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ATELIOTIC DWARFISM IN THE GERMAN SHEPHERD DOG

LOW SOMATOMEDIN ACTIVITY ASSOCIATED WITH APPARENTLY NORMAL PITUITARY FUNCTION (2 CASES) AND WITH PAN-ADENOPITUITARY DYSFUNCTION (1 CASE)

By

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LUND-LARSEN, TATA RINGBERG and JORUNN GRØNDALEN: *Ateliotic dwarfism in the German Shepherd dog. Low somatomedin activity associated with apparently normal pituitary function (2 cases) and with pan-adenopituitary dysfunction (1 case).* Acta vet. scand. 1976, *17*, 293—306. — Two types of ateliotic dwarfism in 3 German Shepherd dog puppies are described. Low somatomedin levels in serum and impaired growth of skeletal tissues were found in all 3 cases.

One dog (case 2) had a histologically undeveloped adenohypophysis, and the dwarfism was apparently due to a generalized lack of adenopituitary function.

The 2 other dogs (cases 1A and 1B) had histologically normal adenohypophyses, and their condition was probably due to a reduced response to endogenous growth hormone in peripheral tissues.

ateliotic dwarfism; German Shepherd dog; growth hormone; somatomedin; skeletal growth.

Hastings & Gilford in 1902 associated the term "ateliosis" with normally proportioned human dwarfs to distinguish them from those with abnormal body proportions (cit. *Rimoin et al.* 1968). They further divided ateliosis into sexual and asexual forms depending on the state of sexual development and function. Autosomal recessive inheritance of sexual ateliotic dwarfism was suggested by the occurrence of affected sibs of both sexes, with unaffected parents, who were frequently related.

The asexual variety is due to pituitary dysfunction with general lack of pituitary hormones and corresponding clinical manifestations.

The sexual type may be due to either an isolated lack of growth hormone with otherwise normal pituitary function (primary GH-deficiency) or to a "peripheral resistance" against a growth hormone present in normal or even supranormal concentrations (secondary GH-deficiency or Laron-dwarfism). This growth hormone may be normal, the tissue being somehow unable to respond adequately to it, or it may be biochemically altered thereby losing its biological activity, even though the immunological properties, as measured by radioimmunoassay techniques, are normal (*Laron et al.* 1966).

Growth hormone is species specific, a fact which complicates the radioimmunoassay of its plasma concentrations in those animal species, for which the purified hormone is not readily available. Accordingly, the characterization of different forms of ateliotic dwarfism in these animal species is based mainly on clinical and/or pathological examinations (*Baker* 1955, *Jensen* 1959, *Alexander* 1962, *Muller & Jones* 1973, *Andresen et al.* 1974).

However, the discovery by *Salmon & Daughaday* in 1957 that the growth promoting effect of growth hormone is mediated via a family of GH-dependent, non species-specific, peptides, the Somatomedins (see reviews by *Hall & Luft* 1974 and *Van Wyk et al.* 1974) has made possible the indirect estimation of growth hormone activity. Thus, the clinical and pathological diagnosis of 4 cases of ateliotic dwarfism in the German Shepherd dog was recently confirmed biochemically by the finding of subnormal plasma somatomedin levels (*Willeberg et al.* 1975).

Correspondingly low growth hormone and somatomedin levels are to be expected in cases of asexual ateliosis (pan-hypopituitarism) and of sexual ateliosis due to primary lack of growth hormone. In cases of "peripheral resistance" to growth hormone (secondary GH-deficiency), however, low somatomedin levels and dwarfism are found in spite of a normal pituitary function and normal, or even elevated plasma levels of growth hormone (*Laron et al.* 1966, 1971).

In this report, 3 cases of ateliotic dwarfism in the German Shepherd dog are presented. Two of the cases (cases 1A and 1B) were siblings, while the third (case 2) was unrelated to the

others. Data on clinical, radiographical, pathological and histological examinations and on serum somatomedin and thyroxin levels are presented.

MATERIALS

Cases 1A and 1B: Two German Shepherd dogs, littermates, 4½ months old, male and female, weights 14 and 12½ kg. The dogs were admitted for radiographical examinations because of short and oblique extremities.

Case 2: A German Shepherd dog, 8 months old, female, weight 14 kg. The dog was admitted for clinical and radiographical examinations because of retardation in growth and abnormal movements.

Controls: Four littermates of case 2, 2 male and 2 female. The parents of case 2, and 3 randomly selected adult German Shepherd dogs.

METHODS

Radiographical examinations

Cases 1A and 1B, case 2 and one littermate of case 2 were submitted to radiographical examination. The thoracal and lumbal columna and the skull were radiographed in the dorso-ventral and the latero-medial position. The radius and ulna, the tibia and fibula were radiographed in the dorso-palmar/plantar and the lateral-medial position.

Serum analyses

Serum somatomedin was measured according to the embryonic chicken pelvis method of *Hall* (1970) as modified by *Lund-Larsen & Bakke* (1975). Sulphation activity was measured at 4 different serum concentrations (1.25 %, 3.2 %, 6.3 % and 12.5 %), each in quadruplicate, and the activity of the test sera was compared to that of a human standard serum run in each assay at the same concentrations. The somatomedin activity of this standard serum is defined as 1 unit/ml. Serum thyroxin was measured according to the method of *Webb* (1972) as modified by *Foss* (1973). Serum glucose was measured as described by *Blom & Halse* (1975).

Pathology

The dogs were euthanized and subjected to necropsy. Tissue specimens for histological examinations were taken from the distal part of radius, ulna, tibia, the liver, myocardium, thyroid and pituitary gland. In case 2, specimens from vertebral body, an intervertebral disc and the spinal cord were added. The tissue specimens were immersed in 10 % buffered neutral formalin and submitted to routine histological processing and paraffin embedding. Bones were decalcified before processing. The sections were stained using the haematoxylin eosin (H.E.) and the van Gieson (V.G.) methods. The sections from the hypophysis were, in addition, stained according to the Trichrom Periodic Acid Schiff (PAS) method.

RESULTS

Case histories

Cases 1A and 1B were admitted because of short and oblique extremities. They were from a litter of 7. No abnormalities were observed among the other 5 littermates. The mother had been mated once previously. According to the breeder no abnormalities were noted among the offspring. The 2 dogs in question had been in a kennel since they were 2 months old. Deviations from normal with regard to the nutrition were not recorded.

Case 2 was admitted because of retardation in growth and sudden difficulties in walking. The dam had been mated once before, and the litter consisted of 9 puppies. Of these, 1 died from meningitis, while no abnormalities were observed in the remaining 8 dogs. Both the dam and the sire of this litter were imported from Denmark. The litter with case 2 was the offspring of a mother $\times$ son copulation. The litter consisted of 9 puppies, 3 males and 6 females. One female suffered from scizosoma reflexum and was stillborn. Another was apathic and died 1 day old. A third died from gastroenteritis 4 months old. Except for the dwarf, the rest of the litter appeared normal when examined at 10 months of age.

Clinical findings

Cases 1A and 1B. The general appearance was that of a normal dog, except for the extremities, which appeared shorter

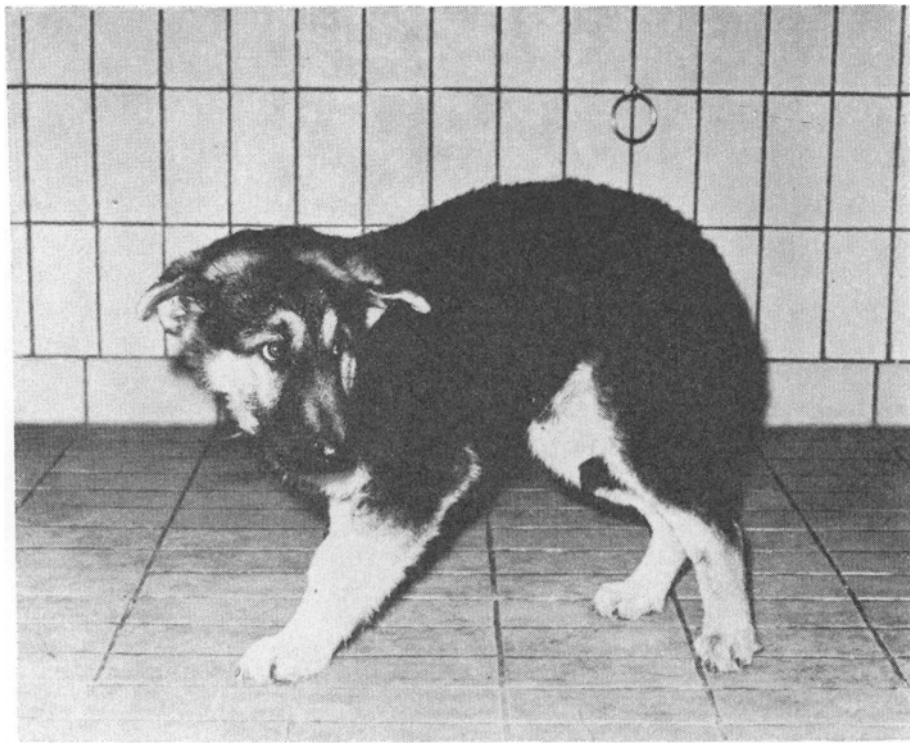


Figure 1. Case 2. German Shepherd dog, female, 8 months old.

than normal. The forelegs were deformed by lateral deviation of the carpus and bending of the radius and ulna. Alertness and movements were normal.

Case 2. The dog was undersized, weight 14 kg. The coat was puppyish. It gave the impression of mental dullness (Fig. 1). The food intake was normal. The mucous membranes, the lymph nodes and the rectal temperature were normal. Both the deciduous and the permanent incisors and canine teeth were present. Upon heart auscultating, a murmur was heard on the left side. The dog had a marked kyphosis and was not able to get to its feet without help. When standing, it very easily tumbled over. The feet seemed stiff. The proportions between the extremities and the back were normal, but all bones were short. The head was broad and dorsoventrally flattened. When examining the skeleton, the dog registered pain when the extremities were passively extended. No signs of pain were observed when pal-

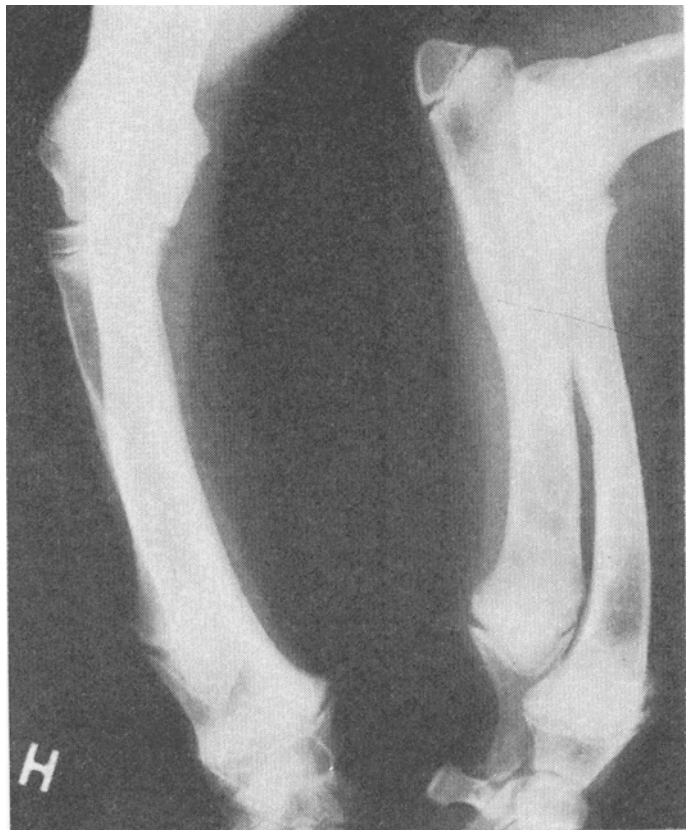


Figure 2. Case 1A. Radiographs of the radius and ulna, dorso-palmar and latero-medial position.

pating the bones. The muscles were atrophic. According to the owner, the dog had, until recently, been normal except for retardation in growth. The littermates and the parents of case 2 revealed no abnormalities when examined clinically.

Radiographic findings

Cases 1A and 1B. Uneven density of the bones was noted. The shapes of the skull, the vertebrae and the rear limbs were normal. The bending of the radius and ulna was similar to the picture seen on premature epiphyseal closure of the distal ulna (Fig. 2), with a retardation in growth of ulna compared to radius. The epiphyseal plates were of about normal width, with an increased density in the metaphyseal region.

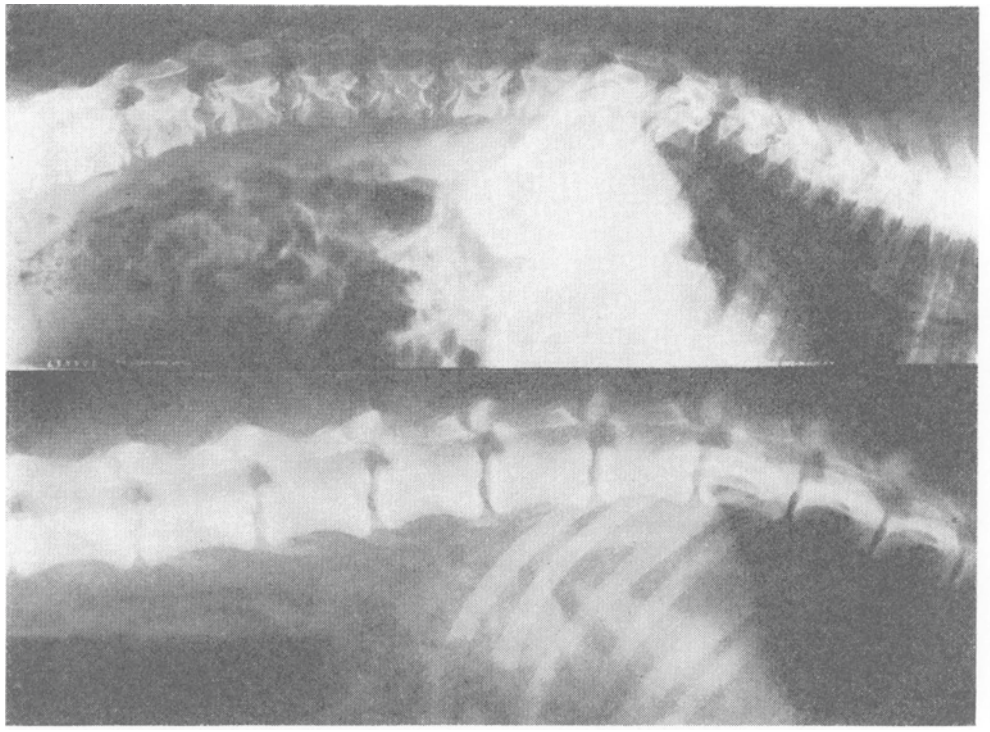
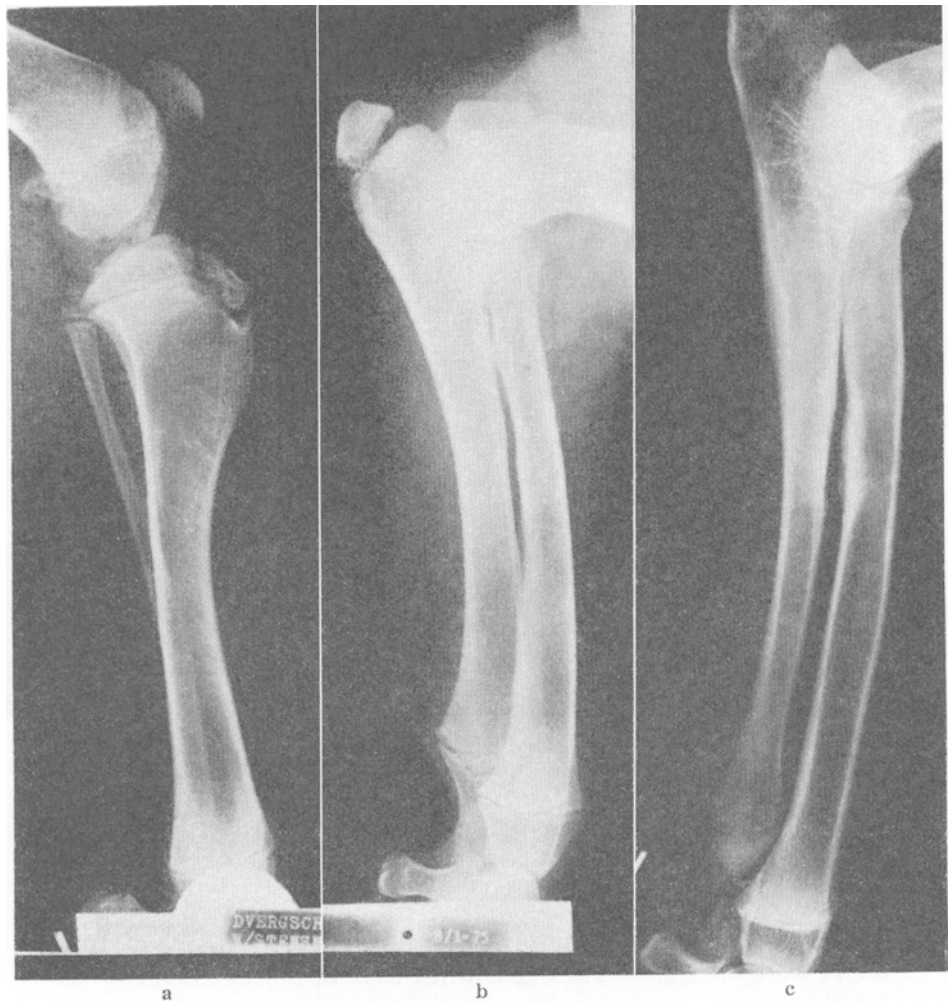


Figure 3. Case 2 (a) and control, the sister of case 2 (b), about same age. Radiographs of the lumbal columna showing the abnormal shape of the vertebrae of case 2 compared to the normal sister.

Case 2. Abnormalities with regard to the density of the bones were not noted. The extremities were of normal shape. The epiphyseal plates had an infantile appearance and could be compared to those of a 3 months old dog (Figs. 3 and 4). The apophyses of tuberositas tibia and olecranon were uneven compared to normal 3 months old dogs. The distal joint surfaces of the femur were uneven as seen in dogs younger than 3 months. In the lateral view, the vertebral bodies were not rectangular but more like the shape of an x (Fig. 3a). The growth of the middle parts of the bodies seemed to be retarded. The epiphyseal plates were open.

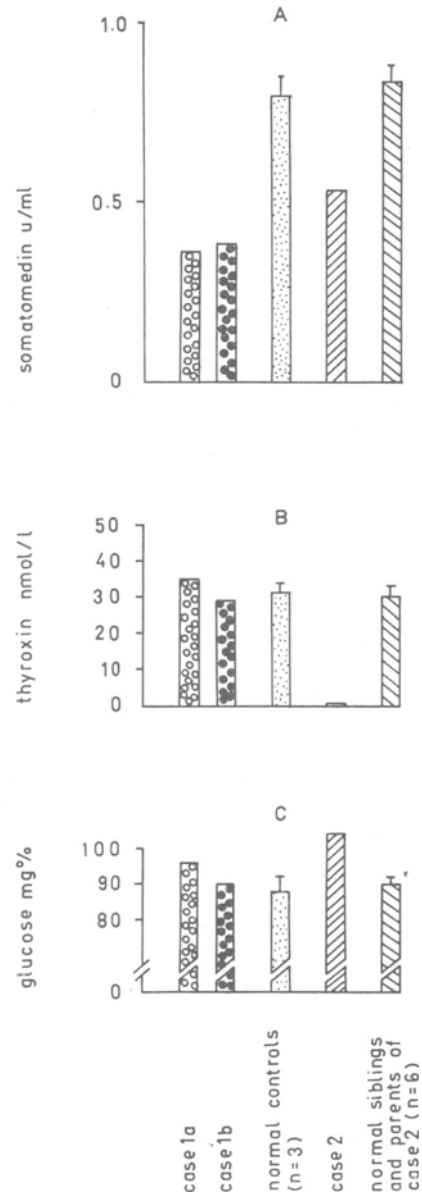
The sister of case 2 was radiographed. No abnormalities were noted (Figs. 3b and 4c).



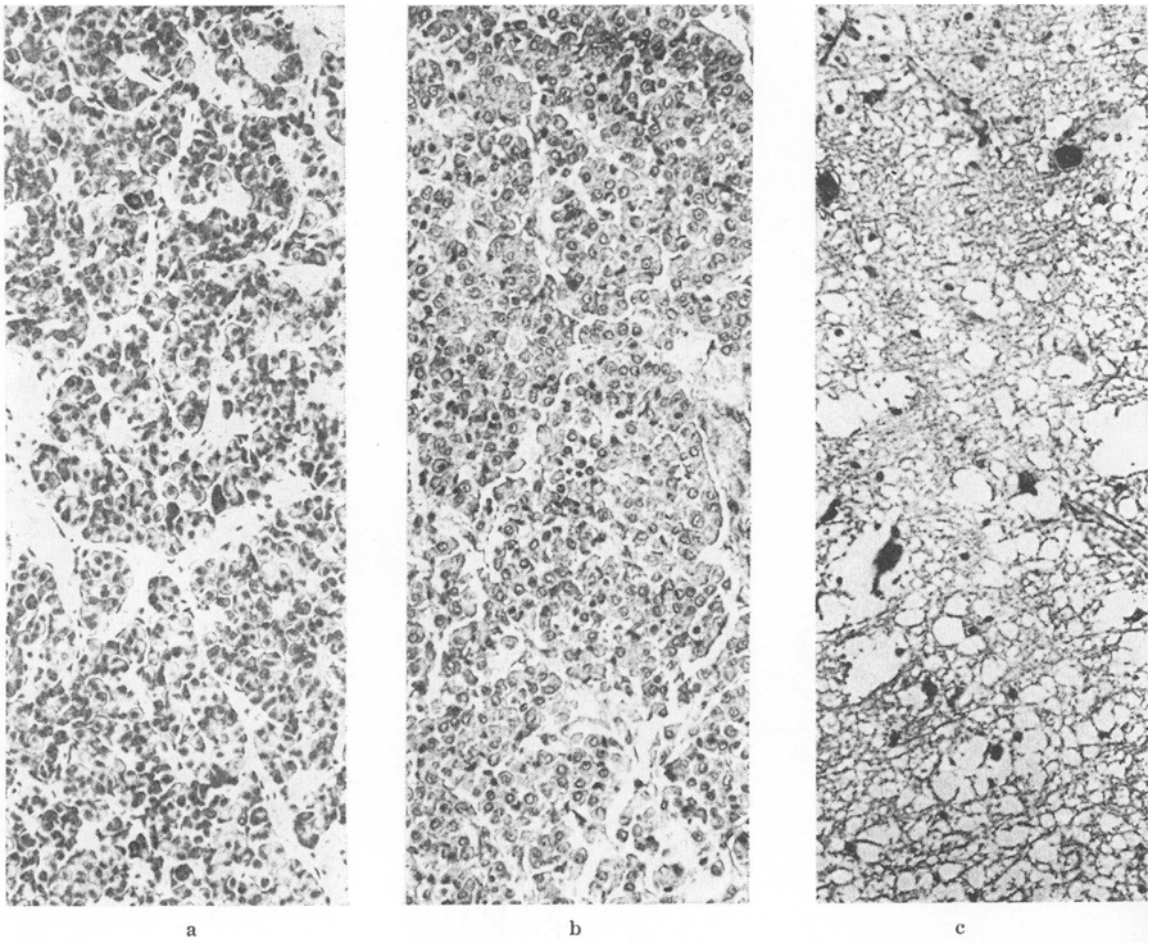
Figures 4a, b, c. Case 2 (a, b) and normal sister (c). Radiographs of
a. The femoro-tibial joint and tibia of case 2.
b. The radius and ulna of case 2.
c. The radius and ulna of the normal sister of case 2.

Serum analyses

Fig. 5 illustrates the results of the serum analyses. Cases 1A, 1B and case 2 had markedly lower somatomedin activity levels than the normal controls, indicating either reduced levels of growth hormone, or reduced response to endogenous GH (Fig.



Figures 5a, b, c. Serum somatomedin (u/ml), serum thyroxin (nmol/l) and serum glucose (mg%) levels in the cases reported. The group of 3 normal controls represents healthy, adult German Shepherd dogs, 2 males and 1 female, from the age of 8 months to 8 years.



a b c

Figures 6 a, b, c. Histological sections of the adenohypophysis of
a. 8 months old normal rottweiler.
b. Case 1A. Histologically, no deviations from normal are observed.
c. Case 2. The normal appearance of lobuli and cell differentiation is totally lacking.

5a). Of the animals examined, only case 2 proved to be hypothyroid with a serum thyroxin level below 20 nmol/l. Both case 1A and 1B were euthyroid with normal thyroxin values (Fig. 5b).

Serum glucose levels were within normal limits for all the animals (Fig. 5c).

Pathology

Cases 1A and 1B. Both dogs were undersized, but with normal body proportions. The radius and ulna on both sides showed lateral bowing as described in the radiographical findings. Endocrine glands were of normal size. Histological examinations of the endocrine glands did not reveal any abnormalities. The decalcified sections of the radius and ulna showed normal structures.

Case 2. The dog was undersized. The vertebral bodies appeared shortened. The thyroid glands on both sides were enlarged. The heart was rounded apically and both ventricles were dilated. There also was a slight thickening of the atrioventricular valves. Histological examinations of the vertebral body showed disorganization of the chondrocytes in the proliferative zone, and the normal columnal arrangement was lacking. Sagittal sections through the dorsal part of the lumbar disc showed quite well differentiated fibrous laminated cartilage. In the thyroids, follicle-like structures were separated by well-developed fibrous tissue. Colloid was absent in most of the follicles. The epithelial cells were rounded and often desquamated. In the pituitary gland, the neurohypophysis seemed normally developed. The intermediate lobe was composed of groups of faintly basophilic staining cells. The adenohypophysis was atrophic and, in serial sections, the cells appeared rounded, vacuolated or with homogenous amphophilic cytoplasma. The size of the adenohypophysis and the total number of cells were greatly reduced, and cells showing the normal differentiation into acidophils and basophils were not observed.

DISCUSSION

It is well established that the activity of serum somatomedin is partly under pituitary growth hormone control and that a certain positive relationship exists between serum somatomedin levels and skeletal growth.

Serum somatomedin activity is often elevated in conditions with high plasma growth hormone concentrations and always reduced in conditions where the supply of metabolically active growth hormone is reduced, either because of a primary lack of growth hormone, or because of alterations in the growth hormone itself or its receptors on the cell membranes.

In the cases presented, no direct determination of plasma growth hormone concentrations was done due to technical limitations. However, the histological examinations of the pituitary glands of cases 1A and 1B revealed no abnormalities of the growth hormone producing cells, and the serum thyroxin levels were normal. In contrast, the adenohypophysis of case 2 consisted of few, unidentifiable and disorderly arranged cells, and a generalized adenohypopituitary condition was confirmed by the finding of serum thyroxin levels below measurable values.

Low serum somatomedin activities were found in all 3 cases. The somatomedin levels of cases 1A and 1B were, however, even lower than that of case 2 in spite of higher rates of weight gain: The body weights of cases 1A and 1B at the age of 4 months were equal to that of case 2 at 8 months' age (∞ 14 kg).

This discrepancy between growth rate and apparent somatomedin activity is, however, not an uncommon finding both in cases of physiological and pathological growth, and probably emphasizes the importance of other growth factors in gross growth promotion.

Concerning the skeletons of cases 1A and 1B, it is difficult to explain the oblique shape and uneven densities of the extremities, although these abnormalities may, at least partly, be the result of impaired epiphyseal growth due to low levels of somatomedin.

With regard to case 2, the skeleton had a generalized infantile appearance as may be expected in the pan-adenohypopituitary condition. However, some of the changes of the vertebrae seen histologically in the proliferative zone of the cartilage resembled those found in "chondrodystrophic" dogs. Whether these findings can be attributes to the reduced levels of somatomedin is not known.

Based on the data presented it is concluded that cases 1A and 1B may represent the canine analogue of the human "Laron-Dwarf". Case 2 represents the well known syndrome of asexual ateliotic dwarfism due to lack of adenopituitary function.

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SAMMENDRAG

Ateliotisk dværgvækst hos schæferhund.

Lav somatomedin aktivitet forbundet med tilsyneladende normal hypofysefunktion (2 tilfælde) og med dysfunktion af hypofyseforlappen (1 tilfælde).

To former for ateliotisk dværgvækst hos tre schæferhundhvalpe, hvoraf to var kuldsøskende, beskrives.

Den ene form, fundet hos 1 hvalp (Case 2), antages at skyldes generel manglende hypofyse-forlap funktion. d.v.s. en primær vækst-hormonmangel. Den anden form, fundet hos de 2 andre (bror og søster, Cases 1A og 1B), antages at være forårsaget af nedsat reaktionsevne for vækstthormon i de perifere væv, d.v.s. en sekundær vækst-hormonmangel.

Antagelserne bygger på radiologiske undersøgelser af skelet, målinger af somatomedin og thyroxin koncentrationer i serum, samt histologiske undersøgelser af hypofyse i alle 3 tilfælde.

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