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Abstract

Case summary A male neutered Ragdoll cat aged 11 years and 9 months presented with a 6 month history of weight loss and a 1 month history of lethargy and adipsia. A thorough clinical investigation confirmed a diagnosis of primary adipsia and hypernatraemia secondary to a non-secretory neuroendocrine pituitary macroadenoma.

Relevance and novel information Primary adipsia is a very rare clinical entity. This report is the first to describe primary adipsia secondary to a non-secretory pituitary macroadenoma in the cat. The veterinary literature available in this field is very limited and this report adds a new differential diagnosis for cats presenting with primary hypodipsia.

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Introduction

Intracranial neoplasia is uncommon in cats, with a reported incidence of between 0.0035% and 2.2%.^{1,2} Pituitary tumours are the third most common feline brain tumour after meningioma and lymphoma, accounting for approximately 9% of all brain tumours.^{3,4} The most common neurological signs reported are blindness, altered consciousness or behavioural change.³ Non-specific clinical signs of lethargy, anorexia, weight loss and polyuria/polydipsia are also commonly reported. Concurrent endocrinopathies are frequently encountered, with diabetes mellitus identified in 50% of cases.³

This case report describes a cat with a non-secretory neuroendocrine pituitary macroadenoma presenting with adipsia and subsequent hypernatraemia. There are five reported cases of primary adipsia in cats;^{5–8} one case of thalamic and hypothalamic B-cell lymphoma with hypothalamic dysfunction and adipsia attributed to neoplasia;⁵ adipsia secondary to hydrocephalus in a 7-month-old cat;⁶ a case of cerebral trauma; and in the final two reported cases, a definitive diagnosis was not reached.^{7–9} Primary adipsia is equally rare in the dog, with only seven cases reported.^{8–14} To our knowledge, this is the first case report in cats describing a pituitary neuroendocrine tumour presenting with primary adipsia and hypernatraemia.

Case summary

A male neutered Ragdoll cat aged 11 years and 9 months was referred for evaluation of a 6 month history of weight loss and a 1 month history of lethargy and cessation of normal drinking.

A fortnight previously, the cat was examined at the referring veterinary practice. Investigations identified severe hypernatraemia (184 mmol/l [reference interval (RI) 138–155 mmol/l]), hyperchloraemia (139 mmol/l [RI 112–129 mmol/l]) and azotaemia (urea 13.1 mmol/l [RI 6–10 mmol/l], creatinine 173 µmol/l [RI 40–150 µmol/l]). The patient was hospitalised and received intravenous (IV) crystalloid fluid therapy. The cat's sodium concentrations normalised and the azotaemia reportedly resolved. No clinical abnormalities were reported at discharge.

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At presentation, the owner reported that they had not witnessed the cat drinking since the time of discharge from the referring vets. The cat was predominantly an indoor cat but occasionally went outside for short periods, during which time drinking activity was unknown. On examination, the patient was thin (body condition score 2/5) and demonstrated a depressed mental status. Based on clinical examination the patient was estimated to be 8% dehydrated. Abdominal palpation identified bilaterally small but normally shaped kidneys. Clinical and neurological examinations were otherwise within normal limits.

Serum biochemistry revealed a severe hypernatraemia (170 mmol/l [RI 138–155 mmol/l]) and borderline hyperchloraemia (130 mmol/l [RI 112–129 mmol/l]). A mild pre-renal azotaemia was identified: urea 12.7 mmol/l (RI 6–10 mmol/l), creatinine 174 μ mol/l (RI 40–150 μ mol/l) and urine specific gravity >1.050. Other haematological and serum biochemical abnormalities suggested haemoconcentration: total protein 79 g/l (RI 54–78 g/l), haematocrit 0.44 l/l (RI 0.29–0.46 l/l). The patient's serum osmolality was calculated using the formula ($2[\text{Na}^+] + \text{glucose} + \text{blood urea nitrogen}$), in accordance with recently published recommendations.¹⁵ This was elevated at 359 mOsm/kg (RI <330 mOsm/kg).

Treatment was initiated with IV 0.9% NaCl at 4.8 ml/kg/h, aiming to restore hydration over 24 h and providing ongoing maintenance requirements. Isotonic crystalloids were chosen with the aim of gradual sodium reduction of no more than 0.5 mEq/l/h to reduce the risk of cerebral oedema and increased intracranial pressure. The patient's electrolytes were monitored every 4–6 h, and a gradual reduction in sodium concentration was identified. After 24 h the patient's IV fluid rate was reduced to maintenance requirements and by 36 h serum sodium concentrations had reduced to 155 mmol/l (RI 138–155 mmol/l). The azotaemia resolved during this time. The cat's mental status was by now normal and clinical examination was within normal limits. The depressed mental status initially observed was therefore considered likely to be due to the dehydration and hypernatraemia. While hospitalised the patient continued to receive IV crystalloid fluid therapy at maintenance rates. Sodium concentrations were checked twice daily and remained within the RIs.

During the initial 72 h period of hospitalisation, and despite being dehydrated initially, the cat did not drink.

Thoracic radiography and abdominal ultrasonography were performed to exclude third space fluid loss as a cause of hypotonic fluid loss and hypernatraemia. Right lateral and dorsoventral thoracic radiographs were unremarkable. Abdominal ultrasonography identified bilaterally abnormal renal architecture with hypochoic renal cortices and complete loss of corticomedullary

definition. No other abnormalities were seen. Urinalysis obtained by cystocentesis identified hypersthenuria (urine specific gravity 1.038) and haematuria (>100 red blood cells per high power field) with no evidence of infection or inflammation. Although ultrasonographical changes reported were suggestive of chronic renal pathology, given the normal urine concentrating ability, renal failure was excluded as a cause of hypotonic fluid loss and hypernatraemia. There was no evidence of gastrointestinal disease and gastrointestinal fluid loss was excluded.

Assessment of the patient's aldosterone concentration at the time of severe hypernatraemia (170 mmol/l) revealed a physiologically appropriate suppression <20 pmol/l (RI 195–390) excluding hyperaldosteronism. Other causes of sodium gain such as salt ingestion and hypertonic fluid administration were excluded based on the history. The patient had full access to water at all times and given the persistent hypersthenuria documented, central and nephrogenic diabetes insipidus were excluded.

In the light of the initial findings, the patient's hypernatraemia was considered to be secondary to primary adipsia and associated dehydration.

Magnetic resonance imaging of the brain was performed using a 0.4 T unit (Hitachi Aperto). A large ($10 \times 12 \times 12$ mm), extra-axial, suprasellar mass was seen, with extension ventrally into the sphenoid bone (Figure 1a). Compared with the surrounding cerebral grey matter the mass was T1 hyperintense and T2 isointense. The mass had a heterogeneous cystic appearance with loculated T1 hypointense foci and was strongly contrast enhancing on T1-weighted sequences in response to IV administration of a gadolinium-based agent (0.01 mg/kg Gadovist [gadobutrol]; Bayer Healthcare Pharmaceuticals) (Figure 1b). The fluid-attenuated inversion recovery sequence identified an irregular hyperintensity surrounding the mass and extending through the right thalamus into the right caudate nucleus rostrally, consistent with peritumoural oedema (Figure 2). Oedema secondary to correction of the patient's hypernatraemia was considered unlikely given the asymmetrical distribution. There was a marked mass effect, with local compression of the thalamus and hypothalamus, mild caudal transtentorial herniation, and mild caudal cerebellar herniation (Figure 3).

Owing to the guarded prognosis, the cat was euthanased.

Post-mortem examination was performed and histopathological assessment of the brain confirmed the presence of a neuroendocrine pituitary macroadenoma (Figure 4). Focal compressing encephalopathy was identified with extensive, bilaterally asymmetric deformation of the ventral diencephalon, vasogenic oedema throughout the pituitary gland, hypothalamus, subthalamus and thalamus, and some degenerative neuronal

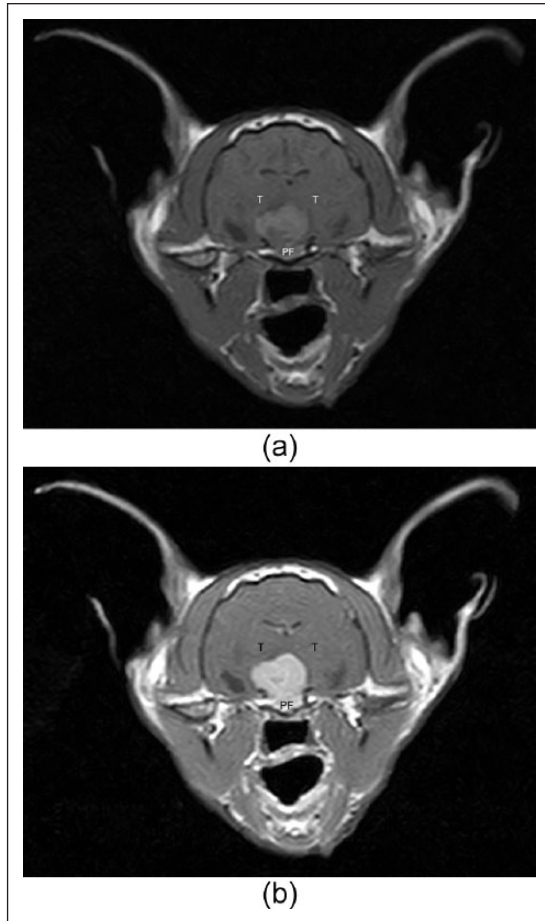


Figure 1 Transverse T1-weighted magnetic resonance images at the level of the pituitary fossa (PF) with (a) pre- and (b) post-contrast (gadolinium) sequences. The suprasellar mass is hyperintense relative to the surrounding parenchyma and strongly contrast enhancing. There is a moderate degree of asymmetrical compression of the thalamus (T)

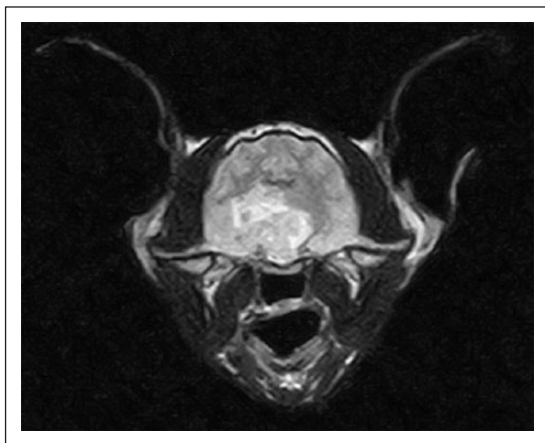


Figure 2 Transverse fluid-attenuated inversion recovery image at the level of the middle cranial fossa. An irregular hyperintensity (consistent with oedema) is seen surrounding the mass and extending into the right thalamus and corona radiata

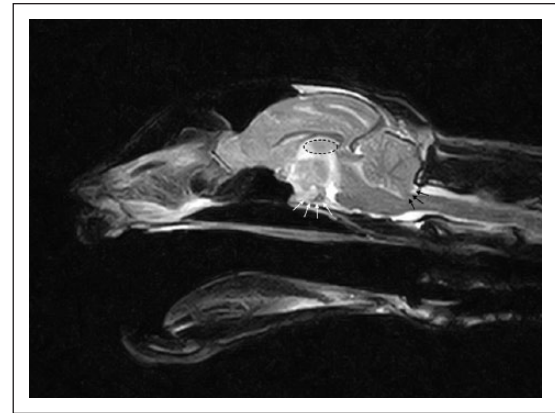


Figure 3 A sagittal T2-weighted magnetic resonance image at the midline. An intracranial mass is seen protruding dorsally from the pituitary fossa (white arrows). The fossa is widened owing to invasion of the sphenoid bone locally. A 'mass effect' is resulting in mild caudal cerebellar herniation through the foramen magnum (black arrows) and compression of the interthalamic adhesion (circled). Mild caudal transtentorial herniation is also seen

changes accompanied by astrogliosis in the hypothalamic nuclei. Renal histopathology identified a bilateral chronic active pyelonephritis and bilateral periurethral lipomatosis.

Although functional assessment of the pituitary gland was not performed ante-mortem, immunohistochemical staining of the tumour cells was positive for chromogranin and synaptophysin, confirming their neuroendocrine origin (Figure 4). Tumour cells did not stain for adrenocorticotropic hormone, somatotropin, somatostatin, prolactin, thyroid-stimulating hormone or luteinising hormone. Therefore, this tumour was considered to be a non-secretory neuroendocrine tumour.

Discussion

Differential diagnoses for hypernatraemia are grouped into those caused by hypotonic fluid loss (eg, renal loss, gastrointestinal loss or third space loss), which is most common in veterinary patients.¹⁶ Less commonly, hypernatraemia is caused by sodium gain (salt ingestion, hypertonic fluid administration, hyperadrenocorticism and hyperaldosteronism) or pure water loss (eg, central or nephrogenic diabetes insipidus, insensible fluid losses or hypodipsia/adipsia).¹⁶

In this case, the patient remained adipsic despite hypernatraemia and dehydration, and having excluded all other differentials of hypernatraemia, a diagnosis of primary adipsia was reached.

In a healthy cat, the normal physiological response to hypovolaemia and hyperosmolality is release of antidiuretic hormone (ADH) and stimulation of thirst. Osmoreceptors in the organum vasculosum of the lamina terminalis and the subfornical organ will, in response to

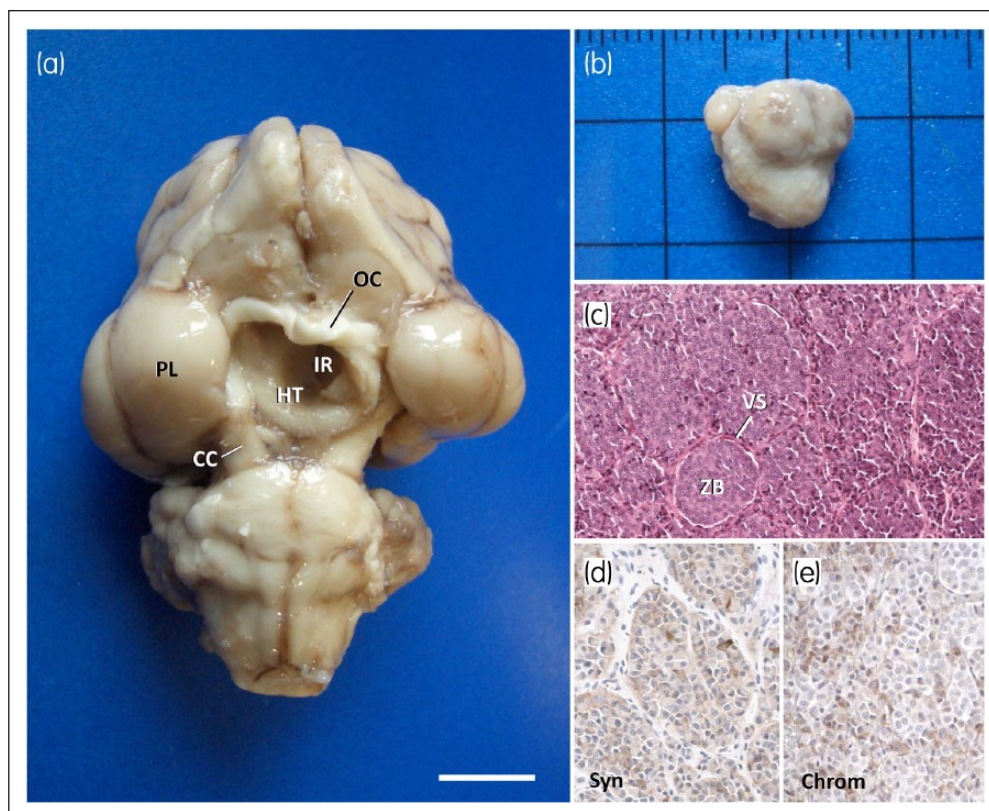


Figure 4 Post-mortem examination. (a) Ventral view of the fixed brain after the tumour had been shelled out. Note the asymmetric impingement on the hypothalamus (HT) and right-sided crus cerebri (CC) with dilation of the infundibular recessus (IR) and oblique caudal compression of the optic chiasm (OC) and tracts. Scale bar = 1 cm. (b) Macroscopic appearance of the pituitary tumour. Scale bar = 0.8 cm. (c) Histology of the mass is characterised by a proliferation of neuroendocrine cells, often confined to Zellballen (ZB), surrounded by vascular septa (VS). Scale bar = 200 µm. (d,e) Tumour cells stain positive for synaptophysin (Syn) and chromogranin (Chrom). Scale bar = 100 µm. PL = piriform lobe

angiotensin II or a rise in plasma osmolality, stimulate the median preoptic nucleus in the hypothalamus (the thirst centre), which will, in turn, cause water seeking and ingestion. Primary adipsia occurs because of a lack of recognition of thirst and in this patient is attributed to compression and damage of the osmoreceptors and the median preoptic nucleus secondary to infiltrative disease.

Pituitary dysfunction resulting in permanent alterations in ADH production and secondary hypernatraemia were excluded in this patient owing to the identification of persistent hypersthenuria, indicating an adequate response to ADH. Some studies evaluating the pathogenesis of hypernatraemia in human patients with hypothalamic dysfunction describe partial central diabetes insipidus and sporadic and paradoxical ADH release, which, along with an increased threshold for thirst centre activity, result in hypernatraemia. This pathomechanism was not evaluated and therefore cannot be fully excluded in this patient.^{17,18}

In relation to the renal pathology documented, it is our hypothesis that chronic pyelonephritis may have

been caused by chronic adipsia and dehydration causing reduced ureteral flow and therefore increasing the risk of ascending urinary tract infection.¹⁹ The clinical significance of the patient's periurethral lipomatosis is not known but it is possible that this, via ureteral compression, might also have predisposed to pyelonephritis.

Conclusions

This is the first reported case of neuroendocrine pituitary macroadenoma with a clinical presentation of primary adipsia and hypernatraemia. Primary adipsia is very rare in cats and this report adds a further differential diagnosis for this presentation, and provides valuable information to an area in which veterinary knowledge is currently lacking.

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Conflict of interest The authors do not have any potential conflicts of interest to declare.

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