Hyperreninaemic hypoaldosteronism in a dog

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ABSTRACT

A 9-year-old male German shepherd dog was evaluated for clinical and clinico-pathological changes that were suggestive of Addison's disease. On further investigation the basal plasma cortisol concentration was high, a normal cortisol response to ACTH stimulation occurred, plasma renin activity was elevated and low serum aldosterone concentration was present. A diagnosis of hyperreninaemic hypoaldosteronism was made. Replacement fludrocortisone resulted in complete normalisation of the electrolyte and fluid imbalances. Hyperreninaemic hypoaldosteronism has never been reported in the dog.

Key words: aldosterone deficiency, canine, dog, hyperreninaemic hypoaldosteronism.

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INTRODUCTION

The secretion of aldosterone by the zona glomerulosa of the adrenal gland is of critical importance for the regulation of sodium, potassium, and fluid balance in the body, and therefore severe electrolyte and fluid imbalances can occur with aldosterone deficiency[1]. Aldosterone regulates electrolyte excretion and intravascular volume mainly through its effects on the renal distal tubular and cortical collecting ducts, in which it increases tubular sodium resorption and potassium excretion into the filtrate[13]. Aldosterone secretion is regulated by the renin-angiotensin system, serum potassium concentration and corticotrophin, although the latter's effect is short-lived[13]. Although aldosterone deficiency with concurrent normal cortisol concentration has been well described in man, in the dog it has been alluded to[12] but never reported in the veterinary literature.

CASE HISTORY

A 9-year-old male German shepherd dog was referred to the Onderstepoort Veterinary Academic Hospital (OVAH) with acute onset of generalised weakness and possible renal failure, the latter based on the referring veterinarian's findings of isosthenuria and azotaemia. According to the owners, the dog had shown episodic weakness for the past 4 months. On clinical examination there was generalised weakness, weak femoral pulses, muffled heart sounds, and flaccid abdominal muscles. Although there was haematochezia, no abnormalities could be found on faecal examination. The only abnormality on urine analysis was persistent isosthenuria. Abnormalities on full blood count and biochemical profile were a stress leukogram, panhypoproteinaemia, hyperkalaemia, hyponatraemia, hypochloridaemia and azotaemia (Table 1). An ECG tracing was consistent with hyperkalaemia (absent P waves and tented T waves; bradycardia was, however, not present). Survey thoracic radiographs showed generalised cardiomegaly and a mild interstitial-bronchial lung pattern. Echocardiography revealed a heart base tumour with moderate pericardial effusion. Survey abdominal radiographs and abdominal ultrasonography were both within normal limits. Basal cortisol concentration was high and on ACTH stimulation there was an adequate post-stimulation cortisol concentration. Serum aldosterone concentration (determined using a radioimmunassay method) was low, whereas plasma renin activity (PRA) was elevated (Table 1). Plasma renin activity is defined as the rate of angiotensin I produced by renin in a patient's plasma, and is expressed in nanograms of angiotensin I produced per mℓ of plasma per hour[10].

The dog was treated with intravenous dextrose-saline fluids and replacement mineralocorticoid therapy (fludrocortisone: Florinef, Bristol-Myers Squibb Pharmaceuticals), the latter initially at a dose of 0.5 mg once a day (oid) but then reduced to 0.3 mg oid on Day 5, as hypokalaemia was developing. As no cardiac tamponade was present, the pericardial effusion was not drained. Within 3 days, the weakness and sodium and potassium abnormalities had resolved. At discharge, 7 days after admission, the azotaemia was resolving and the pericardial effusion had resolved. Re-evaluation on Days 24 and 145 showed no clinical, echocardiographic or biochemical abnormalities (Table 1). On Day 145 the aldosterone concentration was at the low end of normal, whereas the PRA was still elevated (Table 1). The dog had been maintained on 0.3 mg fludrocortisone oid.

One hundred and sixty days after the initial presentation, the dog was re-admitted to the OVAH for an acute onset of dyspnoea. On clinical examination there was hepatomegaly and the heart and lung sounds were muffled. Survey thoracic radiographs showed moderate pleural effusion and multiple pulmonary nodules (5–20 mm in diameter) on the visible lung parenchyma. Hepatomegaly and ascites were confirmed on abdominal radiographs. Pleural fluid analysis showed a modified transudate with the presence of anaplastic cells. As the prognosis was guarded, the dog was euthanased at the owner's request.

Autopsy revealed generalised fluid accumulation (ascites, hydropericardium, hydrothorax), cyanotic induration of the liver, a single, large, locally extensive heart base tumour, and several round, well circumscribed pulmonary neoplasms. Both the heart base tumour and the pulmonary neoplasms were diagnosed as chemodectomas on histopathology. No abnormalities were noted in the adrenal sections.

The cause of the sudden deterioration was attributed to decompensated congestive heart failure and metastatic lung disease.

DISCUSSION

The clinical features, isosthenuria, electrolyte and ECG abnormalities that this case showed were all typical of classical

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Table 1: **Serial biochemical and hormonal parameters.**

Parameters	Normal	Day 1	Day 3	Day 5	Day 7	Day 24	Day 145
Total serum protein	53–75 g/ℓ	45	—	—	—	50	58
Albumin	27–35 g/ℓ	25	—	—	—	28	25
Globulin	20–37 g/ℓ	20	—	—	—	22	33
Alanine transaminase (ALT)	5–40 mμ/ℓ	34	—	—	—	—	36
Alkaline phosphatase (ALP)	40–190 mμ/ℓ	140	—	—	—	—	180
Glucose	3.3–5.5 mmol/ℓ	5	—	—	—	—	—
Sodium	140–155 mmol/ℓ	131	140	139	140	149	145
Potassium	3.6–5.1 mmol/ℓ	8	4.1	3	3	5.4	5.5
Calcium	2.2–2.9 mmol/ℓ	2.2	—	—	—	—	—
Inorganic phosphate	0.9–1.6 mmol/ℓ	5.6	—	—	—	—	1.51
Chloride	105–120 mmol/ℓ	98	87	97	94	94	121
Urea	3.6–8.9 mmol/ℓ	77	82	53	32	6.2	9.5
Creatinine	40–133 μmol/ℓ	425	333	293	230	131	134
Serum aldosterone	0.1–0.8 nmol/ℓ	0.01	—	—	—	—	0.1
Plasma renin activity (PRA)	1.3–3.95 ng/mℓ/hr	5.77	—	—	—	—	6.23
PRA:aldosterone ratio	4.9–13.0	577	—	—	—	—	42
Basal plasma cortisol	80–120 nmol/ℓ	177	—	—	—	—	145
Post ACTH plasma cortisol	240–360 nmol/ℓ	357	—	—	—	—	306

Addison's disease[2]. The hypoproteinaemia was attributed to the haemorrhagic enteritis, which probably also contributed to the high serum urea concentration. Haemorrhagic enteritis has been reported with Addison's disease[2] and it was initially thought that this dog had early Addison's disease. However, cortisol deficiency never developed, and on histological examination of the adrenal glands, no light or electron microscopic changes were present, suggesting a biosynthetic defect of the adrenal cortex zona glomerulosa. The resolution of the pericardial effusion was attributed to normalisation of the intravascular blood volume.

An aldosterone deficiency will result in hyponatraemia, hypochloridaemia, hypovolaemia and hyperkalaemia[9]. In man, an aldosterone deficiency without concurrent cortisol deficiency is rare[3]. In the veterinary literature, to the author's knowledge, there are only 2 references to an aldosterone deficiency. One involved pigs fed olaquindox (used as a growth promoter)[8], which resulted in destruction and fibrosis of the zona glomerulosa of the adrenal cortex, and the other a dog[12] that had hypoaldosteronism with a normal response to ACTH stimulation. Further investigation in the latter case was, however, not undertaken.

As aldosterone is closely linked to the renin-angiotensin system, the interpretation of an aldosterone deficiency accompanied by normal cortisol production must be based on PRA. PRA is usually elevated in aldosterone biosynthetic disorders or situations where there is failure of the adrenal cortical zona glomerulosa function, while disorders that are associated with alterations in the renin-angiotensin system are generally characterised by low or undetectable PRA[5]. Hyporeninaemic hypoaldosteronism occurs with renal failure and diabetes mellitus, whereas hyperreninaemic hypoaldosteronism occurs with adrenal gland biosynthetic defects or in hypotensive, critically ill patients[8,13]. Pseudohyperkalaemia must also be excluded[13]. In this dog, high PRA with low serum aldosterone concentration were present, consistent with either an aldosterone biosynthetic defect or critical, hypotensive disease. Primary disorders of the adrenal gland are characterised by elevated PRA to aldosterone concentration ratio, whereas with extra-adrenal disorders the ratio between these 2 hormones is normal[4]. The ratio in this dog was severely elevated, which suggested that the possible aetiology was a primary adrenal gland disorder. Isolated hypoaldosteronism has also been described in man, but is rare and is associated with both low serum aldosterone concentration and low PRA[7]. Adrenal insufficiency (immune mediated or infectious) may cause hypoaldosteronism. However, cortisol secretion is also affected. Drugs such as ketoconazole, rifampicin, mitotane, polysulphated glycosaminoglycans or heparin, when given for a prolonged period, can all suppress aldosterone biosynthesis and/or aldosterone secretion[3,5]. Neither adrenal gland destruction nor previous drug therapy were present in this case.

In man, hyperreninaemic hypoaldosteronism is well-described in the neonate and is associated with an adrenal biosynthetic defect where there is an inability to transform the C18 methyl group of corticosterone to the C18 aldehyde of aldosterone owing to a deficiency of the 18-hydroxysteroid dehydrogenase enzyme[3]. Other biosynthetic defects that have been reported are 21-hydroxylase enzyme deficiency, associated with congenital adrenal hyperplasia, renal salt wasting, and virilisation[9,11]; and aldosterone synthetase enzyme deficiency[9], which is further subdivided into type I (defect in corticosterone conversion to 18-hydroxycorticosterone) and type II (impaired conversion of 18-hydroxycorticosterone to aldosterone)[3]. Type II is more common and usually presents as a life-threatening, salt-wasting crisis. However, a less dramatic presentation has also been described[6]. The definitive diagnosis of an aldosterone synthetase enzyme deficiency is the demonstration of elevated serum concentrations of corticosterone, deoxycorticosterone, 18-hydroxycorticosterone and PRA combined with low serum aldosterone concentration[3,6,9]. If the precursor hormones cannot be determined, the diagnosis can still be made if a high PRA:aldosterone ratio is present, congenital adrenal hyperplasia is ruled out, and response to replacement mineralocorticoid therapy occurs[6]. In this dog there was a high PRA:aldosterone ratio, congenital adrenal hyperplasia was not present, and a dramatic response to replacement mineralocorticoid therapy occurred.

Another major cause for hyperreninaemic hypoaldosteronism in man is severe illness, associated with sepsis and/or hypotension[3,13]. Hyperkalaemia is, however, not part of this syndrome[13]. The proposed pathogenesis is ischaemic adrenal gland damage as a result of hypo-

tension or inflammatory mediators (tumour necrosis factor, interleukin 1) that stimulate renin and ACTH release, but inhibit the effect of angiotensin on the adrenal gland. Treatment of the underlying disease will resolve the hyperreninaemic hypoaldosteronism, without mineralocorticoid replacement therapy being necessary. Although this dog was ill at presentation, all the clinical signs could be attributed to an aldosterone deficiency, recovery occurred with mineralocorticoid supplementation, and severe hyperkalaemia was also present.

It is speculated that this dog could have had a Type II aldosterone synthetase deficiency, which, although it was present from birth, only manifested later in life. Another possibility is that a biosynthetic defect developed as a result of suppressive factor(s) produced by the chemodectoma. This is feasible in the present case, as a G-protein mutation has been identified in a person with concurrent corticotroph adenoma, chemodectoma and unilateral nodular hyperplasia of the adrenal gland[14]. Hyperreninaemic hypoaldosteronism was, however, either not present or not documented. G-proteins are transducers that link extracellular receptor-bound ligands to intracellular messenger systems, stimulating adenyl cyclase activity[14]. G-protein mutation thus results in the constitutive activation of adenyl cyclase. It is therefore possible that, in the dog described in this report, the chemodectoma resulted in a G-protein mutation which led to a biosynthetic defect in the adrenal glands.

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