MYASTHENIA GRAVIS *REVIEW AND CURRENT PERSPECTIVES*

Kathryn Winger, DVM, Diplomate ACVIM (Neurology)
Assistant Professor of Neurology
Department of Small Animal Clinical Sciences
College of Veterinary Medicine
Veterinary Medical Center, D-208
Michigan State University
East Lansing, MI 48824

The neuromuscular junction is the point of contact between the axon terminal and the muscle cell. As an action potential reaches the nerve terminal, a decrease in membrane potential occurs. This leads to a transient opening of pre-synaptic voltage-gated calcium channels. Calcium influx stimulates the release of acetylcholine in synaptic vesicles. Acetylcholine traverses the synaptic cleft and binds to post-synaptic receptors in the muscle sarcolemma. This binding opens sodium channels and the subsequent influx, should enough channels be open, results in muscle cell contraction. Each signal must be rapidly terminated in order to prepare the muscle for the next signal. The acetylcholine in the synaptic cleft is therefore rapidly eliminated by acetylcholinesterase.

Disorders of the neuromuscular junction, or junctionopathies, can be categorized as pre-synaptic, synaptic, or post-synaptic. These disorders often lack specific changes on routine histopathology, making them a diagnostic challenge. A clinical diagnosis is typically made based on patient history, examination findings, and biochemical, immunological, toxicological, and/or electrodiagnostic testing. Myasthenia Gravis is a junctionopathy that can be either congenital or acquired. It is characterized by focal or generalized muscle weakness, usually exacerbated by exercise. Facial, pharyngeal, laryngeal, and esophageal weakness can lead to dysphagia and regurgitation. Pelvic limb lameness, episodic collapse, hypersalivation, and regurgitation are frequent presenting complaints.

The neurological examination may be normal when the patient is rested. Myasthenia Gravis should be strongly considered in a non-ambulatory patient with normal postural reactions. With exercise, muscle weakness becomes more evident and reflexes may become fatigued. This is most apparent with the palpebral reflex, wherein repeated stimulation leads to poor palpebral fissure closure. A rare fulminant form of the disease exists. This remains a differential for acute lower motor neuron tetraparesis or tetraplegia.

ACQUIRED MYASTHENIA GRAVIS

Acquired Myasthenia Gravis is an immune-mediated disease that occurs spontaneously in adult dogs, and less commonly in cats. The incidence in dogs is bimodal, affecting predominantly young adult (2-4 years) and geriatric (9-13 years) patients, though animals of any age can be affected. Antibodies are directed against the acetylcholine receptors of the neuromuscular junction. More than half of the antibodies in clinical and experimental

cases develop against a conformation dependent subunit of the receptor called the main immunogenic region[1]. Antibody binding and crosslinking leads to receptor blockade, increased rate of receptor degradation, and complement-mediated lysis of the post-synaptic membrane[1,2].

While any breed can be affected, Golden Retrievers, German Shepherd Dogs, Akitas, German Short Hair Pointers, Terriers, Chihuahuas, Great Danes and Newfoundlands appear predisposed[3,4,5]. The focal form of Myasthenia Gravis, consisting solely of weakness of the facial, pharyngeal, laryngeal, and/or esophageal muscles, occurs in 36–43% of dogs[2]. Generalized weakness occurs in 57–64% of dogs, 90% of which will have concurrent megaesophagus[2]. Paraneoplastic disease can occur, most commonly associated with thymomas. The latter appears to be more common in cats with studies reporting a cranial mediastinal mass in 26% of cats and only 3% of dogs[3,6].

A clinical diagnosis can be reached based on presenting signs and pharmacological testing. Tensilon (edrophonium chloride) is a short-acting anticholinesterase. A dose of 0.1-0.2 mg/kg is administered intravenously. A positive response is a brief resolution in muscular weakness. This test is neither sensitive nor specific for Myasthenia Gravis thus a negative response does not rule out the disease. If patients respond favorably, this does provide sufficient evidence to begin long-acting therapy while serological testing is pending. Electrodiagnostics, namely repeated nerve stimulation and single fiber EMG, are more sensitive but may not be readily available.

Definitive diagnosis is based on serologic testing for antibodies directed against acetylcholine receptors. Immunoprecipitation allows for measurement of the amount of receptor bound immunoglobulin. While this test is highly sensitive and specific, each assay is species-specific. While the antibody level within a given patient will reflect disease severity, there is significant variability between patients. Serum samples should be submitted to the UCSD Comparative Neuromuscular Laboratory[a]. An antibody titer > 0.6 nmol/L is diagnostic for acquired Myasthenia Gravis in dogs, while an antibody titer > 0.3 nmol/L is diagnostic in cats.

The acetylcholine receptor binding antibody assay has been shown to positively identify 98% of dogs with generalized immune-mediated Myasthenia Gravis[1]. Patients early in the course of the disease, or those treated with immunosuppressive therapy for longer than 7-10 days prior to testing, may have false negative results[1]. If the clinical picture is highly suggestive of Myasthenia Gravis, repeat serologic testing in two weeks may be beneficial.

Seronegative Myasthenia Gravis refers to cases where the clinical signs, response to therapy, and electrophysiologic findings are suggestive of the disease but serum acetylcholine receptor antibody testing is negative on at least two separate occasions. Seronegative Myasthenia Gravis may reflect antibodies that have a very high affinity for receptors rather than being in circulation. Alternatively, this may reflect antibodies directed against non-acetylcholine receptor skeletal muscle proteins on the post-synaptic membrane.

The mainstay of therapy for acquired Myasthenia Gravis in dogs remains long acting anticholinesterase agents. Since adequate acetylcholine is present in the neuromuscular junction, delaying hydrolysis allows for acetylcholine accumulation within the synaptic cleft and increased cholinergic activity. In the actively regurgitating patient, parenteral therapy is preferred. Neostigmine bromide can be administered at a dose of 0.04 mg/kg IM or SC q6 hours while pyridostigmine bromide can be administered as a constant rate infusion of 0.01-0.03 mg/kg/hour.

Oral therapy with pyridostigmine bromide is advised for maintenance therapy in dogs but is not advised in cats. It is well distributed throughout the body and does not typically cross the blood brain barrier[7]. The adverse effects of pyridostigmine are cholinergic and dose related. As these signs include hypersalivation, nausea, and vomiting, it can be difficult to distinguish between signs of uncontrolled disease as opposed to overdose. Severe overdose may induce a cholinergic crisis[7]. Therapy should be tailored to the individual patient. A starting dose of 0.5-1 mg/kg PO q8 hours is advised.

Although anticholinesterase agents only provide symptomatic relief, this may be sufficient in dogs until remission occurs. Immunotherapy is often used in the treatment of human Myasthenia Gravis and is the preferred choice in cats. Prednisolone with a starting dose of 2-4 mg/kg/day is advised. Immunotherapy remains controversial in dogs given its adverse effects and reports suggesting that dogs managed without immunosuppression are more likely to stay in remission[2]. Other immunosuppressants that have shown promise in all species include cyclosporine, mycophenolate mofetil, and azathioprine.

In the paraneoplastic form of the disease, thymectomy is recommended to remove the antigenic stimulus. While tumor recurrence is possible, the prognosis is reported to be good even in patients undergoing a second procedure and the presence of Myasthenia Gravis does not appear to affect survival time[8]. Other therapeutic considerations include intravenous immunoglobulin (IVIG) and plasmapheresis.

Another feature for the management of Myasthenia Gravis is preventing life threatening complications. As up to 60% of canine deaths are related to respiratory complications, implementing strategies to reduce the risk of aspiration pneumonia is of the utmost importance[2]. Elevated feeding is advised to allow food time to move passively into the stomach. Patients should be kept upright for at least 15 minutes after meals. When aspiration pneumonia develops, antibiotics should be carefully selected as some antibiotics (in addition to numerous other drugs) may exacerbate neuromuscular blockade and should be avoided. In severe cases, mechanical ventilation may be necessary.

The typical course of canine Myasthenia Gravis includes both clinical and immune remission. Clinical remission is represented by resolution of clinical signs of weakness without the need for pharmacologic therapy. Immune remission is represented by negative serologic testing. Evaluation of the serum titer is advised every 2-3 months following diagnosis to help guide the duration of therapy. Despite this, the long-term prognosis for the disease is poor due to respiratory complications. Even in cases where generalized

weakness resolves, esophageal dilatation can persist leading to a life-long risk for aspiration pneumonia.

CONGENITAL MYASTHENIC SYNDROMES

Congenital myasthenic syndromes are a diverse group of hereditary disorders that involve disruption of neuromuscular transmission by pre-synaptic, synaptic, or post-synaptic mechanisms[9]. Affected breeds reported include Jack Russell Terriers, Springer Spaniels, Smooth Fox Terriers, Dachshunds, Labrador Retrievers and Golden Retrievers, among others[9]. Dogs with congenital myasthenic syndromes have an onset of signs around 6-8 weeks of age. While most patients present with generalized weakness similar to the acquired form of the disease, megaesophagus is uncommon. As congenital myasthenic syndromes are not immune-mediated in origin, serological testing is not performed in patients this young. Several genetic mutations have been recently reported and identification of these specific mutations should be considered when breeding[9]. Few congenital myasthenic syndromes are responsive to anticholinesterase agents and their long-term prognosis is poor.

[a] UCSD Comparative Neuromuscular Laboratory http://vetneuromuscular.ucsd.edu/

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