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Four forms of growth hormone excess in the dog

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Introduction

Increased growth hormone (GH) release may be due to an abnormality in the pituitary gland itself (a tumor of GH-producing cells) or due to extra-pituitary causes. Dr. Charles C. Capen performed several studies on the canine pituitary gland in health and disease. In 1967 he reported, together with his wife Dr. Sharron L. Martin and Dr. A. Koestner, on a series of 26 neoplasms of the adenohypophysis.¹ This has become a classic paper, particularly because of the emphasis on functional and morphological interrelations. The article is an early illustration of his life-long striving for pathobiological thinking, an approach that has resulted in many valuable contributions to our present knowledge of endocrine disease. It is very regrettable that Charles died at a relatively young age and that the profession, his colleagues, and students can no longer benefit from his expertise, which was always transmitted in a very thorough and thoughtful way.

Acromegaly

In 1886 the French physician Pierre Marie introduced the term acromegaly in the description of two patients with enlargements of the hands, feet, and face (Greek: akron = extremity, mega = large).² By the following year Minkowski had related this syndrome to a tumor in the pituitary gland.³ In humans the most common form of the disease is now known to be caused by a tumor of the GH-producing cells (somatotropic cells) of the pituitary gland. Acromegaly is an insidious, chronic debilitating disease associated with bony and soft tissue overgrowth. Many of the growth effects of GH are indirect effects through the action of insulin-like growth factor-I (IGF-I). GH stimulates IGF-I production in most tissues, where it then exerts autocrine and paracrine effects in association with IGF-binding proteins (IGF-BPs). The metabolic effects of GH excess, primarily insulin resistance, are direct effects.⁴

The first indication of the spontaneous occurrence of the syndrome of acromegaly in dogs was the detailed description in 1964 by Groen et al. of the case history of a dog in which diabetes mellitus had developed during the luteal phase of the estrous cycle.⁵ The dog was observed to have a large broad head, a wide and deep chest, and heavy legs. Both the coarsening of the physical features and the insulin resistance pointed to an excess of GH, but no pituitary tumor was found at autopsy and thus uncertainty remained as to whether the dog really had acromegaly.

In recent years four conditions have been identified in dogs in which growth hormone excess is responsible for all or some of the morphological and biochemical changes.
GH excess due to pituitary tumor

Pituitary tumors that might have secreted excessive amounts of GH have been reported in dogs, but only very recently has GH hypersecretion been confirmed in a dog with acromegaly and a somatotroph adenoma. This dog had very pronounced characteristics of longstanding GH excess. The soft tissue overgrowth included thickening of the skin, particularly of the head and neck, and enlargement of the tongue with respiratory stridor. The osseous changes had caused widening of the interdental spaces, increasing stiffness, difficulty in standing up, and neck rigidity – due to articular cartilage proliferation, periarticular periosteal reaction, and severe spondylosis deformans.

Metabolic changes were manifested in polyphagia, weight gain, excessive panting, and polyuria and polydipsia. Laboratory examination revealed normoglycemia with impaired glucose tolerance. The only remarkable finding in routine blood examination was mild anemia. Normochromic normocytic anemia has been found in dogs treated with pharmacological doses of GH, and is associated with a depletion of the erythroid cell series as well as cellular atrophy in the bone marrow. GH and IGF-I have been reported to decrease the secretion of erythropoietin from rat kidneys.

Acromegaly due to a tumor originating from pituitary somatotrophs seems to be an extremely rare condition in dogs. In cats the disease is less rare and probably underdiagnosed.

Transient GH excess in large breed dogs

Selection and mixing within the wolf gene pool over many millennia have yielded several hundred dog breeds. The domestic dog is unique among mammalian species in the extent of its variation in height, weight and shape as well as in its behavior. Human interference in the genetic make-up by selective breeding with fixation of mutant genes has led to extreme variations in size as exemplified by the Chihuahua and the St. Bernard. Adult dogs at the opposite ends of the scale may differ nearly 100-fold in weight. Within each breed, key traits are inherited within extremely narrow limits.

In the 1930s, the medical anatomist Charles R. Stockard and his co-workers were the first to study a possible endocrine basis for differences in the size and shape of dogs of different breeds. This hypothesis was based upon the similarities between some endocrine diseases known in humans and some characteristics of dog breeds. For example, posture, voice, large size and skin overgrowth in breeds such as the St. Bernard dog and the bloodhound made the investigators think of acromegaly. In their attempt to substantiate the hypothesis morphologically, they found no correlation between pituitary size and the type of the dog, but histological examination of the anterior pituitary lobe of large dogs revealed an abundance of acidophilic cells. The first biochemical data to support an endocrine basis for differences in body size among dog breeds were provided in the 1980s. In a study of adult dogs of different breeds, circulating concentrations of IGF-I correlated with body size. Also, among genetic subgroups within one breed IGF-I levels paralleled body size; whereas, basal and clonidine-stimulated plasma concentrations of GH were similar among dogs of different sizes. Recently it has been reported, that a single IGF-I
nucleotide polymorphism haplotype is common to all dogs of small breeds and nearly absent in those of giant breeds.\textsuperscript{20} Yet it may be questioned whether IGF-I is the main determinant of body size. Thus far only total IGF-I concentrations have been measured. Without measurement of free IGF-I and/or IGF-BPs, no insight is gained into possible differences in IGF exposure among dogs of different body size. The six IGF-BPs are known as important modulators of IGF actions.\textsuperscript{21} In addition, serial measurements of plasma GH concentration have revealed that the initially very high levels in Great Dane pups decrease to adult levels by about half a year of age. In miniature poodles the GH concentration does not change significantly with time and values in young animals are within the reference range for adult dogs.\textsuperscript{22,23} Long-term infusion of IGF-I does not stimulate growth of miniature poodles, but GH administration does.\textsuperscript{24,25} In a comparative study in Great Dane and Beagle pups the nutritional conditions were such that the plasma IGF-I concentrations were not significantly different. In the Beagles GH secretion was high until the age of seven weeks, whereas in the Great Danes it remained high for much longer.\textsuperscript{26} These observations indicate that hypersecretion of GH at young age, i.e., juvenile hypersomatotropism, rather than of IGF-I is the main determinant of body size.

GH hypersecretion in dogs with primary hypothyroidism

When a pituitary-dependent endocrine gland is hypofunctional, pituitary cells can adapt by different mechanisms. First, the decreased hormone production by a peripheral gland can lead to increased production of the corresponding pituitary hormone and increased numbers of specific pituitary cells, according to the classic one-cell-one-hormone concept. This concept represents the view that each adenohypophyseal cell type produces a single hormone that is secreted upon stimulation by a particular hypothalamic-releasing hormone. Second, cells of one cell line may be transformed into another to contribute to the demand for a specific pituitary hormone. Thus, contrary to the restrictive one-cell-one-hormone concept, adenohypophyseal cells are not irrevocably monohormonal but may be or become polyhormonal. The alteration of the morphologic features and the secretory capacity of mature cell types without cell division has been called transdifferentiation,\textsuperscript{27,28} in which probably the recently identified multifunctional cells play an important role.\textsuperscript{29} In recent years it has become clear that such adenohypophyseal changes may occur in dogs with primary hypothyroidism. Similar to in rats made hypothyroid by administration of propylthiouracil,\textsuperscript{30} in hypothyroid dogs somatotrophs seem to transform into stimulated thyrotrophs. These so-called thyroid deficiency cells are bihormonal, in that they are immunoreactive for both GH and TSH. Thus transdifferentiation of somatotrophs into thyrosomatotrophs seems to contribute to the demand for an increase in the secretory capacity of TSH. However, with time this may change to some extent. In a study in ovariectomized female beagle dogs with induced primary hypothyroidism the initial increase in plasma TSH concentration was followed by a gradual loss of the feedback response of TSH to low plasma thyroid hormone concentrations. This was accompanied by hypersecretion of GH and hyposecretion of prolactin. The associated pituitary enlargement was characterized by thyrotrope hyperplasia, large vacuolated thyroid deficiency cells, and double-staining (GH and TSH) cells. The pituitary enlargement was reversible upon treatment with thyroxine.\textsuperscript{31}
Similar changes are observed in dogs with spontaneous hypothyroidism, with the omission of hypoprolactinemia in intact males and females. On the contrary, plasma prolactin concentration may be elevated in intact females that have recently entered an estrous cycle and the hypothyroidism may even be associated with galactorrhea.32 The altered GH secretion is characterized by elevated basal GH secretion and less GH secreted in pulses. This elevated GH secretion has endocrine significance as illustrated by elevated plasma IGF-I levels and physical changes of acromegaly.33 Most likely as a result of the transdifferentiation of somatotropic pituitary cells to thyrosomatotropes, primary hypothyroid dogs respond to the administration of thyrotropin-releasing hormone with a significant increase in the plasma GH concentration, whereas healthy dogs do not.34

Mammary growth hormone

In the 1980s the administration of progestins to dogs was found to be the cause of elevated plasma GH levels and physical changes of growth hormone excess.35,36,37 Progestin-induced GH is not released in a pulsatile manner, does not respond to stimulation with GH-releasing hormone, and is not inhibited by the administration of somatostatin.38 The progestin-induced GH originates from foci of hyperplastic ductular epithelium in mammary tissue.39 The gene encoding mammary GH is identical to the gene encoding GH in the pituitary gland.40 Progestins stimulate GH promoter activity in the mammary gland indirectly rather than directly. In contrast to the adenohypophysis, the mammary gland lacks expression of the transcription factor Pit-1.41

Progesterone-induced release of mammary GH is a normal physiological process during the luteal phase of the estrous cycle, which has consequences for the pulsatile secretion pattern of pituitary GH. The plasma GH profile during the first half of the luteal phase is characterized by higher basal plasma GH levels and lower GH pulses than during anestrus.42,43

The local production of GH, the expression of the GH receptor, and the associated production of IGF and IGF-binding proteins appear to participate in the cyclic changes in the mammary gland. The presence of the highly proliferative environment may also enhance the risk of malignant transformation and promotion of tumor growth, with an associated inhibition of programmed cell death.44 In both humans and dogs with mammary cancer there is evidence that locally produced GH enhances malignant transformation in an autocrine manner.45,46,47 The increasing awareness of the importance of the GH/IGF-I axis in mammary development and in the formation of neoplastic mammary lesions has led to the suggestion of using agents such as somatostatin analogs and the GH antagonist pegvisomant in attempts to block the formation and progression of mammary tumors.48

In some middle-aged and older bitches in the luteal phase of the estrous cycle sufficient amounts of GH may be released into the systemic circulation to result in acromegaly (and diabetes mellitus).49 Progesterone levels in bitches during nonpregnant metestrus and pregnancy are similar.50 The occurrence of acromegaly and diabetes mellitus during pregnancy has also been reported.51

References:


