Antibodies Gone Wild

A case of myasthenia gravis in the dog

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Introduction

Myasthenia gravis (MG) is the most commonly diagnosed neuromuscular disease in dogs and can be seen less commonly in cats.[2,7,8] It can be seen, rarely, as a congenital disease or, more commonly, as an acquired autoimmune disease.[1,6] In both the congenital and acquired form, the cause of the disease is a decreased number of functional acetylcholine receptors (AChR) at the neuromuscular junction (NMJ).[1,6] There are three different presentations of MG depending on distribution and severity of clinical signs: focal, generalized and acute fulminating.[1-4,6] A paraneoplastic form can also occur with the presence of a thymoma.[1-3,6]

Congenital MG is typically seen in puppies and kittens, but acquired MG has a bimodal age distribution.[1] Several breeds are overrepresented or have a higher risk of developing MG.[1,3,7] Common clinical signs with congenital and acquired MG include focal to generalized muscle weakness, regurgitation due to megaesophagus (ME), dysphagia, weak or absent palpebral reflex, exercise intolerance, and aspiration pneumonia.[1,5] Cats can also have ventroflexion, are less likely to have ME, and have a higher incidence of thymoma associated MG.[5,7]

There are several diagnostics that can be suggestive of MG, however, gold standard for diagnosing acquired MG is identification of AChR antibodies via immunoprecipitation radioimmunoassay.[1,6,8] The mainstay of treatment is anticholinesterase therapy and supportive care for management of ME and potential aspiration pneumonia.[1,2,6] In more severe cases, immunosuppressive therapy may be needed.[1,2,6] Serial monitoring of antibody titers should be performed to assess disease status and to help determine the duration of treatment.[2]

History and Presentation

June Bug is a 9 year old, female spayed, mixed breed dog who presented to Emerson Animal Hospital on August 13th, 2019 for coughing. She was seen by another veterinarian the

previous week and was prescribed amoxicillin and then cephalexin, and later an unknown cough tablet, for a suspected upper respiratory infection. She regurgitated after drinking or eating during this past week, which had progressively worsened. Radiographs taken at Emerson Animal Hospital revealed ME. She was hospitalized for the afternoon and given maropitant, metoclopramide and intravenous (IV) fluids. Due to the regurgitation over the past week she was fed a small amount of wet food in an upright position. After this she began coughing and struggling to breathe. She was kept on flow-by oxygen with little improvement. It was recommended at that time to bring her to Mississippi State College of Veterinary Medicine for 24-hour care.

June Bug presented to MSU-CVM on August 13th. On presentation to MSU-CVM, she was in respiratory distress and was immediately placed on flow-by oxygen. Suction was used to remove white foam and food particles from her airway. Her temperature was normal at 102.1 F. Her heart rate was 60 beats per minute and she was panting with an increased respiratory effort. Her mucous membranes were pink and moist with a capillary refill time of less than 2 seconds. On auscultation, crackles and increased bronchovesicular sounds were heard. Due to increased bronchovesicular sounds, the heart could not be heard. With supplemental oxygen she was appropriately oxygenating with a pulse oximetry of 98-100%. The remainder of her exam was unremarkable. Aspiration pneumonia was suspected secondary to her ME. She was started on ampicillin/sulbactam, enrofloxacin, pantoprazole and IV fluids. She was kept in 50% oxygen overnight and then was transferred to the Internal Medicine service. Differential diagnoses for the cause of her ME included idiopathic, acquired MG, hypothyroidism, and hypoadrenocorticism.

Diagnostic Approach

When a neuromuscular disorder is suspected, a minimum database including CBC, biochemistry panel, urinalysis, thyroid panel, and adrenal function testing should be performed.[1,6,8] These tests will help to determine if any electrolyte imbalances or other underlying disease process could be causing the muscle weakness.[6,8] Other helpful tests include serum CK and evaluation for myoglobinuria which may indicated muscle damage, cardiac troponin 1 to assess for myocardial damage, and lactate to assess for the presence of anaerobic metabolism.[8] Thoracic radiographs should also be performed to assess for ME, a cranial mediastinal mass, and aspiration pneumonia.[1,6] In one study that surveyed owners of dogs with ME, it was found that the top three diseases found concurrently with ME were myasthenia gravis, esophagitis, and hypothyroidism.[9] These should be high on the differential list and diagnostic plan when a patient presents with ME. The neurologic exam in patients with MG is typically normal, but a weak or absent palpebral reflex may be seen.[1,6]

Specific diagnostics for MG include a pharmacological test with an anticholinesterase, repetitive nerve stimulation or EMG, and demonstrating an increased level of AChR antibodies via immunoprecipitation radioimmunoassay (RIA).[1,6,8] Historically, edrophonium chloride (Tensilon test), an ultra-short acting anticholinesterase, was used for the presumptive diagnosis of MG.[10] This drug was discontinued in 2017, so now some specialists use neostigmine instead.[10] In an unpublished study, the sensitivity and specificity of neostigmine for diagnosis of MG was 88.9% and 80% respectively.[10] This sensitivity and specificity are for strong positive results only and the neostigmine being given via the intravenous route.[10] While repetitive nerve stimulation or EMG can demonstrate a decremental response to repeated stimuli and are useful in the diagnosis of MG, they both require special equipment and general anesthesia.[1,6] These are not performed very often due to the risk of putting a patient with ME under general anesthesia.[1,6]

The gold standard for diagnosing acquired MG is finding an increased level of AChR antibodies via RIA.[1,6,8] There is some cross-reactivity between species, but it is recommended that a species-specific assay be used.[1,8] An AChR antibody titer of >0.6nmol/L is diagnostic for acquired MG in dogs and >0.3nmol/L is diagnostic for acquired MG in cats.[1,6,8] The level of antibodies does not correlate well to severity of disease or degree of weakness.[1,6]

Approximately 2% of dogs with clinical signs consistent with MG and a positive response to an anticholinesterase will be seronegative.[1,2,6] A dog can be classified as having seronegative MG if (1) clinical signs are consistent with MG, (2) they have a consistent pharmacologic response and electrophysiologic findings, (3) they have normalization of muscle weakness with anticholinesterase therapy, and (4) they have at least two negative serum AChR antibody titers determined by RIA.[1,6,8] Theories for why this occurs includes high-affinity antibodies or antibodies against non-acetylcholine skeletal muscle proteins such as titin and ryanodine receptors.[1,6,8] The latter can occur in older onset and thymoma associated MG.[1,6,8]

In June Bug's case, radiographs repeated the morning after presentation revealed aspiration pneumonia and the previously diagnosed ME. A cranial mediastinal mass was not seen. A CBC revealed a mild neutrophilia and moderate lymphopenia, which was consistent with a stress leukogram. Her chemistry panel revealed a mild to moderate hypernatremia and hyperchloremia, a mild hypokalemia, a mild decrease in BUN, and a mild hypocholesterolemia. These changes were consistent with dehydration and her inability to take in food. A thyroid panel showed a decrease in total T4, but her free T4 was normal. This ruled out hypothyroidism. A normal baseline cortisol, ($\geq$3 ug/dL), ruled out hypoadrenocorticism. The remaining differentials were idiopathic and acquired MG. She became increasingly weak and unable to rise with exercise. In addition, her palpebral reflex was repeatedly tested with a decreasing response seen.

A neostigmine challenge was performed and she regained muscle strength, so she was presumptively diagnosed with MG. Acetylcholine receptor antibody titers returned a week later at 1.86 nmol/L, which was diagnostic for MG.

Pathophysiology

MG can be congenital or acquired in dogs and cats.[1,5,6] In the congenital form, there is a decreased number of AChR at the NMJ.[1,6] The acquired form is an autoimmune disease in which antibodies target the nicotinic AChR at the NMJ of skeletal muscle.[1,3,5-8] The majority of antibodies target the main immunogenic region (MIR) of the AChR.[1,6,8] The MIR is adjacent to the acetylcholine binding site on the AChR which leads to cross-linking and induction of antigenic modulation.[1,6,8] There are 3 mechanisms that lead to the loss of AChR at the NMJ which include (1) antibodies may bind directly to the AChR which inhibits its function, (2) complement mediated lysis of the postsynaptic membrane or (3) antibodies cause cross-linkage of AChR leading to an increased rate of degradation of AChR at the postsynaptic membrane.[1,6] Spontaneous remission of disease is common in dogs with 88.7% of dogs achieving remission in an average of 6.4 months.[4]

In congenital MG, clinical signs are typically seen in puppies between 6 and 9 weeks old.[1] Breeds predisposed include Springer Spaniels, Jack Russell Terriers, Smooth-haired Fox Terriers, Gammel Dansk Honsehunds, Samoyeds, and Miniature Dachshunds.[1,6] Genetic mutations have been identified in Jack Russel terriers, Old Danish Pointing dogs, Labrador Retrievers, and Golden Retrievers.[1,5] Congenital MG is a progressive disease and clinical remission is unlikely.[1] Miniature Dachshunds, however, can have spontaneous remission by 6 months old.[1,6] Due to a lack of antibodies, diagnosis of congenital MG is based on signalment, history, and response to anticholinesterase medications.[1]

Acquired MG has a bimodal age distribution in dogs and cats.[1] In dogs, the disease is typically diagnosed between 4 months and 4 years old and between 9 and 13 years old.[1] Breeds at a higher risk of developing acquired MG include Akitas, terrier breeds, German Shorthaired Pointers and Chihuahuas; however, German Shepherd dogs and Golden Retrievers represent the breeds with the highest absolute morbidity.[1,3] Familial breed predispositions have been seen in Great Danes and Newfoundlands.[1,5]

Clinical signs vary depending on if the patient has focal, generalized or acute fulminating MG.[1,3,6] In focal MG, there is weakness of one or more muscle groups which can include esophageal, pharyngeal, laryngeal and facial muscles.[1,3,6] With focal MG there is an absence of generalized appendicular muscle weakness.[1,6] Clinical signs with focal disease may include regurgitation due to ME, dysphagia, dropped jaw, weak or absent palpebral reflexes, or voice changes.[1] In dogs with MG, about 36-43% present with focal signs.[1,6] In generalized MG, there is mild to severe appendicular weakness that is either brought on by or worsened with exercise.[1,6] Other signs such as ME and regurgitation can also be seen.[1,6] In dogs, the pelvic limbs are more commonly affected than the thoracic limbs.[1,6] In dogs, about 57-64% present with generalized signs and 90% of those have ME.[1,6] Acute fulminating is a more severe form of generalized MG that is acute in onset and rapidly progressive.[1,6] These patients can collapse and become non-ambulatory, have severe respiratory distress, and have aspiration pneumonia.[1,6] Mechanical ventilation may be needed.[1,2,6] Less than 5% of MG cases in dogs present with acute fulminating signs.[6] A paraneoplastic form is associated with thymomas, and 30-50% of dogs with thymomas have MG.[1-3,6] Clinical signs may be exacerbated by vaccination or surgical stresses.[4,8]

There are several differences seen in cats with MG. In cats, the disease in typically diagnosed between 2 and 3 years old and between 9 and 10 years old.[1] Abyssinian and Somali

breeds are overrepresented.[1,3,7] Congenital MG is rare in cats, but genetic mutations have been documented in Devon Rex and Sphynx cats.[5] Only about 15% of cats with MG present with focal signs and about 80% present with generalized signs.[1] Cats are less likely to have ME associated with MG, most likely due to a larger portion of their esophagus being smooth muscle.[1,7] Another clinical sign that can be seen in cats is ventroflexion.[5,7] Of cats diagnosed with MG, 25.7% have a cranial mediastinal mass, compared to only 3.4% of dogs.[1,2,7] One report suggested that as high as 52% of cats with MG had thymomas.[5,7] Spontaneous remission of disease is uncommon in cats.[5] While treatment with an anticholinesterase can be successful in cats, they may respond better to immunosuppressive therapy.[1]

Treatment and Management

The goal of treatment of MG is to improve muscle strength and minimize side effects until the disease goes into remission.[6] One study showed clinical remission, meaning resolution of clinical signs, and immune remission, meaning return of antibody titers to the normal range, in 88.7% of dogs in an average of 4.1 months and 6.4 months respectively.[4] Supportive care is an important part in treatment of myasthenia gravis. Aspiration pneumonia should be treated aggressively; however, antibiotics that are associated with NMJ blockade should be avoided.[1,2] Drugs that should be avoided in patients with MG include aminoglycosides, ampicillin, lidocaine, propranolol, quinidine, procainamide, penicillamine, magnesium, contrast agents, phenothiazines, narcotics, and muscle relaxants.[1,6] Nebulization and coupage can be a useful addition to the treatment of aspiration pneumonia.[1] Maintaining hydration in patients with significant regurgitation may require intravenous fluid therapy.[1] For patients with ME, elevated feedings are an important aspect of managing regurgitation.[1,2] A “Bailey chair” is a specially designed chair to keep a dog in an upright position during feedings and dogs should be kept in

this upright position for 10 to 15 minutes after eating.[1] If regurgitation is unmanageable, a feeding tube, ideally a gastrostomy tube, can be placed to aid in maintaining hydration and nutrition as well as giving medications.[1,2] Increasing the pH of the gastric content with the use of H_2 blockers or proton pump inhibitors can decrease the severity of esophagitis secondary to regurgitation.[1] Respiratory support, including ventilation, may be necessary in severe cases.[1]

The treatment of choice in MG is acetylcholinesterase inhibitors, such as neostigmine and pyridostigmine.[1,2,6] Acetylcholinesterase inhibitors slow the degradation of acetylcholine at the NMJ prolonging the effect of acetylcholine.[1,2,6] This medication does not treat the disease, but manages the clinical signs.[1,2,6] Animals on this medication can develop a cholinergic crisis which can include weakness, hypersalivation, vomiting, diarrhea, abdominal pain, lacrimation, muscle fasciculations, and bradycardia.[1,2,6] The dose should be decreased if these adverse signs occur.[1]

If anticholinesterase therapy alone is not enough to manage the clinical signs, immunosuppressive therapy may be needed.[1,2,6] Glucocorticoids are the first immunosuppressive typically used; however, the anti-inflammatory dose is used to minimize the side effects.[1,2,6] Glucocorticoids may worsen the muscle weakness, cause polydipsia and polyphagia in a patient with dysphagia and regurgitation, and predispose patients to infection.[1,2,6] The use of glucocorticoids is contraindicated in patients with aspiration pneumonia.[2,6] Other immunosuppressive drugs that have been used in treatment of MG include azathioprine, cyclosporine and mycophenolate mofetil.[1,2,6] There are conflicting studies on the efficacy of mycophenolate mofetil in the treatment of MG.[1,6] Leflunomide and cyclophosphamide have not been studied in the treatment of MG.[1,2,6]

Other suggested treatments, although not frequently used in veterinary medicine, include intravenous immunoglobulin and plasmapheresis.[1,6] A thymectomy in patients with a cranial

mediastinal mass can lead to a shorter survival time if ME is present at the time of surgery.[1,6] Radiation therapy has been reported to be successful in managing thymomas in dogs.[1] One study about a vaccine showed promise in decreasing the time to clinical and serologic remission, but further studies need to be performed to assess the efficacy.[1,6]

June Bug was hospitalized for treatment of her aspiration pneumonia and for initial control of her MG. On August 14th, June Bug had not shown any interest in food since her presentation but was able to drink water in a standing position. In addition to her antibiotics started by the emergency service, nebulizing and coupage were added to her treatments. Due to her lack of interest in food, she was also started on Entyce.

On August 15th, the neostigmine challenge was performed and she was presumptively diagnosed with MG. She was then started on pyridostigmine at a low dose to monitor for side effects. She was noted to have overflow urinary incontinence due to her inability to walk outside. She had continued to regurgitate and was started on sucralfate for treatment of esophagitis. Her overall condition had declined from her initial presentation.

On August 16th, a PEG tube and urinary catheter were placed under general anesthesia to aid in her nutrition and comfort. N-acetylcysteine was added to her saline for her nebulizing and coupage treatments. She was also started on ranitidine to help manage esophagitis. Her medications, with the exception of sucralfate, were given via her PEG tube. She was handling her feedings well through her PEG tube. She was given a slurry of canned Hill's i/d low fat. She started to exhibit some side effects of the pyridostigmine including hypersalivation and diarrhea. However, she was noted to be getting stronger on the pyridostigmine.

On August 17th, she continued to do well with her PEG tube feedings and her regurgitation had stopped. She had normal urine output through her urinary catheter. The side effects from the pyridostigmine were still present, but improving.

On August 18th, June bug was doing well enough to be moved out of the intensive care unit. Her urinary catheter was removed. She was able to walk outside to urinate and defecate. She did not have any more diarrhea, regurgitation, or episodes of increased respiratory rate and effort. Her medications were switched to oral medications, given through her PEG tube. Her pyridostigmine dose was increased to help with her strength.

On August 19th, June Bug was doing well and was discharged from the hospital. She was sent home with pyridostigmine, ranitidine, omeprazole, sucralfate, enrofloxacin and amoxicillin/clavulanic acid. Her owner was instructed to monitor for regurgitation or signs of respiratory distress and to monitor her ability to urinate and defecate normally. Her owner was also given information on Bailey chairs and was told that June Bug should be fed in an upright position to prevent regurgitation of her food. A recheck was scheduled for a week later to reassess her aspiration pneumonia.

Case Outcome

June Bug returned on August 26th for a recheck of her aspiration pneumonia. She had been doing well at home and gaining more strength each day. Her owner noted no episodes of regurgitation since her being discharged. Her recheck radiographs showed her aspiration pneumonia had significantly improved and her ME was still present. All of her medications were continued for another month. A recheck was scheduled for a month later to reassess her aspiration pneumonia and response to the pyridostigmine.

She returned for her recheck on September 23rd for recheck radiographs. Her owner noticed occasional episodes of weakness, but she had otherwise been doing well at home. Her recheck radiographs showed that her aspiration pneumonia had resolved and there was significant improvement in her ME. Her antibiotics were discontinued at this time. Her owner was going out of town, so she was medically boarded over the next week with no complications. She was not noted to have any episodes of weakness during her boarding so the pyridostigmine dose was kept the same. She went home on pyridostigmine, omeprazole, and ranitidine with all other medications discontinued. Her owner elected to keep her PEG tube in for ease of giving medications. Since PEG tubes can be left in for a prolonged period of time, her owner was instructed to have the PEG tube site checked monthly to make sure it is still appropriate to leave it in place. It was recommended that June Bug return in 4-6 weeks to recheck her acetylcholine receptor antibody titers.

June Bug returned on November 4th to have her antibody titers rechecked. Her owner said she had been doing great at home. The PEG tube was not needed for feeding or medications for the past 3 weeks. June Bug had accidentally pulled out her PEG tube 3 days prior to this recheck appointment. Her PEG tube stoma site was cleaned and looked normal, so her owner was instructed to monitor it for any signs of redness, swelling or pain. Her titers returned just over a week later at 0.34 nmol/L, which is considered normal in dogs. The omeprazole and ranitidine were discontinued at this time, but the pyridostigmine was continued at the same dose. It was recommended that June Bug return in 2 to 3 months to recheck her titers again. If the results come back normal again, June Bug could begin tapering off the pyridostigmine. June Bug should return this month to recheck her titers, but her appointment has not yet been scheduled.

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