated with CTS.

Pathophysiology. CTS results from compression of the median nerve as it passes through the carpal tunnel created by the rigid carpal bones, nine flexor tendons, and the transverse carpal ligament.[36,38] This compression causes pain, paresthesias, and weakness in the median nerve distribution.

Diagnosis. The earliest manifestations of CTS are pain, paresthesias, burning, or numbness in the distribution of the median nerve, which involves the volar aspects of the thumb, index, and middle finger in addition to the radial one-half of the ring finger.[37] The pain usually worsens with activity and can also wake the patient from sleep at night. Patients frequently report shaking their hand when the pain is present. Symptoms can be bilateral, but the dominant hand is usually affected more severely.[39]

Motor. While sensory symptoms predominate, the patient may develop weakness of thumb abduction and later develop atrophy of the thenar eminence.[39]

Sensory. Sensory complaints, such as numbness and tingling, are the most common complaints with CTS. Sensory deficits to light touch and two-point discrimination occur over the distribution of the median nerve as described previously.

Reflexes. There are no specific reflex changes

Autonomic Dysfunction. There are no specific autonomic findings.

Diagnostic Testing. There is no diagnostic test that is specific or sensitive for CTS. Positive findings on Tinel's sign and Phalen's maneuver are suggestive for CTS. Tinel's sign involves tapping over the volar surface of the wrist to see if it causes paresthesias in the digits in the median nerve distribution.[37] Phalen's maneuver consists of the patient flexing the wrist for at least 60 seconds. A positive result is the creation of pain or paresthesia in the median nerve distribution. The sensitivities of each test are poor (25%-60% for Tinel's and 10%-91% for Phalen's).[36,37] Electrodiagnostic testing can be performed to verify the diagnosis as an out-patient.

Clinical Management. Treat the patient with a neutral wrist

splint. This has been shown to be effective in mild cases, and is the least invasive treatment option.[40] Splinting is most effective when used continuously, although patients will frequently only use the splint at night. While nonsteroidal anti-inflammatory drugs commonly are prescribed, most studies have shown them to be ineffective.[40] Patients should be directed to follow up with their primary care provider, where a steroid injection into the carpal tunnel can be performed. Steroids have been shown to be effective in the short term,[41] but surgery is the definitive treatment in refractory cases.[42]

Ulnar Neuropathy at the Elbow. *Epidemiology.* Ulnar neuropathy at the elbow is the second most common entrapment neuropathy of the upper extremity.[43,44] In one electrodiagnostic laboratory, it accounted for 9% of all diagnoses and 20% of focal neuropathies.[43]

Pathophysiology. There are many potential areas around the elbow that can cause the ulnar nerve entrapment or neuropathy. In general, the ulnar neuropathy occurs as a result of either external compression, entrapment in the cubital tunnel or at the flexor carpi ulnaris, or by acute or chronic traction injury.[24,44] Risk factors include activities that require repetitive flexion and extension at the elbow and prolonged pressure on the elbows.

Diagnosis. Patients complain of elbow pain that radiates down the ulnar portion of the forearm, hand weakness, and numbness or paresthesias in the ulnar side of the hand and the ring and small fingers.[39] Elbow flexion often exacerbates the symptoms. Patients who tend to sleep in the fetal position will notice nocturnal symptoms as well.

Motor. Similar to CTS, motor involvement is less common or appears later in the disease process. Patients may have a reduced grip strength associated with atrophy of the interosseous or hypothenar muscles. Weakness of the first dorsal interosseous and flexor carpi ulnaris are the more common findings. Finally, weakness of flexor digitorum profundus of the small and ring fingers occurs later.[43,44]

Sensory. Decreased sensation of the small finger and the ulnar half of the ring finger, ulnar palm, and dorsum of the hand is present.

Reflexes. There are no specific reflex changes.

Autonomic Dysfunction. There are no autonomic findings.

Diagnostic Testing. Electrodiagnostic testing is the primary way to confirm the diagnosis. Provocative maneuvers that may help in the diagnosis include tapping over the nerve in the ulnar groove for reproduction of paresthesias. Also, sustained elbow flexion, possibly with manual pressure over the ulnar groove may also reproduce the symptoms.[43] Consider plain radiographs of the elbow if there is an injury or concern of arthritis or bony tumor that may be compressing the nerve.

Clinical Management. Management of ulnar neuropathy at the elbow should be conservative.[43] Elbow pads can provide protection and a splint can be applied to prevent sustained flexion. Patients should be educated to avoid activities associated with repetitive or sustained elbow flexion and to avoid putting pressure on the elbow.[39] Patients should be referred to their primary physician for electrodiagnostic testing to better localize the etiology and location of the injury. Surgery is considered as a last resort in severe lesions or in those who fail to respond to conservative management.[43]

Compressive Radial Neuropathy. *Epidemiology.* Compressive radial neuropathy (CRN), commonly referred to as "Saturday Night Palsy," is caused by compression of the radial nerve as it passes through the spiral groove of the humerus. This condition gets its name because it classically occurs when an intoxicated person falls asleep with his or her arm draped over a chair or bench, compressing the nerve. It is less common than median or ulnar nerve compression.

Pathophysiology. Prolonged compression of the nerve leads to demyelination and, in severe cases, axonal degradation.[39] CRN has been less commonly associated with humerus fractures and the use of crutches. Sensory loss may also occur on the lateral portion of the dorsal hand and the dorsal aspect of the first four fingers.[24] Elbow strength is intact because the branch of the radial nerve supplying the triceps branches off proximal to the radial groove.

Motor. The predominant result of CRN is weakness of the wrist and finger extensors, which results in a wrist drop. The triceps has normal strength because its innervations occur proximal to the radial groove.

Sensory. Decreased sensation over the radial portion of the dorsum of the hand and the dorsal aspects of the thumb through the ring finger.

Reflexes. There will be diminution of the brachioradialis reflex but a normal triceps reflex.

Autonomic Dysfunction. There are no autonomic findings.

Diagnostic Testing. Electrodiagnostic testing is the primary way to confirm the diagnosis and to render a prognosis for recovery.

Clinical Management. CRN is almost always treated conservatively. Symptoms usually resolve spontaneously within a few days or weeks. However, in severe cases where axonal damage has occurred, symptoms can last for more than a year.[39] Outpatient referral for electrodiagnostic testing can help establish a prognosis in these cases. In patients with significant wrist or finger drop, a cock-up wrist splint can help keep them in extension.[39,44]

Toxic Neuropathies

There will be situations when the patient presents with a definite peripheral neuropathy on history and examination but it does not fit any well described disorder. In those cases the physician needs to broaden the differential diagnosis and consider toxin-induced peripheral neuropathy. Toxins that should be considered include the following: arsenic, colchicine, dapsone, ethanol, lead, lithium, mercury, organophosphate pesticides, phenytoin, thallium, toluene, and L-tryptophan.[45] Even though these conditions are rare, they are potentially reversible with removal of the offending agent, so it is important to consider them in those unusual cases.[45] In these difficult cases, the patient should be questioned on toxin exposure by reviewing potential pharmaceutic, industrial, recreational, and environmental exposures. When there is a suspicion of a toxin-induced

neuropathy the case should be discussed with a toxicologist who has the skills, knowledge, and expertise to best determine the next step for the patient.

Summary

There are several life-threatening and benign neuromuscular disorders and peripheral neuropathies that will be encountered. A focused history and structured neurological examination of the patient concentrating on the strength, sensation, and reflexes as well as a search for autonomic dysfunction will allow the physician to narrow the differential diagnosis.

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Physician CME Questions

32. A 35-year-old woman presents complaining of left hand tingling with weakness and numbness over the middle and index fingers. She works as a computer programmer and complains that typing and driving her car worsen her symptoms. On examination, she has weakness of thumb abduction and diminished sensation over the index and middle fingers. Which one of the following is the best prescribed to manage this patient?
    A. Dexamethasone 4 mg twice daily
    B. Ibuprofen 800 mg three times daily
    C. TENS unit placed over the carpal tunnel
    D. Wrist MRI to better evaluate the carpal tunnel
    E. Wrist splint that places the wrist in a neutral position

33. Three family members present with a chief complaint of a very sore throat and visual disturbances to include diplopia. On examination each has very dry mucus membranes with otherwise normal mucosa. There is no exudate or erythema. They each have bilaterally fixed dilated pupils at 8 mm and ptosis. Which one of the following is the most likely etiology for their symptoms?
    A. Botulism
    B. Guillain-Barré
    C. Lambert-Eaton syndrome
    D. Mononucleosis
    E. Streptococcal pharyngitis

34. A 22-year-old male presents with a 3-day history of progressive leg weakness. He is weak over his legs bilaterally with no reflexes of his Achilles and patellar reflexes. Which one of the following tests is the best to help you to determine the diagnosis for this patient?
    A. Complete blood count (CBC)
    B. Erythrocyte sedimentation rate (ESR)
    C. Lumbar puncture
    D. Serum protein electrophoresis
    E. Serum magnesium level

35. A 6-year-old girl presents with a complaint of weakness and difficulty walking. She is a healthy child with no medical history. The only remarkable history is that she was camping with her family earlier in the week. On examination she has an ataxic gait and weakness and areflexia of her legs. She has normal sensation. What is the most important step to perform next?
    A. CBC
    B. ESR
    C. Head to toe examination for a tick
    D. Lumbar puncture
    E. Serum electrolyte determination

36. Which one of the following is the most commonly identified event that is associated with Guillain Barré syndrome?
    A. Gastroenteritis due to *Campylobacter jejuni*
    B. Pneumonia due to mycoplasma
    C. Thyroid surgery
    D. URI due to influenza B
    E. Vaccination for influenza

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

37. Which one of the following medications can cause worsening of myasthenia gravis?
    A. Beta-blockers
    B. Corticosteroids
    C. Erythromycin
    D. Lidocaine
    E. All of the above can cause worsening of myasthenia

38. A 22-year-old injection drug user presents with a chief complaint of diplopia, ptosis, and generalized weakness of one day duration. He last "skin-popped" heroin 8 hours ago. He also has a very dry mouth and pupils that are fixed and dilated. He has normal sensation on examination. Which one of the following is the most likely etiology for his symptoms?
    A. Bell's palsy
    B. Lambert-Eaton myasthenic syndrome
    C. Myasthenia gravis
    D. Tick paralysis
    E. Wound botulism

39. A 28-year-old male presents with a complaint of elbow pain that radiates down the ulnar side of his forearm. He has decreased sensation over the small finger and the ulnar side of his ring finger. He has normal strength. Which one of the following is the most appropriate treatment for this condition?
    A. Dexamethasone 4 mg injected into the carpal tunnel
    B. Elbow pads to decrease pressure on the elbow
    C. Neutral wrist splint
    D. Prednisone 50 mg daily for 7 days
    E. Referral for urgent surgery

40. A 65-year-old male with known small cell lung cancer presents with weakness for several days. Specifically, he has difficulty walking and going up stairs. On examination he has 3/5 weakness in his legs. He has no Achilles and patellar reflexes. His upper extremity exam is normal. Which one of the following is the most likely etiology for his symptoms?
    A. Chemotherapy induced neuropathy
    B. Dehydration
    C. Lambert Eaton Myasthenic Syndrome
    D. Myasthenia gravis
    E. Steroid-induced myopathy

41. A 35-year-old woman with a recent diagnosis of myasthenia gravis presents for worsening weakness. On examination she has mild ptosis and feels slightly short of breath. She has a forced vital capacity of 45.

Which one of the following is the most appropriate in the management of this patient?

A. Ampicillin, gentamicin, and clindamycin for presumptive infection
B. Dexamethasone 8 mg IV
C. Solu-Medrol 125 mg IV
D. Stop all medications
E. Tensilon (edrophonium) IV

CME Answer Key

32. E
33. A
34. C
35. C
36. A
37. E
38. E
39. B
40. C
41. D

In Future Issues:

Obesity

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

New Study on Thiazolidinediones May Show Benefits

In this Issue: Pioglitazone and heart disease; ARBs manufacturers spend millions to show the non-inferiority of their products compared to less expensive, generic ACE inhibitors; some athletes turn to growth hormone because it is difficult to detect; FDA Actions

The thiazolidinediones rosiglitazone (Avandia) and pioglitazone (Actos) have taken their lumps in the last year, with evidence associating drugs with increased risks of heart failure. Rosiglitazone has also been associated with increased cardiovascular mortality, while evidence suggests that pioglitazone may actually improve cardiovascular outcomes. Now a new study compares pioglitazone with the sulfonylurea glimepiride measuring the progression of coronary atherosclerosis in patients with type 2 diabetes. A total of 543 patients with type 2 diabetes and coronary disease underwent coronary intravascular ultrasonography and were then randomized to receive glimepiride 1 to 4 mg daily or pioglitazone 15 to 45 mg daily for 18 months with titration to a maximum tolerated dosage. Intravascular ultrasonography was repeated in 360 patients at completion of the study. The primary endpoint was percent change in atheroma volume (PAV). Patients were also treated with standard therapy (statins, renin-angiotensin blockers, and aspirin). Glimepiride resulted in an increase in PAV of 0.73% (95% CI, 0.33%-1.12%) while pioglitazone decreased PAV by 0.16% (95% CI, -0.57% to 0.25%) (*P*=.002). Blood sugar control as measured by HbA1c was similar in both groups. Pioglitazone also resulted in increase in HDL cholesterol of 5.7 mg/dL compared to 0.9 mg/dL for glimepiride (P<.001), and pioglitazone lowered triglyceride levels an average of 16.3 mg/dL compared to an increase of 3.3 mg/dL with glimepiride (*P* <.001). Hypoglycemia was more common in the glimepiride group while edema, fractures, and decreased hemoglobin levels were more frequent in the pioglitazone group. The authors conclude that in patients with type 2 diabetes and coronary artery disease, pioglitazone slows progression of coronary atherosclerosis compared to glimepiride (*JAMA* 2008; 299: 1561-1573). An accompanying editorial points out that outcomes such as those found in the study may not translate to improving cardiovascular outcomes, however the results are consistent with a modest clinical benefit demonstrated in the PROACTIVE trial (*JAMA* 2008; 299:1603-1604).

ARBS effective as ACE?

Are angiotensin-receptor blockers (ARBs) as effective as angiotensin-converting-enzyme (ACE) inhibitors in reducing vascular events in high-risk patients? Manufacturers of ARBs have spend millions trying to show the non-inferiority of their products compared to the less expensive, generic ACE inhibitors. The current entry funded by Boehringer Ingelheim, the ONTARGET trial, com-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5413. E-mail: iris.young@ahcmedia.com.

pares their product telmisartan (Micardis) with the ACE inhibitor ramipril. In this large double-blind randomized trial of 25,000 patients with vascular disease or high risk diabetes, over 8500 patients received ramipril 10 mg per day, telmisartan 80 mg per day, or the combination of both drugs. The primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Mean blood pressure was slightly lower in the telmisartan and combination therapy group than in the ramipril group. After a median follow-up of 56 months, the primary outcome occurred in 16.5% of the ramipril group, 16.7% of the telmisartan group, and 16.3% of the combination group. The ramipril group had a higher incidence of cough and angioedema, while the telmisartan group had a higher rate of hypotensive episodes. The combination group had a higher risk of hypotensive episodes, syncope and renal dysfunction compared to the ramipril group. The authors conclude that valsartan was equivalent to ramipril in patients with vascular disease or high risk diabetes, and was associated with less angioedema. There was no benefit in the combination of the two drugs (*NEJM* 2008; 358: 1547-1559). An accompanying editorial points out the difficulty in interpreting non-inferiority trials. In this study telmisartan preserved 94% of the benefit of 10 mg of ramipril (95% CI, 85 to 105). It is also the fourth trial showing that combinations of ACE inhibitors and ARBs are of no value in reducing cardiovascular events compared to ACE inhibitors alone. The author concludes that the ARBs provide a similar benefit to prevent ACE inhibitor therapy; however "because ARBs are more costly than ACE inhibitors and have more side effects, their primary value is as an alternative for patients who cannot tolerate ACE inhibitors because of cough." (*NEJM.* 2008; 358:1615-1616).

Athletes and Growth Hormone

As testing for performance-enhancing drugs becomes more prevalent in sports, some athletes have turned to growth hormone because it is difficult to detect. Touted as an anabolic agent that improves athletic performance, the drug is also associated with significance side effects including diabetes, hepatitis, and acute renal failure. Recently a group from Stanford performed a meta-analysis of 44 articles describing 27 study samples in which 303 participants received growth hormone representing 13.3 person-years of treatment. Participants were average 27 years old with lean body mass and physically fit. Lean body mass increased with growth hormone compared to participants who did not receive it (increase 2.1 kg 20.1 kg [95% CI, 1.3 to 2.9 kg]), however strength and exercise capacity did not improve. Lactate levels during exercise were statistically significantly higher in two of three studies, and growth hormone treated participants experienced soft tissue edema and fatigue more often than those who did not receive it. The authors conclude that claims that growth hormones enhance physical performance are not supported by the scientific literature. The drug may increase body mass but it is does not improve strength, and it may worsen exercise capacity and adverse events (*Ann Int Med,* early online release 18 March 2008, print date 20 May 2000).

FDA Actions

Cefixime (Suprax), the only CDC recommended oral treatment for gonorrhea, is now available for the first time since 2002 in a 400 mg tablet. Wyeth Pharmaceuticals discontinued production of the drug when its patent expired. Now Lupin Pharmaceuticals has received FDA approval to market the 400 mg tablets. The company has been marketing the oral suspension since 2004. Cefixime 400 mg as a single dose is recommended treatment for all types of gonorrhea infections (urogenital, rectal, and pharyngeal).

The FDA has approved methylnaltrexone bromide (Relistor) for the treatment of opioid-induced constipation in patients with late stage, advanced illness who are receiving opiates on a continuous basis. The injectable medication is started on an every-other-day basis, then increased to once a day as needed.

The FDA has approved a new biologic, certolizumab (Cimzia) for the treatment of Crohn's disease. Certolizumab is a TNF blocker similar to other drugs used for this indication. The initial dose is one injection every two weeks for the first three injections, then decreasing to once every four weeks. Like other TNF blockers, certolizumab is associated with increased risk of serious infections, lymphomas, and other malignancies.

The FDA has investigated reports of increased depression in patients switched from Wellbutrin XL 300 mg to Teva's generic bupropion XL 300 mg (Budeprion). Nearly 80 patients of the thousands who were changed to the generic noted loss of antidepressant effect following the switch. The agency reevaluated bioequivalency studies and concluded that, although there are small differences in the kinetic profiles the two formulations they were within the establish boundaries of equivalents. They conclude that the generic is bioequivalent and therapeutically equivalent to the branded product. ■