The Flaccid Dog

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The peripheral nervous system (PNS) consists of those structures (including cranial nerves and spinal nerves) containing motor, sensory and autonomic nerve fibers or axons that connect the central nervous system (CNS) with somatic and visceral end organs. Lower motor neuron weakness refers to a lesion of the ventral spinal cord gray matter and its axon coursing to the muscle through the spinal nerve roots, peripheral nerve and across the neuromuscular junction.

A motor unit is composed of a neuron cell body, its axon, the neuromuscular junction, and associated muscle fibers. A group of myofibers innervated by one neuron is considered a motor unit. An abnormality in any portion of the motor unit can result in clinical signs of neuromuscular disease – lower motor neuron. The functional component of the motor unit involves the reflex arc. The arc consists of a sense organ, an afferent neuron (cell body in dorsal root ganglion), one synapse or more centrally, an efferent neuron, and an effector organ. An all-or-none action potential is generated in the afferent nerve and modulated centrally to be generated again as an all-or-none potential in the efferent nerve. The arrival of the action potential at the axon terminal triggers release of acetylcholine, producing an end-plate potential which if enough causes the postsynaptic membrane to depolarize.

Establishing an accurate diagnosis is based on following a logical sequence of diagnostic tests. History provides the signalment, presenting clinical signs, background, and time of onset and temporal progression of clinical signs. Specifically, disorders of the motor unit with acute onset include polyradiculoneuritis, tick paralysis, botulism and fulminant myasthenia gravis. Myopathic and neuromuscular junction (i.e., myasthenia gravis) diseases often are episodic in onset. The term fatigability describes when one or more muscles become weaker with repetitive but normal use and may imply neuromuscular junction disease. History is especially important for determining exposure to toxins. Often the diagnosis of an acute neuromuscular disease is determined by the history.

A physical examination is performed to localize the clinical signs and detect other systemic abnormalities. The neurologic examination will establish existence of peripheral nervous system disease and further assist with determining disease symmetry and distribution (focal, multifocal or diffuse). The neurologic examination should include sensory testing especially when determining the extent of traumatic neuropathy. Clinical signs of lower motor neuron weakness manifest as paresis or paralysis, hyporeflexia to areflexia and muscle atrophy that is severe and rapid in onset. Acute onset lower motor neuron diseases often have muscle flaccidity. Acute peripheral neuropathy of cranial nerves can occur with focal, multifocal or diffuse (polyneuropathy) disease. Proper neuroanatomic localization is crucial to the direction of the diagnostic approach.

Neuropathy. Peripheral neuropathies that involve the motor nerve and nerves roots often manifest hallmark signs of LMN disease with impairment of motor function. Motor neuropathies are characterized by a flaccid paresis or paralysis, postural reaction deficits, neurogenic muscle atrophy and reduced to absent spinal reflexes. Muscle fasciculations, spasms, and cramps also can occur. Neurogenic muscle atrophy is rapid and severe occurring within 1 to 2 weeks from onset of clinical signs and can progress to joint contracture in chronic cases.
Neurogenic atrophy results from a loss of the trophic influence of the axon; denervation results in a loss of this trophism and consequently atrophy develops. As an aside, muscle atrophy is a clinical feature for Wallerian degeneration and axonal degeneration, but not for pure myelopathies (axons still remain intact). Tremors also can be a clinical feature with some pure myelopathies.

Gait disturbances are a reflection of weakness and are not a result of incoordination. Often animals with lower motor neuron dysfunction will have a shortened stride and an inability to support weight associated with the appendicular and axial musculature. Limb tone is reduced and flaccidity often becomes more apparent in the distal limbs. Limb posture will be crouched with tendency for joints to be flexed. Neck flexion also signifies generalized weakness. Dogs with just distal polyneuropathy often show a high-steppage or pseudohypermetric pelvic limb gait. This represents a compensatory response to allow the carpi or tarsi to “flip” forward for limb placement. It is not uncommon for polyneuropathy to first manifest as paraparesis before tetraparesis because the longer (sciatic nerve) and more myelinated proprioceptive fibers usually are affected first.

Loss of tendon and flexor withdrawal reflexes is a sign of peripheral nerve disease. Early in acute polyneuropathy, the reflexes may be diminished but not absent, but become more reduced over time. Reflexes can be diminished out of proportion to weakness because of greater involvement of the large afferent fibers of muscle spindles. Consequently, the loss of reflexes is a result of greater dysfunction of the afferent limb of the reflex arc.

Polyneuropathy can also present with multiple cranial nerve deficits. Cranial nerves V, VII, VIII, IX, X, and XI usually are involved.

Myopathy. Skeletal muscle is composed of slow (type I) and fast (type II) twitch myofibers relatively resistant to fatigue. Cats also have fast twitch fatigable myofibers. Myofibers utilize energy from glycogen in anaerobic conditions. Mitochondrial fatty acid oxidation is ideal for sustained exercise requiring endurance. The hallmark clinical sign of myopathy is weakness. Clinical signs can be persistent or episodic and exercise-induced. Gait often is stiff and short-strided. Cats will show an inability to jump. A unique clinical sign in cats is flexion of the neck. Generalized muscle atrophy can be a feature for some myopathies; alternatively muscle hypertrophy develops in some conditions. Likewise, the distribution can be focal or generalized. Muscle pain (myalgia), failure of muscles to relax (myotonia), and sudden muscle contraction (cramp) also suggest muscle disease. Proprioception and spinal reflexes are normal unless the disorder is severe and diffuse.

Neuromuscular Junctionopathy. Electrical transmission of impulses down the motor nerve is converted to chemical transmission as the nerve synapses with the muscle – neuromuscular junction. As the impulse conveys to the end of the motor terminal, calcium is released into the presynaptic bouton. Increased Ca²⁺ concentration destabilizes the storage vesicles which allow fusion of the vesicle to the presynaptic terminal membrane. The acetylcholine (ACh) containing vesicles dock and fuse with the plasmalemma at the synaptic cleft region. The process results in exocytosis of ACh into the synaptic cleft. Nicotinic receptors are located in skeletal muscle. Once released from the presynaptic terminal, ACh diffuses to the post synaptic membrane of the myofiber and binds to nicotinic ACh receptors (AChR). Binding of ACh to these receptors increases Na⁺ and K⁺ conductance of the membrane and resultant influx of Na⁺ produces a depolarizing potential called the end plate potential (EPP). The EPP causes depolarization of the
adjacent muscle membrane. The muscle action potential subsequently initiates a muscle contraction. There is an overabundance of available ACh and AChRs; this excess is referred to as the safety margin of neuromuscular transmission. The safety margin insures that there will be more than enough ACh to perform neuromuscular transmission. At higher concentrations of ACh, the accumulation of ACh may result in fibrillation of muscle fibers. This is a result of sustained muscle membrane depolarization causing neuromuscular junction blockade.

Disorders affecting the neuromuscular junction are presynaptic or postsynaptic and sometimes both. These processes may increase or decrease the activity at the NMJ by the following: 1) increasing or decreasing presynaptic ACh release by altering ACh synthesis, transport, reuptake or presynaptic release; 2) altering the concentration or duration of ACh in the synaptic cleft by altering removal of ACh from the synaptic cleft; and 3) acting as an ACh agonist or antagonist at the NMJ by affecting the interaction between ACh and the postsynaptic receptor.

**Diagnostic Approach**

Establishing an accurate diagnosis is based on following a logical sequence of diagnostic tests. History provides the signalment, presenting clinical signs, background, and time of onset and temporal progression of clinical signs. Specifically, disorders of the motor unit with acute onset include polyradiculoneuritis, tick paralysis, botulism and fulminant myasthenia gravis. Myopathic and neuromuscular junction (i.e., myasthenia gravis) diseases often are episodic in onset. Signalment is especially important in young animals with a predilection for breed-specific neuropathies. A physical examination is performed to localize the clinical signs and detect other systemic abnormalities. The neurologic examination will establish existence of peripheral nervous system disease and further assist with determining disease symmetry and distribution (focal, multifocal or diffuse). The neurologic examination should include sensory testing.

A complete blood count, serum chemistry (including creatine kinase concentration and electrolytes) and a urinalysis serve to establish a baseline health profile and further identify other systemic abnormalities. Thoracic radiography may show evidence of concurrent megaesophagus and aspiration pneumonia which can be a sequela of peripheral neuropathy. Additionally, thoracic radiography and abdominal ultrasonography are used to screen for underlying metastatic disease and evidence of paraneoplastic neuropathy. CSF analysis will show abnormalities in cellularity and protein concentration with some peripheral neuropathies. Serology is useful to evaluate for infectious and immune mediated diseases. Endocrine function testing, especially thyroid hormone will further delineate underlying cause of the neuropathy.

Electrophysiology is useful for determining disease localization within the motor unit and extent of the disease process. Temporal development of neuropathies has important implications for diagnostic yield of the electrophysiologic examination. Neuropathic disease needs to be present for 3 to 7 days before evidence can be detected by electrodiagnostic examination.

Briefly, electromyography (EMG) will assess electrical activity within a discrete region of an accessible muscle. The activity is recorded by inserting a needle electrode into the muscle. The pattern of electrical activity in muscle has been characterized and abnormalities have been correlated with some disorders at different levels of the motor unit. Relaxed muscle normally shows no spontaneous electrical activity except in the end-plate region, but various types of abnormal activity occur spontaneously in diseased muscle. Typically, abnormalities caused by denervation occur on EMG with axonal disease but not pure demyelinating disorders.

Nerve conduction studies provide a technique of confirming presence and extent of
peripheral nerve damage. Studies of several types of acquired and hereditary axonal and demyelinating neuropathies have shown different patterns of distribution to further assist with differential diagnosis. **Motor nerve conduction studies** are performed by recording the electrical response of a muscle to stimulation of its motor nerve at two or more points along its course. This permits the conduction velocity, amplitude and duration of action potentials to be determined in the fastest-conducting motor fibers between the points of stimulation. Results may give an indication of altered function of axons and myelin. **Sensory nerve conduction studies** are performed by determining the conduction velocity and amplitude of action potentials in sensory fibers when these fibers are stimulated and responses recorded at another point along the course of the nerve.

Histopathologic examination of a muscle biopsy specimen is a critical part of the evaluation of a motor unit disease and can indicate whether the underlying weakness is neurogenic or myopathic in origin. With neuropathic disease, myofibers can show angular atrophy, small and large grouped atrophy, fiber-type grouping if denervation has been followed by reinnervation, replacement of muscle fibers by fatty tissue, and pyknotic nuclear clumps in end-stage disease. In myopathic disease, pathologic changes can include variability in fiber size, necrosis and phagocytosis, cellular infiltrations, connective tissue expansion, cytoarchitectural abnormalities, and inclusions and vacuoles.

A properly processed peripheral nerve biopsy often provides insight into the pathologic process of peripheral nerve disease. Techniques for collection of nerve biopsies have been described in detail, but often consist of a fascicular biopsy. Evaluation of resin embedded semi-thin sections provides the most information regarding axonal degeneration and regeneration, demyelination and remyelination, and abnormalities of supporting structures. In selected cases electron microscopy, teased nerve fibers, and nerve fiber morphometry can provide additional information. Processing of peripheral nerve biopsies for only paraffin or frozen sectioning provides very limited information.
### Differential Diagnosis of Acute Generalized Lower Motor Neuron Disorders

<table>
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<th>Pathophysiology</th>
<th>Clinical Signs</th>
<th>Tests/Treatment</th>
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<tr>
<td>Polyradiculoneuritis</td>
<td>Immune-mediated disease of the ventral roots and spinal nerves causing segmental demyelination and degeneration of both axons and myelin.</td>
<td>Develop in 7 to 14 days after raccoon exposure (or not); early signs include pelvic limb paresis progressing as ascending weakness or paralysis; develops quickly over 24 to 48 h; cranial nerve involvement uncommon; some animals show hyperesthesia.</td>
<td>Clinical course is 3 to 6 weeks and longer; may need to support respiration; muscle atrophy may not resolve; supportive care.</td>
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<td>Rabies</td>
<td>Transmitted by saliva of an infected animal with rabies virus. Retroaxonal transport of the rabies virus.</td>
<td>Average incubation 3-8 weeks; Acute ascending flaccid paralysis. Incubation period is &lt;3 weeks; multiple animals exposed; progressive, symmetric LMN disorder with both cranial and spinal nerve involvement; severity varies with amount of tissue.</td>
<td>Diagnosed by history / clinical signs; LMN paralysis with behavior changes; post-mortem direct FA nervous tissue.</td>
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<td>Botulism</td>
<td>Most cases in dogs is type B toxin from clostridium botulinum, inhibits release of acetylcholine from the terminals of cholinergic nerve fibers.</td>
<td>Incubation period is &lt;6 days; multiple animals exposed; progressive, symmetric LMN disorder with both cranial and spinal nerve involvement; severity varies with amount of tissue.</td>
<td>Can identify toxin in feces and serum; supportive care; clinical course 1-3 days.</td>
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<td>Tick paralysis</td>
<td>Neurotoxin secreted by feeding ticks that inhibits depolarization at the terminal or blocks presynaptic release of Ach at the neuromuscular junction. USA – <em>Demacentor andersoni a variabilis</em>; clinical signs develop 7 to 9 days after tick attachment; early ataxia that rapidly progresses to paralysis; cranial nerve involvement rare.</td>
<td>USA – <em>Demacentor andersoni a variabilis</em>; clinical signs develop 7 to 9 days after tick attachment; early ataxia that rapidly progresses to paralysis; cranial nerve involvement rare.</td>
<td>Diagnosed by rapid improvement after tick removal.</td>
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<td>Myasthenia gravis</td>
<td>Acquired form is an immune-mediated blockade of nicotinic AchR resulting in depletion of receptors of the postsynaptic portion of the NMJ.</td>
<td>Acute fulminant MG can cause: LMN disease causing generalized weakness and cranial nerve abnormalities.</td>
<td>Serologic testing for AchR antibodies, tensilon testing, support ventilation; pyridostigmine (1-3 mg/kg q 8-12h); Immunosuppression (controversial).</td>
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<tr>
<td>Organophosphate/ carbamate</td>
<td>Long acting anti-cholinesterase irreversibly binds in nervous tissue, muscle. ACh accumulates and receptors causing blockade.</td>
<td>Overstimulation of autonomic nervous system and NM dysfunction; stiff, rigid gait, muscle tremors and fasciculation.</td>
<td>Atropine sulfate 0.2 mg/kg total; PAM 10-15 mg/kg IM q 8 to 12 h; diphenhydramine counters nicotinic effects.</td>
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<tr>
<td>Coral snake evenomation</td>
<td>NMJ blockade.</td>
<td>Acute ascending flaccid paralysis, hypothermia, depression, reduced nociception, loss of reflexes.</td>
<td>Supportive care; ventilatory support may be needed. Prognosis - excellent.</td>
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**Polyradiculoneuritis (Coonhound Paralysis)**

Frequently occurs in hunting dogs that have been exposed to raccoons. Raccoon saliva is believed to alter the peripheral nerve antigenicity, resulting in inflammation and demyelination. Also is seen in dogs with no exposure to raccoons, suggesting that other factors (viruses, drugs, vaccines) can incite a similar immune reaction. *Ventral roots and motor axons* are preferentially involved. Analogous to a peripheral neuropathy of humans referred to as Landry-Guillain-Barré syndrome.

*Clinical Signs* – Typical ascending LMN paralysis, with paresis occurring 7 to 14 days after the raccoon bite and progressing to tetraplegia in 2-10 days. Diffuse spinal hyporeflexia and hypotonia. Neurogenic muscle atrophy is evident after 7-10 days. Generalized hyperesthesia may be seen. No sensory deficits. Cranial nerves usually are spared. The recurrent laryngeal nerve may be affected.

*Diagnosis* – Diagnosis is based on clinical signs and exclusion of other causes of acute onset tetraparesis. Characteristic EMG findings distinguish coonhound paralysis from other acute progressive LMN diseases. Denervation activity on EMG is seen after 5-7 days from onset of signs. Motor nerve conduction velocity is decreased indicating myelin involvement. Serology is used to rule out other infectious causes, i.e. protozoal.

*Treatment* – There is no definitive treatment. Supportive care is necessary to prevent decubitus ulcers and urine scald. Rarely, assisted ventilation may be indicated if respiratory compromise is severe. Physical therapy includes hydrotherapy, ROM exercises and sling support.

*Prognosis* – The prognosis for recovery is usually good. The clinical course is usually 3 to 6 weeks but may be prolonged up to 2 to 4 months or longer. Improvement begins by the third week, and complete recovery may take 6 to 8 weeks. In patients that develop severe muscle atrophy, recovery will be prolonged and may not be complete. Neurologic signs usually abate in the reverse order of development. Relapses have been observed. Some dogs appear to be particularly susceptible to recurrences.

**Tick Paralysis**

Neurotoxin secreted by tick species, *Dermacentor andersoni*, *D. variabilis*, and *Ixodes spp.* Blocks the release of acetylcholine at the neuromuscular junction. The toxin may also alter ionic fluxes that mediate action potential production. Clinical signs are acute and develop 7 to 9 days after attachment of the tick.

*Clinical signs* – Clinical signs develop 7 to 9 days after attachment of the tick. The earliest clinical sign is marked ataxia with rapid progression to paresis, paralysis, areflexia, and hypotonus. In the United States, cranial nerve involvement is rare. Nystagmus is occasionally observed. Death can occur from respiratory failure if the ticks are not removed. Painful stimuli normally are perceived. In Australia, affected dogs or cats develop more severe signs. Asymmetric signs are not uncommon with *Ixodes holocyclus*. Respiratory failure and autonomic signs occur with greater frequency in these animals than in those from the United States. In the Australian syndrome, clinical signs may progressively worsen, even though the ticks have been removed. In the U.S. syndrome, dramatic improvement follows tick removal.

*Diagnosis* – is based on clinical findings, identification of a tick and reversal of clinical signs after removal of the tick.

*Treatment* – Paresis is usually improved within 24 to 48 hours after bathing with insecticide and tick removal.

*Prognosis* – Prognosis is favorable in cases without respiratory signs.
Botulism
Clinical signs of botulism occur from ingestion of spoiled food or carrion contaminated with the exotoxin of Clostridium botulinum. Types C and D are most common carnivores. The toxin is internalized in the presynaptic terminal and blocks the presynaptic release of acetylcholine which subsequently blocks neurotransmission at both somatic and autonomic neuromuscular junctions. Clinical signs – The incubation period is less than 6 days. Clinical signs are those of a progressive, symmetric, generalized LMN disorder. Severity varies with the amount of toxin ingested and ranges from mild generalized weakness to tetraplegia with respiratory failure. Both cranial and spinal nerves are affected. Cranial nerve signs include mydriasis with decreased pupillary light reflexes, decreased jaw tone, decreased gag reflex, decreased tongue movements, decreased palpebral reflexes and change in bark and vocalization. Megaesophagus and intestinal ileus also can occur in dogs with botulism. Decreased anal sphincter tone and urinary bladder function also occur. In dogs, the usual clinical course is less than 14 days. Diagnosis – Botulism must be suspected in animals with acute progressive LMN disease. Botulism is especially likely when multiple animals are affected. Given the clinical similarities to other acute LMN diseases such as tick paralysis and polyradiculoneuritis, a definitive diagnosis of botulism is difficult to make. The toxin may present in feces early in the disease course. Treatment – Treatment of botulism is largely supportive. To be effective, the specific antitoxin must be administered before the botulinum toxin binds to receptors at the neuromuscular junction. This approach is rarely possible because signs usually are present before the animal is treated. Polyvalent products that contain type C antitoxin generally are not available. The efficacy of antibiotic therapy has not been proven. Ventilatory support may be necessary in some dogs. Mildly affected animals recover without therapy. Prognosis – Prognosis is generally favorable but guarded in animals with signs of respiratory distress and dysautonomia.

Myasthenia Gravis
Acquired myasthenia gravis (MG) is an immune-mediated disorder in which autoantibodies against nicotinic acetylcholine (ACh) receptors of skeletal muscle result in impairment of neuromuscular transmission. This is manifested clinically as muscle weakness. Antibodies bind to the ACh receptor which is amplified by release of complement and a cell-mediated cytotoxic response at the endplates. The postsynaptic membrane is destroyed and neuromuscular transmission is disrupted. The decreased number of functional ACh receptors increases chance of failure of neuromuscular transmission. With repetitive firing of a motor nerve ending, stores of ACh are depleted; the few available ACh receptors are soon bound with ACh molecules and desensitized to further stimulation. This is the physiologic basis for fatigability which is a common clinical sign of patients with MG. It has been suggested that molecular mimicry of the ACh receptor by a short sequence of a bacterial or viral protein could initiate the immune response. The thymus is suspected to be the site of initiation of the autoimmune response to ACh receptors in MG. Clinical Signs – Classic presentation of a dog with acquired MG is episodic, generalized muscle weakness that is worsened by exercise and improves with rest.
### Diagnosis

**Diagnosis – Immunoprecipitation Radioimmunoassay** is the **gold standard test** which uses radioactive iodinated α-bungarotoxin-labeled canine ACh receptors to quantitatively identify circulating antibodies directed against ACh receptors [Comparative Neuromuscular Laboratory, Dr. Diane Shelton, University of California-San Diego]. A titer result of > 0.6 nmol/L in dogs and > 0.3 nmol/L in cats is compatible with a diagnosis of acquired MG. This test should be performed before administering corticosteroids to prevent false negative results.

Edrophonium chloride (Tensilon) is an ultra-short-acting anticholinesterase agent. The drug provides more ACh molecules to interact with the available ACh receptors to improve muscle strength. A presumptive diagnosis of acquired MG may be made if a patient responds positively to IV injection of 0.1 to 0.2 mg/kg of edrophonium. A patient that demonstrates obvious improvement in muscle strength shortly after edrophonium is considered to have a positive response but the improvement only lasts for a few minutes. Administering edrophonium is not without risk. Overadministration of anticholinesterase agents is referred to as **cholinergic crisis**. Overstimulation of ACh receptors can produce depolarizing neuromuscular blockade and subsequent worsening of muscle weakness. Overstimulation of muscarinic ACh receptors can cause bronchoconstriction and bradycardia along with the SLUDD effect. The clinician should pretreat the patient with IM or SC atropine (0.02-0.04 mg/kg) and have the drug available for immediate IV administration to counteract undesirable muscarinic side effects. Since atropine is an antimuscarinic agent, the nicotinic receptors will still respond to the effects of edrophonium.

### Therapeutic Options

**Therapeutic Options** – In acquired MG, there are 3 major aspects of therapeutic intervention: anticholinesterase therapy, immunomodulatory therapy, and thymectomy. Approximately, 50% of cases may go into spontaneous remission given time. In veterinary medicine, anticholinesterase therapy is most widely accepted. Long-acting anticholinesterase drugs prolong the action of ACh at the neuromuscular junction by reversibly inhibiting acetylcholinesterase. This often provides improvement in muscle strength within the first few days of therapy. The agent most often used is pyridostigmine bromide (0.5 to 3.0 mg/kg every 8 to 12 h by mouth). To avoid overstimulation of ACh receptors, patients are started at the low end of the dose which is gradually increased as needed. Oral pyridostigmine is available in tablet and syrup form. In dogs with severe megaesophagus, intramuscular neostigmine bromide can be administered at 0.4 mg/kg. The dosages are titrated based on changes in muscle strength.

Excessive amounts of anticholinesterase drugs, results in the accumulation of ACh and cause fibrillation of muscle fibers. Paradoxical muscle weakness may occur as a result of this neuromuscular blockage of the motor endplate. Additionally, excessive stimulation of muscarinic receptors also will cause SLUDD (cholinergic crisis). This may be difficult to distinguish from worsening of the MG (myasthenic crisis) which also will reflect as profound muscle weakness. Edrophonium can be used to differentiate between these conditions. If the patient shows no relief or worsens with edrophonium, most likely anticholinesterase therapy is excessive. The drug should be temporarily discontinued and dosage lowered.

It also is important to avoid drugs that may affect the neuromuscular junction. These agents may act presynaptic, synaptic, postsynaptic or in combination. These drugs include

| Megaesophagus alone or with facial, pharyngeal and laryngeal weakness | Predominantly pelvic limb involvement with mild to moderate weakness. Weakness also in thoracic limb. Megaesophagus often present. | Profound appendicular muscle weakness with varying degrees of cranial nerve involvement; acute onset and rapid ascending tetraparesis and respiratory distress |
penicillamine, antimicrobial agents (aminoglycosides, ciprofloxacin, erythromycin, imipenem), pyrantel pamoate, β adrenergic antagonists, calcium channel blockers, antiarrythmic drugs, neuromuscular blocking drugs, and others.