Myasthenia gravis and masticatory muscle myositis in a dog

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Abstract — A 21-month-old, castrated male Vizsla was presented for pelvic limb weakness, difficulty opening his mouth, ptyalism, voice change, and urinary incontinence. Myasthenia gravis and masticatory myositis were diagnosed. The unusual clinical findings, diagnosis, treatment, and case outcome are described, followed by a brief discussion of myasthenia gravis and masticatory myositis.

Résumé — Myasthénie grave et myosite des muscles masticateurs chez un chien. Un vizsla mâle castré âgé de 21 mois présente une faiblesse des membres pelviens, de la difficulté à ouvrir la bouche, du ptyalisme, une modification de la voix et une incontinence urinaire. Une myasthénie grave et une myosite des muscles masticateurs ont été diagnostiquées. Les signes cliniques inhabituels, le diagnostic et le traitement sont décrits; vient ensuite une brève description de la myasthénie grave et de la myosite des muscles masticateurs.

A 21-month-old, 18.4 kg, castrated male Vizsla was presented to the Veterinary Teaching Hospital, University of Guelph, with the complaint of progressive gait abnormality, dribbling of urine, and voice change, progressing over the previous 3 to 4 d. The gait abnormality was described as hindend weakness with an unwillingness to take more than a few steps, followed by sitting. The onset of the gait abnormality coincided with a fall while the dog was playing with another dog. The day prior to presentation, the referring veterinarian noted that the dog had a hunched back and delayed proprioception of the pelvic limbs. Trismus, drooling, and inefficient drinking and eating behavior were also noted 7 d prior to referral. Similar signs, first appearing 4 mo earlier, were attributed to suspected masticatory myositis; however, further diagnostic testing was not pursued and treatment with amoxicillin (Apo-Amoxi; Apotex, Toronto, Ontario) and meloxicam (Metacam; Boehringer Ingelheim, Burlington, Ontario) appeared to resolve the clinical signs. The dog had been assessed to be healthy at the time of vaccination 8 mo earlier.

Physical examination revealed a thin body condition, severe atrophy of the muscles of mastication, and constant ptyalism. Pain and trismus prevented a thorough oral examination. The dog could prehend and swallow food normally, but he drank with difficulty. A grade II/IV left apical systolic heart murmur was detected on cardiac auscultation. The murmur had not been noted previously, and although not typical for the breed, mitral

valve endocardiosis with regurgitation was suspected. Intermittent urine dribbling was observed during the examination; the bladder was large and easily expressed. Neurologic examination revealed that the dog was quieter than normal. The palpebral reflex was absent bilaterally; however, vision and a pupillary light reflex were present. There was a 2- to 3-mm corneal opacity in the left eye, which did not take up fluorescein stain. The dog was ambulatory, but obviously weak and reluctant to bear weight on the hind limbs. Despite having an arched back, the dog did not react painfully to spinal palpation. Proprioception was reduced in the pelvic limbs and normal in the thoracic limbs. Spinal reflexes were present; however, flexor reflexes in all limbs were decreased, with the pelvic limbs being more affected than the thoracic limbs. Deep pain sensation was present in all limbs and perineum. No orthopedic abnormalities were detected. The neurologic examination indicated a diffuse hyporeflexia involving the spinal nerves, cranial nerve VII, and, possibly, the laryngeal innervation. The signs were most consistent with masticatory myositis and a peripheral neuropathy; the differential diagnoses included polyradiculoneuritis (Coonhound paralysis), metabolic disorders (adrenocortical insufficiency, hypothyroidism, hypoglycemia), paraneoplastic syndrome, and idiopathic causes. Atypical myasthenia gravis, a primary myopathy, immune-mediated or infectious polymyositis (toxoplasmosis, neosporosis), and a diffuse or multifocal encephalomyelitis were also considered. A concomitant thoracolumbar spinal cord lesion, possibly due to trauma, could not be ruled out.

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Initial diagnostic tests, consisting of an acid-base analysis, an electrolyte panel, blood urea nitrogen and glucose estimations, and an electrocardiogram, were normal. Palliative support care consisted of IV fluid therapy (50 mL/kg bodyweight (BW)/24 h + 20 meq/L KCl, PlasmaLyte 148; Baxter, Toronto, Ontario), intermittent bladder expression, and application of ophthalmic lubricating ointment (Duralube; Alcon, Mississauga, Ontario) q6h OU. On day 2, results from a complete blood cell count and serum biochemistry were normal, except for a low urea level (1.9 mmol/L; reference range, 3.5 to 9.0 mmol/L). Serum creatine kinase activity was 130 U/L (reference range, 40 to 255 U/L). Analysis of urine obtained by cystocentesis revealed normal. Palliative support care consisted of IV fluid and resumption of urinary continence. Nutritional management included small frequent feedings from an elevated position of a canned food diet (Eukanuba Nutritional Recovery Formula; The Iams Company, Dayton, Ohio, USA).

Histopathologic examination of the masseter muscle revealed moderate multifocal areas of mononuclear cell infiltration (lymphocytes, macrophages). Fibrosis was not observed. Positive staining for type 2M fiber antibodies was detected within the muscle biopsy section. Circulating antibodies against type 2M muscle fibers were also detected in the serum. Based on these findings, a diagnosis of masticatory myositis was made. Histopathologic examination of the biopsy of the hypoglossal muscle was unremarkable, ruling out myositis as a cause of the abnormal EMG findings in the tongue. The titer of the ACh receptor antibody was positive (6.89 nmol/L; reference range, less than 0.6 nmol/L) confirming myasthenia gravis. Titers of antibody to Toxoplasma and Neospora were negative.

Following discharge, the dog exhibited intermittent episodes of muscle weakness, exercise intolerance, and urine dribbling. The dose of pyridostigmine was increased to 2 mg/kg BW, PO, q8h on day 9, and prednisone (Apo-Prednisone; Apotex, Westin, Ontario) was added to the treatment at 0.5 mg/kg BW, PO, q24h, following resolution of the aspiration pneumonia (day 21). The dose of prednisone was gradually increased to 2 mg/kg BW, PO, q24h over 4 wk. A second episode of aspiration pneumonia occurred 10 wk after discharge; this was treated empirically with enrofloxacin (Baytril, Bayer Animal Health), 5 mg/kg BW, PO, q12h. After 12 wk of therapy, serial titers of antibodies to ACh receptor and type 2M muscle fiber were 1.07 nmol/L and negative, respectively. At that time, the dog appeared to be in clinical remission, except for radiographic evidence of megaesophagus.

This case report emphasizes some unusual clinical aspects of the presentation of acquired myasthenia gravis. Hyporeflexia is an uncommon finding and may represent a more severe form of myasthenia gravis. The urinary incontinence is also a unique feature. Disorders associated with generalized muscle weakness can affect bladder function and, in association with decreased urethral sphincter function, may lead to incontinence; the incontinence would seem unlikely to be due to the involvement of neuromuscular transmission of muscarinic type of ACh receptor in the smooth muscles. In a study by King et al (1), 2 of 5 dogs presenting with acute fulminating myasthenia gravis were noted to have bladder distension requiring assistance to urinate. Other causes of urinary incontinence were not pursued in this case following the rapid clinical resolution of the incontinence following therapy for myasthenia gravis. In humans, voiding dysfunction in conjunction with myasthenia gravis is rare and seems to be associated with a recent diagnosis of myasthenia or an exacerbation of the disease process (2). It has been hypothesized that autonomic dysfunction in patients with myasthenia gravis might indicate a unique subset with a worse prognosis (2).

The clinical presentation of an arched spine with pelvic limb proprioceptive deficits, representing profound muscle weakness, is also an unusual finding in a nonrecumbent animal. Most ambulatory patients with...
myasthenia gravis present with normal proprioception. The proprioceptive deficits in this patient, however, may have been attributable to an additional disorder, such as a polyneuropathy, in which case, a nerve biopsy might have proven useful. Interestingly, following treatment for myasthenia gravis, the proprioceptive deficits resolved. In addition, this patient initially did not have the typical historical complaint of fatigue associated with exercise seen in many cases of generalized myasthenia gravis. If fatigue had been present, it might have aided in an earlier diagnosis of myasthenia gravis. It was also unusual that with rest while hospitalized, the progressive weakness was unabated.

The masticatory myositis was likely chronic, given the patient’s previous history; however, there was no histopathologic evidence of fibrosis, which is often seen with chronicity (3). The excessive ptyalism on initial presentation was attributed to the esophageal disease associated with the myasthenia gravis and not to masticatory myositis.

Previously, Hackett et al (4) reported myasthenia gravis and concurrent masticatory muscle myositis in a 10-year-old dog presenting with regurgitation, cough, and a thymoma. Myasthenia gravis was diagnosed, based on a high antibody titer to ACh receptor. Histologic examination of the masticatory and extraocular muscles revealed extensive lymphoplasmacytic infiltration, and circulating antibodies against temporalis muscle proteins were documented by immunohistochemical staining.

The unusual clinical presentation of this case and the presence of autoantibodies to ACh receptors and type 2M muscle fibers prompted testing for concurrent or underlying autoimmune disease. Human myasthenics have an increased occurrence of several associated disorders, including autoimmune diseases such as hypothyroidism, lupus erythematous, and rheumatoid arthritis (5). Although not as well characterized in the dog, some of these conditions are believed to be associated with canine myasthenia gravis (3,6). In this case, antinuclear antibody (ANA) testing was negative and total thyroxine, free thyroxine, and thyroid stimulating hormone were normal.

Acquired myasthenia gravis is an immune-mediated disease in which autoantibodies that react with nicotinic acetylcholine receptors of the skeletal muscle neuromuscular junction are produced (5,7). Clinical signs of myasthenia gravis vary depending on the muscle groups involved. Appendicular muscle weakness can manifest as weakness, stiff gait, or collapse. Facial muscle weakness can manifest as reduced or absent palpebral reflex; esophageal muscle weakness as megaesophagus with regurgitation; pharyngeal weakness as dysphagia; and laryngeal muscle weakness as voice change or inspiratory stridor (7,8). Less common clinical signs that have been associated with myasthenia gravis include hyporeflexia, lameness, shortening of stride, collapse, tremors, and distended bladder (1).

The preferred diagnostic test for canine acquired myasthenia gravis is the detection of circulating autoantibodies to ACh receptors (6). This immunoprecipitation radioimmunoassay carries a high sensitivity and specificity, detecting approximately 98% of dogs with generalized acquired myasthenia gravis (6). False positive results are rare. A positive response to the short-acting anticholinesterase drug edrophonium chloride is suggestive of myasthenia gravis; however, false positive and false negative results are possible (3,8). Therapy for myasthenia gravis involves the use of anticholinesterase medication. In many dogs, muscle weakness is not adequately controlled with anticholinesterase therapy alone, in which case immunosuppressive therapy is recommended either in conjunction with anticholinesterase treatment or as the sole therapy (5,6,9). Prednisone is the most commonly used immunosuppressive agent; however, azathioprine, cyclophosphamide, and cyclosporine therapy have been reported to be efficacious (6,7,9). Dogs with megaesophagus are managed with small, frequent feedings in the upright position, of a solid or semiliquid diet, depending on individual response, and are monitored closely for signs of aspiration pneumonia. The prognosis for dogs with myasthenia gravis is variable; however, severe aspiration pneumonia, persistent megaesophagus, acute fulminating myasthenia gravis, and the presence of a thymoma carry a poor prognosis (3,10).

Masticatory muscle myositis (MMM) is an inflammatory disorder selectively involving the muscles of mastication (3). It is presumed to be immune-mediated, based on the detection of autoantibodies reacting with type 2M muscle fibers, the presence of a mononuclear inflammatory cell infiltrate, and the clinical response to immunosuppressive doses of corticosteroids (3). Masticatory muscles are composed primarily of unique type 2M myofibers that are not present in limb muscles (11). Masticatory muscle myositis is usually bilaterally symmetrical, and affects dogs of any age, sex, or breed; however, large breed dogs are most commonly affected (3). Acute and chronic forms of MMM have been described. In the acute form, swelling of the muscles of mastication is observed with myalgia. The animal is reluctant to open its mouth, has difficulty eating, and may exhibit ptalmism. Exophthalmos, linked to enlargement of the temporal muscles, can lead to exposure keratitis and conjunctivitis (10,12). In most cases, such as in this case, MMM is a chronic condition with severe progressive muscle atrophy and reduced ability to open the mouth (10,11). Clinicopathologic evaluation in affected dogs is typically nonspecific; however, the serum creatine kinase (CK) activity may be increased and a leukocytosis attributable to a neutrophilia or, less commonly, an eosinophilia may be present (3). Diagnosis is based on biopsy of the affected muscles and documenting the presence of antibodies to type 2M muscle fibers, which can be demonstrated in more than 85% of affected dogs (11,12). Histopathologic findings commonly include sites of necrosis and phagocytosis of the 2M fibers with perivascular infiltration of mononuclear cells. Abnormalities in the EMG may include increased insertional activity, fibrillation potentials, positive sharp waves, and bizarre high-frequency discharges (3). The treatment for MMM is prednisone, initially at 1–2 mg/kg BW, PO, q12h; however, the dosage can be tapered gradually in accordance with improvement in clinical signs. Azathioprine (2 mg/kg BW, PO, q24h) may be required, if clinical signs are not well controlled (3). Treatment for MMM was delayed in
this patient due to the presence of complicating aspiration pneumonia. It has also been documented in human and canine myasthenics that initial immunosuppressive dosages of prednisone can exacerbate muscle weakness; therefore, the dose was gradually increased (5,7,9). The prognosis for MMM, if treated appropriately, is good; however, relapse may occur (3,10,12).

References

The atlas is also excellent in that each case is presented in a format that includes the history, the physical examination findings, the likely differential diagnoses, the appropriate diagnostic plan and corresponding diagnostic techniques, the treatment and management, and the outcome and discussion. In the majority of cases, the differential diagnoses are prioritized, and the reasons for the prioritization are discussed. This type of format complements the problem-solving-oriented approach to veterinary medicine that is emphasized in many veterinary colleges.

Despite these aforementioned strengths, there are a number of flaws in this atlas. These deficiencies are not present throughout the text, but they are of sufficient quantity that I found the atlas disappointing. The discussions for each case are informative, but because the text is not comprehensive, certain important details are occasionally left out. For example, in case 1, the cat is placed on itraconazole for Microsporum canis. The side effects of other antifungal drugs are mentioned in the discussion, yet the side effects of itraconazole are not mentioned. In case 1.12, thoracic radiographs are taken, presumably for metastasis, yet this simple explanation is excluded. Later on in the text, within different chapters, the reason for thoracic radiographs are mentioned. A veterinary student may not initially recognize why the chest radiographs were taken. In a case of otitis media with a suspected ruptured tympanum, it is recommended, as part of the treatment, to clean the ear. There is no recommendation as to the type of cleaner that should be used if the tympanum is ruptured. In subsequent cases, a neutral pH cleaner is used in one case and a dilute povidone-iodine solution is recommended in another. In addition, the abbreviation SID is used frequently; this abbreviation is no longer taught to veterinary students, q24h is used instead to avoid prescription errors.

Although the overall format of the atlas is very good, there are inconsistencies. In cases 5.1 and 5.2, a generic list of differential diagnoses for an oral mass are given, yet, if one looks at the pictures, the list could have been modified and prioritized differently in accordance with the appearance and location of the mass in each case. Later on in case 5.5, the list of differential diagnoses present in certain cases and in certain areas. If one reads the entire chapter, some of these deficiencies are remedied, but it would seem logical to discuss certain considerations when they first arise or, at least, to make reference to future cases for further details.

The main strengths of the atlas are the numerous photographs that complement each case and introductory chapter. The anatomical photographs of the canine and feline nose and paranasal sinuses are exceptional and well labeled. Overall, the photographs in the chapters on the nose and paranasal sinuses, and the larynx are the best; they provide the reader with an invaluable amount of information and insight into each case that text alone could not provide. The cases presented in each chapter include the common presenting complaints that one would encounter in the particular area of interest.