Hypoadrenocorticism Diagnosed by Adrenocorticotropin Stimulation Test for Aldosterone in a Diabetic Cat

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ABSTRACT

A 6-year-old male neutered cat was referred with a 3-month history of lethargy, chronic constipation, intermittent vomiting, inappetence, progressive weight loss, dysphagia and polyuria. Previous treatment with intravenous fluids, antimicrobials, glucocorticoids, laxatives and appetite stimulants [megestrol-acetate (MgAc)] resulted in partial response. During the treatment course, the cat developed diabetes mellitus (DM). Physical examination revealed obtundation, cachexia, dehydration, pale mucosal membranes, generalised muscle atrophy, sialoadenomegaly and thoracolumbar pain as well as pain upon opening the mouth. Serum electrolyte analysis showed severe hypochloridaemia, hyperkalaemia and hyponatraemia, with a sodium to potassium (Na:K) ratio of 19.6. As the cat had been chronically treated with prednisolone at presentation cortisol concentration could not be reliably interpreted. Therefore, ACTH-stimulation was performed and pre- and post-ACTH aldosterone concentrations were measured, and were consistent with hypoadrenocorticism. Fludrocortisone treatment was initiated, and the clinical signs and electrolyte imbalances resolved; however DM persisted. Feline hypoadrenocorticism is rare, and unlike dogs, cats with this disease may present with dysphagia as a major clinical sign. Although MgAc may induce glucocorticoid deficiency and DM in cats, it has not been reported to induce mineralocorticoid deficiency with subsequent electrolyte imbalance, and its role in the pathogenesis of hypoadrenocorticism in this cat is questionable.

Keywords: Feline; Addison's Disease; Glucocorticoid; Megestrol-Acetate; Diabetes Mellitus; Hyperkalaemia; Hyponatraemia; Hypoadrenocorticism.

INTRODUCTION

Hypoadrenocorticism is a rare endocrinopathy in cats. Primary hypoadrenocorticism is hypothesized to result from immune-mediated destruction of the adrenal cortex, leading to inadequate glucocorticoid and mineralocorticoid production (1,2). At least 85-90% of the adrenal cortices must be impaired for clinical signs to develop (1,2). Spontaneous, secondary hypoadrenocorticism, unreported in cats so far, results from inadequate pituitary adrenocorticotropin (ACTH) secretion, leading to deficient glucocorticoid secretion (1, 2). Iatrogenic hypoadrenocorticism can occur after withdrawal of potent glucocorticoids or progestins, however, clinical signs are rarely seen in cats (2).

Cats with hypoadrenocorticism typically show lethargy, anorexia, weight loss, (nonspecific signs which are common to many other illnesses) and may also present vomiting, polydipsia and polyuria, while unlike dogs, collapse and bradycardia are rare (2-4). Dysphagia occurs uncommonly, and is believed to result from muscle weakness, secondary to electrolyte disturbances and generalised atrophy (5). Laboratory abnormalities may include an "anti-stress leukogram" (eosinophilia, lymphocytosis and neutropenia) , anaemia, azotae-

mia, hyperphosphatemia, hypocholesterolaemia and evidence of dehydration (1). Hyponatremia is reported in 100% of cases whilst hyperkalemia occurs in 90% of such cats, and the Na:K ratio is typically <24 (2).

Definitive diagnosis of hypoadrenocorticism is mostly based on measurement of pre- and post-ACTH serum cortisol concentrations. To the best of our knowledge, an ACTH stimulation of serum aldosterone concentrations for confirmation of hypoadrenocorticism in cats was previously reported only once (4). The present report describes a case of hypoadrenocorticism in a diabetic cat, diagnosed using pre- and post-ACTH serum aldosterone concentrations.

CASE REPORT

A 6-year-old male neutered domestic shorthair cat was referred to the Hebrew University Veterinary Teaching Hospital (HUVTH) with chief complaints of chronic constipation, weight loss and intermittent vomiting. During the three months prior to presentation, the cat was vocal when defecating, passed overly firm stools, progressively lost weight, and presented with selective appetite, polyuria and dysphagia. The cat appeared to be interested in food, but had difficulties prehending and chewing it. Two weeks after the initial clinical signs were first noted, blood samples for CBC and serum biochemistry (electrolytes measurement excluded) were performed by the referring veterinarian. Results were unremarkable, with exception of increased haematocrit [47.4% reference interval (RI) 30-45%; 0.474 L/L, RI 0.30-0.45]. Serum cholesterol concentration was low within RI (68 mg/dL, RI 65-225; 1.76 mmol/L RI 1.68-5.83). Urine was obtained by cystocenthesis, and urinalysis showed a SG of 1.025 and mild proteinuria (25 mg/dL). Oral examination findings, performed under sedation, thoracic radiographs and abdominal ultrasound were unremarkable. The cat was treated at the referring clinic with intravenous (IV) fluids, cefovecin (Convenia, Zoetis, Madison, NJ, USA; 80 mg SC), lactulose (Avilac, Perrigo, Allegan, MI, USA; 330 mg PO, q12h) and megestrol-acetate (MgAc) (Ovarid, Jurox Pty Ltd., Silverwater, NSW, Australia; 5 mg PO, q48h for one week, followed by q72h for four additional weeks and followed by q96h for two additional weeks). Mineral oil and an oral fat additive (Nutri-cal, Toymlin, Fort Worth, TX, USA) were added to the cat's diet. Despite treatment no improvement was noted.

Total serum thyroxine concentration, measured seven days later by the referring veterinarian was within RI (0.9 µg/dL, RI 0.8-4.7; 11.5 nmol/L, RI 10.3-60.4). The cat continued to show eating difficulties, and was therefore referred for computed tomography of the head which was reviewed by a board certified radiologist, and was unremarkable. Four weeks after noting the initial signs, prednisolone (Danalone, Trima, Maabarot, Israel; 6 mg PO, q12h for five days, followed by 6 mg PO q24h) was empirically initiated, and the cat showed improvement in his eating ability, although he still suffered from dysphagia and did not gain weight. Treatments with prednisolone and MaAc overlapped for three weeks.

After five weeks of prednisolone treatment, during a check-up, hyperglycemia was noted, and was persistently present later on (glucose 223-330 mg/dL, 12.38-18.32 mmol/L measured several times over a 2.5-week period; RI 74-159, RI 4.11-8.82). Serum fructosamine concentration was increased (634 µmol/L, RI 0-375; 6.34 mmol/L, RI 0 – 3.75). The cat was tentatively diagnosed with glucocorticoid / MgAc-induced diabetes mellitus (DM), and treatment with NPH insulin (Humulin-N, Eli Lilly, IN, USA; 3 IU SC, q12h) was initiated, and the cat was then referred to the HUVTH.

At presentation to the HUVTH, the cat showed cachexia (body condition score: 2-3/9; body weight: 4.06 Kg.), general muscle atrophy, obtundation, pale mucous membranes, hypothermia (rectal temperature 36.5° C), mild gingivitis, bilateral sialoadenomegaly and 8% dehydration. Pain was noted upon palpation of the lumbar-sacral spine and upon opening the mouth. Abdominal palpation, thoracic auscultation and neurological examination were unremarkable. At presentation, the cat was still being treated with prednisolone (6 mg PO, q24h), but had not received MgAc for three weeks.

A CBC showed microcytic normochromic anaemia, lymphopenia and eosinopenia, with an unremarkable leucocyte count (Table 1). Polychromasia was absent upon examination of a stained blood smear. Abnormal serum biochemistry results (Table 2) included hyperglycemia, hypertriglyceridemia, hypochloridemia , hyperkalemia, hyponatremia, decreased Na:K ratio (19.6, RI 27.0-40.1) and increased fructosamine and β-hydroxybutyric acid (BHBA) concentrations. Serum cobalamine and folate concentrations were within RI. Feline pancreatic lipase like immunoreactivity assay (SNAP fPL, Idexx, Westbrook, ME, USA) was negative. Fine needle as-

Table 1: Complete blood count results* of a 6-year-old male cat with hypoadrenocorticism and diabetes mellitus at presentation at HUVTH.

Analyte	Day 0	RI[1] (US units)	RI[1] (SI units)
White blood cells ($x10^3$ /μL) [$x10^9$ /L]	9.4	6.3 – 19.6	6.3 – 19.6
Red blood cells ($x10^6$ /μL) [$x10^{12}$ /L]	7.3	6.0 – 10.2	6.0 – 10.2
Haemoglobin (g/dL) [g/L]	9.6 [96]	8.1 – 14.2	81 – 146
Haematocrit (%) [L/L]	27.2 [0.27]	27.7 – 46.8	0.27 – 0.46
Mean corpuscular volume (μm3) [fL]	37.3	41.3 – 52.6	41.3 – 52.6
Mean corpuscular haemoglobin (pg)	13.2	12.0 – 16.0	12.0 – 16.0
Red cell distribution width (%)	15.9	15.9 – 19.4	15.9 – 19.4
Haemoglobin distribution width (g/dL)	2.0	1.6 – 2.9	1.6 – 2.9
Platelets ($x10^3$ /μL) [$x10^9$ /L]	272	156 – 626	156 – 626
Mean platelet volume (fL)	16.4	8.6 – 18.9	8.6 – 18.9
Neutrophils ($x10^3$ /μL) [$x10^9$ /L]	7.4	3.0 – 13.4	3.0 – 13.4
Lymphocytes ($x10^3$ /μL) [$x10^9$ /L]	1.7	2.0 – 7.2	2.0 – 7.2
Monocytes ($x10^3$ /μL) [$x10^9$ /L]	0.1	0 – 1.0	0 – 1.0
Eosenophils ($x10^3$ /μL) [$x10^9$ /L]	0.1	0.3 – 1.7	0.3 – 1.7
Basophils ($x10^3$ /μL) [$x10^9$ /L]	0.02	0 – 0.10	0 – 0.10
Leucocytes ($x10^3$ /μL) [$x10^9$ /L]	0	0 – 0.2	0 – 0.2
Reticulocytes ($x10^9$ /μL) [$x10^9$ /L]	1.9	15 – 81	15 – 81

* US units are depicted in parentheses, while SI units (when different from the US ones) depicted in square brackets; 1, reference interval.

piration from the enlarged salivary glands was cytologically unremarkable. Abdominal ultrasound revealed increased hepatic echogenicity, with no other abnormalities.

In view of the low Na:K ratio and the chronic, waxing and waning clinical signs, hypoadrenocorticism was suspected. As the cat had been treated with prednisolone. the continued clinical signs were attributed to the lack of mineralocorticoid treatment. Because the cat had been treated with prednisolone continuously for five weeks at the time of presentation, measurement of cortisol concentrations pre- and post-ACTH was deemed unreliable for diagnosing hypoadrenocorticism, due to the expected suppression of adrenal cortisol secretion (6). Blood samples were collected pre- and one hour post-ACTH (Cortosyn, Amphastar Pharms, Rancho Cucamonga, CA, USA; 0.125 mg, IV) administration, and the harvested sera were sent, at 2-8°C, to the Diagnostic Center for Population and Animal Health, Michigan State University Veterinary School Laboratory, for measurement of aldosterone concentration. Aldosterone concentration was not expected to decrease in response to administration of glucocorticoids as the main determinants of aldosterone secretion are concentrations of angiotensin II and potassium (1, 7). Pending results, fludrocortisone (Florinef, Pfizer, New York, NY, USA; 0.1 mg PO, q24h) treatment was initiated, and prednisolone (5 mg, PO, q12h) and NPH-insulin were continued. The cat was then referred back to the referring clinic for further treatment and monitoring. Over the next four days, progressive improvement was noted. The cat began eating voluntarily, and the diet was subsequently changed to a diabetic prescription veterinary diet (DM, Nestlé-Purina PetCare Company, St. Louis, MI, USA). Electrolytes concentrations four days after initiation of fludrocortisone were within RI (Table 2), with a Na:K ratio of 33. Pre- and one hour post-ACTH aldosterone concentrations were both below the assay's detection limit (< 14 pmol/L pre and post- ACTH; RI pre-ACTH 194-388; RI post-ACTH, 277-721), confirming hypoadrenocorticism.

Follow up was performed by the referring veterinarian. The cat progressively improved over the next three months, and gained 1.5 kg of body weight. Prednisolone was tapered down several weeks post diagnosis, while fludrocortisone dose was increased to 0.125 mg PO q24h. He remained diabetic despite prednisolone tapering, and was therefore constantly treated with NPH insulin (4 units SC q12h).

DISCUSSION

Primary hypoadrenocorticism is a rare endocrinopathy in cats, reported sporadically in the veterinary literature (3-5,8,9). Megastrol-acetate can induce adrenal insufficiency by its glucocorticoid activity (10,11), however, to the best of our knowledge, it has not not reported to affect adrenocortical mineralocorticoid production neither in cats and dogs, nor in humans. Adrenal suppression induced by prednisolone, given at a dose of 2 mg/kg q24h, was compared to that induced by MgAc at 5 mg (total dose) q24h in cats (11). The severity of adrenal suppression and the decrease in circulating serum cortisol levels were more profound when induced by MgAc compared to prednisolone. Moreover, while adrenal suppression induced by prednisolone resolved in 85% of the cats at two weeks after its discontinuation, it was still evident

Table 2: Serum biochemistry results* of a 6-year-old cat with hypoadrenocorticism and diabetes mellitus at presentation, and repeat electrolyte results four days later.

Analyte	Day 0	Day 4	RI[1] (US units)	RI[1] (SI units)
Albumin (g/dL) [g/L]	4.1 [41]		2.0 – 4.6	22 – 46
Alkaline phosphatase (U/L)	39		14 – 71	14 – 71
Alanine transaminase (U/L)	65		27 – 101	27 – 101
Amylase (U/L)	870		500 – 1800	500 – 1800
Aspartate transaminase (U/L)	50		17 – 58	17 – 58
Total bilirubin (mg/dL) [µmol/L]	0.2 [3.4]		0.0 – 0.2	0.0 – 3.4
Calcium (mg/dL) [mmol/L]	9.6 [2.4]		9.0 – 10.9	2.2 – 2.7
Cholesterol (mg/dL) [µmol/L]	211 [5.4]		89 – 258	2.3 – 6.6
Creatine kinase (U/L)	60		73 – 260	73 – 260
Chloride (mmol/L) [mEq/L]	91	115	117 – 126	117 – 126
Total CO_2 (mmol/L) [mEq/L]	14.3		15.0 – 21.0	15.0 – 21.0
Createnine (mg/dL) [µmol/L]	0.9 [83.9]		1.1 – 2.2	97.2 – 194.4
Fructosamine (µmol/L) [mmol/L]	387 [3.87]		0 – 375	0 – 3.75
γ-glutamyl transpeptidase (U/L)	<0.0		0.0 – 6.0	0.0 – 6.0
Glucose (mg/dL) [mmol/L]	297.6 [16.4]		63.0 – 118.0	3.5 – 6.5
Potassium (mmol/L) [mEq/L]	6.2	4.6	3.6 – 4.9	3.6 – 4.9
Sodium (mmol/L) [mEq/L]	122	150	151 – 158	151 – 158
Sodium:potassium ratio	19.6	33	>24	>24
Phosphorus (mg/dL) [mmol/L]	4.8 [1.5]		3.2 – 6.3	1.0 – 2.0
Total protein (g/dL) [g/L]	6.8 [68]		6.6 – 8.4	66 – 84
Triglycerides (mg/dL) [µmol/L]	377 [4.26]		8.0 – 88.0	0.09 – 0.99
Urea (mg/dL) [mmol/L]	37.4 [13.3]		38.5 – 70.6	13.7 – 25.2
b-hydroxybutyric acid (md/dL) [mmol/L]	29.8 [2.87]		0 – 4.8	0 – 0.47
Cobalamine (pg/mL) [pmol/L]	308.8 [227.8]		100.0 – 350.0	73.8 – 258.3
Folate (ng/mL) [nmol/L]	11.7 [26.5]		10.4 – 20.7	23.5 – 46.9

* US units are depicted in parentheses, while SI units (when different from the US ones) depicted in square brackets; 1, reference interval.

in 57% of the MgAc-treated cats at two weeks after its discontinuation (11). Nevertheless, no clinical signs of adrenal insufficiency were noted in any of the cats in that study (11).

Signs of hypoadrenocorticism in cats may be noted from several days and up to four months prior to its diagnosis, as was seen in this cat. In some cats, the disease is diagnosed only when a hypoadrenal crisis occurs, which is considered a medical emergency (2). The present cat exhibited weakness, weight loss and selective appetite for three weeks before MgAc therapy was initiated. Overall, the cat was treated with MgAc for seven weeks and treatment was discontinued three weeks prior to presentation to the HUVTH. Therefore it is unlikely that MgAc treatment contributed to the electrolyte imbalance noted at presentation. The presence of decreased sodium concentration and increased potassium concentration, along with aldosterone deficiency is suggestive of primary, rather than iatrogenic hypoadrenocorticism. Additionally, MgAc was tapered gradually, decreasing the likelihood of inducing iatrogenic hypoadrenocorticism. Nevertheless, it is very likely that concurrent MgAc and prednisolone treatment in this cat had a role in induction of DM (12,13). Jaw and back pain, exhibited in this cat has not been reported previously and was attributed to muscle atrophy.

Definitive diagnosis of hypoadrenocorticism is based on measurement of low pre- and post-ACTH stimulation serum cortisol concentrations (1,2). Combining these with baseline endogenous serum ACTH concentration or pre- and post-ACTH stimulation serum aldosterone concentrations allows differentiation between primary and secondary hypoadrenocorticism (1).

Prednisolone or methyl-prednisolone administration prior to ACTH stimulation testing interferes with the diagnosis, and make interpretation of the test results difficult to impossible, as both drugs are detected, along with endogenous cortisol, in the cortisol assay (6). Moreover, if used long-term, both glucocorticoids lead to adrenal gland suppression, thereby resulting in low pre- and post-ACTH stimulation cortisol concentration, thereby mimicking hypoadrenocorticism (14,15). Aldosterone is the primary hormone responsible for maintaining sodium, potassium, chloride, and acid-base homeostasis (1), and its deficiency accounts for some of the major clinical signs of hypoadrenocorticism (1,2). Serum aldosterone concentration is seldom measured in the diagnostic work-up of feline hypoadrenocorticism, mostly because the availability of the aldosterone assay has been limited for some time (1). To our knowledge, feline hypoadrenocorticism has been diagnosed previously by ACTH stimulation and aldosterone

concentration only once (4). Serum aldosterone concentrations in dogs with primary hypoadrenocorticism are usually below RI, although they overlap the lower RI (16). Similar data for cats are unavailable. In the present cat, due to the need to ship the serum samples for aldosterone measurement overseas, some degradation cannot be completely ruled out, but was considered unlikely to be significant. Nonetheless, considering the clinical signs and, most importantly, the excellent response to treatment, the measured aldosterone concentrations were likely actually very low.

While dogs with hypoadrenocorticism typically respond quickly to treatment, the response of cats may take up to 3-5 days (2). In the present case, electrolyte concentrations normalised within four days from initiation of fludrocortisone therapy. Hypoadrenocorticism in cats requires life-long mineralocorticoid and to a lesser extent glucocorticoid treatment, and can be usually treated with fludrocortisone (0.05–0.1 mg/cat PO q 12 h) which supplements both glucocorticoids and mineralocorticoids. Some cats will require additional glucocorticoid supplementation (e.g., prednisolone at 0.25-1 mg/cat PO, q12h) either for life, or at times of stress (2). The prognosis is usually good to excellent with proper treatment (2), as was observed in this case.

Increased serum BHBA concentration typically occurs in cats in states of negative energy balance, such as DM (i.e., diabetic ketosis), diabetic ketoacidosis (DKA) or hepatic lipidosis (HL) (17). In this cat, in light of the dysphagia, prolonged anorexia and hyperechoic liver it is likely that hyperketonemia resulted from both DM (or DKA) and HL; however, additional diagnostic tests, such as fine needle aspiration of the liver, venous blood gas analysis and additional serum BHBA measurements overtime were not performed, being deemed unnecessary in light of the cat's clinical improvement.

In conclusion, hypoadrenocorticism should be considered in cats presenting chronic dysphagia, weight loss and inappetance, when other causes of dysphagia are ruled out. If prior glucocorticoid supplementation precludes measurement of pre- and post-ACTH stimulation serum cortisol concentrations, measurement of pre- and post-ACTH stimulation serum aldosterone concentrations can aid in the definitive diagnosis of hypoadrenocorticism.

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