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CASE REPORT



Mucopolysaccharidosis VI in a European Shorthair cat: Neurological presentation, computed tomography findings and genetic investigation

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ABSTRACT

The present case report describes the clinical signs of a 10-month-old, intact female, Domestic Shorthair cat presented with a history of chronic progressive difficulty to walk with the four limbs. The physical and neurological examinations revealed skeletal deformities, corneal opacity and a severe spastic non-ambulatory tetraparesis. Complete blood count and biochemistry profiles were unremarkable. Diffuse bone rarefaction, hyperostosis and an apparent fusion of the vertebral bodies were observed on spinal radiographs. A non-contrast computed tomography (CT) exam of the whole body of the patient was performed. Based on the medical history, clinical findings, laboratory analysis, spinal radiographs and CT findings, a lysosomal storage disorder was suspected. Genetic testing for mucopolysaccharidosis VI and VII revealed a genetic mutation, ARSB variant L476P, confirming the diagnosis of mucopolysaccharidosis VI.

KEYWORDS

mucopolysaccharidosis, lysosomal storage disease, computed tomography, genetic testing, cat

INTRODUCTION

Mucopolysaccharidosis is one of the main subgroups of pathologies known as 'lysosomal storage diseases' (Skelly and Franklin, 2002; Crawley et al., 2003; Lyons et al., 2016). These diseases are mostly inherited in an autosomal recessive pattern and involve single enzyme deficiencies within the lysosomal catabolic pathway (Skelly and Franklin, 2002; Lyons et al., 2016). In particular, mucopolysaccharidosis VI (MPS VI) is characterised by a deficiency of arylsulphatase B (ARSB) due to a thiamine to cytosine transition (c. 1427 T<C) and replacement of the wild-type leucine by proline (L476P) (Yogalingam et al., 1996; Lyons et al., 2016). MPS VI has been found to be analogous in humans and in the cat population (Aguirre et al., 1983). This deficiency leads to lysosomal accumulation and urinary excretion of the glycosaminoglycan (GAG) dermatan sulphate (Skelly and Franklin, 2002; Lyons et al., 2016).

GAG accumulation leads to cell injury, in particular interferes with the ossification of bones, affecting growth, gait and appearance (Lyons et al., 2016).

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Cats with this pathology present facial dysmorphism, corneal opacity, cardiac valvular thickening, dwarfism and severe degenerative joint disease (Konde et al., 1987).

The clinical phenotype of patients range from mild to severe which is characterised by growth retardation, coarse facial features, skeletal deformities and organ and soft tissue involvement (Yogalingam et al., 1996; Crawley et al., 1998).

In human medicine, MPS VI is a rare pathology which is also called 'Maroteaux-Lamy syndrome' (Aguirre et al., 1983; Yogalingam et al., 1996; Lyons et al., 2016).

In the veterinary literature, MPS VI was initially described by Cowell et al. (1976) in a Siamese cat reported to be 'reluctant to walk', 'smaller than normal' and 'with shortened and broadened appearance' (Lyons et al., 2016). Further case reports have been published, along with genetic studies, in order to investigate the genetic mutation in Siamese families and crossbreeds (Crawley et al., 1998). However, the description of advanced imaging findings of mucopolysaccharidosis VI is lacking.

Hence, the aim of this case report is to describe the general features, the computed tomography (CT) findings and the genetic investigations of a feline case of MPS VI and compare them with what was previously described in the veterinary literature.

CASE PRESENTATION

A 10-month-old, intact female, Domestic Shorthair cat was referred because of a history of chronic progressive difficulty to walk with the forelimbs. At the time of presentation, the general physical examination showed mild hypothermia, bilateral corneal opacity and skeletal deformities with facial dysmorphism. The neurological examination revealed lateral recumbency, generalised stiffness, thoracolumbar kyphosis, severe spastic non-ambulatory tetraparesis and absent proprioception on the four limbs (Fig. 1). No hyperalgesia was evoked on the extension and flexion of the joints and palpation of the vertebral column. Cranial nerves and spinal reflexes were normal. The neurological localisation is primarily cervical spinal cord (C1–C5 segments) with also a diffuse and generalised vertebral and bone involvement.

The neurologic examination was followed by an extended laboratory analysis, including blood counts, serum biochemical profile, coagulation and urinary analysis, associated with a radiographic study of the vertebral column.

The bloods count was within normal limits. Biochemistry revealed a mild hyperproteinaemia (8.0; 6.1–7.4 g dL⁻¹) with an increased in albumin (4.2; 2.9–3.8 g dL⁻¹) and mild hypercalcaemia (11.1; 9.3–10.6 mg dL⁻¹) secondary to hyperalbuminaemia.

The haemostatic profile showed an increase in activated partial thromboplastin time (47.5; 11–16.5 s). This finding was compatible with a genetic deficiency of coagulation factor XII which, in cats, is considered an alteration without clinical significance. Urinalysis showed a moderate decrease in urinary osmolarity (545; 1465–2473 mOsm kg⁻¹).

The cervical and thoracolumbar spinal radiographs (right latero-lateral projections) showed diffuse bone rarefaction, shortening and an apparent fusion of the vertebral bodies, facet joints hyperostosis and increased intervertebral distance.

Taking into account these findings, the differential diagnoses considered were degenerative diseases (such as lysosomal storage diseases) and metabolic diseases (such as hyperparathyroidism, vitamin D intoxication, primary hypothyroidism, hypervitaminosis A).

Hyperparathyroidism was ruled out because ionised calcium was normal (1.27; 1.23–1.38 mmol L⁻¹) and the parathyroid hormone level (PTH) was low (3; 10–55 pg mL⁻¹). Vitamin D intoxication was excluded because cholecalciferol (1.38; 0.25–4.75 ng mL⁻¹) and its metabolites (25-cholecalciferol 7.29; 4.50–18.75 ng mL⁻¹; 1-25 cholecalciferol 0.62; 0.01–0.80 pg mL⁻¹) were within reference ranges. Primary hypothyroidism was also excluded because the tests evaluating thyroid function were normal (TSH 0.03, 0.03–0.15 mg mL⁻¹; FT4 11.0, 8.1–16.9 pmol L⁻¹; TT4 1.59, 1.21–3.29).

Hypervitaminosis A was ruled out because the cat is fed with a commercial wet and dry diet and no raw liver intake was reported. Furthermore, the presence of corneal opacity and facial dysmorphism is not described in cases of hypervitaminosis A. For a better investigation of the typical alterations caused by the suspected lysosomal disease, a non-contrast CT exam of the whole body of the patient was

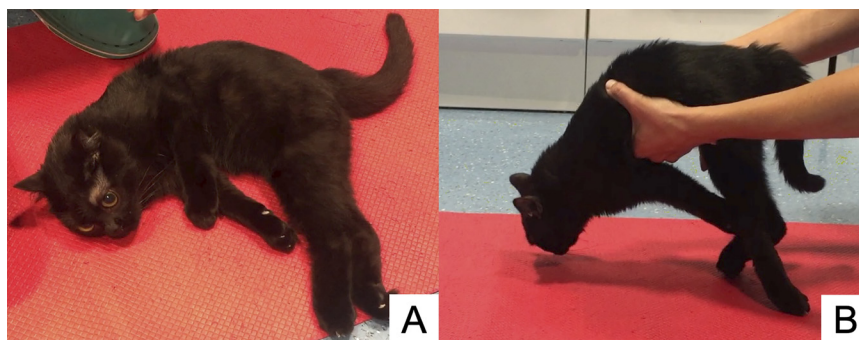


Fig. 1. Images of the cat during the neurological examination showing lateral recumbency (A), generalised stiffness, low head carriage and severe spastic non-ambulatory tetraparesis (B)

performed. A third-generation dual-source computed tomography (192×2 DSCT) (Somatom Definition Force; Siemens, Erlangen, Germany) was used with a high-pitch flash modality scan protocol, with two tubes set at the same energy level (120 kVp), a gantry rotation time of 0.28 s/r, and a pitch of 3.4 and $2 \times 128/192$ slices. The reconstructed slice thickness was 0.6 mm with a 0.3 mm interval). The cat was placed in right recumbency with the head first.

The CT showed a generalised osteopenia, an alteration of the morphology of the sternum described as '*pectus excavatum*' with a consequent more distended heart, and could evaluate the spinal alterations seen in the radiographs with a better resolution: wider intervertebral spaces (particularly between lumbar vertebrae), elongated pedicles and malformed articular processes of the vertebrae, a remodelling of the shape of the vertebral bodies characterised by a shortened and cuboid aspect (particularly in the cervical and thoracic vertebrae), an epiphyseal dysplasia characterised by ill-defined, small and irregular vertebral epiphyses, and a malformation of the dens that appeared shorter than normal (Fig. 2).

At the level of the limbs a dysplasia of shoulders, elbows, carpal joints, knees, hips and tarsal joints was seen, characterised by a delayed and incomplete mineralisation of the epiphyseal cartilage. Ossified regions of the epiphyses were smaller than normal and had a nonuniform opacity with

granular appearance, while the subchondral bone of the articular surfaces was distorted (Fig. 3).

At the level of the hip, a femoral head epiphysis remodelling with a coxofemoral bilateral subluxation was seen, while at the level of the knees a bilateral medial patellar luxation was found.

Moreover, a facial dysmorphism characterised by shortened nasal conchae, absence of the left frontal sinus and reduction of the right frontal sinus was found (Fig. 4).

Also, a hypoplastic hyoid apparatus and shortened incisive and maxillary bones were noted.

In addition to all these skull alterations, a dysplasia of the bone component of the tympanic bulla was discovered, characterised by a mild asymmetrical triangular shape and an irregular multifocal thickness of the ventrolateral aspect of the bulla, and a bilateral dysplastic temporomandibular joint was seen.

At the level of the brain, a diffuse accentuation of the cerebral sulci and a diffuse mild ventriculomegaly were found.

After the CT, cytological exam of spleen and liver was performed and the findings were unremarkable.

The diagnostic suspicion based on the medical history, clinical findings, laboratory analysis, spinal radiographs and CT findings was a degenerative disease, in particular feline mucopolysaccharidosis VI or VII.

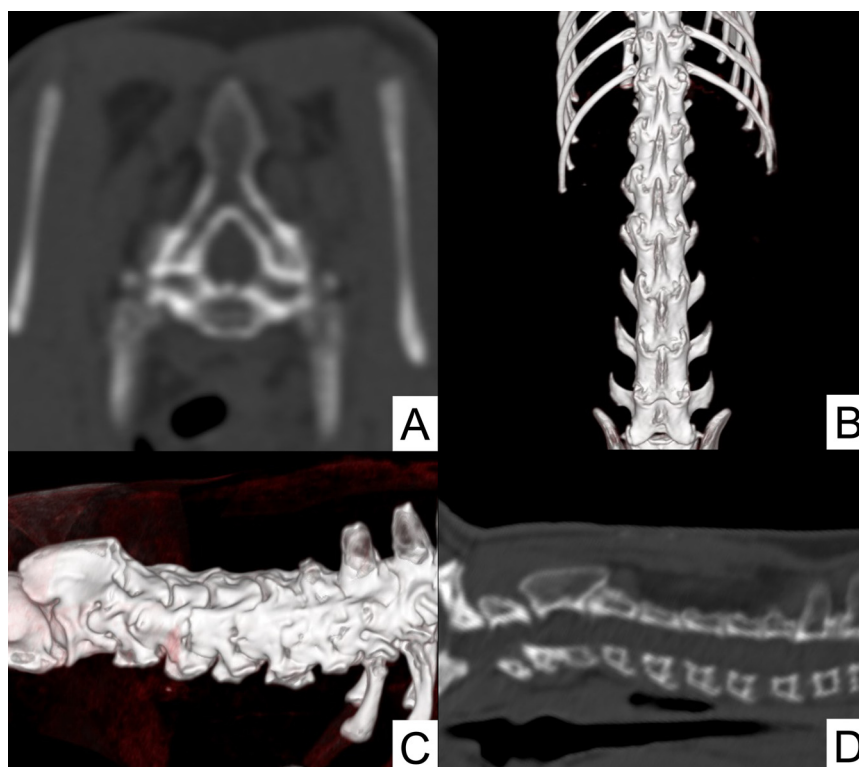


Fig. 2. An (A) multiplanar reconstructed (MPR) transverse image of T2, bone window, a (B) 3D volume rendering reconstruction of the lumbar column, dorsal view, a (C) 3D reconstruction of the cervical column, left lateral view, and an (D) MPR of the cervical column, sagittal view, bone window, are shown. The general osteopenia can be visualised in (A) and (D), wider vertebral interspaces in (D), and a remodelled shape of the vertebral bodies with a cuboid aspect and an epiphyseal dysplasia in (A) and (D). Elongated pedicles and malformed articular processes can be seen in (B) and (C). The malformed dens of the axis can be noted in (D)

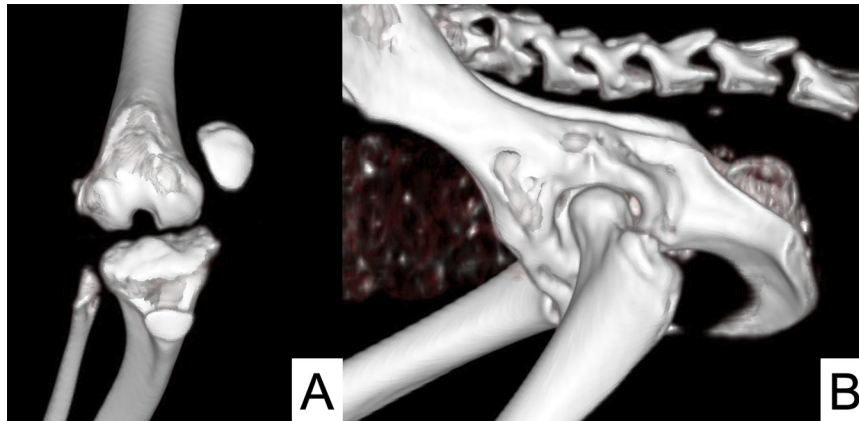


Fig. 3. A 3D volume rendering of the right knee (A) and of the left coxofemoral joint (B) showing the medial patellar luxation (A) and a coxofemoral dorsal subluxation (B). Note the smaller ossified regions of the epiphyses with a non-uniform opacity

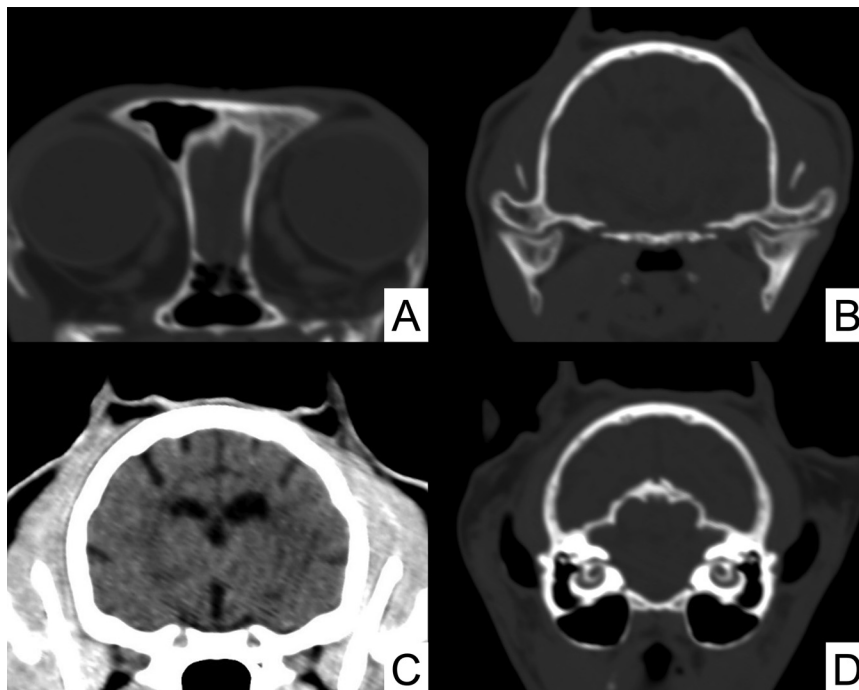


Fig. 4. An MPR transverse image of the skull, bone window (A, B, D) and of the brain, soft tissue window (C) showing the absence of the left frontal sinus (A), a bilateral dysplastic temporomandibular joint (B) and a bilateral dysplasia of the tympanic bullae, characterised by a mild triangular shape and an irregular multifocal thickness of the ventrolateral aspect of the bulla (D). In (C) a diffuse accentuation of the cerebral sulci and a mild lateral ventriculomegaly is shown

A genetic testing for mucopolysaccharidosis VI and VII was performed and the cat was found to be affected by the gene mutation ARSB variant L476P, indicative of mucopolysaccharidosis type VI. The recheck one month later showed unchanged clinical signs. Unfortunately, the long-term follow-up went lost and the owner did not answer the phone calls.

DISCUSSION

Lysosomal storage diseases are inherited disorders which involve the cellular metabolism (Crawley et al., 2003).

MPS VI is one of the main subgroups of these pathologies and it is caused by a deficiency of the enzyme N-acetylgalactosamine 4-sulfatase, arylsulfatase B (ARSB) (Aguirre et al., 1983; Abreu et al., 1995). This enzyme degrades the glycosaminoglycan dermatan sulphate by cleaving the terminal sulphate of N-acetyl glucosamine; enzyme deficiency results in intralysosomal storage of this GAG (Aguirre et al., 1983). The GAGs are present in various connective tissues, in particular in bone and cartilage, and skeletal disease is the predominant abnormality associated with this disorder (Crawley et al., 2003).

Previous studies described a missense mutation (c. 1558 G>A) with the amino acid substitution of the wild-type aspartic acid to an asparagine at codon 520 (D520N) in a colony of Siamese cats (Crawley et al., 1998; Yogalingam et al., 1998). The ARSB D520N variant alone has no evidence of association with the disease, but in combination with the L476P variant it can result in a mild form of MPS VI (Lyons et al., 2016). Cat heterozygotes (L476P/D520N) have been described with a high incidence of degenerative joint disease with normal skeletal growth (Crawley et al., 2003).

Clinical features of MPS VI in cats are evident at 6–8 weeks of age and involve the musculoskeletal system, joints, eyes, central nervous system and cardiovascular system. In particular, the musculoskeletal alterations affect areas of endochondral ossification and result in spondylosis, arthritis and ankylosis, hip and patella subluxation, reduced flexibility of the cervical spine, pathological fractures and *pectus excavatum*. Cats can also have a broad face, shortened nose, smaller ears, stunted growth and dwarfism (Crawley et al., 2003). Corneal opacity and cardiac valvular thickening have also been described (Konde et al., 1987). The central nervous system alterations, due to the bony compression of the spinal cord, result in progressive difficulty walking with hindlimb paresis or paralysis (Crawley et al., 2003). In our case the hypothesis of a compressive myelopathy was suggested due to bony alterations reported in the CT. This finding could be better evaluated by an MRI investigation.

Regarding changes in blood exams, as suggestive of a storage disease in the veterinary literature, the presence of dark purple cytoplasmic granules in granulocytes, lymphocytes and monocytes has been described (Wang et al., 2018). Unfortunately, in our case the blood smear was unremarkable.

The radiographic examination can help in showing the bony malformations and rarefaction, including a generalised osteopenia, with a coarse trabecular pattern and severe epiphyseal dysplasia of the vertebrae (Skelly and Franklin, 2002; Crawley et al., 2003).

Progressive degenerative joint disease was evidenced radiographically by an irregular subchondral bone outline and osteophyte development (Crawley et al., 2003).

The shortening and an apparent fusion of the vertebral bodies, facet joints hyperostosis and increased intervertebral distance described in our case have similarities with what has been reported in human patients with Maroteaux–Lamy syndrome (Konde et al., 1987).

In our case, for the first time in the veterinary literature, a non-contrast CT exam of the whole body of a cat with MPS VI is described, supporting and expanding the radiographic results.

The final diagnosis of MPS VI is made by demonstration of a particular enzyme deficiency with the determination of the lack of the enzyme activity using artificial substrates like blood cells, cultured fibroblasts or liver, or by demonstrating the DNA genetic mutation (Haskins and Giger, 2008).

In clinical veterinary practice, currently no medical treatment is available and supportive care is desirable. Recent studies, based on animal models, are trying to

investigate novel therapies for human lysosomal storage diseases (Haskins and Giger, 2008). The target of these therapies is to provide a normally functional enzyme to a patient's cells involving three different approaches: enzyme replacement therapy (ERT), bone marrow transplantation (BMT) and gene therapy (Haskins and Giger, 2008). ERT and BMT have been used and tested in several experimental studies in cats with MPS VI (Haskins and Giger, 2008). Veterinarians and breeders are encouraged to control the mating of cats using genetic tests, trying to eliminate problems before they occur, in particular in breeds with Siamese derivations and outcrosses (Lyons et al., 2016).

In conclusion, this case report describes an inherited autosomal recessive disorder, rare in veterinary clinical practice, and can help the clinicians to set up a proper work-up for the correct diagnosis of MPS VI.

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