Canine Acquired Myasthenia Gravis

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Acquired myasthenia gravis is a disease characterized by autoantibodies directed against nicotinic acetylcholine receptors of skeletal muscle neuromuscular junctions. Neuromuscular transmission is disrupted when acetylcholine released from presynaptic vesicles at the nerve terminal are unable to bind receptors on the postsynaptic muscle fiber membrane. Disruption of neuromuscular transmission can lead to muscle weakness and excessive fatigability. Severe cases of myasthenia gravis are associated with nonambulatory tetraparesis and respiratory failure. Myasthenia gravis should be on the list of differential diagnoses for any patient with focal or generalized neuromuscular weakness. Early diagnosis and treatment may improve the clinical outcome.

DIAGNOSTIC CRITERIA

Historical Information

Gender Predisposition: Myasthenia gravis can affect either gender.

Age Predisposition: There appears to be a bimodal age distribution (those 2 to 3 years of age and those older than 9 years of age), but all ages can be affected.

Breed Predisposition: German shepherds, Labrador retrievers, dachshunds, and Scottish terriers are the breeds most commonly diagnosed with myasthenia gravis. Akitas, terriers, German shorthaired pointers, and Chihuahuas have the highest relative risk for developing myasthenia gravis.

Owner Observations: Clinical signs include generalized muscle weakness that worsens with exercise and improves with rest, collapse, regurgitation, hypersalivation, voice change, dysphagia, and facial muscle weakness. Owners may describe that the dog sleeps with its eyes open.

Other Historical Considerations/Predispositions: Myasthenia gravis can be a paraneoplastic syndrome associated with thymoma, thymic hyperplasia, and other neoplasms. All dogs diagnosed with a cranial mediastinal mass should be tested for the presence of acetylcholine receptor (AChR) antibodies. Third-degree heart block and hypothyroidism have also been associated with myasthenia gravis.

Physical Examination Findings

- About 50% of affected dogs will have generalized muscle weakness.
- Dogs with focal myasthenia gravis can exhibit facial muscle weakness demonstrated by decremental palpebral reflexes and/or decreased arytenoid and vocal-fold abduction demonstrated by inspiratory stridor or decreased gag reflex due to pharyngeal muscle weakness.
- These patients can develop dyspnea and harsh lung sounds secondary to respiratory muscle weakness and/or aspiration pneumonia associated with megaesophagus and/or laryngeal/pharyngeal dysfunction.
- Spinal reflexes and proprioceptive placing reactions are normal but may be difficult to interpret in patients with profound weakness. Spinal reflexes may be fatigable.
- Bradycardia has been reported in dogs with a third-degree heart block.

Laboratory Findings

- The gold standard for the diagnosis of acquired myasthenia gravis is the demonstration of serum autoantibodies directed against AChR. An immunoprecipitation radioimmunoassay using 125α-bungarotoxin labeled canine AChR can be used to quantify circulating antibodies that bind to the receptors. Immunosuppressive doses of corticosteroids may

lower antibody concentrations; therefore, testing should be performed prior to initiation of steroid therapy. An AChR antibody concentration ≥0.6 nmol/L is considered positive for myasthenia gravis. Titers do not necessarily correlate with severity of disease. There is good correlation between antibody titer and disease progression or remission in an individual animal.

- A complete blood count (CBC), serum chemistry analysis, and urinalysis should be performed in all patients. The results do not provide specific information about myasthenia gravis but may help rule out other causes of muscle weakness or concurrent disease.
- Serum creatine kinase activity should be measured as an indicator of muscle damage. Repeated elevated creatine kinase activity is a sensitive indicator of inflammatory, necrotizing, and dystrophic myopathies but may be elevated following muscle trauma, extended recumbency, in chronic neuropathies, or following needle injections. A normal creatine kinase does not rule out a myopathy. Elevations in creatine kinase (>2,000 U/L) can be clinically significant for a myopathy (normal 40 to 254 U/L). Creatine kinase levels lower than 2,000 U/L may indicate muscle trauma or extended recumbency.
- Megaesophagus has been associated with hypothyroidism and hypoadrenocorticism. Evaluation of thyroid and adrenal gland function should be included in the diagnostic workup. Hypothyroidism and hypoadrenocorticism have been anecdotally associated with myasthenia gravis, but the association has not been proven.
- The AChR blocking antibody assay detects antibodies near the AChR's binding sites for 125α-bungarotoxin. The assay is not sensitive or specific for myasthenia gravis.
- The AChR modulating antibody assay measures AChR blockage and degradation in tissue culture. False-positive results can occur.
- Arterial blood gas analysis can be used to further define the degree of respiratory compromise from aspiration pneumonia and/or respiratory failure.

Other Diagnostic Findings

- About 90% of dogs with myasthenia gravis have radiographic evidence of megaesophagus. Aspiration pneumonia can be present.
- A presumptive diagnosis of myasthenia gravis can be made by a positive response to an edrophonium challenge test (Tensilon test). An ultra short-acting anticholinesterase agent, edrophonium chloride, is administered IV at 0.1 to 0.2 mg/kg. Response is based on dramatic improvement in muscle strength shortly after administration. Patients with other myopathic and neuropathic disorders may also have a subjectively positive response. Not all myasthenic dogs will show a positive response to the edrophonium challenge test because of insufficient number of AChR. Overdose or use of edrophonium in a non-myasthenic patient can lead to bronchoconstriction, bradycardia, salivation, lacrimation, retching, vomiting, and diarrhea. In the event of a cholinergic crisis, 0.02 to 0.04 mg/kg of atropine sulfate should be administered IV.
- A presumptive diagnosis of acquired myasthenia gravis can be made from a decremental response to repetitive nerve stimulation during electrodiagnostics. Nerve stimulation requires anesthesia and may be contraindicated in a critical patient.
- A transtracheal wash or bronchoalveolar lavage with culture and sensitivity is indicated in patients with aspiration pneumonia to determine the appropriate antibiotic choice.

Summary of Diagnostic Criteria

- Clinical signs stem from generalized appendicular muscle weakness or focal weakness involving the esophageal, facial, pharyngeal, and/or laryngeal muscles.
- There is a bimodal age distribution with peaks at 2 to 3 years and 9 years of age.
- The gold standard diagnostic test is the identification of serum antibodies against muscle AChR.

CHECKPOINTS

- The use of corticosteroids in the treatment of myasthenia gravis is controversial.
- Improvement in neuromuscular function can be related to prednisone's inhibitory effects on lymphocyte division, leukocyte chemotaxis, and release and production of inflammatory mediators.
- Relative contraindications for corticosteroid therapy include severe obesity, diabetes mellitus, uncontrolled hypertension, GI ulceration, and aspiration pneumonia.
- High doses of glucocorticoids can exert a negative effect on neuromuscular transmission and can cause a transient worsening of clinical signs.
- As a general rule, the greater the degree of weakness the lower the dose of glucocorticoids.
- Patients on immunosuppressive therapy should be monitored very closely for signs of aspiration pneumonia.

ON THE NEWS FRONT

- In humans with myasthenia gravis, autoantibodies to other striated muscle proteins (striational antibodies) have been described. When tests for AChR antibodies are negative, positive assays for striational antibodies in humans may support a clinical diagnosis of acquired myasthenia gravis.
- Ryanodine receptors are sarcoplasmic reticulum calcium release channels and are involved in striated muscle contraction. Autoantibodies to ryanodine receptors have been described in human patients and dogs with late onset myasthenia gravis and thymoma.
- MMF is being used to prevent allograft rejection in human renal transplant patients and may show some promise in the treatment of canine myasthenia gravis. MMF inhibits purine synthesis primarily in lymphocytes (T and B cells) with minimal effects on other cell lines. Side effects are usually GI upset and bone marrow suppression. Clinical trials are needed to further support the use of MMF as a potential immunosuppressive agent for acquired myasthenia gravis in dogs.

- Thoracic radiographs will often reveal megaesophagus and secondary aspiration pneumonia.

Differential Diagnoses

- Myasthenia gravis should be differentiated from other causes of tetraparesis with lower motor neuron disease such as acute polyradiculoneuritis, tick paralysis, or botulism. Animals with these disorders often have depressed or absent spinal reflexes.
- Other causes of megaesophagus include hypothyroidism, hypoadrenocorticism, lead intoxication, organophosphate ingestion, polymyositis, or idiopathic megaesophagus. Blood lead concentrations, creatine kinase activity, thyroid and adrenal function tests, and clinical history may help diagnose these disorders.
- Other conditions that cause weakness, such as hypoglycemia, endocrinopathies, or electrolyte abnormalities can be ruled out through a CBC, serum chemistry profile, thyroid, and adrenal gland function tests.
- A muscle biopsy is necessary to diagnose myopathies. Biopsies are indicated if muscle atrophy/hypertrophy is present or if the creatine kinase is persistently elevated.
- A physical examination, thoracic radiographs, electrocardiogram, and/or echocardiogram can diagnose cardiac disease as the cause of weakness.

TREATMENT RECOMMENDATIONS

Initial Treatment

- **Elevation of food and water** may aid in their transport into the stomach. If regurgitation persists, a gastrostomy tube should be placed.
- **Anticholinesterase agents** are the primary mode of treatment. Available drugs are pyridostigmine bromide (1 to 3 mg/kg PO q8–12h or 0.01 to 0.03 mg/kg/hr as a constant-rate IV infusion) or neostigmine bromide (2 mg/kg/day PO in divided doses to effect or 0.04 mg/kg administered IM q6h). Therapy should begin at the low end of the dosage range and gradually increased to the desired effect. $
- **Immunosuppressive doses of corticosteroids should be avoided** early in the course of myasthenia gravis because they can exacerbate weakness. Low-dose prednisone (0.5 mg/kg every other day) can be used in mild to moderately affected myasthenic dogs. The dosage can gradually be increased to an immunosuppressive level (2 to 4 mg/kg q12h) if indicated. Glucocorticoid therapy is not without risk and can worsen clinical signs. Patients with megaesophagus are at risk for aspiration pneumonia, and glucocorticoids can have a negative impact on their recovery. $
- **Broad-spectrum antibiotics** should be administered to treat aspiration pneumonia. The antibiotic choice should be based on culture and sensitivity with avoidance of those antibiotics that interfere with neuromuscular transmission. $

Alternative/Optional Treatments/Therapy

- If elevation feedings and anticholinesterase drugs do not control clinical signs, other alternative therapies may be tried.
- **Glucocorticoids** are contraindicated in some patients, and azathioprine (2 mg/kg PO q24h, then tapered to every other day once in clinical remission) can be used as the sole immunosuppressive drug. Potential side effects of azathioprine include bone marrow suppression, pancreatitis, gastrointestinal (GI) irritation, and hepatotoxicity. A CBC is recommended every 1 to 2 months during therapy. **Cyclophosphamide** and **cyclosporine** have some efficacy in human myasthenia gravis patients, but the side effects and cost may outweigh the benefits. **Mycophenolate mofetil (MMF)** is an immunosuppressive drug specifically for lymphocytes. MMF has shown some promise in human myasthenic patients but controlled studies in dogs are lacking. $
- **Plasmapheresis** involves the removal of plasma from whole blood and returning the patient's packed red blood cells along with plasma from a healthy donor. It is hypothesized that plasmapheresis increases the sensitivity of antibody-producing cells to cytotoxic

effects of immunosuppressive drugs and reduces the AChR antibody load. **$$$$**

- **Intravenous immunoglobulin** therapy is thought to improve the clinical outcome by AChR antibody neutralization with anti-idiotypes and other down-regulating mechanisms. **$$$$**

Supportive Treatment

- **IV crystalloid fluid therapy** may be needed in myasthenic patients because constant regurgitation may make oral nutrition or drug therapy impossible. Maintenance and ongoing fluid losses should be met. **$**
- Treatment of secondary esophagitis and gastritis involves **histamine receptor antagonists** and **gastric protectants**. Ranitidine (0.5 to 2 mg/kg IV, IM, or PO q8–12h) or famotidine (0.5 mg/kg IM, SQ, IV, or PO q12–24h) and sucralfate (0.5 to 1 g/dog PO q8h) can be used. Sucralfate should not be given 2 hours before or after any other oral medication, including histamine receptor antagonists. **$**
- **Gastric motility modifiers** have been used in the treatment of myasthenia gravis. Metoclopramide (0.2 to 0.4 mg/kg IV, IM, or PO q6–8h or 1 to 2 mg/kg/day via a continuous IV infusion) increases the tone of the lower esophageal sphincter. Metoclopramide may be contraindicated in patients with severe megaesophagus and regurgitation because it can worsen the clinical signs. Cisapride also has prokinetic effects on the GI smooth muscle. Cisapride may prolong the esophageal transit time of a food bolus and worsen the regurgitation. There is no evidence that either drug has any effect on canine esophageal motility. **$**
- **Nutritional support** can be provided by either elevating the head during oral feedings or by feeding though a gastrostomy tube. Gastrostomy tubes reduce the risk of aspiration pneumonia when compared to oral feedings. **$$$**
- **Ventilatory support** is indicated in patients with severe aspiration pneumonia and/or respiratory muscle failure based on arterial blood gas analysis.

Patient Monitoring

- Serum AChR antibody concentrations should be measured every 4 to 6 weeks in myasthenic dogs. As long as the titers are positive (≥0.6 nmol/L), treatment should continue. Immunosuppressive therapy can lower antibody concentrations, so a decrease in the antibody titer may be drug induced and not indicative of remission. Pyridostigmine bromide does not lower antibody titers but should control clinical signs.
- Patients on immunosuppressive therapy should have a CBC performed every 4 to 8 weeks.

Home Management

- Owners should be educated on nutritional support. The patient's head should be elevated relative to the thorax during feedings and remain elevated for 10 to 15 minutes afterward. The food selection will depend on the patient. Some dogs tolerate semi-liquid gruel while others prefer solid food. Elevated feedings may fail to provide the dog with adequate nutritional support. Gastrostomy tube feedings can be done at home for an indefinite time period.
- Do not breed any myasthenic dog.

Milestones/Recovery Time Frames

- Improvement in clinical signs and resolution of weakness should occur rapidly following anticholinesterase therapy.
- The natural course of disease in the absence of neoplasia is for clinical and immunologic remission. The average time for remission of the disease is 4 to 6 months with a range of 1 month to 1.5 years.
- The dog should be clinically normal, AChR antibody concentration should return to the normal range, and megaesophagus should be resolved radiographically at the time of complete remission.

Treatment Contraindications

There are various drugs that may hinder neuromuscular transmission, including:

- Aminoglycosides
- Ampicillin
- Ciprofloxacin
- Erythromycin
- Imipenem
- Pyrantel pamoate
- β-adrenergic antagonists
- Calcium-channel blockers
- Antiarrhythmic agents
- Neuromuscular blocking drugs
- Phenothiazines
- Tropicamide

RESOURCE LIST

- **Edrophonium chloride** (Tensilon, ICN Pharmaceuticals): 0.1–0.2 mg/kg IV.
- **Pyridostigmine bromide** (Mestinon, ICN Pharmaceuticals; Regonol, Organon): 1–3 mg/kg PO q8–12h or 0.01–0.03 mg/kg/hr as a constant-rate infusion.
- **Neostigmine bromide** (Prostigmin, ICN Pharmaceuticals): 2 mg/kg/day PO in divided doses to effect or 0.04 mg/kg IM q6h.
- **Azathioprine** (Imuran, GlaxoSmithKline): 2 mg/kg PO q24h, then tapered to every other day once in clinical remission.
- Assays for **acetylcholine receptor antibody** are available at the Comparative Neuromuscular Laboratory, Basic Science Building, Room 2095, University of California–San Diego, La Jolla, CA 92093-0612, (858) 534-1537.

- Methoxyflurane

Overvaccination can potentially exacerbate active myasthenia gravis.

PROGNOSIS

Favorable Criteria

Early diagnosis and treatment is associated with a better outcome.

Unfavorable Criteria

- Aspiration pneumonia is the primary cause of death.
- Hormonal influences such as heat cycles in female dogs may exacerbate myasthenia gravis. Neutering is advised as soon as the dog is stable.
- Vaccination may exacerbate the clinical signs of myasthenia gravis. Do not vaccinate a dog with active myasthenia gravis unless absolutely necessary.

RECOMMENDED READING

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