

Chondrodysplasia in five Great Pyrenees

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- Chondrodysplasia in Great Pyrenees appears to be a simple autosomal recessive trait.
- Radiographic abnormalities in chondrodysplastic Great Pyrenees are restricted to the metaphyses of long bones and vertebrae.

Two male and 1 female, 8-week-old Great Pyrenees pups from a litter of 10 (litter 1) and 1 male and 1 female, 9-week-old Great Pyrenees pups from a litter of 9 (litter 2) were examined because of chondrodysplasia. Pedigrees for these 5 pups and for 1 other male pup from a litter of 10 (litter 3) were obtained (Fig 1). Analysis of the pedigrees suggested that the chondrodysplasia in these pups was a simple autosomal recessive trait. However, information concerning ancestors was equivocal and often consisted of hearsay. Individual dogs suspected to be carriers were phenotypically normal.

According to the breeders, the pups did not appear physically abnormal at birth. The affected pups from litter 2 weighed 623 and 509g at birth, whereas unaffected litter-mates weighed between 679 and 850g. By the time the pups were 14 days

old, they were obviously physically abnormal. They had failed to gain weight at the same rate as their littermates and were not as tall. The limbs, trunk, and muzzle of affected pups appeared shorter than normal (Fig 2).

On physical examination, the pups did not have hypermobility of any joints, nor did they have thin or hyperextensible skin. Ocular examinations of all pups failed to reveal any abnormalities. Three pups were deaf, and evoked auditory brain stem responses were measured in 1 pup when it was 5 months old. Results suggested that conduction did occur in the auditory nerve; however, conduction within the cochlear nucleus, the nucleus dorsalis, corporis trapezoidei, or the caudal colliculus may have been abnormal.^{1,2}

Mature dwarfs were less than half as tall as their unaffected littermates. Semen examinations performed on 2 of the pups when they were 1 year and again when they were 1.5 years old revealed

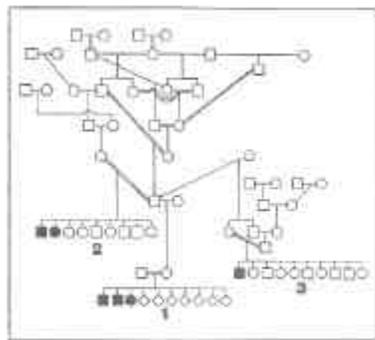


Figure 1—Pedigree for 4 male (■) and 2 female (●) chondrodysplastic Great Pyrenees. Double lines indicate that the dogs have a common ancestor within the 2 previous generations.



Figure 2—Five-year-old male chondrodysplastic Great Pyrenees.

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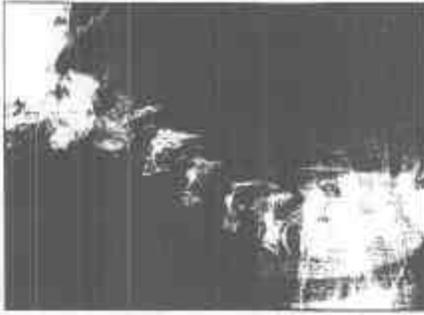


Figure 3—Lateral radiographic view of the cervical spine of an 8-week-old chondrodysplastic Great Pyrenees pup. Vertebral bodies were poorly developed and ossification was delayed compared with normal. The central border of vertebral bodies was plicated, and there were bony projections at the caudoventral aspect of the vertebral bodies. Ossification centers of the vertebral endplates were narrow.

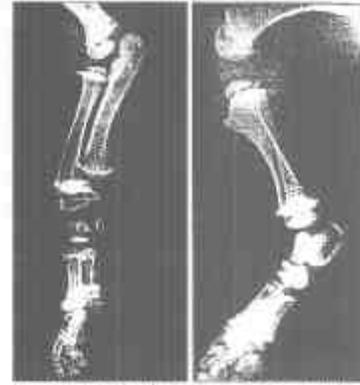


Figure 4—Lateral radiographic views of the right forelimb (left) and right hind limb (right) of an 8-week-old chondrodysplastic Great Pyrenees pup. Metaphyses of the radius, ulna, and tibia were flared, but had smooth, regular borders. Cortical thickness of the diaphyses appeared normal.

low numbers of sperm; however, sperm that were seen appeared normal.

Serum growth hormone concentrations were measured before and after IV administration of xylazine hydrochloride (0.3 mg/kg of body weight)³ in 1 female and 1 male pup when they were 6 months old. Baseline and xylazine-stimulated serum concentrations of growth hormone in the male pup were within reference ranges. In the female pup, xylazine administration resulted in a transient rise in serum growth hormone concentration, which quickly returned to baseline concentration. The response was considered to be normal or marginally low in this dog.

Thyroid stimulation tests were performed on 3 of the pups when they were 12 weeks old. Baseline concentrations of triiodothyronine and thyroxine were measured, thyrotropin (0.1 g/kg, IM) was administered, and serum thyroxin concentrations were measured again 8 hours later.⁴ Results for these 3 pups were normal. Gamma scintigraphy of the thyroid was performed in 1 male pup, using technetium Tc 99m, and uptake was normal.

Results of CBC, performed when pups were 8 to 9 weeks old, were normal. Serum biochemical analyses were performed when pups were 8 to 14 weeks old. Serum alkaline phosphatase activity (range, 135 to 421 IU/L; reference range, 111 to 155 IU/L) and serum potassium (range, 6.6 to 7.1 mEq/L; reference range, 3.8 to 5.7 mEq/L) and phosphorous (range, 5.3 to 9.6 mg/dl; reference range, 3.0 to 7.0 mg/dl) concentrations were high, whereas, serum total protein (range, 4.6 to 5.2 g/dl; reference range, 5.7 to 7.5 g/dl) and globulin (range, 1.9 to 2.1 mg/dl; reference range 2.7 to 4.4 mg/dl) concentrations were low.

Urinary excretion of chondroitin sulfate was excessive in all pups.⁵ Affected pups also had higher concentration of triglycerides in their urine than did clinically normal dogs. Repeated attempts to impregnate the pups by natural means and by artificial insemination were unsuccessful. Postmortem examination was performed on 2 of the dogs (1 when it was 16 months old and the other when it was 7 years old), and lesions were confined to the skeletal system, with the exception of testicular atrophy in 1 dog. Neither dog had evidence of degenerative joint disease.

On radiographs obtained when pups were 8 weeks old, vertebral bodies appeared poorly ossified, and cervical vertebrae had an extension of bone from the caudoventral aspect of the vertebral bodies. All vertebral end-plates were thin, irregular, and incompletely ossified, vertebral physes were ragged and indistinct (Fig 3). Metaphyses of all long bones, especially the distal metaphyses of the tibia, radius, and ulna and the metaphyses of the metacarpal and metatarsal bones, were greater in diameter than normal, but metaphyseal margins were smooth and regular. On subsequent radiographs, epiphyseal development appeared delayed (Fig 4), but ossification of skull bones and development of teeth did not. Ribs were short, and the costochondral junctions were flared. The pelvic bones had exaggerated curvature, but ossification of these bones was well organized. Angular deformities were not evident on radiographs obtained when pups were 8 weeks old, but were seen on radiographs obtained when pups were 12 weeks old. Long bones were noticeably shorter than expected when the pups were 16 weeks old. Although skeletal maturation was delayed, concrescence of physes at the distal radii and ulnae occurred by 1 year of age.

Growth plates of the sixth rib and distal ulna of 1 pup were biopsied when it was 12 weeks old.

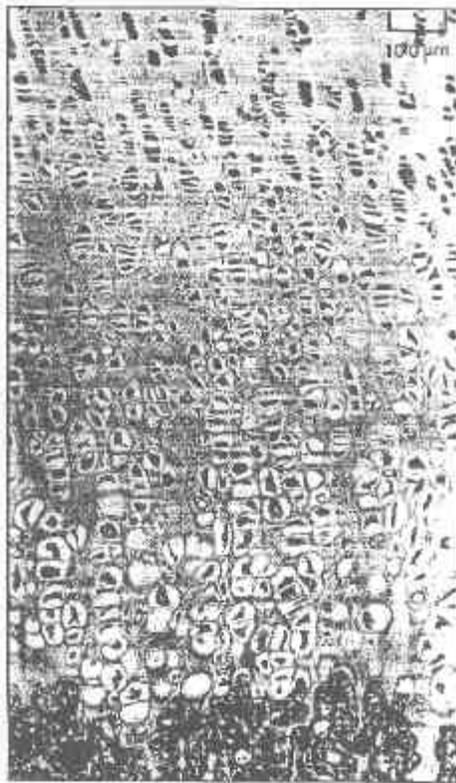


Figure 5—Photomicrograph of a section of growth plate from the distal ulna of a 12-week-old chondrodysplastic Great Pyrenees pup. Chondrocyte columns are disorganized. H&E stain, bar = 100 μ m.

A portion of each physis was processed for routine histologic examination. The remaining portion of each physis was fixed for 3 hours in half-strength Karnovsky's fixative containing 0.2% ruthenium red and then fixed in cacodylate-buffered osmium tetroxide containing 0.05% ruthenium red 6,7 and examined by means of transmission electron microscopy.

Histologically, the organization of chondrocyte columns was disrupted (Fig 5), and chondrocytes appeared as clusters of cells separated by wide areas of matrix. Numerous chondrocytes in the proliferating zone appeared to have highly vacuolated cytoplasm. Some also had hyperchromatic nuclei and resembled cells in the zone of chondrocyte degeneration. Blood vessels penetrated into the last lacunae; however, the process appeared irregular as a result of the disorganization of chondrocyte columns. Trabeculae in the primary and secondary spongiosa were thicker than normal and irregular, and there was marked lateral bridging between trabeculae.

Ultrastructurally, numerous chondrocytes in the zone of chondrocyte proliferation had dilated profiles of rough

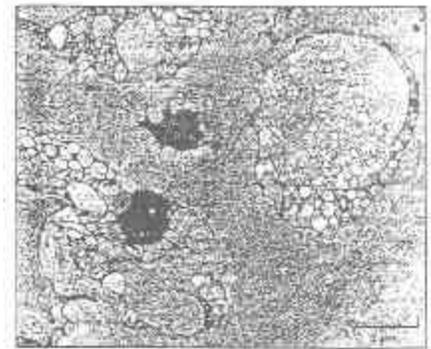


Figure 6—Electron micrograph of a section of growth plate shown in Figure 5, showing chondrocytes in the upper half of the proliferative zone. Notice variably dilated rough endoplasmic reticulum. Bar = 5 μ m.

endoplasmic reticulum containing ruthenium red-staining granules (Fig 6). Often cells above and below these chondrocytes appeared morphologically normal. Chondrocytes that appeared to be undergoing hypertrophy and degeneration could be found throughout the proliferative zone. These cells contained extensively dilated endoplasmic reticulum and numerous large irregular vacuoles.

The first report of chondrodysplasia in dogs was that by Hansen,⁸ who described chondrodysplastic Dachshunds and French Bulldogs. Subsequently, various forms of chondrodysplasia affecting a Cocker Spaniel,⁹ a German Shorthair Pointer,¹⁰ and Norwegian Elkhounds¹¹ have been described. Oculoskeletal dysplasias have been described in Labrador Retrievers^{12,13} and Samoyeds.¹⁴ A form of spondyloepiphyseal dysplasia in Miniature Poodles was described by Gardner,¹⁵ Amloff,¹⁶ and Riser et al.¹⁷ Subsequent studies have shown that this dysplasia is a result of under-sulfated chondroitin sulfate.¹⁸ An autosomal recessively inherited chondrodysplasia in Alaskan Malamutes has been described.¹⁹⁻²³ The clinical,^{19,20} radiographic²¹ histopathologic, and ultrastructural features of the disorder^{22,23} have been documented. Biochemical studies have demonstrated that there is a less mature form of cartilage matrix macromolecules in the dwarf growth plates.²⁴

More than 100 different types of skeletal dysplasias have been described in human beings, and an internationally recognized system of classification has been developed.²⁵ According to this system, the chondrodysplasia in these Great Pyrenees would best be classified as an osteochondrodysplasia with abnormalities of cartilage and bone growth and development and with defects in the growth of tubular bones and spine. The disease was not lethal and was identifiable in later life. The lack of epiphyseal disturbance, restriction of errors in remodeling of bone to the metaphyses, and dramatic changes in the vertebral bodies would place this

condition in the category of spondylometaphyseal dysplasia. Because the condition was not autosomal dominant, it could not be considered the Kozlowski type and, therefore, would belong to the broad category of "other forms."²⁵⁻²⁷ The short, broad ilia, pointed vertebral bodies, metaphyseal flaring of tubular bones, and autosomal recessive transmission were similar to Dyggve-Melchior-Claussen disease²⁸; however, unlike people with that disease, these pups had normal epiphyseal ossification, and none of the human spondylometaphyseal dysplasias have been associated with deafness.²⁹ The form of chondrodysplasia in these pups was not similar to that described in other breeds of dogs. The excessive excretion of chondroitin sulfate in the urine of these pups was believed to be a nonspecific finding and probably resulted from excessive skeletal remodeling. Dilatation of the rough endoplasmic reticulum of physeal chondrocytes is common in chondrodysplastic Alaskan Malamutes,¹⁶ and in people with Kniest dysplasia, spondyloepiphyseal congenita, dysplasia, and pseudoachondroplasia.^{26,30-32}

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