A case of hypertrophic feline muscular dystrophy in a Belgian domestic shorthair cat

Een geval van feliene hypertrofische spierdystrofie bij een huiskat in België

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ABSTRACT

A 3-year-old, male domestic shorthair cat was presented with signs of progressive muscular hypertrophy. A diagnosis of hypertrophic feline muscular dystrophy was made on the basis of the typical clinical presentation in cats and on the basis of the results of medical imaging, the electrodiagnostics and the findings on histopathology and immunohistochemistry of muscle biopsies. The cat was initially successfully treated with prednisolone. Eight months after presentation, however, the cat was euthanized because of acute renal failure. To the author's knowledge, this is the first report of hypertrophic feline muscular dystrophy in a domestic cat in Belgium.

SAMENVATTING

Een korthaar huiskat van 3 jaar oud werd aangeboden met progressieve symptomen van spierhypertrofie. De diagnose van feliene hypertrofische spierdystrofie werd gesteld op basis van de typische klinische presentatie bij katten en op basis van de bevindingen van de medische beeldvorming, een elektrodiagnostisch onderzoek en histopathologie en immunohistochemie van spierbiopten. De kat werd initieel succesvol behandeld met prednisolone maar werd 8 maanden na het eerste bezoek geëuthanaseerd wegens acute nierinsufficiëntie. Voor zover bekend bij de auteurs is dit het eerste geval van feliene hypertrofische spierdystrofie beschreven bij een huiskat in België.

INTRODUCTION

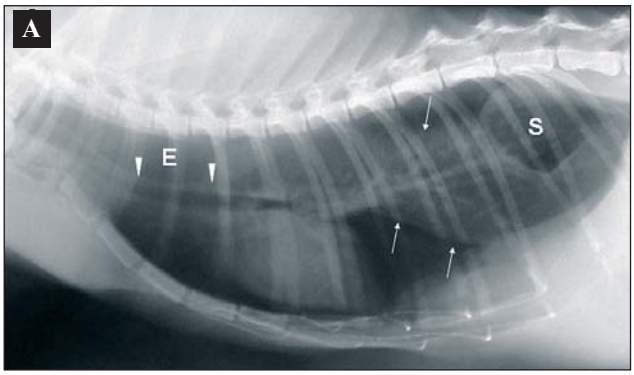
Dystrophin-deficient feline muscular dystrophy is a myopathy caused by the absence of dystrophin, a large protein found in the cardiac and skeletal muscles. The structural components of dystrophin mediate a mechanical function that stabilizes and links the muscle cell membrane and the cytoskeleton. Thus, the lack of functional dystrophin leads to instability of the sarcolemma and therefore to chronic muscle damage and degenerative pathology (Carpenter *et al.*, 1989; Gaschen *et al.*, 1992; Kohn *et al.*, 1993; Gaschen *et al.*, 1998; Verhaeghe *et al.*, 2008).

As with dystrophinopathies in other animals, the deficiency is due to a mutation in the dystrophin gene, which is located on the X chromosome. Therefore, the disorder is transmitted according to an X-linked recessive inheritance pattern (Carpenter *et al.*, 1989; Gaschen *et al.*, 1992; Kohn *et al.*, 1993; Gaschen *et al.*, 1998; Shelton and Engvall, 2002; Shelton and Engvall, 2005; Verhaeghe *et al.*, 2008).

Dystrophin deficiency is the most common cause of muscular dystrophy in animals, and thus in cats. A major reason for this is that the extremely large dystrophin gene is the target of more frequent mutations than a smaller gene (Shelton and Engvall, 2002).

The prominent clinical sign in defective cats is a marked muscular hypertrophy; therefore the term hypertrophic feline muscular dystrophy (HFMD) is used (Gaschen *et al.*, 1992). Diagnosis is based on the typical clinical features and on the results of histopathology and immunohistochemistry of muscle biopsies. Until now, no specific treatment is known. Life-threatening complications such as acute renal failure and peracute rhabdomyolysis can develop in the course of the disease.

Cases of hypertrophic feline muscular dystrophy have been reported in the US and Germany (Carpen-



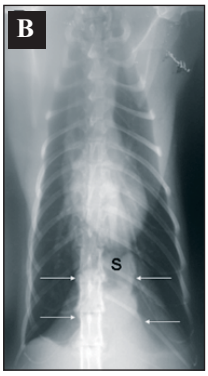


Figure 1. Right-left (A) and ventro-dorsal (B) projections of the thorax. (A) The esophagus (= E) is dilated which is indicated by the presence of a stripe sign (dorsal wall of the trachea is visible) (arrowheads). There is a soft tissue opacity in the caudo-dorsal part of the thorax, extending from T8 to T13 (arrows) and including a thick-walled, pear-shaped gas-filled structure (stomach = S) visible starting at T11 and stretching till the abdomen. (B) The caudal mediastinum appears enlarged (arrows) and contains a gas-filled structure (stomach=S). The stomach is still visible within the soft tissue opacity (arrows). These findings are compatible with a mega-esophagus and a hiatal hernia.

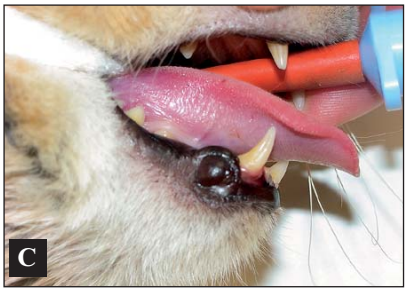


Figure 2. Images of the cat showing the muscular hypertrophy of the skeletal muscles and of the tongue: (A) marked muscular hypertrophy of the muscles of the neck; (B) protrusion of the tongue due to the hypertrophy of the tongue; (C) hypertrophy of the tongue clearly visible after intubation.

ter *et al.*, 1989; Gaschen *et al.*, 1992; Kohn *et al.*, 1993). The present report is the first description of a case of HFMD in a cat in Belgium.

CASE DESCRIPTION

A 3-year-old male, domestic shorthair cat was presented with symptoms of hypertrophic skeletal muscles and a stiff gait. Since the age of 6 months the cat had suffered from intermittent gastro-intestinal symptoms such as vomiting and diarrhea. Hypertrophic muscles had been seen since youth, but had increased with time. Clinical examination revealed no significant abnormalities. At the age of 10 months, the results of serum biochemical analysis showed increased values of alanine aminotransferase (ALT: 361 iu/l; reference < 43 iu/l), aspartate aminotransferase (AST: 1250 iu/l; reference < 46 iu/l), alkalic phosphatase (AP: 218 iu/l; reference < 144 iu/l), potassium (K: 5.5 mmol/l; reference values 3 to 5 mmol/l) and bile acids (21 µmol/L; reference < 8 µmol/L). The cat was symptomatically treated for the gastro-intestinal signs with amoxicillin-clavulanic acid (Synulox; Pfizer), metoclopramide (Primperan; Sanofi-Synthelabo), metronidazole (Flagyl; Aventis) and prednisolone (Prednisolone; Kela). By the age of 12 months, the gastro-intestinal signs had disappeared. However, the hypertrophy of the skeletal muscles had increased. Thoracic radiographs at the age of 2 years and 8 months revealed the presence of a mega-esophagus and a sliding hiatal hernia (Figures 1A, B).

At that time, the cat was referred to the Small Animal Clinic of the University of Ghent. The cat showed a stiff gait and marked skeletal muscle hypertrophy. Especially the muscles of the neck (Figure 2A) and, to a lesser extent, the dorsal and pectoral muscles, the suprahyoid muscles and the muscles of the pelvic limbs were hypertrophic. Sometimes the cat was panting with protrusion of the tongue (Figure 2B), and after intubation, a hypertrophic tongue was clearly visible (Figure 2C). A general physical and neurological examination revealed no significant abnormalities. The biochemistry results showed increased values of alanine aminotransferase (ALT: 228 iu/l; reference < 43 iu/l), aspartate aminotransferase (AST: 993 iu/l; reference < 46 iu/l), lactate dehydrogenase (LDH: 3535 iu/l; reference < 188 iu/l), creatine kinase (CK: 207 iu/l; reference < 127 iu/l) and potassium (K: 5.5 mmol/l; reference values 3 to 5 mmol/l).

Based on the history, the results of the laboratory examinations and the extensive muscle hypertrophy, HFMD was suspected.

Electrophysiological examination and muscle biopsy were performed under general anesthesia. Pre-anesthetic electrocardiographic examination revealed normal P-QRS-T waves and on echocardiography no abnormalities were noticed on dimension, function and appearances of the myocardium. The cat was premedicated with xylazine hydrochloride 2% (XYL-M®, VMD), 1 mg/kg IM. Induction of anesthesia was per-

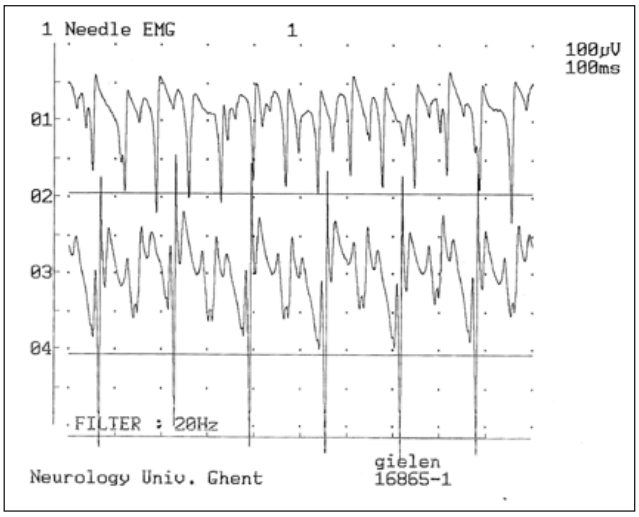


Figure 3. EMG findings in the appendicular muscles and the muscles (trace 01) of the neck (03): complex repetitive discharges.

formed using propofol (Rapinovet®, Schering-Plough) 4 mg/kg on effect until intubation was possible. Anesthesia was maintained with isoflurane (Isoflo, Abbott Lab) in oxygen using a commercial circle system.

On electromyography (EMG), complex repetitive discharges (Figure 3) were seen in the appendicular muscles and the muscles of the neck. To avoid artefacts due to EMG needle insertion, muscle biopsy specimens were taken on the opposite side from where the EMG was performed. Muscle biopsy samples were taken from the triceps muscle using a biopsy punch (Acu-Punch, Acuderm). Fresh specimens were kept cool using cold packs and shipped overnight to a specialized laboratory.

Histopathological findings included disseminated irregular myofiber atrophies and massive hypertrophies, myofiber splitting, multiple central nuclei and individual myofiber necrosis (Figure 4A, B). Immunohistochemistry revealed deficits in the expression of dystrophin 1 and 2 (Figure 5A, B, C). A final diagnosis of HFMD was made.

Treatment with prednisolone was initiated (1mg/kg/day). The dose was gradually diminished over 2 months (1mg/kg/day every 2 days) and discontinued after 5 months on the owner's request. One year after presentation, the cat's condition deteriorated; she refused to eat and drink and started to vomit and regurgitate. The owner refused further treatment and the animal was euthanized.

Necropsy showed generalized muscular hypertrophy, especially of the muscles of the neck, the thoracic limbs and the diaphragm. In addition, hypertrophy of the tongue, dilatation of the distal part of the esophagus and a hiatal hernia were seen macroscopically (Figures 6A, B, C). The heart weighed 16g (normal weight < 16g) and had white patches on the myocardium. No other significant abnormalities were found on gross examination. Histopathology results of striated muscles included myofiber degeneration and regeneration, mild fibrosis, swollen myocytes and the presence of central nuclei in the myocytes. Cardiac histopathology was restricted to a mild focal suppurative myocarditis. The kidneys showed tubular mineralization.

DISCUSSION

In 1989, hypertrophic feline muscular dystrophy was described for the first time in two male littermates of domestic cats (Carpenter *et al.*, 1989). More recent reports (Gaschen *et al.*, 1992; Kohn *et al.*, 1993; Gaschen *et al.*, 1998) all describe affected male cats with familial relationship suggesting an X-linked recessive mode of inheritance. For the cat in the present

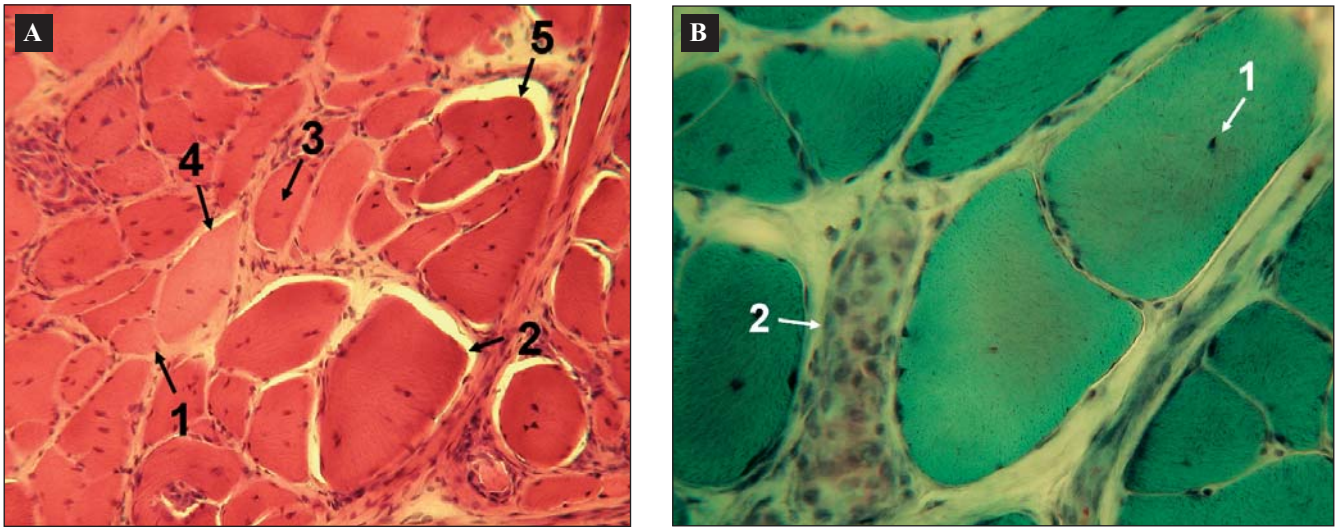


Figure 4. Section of the triceps muscle: (A) a wide variation of myofiber distribution is noticeable: myofiber atrophies (1) and massive hypertrophies (2). There are multiple central nuclei (3) and groups of degenerating (4) and basophilic regenerating fibers (5). Hematoxylin and eosin, original magnification x120; (B) dystrophic muscle fibers with some central nuclei (1) and a myogenic regenerative nuclear cluster (2). Engel stain, original magnification x120.

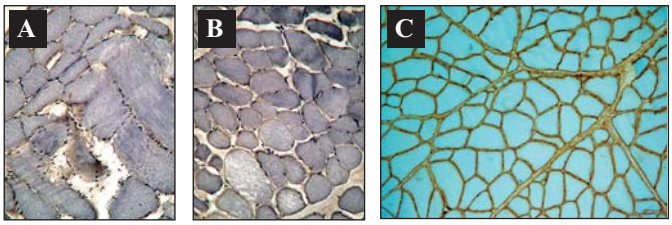


Figure 5. Section of the triceps muscle: histochemistry. (A) Immunohistochemical reaction with dystrophin-1 antibody: partial loss of membrane-associated protein in comparison to the control; original magnification x 54. (B) Immunohistochemical reaction with dystrophin-2 antibody: partial loss of membrane-associated protein in comparison to the control; original magnification x 54. (C) Dystrophin control stain of a normal skeletal muscle; original magnification x 54.

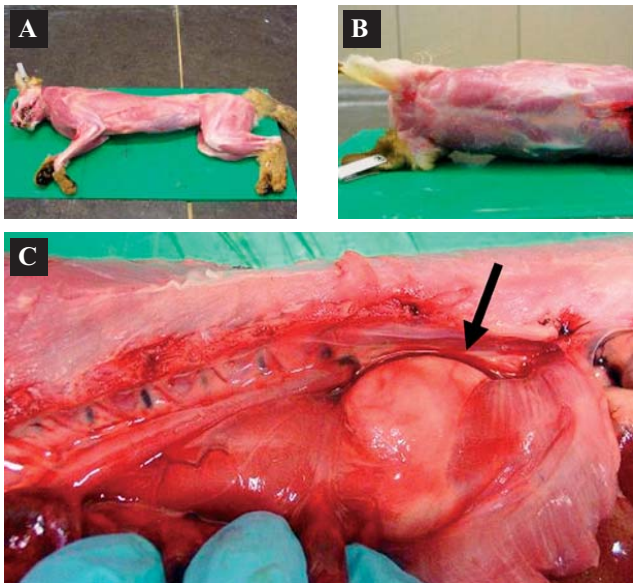


Figure 6. Images of the cat on necropsy: (A) marked muscular hypertrophy; (B) muscle hypertrophy of the muscles of the neck; (C) dilatation of the distal part of the esophagus (arrow) and a hiatal hernia.

study, however, no information regarding its littermates or its genetic background was available.

Clinical symptoms in cats with HFMD are seen in male cats from 3 to 6 months of age (Gaschen *et al.*, 2004; Shelton, 2004; Shelton and Engvall, 2005). The hallmark of the disorder in cats is the prominent hypertrophy of the axial and appendicular skeletal muscles starting at 10 weeks of age. The cat in the present study showed progressive muscular hypertrophy located in the muscles of the neck and the proximal muscles of the four limbs. Protrusion of the tongue was visible in the later course of the disease, indicating hypertrophy. Functionally, the cats have a stiff gait with a tendency to bunny-hop (Carpenter *et al.*, 1989; Gaschen *et al.*, 1992; Gaschen *et al.*, 2004). The gastrointestinal symptoms of this cat might have been caused by the mega-esophagus and hypertrophy of the lingual and diaphragmatic musculature.

The diagnosis of HFMD is based on the typical clinical presentation and on the results of histopathology and immunohistochemistry. In any young cat with progressive muscular hypertrophy and gait abnormalities beginning in the first months of life, HFMD should be considered. Additionally, increase in the activity of serum CK, AST and ALT are indicative for HFMD. Release of these enzymes from the myofibers occurs from myofiber necrosis or from leakage of the cytoplasm due to generalized instability of the myofiber membrane (Shelton and Engvall, 2002; Gaschen *et al.*, 2004).

The results of thoracic radiographs (Gaschen *et al.*, 1999), echocardiography (Chetboul *et al.*, 2006) and electrodiagnostic testing (Howard *et al.*, 2004) provided more diagnostic and prognostic information. Radiographs of the thorax revealed a mega-esophagus and a hiatal hernia, typical lesions in HFMD cats. In contrast to other reports, no enlarged cardiac silhouette was visible on radiography (Gaschen *et al.*, 1999). Conventional echocardiography could not detect any significant abnormalities in the cat in the present study, such as have been described in the literature (Chetboul *et al.*, 2006). EMG showed complex repetitive discharges in the appendicular muscles and the muscles of the neck. Differences in EMG findings between proximal and distal appendicular muscles, as described in a study by Howard (2004), were not found in the present cat.

The most striking aspect on gross pathology was the marked hypertrophy of different muscle groups and, on immunohistochemistry, the absence of dystrophin, which provides a conclusive diagnosis for HFMD (Carpenter *et al.*, 1989; Gaschen *et al.*, 1992; Gaschen and Burgunder, 2001; Shelton and Engvall, 2002; Shelton and Engvall, 2005).

The prognosis of HFMD is guarded to poor. Affected cats do not loose their ability to ambulate or breed, though as a result of the lingual, esophageal and diaphragmatic hypertrophy; the animals may suffer from regurgitation and dysphagia, which in turn may cause decreased water intake and hyperosmolar syndrome with acute renal failure (Gaschen *et al.*, 1992; Shelton and Engvall, 2002). Another fatal complication of the disorder is peracute rhabdomyolysis associated with stress and anesthesia with volatile anesthetics. An increased sensitivity of the dystrophin-deficient sarcolemmal membrane to the aforementioned factors is suspected (Gaschen *et al.*, 1998). Rarely, cardiac failure due to cardiomyopathy will develop in cats with HFMD (Gaschen *et al.*, 1999). The cat in the present report remained in good condition until the age of 3 years and 8 months, when it developed regurgitation and anorexia, presumably with dehydration and hyperosmolality, which resulted in acute renal failure.

Specific therapies for HFMD are not currently available. As for all inherited disorders, the affected animals should be excluded from breeding programs. In accordance with the recommendations of human and animal model studies, the cat in the present report

was treated with prednisolone. As recent evidence suggests that a chronic inflammatory reaction contributes to the progression of the pathology, immunosuppressive drugs are thought to be beneficial in dystrophies (Porter *et al.*, 2002). Human patients with Duchenne muscular dystrophy treated with low dose prednisolone improved significantly for a period of at least 2 to 4 months, and the deterioration of the symptoms at 2 years was less than the natural course of events noted in control patients (Pradhan *et al.*, 2006). Another potential immunosuppressive drug, cyclosporine, has also proven to reduce the severity of muscular dystrophy (De Luca *et al.*, 2005; Davies and Grounds, 2006; Grounds and Davies, 2007).

In conclusion, hypertrophy of muscles and a stiff gait are typical clinical features in cats with muscular dystrophy. Definitive diagnosis is based on the results of the immunohistochemistry of muscle biopsies. Prednisolone might temporarily improve the quality of life in cats with HFMD.

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