Atypical Cushing’s Syndrome in Dogs: Arguments For and Against

Ellen N. Behrend, VMD, PhD*, Robert Kennis, DVM, MS

Hyperadrenocorticism (HAC), also known as Cushing’s syndrome, is one of the most common, if not the most common, endocrinopathies of older dogs. Due to the high incidence and relatively nonspecific clinical signs, older dogs are commonly screened for HAC. Diagnosis requires testing with the low-dose dexamethasone suppression test (LDDST) or the standard corticotropin (ACTH) stimulation test with measurement of serum cortisol pre- and post-ACTH injection.1 Unfortunately, neither test is perfect, however.

To understand how good a test is, comprehension of the statistical terms sensitivity and specificity is helpful. Sensitivity is the percentage of individuals with the disease who are correctly identified by the test. For example, if the LDDST is 95% sensitive for diagnosing HAC, then of all dogs with the disease, 95% would have abnormal LDDST results consistent with HAC and the other 5% would not. Specificity is the percentage of individuals without the disease who have a negative result. For example, if the ACTH stimulation test has a specificity of 86% for diagnosing HAC, then, of all dogs with positive ACTH stimulation test results, 86% would have the disease and 14% would have a false-positive result.

For diagnosing HAC, the LDDST offers a sensitivity of approximately 95%, while the ACTH stimulation test offers a sensitivity of approximately 80%. For pituitary-dependent HAC (PDH) alone, the sensitivity of the ACTH stimulation test is 87%. Meanwhile, for HAC due to adrenal tumor alone, the sensitivity of the ACTH stimulation test is 61.3%.1 The specificity of the LDDST has been estimated to be 44% to 73%2–5; for the ACTH stimulation test, specificity is 64% to 86% (Table 1).2,6 Since HAC occurs in older dogs, patients tested for HAC often have concurrent disease. If they do not have HAC, they at least have a nonadrenal illness causing the clinical signs. In general, the more severe the nonadrenal illness present, the more likely a false-positive test result for HAC.2

Department of Clinical Sciences, College of Veterinary Medicine, Auburn University, Auburn, AL 36849, USA
* Corresponding author.
E-mail address: behreen@auburn.edu (E.N. Behrend).

Key Words
- Hyperadrenocorticism
- Sex hormones
- Cushing’s syndrome
- Adrenal gland
- Alopecia X

vetsmall.theclinics.com
0195-5616/10/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
Due to imprecision of the tests, HAC can be a difficult diagnosis to make at times. Clinicians are faced with the situation where their clinical impressions are that patients have HAC, but the tests performed do not confirm the diagnosis and no alternative diagnosis is identified. Recently, to explain such circumstances, much interest has focused on a syndrome termed occult HAC. Dogs with occult HAC allegedly have clinical signs and/or routine laboratory abnormalities consistent with classic HAC but have normal serum cortisol concentrations on LDDST and/or ACTH stimulation tests. Alopecia X has been used to describe dogs with occult HAC with dermatologic changes only, mainly bilaterally symmetric alopecia and hyperpigmentation with a puppy coat (Fig. 1). Alopecia X is commonly seen in the Nordic breeds, Pomeranians, and chow chows, which may exhibit a telogen-predominant hair cycle with seasonal shedding. In theory, occult HAC is caused by diversion of the normal adrenocortical pathways for cortisol and aldosterone synthesis into overproduction of sex hormones instead (Fig. 2). The syndrome is diagnosed by an ACTH stimulation test with measurement of serum sex hormones (ie, androstenedione, estradiol, progesterone, and 17-hydroxy-progesterone [17OHP]) and aldosterone concentrations pre- and post-ACTH.

However, in these authors’ opinion, conclusive evidence for the existence of occult HAC as a sex hormone–mediated condition is lacking. Here we evaluate the evidence both for and against. In evaluating adrenal secretion of sex hormone and cortisol precursors (eg, 11-deoxycortisol) in dogs, it must be taken into account whether basal or ACTH-stimulated concentrations were measured. For the diagnosis of standard HAC, determination of basal cortisol concentration is not reliable and never used by

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test</th>
<th>LDDST Sensitivity</th>
<th>LDDST Specificity</th>
<th>ACTH Stimulation Sensitivity</th>
<th>ACTH Stimulation Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAC</td>
<td>95%(^1)</td>
<td>44%-73%(^2,5)</td>
<td>80%(^1)</td>
<td>64%-86%(^2,6)</td>
<td></td>
</tr>
<tr>
<td>PDH</td>
<td>Not determined</td>
<td>Not determined</td>
<td>87%(^1)</td>
<td>Not determined</td>
<td></td>
</tr>
<tr>
<td>Adrenal tumor</td>
<td>Not determined</td>
<td>Not determined</td>
<td>61%(^1)</td>
<td>Not determined</td>
<td></td>
</tr>
<tr>
<td>Occult HAC</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not determined</td>
<td>70%(^a,7,8)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Determined only for 17OHP.

Fig. 1. Typical appearance of a Pomeranian with Alopecia X. (Courtesy of Dr Randy Thomas.)
No evidence has shown that measurement of basal serum sex hormone concentrations are any more reliable for diagnosis of adrenal dysfunction; thus, the following discussion will focus on ACTH-stimulated concentrations, which are a measure of adrenal reserve.

**ADRENAL SEX HORMONE AND CORTISOL PRECURSOR SECRETION AS A CAUSE OF BILATERALLY SYMMETRIC ALOPECIA**

**Evidence in Favor**

Sex hormones secreted from sources other than the adrenal glands can cause alopecia. A syndrome of castration-responsive alopecia has been recognized. Hyperestrogenism as well as hyperprogesteronism associated with Sertoli cell tumors, for example, can lead to bilaterally symmetric alopecia. Administration of estrogen for treatment of urinary incontinence has led to bilaterally symmetric alopecia and histopathological changes consistent with endocrine alopecia.

The first report of clinical signs thought to be due to elevations in adrenal-derived sex hormone concentrations described diffuse bilaterally symmetric alopecia and hyperpigmentation in seven Pomeranians. Classic HAC was ruled out on the basis of normal ACTH stimulation test and LDDST results. Progesterone, 17OHP, 11-deoxycorticisol, 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 with the controls. Given the constellation of abnormalities in both affected and unaffected Pomeranians, Schmeitzel and Lothrop 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, cortisol is not synthesized and cortisol precursors, most notably 17OHP and androgens, accumulate. Because affected Pomeranians had normal serum cortisol concentrations, the enzyme deficiency was assumed to be partial. Family members of people with congenital adrenal hyperplasia have sex hormone elevations to a lesser magnitude and no clinical signs, thus explaining the abnormalities in the unaffected Pomeranians.

---

**Fig. 2.** The adrenocortical hormone synthesis pathway. (Courtesy of Dr Lauren Reid.)
(many of the affected and unaffected Pomeranians in the study by Schmeitzel and Lothrop\textsuperscript{13} were related). Subsequently, 3 Alaskan malamutes with Alopecia X were reported to have ACTH-stimulated 17OHP concentrations above the reference range and significantly higher than those in 3 normal Alaskan malamutes.\textsuperscript{15}

**Evidence Against**

Of six sex hormones assessed by Schmeitzel and Lothrop\textsuperscript{13} in the 7 Pomeranians with Alopecia X, only ACTH-stimulated serum 17OHP concentrations were significantly different between affected and unaffected dogs. However, when affected males and females were assessed separately, the males did not have elevated serum 17OHP concentrations. In 276 dogs with Alopecia X, including 63 Pomeranians, 73\% had at least one basal or post-ACTH sex hormone concentration above the normal range. Despite the preponderance of elevations in sex hormone concentrations, though, no consistent sex hormone abnormalities were identified, and Frank and colleagues\textsuperscript{16} concluded that it is more appropriate to refer to Alopecia X as “alopecia associated with follicular arrest” rather than equating it with an adrenal hormone imbalance.

Due to the postulation by Schmeitzel and Lothrop\textsuperscript{13} that the alopecia in Pomeranians was due to partial 21-hydroxylase deficiency, Takada and colleagues\textsuperscript{17} cloned the canine 21-hydroxylase gene and evaluated genetic polymorphisms. No mutations affecting the primary structure of the enzyme or gene expression were identified.

**Assessment**

Although 21-hydroxylase abnormalities were not documented in dogs with Alopecia X,\textsuperscript{17} another enzyme could be involved. Abnormalities of other enzymes in the cortisol synthesis pathway have been documented to cause congenital adrenal hyperplasia in people.\textsuperscript{14} To date, however, no search for genes outside of the cortisol synthesis pathway has been successful either.\textsuperscript{18,19} More importantly, sex hormone abnormalities appear to be easily documented in dogs with Alopecia X, but no correlation exists between elevations in any hormone and a clinical abnormality. Sex hormones are no longer believed to be related to Alopecia X.

**17-HYDROXY-PROGESTERONE, OTHER SEX HORMONES, AND CORTISOL PRECURSORS AS CAUSES OF OCCULT HYPERADRENOCORTICISM**

**Evidence in Favor**

A study of 23 dogs with clinical and routine laboratory findings suggestive of HAC was reported recently. Of the 23 dogs, 11 assigned to group 1 had typical HAC with elevated cortisol responses to ACTH. Of 10 dogs with normal ACTH response test results, 6 had positive LDDST results (group 2A), 4 had negative LDDST results (group 2B), and 3 had low plasma cortisol concentrations throughout testing (group 2C). Despite the variation in serum cortisol concentrations on the tests for standard HAC, all 23 dogs had elevated ACTH-stimulated 17OHP concentrations. Thus, Ristic and colleagues\textsuperscript{20} concluded that ACTH-stimulated serum 17OHP concentration is elevated in dogs with classic as well as occult HAC and measurement of serum 17OHP concentrations 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 PDH or adrenal tumor. In 11 dogs with hypercortisolemia, ACTH-stimulated DHEAS was elevated in 4 of 9, androstenedione was elevated in 7 of 10, progesterone was elevated in 11 of 11, and 17OHP concentrations were elevated in 6 of 11. No dog had elevated ACTH-stimulated testosterone concentrations.\textsuperscript{21} In 14 dogs with PDH, at least 6 and as many as 9 had elevated ACTH-stimulated 17\alpha-hydroxypregnenolone, 17OHP,
21-deoxycortisol, or 11-deoxycortisol concentrations. Of dogs with suspected HAC and elevated ACTH-stimulated serum cortisol concentrations, 71% of 59 had elevated ACTH-stimulated 17OHP and 60% of 53 had elevated corticosterone concentrations. In 9 dogs with cortisol-secreting adrenal carcinoma and 10 dogs with PDH, 1 or more had elevations in serum ACTH-stimulated androstenedione, progesterone, 17OHP, testosterone, or estradiol concentrations. Lastly, in 53 dogs with confirmed HAC, 69% had elevated ACTH-stimulated 17OHP concentrations. An additional 2 dogs had elevated 17OHP concentrations despite normal cortisol concentrations on both the ACTH stimulation test and LDDST. One of those 2 dogs had confirmed occult HAC based on response to mitotane. In the other, the diagnosis of occult HAC was not verified.

More specifically to the point, in cases in which cortisol and sex hormones are both elevated, determining which hormones are causing clinical signs of HAC is difficult or impossible. However, sporadic reports exist of dogs with sex hormone–secreting adrenal tumors and low serum cortisol concentrations but in which clinical signs of HAC were present, ostensibly due to the sex hormones. Two dogs with adrenal tumors had clinical signs of HAC despite markedly suppressed ACTH-stimulated serum cortisol concentrations. One tumor secreted progesterone, 17OHP, testosterone, and DHEAS, while the other secreted androstenedione, estradiol, progesterone, and 17OHP. In a report of eight dogs with adrenal tumor and signs of HAC, three had suppressed ACTH-stimulated serum cortisol concentrations and one had elevated 17OHP concentrations; no other sex hormones were measured in any dog nor in the other two with subnormal cortisol concentrations.

**Evidence Against**

It is difficult to understand how sex hormones would cause clinical signs of HAC. The sex hormone most mentioned as a cause of occult HAC is progesterone. Due to progesterone’s short half-life, however, little is known about the effects of elevated serum concentrations. Chronic excesses in progesterone concentration are not unique. In estrus and diestrus, serum progesterone is elevated for 60 to 90 days and often approaches or exceeds 50 to 100 times anestrus concentrations, yet no clinical signs of HAC develop. In humans, clinically silent 17OHP-secreting adrenal tumors occur. Massive elevations in serum 17OHP occur with 21-hydroxylase deficiency in people, yet clinically affected patients show signs either of aldosterone deficiency or androgen excess. Clinical signs of HAC do not occur despite 17OHP concentrations ranging from 3000 to 40,000 ng/dL (reference range 20–600) in people. Lastly, a “cryptic” syndrome of 21-hydroxylase deficiency exists in which affected people lack 21-hydroxylase and have hormonal abnormalities but no clinical signs. The factors that impose the phenotypic variability on the genotypic abnormality are unknown, but abnormal sex hormone elevations by themselves are not sufficient to cause clinical disease. Similarly, in dogs with Alopecia X, serum 17OHP concentrations can be quite elevated, similar to what is seen with dogs with purported occult HAC, yet none of the classical systemic clinical signs, such as polyuria/polydipsia, polyphagia, pot belly, and panting, are reported.

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 because of negative feedback effects of glucocorticoids on the pituitary. Indeed, for dogs with proven sex hormone–secreting tumors and signs of HAC despite hypocortisolemia, measured endogenous ACTH concentrations were low. However, not all dogs with clinical signs supposedly due to sex hormones have suppression of ACTH secretion. To the contrary, Pomeranians with elevated serum 17OHP concentrations had higher plasma ACTH concentrations than did healthy dogs. Similarly, during diestrus, when serum progesterone concentrations are highest, adrenal secretion of cortisol in response to ACTH is greatest. Lastly, in the report of eight dogs with adrenal tumor, another dog had elevated ACTH-stimulated 17OHP concentrations, but cortisol secretion was not suppressed.

How adrenal tumor could have a shift in hormone synthesis activity can be understood easily. Tumor cells are not normal and can undergo loss of differentiation, losing the ability to synthesize enzymes in the hormone synthesis pathways. In cases of pituitary-dependent occult HAC, how or why normal adrenocortical tissue should alter steroid synthesis is unexplained.

The number of published cases of dogs with purported true occult HAC (ie, presence of consistent clinical signs, ACTH stimulation test and LDDST both normal, and response to appropriate therapy) is actually quite small. Problems exist with the initial study that attributed occult HAC to elevated 17OHP concentration. Classifying all 23 dogs as having occult HAC was inappropriate because 17 had standard ACTH stimulation test or LDDST results consistent with HAC and were not occult. Three dogs had normal ACTH stimulation test results and low plasma cortisol concentrations throughout the LDDST. These results are not unusual in dogs with an adrenal tumor. Only 3 dogs were diagnosed with PDH despite having both normal ACTH stimulation test and LDDST results. In 64 dogs documented to have HAC, no dog was negative on both the ACTH stimulation test and LDDST. Out of 57 dogs evaluated recently for HAC with cortisol measurements on a ACTH stimulation test and LDDST, 40 were diagnosed as having PDH, 12 as having adrenal tumor, and 5 as possibly having occult HAC. The diagnosis of occult HAC was bolstered by a positive response to therapy in only 1 dog in the latter group, suggesting that only 1 of 57 dogs may have had occult HAC.

Assessment

Sex hormone concentrations have been reportedly elevated in dogs with either PDH or adrenal tumors. In most cases, it is impossible to tell whether excess cortisol or sex hormones are causing the clinical signs. Sex hormone elevations, however, have been documented to cause clinical signs of HAC even in cases in which cortisol concentrations are suppressed. On the other hand, in humans, sex hormone elevations either cause no clinical signs or signs associated with the reproductive function of the hormones, but never signs of occult HAC. A mechanism by which sex hormones could cause the signs of occult HAC, or by which adrenal glands could shift their hormone production in PDH, is lacking. Occult HAC, if it does exist, has been possibly documented in only a handful of cases.

SEX HORMONE PANEL TESTING

Evidence in Favor

Measurement of serum sex hormone concentrations has been advocated as a means of diagnosing occult HAC. Use of a panel of hormones has been stated to increase
sensitivity and specificity of the test over measurement of a single hormone alone.\textsuperscript{37}

Elevations in concentrations of any hormone can be common, with estradiol elevations noted in approximately 40% of panels submitted to one reference laboratory.\textsuperscript{37}

**Evidence Against**

Unfortunately, sensitivity and specificity of adrenal sex hormone panel testing have not been published in a peer-reviewed journal. Neither have elevations in sex hormone concentrations been evaluated in the context of occult HAC, as was done for Alopecia X; although sex hormones previously were believed to cause Alopecia X, retrospective analysis of sex hormone panel results identified the abnormalities as coincidental and not causative.\textsuperscript{16}

The specificity of sex hormone panel testing must be considered. It is reasonable to assume that dogs with nonadrenal illness (eg, a dog with diabetes mellitus) might not have the same ACTH response as healthy dogs because of adaptation of adrenocortical function to the stresses of chronic illness.\textsuperscript{6} Indeed, two landmark studies assessed the response to ACTH in dogs not suspected to have HAC but that did have nonadrenal illness,\textsuperscript{2,6} and their results revolutionized how ACTH stimulation test results are evaluated. Many stressed and sick dogs have increased cortisol concentrations and an exaggerated ACTH response, but do not have HAC. Dogs with chronic nonadrenal illness had a 14%\textsuperscript{2} or 36%\textsuperscript{6} chance of having ACTH stimulation test results consistent with HAC. In other words, if testing a dog with nonadrenal illness to see if it also has HAC, a dog with an ACTH stimulation test result consistent with HAC still has up to a 36% chance of not having HAC! Similarly, if chronic nonadrenal illness is present and causing clinical signs similar to those of HAC even though HAC is not present, a positive ACTH stimulation test may yield a false diagnosis of HAC in up to one-third of patients and the real disease may be missed.

As such, the likelihood that activation of the pituitary-adrenal axis in nonadrenal illness would also cause a shift toward synthesis and secretion of sex hormones is unknown. In one study, post-ACTH serum cortisol, 17OHP, and corticosterone concentrations were significantly correlated both in dogs with neoplasia and those suspected of having HAC, suggesting that as adrenal function is increased either by adrenal disease or nonspecifically by nonadrenal illness, production of all hormones increases proportionately.\textsuperscript{7}

With regard to 17OHP, the specificity of the test may be as low as 70% (ie, the chance of a false-positive result is 30%) (see Table 1).\textsuperscript{7,8} In one study of 35 dogs with neoplasia but without adrenal disease, 30% had elevated serum 17OHP concentrations post-ACTH stimulation.\textsuperscript{7} When dogs suspected to have HAC but proven not to were compared with those that did have HAC, cortisol distinguished the two groups more clearly than did either 17α-hydroxypregnenolone\textsuperscript{22} or 17OHP.\textsuperscript{8,22} In 30% of dogs suspected to have HAC but for which alternate diagnoses were found, serum ACTH-stimulated 17OHP concentrations were elevated.\textsuperscript{8} Thus, if 17OHP were measured to make the diagnosis in a similar population of dogs, 30% would be mistakenly misdiagnosed as having HAC. In 6 dogs with either pheochromocytoma or a nonfunctional adrenal tumor, concentrations of androstenedione, progesterone, 17OHP, testosterone, or estradiol were elevated in all.\textsuperscript{23} Therefore, dogs without adrenal disease clearly can have elevated sex hormone concentrations as they do cortisol concentrations, and sex hormones may be more likely to be falsely elevated by nonadrenal illness as compared with cortisol.

Unfortunately, the ability of chronic nonadrenal illness to affect sex hormone testing has not received critical appraisal as has the ability of chronic nonadrenal illness to
affect the standard ACTH stimulation test. Besides 17OHP, other sex hormones measured to diagnose occult HAC include basal and ACTH-stimulated estradiol, progesterone, testosterone, and androstenedione. However, the accuracy of this test remains to be determined.

**Assessment**

Numerous dogs have been documented to have elevated sex hormone concentrations with signs of occult HAC, but the association between hormone abnormalities and the clinical signs has not undergone rigorous assessment. Similarly, the specificity of adrenal sex hormone panel testing has not been evaluated. Elevations at least in serum ACTH-stimulated 17OHP concentrations apparently are more often due to non-adrenal illness than to cortisol.

**RESPONSE TO TREATMENT**

**Evidence in Favor**

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 is a neurohormone produced by the pineal gland, which controls seasonal reproductive and hair growth cycles and alters sex hormone concentrations in intact dogs. In 29 dogs with Alopecia X, melatonin was administered initially at 3 mg/kg every 12 hours to dogs weighing 15 kg or less, and 6 mg/kg every 12 hours to dogs weighing more than 15 kg. Dogs were reevaluated approximately every 4 months and, based on clinical response, melatonin therapy was continued at the same or at an increased dose (if ≤15 kg, 4.5 mg every 12 hours; if >15 kg, 9–12 mg every 12 hours), or therapy was switched to mitotane, an adrenocorticolytic agent with preference for the adrenal zonae reticulata and fascicularis, the zones that secrete cortisol and sex hormones (25 mg/kg orally daily or divided twice daily for 5–7 days followed by 25 mg/kg orally divided twice weekly). Of the 29 dogs, 15 had partial hair regrowth at first reevaluation. In 3 Alaskan malamutes with Alopecia X, treatment with trilostane (3.0–3.6 mg/kg daily by mouth), a drug that inhibits the adrenal enzyme 3β-hydroxysteroid dehydrogenase and inhibits adrenal hormone synthesis, 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; the mean dose that caused hair regrowth was 11.8 mg/kg (range 5–23.5) in Pomeranians and 9 mg/kg (range 6.1–15.0) per day in the poodles. In the study on occult HAC by Ristic and colleagues, 9 dogs in groups 2A, B, or C (ie, 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 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.

**Evidence Against**

The response to mitotane, melatonin, or trilostane has not been uniform or predictable. In 15 Pomeranians with Alopecia X, melatonin (mean 1.3 mg/kg by mouth twice a day; range 1.0–1.7) for 3 months, only 6 (40%) had mild to moderate hair regrowth.

In the study evaluating 29 dogs that were diagnosed with Alopecia X and treated with melatonin or mitotane, partial or complete hair regrowth was seen in only 62% overall. After the first recheck, melatonin dosage was increased in 8 dogs, but only 1 had improved hair growth. On mitotane, 4 of 6 dogs had partial to complete hair regrowth.
and 2 had none. More importantly, serum sex hormone concentrations did not change significantly in response to treatment nor correlate with whether response was seen. Of the dogs with partial or complete hair regrowth, androstenedione was still elevated in 21%, progesterone was still elevated in 64%, and 17OHP was still elevated in 36%. In 16 Pomeranians and 8 miniature poodles with Alopecia X that responded to trilostane therapy, 17OHP concentrations were significantly elevated by therapy. Similarly, 2 dogs with occult HAC treated with trilostane had clinical signs resolve despite 17OHP concentrations being higher with therapy. Thus, hair coat and other clinical signs improve despite further increases in concentrations of the sex hormones purportedly underlying the clinical signs.

**Assessment**

Although successful therapy has been reported, three main problems exist. First, not all dogs respond to melatonin, mitotane, or trilostane. Second, response does not correlate with sex hormone concentrations. Hair regrowth can occur even in dogs in which serum sex hormone concentrations do not improve. Third, serum sex hormone concentrations can even increase while the clinical signs resolve. If the sex hormones are causing the clinical signs, it is hard to explain how lack of change or even further elevations in sex hormones can be associated with remission if the sex hormones are causing the clinical signs.

**SUMMARY**

Occult HAC due to adrenal secretion of sex hormones has never been 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 although elevations in sex hormone concentrations were widely documented in dogs with Alopecia X, later research was unable to correlate elevations in any hormone with a clinical abnormality. The specificity of adrenal sex hormone panel testing needs to be carefully evaluated because evidence suggests that nonadrenal illness may commonly and nonspecifically increase sex hormone concentrations. Furthermore, not all dogs diagnosed with occult HAC respond to therapy directed at minimizing adrenal hormone secretion. Sex hormones may be elevated even further by therapy, yet dogs may 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 some cases of Alopecia X 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 adrenal glands to manifest the clinical signs. The same could be true of occult HAC. For example, abnormal local tissue response to cortisol could cause the syndrome. Alternatively, occult HAC may represent the canine form of metabolic syndrome as seen in people and horses. Much work remains to be done to understand both the adrenal and local tissue contribution to the syndrome of occult HAC.

**REFERENCES**


