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WHAT EVERY PRACTITIONER SHOULD KNOW ABOUT MUSCLE DISEASE

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INTRODUCTION
It is easy to overlook myopathies in dogs and cats unless the signs are extreme because patients do not complain of muscle pain, and measurement of creatine kinase (CK) is often used as the sole determinant of the presence of muscle disease. However, the early recognition and detailed evaluation of skeletal muscle disease is important in animals with a variety of systemic diseases as it can be the first sign of a serious underlying disorder (e.g., hypokalemic myopathy and renal disease in cats).1 This manuscript will review the physiology of skeletal muscle contraction and discuss the diagnostic approach to myopathies using clinical examples to provide context.

PHYSIOLOGY OF MUSCLE CONTRACTION
Myofibers are filled with contractile protein filaments (primarily actin and myosin) that lie adjacent to each other and are linked to each other and to the sarcolemma (the cell membrane) by complex groups of associated proteins. Muscle contraction is a result of depolarization of the excitable membrane (sarcolemma) by rapid influx of sodium ions causing release of calcium from large intracellular stores into the intracellular space. Calcium triggers energy dependent movement of actin and myosin filaments relative to each other via conformational changes in the associated proteins. Relaxation occurs when the calcium is removed from the intracellular space by energy dependent pumps. For efficient functioning, skeletal muscle is dependent on the correct extracellular ion concentrations and functional ion channels (for depolarization and calcium release to occur), adequate energy supplies, and correct linkage of the intracellular and transmembrane proteins. The primary source of energy within myofibers is oxidative phosphorylation occurring in mitochondria using fatty acids as the primary energy source, but anaerobic metabolism producing lactic acid as a by product can also occur. Muscle dysfunction occurs when there are disturbances of energy supply, electrolyte imbalances, ion channel disorders and abnormalities in many of the different proteins that produce effective contraction while maintaining the integrity of the cell (e.g. dystrophin).2,3 As a result, a wide variety of metabolic, toxic, infectious, inflammatory and degenerative myopathies occur. Table 1 below lists the more common myopathies by disease mechanism.

Many different myopathies have been recognized in specific breeds of dog and cat and these are regularly updated in neurology texts. If faced with a young animal exhibiting signs of a progressive myopathy, it is worthwhile to do a literature and a web search under the breed of dog/cat to see if there have been recent descriptions of new disease syndromes in particular breeds.

<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>DISEASE</th>
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<tr>
<td>Degenerative</td>
<td>Muscular dystrophies, Labrador retriever myopathy, Myotonia</td>
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<tr>
<td>Metabolic</td>
<td>Mitochondrial myopathies, Hyper and hypothyroidism, Hyper and hypoadrenocorticism, Hypokalemia</td>
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<td>Nutritional</td>
<td>Vitamin E deficiency</td>
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<td>Inflammatory</td>
<td>Polymyositis, Masticatory myositis, Extraocular myositis, Dermatomyositis</td>
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<td>Infectious</td>
<td>Protozoal, viral, bacterial and rickettsial</td>
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<td>Idiopathic</td>
<td>Fibrotic myopathy, Exercise induced collapse in Labrador retrievers</td>
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<tr>
<td>Vascular</td>
<td>Thromboembolic disease. (e.g. iliac thrombosis)</td>
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CLINICAL SIGNS
Signs of skeletal myopathies include generalized weakness, exercise intolerance, muscle atrophy or hypertrophy, muscle cramps, stiff gait, regurgitation (as a result of megaesophagus), muscle fasciculations and muscle pain. It is important to recognize that muscle hypertrophy can occur with myopathies. This can result either from increased or repeated muscle contraction (as occurs with myotonia) or from sarcolemmal tearing (because the response of the myofiber to tearing is to hypertrophy).3 By the same token, it is easy to understand why animals with myopathies may be weak and exercise intolerant, but it is important to remember that some myopathies result in a stiff gait that improves with exercise (such as myotonia). Signs of pneumonia are not uncommon in myopathic animals because of mega-esophagus and regurgitation. Animals that also have dysfunction of the pharyngeal muscles will be particularly at risk of aspiration and owners will often report that their pet seems to choke when it tries to eat.

DIAGNOSIS
Initial evaluation of the myopathic case includes careful examination of the gait, exercise tolerance and a full neurological examination (to rule out a primary neuropathic cause of the problem). Muscle disease should not be ruled out if muscles do not appear to be painful, as this is an insensitive test in companion animals. The heart should be evaluated as many generalized myopathies can affect cardiac muscle, and special attention should be paid to any mention of vomiting, regurgitation or dyspnea, as involvement of the esophagus can lead to potentially fatal aspiration pneumonia. Routine laboratory tests include a complete blood cell count, a serum biochemistry panel (that includes creatine kinase [CK]), and urinalysis. Mild elevations of CK are non-specific and often not significant, however, they should not be ignored in animals with other signs of generalized muscle disease, particularly if they are persistently elevated. It is important to note that serum CK levels increase when the sarcolemma becomes permeable.
(CK is a cytosolic enzyme). Thus, myopathies that do not affect the sarcolemmal integrity do not cause a significant elevation in CK. CK has a short half life (2-4 hours) and is therefore rapidly cleared from the circulation. By contrast, aspartate amino transferase, (AST), while not as specific as CK, is also released into the circulation when muscle damage occurs and has a longer half life the CK (12 hours). AST concentrations may therefore remain elevated after CK concentrations have returned to normal. Alanine amino transferase (ALT) serum concentrations may also be elevated with very severe muscle necrosis (for example, in X-linked muscular dystrophy). Thoracic radiographs should always be obtained in dogs to rule out megaesophagus. In some animals, endocrine testing such as a thyroid panel (with both free T4 and TSH levels measured), or an ACTH stimulation test may be indicated. If a systemic disease that could cause the myopathic signs is identified it should be addressed at this point. If not, further diagnostic testing is indicated. Genetic tests are becoming available for inherited diseases, and there is a test available for myotonia in the Miniature Schnauzer at the University of Pennsylvania.

The main alternatives for further evaluation of muscle include electrophysiological testing, muscle biopsy and metabolic testing. Electrophysiological testing, primarily electromyography (EMG), is usually performed by neurologists and is not routinely available to general practitioners. An EMG records the electrical activity within the muscle, and is most commonly performed with the animal under general anaesthesia. Voluntary muscle contraction cannot be evaluated in the anaesthetized animal but the presence of spontaneous electrical activity can be recorded and the type and distribution of spontaneous activity can help to establish a diagnosis or simply to identify which muscles are affected. EMG findings provide specific diagnosis of diseases in which involuntary muscle contraction occurs such as myotonia. Myopathies as diverse as muscular dystrophy and polymyositis result in less specific electrophysiological changes (fibrillation potentials, positive sharp waves, complex repetitive discharges) that facilitate mapping the extent of the disease. Nerve conduction studies can be performed to determine the amplitude of the motor unit potential that can be elicited by stimulation of the nerve, and to rule out a neuropathic component.

Muscle biopsy is the only method of determining the presence and type of muscle pathology and as such is an invaluable diagnostic tool. It is important that the correct muscle is selected for biopsy and that arrangements have been made for appropriate tissue processing and evaluation. The muscles biopsied should be affected but not end stage, and so severely atrophied fibres with no electrical activity on EMG should be avoided. It is advisable to biopsy both a thoracic and pelvic limb muscle. The biopsy should be at least 1cm long (running parallel to the myofibres) and 0.5cm wide, and should be handled only at the ends to avoid damaging the tissue. Prior to performing the biopsy, a laboratory experienced at muscle histopathology should be identified. Typically they will request that the muscle sample is placed in a gauze swab moistened with saline and shipped overnight on ice. At the laboratory the muscle will be snap frozen and sectioned using a cryostat. Working with frozen tissue allows the different enzymes important to muscle function to be evaluated histochemically: this is not possible in formalin fixed tissue. The pathologist may be able to establish a definitive diagnosis from the muscle biopsy (e.g. protozoal myositis, muscular dystrophy) or may be able to classify the pathology for example as inflammatory, metabolic, or degenerative and recommend further tests if appropriate.

Further metabolic evaluation is indicated in animals with exercise intolerance or pathological changes indicative of a primary metabolic problem (for example, changes in mitochondrial numbers, morphology and distribution, excess lipid accumulation). Skeletal muscle relies primarily on beta oxidation of fatty acids to generate ATP and disorders of beta oxidation may result in accumulation of fatty acids in the urine. A sample of frozen urine can be sent to certain laboratories for measurement of organic and amino acids. Failure of oxidative phosphorylation may cause depletion or accumulation of lactic or pyruvic acid and acidaemia. This can be determined by measuring arterial blood pH and lactate and pyruvate levels before and immediately after exercise. It is important to exercise until clinical signs appear and to identify a laboratory that can perform these assays prior to taking the samples. It is also important to be prepared to provide supportive care in case of emergency.

**TREATMENT GUIDELINES**

Treatment of myopathies is dependent on the disease, and the success of treatment will depend both on the disease type (for example, X-linked muscular dystrophy carries a poor prognosis) and the severity of the disease. The presence of regurgitation complicates treatment and worsens prognosis because aspiration pneumonia can be fatal. Severe muscle atrophy, particularly if contractures develop, can seriously impact the animal's motor function in the long term, whether or not the underlying disease is successfully treated. Protozoal infections are treated with a prolonged course (4 - 6 weeks) of antibiotics such as clindamycin, or trimethoprim sulfadiazine. Systemic metabolic disorders causing myopathic signs should be treated primarily (for example, treatment of hyperadrenocorticism) and electrolyte imbalances should be corrected (e.g. hypokalaemia). Immune mediated myositis is treated using immunosuppression⁷ (for example, prednisone at 2 - 4 mg/kg/day for 2 weeks, then half the dose every month until on 0.25-0.5mg/kg every other day). All patients need supportive care including range of motion exercises and controlled exercise to maintain or improve muscle mass. Supplements such as L-carnitine (50 mg/kg PO q12hrs), and co-enzyme Q10 (100 mg PO q24hrs) are commonly recommended in animals with myopathies no matter what the cause, and are particularly appropriate if a metabolic myopathy is suspected. Feeding from a height or placement of a PEG tube may be indicated in animals with megao-esophagus.

**SUMMARY**

It is important to note that many different systemic diseases affect muscle and to be aware of the emerging breed specific myopathies. Although general practitioners cannot perform an electrophysiological examination of muscle function, if the specialist laboratories are identified to process and interpret samples, it is possible to obtain muscle biopsies and perform a metabolic screen. Early identification and treatment of myopathies before severe muscle loss occurs increases the chances of recovery and can avoid potentially fatal complications such as aspiration pneumonia.
REFERENCES


