Canine Pituitary Dwarfism

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Introduction:

Canine pituitary dwarfism (CPD) is an autosomal recessive inherited disorder of the pituitary gland caused by a mutation of the LHX3 gene on chromosome 9. It is most often reported in German shepherds (GSD) where it is estimated that 18-20% of GSD are now carriers of the faulty gene.[1] First reported in 1951, is it believed to arise due to the intense inbreeding programs to rebuild the GSD population after numbers were depleted due to breed utilization in World War II.[2] This disorder can be easily recognized soon after birth as puppies with CPD will be proportionately smaller than their littermates and frequently suffer from additional physical and medical abnormalities. Patients diagnosed with canine pituitary dwarfism tend to have shorter lifespans and require intensive medical care and monitoring. Owners should purchase these patients with caution as their care can be time consuming and financially demanding.

History and Presentation:

Given the CPD abnormality has been associated with a recessive gene, canines that are carriers of the gene typically do not have visible symptoms. The birth of an affected canine indicates a carrier state in both the Dam and the Sire. Within the carrier mated litter, 50% of the progeny will be carriers, 25% will be free of the gene, and 25% of their offspring will be affected.[1]

Patients with canine pituitary dwarfism typically present due to small stature and a lack of growth. Patients with CPD will be smaller in size; however, their skeleton is of appropriate proportions. Aside from growth retardation, which can be appreciated at a young age, patients may additionally present for retention of secondary hairs and a lack of primary (guard) hairs, bilateral symmetric alopecia, maxillary prognathism, and retention of deciduous teeth past appropriate age. Dermatologically, patients may present with squamous, hyperpigmented skin

and can have difficulty clearing pyoderma infections due a deficiency in IgA production.[2] A deficiency of essential fatty acids has additionally been reported, leading to increased trans-epidermal water loss and a dry appearance to the skin. Common internal abnormalities include underdevelopment of the liver, cardiovascular problems (such as patent ductus arteriosus), in addition to a multitude of neurological conditions. Frequently, development of the kidneys is retarded due to a lack of growth hormone and IGF-1. This underdevelopment manifests as impaired renal tubular function and low glomerular filtration rates which can ultimately lead to renal failure.[3] With regards to skeletal development, patients are proportional, however they can be prone to abnormalities in bone development. The most commonly reported osseous abnormality involves the cervical spine, where patients with CPD frequently experience atlanto-axial subluxations.[4] Aggressive behavioral problems have been reported in patients diagnosed with canine pituitary dwarfism, however behavioral problems have additionally been associated with secondary hypothyroidism.[3]

Pathophysiology:

Canine pituitary dwarfism has a genetic trace to working lines of German Shepherd Dogs due to heavy inbreeding during World War II as these dogs were utilized to fulfill military roles. The first documented case was reported in Germany in 1951 at the University of Hannover, in a GSD at 11 months old standing only 34 cm at the shoulder and weighing only 10 kgs.[5] Later, a genetic cause was discovered, which was linked to the LHX3 Intron 5 located on Chromosome 9. This region codes for a transcription factor that is essential for the development of the pituitary gland. Patients presenting with CPD will have a deletion of a 7 base pair repeat (base pair sequence GCGCCC) in intron 5 of LHX3 which results in deficient splicing and is associated with a low RNA expression level for pituitary development.[6,7,8]

Abnormalities present within the pituitary gland from this deletion include pituitary hypoplasia and pituitary cysts. It was originally suspected that the condition could be related to a pressure atrophy of the anterior lobe of the pituitary gland caused by cystic enlargement of the residual craniopharyngeal duct or Rathke's clefts. Developments in imaging techniques and further investigation have shown canines with pituitary dwarfism do produce cysts within the anterior pituitary gland; however, these were small in size and therefore unlikely to be responsible for pressure atrophy. In addition, ACTH secretion is maintained in canines with pituitary dwarfism which would argue against cyst formation in Rathke's pouch as a principal cause of pituitary dwarfism. It has been concluded that cyst formation can be seen as a consequence of the underlying genetic defect; however, a failure of differentiation of the craniopharyngeal ectoderm into normal hormone-secreting cells is more likely as the primary cause. [2]

A lack of pituitary gland development causes a combined deficiency in production of growth hormone (GH), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin and gonadotropins.[3] Decreased production of growth hormone which is essential in the development and reproduction of cells, leads to underdevelopment of internal organs and osseous structures.[9] The deficiency of thyroid stimulating hormone will result in an underactive thyroid gland that can lead to clinical secondary hypothyroidism.[2] In male patients, a lack of gonadotropin release can lead to retention of one or both testes in addition to sterility. Female CPD patients may have shortened estrous cycles without ovulation due to a lack of luteinizing hormone (LH) and follicle stimulating hormone (FSH).[10]

Differential Diagnoses:

Differential diagnoses include chondrodysplasia, hypothyroidism, megaesophagus, persistent right aortic arch, and nutritional deficiencies. A full biochemical workup is typically warranted in patients presenting with small stature and additional abnormalities discussed above. Radiographs of the cervical spine and abdomen in addition to abdominal ultrasonography may additionally aid in ruling in or out CPD. Definitive diagnosis of CPD is discussed below.

Diagnostic Approach/Considerations:

Diagnosis of CPD can be definitively attained with several different endocrine tests in addition to presenting clinical signs and symptoms. Definitive diagnosis should rely on the evaluation of responsiveness of the pituitary gland to stimulation. Combined pituitary function testing detects deficiencies in secretion of growth hormone, thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin (PRL) or gonadotropins by the anterior pituitary gland. Patients are administered growth hormone-releasing hormone, corticotropin-releasing hormone, thyrotropin-releasing hormone, and gonadotropin-releasing hormone. In healthy patients, plasma growth hormone concentrations should have a twofold to fourfold increase. In patients with pituitary dwarfism, no significant rise in plasma growth hormone concentration can be appreciated. With respect to TSH, ACTH, PRL or gonadotropins, in patients with CPD mild increases after stimulation may be appreciated; however, these with be significantly lower to that seen in a healthy patient.[2]

Another test to determine responsiveness of the anterior pituitary gland is the Ghrelin Stimulation Test. Ghrelin is a peptide hormone produced in the gastrointestinal tract that functions as a neuropeptide within the central nervous system leading to growth hormone release. In young dogs, ghrelin acts as a stimulator of growth hormone secretion and is even more potent than growth hormone-releasing hormone. To perform the test, human ghrelin is

administrated, and a post-ghrelin plasma growth hormone concentration more than 5 µg/L will exclude pituitary dwarfism as a diagnosis.[11]

Insulin-like growth factor (IGF-1) is a protein similar in molecular structure to insulin that is closely associated with growth hormone. IGF-1 is synthesized in the liver under regulation by growth hormone secretion and is essential in stimulating amino acid uptake and activating enzymes for protein synthesis. Canines presenting for pituitary dwarfism will have a lower baseline blood concentration of IGF-1 when compared to healthy patients, which is due to a primary growth-hormone deficiency. Insulin-like growth factor levels are breed dependent, and laboratories that perform analysis will be able to provide reference for appropriate values. A low baseline IGF-1 can confirm suspicion of canine pituitary dwarfism, however additional stimulation tests should be performed to fully assess pituitary function. Insulin-like growth factor is frequently used for assessment during treatment with growth hormone supplementation as IGF-1 levels are easily measured in a blood sample and testing is economically feasible for owners.[5]

Additional testing regarding the physiological status of canines with pituitary dwarfism should be explored to gain a full clinical picture of the patient. As discussed previously, a decrease in glomerular filtration is common therefore an increase in blood urea nitrogen (BUN) and creatinine may be present.[3] A thyroid panel should be completed to assess for secondary hypothyroidism in addition to a complete blood count and serum chemistry for assessment in changes with regards to the liver, musculature and any concurrent infectious processes.

Diagnostic imaging is warranted in cases of suspected canine pituitary dwarfism. Abdominal radiographs can be performed to evaluate the size of the liver and any surface irregularities of the kidneys. Ultrasound can additionally be performed to evaluate any

parenchymal changes or aplasia within the kidneys.[3] Radiographs of the cervical spine are frequently performed to assess for any significant osseous changes that may predispose the patient to atlanto-axial subluxation.[4] Computed tomography (CT) may be performed to assess for additional osseous abnormalities. Ideally, magnetic resonance imaging (MRI) is performed to assess the size of the pituitary gland and to identify any cystic structures present. Minimal data is currently available with regards to the appropriate size of pituitary glands through development, however it has been shown that canines with pituitary dwarfism have significantly smaller pituitary glands when compared to a clinically normal dog of the same age.[9]

Treatment and Management Options:

In cases of CPD, few treatment options are currently available. Logically, patients with canine pituitary dwarfism would be treated with canine growth hormone. This hormone, however is not currently available for therapeutic use. A secondary option exists in the administration of porcine growth hormone. The amino acid sequence of porcine growth hormone is identical to that of the canine, therefore, administration will not lead to the formation of antibodies.[12] It is recommended that dosages start at 0.1 to 0.3 IU/kg subcutaneously three times weekly. Monitoring of plasma concentrations of growth hormone and glucose is highly recommended as an excess of growth hormone is possible, and side effects including diabetes mellitus can occur.[13] Long-term treatment and dosages should be dictated by measurements of plasma insulin-like growth factor-1. Initiation of treatment dictates any further skeletal growth the patient may experience.[2]

An alternative treatment to porcine growth hormone includes the use of medroxyprogesterone acetate or proligestone (progestins). Progestins induce expression of the growth hormone gene located within the mammary gland of canines. The induced expression,

was found to drastically increase plasma insulin-like growth factor-1 concentrations.[10] Patients can be treated with subcutaneous injections of medroxyprogesterone acetate at dosages of 2.5-5.0 mg/kg at three-week intervals initially then tapered down to six-week intervals. Side effects to treatment have included slight acromegalic features, pyoderma, and cystic endometrial hyperplasia in females.[14]

In addition to treatment of the underlying pituitary dwarfism, patients should receive additional care for any secondary medical conditions, with the most common being secondary hypothyroidism. Serial thyroid level monitoring should be performed, and initiation with thyroid supplementation should be initiated. Dosages should be adjusted as needed based on observed levels. Blood glucose and renal values should be monitored for diabetes mellitus and renal failure, and appropriate therapies initiated as needed.[13] Frequent skin infections can occur, and diagnosis and treatment should be initiated as warranted. Patients may additionally need medicated shampoos and dietary supplementation to aid in prevention of further integumentary complications.[3]

Expected Outcome and Prognosis:

In patients with CPD the long-term prognosis is poor. Treatment differentiates survival times by only a few years. In patients receiving no treatment, the average lifespan ranges from three to five years of age. Changes commonly appreciated at this point include alopecia, emaciation, and mental dullness. These changes are frequently associated with progressive loss of pituitary function, expansion of any cysts present within the pituitary gland and eventual renal failure. Prognosis and quality of life improves significantly in patients properly treated with thyroid supplementation and either porcine growth hormone or progestins, however their lifespan averages only five to seven years of age.[3]

Conclusion:

In summary, canine pituitary dwarfism is an autosomal recessive trait most commonly appreciated in German Shepherd Dogs that leads to underdevelopment of the pituitary gland and frequent cystic formation within the gland. Canines presenting with a history of small stature when compared to litter mates and abnormalities including retention of secondary hairs, alopecia, lack of weight gain, maxillary prognathism, and skin infections should be considered for canine pituitary dwarfism. Diagnosis of CPD alone can be attained with several blood tests, however, assessment of thyroid and kidney function should also be performed. Additionally, diagnostic imaging may be warranted to rule out secondary manifestations of canine pituitary dwarfism including atlanto-axial subluxations, congenital cardiac abnormalities, and osseous malformations. Treatment regarding the pituitary dwarfism may be limited, and a significant amount of secondary therapies may be necessary for full maintenance of these cases. Canines with pituitary dwarfism tend to have short life-spans and have a poor prognosis with no treatment. Initiation of treatment may extend the life-span however they are still significantly shorter than that of a normal canine, and patients will encounter frequent additional medical conditions secondary to a lack of development of the pituitary gland.

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