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DIAGNOSIS AND TREATMENT OF ACQUIRED MYASTHENIA GRAVIS IN AN AMERICAN STAFFORDSHIRE TERRIER DOG

Cristina FERNOAGĂ, Raluca Mihaela TURBATU, Alexandru Gabriel NEAGU, Tudor NICULAE, Constantin VLĂGIOIU

University of Agronomic Sciences and Veterinary Medicine of Bucharest, 59 Marasti Blvd, District 1, Bucharest, Romania

Corresponding author email: raluca.tbt@gmail.com

Abstract

Myasthenia gravis is an immune-mediated disease that affects the neuromuscular junction due to the increased production of antibodies directed against the acetylcholine receptors of skeletal muscles. The consequence is the impairment of action potential transmission from nerve to muscles. Although in human medicine, Myasthenia gravis is a well-known condition with diagnostic protocols and several therapeutic strategies, in veterinary medicine diagnosis and therapy for this condition are still challenging. This study presents the case of a 5-year-old male American Staffordshire Terrier referral to the Clinic of Faculty of Veterinary Medicine in Bucharest for a neurological consultation due to a history of fatigue, limb tremor and reluctance to exercise. After the complete physical and neurological examination, the findings were consistent with Myasthenia gravis, so neostigmine methylsulfate was administered intravenously to confirm the diagnosis. Considering the positive clinical reply that was obtained after 15 minutes, a long-term therapeutic scheme was established and the patient was reassessed periodically.

Key words*: myasthenia gravis, neuromuscular disease, neostigmine methylsulfate, weakness, veterinary neurology.*

INTRODUCTION

Acquired myasthenia gravis (MG) is an immune-mediated disease that implies the production of autoantibodies that act against acetylcholine receptors of skeletal muscles (Shelton, 2002; Plat & Olby, 2004). In dogs, this pathology is documented by several case studies and retrospective case series, and it exhibits many similarities to the corresponding disorder of people (Dewey et al., 1997).

From the clinical perspective, the symptomatology of MG is subsequent with a generalized peripheral nervous system (PNS) disorder and very often its diagnosis is a challenge even for experienced neurologists. The difficulty lies in the variability of PNS symptoms that do not follow a clear pattern, considering that they are influenced by factors like the moment of onset, clinical course, severity and extent of the disease (Shelton et al., 1997). However, most systemic neuropathies, including MG, are characterized by an insidious onset and a chronic course, so whenever a disease of the peripheral nervous system is suspected, a differential diagnosis between polyradiculoneuritis, MG, megaoesophagus or disorders of neuromuscular transmission like tick paralysis, botulism or organophosphate toxicity must be performed (Platt & Olby, 2004). Although the gold standard for the diagnosis of MG is the detection of serum autoantibodies against muscle acetylcholine receptors by immunoprecipitation radioimmunoassay, in the absence of this method, other testing procedures can be used (Conti-Fine, 2006). An example is a pharmacological test that implies the administration of an ultra-short acting anticholinesterase drug. A positive response with an obvious improvement of muscle strength within several minutes of administration is very suggestive for MG (Shelton, 2010).

This study presents the clinical signs, the diagnostic approach and the therapeutic management of a 5-year-old American Staffordshire Terrier dog with a presumptive diagnosis of MG.

MATERIALS AND METHODS

The dog included in this case study was referred to the Clinic of the Faculty of Veterinary Medicine of Bucharest during 2018

for a neurological assessment. The evaluation was performed according to the protocol already implemented in our clinic that involves strict follow-up of the following stages: animal signalment, history, physical and neurological examination, neurolocalization of the disease, differential diagnosis using the acronym VITAMIND (vascular, inflammatory/ infectious, traumatic, anomalous, metabolic, idiopathic, neoplastic, degenerative), recommendations of paraclinical investigations, diagnostic and treatment (Thomas, 2010; Dewey & da Costa, 2016).

After the positive response obtained at the pharmacological test, for this patient, the therapeutic goal was to improve muscle strength and to minimise the adverse effects of the medications until remission of the disease was obtained, so we use pyridostigmine bromide as an acetylcholinesterase inhibitor (Dissanayake et al., 2006; Engel et al., 2015; Stanciu & Solcan, 2016). In addition, we completed the treatment with a product that supports the function of the liver (administered to diminish the adverse side effects of pyridostigmine bromide) and Omega-3 supplementation for its effect on functional brain activation and reduction of inflammation in autoimmune diseases.

For two years and a half, the dog was reassessed every 3 months, even after complete remission of the disease. In addition, the treatment dose was adjusted periodically according to the patient's evolution.

Animal signalment and history

A 5-year-old dog, intact male, American Staffordshire terrier was referred for neurological consultation. The dog came to the Clinic of the Faculty of Veterinary Medicine of Bucharest in September 2018. After the discussion with the owner, we discover that ten days before consultation, the patient started to manifest difficulty in getting up and walking, a need to rest after minimal efforts and stiffness of the limbs (first the hind limbs were affected and after several days the same symptoms were observed on the thoracic limbs, too). The appetite for food and water remained unchanged during this period and the macroscopic aspect of urine and faeces was normal. Vaccination and deworming schemes were completed and updated according to standard protocols. The history did not reveal signs of another recent illness (coughing, lack of appetite, vomiting, inactivity or agitation), trauma or exposure to toxins. Initially, the owner suspected an orthopaedic problem and asked for a surgeon opinion, at another clinic. No abnormalities of the locomotory system were detected, so the dog was referred for a neurological examination. The treatment received after the initial evaluation consisted of supplementation with B vitamins, in injectable form, as an attempt to reduce the weakness manifested throughout the patient's body. The evolution of the disease was progressive and the owner did not observe any improvements after the administration of the vitamins.

Because the clinical presentation was compatible with a neuromuscular disease, we performed a full physical examination, that was completed by neurological assessment to identify and establish the localisation of the lesion within the nervous system. Based on the corroboration of the results, we requested a series of paraclinical investigations for diagnostic confirmation. Findings were recorded in the neurological examination sheet, which has been used to monitor the subsequent evolution of the case. Finally, we established the treatment protocol and we settled on the following check-ups.

RESULTS AND DISCUSSIONS

Physical and neurological examination findings

Physical examination revealed a normal temperature (38.8°C), a heart rate of 87 beats per minute and a synchronous femoral pulse, present bilaterally. The respiratory rate was mildly elevated (43 respirations per minute), but we associated this value with the stress trigger by the environmental change, considering that at home the dog's respiratory rate was normal. All palpable lymph nodes were mobile, painless and normal size. The colour of the mucous membranes was pale pink and we obtained a capillary refill time of 1.5 seconds. The patient did not express pain when the abdomen was deeply palpated. The physical examination was followed by neurological examination, which included an evaluation of

the mental status, posture, cranial nerves, proprioception, gait, spinal reflexes and sensory testing to establish the localization of the lesion within the nervous system. For this dog, neurological evaluation showed several deficits:

- The **posture** was characterised by permanent sternal recumbency. However, when the patient was encouraged to move, he could support his weight and walk only for a short period (seconds), after which he displayed progressively over flexion of the joints and a crouched stance that forced him to rest and recover the strength needed to walk again (Figure 1).

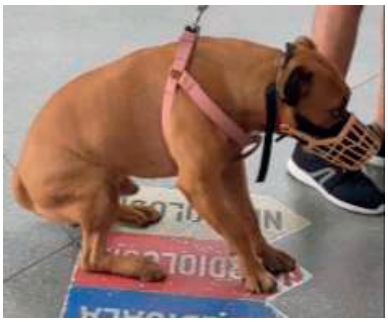

Figure 1. The dog showed progressive overflexion of the joints and crouched stance

- Regarding the gait, we observed tetraparesis, a narrow base of support on the thoracic limbs and the tendency to step on the dorsal surface of the paw on the forelimbs. The examination showed also hypometria, short steps with hyperflexion of the joints, dragging of the nails (with consequent noise of rubbing the nails on the ground), crouched stance with lowered tail, emprosthotonus and decreased ability to support the weight. Also, during gait, the whole musculature of its body was tense.
- Postural reactions were difficult to be assessed due to the patient's inability to support his weight.
- Mental status, behaviour, cranial nerve, spinal reflexes and sensory testing were normal for this dog.

The next step after the neurological examination was to establish the localization of the lesion within the nervous system. For this case, our differential diagnosis was made between a C1-C5 lesion (that would have evolved also with tetraparesis) and a peripheral nervous system lesion (which could have affected the nerve, the neuromuscular junction or the muscle).

Taking into consideration the acute onset, the deteriorating clinical course, the symmetry of the deficits, the lack of pain involvement and the signalment of the patient, according to, "VITAMIND" acronym, we ruled out most of the causes that could have generated exercise intolerance, but instead, we kept the suspicion of congenital or metabolic causes. The differentiation between the two will be made based on paraclinical investigations.

Paraclinical investigations and diagnosis

To obtain an aetiological diagnosis, we recommended a complete cell blood count (CBC), a serum chemistry panel, a cardiologic examination and radiography of the cervicothoracic chest to rule out megaoesophagus. No abnormalities were detected on blood analysis and the cardiologist did not identify any modification of the heart that could have produced the symptomatology.

On radiological examination of the cervical spine at the level of C1-C5 area was excluded any radiological signs such as narrowing of the intervertebral space, mineralization of the discs or other signs consistent with initial suspicion.

The radiological signs specific for megaoesophagus such as ventral deviation of the trachea, the radiolucent band superimposed on its projection area with the highlighting of the oesophageal wall in the form of a narrow radiopaque band, well delimited, which surrounds the radiolucent area resulting from aerophagia were not visible in this case and ruled out.

Due to the suspicion of acquired Myasthenia gravis, we decided to perform a pharmacological test by the administration of 1 ml neostigmine methylsulfate intravenously (iv) (Miostin® - 0.5 mg/ml) as an acetylcholinesterase inhibitor. Although the recommended substance for this test is edrophonium chloride, this drug is not available in Romania, so we use the alternative anticholinesterase agent.

Before the Miostin® administration, the dog was reluctant to move and had difficulty sustaining its bodyweight. Approximately 5

minutes later, he left decubitus and started to move and after another 10 minutes, we observed an obvious improvement of strength and better movement coordination.
Considering the positive response to the pharmacological test, the suspicion of Myasthenia gravis was confirmed.

Treatment and follow-up

Established treatment consisted of an oral anticholinesterase drug (pyridostigmine bromide - Mestinon®) at an initial dose of 2 mg/kg every 8 hours. In addition, we added silymarin for his role in diminishing hepato-toxic reactions and Omega-3 supplementation for its effect on functional brain activation and reduction of inflammation in autoimmune diseases.
The owner was informed that in this early stage of the disease, the prognosis is still guarded and a recidivation can occur even though remission is obtained (Mao et al., 2010). He agreed to follow our recommendations and to come back for a check-up after 2 months of treatment.

Figure 2. First evaluation after the onset of treatment - The posture was improved and the dog was able to walk without any signs of fatigue

On November 11, the dog came back for revaluation and an important progression was noticed. The patient could stand and walk without stopping and without any signs of fatigue. The mental status was normal, alert, the appetite for food and water remained unchanged and no adverse side effects of the pyridostigmine bromide have been reported by the owner (Figure 2).
Under these circumstances, the treatment recommendations remained the same, and the next visit was scheduled after another 8 weeks.
In January 2019, we noticed the same positive evolution, except for the occurrence of vomiting episodes (white foam) at intervals of about 2 weeks. The serum chemistry panel was repeated and we found a mildly increased level of the enzyme γ-glutamyl transferase and a high level of creatine kinase (1220 U/l) - which could be explained on the basis of the generalised muscle inflammation produced by the autoimmune disease (Garlepp et al., 1984). On the same day, abdominal ultrasound was performed and no other internal abnormalities have been found. We added at the previous therapeutic protocol a product containing L-Ornithine Aspartate, L-Arginine Hydrochloride, L-Citrulline and Acetyl Methionine (Ornitil®) as a hepatic metabolism aid. After one year of treatment, the dose of pyridostigmine bromide was reduced to 1 mg/kg every 12 hours. No other side effects have been reported during treatment.
Over the next two and a half years, periodic checks were performed every 3 months. The result was that from the onset of the disease, the dog did not show any episodes of relapse and its general condition remained unchanged.

CONCLUSIONS

1. For this case, the diagnosis of Myasthenia gravis was based on the typical clinical signs: reluctance to exercise, chronic hindlimb's weakness, tetraparesis, hypometria, progressive over flexion of the joints and a crouched stance during the walk.
2. The pharmacological test with neostigmine methylsulfate showed an obvious improvement of strength and better movement coordination, so the initial diagnosis was confirmed.
3. Proper cooperation between doctor and owner is essential since the owner must evaluate the results of treatment with pyridostigmine bromide, whose dose was adjusted according to patient evolution and

no significant side effects have been reported.

4. From the onset of the disease until the present, the patient was reassessed every three months and the evolution remained favourable, without any other episodes of relapse.

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