Identifying and Managing Atypical Hyperadrenocorticism
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(HAC) is one of the most, if not the most, common endocrinopathies of older dogs. Due to the high incidence and relatively non-specific clinical signs, older dogs are commonly screened for HAC. Diagnosis requires testing such as the low-dose dexamethasone suppression test (LDDST) or the standard ACTH stimulation test with measurement of serum cortisol pre- and post-ACTH injection. Unfortunately, neither test is perfect.

Atypical Hyperadrenocorticism

This term is used to describe dogs in which clinical signs and response to treatment are consistent with a diagnosis of HAC, but the standard screening test (ACTH stimulation test, low-dose dexamethasone suppression test) results are within the reference range. The reasons for the clinical signs in these patients are currently unknown. It has been proposed that increased circulating concentrations of steroid adrenal hormones other than cortisol (e.g., progesterone, 17-hydroxyprogesterone, androstenedione, dehydroepiandrosterone) may be responsible for the clinical signs in occult HAC, but this is controversial except in the few documented cases of sex-hormones-secreting adrenal tumors. Sex-hormone-secreting adrenocortical tumors can be identified because of the presence of an adrenal mass; in these dogs cortisol concentration after ACTH administration is typically suppressed below the reference range. Although dogs with apparent, pituitary-dependent occult HAC have been reported in the literature they are rare. Other potential reasons for normal screening test results in occult HAC patients may include individuals with increased sensitivity to glucocorticoids, inappropriately high reference ranges for cortisol in dogs with early or mild HAC, as well as rare forms of HAC such as food-dependent HAC.

The first report of clinical signs thought to be due to elevations in adrenal-derived sex hormone concentrations described diffuse bilaterally symmetrical alopecia and hyperpigmentation in 7 Pomeranians. Classic HAC was ruled out. Progesterone, 17-hydroxy-progesterone (17OHP), 11-deoxycortisol, dehydroepiandrosterone sulfate (DHEAS), testosterone, androstenedione, and estradiol were measured pre- and post-ACTH in 7 affected Pomeranians, 12 unaffected Pomeranians and 19 non-Pomeranian control dogs. Only ACTH-stimulated 17OHP concentrations were different between affected and unaffected Pomeranians, but ACTH-stimulated progesterone and DHEAS concentrations were significantly higher in both affected and unaffected Pomeranians as compared to the controls. Based on the findings, it was hypothesized the alopecia was due to a partial deficiency of 21-hydroxylase, an enzyme needed for cortisol synthesis. In humans with 21-hydroxylase deficiency and resultant congenital adrenal hyperplasia (CAH), cortisol is not synthesized and cortisol precursors, most notably 17OHP and androgens, accumulate. Since affected Pomeranians had normal serum cortisol concentrations, the enzyme deficiency was assumed to be partial. Family members of people with CAH have sex hormone elevations to a lesser magnitude and

no clinical signs, thus explaining the abnormalities in the unaffected Pomeranians (many of the affected and unaffected Pomeranians were related). Subsequently, 3 Alaskan Malamutes with Alopecia X were reported to have ACTH-stimulated 17OHP concentrations above the reference range and that were significantly higher than those in 3 normal Alaskan Malamutes.

More recently, a study of 23 dogs all of which had clinical and routine laboratory findings suggestive of HAC was reported. Of the 23 dogs, 11 were assigned to Group 1 that had typical HAC with an elevated cortisol response to ACTH. Of 10 dogs with a normal ACTH response, 6 had a positive LDDST (Group 2A), 4 had a negative LDDST (Group 2B) and 3 had low plasma cortisol concentrations throughout an LDDST (Group 2C). However, all 23 dogs had elevated ACTH-stimulated 17OHP concentrations. It was concluded that ACTH-stimulated serum 17OHP concentration is elevated in dogs with classic as well as occult HAC and measurement of serum 17OHP concentration is a marker of adrenal dysfunction. Numerous other studies have also documented elevations in sex hormone concentrations in dogs with various forms of hypercortisolemia, either pituitary-dependent HAC (PDH) or due to an adrenal tumor (AT). More specifically to the point, in cases where cortisol and sex hormones are both elevated, which hormones are causing any of the clinical signs of HAC present is difficult to impossible to determine. However, sporadic reports exist of dogs with sex hormone-secreting AT and low serum cortisol concentrations but in which clinical signs of HAC were present, ostensibly due to the sex hormones.

Two mechanisms have been proposed for progesterone's ability to cause signs of glucocorticoid excess. Synthetic progestins, compounds with progesterone-like actions, may either bind glucocorticoid receptors or may displace cortisol from its binding protein, thereby elevating serum free cortisol concentrations. Indeed, progestins suppress endogenous ACTH secretion and cause adrenal atrophy, an action suggestive of glucocorticoid activity. Accordingly, progesterone may do the same. Examination of Pomeranians with Alopecia X, however, refutes the likelihood of either mechanism occurring. If elevated serum 17OHP concentration as seen in those dogs is sufficient to cause clinical disease due to glucocorticoid actions of 17OHP, endogenous ACTH concentration should be suppressed due to negative feedback effects of glucocorticoids on the pituitary. To the contrary, Pomeranians with elevated serum 17OHP concentrations had higher plasma ACTH concentrations than healthy dogs. Similarly, during diestrus when serum progesterone concentrations are highest, adrenal secretion of cortisol in response to ACTH is greatest.

Sex hormones can be elevated in dogs with either PDH or AT. However, in most cases, whether hypercortisolemia or the sex hormones are causing the clinical signs is impossible to distinguish. Sex hormone elevations, however, have been documented to cause clinical signs of HAC even in cases where cortisol concentrations are suppressed. On the other hand, in humans and intact female dogs, sex hormone elevations do not always cause clinical signs or cause signs associated with the reproductive function of

the hormone and not of occult HAC. A mechanism by which sex hormones could cause the signs of occult HAC or by which adrenal glands would shift their hormone production in PDH is lacking. Occult HAC, if it does exist, has only truly been possibly documented in a handful of cases.

In dogs with either Alopecia X or purported occult HAC, treatment with agents that affect pituitary or adrenal function has resulted in resolution of clinical signs. Melatonin alters sex hormone concentrations in intact dogs; it was administered initially in 29 dogs with Alopecia X. Of the 29 dogs, 15 had partial hair regrowth. In 3 Alaskan Malamutes with Alopecia X, treatment with trilostane resulted in complete hair regrowth within 6 months. Of 16 Pomeranians and 8 miniature poodles with Alopecia X, 14 Pomeranians and all poodles had hair regrowth in response to trilostane. In another study on occult HAC, 9 dogs in groups 2A, B or C (i.e., were diagnosed with HAC but had normal ACTH-stimulated cortisol concentrations) were treated with trilostane or mitotane, and all had clinical improvement. Decreased ACTH-stimulated cortisol and/or 17OHP concentrations were documented in 4 of the 9. Lastly, in 1 dog with clinical signs of HAC and normal post-ACTH stimulated cortisol and LDDST results but an elevated ACTH-stimulated 17OHP concentration, clinical signs resolved with mitotane therapy.

Although successful therapy has been reported, 2 main problems exist. First, not all dogs respond to melatonin, mitotane or trilostane. Response has no apparent correlation to sex hormone concentrations; hair regrowth can be seen even in dogs in which serum sex hormone concentrations do not improve. Secondly, serum sex hormone concentrations can even increase yet the clinical signs resolve. It is hard to explain how further elevations in sex hormones can be associated with remission if the sex hormones are causing the clinical signs.

Conclusion

Whether occult HAC is due to adrenal secretion of sex hormones has never been conclusively proven. In the literature, both human and veterinary, evidence exists both in favor and against the theory. Using the research into Alopecia X as an analogy for occult HAC, although occult HAC was originally thought to be due to sex hormone abnormalities and elevations in sex hormone concentrations were widely documented in dogs with Alopecia X, later research was unable to detect a correlation between elevations in any hormone and a clinical abnormality. The specificity of adrenal sex hormone panel testing needs to be closely evaluated as evidence suggests that sex hormone concentrations may be easily elevated non-specifically due to NAI. Furthermore, not all dogs diagnosed with occult HAC respond to therapy directed at minimizing adrenal secretion. Sex hormones may be elevated even further by therapy, yet dogs improve clinically.

The possibility remains that "occult HAC" may exist as a syndrome, but one that is not caused by sex hormone secretion. Given the response of Alopecia X in some cases to therapy directed at hormone secretion, it is possible that local factors such as enzymes, growth factors or hormone receptors may contribute to the hair cycle abnormalities and

be acted upon by substances secreted by the adrenals to manifest the clinical signs. The same could be true of occult HAC - abnormal local tissue response to cortisol, for example, could cause the syndrome. Much work remains to be done to understand both the adrenal and local tissue contribution to occult HAC.