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Acute Fulminating Myasthenia Gravis in a Shih-tzu Dog

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Abstract : A 3-year-old, spayed female Shih-tzu dog was presented due to acute vomiting, diarrhea, and generalized weakness. The dog had generalized weakness, increased respiratory rate, and respiratory muscle effort. Neurologic examination revealed appendicular muscular weakness and decreased in tone of the anal sphincter. Megaesophagus was confirmed by radiographic examinations. Other than type 2 fiber atrophy, no specific abnormalities were identified in histopathologic examinations of muscle biopsies from the left pelvic limb. Serum acetylcholine receptor (AChR) antibody titer was increased (0.78 nmol/L; reference range, less than 0.6 nmol/L), confirming a diagnosis of acute fulminating myasthenia gravis. The dog dramatically responded to pyridostigmine bromide and had marked improvement in muscle strength, megaesophagus, and respiratory function. The dog has been successfully managed for 7 months after initial treatment.

Key words **:** acetylcholine receptor (AChR) antibody titer, acute fulminating myasthenia gravis, megaesophagus, type 2 fiber atrophy.

Introduction

Myasthenia gravis (MG) is a disease characterized by failure of neuromuscular transmission and classified into two forms, such as congenital and acquired. Generally, the nicotinic acetylcholine receptor (AChR) plays a central role in neuromuscular transmission in skeletal muscle (10). Binding of acetylcholine (Ach) to the alpha-subunit of the AChR results in depolarization of the end-plate region, termed the end-plate potential (EPP), that spreads in all directions of the muscle fiber sarcolemma, ultimately leading to muscle contraction (9). Congenital MG is defined as inherited disorder in which the safety of neuromuscular transmission is compromised by an abnormal reduction in the number of AChR on the muscular end plate, resulting in clinical signs of exercise induced weakness (5,9). Acquired MG (AMG) is an immune-mediated disease in which autoantibodies that react with nicotinic AChRs of the skeletal muscle neuromuscular junction are produced, inhibiting neurotransmission and accelerating AChR exocytosis and degradation (1).

Clinical signs of MG 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 (1,2).

AMG may be generalized (resulting in appendicular muscle weakness) with or without oesophageal involvement (12). In addition, clinical manifestations of AMG may be focal (limited to pharyngeal, esophageal, or facial musculature) (11) or acute and fulminating (generalized collapse) (2).

Previously, two cases of generalized form of MG were reported in South Korea (6,8). This case report firstly describes the clinical-, histopathological-findings, and treatment responses of the acute fulminating MG of the dog in Korea.

Case

A 3-year-old, spayed female Shih-tzu dog was presented because of acute vomiting, diarrhea, and generalized weakness. Clinical signs had been acutely shown 1 day before the presentation and progressively increased in severity and frequency, even though supportive cares were done at the local animal hospital. On history taking, the dog defecated flaccid feces and dribbled urine and appetite was acutely decreased. The dog had regularly received all of its vaccinations and heartworm prevention.

Physical examinations revealed that the dog was moderately

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depressed, dehydrated (less than 5%), and had generalized weakness, increased respiratory rate and respiratory muscle effort. On the thoraxic auscultation, abnormal sounds, such as crackles and systolic murmur, were not noted. Neurologic examination revealed appendicular muscular weakness with the hind limbs most severely affected and decreased anal sphincter tone. Proprioceptive positioning reaction was reduced in all limbs. Intracranial neural structures was normal according to the assessment of mental status, gait, posture, postural reaction, and cranial nerve. A position of lateral or sternal recumbency was preferred. Segmental spinal reflexes were normal and evidence of hyperesthesia was not detected. The acute onset and progressive nature of weakness in the absence of localizing signs of CNS dysfunction suggested a generalized neuromuscular problem of paraneoplastic syndrome (e. g. thymoma), metabolic (e. g. hypothyroidism and hypoglycemia), toxic (e. g. botulism, drug), immunologic (e. g. myasthenia gravis), idiopathic (e. g. idiopathic polymyositis) causes.

On complete blood count (CBC), hemoglobin concentration (18.8 g/dL) and packed cell volume (PCV) (58%) were mildly increased due to dehydration. Results of serum chemical profile, urinalysis, and blood gas analysis were normal. On thoracic radiography, the esophagus of dog was dilated and filled with air (Fig 1A, B). Evaluation of a barium esophagram with fluoroscopy revealed lack of primary or secondary esophageal peristalsis, confirming a diagnosis of megaesophagus. Based on the history and clinical findings, MG was strongly suspected. Thus neostigmine methylsulfate (0.04 mg/kg, IM; Kwang Myung Pharma., South Korea) was given as a presumptive diagnosis of AMG. After the administration of anticholinesterase drug, respiratory distress ceased and tone of the anal sphincter, limb strength, and body posture were rapidly and dramatically improved. However clinical signs relapsed 6 hours after drug administration. For definitive diagnosis, serum was tested for anti-AChR antibodies by ^{125}I-labelled α-bungarotoxin immunoprecipitation immunoassay and muscle biopsy of left pelvic limb was performed (Comparative neuromuscular laboratory, University of California, San Diego, La Jolla, CA, USA). Serum AChR antibody titer was increased (0.78 nmol/L; reference range, less than 0.6 nmol/L), confirming a diagnosis of AMG. To evaluate histopathologic features of biopsies, various stain methods, such as hematoxylin-eosin, modified trichrome, Periodic Acid Schiff (PAS), adenosine triphosphatase (ATPase) at pH 9.8 and 4.3, esterase, NADH-tetrazolium reductase (NADH-TR), acid Pase, alkaline Pase, oil red O, and staphylococcal protein A conjugated to horseradish peroxidase (SPA-HRPO), were employed. Other than type 2 fiber atrophy (Fig 2A, B), no specific abnormalities were identified. Type 2 fiber atrophy may be observed in cases of hypothyroidism and also in occasional muscles of dogs with MG. To rule out hypothyroidism, thyroid-stimulation hormone (TSH) stimulation test was done. A blood sample is obtained immediately before and 6 hours after administration of TSH (Thyrotropic hormone; Sigma-aldrich, St. Louis, USA) (0.1 unit/kg body weight, IV).

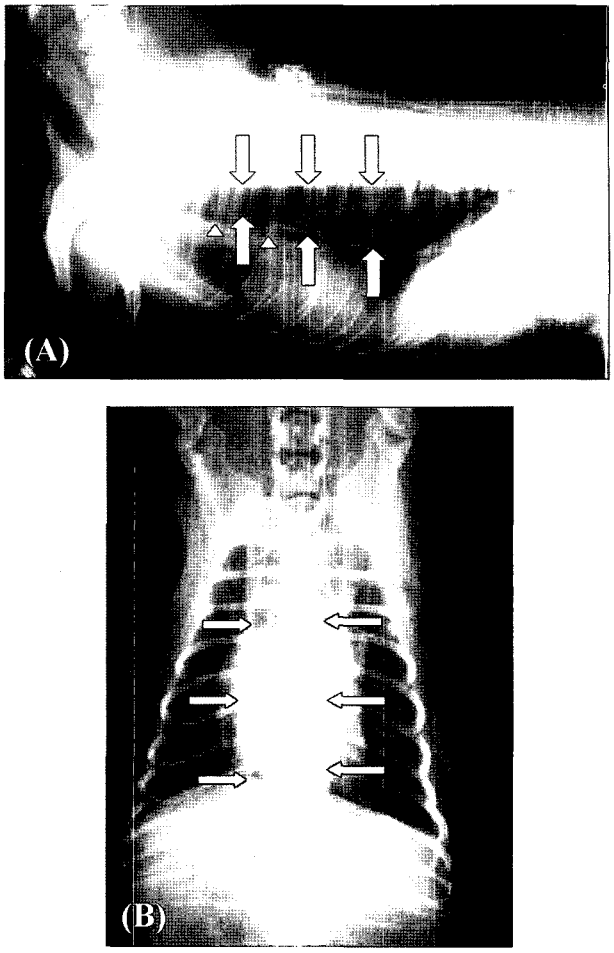

Fig 1. Lateral (A) and ventrodorsal (B) thoracic radiograph demonstrating dilated-, gas filled- esophagus and soft tissue stripe representing esophageal wall (arrows). Tracheal line ventrally displaced (arrow heads).

Pre-TSH serum T4 concentration was 2.3 μg/dL (reference range, 1.1 to 4.0 μg/dL) and post-TSH serum T4 concentration was 4.2 μg/dL (reference range, 1.5 to 4.5 μg/dL). Thus the dog was definitively diagnosed as acute fulminating generalized MG.

Treatment was initiated with pyridostigmine bromide (0.05 mg/kg, PO, TID; Myung moon pharma., South Korea). Even though the clinical response to the long-acting anticholinesterase was striking, the duration of effect was only persisted approximately 2 to 3 hours. Thus the dose was increased to 1 mg/kg (PO, TID), then it was persisted more than 8 hours. The dog responded well to this treatment, had marked improvement in muscle strength, megaesophagus, and respiratory function, and was discharged with instruction to administer pyridostigmine (1 mg/kg, PO) twice daily 2 days after the presentation. The absence of a radiographically demonstrable cranial mediastinal mass does not rule out the possibility of a thymoma. Hence computed tomography (CT) was performed 2 weeks after discharge. Because no occupying mass was found

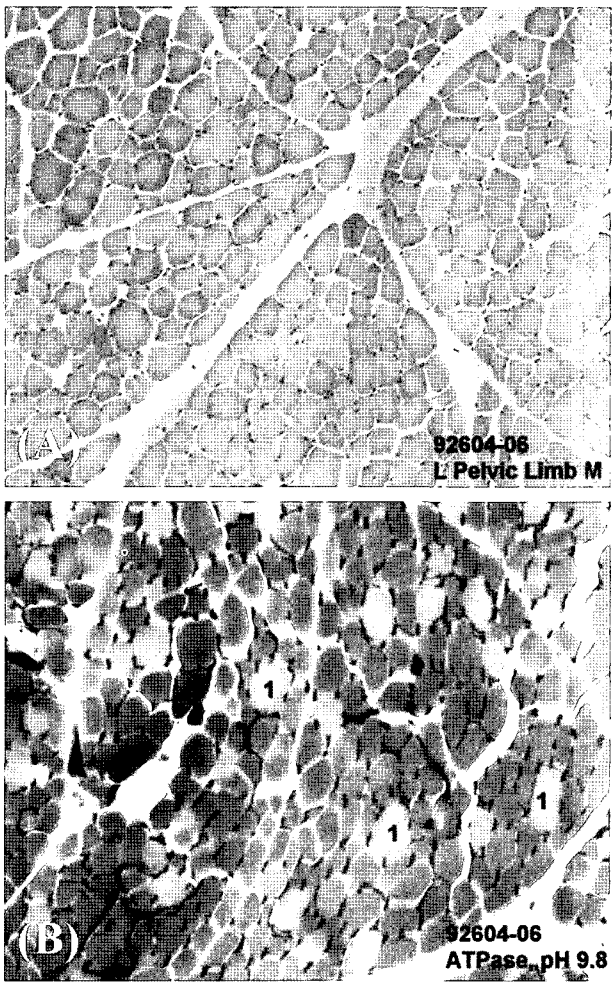

Fig 2. There was a moderate variability in myofiber size with scattered atrophic fibers having a round shape and predominantly of type 2. Type 1 fibers are lighter staining (1) and type 2 fibers are dark staining. (A) Hematoxylin-Eosin stain, ×400. (B) Adenosine triphosphatase (ATP) stain at pH 9.8, ×400.

in mediastinal space, it could be ruled out. Serum AChR antibody titer was monitored on 2 months (0.12 nmol/L) and 5 months (0.22 nmol/L) after the first therapy. The dog has been successfully managed with pyridostigmine bromide for 7 months after initial treatment.

Discussion

Acute fulminating MG in dogs is characterized by sudden onset of regurgitation of large volumes of fluid associated with megaesophagus, rapid progression to quadriparesis, respiratory failure, and high mortality (7,10). Respiratory failure is a consistent complication of acute fulminating MG in dogs and a common cause of death (7). It may result from ventilatory failure caused by weakness of the intercostals muscles or diaphragm or by severe aspiration pneumonia (10). Especially, aspiration pneumonia is the main reason for death or euthanasia in dogs with AMG (2). Accordingly, rapid recognition, accurate diagnosis, initiation of appropriate therapy, and aggressive prevention and/or treatment of aspiration pneumonia are essential to maximize the chance of a favorable outcome (9,10). The prevalence of acute fulminating MG in dogs has been reported as 16% (9). In this case, regurgitation was firstly shown and followed by respiratory failure and rapid loss of muscle strength resulting in recumbency. Clinical signs were progressively worsen, especially generalized muscle weakness continued unabated in spite of the rest. However, aspiration pneumonia was not noted based on physical, laboratory, and radiographic examinations, which suggests that rapid management may contribute to successful treatment.

For diagnosis MG, short acting anticholinesterase drug challenge test, electrodiagnostic assessment, and demonstration of elevated anti-AChR antibody concentrations have been performed (9). Among them, measurement of serum AChR antibody titer is sensitive and specific assay for diasnosis of immune-mediated MG in human beings and animals and a reported study showed seronegative myastehia occurs about 2% and false positive is rare (10). In this case, although electrodiagnostic assessment was not performed, other two assays and histopathologic examinations of muscle biopsies from the pelvic limb were useful to diagnosis of MG.

With the progression of treatment, there has been excellent correlation between resolution of clinical signs, including megaesophagus, and return of AChR antibody titers to less than 0.6 nmol/L (10). Dewey (1999) reported that mean final serum AChR antibody concentration of dogs treated for MG was 0.95 nmol/L (range, 0.61 to 1.49 nmol/L), a decrease of 81%. In this case, a sequential decline in serum AChR antibody concentration was also demonstrated with improving clinical signs over time while receiving therapy. Recent titer was 0.22 nmol/L, a decrease of 72%. Since anticholinesterase drugs have no effect on the immune response in AMG, immunosuppressive agents are commonly and successfully used in myasthenic humans in combination with anticholinesterase therapy (4). In canine myasthenics, esophageal muscle appears to be less responsive than appendicular muscle to anticholinesterase agents (3). However clinical signs, including megaesophagus, were dramatically improved and successfully managed with pyridostigmine bromide only in this case. Immunosuppressive agents should be avoided initially in patients with overwhelming aspiration pneumonia, which frequently associated with acute fulminating MG. Thus single application of anticholinesterase drugs may be useful in acute fulminating MG.

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시츄 견에서 발생한 급성 전격 중증 근육무력증

강병택 · 유종현* · 박효진 · 정동인 · 박 철 · 구수현 · 전효원 · 김주원 · 김하정 · 임채영 · 조수경 · 이소영 · 허라영 · 김정현 · 한성국 · 성주헌 · 박희명[1]

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요 약 : 3년령의 중성화된 암컷 시츄 견이 급성의 구토, 설사 및 전신 쇠약으로 인하여 내원하였다. 환자는 전신 쇠약, 호흡수 증가 및 노력성 호흡을 나타냈으며 신경 검사 상에서는 사지 근육 쇠약과 항문 조임근의 긴장도가 감소하였다. 방사선 검사를 통하여 거대식도가 확인되었다. 좌측 뒷다리 근육의 생검에 대한 조직병리 검사 상에서는 2형 섬유 위축을 제외하고는 특이적인 이상 소견이 발견되지 않았다. 혈청의 아세틸콜린 수용체 항체가가 상승되어 있어 (0.78 nmol/L; 정상 범위, 0.6 nmol/L 이하) 급성 전격 중증 근육무력증으로 확진되어졌다. 환자는 pyridostigmine bromide에 대하여 극적으로 반응하여, 근육 강도, 거대식도, 그리고 호흡 기능이 현저하게 호전되었으며 현재 7개월 동안 환견은 성공적으로 관리되어져 오고 있다.

주요어 : 아세틸콜린 수용체 항체가, 급성 전격 중증 근육무력증, 거대식도, 2형 섬유 위축.