

X-linked spondylo-epiphyseal dysplasia tarda in the Danish-Swedish farm hound

In two litters from the same parents, three out of four males had an abnormally short leg and body length. Affected dogs showed signs of pain when moving, which could be eliminated by analgesia. On radiography, these animals had widened, radiolucent, irregularly bordered intervertebral disc spaces. When examined at seven months of age, the epiphyses appeared widened and irregular in shape and outline. General bone opacity in the vertebral column was lower in the affected male dogs than in the normal littermate. The affected dogs developed spondylosis and arthrosis of the larger limb joints. All affected dogs were euthanased on humane grounds, the eldest at the age of two years nine months. Based on the clinical and radiographic evidence, the condition seen in the male dogs described here resembles X-linked spondylo-epiphyseal dysplasia tarda caused by a collagenopathy due to malformation of COL2A1 as seen in human beings.

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Journal of Small Animal Practice (2007)
48, 36–38
DOI: 10.1111/j.1748-5827.2006.00160.x

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INTRODUCTION

The size of an adult dog is determined by inherited factors and the development of the skeletal system is almost independent of bodyweight. However, if regulation of the development is altered by a local or general disturbance of a biochemical or physical nature, skeletal development can be abnormal. Skeletal deformities can be breed related, for example, in hemi-vertebrae in bulldogs and Manx cats. Affected animals may show no clinical problems associated with their deformities in spite of quite dramatic radiological changes.

Hereditary forms of skeletal disease may be caused by mutation in the genes coding for cartilage proteins in human beings (Jacenko and others 1994). Depending on the position of the mutant-defect, the phenotype can vary from severe achondrogenesis to hypochondrogenesis. Spondylo-epiphyseal chondrodysplasia is a mild form of hypochondrogenesis (Rimoin 1996). Chondrodysplasias, caused by collagen abnormalities particularly involving collagen type COL2A1, are described in

human beings and result in malformation of the spine and larger joints. One such chondrodysplasia is sex linked and is known as X-linked spondylo-epiphyseal dysplasia tarda (Fiedler and others 2004).

Dogs from a kennel breeding Danish-Swedish farm hounds in which male dogs showed spine and joint abnormalities were followed over a total period of 3·5 years and similarities with X-linked spondylo-epiphyseal dysplasia tarda are discussed.

CASE HISTORIES

First litter

A phenotypically and radiologically normal female Danish-Swedish farm hound had two litters by the same phenotypically normal sire (two females and two males in the first litter and three females and three males in the second). One male dog from the first litter was euthanased at four months of age following a road accident. The remaining male from the first litter, 'Luffe 1', was referred to the authors' clinic at the age of nine months as he seemed dwarfed and following referral, the entire litter was examined and radiographed. The second litter was monitored from birth to 2·9 years because two of the three males also seemed dwarfed.

On examination, Luffe 1 had abnormally short limbs and body. Its head conformation was typical for the breed. The dog weighed 9 kg at the age of nine months compared with the 11·5 and 12 kg of the female littermates and the 14 and 15 kg of the dam and sire. The dog walked stiffly and was reluctant to exercise. If forced to run, it bunny-hopped. The dog's urine was tested using the Berry spot test for mucopolysaccharides (Berry 1987) and was found to be negative. Skeletal radiography was carried out (Figs 1 and 2). The vertebral bodies were shorter than in the normal female littermates, 2 cm compared with 2·5 cm (Figs 3 and 4).

The vertebral epiphyses were open and poorly mineralised in the affected animals. When visible, they had a folded appearance

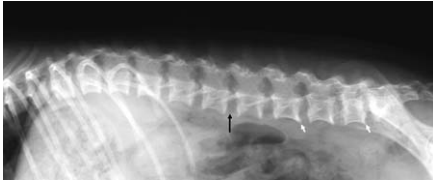


FIG 1. Latero-lateral radiograph of 'Luffe 1' at nine months. Notice the widened radiolucent intervertebral space (black arrow) about a third of the size of the length of the vertebral body, which is smaller than normal. The intervertebral spaces are irregularly bordered. Small spondylitic reactions are indicated with white arrows. No epiphysis can be seen. The vertebral bodies are square instead of rectangular and measure 2 cm in length. The bone density of the vertebral bodies, arches and articular processes is lower than the littermate (Fig 2)

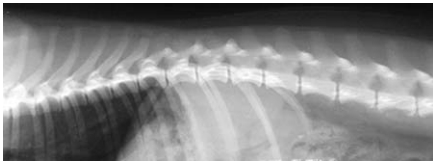


FIG 2. Latero-lateral radiograph of a normal female littermate at nine months. Notice the very small and regularly bordered intervertebral spaces, normal for the age in this breed. The vertebrae are 2.5 cm in length



FIG 3. Ventrodorsal radiograph of the affected male at nine months. The intervertebral spaces are irregular and wide (black arrow). Notice the very narrow hip joint spaces compared with the female littermate in Fig 4



FIG 4. Ventrodorsal radiograph of the normal female littermate. This female has vertebrae, hip joints and joint spaces of normal size and shape

with radiolucent centres. The intervertebral spaces had irregular margins (Fig 1). In comparison, a normal littermate showed greater density of the bone forming the vertebral bodies and neural arches and regular intervertebral spaces (Figs 3 and 4). Spondylosis was visible ventrally. The dog's hindlimbs were shorter, the femora being 13 cm in length compared with the 15 cm of an unaffected female littermate. The articular spaces were considered to be narrower (Fig 2) compared with a normal littermate (Fig 4). Areas of radiolucency gave the metaphyses a mottled appearance in the femoral heads similar to Perthes disease (Fig 2).

The dog was euthanased at the age of nine months because the owner did not wish to continue using analgesic drugs, 4 mg/kg carprofen (Rimadyl; Orion Pharma) once a day for the dog permanently, although the treatment was effective. A postmortem examination was performed. There were no cardiac abnormalities. The articular cartilage within the

limb joints was considered thinner than normal, which was shown on the histological examination of the hip joint and observed on the radiographs (Fig 2). Microscopy of the diaphyses was considered normal in the long bones. For technical reasons, the rest of the histopathology could not be evaluated.

Second litter

The two affected male dogs from the second litter, 'Luffe 2' and 'Ferdinand', showed similar clinical and radiographic changes at nine months of age as the affected animals in the first litter and continued to do so after maturity, if not treated constantly with analgesic drugs, 4 mg/kg carprofen (Rimadyl) once a day. Urine samples tested negative for mucopolysaccharidosis using the Berry spot test.

The dogs were radiographed regularly and the irregular intervertebral spaces still remained wider than normal, but did become smaller with age (Fig 5). In the endplates, spotted calcification slowly developed in the epiphyses. The spondylosis developed increasingly, but never made a bridge under the intervertebral spaces (Fig 5). The bigger joints, such as the hip and shoulder joints, slowly developed osteoarthritis (Fig 6).

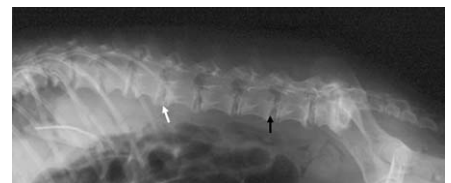


FIG 5. Latero-lateral radiograph of a brother, 'Luffe 2', of the affected male in the first litter (Fig 1). Notice the irregular and wide intervertebral space (black arrow) with some calcification of the epiphysis. The white arrow is pointing to an area of spondylosis ventral to the irregular intervertebral spaces. The bodies of the vertebrae remain small measuring about 2 cm in length at the age of 2.5 years



FIG 6. Mediolateral radiograph of 'Luffe 2' at the age of 2.5 years. Osteoarthrosis is present in the left shoulder joint (black arrow) and a less severe osteoarthrosis in the elbow (white arrow)

The dogs were successfully clinically treated with analgesic drugs for the lameness until the age of two years five months for Luffe 2 and two years nine months for Ferdinand and then they were euthanased.

DISCUSSION

The clinical and radiological findings described in the affected dogs from these two litters are very much like the findings seen in human beings with sex-linked collagenopathia (Jacenko and others 1994, Freisinger and others 1996). In spondylo-epiphyseal dysplasia tarda in human beings, DNA screening shows a molecular based mutation in the type II collagen gene (COL2A1) located at the Xp22.12-p22.31 sequence (Fiedler and others 2004). Unfortunately, at the time of writing, this sequence is not yet defined in the dog genome. A similar dwarfism in pigs has been found to be caused by a defect in collagen type X (Nielsen and others 2000).

Spondylo-epiphyseal dysplasia tarda is so called in human beings because the symptoms and signs from the joints do not become significant until the patient

gets older and is nearly mature, compared with other abnormalities that show some degree of dwarfism where symptoms begin much earlier in life (Iceton and Horne 1986, Nielsen and others 2000).

The findings in the dogs in the present case are significantly different from those found in cases with mucopolysaccharidosis (Haskins and others 1984, Rimoin 1996), where the arthroses is more pronounced and the epiphyses in the vertebrae are visible but irregularly calcified and nearly normal in size, but floppy in their conformation.

In this condition, in contrast to mucopolysaccharidosis, the epiphyses in the dogs from a few months of age are thickened and non-calcified, causing the intervertebral space to appear widened on the radiographs (Fig 1 and 2). In the older dogs, the epiphyses start to calcify abnormally in the ventral part of the intervertebral space, and spondylosis develops with age below the intervertebral spaces (Fig 5). It is not typical for dogs with mucopolysaccharidosis to develop as severe a spondylosis as seen in the present case in these male dogs.

None of the examined dogs showed clinical signs or laboratory findings typical of mucopolysaccharidosis (Berry 1987). In cases of mucopolysaccharidosis, the arthroses are more severe than seen in the present case in these dogs. Hepatomegaly and cardiac abnormalities are commonly seen in mucopolysaccharidosis (Haskins and others 1984, Wilkerson and others 1998), but were not seen in these dogs on the clinical and radiological examinations nor on the macroscopic post-mortem examination. Later, the older affected dogs developed spondylosis under some of the intervertebral spaces (Fig 5), but to a degree that was not as severe and at a later onset than the spondylosis seen in a collagenopathia of Cairn terriers,

probably caused by collagen type IX anomaly (J. Arnbjerg, personal communication).

Conclusions

It can be stated that in young dogs of small stature, without major clinical signs, dwarfism should be recognised and verified radiologically. If the changes in the vertebrae are generalised or severe, the prognosis is poor.

Acknowledgements

The authors would like to thank the staff at the Institute for Small Animal Diseases, Diagnostic Imaging and Clinical Pathology sections for their technical support.

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