INTRODUCTION

Hyperadrenocorticism (HAC) is one of the commonest canine endocrinopathies. In first opinion practice it is probably more common than hypothyroidism and less common than diabetes mellitus, though meaningful figures are hard to obtain. In the first article in this series the author presented a brief overview of the causes and effects of HAC. This article focuses on the presentation and diagnosis of this disease. Further details and references can be found in the reading list.

The diagnosis of HAC depends on the recognition of the clinical signs, the identification of any concurrent disorders that might interfere with the diagnostic tests or with the subsequent treatment and then the performance of the appropriate diagnostic tests. However before embarking on this process a few considerations may need to be addressed by the clinician and their client.

CONSIDERATIONS BEFORE DIAGNOSING HAC

Is it really significant?

Dogs are now being recognised as having developed HAC without having any clinical signs of the condition. These cases are identified as a result of the increase in pre-operative or ‘geriatric’ biochemical profiles being obtained from otherwise healthy animals. Cases are also identified during consultations for non-endocrine problems as a result of the high levels of awareness of HAC. The problem is that the performances of many of the diagnostic tests in this article have only been assessed in populations showing signs of disease. The diagnostic value of these tests in animals showing no clinical signs is at best poorly defined. Not all such cases – even if confirmed - require treatment. Some cases may be monitored without treatment.

Even if it is significant, is treatment an option?

The diagnosis, treatment and associated monitoring of HAC are expensive. The disease is frequently not life-threatening even though the clinical signs may be debilitating to the dog and of considerable concern to the owner. The costs and benefits in treating dogs for HAC need to be discussed with an owner before embarking on diagnostic tests to confirm the condition. What is the value of an ACTH stimulation test and an ACTH assay if the owner cannot afford any treatment or the associated monitoring? The money would be better spent treating the complications (e.g. recurrent cystitis) of the suspected underlying disease.

How much is ‘enough’ for a diagnosis?

The wide range of diagnostic tests that are available for the confirmation of HAC can be perplexing and what constitutes an adequate work-up sometimes seems to vary from author to author and from case to case. The diagnostic criteria presented in research papers or used by referral practices may not be appropriate in a first opinion practice. In general, the greater the number of clinical signs that are consistent with HAC, the less rigorous the confirmation of the diagnosis is required to be. Academic institutions working with rare presentations or unusual cases require higher standards of diagnosis than the ‘standard’ case presented to a first opinion practice. In many cases of HAC the option of surgical intervention to treat an adrenal tumour is not available and in such cases there is little need to distinguish the two forms of HAC (pituitary dependent or PD-HAC and adrenal dependent or AD-HAC).
CLINICAL PRESENTATION
PD-HAC occurs in middle-aged to older animals with no sex predisposition. In dogs PD-HAC is seen most frequently in small breeds. The disease is usually insidious and slowly progressive. Clinical signs are shown in Table 1 and illustrated in Fig. 1. Clinical signs do vary considerably between individual animals and some cases may only show one or two signs. In addition neurological signs related to an intracranial mass may be present. The clinical presentation of AD-HAC is indistinguishable from PD-HAC. AD-HAC is commoner in larger breeds when compared to PD-HAC. AD-HAC is also more common in female dogs (about 70% of cases are female).

Routine haematology, biochemistry and urinalysis
It is important to obtain a full blood and urine profile before proceeding to further diagnostic tests to exclude other causes of polyuria/polydipsia, polyphagia etc. and to identify any evidence of intercurrent disease that might affect subsequent therapy. The profiles may also identify some non-specific indicators of the disease. The commoner changes that are seen are shown in Table 2.

TABLE 1: Clinical signs of HAC

<table>
<thead>
<tr>
<th>Common signs of hyperadrenocorticism</th>
<th>Uncommon signs of hyperadrenocorticism</th>
</tr>
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<tbody>
<tr>
<td>Polydipsia, polyuria, polyphagia</td>
<td>Dermatological changes: coat colour changes, hyperpigmentation, calcinosis cutis</td>
</tr>
<tr>
<td>Lethargy</td>
<td>Chronic infections / non healing wounds (e.g. cystitis, decubital ulcers)</td>
</tr>
<tr>
<td>Dermatological changes: symmetrical alopecia, poor hair regrowth, comedones, skin thinning</td>
<td>Pseudomyotonia (leading to a stiff hindlimb gait)</td>
</tr>
<tr>
<td>Abdominal distension (‘pot belly’)</td>
<td>Pulmonary thromboembolism (causing dyspnoea)</td>
</tr>
<tr>
<td>Excessive panting</td>
<td>Neurological signs (due to rapid tumour growth): ataxia, depression, apparent blindness</td>
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<tr>
<td>Muscle weakness</td>
<td>Anoestrus and genital atrophy</td>
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SPECIFIC ENDOCRINE TESTS
These should only be undertaken in animals with clinical evidence of HAC. Some cases of HAC are presented with clinical signs of the condition but diagnostic tests prove equivocal or negative. In these circumstances it is sensible to check for other endocrine diseases (particularly hypothyroidism) and then to repeat the tests detailed below from one to
three months later (depending on the severity of the clinical signs).

**ACTH stimulation test**
This is the author’s first choice of the available diagnostic tests. This is mainly because it is the quickest confirmatory test for HAC. However it is relatively insensitive when compared to other confirmatory tests. It should be performed in all dogs with suspected HAC as the results will be used to monitor the success of any medical therapy. This test is of no value in determining the cause (pituitary or adrenal) of the HAC.

To perform the test, obtain a heparinised blood sample (2 ml) and then administer 0.25 mg synthetic ACTH (Synacthen) intravenously (preferred) or intramuscularly. A second heparinised sample is then obtained 30–90 minutes (if given IV) or 1–2 hours (if given IM) later. Normal dogs show a 2–3-fold increase in cortisol concentrations, but these remain <450 nmol/l. Most dogs with HAC have post-ACTH concentrations that are greater than 550 nmol/l.

False-positive results occur with ‘stressful’ illnesses such as unstable diabetes mellitus (Fig. 2). If no response is seen then the most likely explanation is that the dog has iatrogenic hypercortisolism (iHAC) caused by the administration of exogenous steroids. Alternative explanations are that either the ACTH has not been administered, or the dog has hypoadrenocorticism (which is unlikely as the clinical signs are different).

**Low dose dexamethasone suppression test**
This test takes longer than the ACTH stimulation test but is more sensitive (though less specific) and may indicate the cause of the HAC.

To perform the test, obtain a heparinised blood sample early in the morning and then inject 0.015 mg/kg dexamethasone intravenously. Two further heparinised blood samples are then obtained at 3 and 8 hours after injection. Normal dogs show greater than 50% suppression of cortisol concentrations at 3 hours with values less than 40 nmol/l at 8 hours. Dogs with HAC show little or no suppression at 8 hours. If the dog shows suppression at 3 hours, but then no suppression at 8 hours it is still very likely to have HAC (Fig. 3).

**TABLE 2: Common clinicopathological findings in HAC**

<table>
<thead>
<tr>
<th>Haematology</th>
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<tbody>
<tr>
<td>Increased total WBC count</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>Eosinopenia</td>
</tr>
<tr>
<td>Monocytosis</td>
<td></td>
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<table>
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<tr>
<th>Biochemistry</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolaemia</td>
<td>Hyperglycaemia: overt diabetes mellitus is uncommon in dogs</td>
</tr>
<tr>
<td>Increased alanine transferase (ALT)</td>
<td>Increased alkaline phosphatase</td>
</tr>
<tr>
<td>Decreased circulating total T4 (normal endogenous TSH)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Urinalysis</th>
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<tbody>
<tr>
<td>Specific gravity generally low (&lt;1.015); sometimes very low</td>
<td>Glucosuria: uncommon in dogs</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Urinary tract infections (blood, protein, pH changes, active sediment)</td>
</tr>
</tbody>
</table>

![Fig. 2: ACTH stimulation test.](image)
![Fig. 3: Low dose dexamethasone suppression test.](image)
If the values remain persistently increased then the dog may have PD-HAC or AD-HAC (or the dexamethasone has not been administered correctly). If the values remain persistently low throughout the test then the most likely explanation is that the dog has iatrogenic hypercortisolism (iHAC) caused by the administration of exogenous steroids. Alternative explanations are that the dog has an adrenal tumour that is only intermittently secreting steroids or that it has iatrogenic hypercortisolism (which is unlikely as the clinical signs are different). The test is interpreted as shown in Fig. 3.

Other tests for HAC
Measurement of the urine creatinine:corticoid ratio on a urine sample comprising of an equal volume from three different samples obtained over a 24-hour period may be used to exclude the diagnosis of HAC. It can also be used to help confirm the diagnosis in cases with a high index of clinical suspicion provided the owner obtains the urine samples at home.

Recently, the measurement of 17-hydroxyprogesterone, before and after ACTH stimulation, has been suggested to be useful in helping to confirm the diagnosis of HAC in cases with equivocal results. The sensitivity and specificity of this test is debated and it is not a replacement for the standard tests detailed above. However, in certain specific cases when the standard tests have given equivocal results and there is strong circumstantial evidence of HAC, the test may provide valuable evidence of an adrenocortical problem.

The diagnosis of adrenal tumours can pose particular problems. The neoplastic cells release variable amounts of cortisol and other steroids to a greater or lesser extent under the control of ACTH. They do not behave predictably with any test. Reports vary in the efficacy of ACTH stimulation and low dose dexamethasone suppression tests. Some dogs with functional adrenal tumours can give normal results on both tests. Some low dose dexamethasone suppression tests in these cases can show a pattern of low cortisol production that cannot be suppressed. This pattern should be considered as abnormal and prompt further investigation for an adrenal tumour. The definitive diagnosis of an adrenal tumour requires ultrasonographic or radiographic evidence of an adrenal mass (see below).

Discriminating between PD-HAC and AD-HAC
The low dose dexamethasone suppression test may give an indication of the presence of an adrenal tumour. However, other methods such as the measurement of circulating endogenous ACTH concentrations and diagnostic imaging (see below) are often needed. The high dose dexamethasone suppression test is probably now unnecessary in most situations. Measuring endogenous ACTH is probably the easiest of these techniques, but it is probably less accurate than ultrasonography when performed by an experienced operator. To measure ACTH a single EDTA blood sample is obtained and rapidly separated and frozen (within 15 minutes). Local clinical pathology laboratories should then be contacted to help arrange sample dispatch. Endogenous ACTH concentrations are high or normal in PD-HAC (>25 pg/ml), but low in AD-HAC (< 5 pg/ml). Equivocal results (5-25 pg/ml) are sometimes seen. The assay should be repeated in these circumstances as some of these results are due to poor sampling technique.

**DIAGNOSTIC IMAGING**

Plain abdominal and thoracic radiographs should be obtained in all cases of suspected HAC. The principle value of radiography is the identification of adrenal tumours or their metastatic spread. Approximately 50% of adrenal tumours can be identified on plain radiography (Fig. 4). Adrenal tumours cannot be classified as malignant or benign on the basis of their size or degree of calcification. In addition to adrenal tumours there are also a number of non-specific changes, such as hepatomegaly, abdominal distension and dystrophic calcification of soft tissues (e.g. calcinosis cutis) that may help in the diagnosis of HAC. Radiography may also demonstrate other problems that need to be considered when selecting therapy e.g. urolithiasis (Fig. 4).

Ultrasonography is the best method for the detection and assessment of adrenal tumours. If both adrenals cannot be identified then the examination should be regarded as unreliable. Even if an adrenal tumour is detected it is important to identify the contralateral gland as bilateral tumours have been reported. Ultrasonography will also detect bilateral adrenal hypertrophy consistent with PDH. If an adrenal tumour is detected then the caudal vena cava...
and renal vessels should be carefully checked for evidence of local invasion.

Magnetic resonance imaging (MRI) and computed tomography (CT) can be useful in dogs which have mild neurological signs and suspected PDH. Both will provide evidence of pituitary tumours but CT is less sensitive than MRI at the detection of pituitary masses. CT does have the advantage of being able to examine the adrenal glands simultaneously; however ultrasonography is quicker and more reliable even in institutions where CT is available. The presence of a large intra-cranial tumour should not be regarded as poor prognostic sign per se, but rather the severity of the neurological lesions associated with it. The rate of tumour growth is a more important factor in determining the outcome of the case. Many dogs with large intra-cranial tumours have extended survival times because the rate of tumour growth has decreased to negligible levels. Clearly however the chance of intracranial haemorrhage (pituitary apoplexy) or the sudden expansion of the tumour following treatment is increased with larger tumours.

### Key points
- HAC may be seen in any dog of almost any age
- HAC may present with a wide variety of clinical signs of varying severity
- The ACTH stimulation test remains the best single test for HAC
- The ACTH assay is the most practical method of distinguishing AD–HAC from PD–HAC
- Some form of diagnostic imaging should be performed in all cases

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**FURTHER READING**


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**TABLE 3: Diagnosing canine hyperadrenocorticism**

<table>
<thead>
<tr>
<th>Anorexia, vomiting, diarrhoea and pruritus are all uncommon in HAC.</th>
<th>History and physical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>If S.G &gt; 1.030 then HAC unlikely</td>
<td>Urinalysis (including specific gravity)</td>
</tr>
<tr>
<td>If AP is normal then HAC is unlikely</td>
<td>Routine biochemistry</td>
</tr>
<tr>
<td>If lymphocyte count is greater than 1.5 x 10^9/l then HAC is unlikely</td>
<td>Routine haematology</td>
</tr>
<tr>
<td>Consider other differentials. Proceed only if clinical sings still suggestive</td>
<td>ACTH stimulation test</td>
</tr>
<tr>
<td>If 8 hour cortisol &lt; 40 nmol/l HAC unlikely</td>
<td>Post ACTH cortisol concentration &lt;550 nmol/l HAC not excluded</td>
</tr>
<tr>
<td>Consider other differentials. If clinical signs still suggestive then 17-OH progesterone (pre/post ACTH) and/or urine cortisol creatinine ratio</td>
<td>Low dose dexamethasone suppression test</td>
</tr>
<tr>
<td></td>
<td>Determine if adrenal or pituitary dependent</td>
</tr>
<tr>
<td></td>
<td>Radiography, ultrasonography, endogenous ACTH</td>
</tr>
</tbody>
</table>

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1. Which one of the following clinical signs is not a feature of hyperadrenocorticism:
   a. Polyuria
   b. Alopecia
   c. Polyphagia
   d. Weight loss
   e. Polydipsia

2. Which one of the following biochemical findings is not a feature of hyperadrenocorticism:
   a. Increased cholesterol
   b. Decreased glucose
   c. Increased alkaline phosphatase
   d. Decreased phosphate
   e. Low urine specific gravity

3. Which one of the following haematological findings is not a feature of hyperadrenocorticism:
   a. Decreased lymphocytes
   b. Increased erythrocytes
   c. Decreased eosinophils
   d. Increased neutrophils
   e. Decreased monocytes

4. The ACTH stimulation test is said to be 98% specific but only has a sensitivity of 75%. Which one of the following statements is false:
   a. The test generates very few false positive results.
   b. If 100 dogs with hyperadrenocorticism have ACTH stimulation tests then about 25 will not be identified using the test.
   c. The test is not particularly suited to use in a mass screening programme.
   d. If a positive result is obtained from a normal dog then it is not possible to tell how likely it is that the dog does in fact have hyperadrenocorticism.
   e. The test has a poor negative predictive value.

5. The low dose dexamethasone suppression test is said to be 90% specific but has a sensitivity of 90%. Which one of the following statements is false:
   a. Sensitivity is the number of dogs diagnosed with the disease by the test divided by the total number of dogs with the disease.
   b. The prevalence of the disease does not influence the sensitivity or specificity.
   c. The false positive and false negative rates can be calculated from these figures.
   d. Specificity is the number of dogs diagnosed as being disease-free by the test divided by the total number of dogs that gave a negative result.
   e. All measurements of a test’s ‘value’ (such as sensitivity and specificity) require a second definitive test to act as a gold standard.