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THE WEAK DOG: IS IT MEDICAL OR SURGICAL?

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Generalized weakness, or weakness involving part to the body can provide significant diagnostic challenges. Many body systems can be lead to a clinical picture of weakness, including endocrine, cardiovascular, skeletal and respiratory systems. Determining the origin of the problem will be largely based on taking a history, performing a physical and neurological examination, and judicious use of laboratory testing.

From the perspective of the neurologist, generalised weakness is usually caused by lesions in one of the following locations:

- Cranial
- Cervical spine (C1-C5)
- Cervico-thoracic spine (C6-T2)
- Generalized peripheral neuro-muscular system.

Cranial diseases have the potential to cause generalized weakness, but it would be usual to have other signs indicating brain involvement. Animals with forebrain disorders often walk reasonably well and have good strength, but have significant sensory (proprioceptive) deficits. Lesions in the brainstem cause more severed gait abnormalities with profound hemi-paresis or asymmetrical tetraparesis. In bilateral diseases it can be difficult to determine the location of the lesion.

Cervical spinal disorders involving either C1-C5 or C6-T2 cord segments can lead to weakness, which is sometimes more severe in the forelimbs. Proprioceptive deficits in all limbs are usual, though this function can be spared in C6-T2 lesions. The full range of spinal cord diseases can be involved. Severe cord lesions such as those seen in the thoracolumbar region are not frequently encountered in the cervical spine; animals with such severe disease usually die of respiratory failure. Pain is a common feature of cervical spinal disease.

The peripheral neuromuscular system presents the biggest challenge to most clinicians. Whereas the general clinical picture of spinal disease is familiar to most, peripheral neuromuscular disorders are less well recognized.

DISORDERS OF THE NEUROMUSCULAR JUNCTION

The neuromuscular junction (NMJ) connects the peripheral nervous system to the skeletal muscles. Dysfunction at the neuromuscular junction leads to varying degrees of locomotor disturbance from episodic weakness to flaccid quadriplegia. There are a number of clearly defined disorders of the neuromuscular junction in dogs and cats

Transmission of the electrical impulse from the axon to the muscle fibre may be disturbed at a number of locations. Clinical disorders may be characterized according to the site of the conduction failure. Presynaptic disorders result in a decrease in the quantity of ACh released. This occurs, for example, in tick paralysis, botulism and the Lambert-Eaton myasthenic syndrome in man. Postsynaptic disorders are due to interference with the ACh receptor activation mechanism, as in congenital and acquired myasthenia gravis. Finally, certain toxins, such as organophosphorus compounds interfere with the enzymatic pathways in the neuromuscular junction.

The majority of animals with neuromuscular junction disorders will present with varying degrees of locomotor disturbance. This may be exercise-induced weakness, stiffness or flaccid paralysis. Differential diagnoses for these presenting signs include metabolic, cardiovascular and neurological diseases. Neuromuscular junction disorders may be a later consideration but some conditions have readily defined patterns and thus are more easily recognised. In some circumstances, the presenting signs may not be immediately suggestive of locomotor disease. This is especially true in some cases of myasthenia gravis, which present initially with regurgitation because of megaoesophagus.

The fundamental sources of diagnostic information, the history and clinical examination, are prerequisites in all cases. Care must be taken to eliminate other causes of episodic weakness, particularly cardiovascular and endocrine diseases. The neurological examination must be thorough with particular attention being paid to conscious proprioception, reflex function, muscle tone and muscle size. The animal should be encouraged to walk or run to the limit of its tolerance. A note of the time taken until collapse or cessation of exercise should be made.

Summary of signs that may seen in each of the locations

<table>
<thead>
<tr>
<th>Cranial</th>
<th>Cervical Spine</th>
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<tbody>
<tr>
<td>Locomotor disorders</td>
<td>Hemi- or tetra paresis</td>
</tr>
<tr>
<td>Cranial nerve palsies</td>
<td>Neck pain</td>
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<tr>
<td>Behavioral change</td>
<td>Intact spinal reflexes</td>
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<tr>
<td>Head tilt</td>
<td></td>
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<tr>
<td>Seizures</td>
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<tr>
<td>Cervico-thoracic Spine</td>
<td>Peripheral Neuromuscular</td>
</tr>
<tr>
<td>Hemi- or tetra paresis</td>
<td>LMN signs all limbs (hindlimbs often worse)</td>
</tr>
<tr>
<td>Low neck pain</td>
<td>Dysphonia</td>
</tr>
<tr>
<td>Intact spinal reflexes hindlimbs, LMN signs forelimbs (may be restricted to muscle atrophy)</td>
<td>Dyspnoea</td>
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<tr>
<td></td>
<td>Dysphagia</td>
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Laboratory Assessments. Routine laboratory information is of limited value, although it will assist in eliminating some conditions. The serum creatine kinase (CK) concentration is a useful indicator of muscle diseases and should be part of the data base. Blood for creatine kinase measurement should be collected prior to any electrophysiological tests or muscle biopsy as these procedures may artificially raise the blood concentration. The detection of serum antibodities to ACh receptors strongly suggests a diagnosis of myasthenia gravis. Whilst this test is not absolutely specific, it has an important role in the diagnosis of this disease. Examination of various materials (blood, faeces etc.) for evidence of botulinum toxin may be useful if this disease is suspected. Assessment of serum concentrations of acetylcholinesterase similarly may be informative in cases where organophosphorus toxicity is suspected. However, routine use of these compounds may lower cholinesterase concentrations without clinical signs of toxicity.

Provocative Testing. Another useful diagnostic test in patients with episodic weakness is the "edrophonium response test". Edrophonium chloride is a short acting anticholinesterase agent. Antagonism of cholinesterase potentiates the activity of ACh at the NMJ, thus increasing strength for a short period in some diseases. The animal is exercised to its limit and the time taken to collapse noted. A dose of 0.25 to 10 mg of edrophonium chloride is administered intravenously. Most cases of myasthenia gravis respond dramatically to the drug by rising promptly and walking for several minutes. Some care in the interpretation of this test is necessary as nonspecific improvements may be seen in other neuromuscular disorders.

Electrophysiology. Electrophysiological testing has an important role in the evaluation of neuromuscular junction disorders. Electromyography (EMG), motor nerve conduction and sensory nerve conduction studies will assist in ruling out peripheral neuropathies and myopathies.

PRESYNAPTIC DISORDERS

Botulism

The exotoxins produced by Clostridium botulinum are potent neurotoxins. Ingestion of as little as 0.05mg may be fatal in humans, although dogs are more resistant. A number of exotoxins exist that affect various species differently. Type C toxin most often affects dogs. Ingestion of contaminated foodstuffs is the primary route of exposure, which may account for the high prevalence in foxhounds. Clinically, the animals present with acute, progressive quadriaparesis or quadriplegia. Neurological evaluation reveals lower motor neurone-type deficits in all limbs. There is hypotonia and markedy reduced reflexes in the limbs. Cranial nerves may be involved leading to dysphagia, dysphonia and facial weakness. Affected dogs can also be systemically ill. Pain sensation is preserved (Cornelissen, Haagsm & van Ness, 1985).

Most evidence suggests that the defect in neuromuscular function is presynaptic in origin. Acetylcholine is synthesized appropriately but the toxin interferes with the release mechanism. Although calcium transport is normal, there is a lack of response to the calcium. The toxin may bind irreversibly to a receptor in the nerve terminal. Thus, if recovery occurs, axonal sprouting and reinnervation may be necessary (Pearlman, 1990). Electrophysiological abnormalities have been reported in dogs with botulism, with positive sharp waves and fibrillation potentials seen during the recovery phase. It is speculated that the lack of ACh release and the subsequent reduction in number of miniature end plate potentials may deprive the muscle of some trophic influence, thus resulting in spontaneous electrical activity. Also, evidence of peripheral nerve dysfunction has been documented (Van Ness, 1986). Reductions in amplitude of the compound muscle action potential were seen, with later increase in these amplitudes corresponding to clinical improvement. Also noted were reduced nerve conduction velocities, possibly a result of axonal disease related to interference with retrograde axonal transport.

Diagnosis of botulism may be confirmed by the identification of toxin in serum, vomitus or faeces. Identification of the contaminated foodstuff may be useful. Treatment is essentially supportive although the use of penicillin and polyvalent clostridial antitoxin have been suggested. The antitoxin available in the USA only acts against toxins type A,B & E. Thus it is of no value against the common toxin in dogs, which is Type C. The prognosis is guarded, but affected dogs may improve with aggressive supportive therapy.

Tick Paralysis

Tick paralysis is an acute, progressive lower motor neurone-type quadriaparesis or quadriplegia that occurs following tick attachment to a patient. Various species of tick are incriminated in different parts of the world (Kocan, 1988) with subsequent variation in the severity of the disease produced. In Australia, for example, affected animals may have sensory and autonomic involvement in addition to motor deficits (Ilkiw et al, 1987). The ticks release a salivary neurotoxin, which interferes with ACh release, thus leading to decreased neuromuscular transmission.

Diagnosis is confirmed by finding a tick attached to the affected animal and noting rapid improvement following removal. If tick paralysis is suspected, the animal should be treated topically with a suitable insecticide. Swallowing difficulties may be seen, thus food and fluids should not be given by mouth until recovery has occurred. The prognosis is good if the tick is removed promptly, with recovery occurring rapidly in many patients. However, some more severe cases may have a prolonged recovery, for example, where Ixodes holocyclus is the tick involved as occurs in Australia.

POSTSYNAPTIC DISORDERS

Acquired Myasthenia Gravis

This is the most common neuromuscular junction disorder of dogs but is unusual in cats. The condition closely parallels that seen in man. Typically, affected dogs suffer exercise induced weakness that improves following rest. The weakness may be profound leading to collapse. Many dogs have megaoesophagus with associated regurgitation and possible secondary aspiration pneumonia. Occasional cases present with regurgitation alone. The neurological examination is unremarkable during periods of normality following rest. However, once weakness is present, there are several important abnormalities. Conscious proprioception is intact, but this may be difficult to recognize unless the full weight of the animal is supported during the examination. It is possible to induce muscle fatigue by repeatedly stimulating the palpebral reflex with eventual loss of the ability to blink. In people, ptosis and ocular movement disorders may be the only clinical sign in myasthenia gravis.
Various breeds are affected, although the GSD is over-represented. There are peaks of incidence at 2-3 years old and 9-10 years old with females more frequently affected in the older group (Shelton, 1989b).

Acquired myasthenia gravis is a result of immune-mediated interference with neuromuscular transmission. Antibodies are generated against the postsynaptic ACh receptor. These antibodies fix to the receptor, although not to the ACh binding site itself but to the main immunogenic region, resulting in an immune-mediated lysis of the receptor. Morphological changes including a reduction in the number of ACh receptors, a widening of the synaptic cleft and alterations in the postsynaptic folds are apparent by electron microscopy of the NMJ. The initiating factor that leads to anti-ACh receptor antibody production is unknown, although the possibility that endogenous ACh receptors are responsible has been speculated (Pearlman, 1990).

One interesting relationship in human myasthenia gravis is the presence of thymic abnormalities in a high proportion of patients. Because of this, thymectomy is a common procedure used to treat human myasthenia gravis. Thymic disease has been noted in some animals with the myasthenia gravis. Therefore, thoracic radiography should be performed to investigate this possibility as well as the presence of aspiration pneumonia.

The edrophonium response test is often used to attempt to confirm the diagnosis of myasthenia gravis. Dogs with generalized myasthenia gravis usually improve dramatically following administration and are able to exercise normally for several minutes. However, the test is not completely reliable and should not be used as the sole method of reaching a diagnosis. Repetitive nerve stimulation may show a decremental response. Assay for circulating ACh receptor antibody is useful in confirming the diagnosis, although the concentration of antibody in the serum is not proportional to the severity of the clinical signs. Approximately 15% of myasthenic dogs do not have elevated ACh receptor antibody concentrations, but other immunological tests on serum or muscle biopsy can identify immune complexes at the neuromuscular junction (Shelton, 1989a).

Myasthenia gravis in cats may present in a similar fashion, with exercise induced weakness. Cats may show regurgitation, alterations of voice, muscle tremors, neck flexion and loss of the palpebral reflex (Joseph et al, 1988). The disease preferentially affects Abyssinians and related breeds.

General treatment of myasthenia gravis is by the administration of anticholinesterase drugs, which prolong the action of ACh in the neuromuscular junction and thus improve muscle strength. Pyridostigmine bromide (0.5 - 3.0 mg/kg/day) is given orally. If regurgitation is present, thus making oral dosing difficult, a lower dose may be given by intramuscular injection. The dose of one-thirtieth of the oral dose is suggested in man. The use of corticosteroids is indicated because of the immune mediated nature of the disease. Corticosteroids must be avoided if pneumonia is present and should not be used until the lung disease has resolved. Overdosing with anticholinesterase drugs may precipitate a cholinergic crisis with excessive muscarinic side effects, which may be controlled with atropine.

The prognosis for many dogs with myasthenia gravis is good. They can be managed by drug therapy and in some the medications may be reduced or stopped after several months. However, regurgitation may persist requiring attention to feeding methods and the presence of pneumonia is a poor prognostic sign. Cats appear to carry a rather more guarded prognosis as response to therapy is less predictable. Successful treatment of myasthenia gravis has been reported in the cat, with corticosteroid therapy at immunosuppressive doses (Cuddon, 1989).

Congenital myasthenia gravis

Congenital myasthenia gravis is a rare disease seen in springer spaniels, Jack Russell terriers, smooth fox terriers, samoyeds and occasionally in cats (Palmer, 1980; delLahunty, 1983; Miller et al, 1983; Joseph et al, 1988). The affected animals show weakness at a young age similar to that seen in acquired myasthenia gravis. The congenital form of myasthenia gravis is due to a deficiency or abnormality of the postsynaptic ACh receptor rather than an immune-mediated attack. Thus, circulating receptor antibodies are not present. Treatment with oral anticholinesterase drugs may be successful, but the prognosis is not as favourable as in acquired myasthenia gravis. The condition is inherited in an autosomal recessive mode in Jack Russell terriers and smooth fox terriers (Miller et al, 1984).

ENZYMATIC DISORDERS

Chemical compounds interfere with acetylcholinesterase, the enzyme that inactivates ACh in synapses. Particularly prevalent are the organophosphorus and carbamate insecticides, which irreversibly inhibit acetylcholinesterase. Cats are very susceptible to these compounds. The general clinical signs of organophosphorus toxicity manifest as autonomic nervous system over stimulation and neuromuscular dysfunction. Typically, animals have a stiff, rigid gait with muscle tremors and fasciculation. A peripheral neuropathy may occur in cats some time after exposure (Nafe, 1988). Historical features regarding misuse of insecticides are helpful in reaching the diagnosis. Serum cholinesterase concentrations may be measured, although even routine use of insecticides will depress these concentrations.

Fenthion toxicity differs from classical organophosphorus poisoning in that signs of weakness predominate with little evidence of autonomic dysfunction. Chronic exposure to fenthion may occur before clinical signs appear, and the onset of signs may be delayed (Nafe, 1988). Plasma cholinesterase concentrations are markedly depressed, often to 10% of normal.

Treatment is by reducing further absorption in acute cases, by bathing or gastric lavage as appropriate. Atropine is used to counteract the parasympathetic signs. Pralidoxime hydrochloride releases the acetylcholinesterase from the OP compound and is indicated in OP toxicity. However, it should not be used in carbamate toxicity. It has been reported to be useful, along with atropine, in cases of chlorpyrifos toxicity in cats (Jaggy & Oliver, 1990). Diphenhydramine has been recommended to relieve muscle weakness and tremors in fenthion toxicity (Clemmons et al, 1984). Here, absorption of the toxin is rapid, so attempts to remove it by bathing are unlikely to be useful. Several therapeutic agents are incubinated in neuromuscular junction dysfunction in man and a similar syndrome has been described in a dog following aminoglycoside administration (Oliver & Lorenz, 1983).
REFERENCES