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Pituitary Dwarfism in German Shepherd Dogs

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Pituitary dwarfism in German shepherd dogs is an autosomal, recessive inherited disorder characterized by underdevelopment of the pituitary and a deficiency of growth hormone, thyrotropin, prolactin, and the gonadotropins, but unaffected corticotropin secretion. Probably, a mutation of a gene encoding a transcription factor that precludes effective expansion of pituitary stem cells after differentiation of the corticotropic cells is the cause of this disorder. Identification of the mutation would enable the development of a DNA test for potential breeding animals and could lead to the eradication of this condition. The main clinical manifestations of pituitary dwarfism are proportionate growth retardation and alopecia. Definite diagnosis should ideally rely on the results of a combined pituitary anterior lobe function test. Although the prognosis improves significantly when dwarfs are properly treated with levo-thyroxine and either porcine growth hormone or progestins, the prognosis remains guarded.

Key Words: Growth hormone, adenohypophysis, growth retardation, canine

Introduction

The canine pituitary gland consists of two main parts: the adenohypophysis and the neurohypophysis. The adenohypophysis can be divided into two functional units: the anterior lobe (pars infundibularis adenohypophysis and pars distalis adenohypophysis) and the intermediate lobe (pars intermedia adenohypophysis). The mature anterior pituitary contains a functionally diverse population of highly specialized cell types that are classified according to the tropic hormones they produce: somatotropic cells secreting growth hormone (GH), lactotropic cells secreting prolactin (PRL), gonadotropic cells secreting luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thyrotropic cells secreting thyroid- stimulating hormone (TSH) and corticotropic cells synthesizing the precursor molecule pro-opiomelanocortin (POMC), which gives rise to adrenocorticotropic hormone (ACTH).

The development of the adenohypophysis is a highly differentiated process that is tightly regulated by the coordinated actions of numerous transcription factors.[1,2] During embryogenesis, the adenohypophysis develops from Rathke's pouch, which arises from the oral ectoderm. The individual hormone secreting cells emerge from this pouch in a sequential order. Of the adenohypophyseal endocrine cells, the corticotropic cells are the first to develop.[3]

Any defect in the development of the pituitary gland may result in a form of isolated or combined pituitary hormone deficiency. In dogs, congenital GH deficiency or pituitary dwarfism is the most striking example of pituitary hormone deficiency. Pituitary dwarfism has been mentioned to occur in different dog breeds, including the Carelian bear dog and Saarloos wolfhound. However, the condition is encountered most often in German shepherd dogs.[4-15] German shepherd dwarfs have a combined deficiency of GH, TSH, PRL, and the gonadotropins. In contrast, ACTH secretion is preserved in these animals.[16,17]

Pathogenesis

Pituitary dwarfism is known as a simple, autosomal, recessive inherited abnormality.[18-20] Genealogical investigations indicate that the origin of the recessive gene is a mutation that occurred at about 1940 or sometime prior to that year. Additionally, they point at various champion dogs as being carriers.[19] The genetic defect causing congenital GH deficiency in German shepherd dogs is probably also the cause

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of pituitary dwarfism in Carelian bear dogs and Saarloos wolfhounds, because the disorder in the latter breeds was first recognized after German shepherd dogs had been used in their breeding.[21]

Originally, the condition has been ascribed to pressure atrophy of the anterior lobe of the pituitary gland by cystic enlargement of the residual craniopharyngeal duct or Rathke's cleft.[13] However, a more recent study indicated that this is an unlikely theory since German shepherd dwarfs have been found with only a very small pituitary cyst, unlikely to be responsible for pressure atrophy.[17, 22] Also the finding that ACTH secretion is preserved in German shepherd dogs argues against cyst formation in Ratkhe's pouch as the primary cause of pituitary dwarfism in this breed.[17] It was concluded that cyst formation should be seen as a consequence of an underlying genetic defect and that it is more likely that pituitary dwarfism is caused by a primary failure of differentiation of the craniopharyngeal ectoderm into normal tropic-hormone-secreting pituitary cells.

Because ACTH secretion is unaffected in the German shepherd dwarfs, it was supposed that a mutation of a gene encoding a transcription factor that precludes effective expansion of pituitary stem cells after the differentiation of the corticotropic cells is the cause of this disorder. The identification of this mutation would enable the development of a DNA test for potential breeding animals. In turn, this could lead to the eradication of this condition. Therefore, several genes have been investigated as candidate genes for the mutation that causes pituitary dwarfism in German shepherd dogs.

The candidate gene investigated first was POU1F1 (previously known as Pit-1). POU1F1 is a homeodomain transcription factor, essential for the development and survival of the somatotropic, lactotropic and thyrotropic cells. It is also required for the subsequent expression of the genes encoding GH, PRL and TSH.[23] In humans and mice, a mutation in the POU1F1 gene causes a deficiency of GH, TSH and PRL, whereas gonadotropin and ACTH secretion are unaffected.[23-25] It was unlikely that a mutation in the POU1F1 gene was the cause of pituitary dwarfism in German shepherd dogs, since German shepherd dwarfs also exhibit a deficiency of gonadotropins. In agreement with this supposition, sequence analysis of genomic DNA from German shepherd dwarfs did not reveal a disease-causing mutation in the POU1F1 gene. In addition, linkage analysis of polymorphic DNA markers flanking the POU1F1 gene revealed no co-segregation between the POU1F1 locus and the dwarf phenotype.[26] These observations excluded POU1F1 as a candidate gene.

In contrast to individuals with POU1F1 gene mutations, humans and mice with mutations in the Prop1 gene are not only characterized by a combined deficiency of GH, PRL and TSH, but they also have impaired production of LH and FSH.[27-29] This made Prop1 a very strong candidate gene. However, Prop1 was excluded as candidate gene, since sequence analysis of genomic DNA from these animals showed no alterations in the Prop1 gene. Moreover, linkage analysis revealed no co-segregation between the Prop1 locus and the combined pituitary hormone deficiency phenotype.[30]

Lhx4 is a member of the LIM homeodomain (LIM-HD) factor family. It acts at an earlier stage of pituitary gland development than POU1F1 and Prop1 and plays an important role in the formation of the definitive pouch.[31] In humans, a splice site mutation of Lhx4 has been identified in patients with short stature due to GH deficiency. These patients also displayed pituitary and hindbrain defects and abnormalities in the central skull base.[32] In German shepherd dwarfs Lhx4 was excluded as candidate gene for pituitary dwarfism. Genotyping in 5 litters in which pituitary dwarfism occurred showed absence of linkage between the inheritance of the dwarf phenotype and a nearby DNA marker.[33]

Leukemia inhibitory factor (LIF), a pleiotropic cytokine, and its receptor (LIFR) play a modulating role in the ontogeny of the adenohypophysis.[34] In the developing murine pituitary, LIF inhibits gonadotroph, thyrotroph, lactotroph and somatotroph lineages and induces development of corticotropes. Consistent with the phenotype of German shepherd dwarfs, transgenic mice with early pituitary overexpression of LIF display severe dwarfism and cystic cavities in the adenohypophysis.[35] Impaired development of the somatotropes and lactotropes and formation of pituitary cysts was also found in LIF transgenic mice in which the overexpression of LIF started at a later stage of embryonic development.[36] It was hypothesized that the canine LIFR gene could be involved in the etiology of pituitary dwarfism. Because there was no allelic association between a polymorphic microsatellite marker in the near vicinity of the LIFR gene and the dwarfism phenotype, LIFR was excluded as a candidate gene for pituitary dwarfism in German shepherd dogs.[37]

Clinical Manifestations

Pituitary dwarfism can lead to a wide range of clinical manifestations and not all dwarfs display the same clinical signs and symptoms. The most common clinical manifestations of pituitary dwarfism are marked growth retardation (Figure 1), retention of lanugo or secondary hairs (puppy hair coat) with concurrent lack of primary or guard hairs and bilateral symmetrical alopecia (Figure 2). Affected animals may be of normal size during the first weeks of their life, but they grow more slowly than their littermates after this period. By 3 to 4 months of age, affected dogs are obviously runts of their litter and they never attain full adult dimensions. In these animals, the alopecia mostly occurs at the trunk, the neck and at the proximal extremities.[4-15,38]

Other often-encountered manifestations are skin problems such as hyperpigmentation, scales, and bacterial infections. In addition, the presence of a pituitary cyst can be identified in a large number of dwarfs. These cysts are remnants of Rathke's cleft and they are lined with ciliated columnar epithelial cells and mucin-secreting globet cells.[6,8,10] Pituitary dwarfism is also associated with decreased glomerular filtration.[17] An overview of the clinical manifestations and post mortem findings associated with pituitary dwarfism is given in Table 1.

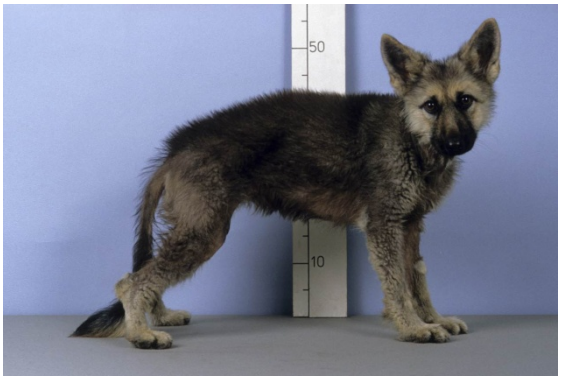

Figure 1 ─ A nine-month-old German shepherd dog with growth retardation due to pituitary dwarfism.

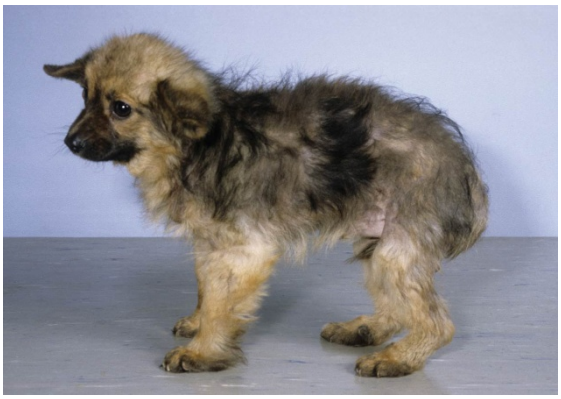
Figure 2 ─ A five-month-old German shepherd dog with pituitary dwarfism. Note the retention of secondary hairs (puppy hair coat) and the alopecia.

Table 1. Clinical manifestations and post mortem findings associated with pituitary dwarfism. (Modified from Nelson, 2003)[38]

Musculoskeletal	**Dermatologic**
Stunted growth	Soft, wooly haircoat
Thin skeleton	Retention of lanugo hairs
Changes in ossification centers	Lack of guard hairs
Delayed closure of growth plates	Isolated patches of guard hair
Delayed dental erupture	Bilateral symmetrical alopecia at
Fox like facial features	trunk, neck and proximal extremities
Muscle atrophy	Hyperpigmentation of the skin
	Thin, fragile skin
Reproduction	Wrinkles
Cryptorchidism	Scales
Flaccid penile sheath	Comedones
Failure to have estrus cycles	Papules
	Pyoderma
Other signs	Seborrhea sicca
Shrill, puppy-like bark	
Signs of secondary hypothyroidism	**Post mortem findings**
Mental dullness	Pituitary cysts
Impairment of renal function	Atrophy adenohypophysis
	Hypoplasia thyroid gland
	Persistent ductus arteriosus

Diagnosis

Combined Anterior Pituitary Function Test

Although the physical features of pituitary dwarfism may seem obvious, the diagnosis of pituitary dwarfism should be based on endocrine test results. The mean plasma insulin-like growth factor-1 concentration of German shepherd dwarfs is considerably lower than that of healthy adult and immature German shepherd dogs, but there may be some overlap. Therefore, the definitive diagnosis should rely on evaluation of pituitary responsiveness to provocative testing, i.e., challenging the adenohypophyseal cell types by stimulation with releasing hormones.[17]

To determine if a dog has GH deficiency, a stimulation test using GH-releasing hormone (GHRH) in an intravenous dosage of 1 μg/kg body weight may be used. Alternatively, α-adrenergic drugs such as clonidine (10 μg/kg body weight) or xylazine (100 μg/kg body weight) can be used. The plasma GH concentration should be determined before and 20 to 30 minutes after intravenous administration of the stimulant. In healthy dogs, plasma GH concentrations should increase at least two-to-fourfold after administration of the stimulant. In the dwarfs there will be no significant rise in plasma GH concentration.[39]

To determine if a dog has a deficiency of ACTH, TSH, PRL or gonadotropins, the pituitary can by stimulated with corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), and gonadotropin-releasing hormone (GnRH).[40] The results of this combined pituitary anterior lobe function test in healthy dogs and German shepherd dogs with pituitary dwarfism are depicted in Figure 3.

Ghrelin Stimulation Test

Another test to determine the responsiveness of the somatotropic cells is the ghrelin stimulation test. Ghrelin is a potent stimulator of GH release in dogs. In young dogs it is an even more potent stimulator

than GHRH.[41] Human ghrelin is administrated intravenously in a dose of 2 µg/kg body weight. A post-ghrelin plasma GH concentration more than 5 µg/l excludes pituitary dwarfism.[42]

Intrapituitary Cysts

The morphology of the pituitary may be investigated with computed tomography or magnetic resonance imaging. In most German shepherd dwarfs, an intrapituitary cyst can be identified at a young age, and the size of this cyst gradually enlarges during life.[22] Because healthy dogs may have pituitary cysts as well, a definitive diagnosis of pituitary dwarfism cannot be based solely upon the presence of pituitary cysts.[39]

Treatment

Heterologous GH

The most logical option would be to treat the dwarfs with canine GH. Unfortunately, this is not possible, since canine GH is not available for therapeutic use. Another option is the use of heterologous GH. In the past, there have been attempts to treat pituitary dwarfs with human GH. Not only is this a very expensive therapy, formation of antibodies directed against human GH also precludes its use.[43] A good option is the use of porcine GH. Administration of porcine GH will not result in the formation of antibodies, because the amino acid sequence of porcine GH is identical to that of canine GH.[44]

The recommended subcutaneous starting dose for any kind of heterologous GH is 0.1 to 0.3 IU per kg body weight, three times a week. This treatment may result in GH excess and consequently side effects such as diabetes mellitus may develop. Therefore, 3-weekly monitoring of the plasma concentrations of GH and glucose is recommended. Long-term dose rates should depend on measurements of the plasma concentration of insulin-like growth factor-1.[39]

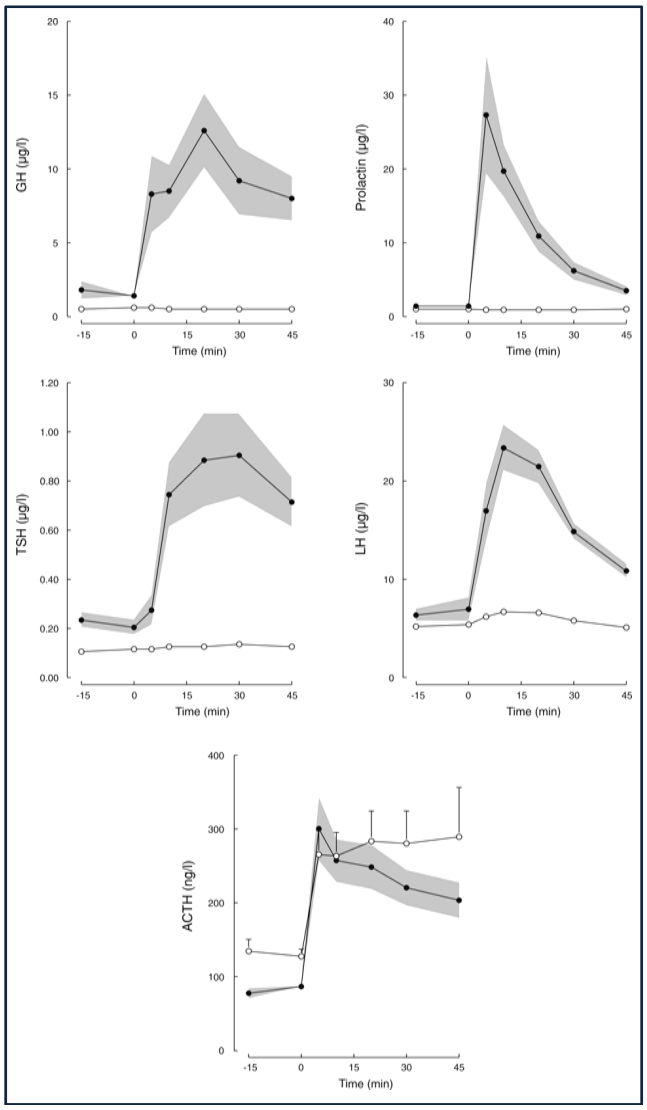

Figure 3 — Mean (± SEM) plasma hormone concentrations during a combined pituitary anterior lobe function test in 8 German shepherd dwarfs (○) and 8 healthy beagle dogs (●).[17]

Whether therapy will lead to linear growth of the dwarf is dependent on the status of the growth plates at the time that treatment is started. A beneficial response in the skin and hair coat usually occurs within 6 to 8 weeks of the start of therapy. The hairs that grow back are mainly lanugo hairs. The growth of guard hairs is variable.[38]

Progestins

Alternatively, long-term treatment with medroxyprogesterone acetate (MPA)[22] or proligestone[45] can be used. Progestins are able to induce the expression of the GH gene in the mammary

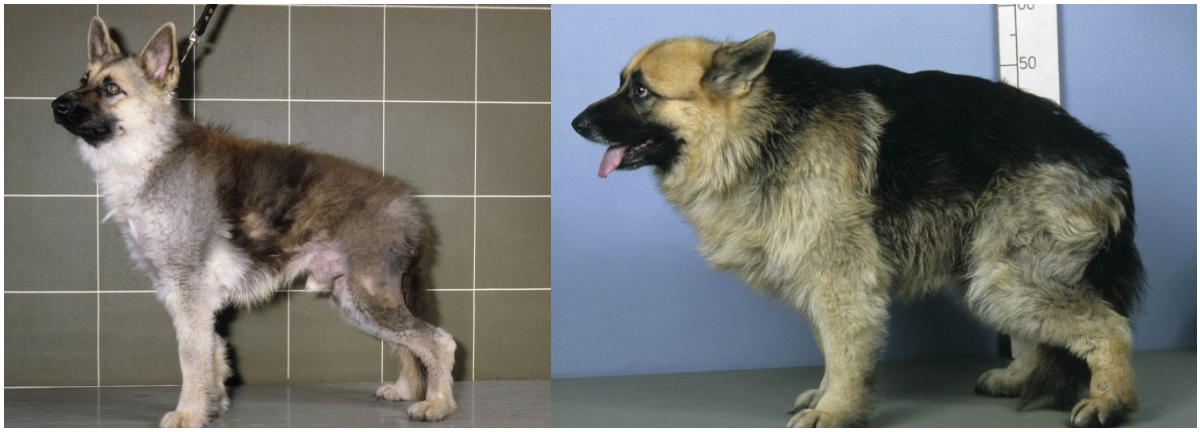

Figure 4 — A male German shepherd dog with pituitary dwarfism before (left) and after 1.5 years of treatment with medroxyprogesterone acetate.

gland of dogs. In 1998, Kooistra *et al.* reported an increase in size and a complete adult hair coat in two German shepherd dwarfs that were treated with subcutaneous injections of MPA (Figure 4).[22] The dogs received doses of 2.5 to 5.0 mg MPA per kg body weight, initially at 3-week intervals and subsequently at 6-week intervals. Undesirable side effects were recurrent periods of pruritic pyoderma in both dogs and cystic endometrial hyperplasia with mucometra in the female dog. Although plasma concentrations of GH did not exceed the upper limit of the reference range, one of the dogs developed slight acromegalic features.

Thyroid Hormones

The recommended therapy to treat the secondary hypothyroidism is synthetic levo-thyroxine. The starting oral dose is 0.02 mg/kg body weight, q12 hours. Because its absorption and its metabolism are variable, the dose of levo-thyroxine may have to be adjusted before a satisfactory clinical response is reached. For this reason, the therapy should be monitored carefully.[46]

Prognosis

Without proper treatment, the long-term prognosis is poor. By the age of 3 to 5 years the animal has usually become a bald, thin, and dull dog. These changes may be due to progressive loss of pituitary functions, continuing expansion of pituitary cysts, and progressive renal failure. At this stage owners usually request euthanasia for their dog, if they have not done so long before this.[47] Although the prognosis improves significantly when dwarfs are properly treated with levo-thyroxine and either porcine GH or progestins, their prognosis still remains guarded.

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