Neuromuscular disorders cause weakness or muscle atrophy due to dysfunction of the lower motor neuron (LMN), nerve root, peripheral nerve, muscle or neuromuscular junction. Abnormalities may be generalized or focal and deficits will reflect the distribution of the lesion. Generalized neuromuscular weakness is characterized by a short, shuffling gait and fatigue with exercise. Acute lower motor neuron or peripheral nerve disease will cause rapid muscle atrophy (denervation atrophy), often within 7-10 days of clinical signs. Muscle tone and segmental spinal reflexes are generally decreased though in some conditions they may be preserved. Ataxia is seen with diseases of the central nervous system but is not a typical feature of neuromuscular disease. Cranial neuropathy such as facial paralysis may be seen with certain neuromuscular disorders such as myasthenia gravis. Dysphagia or megaesophagus may be seen due to dysfunction of skeletal muscle in the orad gastrointestinal tract. Severe generalized neuromuscular disease will cause loss of mobility or even tetraplegia. In these cases, the patient should be monitored carefully for hypoventilation and aspiration pneumonia.

**Diagnosis of Neuromuscular Disease**

The clinical diagnosis of neuromuscular disease is typically based on physical examination. Electrodagnostic testing confirms the presence of neuromuscular disease and localizes the problem to nerve/LMN, muscle or neuromuscular junction. Electromyography (EMG) is the study the electrical activity of muscle. Normal muscle is electrically quiet except when the EMG needle initially enters the muscle (insertional activity). Denervated, inflamed or dystrophic muscle is prone to spontaneous activity often in combination with increased insertional activity. EMG is useful in determining whether muscle atrophy is from disuse, denervation or myopathy. Disuse atrophy does not lead to spontaneous activity unlike denervation or myopathic atrophy. Nerve conduction testing involves stimulating a peripheral nerve at two or more sites and recording a compound muscle action potential (CMAP) from a muscle in the distribution of that nerve. The CMAP waveform is evaluated for onset latency, height, duration and appearance, all of which may be altered by neuropathy. Nerve conduction velocity can be calculated to assess nerve and myelin function. Finally, repetitive nerve stimulation can be performed to test the neuromuscular junction. In animal with myasthenia gravis, no abnormalities are noted on EMG or nerve conduction study, however, there is a successive decrement in amplitude of CMAP with supramaximal repetitive nerve stimulation. Electrodagnostic evaluation may provide presumptive diagnosis in diseases such as polyradiculoneuritis or may direct the clinician to pursue nerve or muscle biopsy.

The differential diagnosis of neuromuscular disease can be complex. The differential list is best generated by looking at the onset of signs (acute vs. chronic) and the distribution of deficits (focal, multifocal, diffuse). Myasthenia gravis, polymyositis, rhabdomyolysis, polyradiculoneuritis, tick paralysis and botulism all cause acute, severe generalized neuromuscular dysfunction. Chronic progressive generalized neuromuscular dysfunction is seen with degenerative myopathies, idiopathic peripheral neuropathy, metabolic neuropathy, and paraneoplastic neuropathy. Focal deficits are seen with disorders such as idiopathic facial paralysis, masticatory muscle myositis and hypothyroid neuropathy. Patchy or multifocal neuropathy is often a characteristic of perineural lymphoma or inflammatory neuropathy.

For any patient with generalized or focal neuromuscular disease, a minimum database of CBC, urinalysis, chemistry profile including creatinine kinase (CK) activity and thyroid profile should be collected. Thoracic radiographs and abdominal ultrasound should be considered to evaluate for a paraneoplastic disorder and to look for megaesophagus. If a diagnosis is not forthcoming then referral for electrodiagnostics, CSF analysis or nerve/muscle biopsy should be considered.
Myopathy

Polyomyositis

Generalized inflammatory muscle disease (polymyositis) may be seen with certain infectious agents but is most commonly seen as an autoimmune disorder. Organisms that have been associated with polymyositis in dogs and cats include *Toxoplasma gondii*, *Neospora caninum*, *Sarcocystis* sp., *Hepatozoon americanum*, *Leptospira* sp. and occasionally rickettsial disease. Autoimmune polymyositis can be seen in any dog but is more commonly seen in Newfoundland dogs, Boxers, Kooikerhondje and Vizlas. In Boxers, polymyositis may be seen a preneoplastic condition that precedes the development of lymphoma. Clinical signs of polymyositis include tetraparesis with a stilted gait, dysphagia or megaesophagus, generalized atrophy, dysphonia, fever and muscle pain (myalgia). Serum creatinine kinase activity is often moderately elevated (>10X normal). Definitive diagnosis of polymyositis is made based on muscle biopsy and infectious disease testing. If infectious etiologies can be excluded, then therapy is directed at immunosuppression. Prednisone (1 mg/kg BID) is usually effective in improving clinical signs in the acute phase. Adjunct therapy with azathioprine, mycophenolate or cyclosporin is often necessary since idiopathic polymyositis is most commonly seen in medium to large breed dogs and these animals do not tend to tolerate high dose prednisone (e.g. severe polyuria, polydipsia, polyphagia).

Rhabdomyolysis

Acute rhabdomyolysis is an occasional cause for severe muscle weakness, muscle swelling, pain and marked elevation of serum CK. Potential causes include drugs (statins, gemfibrozil, azathioprine), toxins (rattlesnake bite, hornet or Africanized bee sting), heatstroke, malignant hyperthermia and metabolic derangements, particularly hypokalemia. Therapy is often directed at supportive care unless a correctable metabolic abnormality is identified. Myoglobin is released following disruption of the muscle fiber cell membrane and is excreted in the urine giving an unmistakable “Coca-cola” appearance. Fluid diuresis is necessary to prevent renal damage from myoglobin (pigment nephropathy). If rhabdomyolysis is recurrent or a cause of rhabdomyolysis cannot be identified, muscle biopsy should be considered to look for underlying myopathies that may cause rhabdomyolysis.

Masticatory muscle myositis (MMM)

Myositis of the muscles of mastication may be seen in dogs because of autoantibodies against type IIM muscle fibers. Most patients present for severe bilateral atrophy of the muscles of mastication and trismus. Unilateral atrophy of the muscles of mastication is more suggestive of a trigeminal nerve sheath tumor. Definitive diagnosis of MMM is usually made based on a positive anti-IIM antibody titer (sensitivity 85-90%, specificity 100%) or muscle biopsy if the titer is negative/equivocal. MMM may be seen alone or in combination with polymyositis or extra-ocular myositis. Treatment is immune suppression usually with a combination of prednisone and azathioprine or mycophenolate mofetil. Antibody titers can be serially followed, and medications tapered or discontinued if there are consistently negative titers. Some dog will have persistent or borderline titer and require long term or lifetime therapy with low dose prednisone and/or azathioprine.

Neuromuscular junction disorders

Myasthenia gravis

Acquired myasthenia gravis (grave muscle weakness) is the most common disorder of the neuromuscular junction in small animals. Clinical signs develop due to autoantibodies against the nicotinic acetylcholine receptors (AChR) disrupting normal neuromuscular transmission. Congenital myasthenia gravis (MG) is rare and stems from a deficiency in the AChR. Myasthenia gravis may be focal, generalized, or fulminating. Focal myasthenia gravis causes primarily dysphagia and megaesophagus leading to clinical signs of regurgitation. Weight-loss and aspiration pneumonia are common sequelae to focal MG. Animals with generalized MG manifest signs of severe, fatigable
muscle weakness. More than 85% of dogs with generalized MG also have megaesophagus or dysphagia. Dysphonia, laryngeal paresis, and facial paralysis or fatigue of the palpebral reflex may also be seen. Fulminating MG is characterized by rapidly progressive generalized weakness, esophageal dilation, hypoventilation and respiratory failure. Myasthenia gravis has been reported in approximately 20% of dogs and 50% of cats with thymoma. The prognosis for generalized myasthenia gravis in dogs is guarded with a reported 41% mortality/euthanasia rate in dogs and 58% in cats.

The diagnosis of MG may be made presumptively by response to acetylcholinesterase inhibitors such as edrophonium (Tensilon) or pyridostigmine (Mestinon). Definitive diagnosis for acquired MG is usually based on a positive serum titer for anti-acetylcholine receptor antibodies. Seronegative acquired MG is uncommon unless the patient has been pretreated with corticosteroids. Repetitive nerve stimulation may be suggestive of MG but requires general anesthesia which puts the patient at risk for aspiration pneumonia.

Treatment for MG usually entails pyridostigmine (1-3 mg/kg BID) since this increases acetylcholine levels at the neuromuscular junction and improves muscle strength. Some dogs with MG will go into spontaneous remission and respond to pyridostigmine as sole therapy. The use of corticosteroids for canine MG is controversial, however, since the underlying etiology is autoimmune, some form of immune suppression should be considered unless contraindicated by severe aspiration pneumonia. In cases with mild aspiration pneumonia, drug such as azathioprine (2 mg/kg PO q 24 hours for 2 weeks then q 48 hours) or mycophenolate mofetil (10-15 mg/kg PO BID) may be used since they do not suppress neutrophil function. Anti-AChR antibody titers should be monitored periodically and if there is clinical and serologic remission then immunosuppressive medications are gradually tapered.

Tick paralysis

Severe neuromuscular weakness may develop secondary to a neurotoxin secreted by certain tick species. In the US, Dermacentor variabilis and andersoni have been associated with tick paralysis, most commonly in the mid-Atlantic coastal states. The onset of signs is 5-9 day post-bite, causing fulminating neuromuscular weakness. Flaccid tetraparesis or tetraplegia develops with decreased spinal reflexes. Recovery is often rapid (2-3 days) after removal of the tick. Unlike polyradiculoneuritis, there is no spinal hyperesthesia. Megaesophagus and cranial nerve deficits are only seen in extremely severe cases. Empiric treatment with fipronil (Frontline) or an isoxazoline (Nexgard, Simparica, Bravecto) should be considered in cases of acute generalized neuromuscular weakness due to the potential for tick paralysis.

Neuropathy

Polyradiculoneuritis

A syndrome of fulminating polyradiculoneuritis (PRN) is seen in dogs causing progressive tetraparesis, flaccid muscle tone, and diminished tendon reflexes. Acute PRN has been well documented in Coonhounds following the bite of raccoon (“Coonhound paralysis”). The disease appears to develop secondary an antigen in raccoon saliva that stimulates autoimmune attack on the ventral nerve root and peripheral nerve. Polyradiculoneuritis may, however, develop in any breed and without interaction with a raccoon. Clinical signs of weakness often start in pelvic limbs and ascend to the thoracic limbs. In severe cases, tetraplegia and hypoventilation may occur. Cranial nerve deficits and megaesophagus are not seen although many dogs will develop signs of hyperesthesia. Diagnosis is often based on clinical signs and the exclusion of other neuromuscular diseases. CSF may demonstrate an elevation in protein but no evidence of inflammation. Electrodiagnostics, particularly F-waves, aid in the diagnosis of PRN. Treatment is supportive care and the prognosis is often good if hypoventilation does not develop. The time for recovery is variable and in severe cases it may take months for the dog to walk again.

Paraneoplastic or Neoplastic neuropathy
Progressive generalized peripheral neuropathy and weakness has been reported as a paraneoplastic syndrome secondary to certain malignancies such as pancreatic beta cell tumor ("insulinoma") and lymphoma. Lymphoma may also cause multifocal peripheral or cranial neuropathy due to lymphoblastic infiltration of the perineurium. Malignant peripheral nerve sheath tumors will typically have a history of insidious lameness and/or monoparesis.

**Metabolic neuropathy**

Hypothyroidism may cause neurologic dysfunction due to cerebrovascular disease or peripheral neuropathy. Sciatic neuropathy, facial paralysis/paresis and peripheral vestibular disease have all been associated with hypothyroidism in dogs. Generalized peripheral neuropathy is seen with hypothyroidism because of demyelination and axonal degeneration although the exact mechanism is uncertain. Cranial neuropathy is thought to develop secondary to myxedematous changes in the tissue around the skull foramina causing nerve compression. Deficits usually improve with thyroid therapy, but residual dysfunction is common.

Diabetes mellitus is a common cause of peripheral neuropathy in both humans and animals. Sciatic neuropathy is the most common manifestation in animals, and this is more frequently seen in cats. Numerous mechanisms have been suggested for diabetic neuropathy and oxidative stress is thought to play a major cause. There is no specific therapy for diabetic neuropathy other than regulation of underlying diabetes mellitus. Gabapentin or pregabalin may help with sensory manifestations of diabetic neuropathy.