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DISORDERS OF THE PERIPHERAL NERVOUS SYSTEM

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INTRODUCTION

This expansive group of disorders includes diseases of peripheral nerve, skeletal muscle, and the neuromuscular junction (NMJ). It is of utmost importance for the clinician to be able to discern a patient as having a peripheral (PNS) versus central (CNS) nervous system disorder. In general, neuropathies are characterized by poor reflex activity and decreased muscle tone. Patients with myopathies often have evidence of weakness (often exercise-related), normal reflexes and sensory function (e.g., proprioception, nociception), muscle atrophy, and myalgia. Neuromuscular junction disorders are often typified by generalized weakness with normal sensory function. These characteristic features are far from absolute; it may be difficult to distinguish whether a particular animal is afflicted by a neuropathy, myopathy, or NMJ disorder (junctionopathy). As a group, the diagnostic tests directed at arriving at a diagnosis are similar, regardless of the specific disease. These tests include electromyography (EMG), nerve conduction velocity (NCV) studies, repetitive nerve stimulation (RNS -mainly for junctionopathies), and muscle/nerve biopsies. A complete discussion of all the PNS disorders is beyond the scope of this presentation. Several selected neuropathies and myopathies will be discussed, in addition to a discussion of acquired myasthenia gravis (MG).

SELECTED NEUROPATHIES

Paraneoplastic neuropathy These neuropathies are believed to develop as an indirect, rather than a primary effect of the underlying neoplasia. The pathogenesis of this phenomenon is unknown, but several hypotheses exist. Potential explanations include elaboration of some neurotoxic factor by the tumor, disruption of axonal and/or Schwann cell metabolism by the tumor, and an immunologic reaction to antigens shared by the neoplasm and peripheral nerve elements (i.e. innocent bystander reaction). A paraneoplastic polyneuropathy has been reported occasionally with pancreatic insulinomas, and the potential exists for the associated hypoglycemia to be responsible for the neuropathy.

However, peripheral nerves are particularly resistant to the effects of hypoglycemia and peripheral neuropathy has not been associated with any other disease that results in hypoglycemia. The hypoglycemia is probably not a major contributing factor to the neuropathy. Clinical signs are variable and may range from a subclinical neuropathy to severe LMN tetraplegia. The existence of this phenomenon makes it imperative to rule out the existence of neoplasia in animals presenting with neuropathies, especially older patients. Diagnosis of an insulinoma is usually based upon an abnormal amended serum insulin/glucose ratio, and sometimes identifying the pancreatic tumor via ultrasound or exploratory laparotomy. Treatment is directed toward the underlying neoplasia. There is no specific treatment for the associated neuropathy.. The prognosis for recovery from paraneoplastic neuropathies (assuming adequate control of the primary tumor) in dogs and cats is presently unknown. In people with paraneoplastic neuropathies, the prognosis is often poor for recovery. Prognosis for control of the underlying neoplasia depends largely upon tumor type and location.

Acute idiopathic polyradiculoneuritis (coonhound paralysis). An idiopathic inflammatory disorder primarily involving both axons and myelin of ventral nerve roots occurs in dogs, and is probably one of the most common polyneuropathies in this species. Although much less common, an analogous polyneuropathy has been described in cats. Varying degrees of axonal and myelin loss in motor nerves explain the characteristic clinical signs. There is evidence that axonal loss is more prominent than demyelination in most dogs with polyradiculoneuritis. Demyelination is thought to be most severe in the ventral nerve roots in dogs, with minimal myelin loss in the major nerve trunks.

Although the pathogenesis is uncertain, an autoimmune process is suspected. The term *coonhound paralysis* refers to those dogs with a history of being bitten or scratched by a raccoon shortly before developing clinical signs of disease. The term *idiopathic polyradiculoneuritis* refers to patients with an identical clinical disorder, but

with no possible exposure to raccoons. These two subcategories probably reflect the same disease syndrome, with the trigger for the inflammatory process being as yet unidentified in the latter subcategory. The typical clinical scenario for acute idiopathic polyradiculoneuritis describes a rapidly developing LMN paresis/plegia, usually beginning in the pelvic limbs, and eventually involving the thoracic limbs. Most affected animals will progress to being either non-ambulatory tetraparetic or tetraplegic within 10 days of initial onset of clinical signs. It is not uncommon for this stage of dysfunction to be reached within a 72 hour period of time. Development of life-threatening respiratory paralysis is a concern, especially in the more rapidly developing cases. Loss of voice (dysphonia, aphonia) is common and some patients will also exhibit facial weakness. Spinal reflexes are typically absent (with the exception of the perineal reflex, which is normal), muscles are hypotonic, and neurogenic atrophy develops quickly in recumbent patients. Proprioceptive placing reactions will be normal in those animals that still have enough motor ability to perform the efferent limb of these tests. These patients retain the ability to urinate and defecate, and will readily eat and drink if the head is supported. Pain sensation also remains intact. In fact, these animals often seem hyperesthetic upon limb manipulation, which may reflect the inflammatory nature of the disease. In dogs with coonhound paralysis, there is a history of an encounter with a raccoon approximately 1-2 weeks prior to the onset of clinical signs. In patients with idiopathic polyradiculoneuritis, identical clinical features are present as described, with no possibility of a raccoon scratch or bite. Many, if not most of these dogs will exhibit abnormal EMG activity with normal motor nerve conduction velocities (MCV).

The patients often do not have enough functional axons to ambulate, but the remaining axons have essentially normal myelination. CSF examination may demonstrate increased protein levels. There is no specific therapy for this disease. Glucocorticoids have been suggested, but there is no evidence of efficacy. Nursing care, physical therapy, and proper nutrition are essential for recovery. The inflammatory phase of this disorder is believed to be transitory, but the damaged axons need to remyelinate and, to some degree, regrow. The prognosis for full recovery is often favorable, but it is typically prolonged, usually taking several weeks to several months. Some patients develop life-threatening respiratory paresis/paralysis in the acute phase of the disease (usually those dogs whose signs progress rapidly over 72 hours) and may need to be mechanically ventilated. Re-exposure to raccoons is to be avoided in dogs having recovered from coonhound paralysis, as this may trigger a relapse of disease symptoms.

Chronic inflammatory demyelinating polyneuropathy (CIDP) This is a suspected autoimmune polyneuropathy of mature dogs and cats (mean age of 67 years) that has recently been described. An analogous neuropathy occurs in people. This disorder is believed to be one of the more common neuropathies in dogs and cats. A polyneuropathy very similar to CIDP, referred to as chronic relapsing polyneuropathy, has been described in cats. Clinical signs of insidiously progressive LMN paresis, with abnormal proprioception and normal sensation have been described in CIDP and chronic relapsing polyneuropathy. The course of the disease is typically chronic, and patients tend to spontaneously recover and relapse. Clinical signs of dysfunction often occur in the pelvic limbs initially, then progress to involve the thoracic limbs. The spectrum of potential clinical signs of dysfunction is broad and may include depressed spinal reflexes, muscle atrophy, paraparesis, tetraparesis, and tetraplegia. Diagnosis is based upon historical and clinical features consistent with the disease, in conjunction with nerve/muscle biopsy results. Response to therapy (see below) also contributes to diagnosis.

The predominant pathologic feature seen in nerve biopsies from these patients is evidence of demyelination and remyelination. Inflammatory cells have consistently been identified in ultrastructural studies of nerve biopsies from CIDP patients. Evidence of inflammation was lacking in nerve biopsies from patients with chronic relapsing polyneuropathy. Axonal degeneration is not a feature of CIDP, but was evident on nerve biopsy of one cat with chronic relapsing polyneuropathy. The prognosis is guarded to good. Most animals with CIDP and chronic relapsing polyneuropathy tend to be responsive to glucocorticoid therapy.

In a recent report, 90% of dogs, and 88% of cats with CIDP exhibited an initial positive response to oral prednisone therapy (1-2 mg/kg body weight, every 12 hours). Patients may relapse coincident with reduction of glucocorticoid dosage or discontinuation of glucocorticoid therapy. Some animals that initially respond to glucocorticoid therapy may subsequently become resistant to such treatment. If a positive response to glucocorticoid therapy is demonstrated in a patient with suspected CIDP or chronic relapsing polyneuropathy, dose reduction should proceed slowly. The author has treated several kittens with a condition very similar to CIDP-these patients responded to immunosuppressive therapy.

Toxic neuropathies: Delayed organophosphate toxicity in cats-a polyneuropathy associated with prolonged exposure to chlorpyrifos has been described in cats. The mechanism by which the organophosphate causes the neuropathy is unknown. The reported cats exhibited varying degrees of decreased thoracic and pelvic limb proprioception, decreased spinal reflexes, generalized hyperesthesia, and paraparesis. Bilateral papillary dilation (partially responsive to light) was also reported. Diagnosis in the reported cases was based upon history (exposure to organophosphates), decreased serum cholinesterase activity, neurologic exam findings, and an

abnormal EMG. Treatment consisted of intravenous pralidoxime (2-PAM) and subcutaneous atropine. The cats recovered completely. *Walker hound mononeuropathy*-An unusual neuropathy involving the peroneal and tibial nerves of one pelvic limb has been described in unweaned Walker hound puppies. There was degeneration of both axons and myelin in the peroneal and tibial nerves. The cause is undetermined, but a toxic agent in well water used to prepare milk replacement is suspected.

Clinical signs occurred at approximately 2 weeks of age and included paresis, lack of proprioception, absent spinal reflexes, muscle atrophy, and analgesia (except on the medial aspect of the limb), all in one pelvic limb. Progressive signs of worsening paresis as well as automutilation of the affected limb occurred over a 6 week period. Diagnosis is based upon history, signalment, clinical findings, and results of histopathologic evaluation. All of the reported puppies were euthanized due to the progressive nature of the disease. *Salinomycin toxicity in cats*- a severe polyneuropathy has been reported in cats in the United Kingdom and the Netherlands that had eaten food contaminated with the chicken ionophore coccidiostat, salinomycin. An acute, progressive polyneuropathy occurred in affected cats.

Clinical signs of neurologic dysfunction included paraparesis, tetraparesis, dysphagia, dyspnea, and generalized muscle atrophy. Paralysis of the pelvic limbs characteristically developed initially, followed by paralysis of the thoracic limbs. Diagnosis was based on clinical signs consistent with a polyneuropathy in cats exposed to food contaminated with salinomycin. Evidence of a distal axonopathy affecting both motor and sensory nerves was evident on histopathologic evaluation of nerve samples. Many of the earliest reported cases were euthanized due to disease severity. However, removal of contaminated food and provision of supportive therapy is likely to lead to a full neurologic recovery in the majority of affected cats.

SELECTED MYOPATHIES

Myotonia congenita -This disorder is probably inherited as an autosomal recessive trait in Chow Chow dogs and Miniature Schnauzers. Other breeds reported with a similar condition include Staffordshire terrier, Rhodesian Ridgeback, Great Dane, West Highland White terrier, Samoyed cross, and Labrador retriever. Myotonia congenita has recently been described in six domestic shorthaired kittens. The four kittens in one report were from separate litters, but the queens of those litters were related. The discerning clinical feature of this disorder is sustained muscle contraction after cessation of voluntary movement. Failure of muscle relaxation is believed to be due to abnormal sarcolemmal chloride conductance.

The decreased chloride conductance leads to hyperexcitability of the muscle membrane. Subsequent accumulation of potassium ions in the T-tubule system is responsible for sustained muscle contraction following initial depolarization. Abnormal sarcolemmal chloride channels, due to an autosomally inherited genetic defect, have been demonstrated as the cause of myotonia congenita in the Miniature Schnauzer. There are several forms of myotonia congenita in humans, some of which are due to abnormal sodium conductance across the sarcolemma. Clinical signs are usually appreciated when affected puppies and kittens begin to ambulate. Affected animals typically appear worse after a period of rest. Cold temperatures also tend to cause exacerbation of clinical signs. The gait is stiff, and tends to improve or even normalize with activity. The pelvic limbs are often more severely affected than the thoracic limbs; in canine myotonia, they may be advanced simultaneously in a "bunny-hopping" fashion. It may be difficult for affected dogs to flex the stifle joints. The thoracic limbs are often held abducted while ambulating, due to decreased ability to flex the proximal limb joints. Myotonic patients may have difficulty rising from a sternal position. Myotonic kittens tend to snag their claws when walking on carpet. When myotonic kittens are startled, they may hyperextend all four limbs and fall into lateral recumbency for approximately 10 seconds. Startling in these kittens may also result in bilateral prolapse of the nictitans, blepharospasm (due to spasm of the orbicularis oculi muscles), flattening of the ears, and retraction of the lips. Generalized muscle hypertrophy (especially proximal appendicular and neck muscles and the tongue in dogs, gastrocnemius muscles most prominent in cats) is often appreciated and percussing the muscle may leave an indentation, referred to as a "myotonic dimple".

Some patients will exhibit dysphagia and respiratory problems (e.g. stridor) because of sustained contraction of pharyngeal and laryngeal musculature, respectively. Affected kittens may exhibit signs of dysphonia, characterized by a hoarse meow and quiet purr. Unusual physical characteristics apparent in all of a group of related myotonic Schnauzers were prognathism (shortened mandible), and medially displaced canine teeth. Diagnosis is based upon signalment, characteristic clinical signs, and electrodiagnostic findings (EMG abnormalities). CK levels are often either normal or only mildly elevated, and changes on muscle biopsy are usually mild and nonspecific (e.g. variation in myofiber size). Muscle biopsy results may contribute to the diagnosis, but may not be worth the risk of anesthesia in these patients. Anesthesia may be both difficult and dangerous due to stenosis of the laryngeal glottis. Also, people with myotonia are predisposed to anesthetic-induced malignant hyperthermia. The characteristic finding on EMG is bizarre high frequency discharges that wax and wane. These discharges are frequently referred to as "dive-bombers", due to their waxing and waning nature. Others have likened their sound to a motorcycle engine. There is some evidence that using membrane-stabilizing

agents may be helpful in relieving clinical signs in myotonic dogs. Procainamide is thought to be more effective than phenytoin or quinidine.

Other drugs that have been used to treat myotonia in dogs include carbamazepine, tocainide, nifedipine, and mexiletine hydrochloride. Environmental modification alone is recommended to control clinical signs in myotonic cats. These kittens tend to be well managed without drug therapy, and drugs typically used to control canine myotonia have unacceptable toxicity risks in cats. Myotonia congenita is not considered a progressive disease, and clinical signs of dysfunction tend to stabilize between 6-12 months of age. In general, most dogs and cats with myotonia congenita are not severely disabled, and therefore the prognosis for long-term survival is favorable. The prognosis for sustained improvement of clinical signs of myotonia is guarded, however.

Autoimmune polymyositis This is an autoimmune inflammatory disease of unknown pathogenesis primarily affecting the appendicular muscles. It is more commonly reported in dogs than cats. While there is usually no identifiable cause for the immune response, systemic lupus erythematosus, the use of trimethoprim-sulfa drugs in Doberman Pinschers, and thymomas (usually in conjunction with acquired myasthenia gravis), have all been associated with the development of this condition. While any age or breed dog can be affected, most are middle-aged large breed dogs of either sex.

A group of seven Newfoundland dogs with autoimmune polymyositis, ranging in age from 6 months to 5 years of age, was recently described. Clinical signs may be acute or chronic and may include generalized weakness that is often worsened by exercise, hyperesthesia upon muscle palpation (myalgia), regurgitation (due to megaesophagus), dysphagia, depression, fever, muscle swelling acutely, muscle atrophy chronically, shifting leg lameness, and voice change. None of the reported Newfoundlands exhibited myalgia. Diagnosis is based upon typical clinical findings, as well as results of various diagnostic tests.

CK levels may be elevated, EMG examination typically reveals abnormalities, and muscle biopsy reveals myofiber necrosis, phagocytosis, and regeneration, with a non-suppurative inflammatory infiltrate. Immunoglobulin localization to the sarcolemma may also be demonstrable immunohistochemically. Treatment consists of oral prednisone therapy at immunosuppressive doses (e.g. 1-2 mg/kg, q 12 hours) until clinical remission is achieved, with subsequent tapering of the dose. The prognosis is generally favorable, although relapses may occur.

Masticatory myositis This is an autoimmune disorder in which antibodies are directed against the muscles of mastication (e.g. temporalis, masseter, pterygoid muscles). The pathogenesis of this disease is uncertain, but the distinct myosin isoform and myofiber type (Type II M) of masticatory muscles may explain why they are preferentially targeted by the immune response. These Type II M myofibers have a different embryologic origin (branchial arch mesoderm) than appendicular myofibers (paraxial mesoderm), and are believed to be antigenically distinct from these latter fiber types. Dogs of numerous breeds (usually large breeds) and both sexes have been reported with this disorder, but the German Shepherd dog seems to be particularly predisposed. Most dogs with masticatory myositis are young adults. Cats are rarely reported with this disorder. Clinical signs typically include painful swelling of the masticatory muscles and varying degrees of trismus. The clinical signs are often acute in onset and may be recurrent.

Exophthalmos and fever are also occasionally observed. Palpation of the masticatory muscles and attempts to force the jaws open often elicit a painful response. Some dogs have a history of chronic masticatory muscle atrophy without obvious painful swelling. These dogs may represent a more chronic form of masticatory myositis, neurogenic atrophy from trigeminal neuritis, or a distinct atrophic myopathy of masticatory muscles. Diagnosis of masticatory myositis is attained by demonstrating antibody localization to Type II M myofibers with the immunoreagent Staphylococcal protein A conjugated to horseradish peroxidase (SPA-HRPO). This can be done using frozen sections of the patient's temporalis muscle, or incubating the patient's serum with normal stored frozen canine muscle and the immunoreagent.

CK levels may also be elevated and EMG examination often reveals abnormalities. Muscle biopsies may reveal varying degrees of inflammatory infiltrates, and myofiber necrosis and phagocytosis. Treatment is immunosuppressive doses of prednisone (1-2 mg/kg per os, q 12 hours) for 3-4 weeks, after which the dosage is tapered to every other day. Tapering is slowly continued in order to achieve the lowest every other day dosage that will control clinical signs. Most dogs will show a favorable response to therapy, but relapses are common. In some cases, prednisone can be replaced by azathioprine as the maintenance immunosuppressant drug, relieving some or all of the side effects associated with glucocorticoid therapy. In general, the prognosis for this disease is favorable.

ACQUIRED MYASTHENIA GRAVIS

Acquired myasthenia gravis (MG) is the quintessential junctionopathy. It is an autoimmune disorder in which autoantibodies directed against nicotinic ACh receptors of skeletal muscle are produced, resulting in muscle

weakness. Focal, generalized, and acute fulminating forms of MG have been described in dogs and cats. Focal MG is characterized by the lack of obvious appendicular (limb) muscle weakness, Generalized MG patients exhibit obvious appendicular weakness. Acute fulminating MG is a rapidly progressing form of the disorder that is often fatal. Definitive diagnosis of MG is typically made via a positive serum test for circulating autoantibodies directed against the nicotinic ACh receptor. Treatment consists of anticholinesterase agents, often combined with immunosuppressive therapy. Prognosis is guarded, generally being more favorable in cases in which megaesophagus is absent or corrected with therapy.

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