COMPANION OR PET ANIMALS

# Neurological signs due to hypoadrenocorticism in two dogs

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## SUMMARY

Primary hypoadrenocorticism, also known as Addison's disease and nicknamed 'the great pretender', is a rare disease in dogs and has been sporadically documented in cats. Documented cases of confirmed hypoadrenocorticism as a cause of neurological signs are limited. This report describes two cases of hypoadrenocorticism primarily referred for neurological signs. In case 1, neurological signs consisted of generalised neuromuscular weakness/paresis. The very noticeable tetraparesis (paraparesis most apparent) in case 2 is an example of the generalised paresis that may be a consequence of hypoadrenocorticism. Both cases responded to treatment for hypoadrenocorticism with resolution of neurological signs. In conclusion, hypoadrenocorticism should be considered a differential diagnosis for dogs presented with neurological signs of (generalised neuromuscular) weakness/paresis (manifesting as a 'wobbly gait' which is easily confused with ataxia), especially when signs are long-standing or vaguely defined.

## BACKGROUND

Primary hypoadrenocorticism, also known as Addison's disease and nicknamed 'the great pretender', is a rare disease in dogs and has been sporadically documented in cats.[1–3] Secondary hypoadrenocorticism is even rarer, accounting for 2–4 per cent of cases of hypoadrenocorticism.[4] Still, compared with other species, dogs have a high prevalence of primary hypoadrenocorticism.[4] Some breeds are reported to be over-represented for hypoadrenocorticism and several genetic factors have been subject to investigation (eg, Nova Scotia Duck Tolling Retriever, Portuguese water dog, (standard) Poodle).[1 4 5] As in human beings, autoimmune mechanisms have been identified and some patients are diagnosed with concurrent autoimmune disorders.[1 2 4 6]

This disease is extensively covered in human and veterinary literature. The nickname for hypoadrenocorticism, 'the great pretender', is aptly chosen since a variety of signs are documented in patients with this disorder. They are often vague and as variable as the laboratory test results.[1] Clinical signs are most often reported to be episodic or progressive in nature. Signs of gastrointestinal, muscular, neurological, cardiovascular and renal disease have all been reported.[1 3 5 7–9] Classically, the presenting signs are vague and consist of prolonged episodes and variable severities of lethargy, anorexia, weight loss and gastrointestinal signs.[1] Laboratory tests typically reveal hyperkalaemia and/or hyponatraemia, non-regenerative anaemia and lymphocytosis.[1–3] Those cases which are presented in a hypoadrenocortical crisis often exhibit signs of hypovolaemic shock. Hypotension with bradycardia due to hyperkalaemia might also be noticed. Although consequences of the disease are well-described, pathogenesis is incompletely understood.[1]

Several small animal neurology textbooks mention hypoadrenocorticism as a 'not to be forgotten' differential diagnosis for a variety of clinical presentations. However, documented cases of confirmed hypoadrenocorticism as a cause of neurological signs are limited. This report describes two cases of hypoadrenocorticism primarily referred for neurological (neuromuscular) signs. The aim of this article is to stress the importance of inclusion of hypoadrenocorticism in dogs presented for vague, possibly neurological signs that are episodic or progressive in nature.

## CASE PRESENTATION

Case 1 is a 1.5-year-old female crossbreed (Fox terrier cross) with a bodyweight of 7.1 kg at presentation. The dog was presented to the referring veterinarian with signs of generalised (muscle) weakness/paresis (with a 'wobbly gait') for the duration of one week. Rest and treatment with NSAIDs by the referring veterinarian had not improved clinical signs and euthanasia was put forward in the discussion at that point. On request of the owner the dog was referred to the university clinic and at that time the owner reported a decreased appetite and lethargy. General physical examination was unremarkable. Gait was slow, and the dog was unwilling to walk long distances and was prone to lie down. Tetraparesis was noted. Head carriage was low, but no signs of (cervical) spinal pain were noted on palpation, flexion and extension. Therefore, this was considered a sign of generalised weakness, which also had resulted in tetraparesis causing the slow gait and unwillingness to stand/walk. Muscle tone was decreased. The remainder of the neurological examination was unremarkable.

Case 2 is a nine-year-old female Cairn Terrier with a bodyweight of 8.5 kg at presentation. The dog was referred for vague, but progressive, signs of (para) paresis (especially in the morning) for the duration of one month. Initial treatment by the referring vet with NSAID had not resolved the clinical signs. Laboratory test results performed at the referring practice had revealed (mild) non-regenerative anaemia, hypoalbuminemia and low urine-specific gravity. Plasma sodium and potassium concentrations were within reference range. Laboratory test



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**Table 1** Laboratory results of case 2

| Parameter | Case 2 | Reference range |
|---|---|---|
| Glucose | 4.5 | 4.2–5.8 mmol/l |
| Sodium | 140↓ | 141–150 mmol/l |
| Potassium | 5.2 | 3.6–5.6 mmol/l |
| Chloride | 115 | 114–145 mmol/l |
| Calcium (total) | 2.45 | 1.98–2.97 mmol/l |
| Phosphate (inorganic) | 1.35 | 0.6–1.8 mmol/l |
| Alanine transaminase (ALT) | <12 | <70 U/l |
| Blood urea nitrogen (BUN) | 5.2 | 2.3–9.1 mmol/l |
| Creatinine | 47↓ | 50–129 µmol/l |
| Total protein | 60 | 47–69 g/l |
| Creatine kinase (CK) | 134 | <349 U/l |

results from the referring veterinarian are depicted in table 1. At this stage the dog was referred to a referral centre and was seen by a resident in veterinary neurology. Thoracic radiographs revealed no abnormalities. On abdominal ultrasound examination, signs suggestive of a gastric ulcer were noted. The treatment with NSAIDs was discontinued, and as the differential diagnosis included neuromuscular weakness, the case was referred to the university clinic for EMG and/or nerve conduction studies. At referral, the general physical examination was unremarkable. Tetraparesis was apparent, the hindlimbs were more obviously affected than the front limbs. The dog struggled to stand up from recumbency. Spinal reflexes were normal.

## INVESTIGATIONS

### Case 1

Other than slight lymphocytosis (3.9 *$10^9$/l (ref. 1–3.6 *$10^9$/l), no abnormalities were evident in haematology parameters. Biochemical test results are depicted in table 2. Hyponatraemia and hyperkalaemia were striking abnormalities, and hypoadrenocorticism as a possible reason for the neurological signs was suspected. An adrenocorticotropic hormone (ACTH) stimulation test was performed and at the same time 0.9 per cent sodium chloride intravenous fluid therapy was started.

The results of the ACTH stimulation test confirmed hypoadrenocorticism: both pre-stimulation and post-stimulation cortisol levels were <1 nmol/l (ref. for post-stimulation 270–690 nmol/l).

### Case 2

Repeat laboratory tests revealed significant non-regenerative slightly hypochromic and anisocytic anaemia (20 per cent haematocrit (Ht)). Other test results including glucose, potassium, calcium, ALT, CK and creatinine were within reference range. The plasma sodium concentration was just below reference range (140 mmol/l, ref. 141–150 mmol/l). Na/K ratio was >27 at this time.

Anticholinesterase antibody testing was found to be negative. Coombs testing revealed auto-agglutination on the IgM fraction. An ACTH stimulation test was performed in light of the hyponatraemia and non-regenerative anaemia, and the clinical signs of vague, long-standing signs of weakness and decreased appetite. Pre-ACTH cortisol concentration was 11 nmol/l and post-ACTH cortisol was 8 nmol/l (ref. 270–690 nmol/l).

**Table 2** Laboratory results of case 1

| Parameter | Case 1 | Reference range |
|---|---|---|
| Glucose | 4.8 | 4.2–5.8 mmol/l |
| Sodium | 131↓ | 139–149 mmol/l |
| Potassium | 7.4↑ | 3.8–5.5 mmol/l |
| Chloride | 120 | 114–145 mmol/l |
| Calcium (total) | 3.3 | 2.2–3.3 mmol/l |
| Phosphate (inorganic) | 2.74↑ | 0.6–1.8 mmol/l |
| Alanine transaminase (ALT) | 51 | <113 U/l |
| Blood urea nitrogen (BUN) | 23↑ | 2.3–9.1 mmol/l |
| Creatinine | 115 | 40–199 µmol/l |
| Total protein | 59 | 47–69 g/l |
| Creatine kinase (CK) | 124 | <220 U/l |

## DIFFERENTIAL DIAGNOSIS

Localisation in both cases: neuromuscular.

In both cases, a variety of differential diagnoses were considered for the neuromuscular symptoms. In both cases, metabolic, autoimmune (myasthenia gravis)/inflammatory and (less likely) degenerative and (para)neoplastic differential diagnoses were discussed. Diagnostic testing should therefore be performed according to prioritisation in each individual case.

## TREATMENT

### Case 1

After the ACTH stimulation test, the dog was treated with subcutaneous desoxycorticosterone acetate (0.7 µg) and intravenous hydrocortisone (0.5 mg/kg). The same day the dog was discharged from further hospitalisation and oral therapy with cortisone acetate (0.7 mg/kg twice daily), fludrocortisone acetate (13.4 µg/kg twice daily) and supplementary sodium chloride (0.25 g twice daily) was initiated.

### Case 2

The findings were consistent with hypoadrenocorticism, and cortisone acetate (0.6 mg/kg twice daily orally) was prescribed.

## OUTCOME AND FOLLOW-UP

### Case 1

On clinical examination one week after initiation of oral supplementation therapy, the dog was doing significantly better. Appetite had returned and the dog was more active, though still easily tired especially in the afternoon. The dog was still mildly paretic after exercise, but otherwise the clinical neurological examination was unremarkable. Spinal reflexes were normal. Repeated laboratory test results were within normal limits. Specifically, sodium (147 mmol/l) and potassium (4.4 mmol/l) had normalised. Since there were signs of lethargy in the afternoon, the cortisone acetate was adjusted to thrice daily administration of 0.7 mg/kg instead of twice daily. One month later, the dog was completely back to normal, possibly even more active than before. Repeated laboratory testing did not reveal significant abnormalities.

### Case 2

On clinical examination one week later, the dog had improved significantly. Gait had returned to normal and appetite was restored. The anaemia was still evident, but regeneration was now apparent (corrected reticulocyte percentage of 3.4 per cent, ref. <1.5). Sodium and potassium were within reference range (Na/K ratio >27). One month later, the dog was back to normal according to the owner. Clinical examination revealed

no abnormalities. Anaemia was still present, but now haematocrit was 30 per cent. Again, sodium and potassium were within range (Na/K ratio >27). Cortisone acetate dosage was tapered to starting dose (0.6 mg/kg twice daily orally). One month after the initial visit the dog had returned to normal. All blood values, including the Ht, had returned to values within references values at that time.

## DISCUSSION

The two cases emphasise the importance of inclusion of hypoadrenocorticism in dogs presented for vague neurological signs that are episodic or progressive in nature. In many small animal neurology textbooks, hypoadrenocorticism is mentioned in discussions of muscle disorders and metabolic derangements.[7 8 10] However, only a few reports have documented hypoadrenocorticism in clinical neurological cases. Those most referenced include a dog with 'exercise-induced seizures' secondary to hypoglycaemia associated with hypoadrenocorticism and two dogs with muscle cramps.[7 8] Other neuromuscular signs (eg, generalised paresis) are usually mentioned in reports pertaining to hypoadrenocorticism in general. As with other neurological disorders of an endocrine/metabolic nature, a generalised, waxing and waning presentation of clinical signs might be expected. However, localised clinical signs have been described in two standard poodles with hypoadrenocorticism. In these two dogs, muscle cramps in the thoracic limbs were observed and eventually resolved with treatment.[7] Conversely, intracranial neurological disorders (trauma, neoplasia, vascular) might result in (secondary) hypoadrenocorticism.[9] In the treatment of hypoadrenocorticism, complications of a neurological nature may occur, most notably when correction of (severe) hyponatraemia is performed too rapidly (ie, myelinolysis).[11] Signs of multifocal/diffuse encephalopathy due to lesions in the pons and other brain (stem) regions are a result of myelin destruction in these regions.[11 12]

The very noticeable generalised neuromuscular weakness/tetraparesis (paraparesis most apparent) in these cases is an example of the generalised paresis that may be a consequence of hypoadrenocorticism. Careful history taking, clinical examinations and laboratory tests identified sufficient key indications to consider hypoadrenocorticism as the cause in these patients. Clinical suspicion is crucial in the work-up of patients with hypoadrenocorticism and many cases might be overlooked, simply because the clinical picture is so variable (ie, 'the great pretender'). Reviews already mention that definitive diagnosis relies heavily on the clinician's index of suspicion.[1 5]

The main question is: what processes underlie the manifestation of neuromuscular signs in patients with hypoadrenocorticism? Hyperkalaemia increases the resting membrane potential and brings it closer to the threshold for an action potential to occur.[10] Muscle cramping might result, but paradoxical muscular weakness is also a possible consequence. This is thought to be due to inability to repolarise and muscle fatigue. Cardiac conduction abnormalities leading to bradycardia are also reported in canine hypoadrenocorticism.[2] Thus, imbalance of electrolytes may lead to weakness of muscular or cardiovascular origin, which might worsen with exercise. Also, cortisol has been attributed many roles in homeostasis, including maintenance of membrane integrity. In human literature, 'encephalopathy addisonienne' is documented.[13] Most theories pertaining to the development of that encephalopathy also focus on electrolyte imbalances. Hypotension is reported in hypoadrenocorticism.[1 3–5] In both cases reported here, blood pressure was not measured. Hence hypotension might contribute to signs of weakness in patients with hypoadrenocorticism.

Regarding laboratory testing when hypoadrenocorticism is suspected, the ratio of sodium and potassium (Na/K) has been put forward as being diagnostically valuable in a first evaluation of the likelihood of primary hypoadrenocorticism in clinical settings.[1 2 14] Na/K ratios of ≤24 have been found to be approximately 100 per cent specific and 79 per cent sensitive for hypoadrenocorticism.[14] The same study revealed a sensitivity of 89 per cent and specificity of 97 per cent for a ratio of <27.[14] In cases of suspected hypoadrenocorticism, a ratio of <27 is used as a diagnostic aid. Still, so-called 'atypical' cases of primary hypoadrenocorticism are characterised by normal electrolyte levels and cases of secondary hypoadrenocorticism are typically not associated with changes in electrolytes.[1 14–16] Haematological findings, such as the absence of a 'stress-leukogram' in a sick dog, eosinophilia, lymphocytosis and varying degrees of anaemia (typically mild, normocytic, normochromic anaemia), are also unreliable but can point clinicians in the direction of further diagnostic tests to exclude or confirm hypoadrenocorticism. Ultrasonographic examination of the abdomen might reveal small adrenal glands. A full discussion of the (possible) diagnostic findings in hypoadrenocorticism is beyond the scope of this report.

For the definitive diagnosis of hypoadrenocorticism in canines, an ACTH stimulation test is necessary.[1 5 9 17 18] It is important that no corticosteroids are administered before testing, as this will influence test results. The basal circulating cortisol concentration is valuable diagnostically as well, mainly due to ease and less costs associated with the test. In one study, very low levels of basal cortisol (≤27.6 nmol/l) had excellent sensitivity (approximately 100 per cent) and specificity (98.2 per cent).[17] Still, since cortisol is secreted in a pulsatile fashion, low basal cortisol levels are logically not to be relied on to diagnose hypoadrenocorticism definitively. Levels higher than 55.2 nmol/l make hypoadrenocorticism highly unlikely and can be used to exclude this disease in clinical settings when patients are not receiving corticosteroids, mitotane or ketoconazole.[17] Determination of endogenous ACTH levels, aldosterone-to-renin and cortisol-to-adrenocorticotropic hormone ratios can be used to differentiate between primary and secondary hypoadrenocorticism, but are cumbersome to perform in most clinical settings due to the short half-life of ACTH and need for cooled transport.[1 2 19] However, this differentiation is important as patients with secondary hypoadrenocorticism do not require mineralocorticoid supplementation. In both cases reported here, these tests were not performed, but preferably would have in hindsight. Most patients with the so-called 'atypical' form of primary hypoadrenocorticism eventually do require mineralocorticoid supplementation in addition to glucocorticoid supplementation. Clinical follow-up and laboratory investigations are of great importance in these cases.

In case 1, hypoadrenocorticism was diagnosed on the basis of abnormal electrolyte levels in patient samples in addition to an ACTH stimulation test. Treatment was initiated with fludrocortisone acetate and cortisone acetate orally after initial parenteral desoxycortisone acetate and hydrocortisone. Supplementation of sodium chloride (twice daily 0.25 mg orally) was also prescribed. Electrolyte levels subsequently normalised.

In case 2, hypoadrenocorticism was diagnosed on the basis of the results of an ACTH stimulation test. Electrolyte levels were fairly normal, except for a minimally low sodium concentration (when tested at the referral practice). When tested at the referring practice, the dog had a Na/K ratio of <27, although sodium

and potassium levels were within reference range. In this case, mineralocorticoid supplementation was not part of the treatment and sodium and potassium levels were normal one month after start of therapy with oral glucocorticoids only. However, definitive classification of the hypoadrenocorticism (secondary vs primary) could not be made in the second case. This dog also had significant anaemia at first presentation, which could have been due to chronic blood loss through a gastric ulcer that had been seen on ultrasonographic examination at the referring practice in combination with hypoadrenocorticism. The regeneration that became apparent only after institution of oral cortisone acetate might indicate recovery of regenerative capacity due to corticoid supplementation or might have been a coincidence. Cortisone might also have had an effect on autoimmune destruction of red blood cells, and this might have contributed to elevation of the haematocrit. Also, one might argue that the anaemia partly could have been a contributor to the (generalised) paresis, most evident in the hindlimbs (paraparesis), in addition to the hypoadrenocorticism, although the anaemia was not severe.

Treatment recommendations in literature vary based on availability of substances, clinical preferences and take into consideration financial aspects.[1 3 5 9] The treatment in both the cases reported here resulted in resolution of neurological clinical signs as well as other signs retrospectively postulated to be due to the diagnosed hypoadrenocorticism.

In conclusion, hypoadrenocorticism should be considered a differential diagnosis for dogs presented with neurological signs of (generalised neuromuscular) weakness/paresis, especially when signs are long-standing or vaguely defined. And, if indicated, the appropriate diagnostics should be performed.

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