Case Report

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Dilated cardiomyopathy in a cat with congenital hyposomatotropism

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Abstract

Case summary A 7-month-old domestic shorthair cat was presented for evaluation of stunted growth, recurrent hypoglycaemia during the first months of its life and altered mentation. Complete blood count and biochemistry were unremarkable, except for mildly elevated serum creatinine concentration (despite low muscle mass) and concurrent isosthenuria. Hyposomatotropism was diagnosed based on persistent low circulating insulin-like growth factor 1 concentrations and a lack of response of circulating growth hormone (GH) concentration after the administration of GH-releasing hormone. Other endocrinopathies such as hypothyroidism and hypoadrenocorticism were excluded. MRI of the brain revealed a fluid-filled empty sella tursica, consistent with a pituitary cyst and atrophy/hypoplasia of the pituitary. Echocardiography was unremarkable at the time of diagnosis of hyposomatotropism. Three months later, ovariohysterectomy revealed immature ovaries, raising the suspicion of luteinising and follicle-stimulating hormone deficiency. At 1 year of age, the cat developed congestive heart failure secondarily to dilated cardiomyopathy (DCM) with severely reduced left ventricular systolic function and died a few days later. Pathology showed atrophy of the adenohypophysis, epithelial delineation of the pituitary cysts, mild cardiomegaly, multifocal fibrosis of the left ventricle and a mild, multifocal, chronic epicarditis.

Relevance and novel information GH deficiency is a very rare endocrinopathy in cats. This is the first case to describe the development of DCM with concurrent hyposomatotropism, which has previously been reported in human medicine. Other notable abnormalities that could be related to GH deficiency are juvenile self-limiting hypoglycaemia, behavioural changes and possible nephropathy.

Keywords: Dwarfism; congestive heart failure; hypoglycaemia; pituitary hypoplasia/atrophy; growth hormone

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Introduction

Congenital hyposomatotropism can be part of panhypopituitarism or a standalone condition, characterised by growth hormone (GH) deficiency or insensitivity to GH. It is a rare feline endocrinopathy, with only a few cases reported.[1–5] GH is produced in the anterior hypophysis and regulated by the hypothalamic stimulating GH-releasing hormone (GHRH) and inhibitory somatostatin. Its deficiency causes a decrease in hepatic insulin-like growth factor 1 (IGF-1) production, resulting in clinical manifestations of proportionate dwarfism with skeletal, haircoat and mentation changes, and – less often reported – intermittent hypoglycaemia and corneal oedema.[1,3,6] Hyposomatotropism-associated dilated cardiomyopathies have not been reported in veterinary

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medicine, but have been described in human medicine, where a link between long-standing GH deficiency and impairment of cardiac function has been established.[7] This case describes a young domestic shorthair (DSH) cat with congenital pituitary dwarfism, associated with pituitary cysts, that developed dilated cardiomyopathy (DCM) and secondary congestive heart failure.

Case description

A 7-month-old female intact domestic shorthair cat was presented to the Small Animal Hospital of the University of Bern for suspicion of stunted growth. After losing its mother and siblings, it was adopted at the age of 5 weeks. At first, it only tolerated bottle feeding and received an adequate daily amount of a commercial, balanced cat milk, spread over multiple feedings per day. Over two weeks it was slowly transitioned to a commercial kitten diet. It was regularly presented to the referring veterinarian for lethargy and hypoglycaemia (glucose at 6 and 11 weeks old <1 mmol/l and 2.3 mmol/l, respectively; reference interval [RI] 3.8–8), which resolved after fluid and glucose supplementation. Between 6 and 13 weeks of age, bloodwork revealed moderate anaemia (haematocrit 18.3% [RI 25–45%]; reticulocyte count not available), moderate hypoalbuminemia (15 g/l; RI 23–35) and mild hyperbilirubinaemia (11 µmol/l; RI 2–7), all of which normalised by 14 weeks of age. Complete blood count (CBC) and other biochemistry parameters were unremarkable. Because of the small stature, the referring veterinarian measured thyroid hormone and IGF-1. Circulating thyroxine (T4) and thyroid-stimulating hormone (TSH) concentrations at 16 weeks of age were not supportive of primary nor secondary hypothyroidism (T4: 16 nmol/l [RI 16–46]; TSH: 0.06 ng/ml [RI <0.2]). The circulating IGF-1 concentration was low (44 ng/ml; RI 50–400).

Despite its young age, the kitten was mildly obtunded and displayed fractious behaviour when approached. It maintained a good appetite and had a smooth transition to several balanced commercial kitten dry diets. The owner was unsure whether the kitten displayed stunted growth and mild polydipsia. Water intake was never quantified.

Upon evaluation at the university hospital, the cat showed a moderately small stature with a small, rounded head and proportional body and limbs (Figure 1). Its body weight was 2.46 kg and its body condition score was 6/9, despite mild muscle wasting (muscle score 2/4). The cat's haircoat was normal and its deciduous teeth were replaced by definitive teeth. Clinical parameters, including lung auscultation and abdominal palpation, were within normal limits. Auscultation of the heart revealed a rate of 200 beats/min (bpm), a rhythmic rhythm and no audible murmur or click. Oestrus was never observed by the owner.

Figure 1 Seven-month-old domestic shorthair cat diagnosed with hyposomatotropism

Considering the history, physical changes and previous bloodwork, a congenital hyposomatotropism was strongly suspected. A concomitant hypoadrenocorticism was deemed possible. Congenital hypothyroidism was considered less likely given the normal T4 and TSH values. Other congenital/metabolic diseases (portosystemic shunt, storage diseases, renal dysplasia and cardiac disease) could not be ruled out at this point.

The CBC was within normal limits. Biochemistry revealed mild hypokalaemia (3.4 mmol/l; RI 3.7–5.3), mildly increased serum creatinine concentration (139 µmol/l; RI 52–138) with normal serum urea concentration (10.4 mmol/l; RI 6.46–12.2), and presumably age-related increased serum phosphate concentration (2.44 mmol/l; RI 0.82–1.91) and alkaline phosphatase activity (153 U/l; RI 0–93 U/l). Urinalysis showed isosthenuria (urine specific gravity [USG] 1.014) with a normal pH (pH 6) and inactive sediment. Shortened echography of the heart was performed under sedation (butorphanol 0.2 mg/kg IV and alfaxalone 2 mg/kg IV) because the patient was fractious and would not tolerate restraint. It showed mild reduced fractional shortening (Table 1), compatible with sedation. No signs of congenital cardiac disease were found. Abdominal ultrasound revealed a slightly decreased liver size without other changes indicative of a portosystemic shunt; both kidneys were within normal limits. Pre- and postprandial serum bile acid concentrations were within the RI (1 µmol/l and 8.8 µmol/l, respectively; RI 0–15). Circulating IGF-1 concentration was persistently low (47 ng/ml; RI 50–400). Basal serum cortisol concentration was <0.5 µg/dl (RI 0.5–8.8), despite the obvious stress of the cat. An adrenocorticotropic hormone (ACTH) stimulation test (Synacthen, 125 µg IV; blood sampling at 0 and 60 mins) showed a prestimulation cortisol concentration <0.5 µg/dl and a post-stimulation cortisol concentration of 3.8 µg/dl,

Table 1 Evolution of echocardiographic measurements

Parameter	First echocardiogram	Second echocardiogram
LA/Ao	1.3	1.7
IVSd (mm)	2.5	4.2
LVIDd (mm)	17.3	22.7
LVPWs (mm)	3.9	3.2
IVSs (mm)	3.9	4.3
LVIDs (mm)	14.7	18.9
LVPWs (mm)	4.8	9.4
FS (%)	15	16
LVOT/Ao Vmax (m/s)	0.6	0.9
RVOT/Ao Vmax (m/s)	0.5	0.8
Additional findings	–	Mild pleural effusion (after thoracocentesis); induced mitral regurgitation through dilatation of the LV
Remarks	Examination performed under sedation; reduced FS compatible with sedation	Examination without sedation (unstable patient)

LA = left atrium; Ao = aorta; IVSd = interventricular septum in diastole; LVIDd = left ventricle internal diameter in diastole; LVPWd = left ventricle posterior wall in diastole; IVSs = interventricular septum in systole; LVIDs = left ventricle internal diameter in systole; LVPWs = left ventricle posterior wall in systole; FS = fractional shortening; LVOT = left ventricle outflow tract; Vmax = maximum speed; RVOT = right ventricle outflow tract; LV = left ventricle

Table 2 Endocrine tests performed in order to investigate growth retardation

Test	Basal value	IV dose	Stimulated values	RI
Endogenous ACTH	ACTH 42 ng/l	–	–	ACTH 10–60 ng/l
ACTH stimulation test	Cortisol 1.75 µg/dl	ACTH 125 µg	+1 h: cortisol 5.77 µg/dl	Cortisol 0.5–8.8 µg/dl
TRH stimulation test	TSH 0.06 ng/ml	TRH 250 µg	+ 30 mins: TSH 0.31 ng/ml	TSH >0.04 ng/ml
GHRH stimulation test	GH 3.4 µg/ml	GHRH 1 µg/kg	+ 1 h: GH 3.1 µg/ml	GH >5 µg/ml

RI = reference interval; ACTH = adrenocorticotropic hormone; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; GHRH = growth hormone-releasing hormone; GH = growth hormone

below the RI (4.5–15). A partial secondary hypoadrenocorticism, as described in people with panhypopituitarism,[8] was suspected and the decision was made to repeat the ACTH stimulation test.

Three weeks later, pituitary functions were assessed by measuring endogenous ACTH, and GH and TSH values pre- and post-GHRH and thyrotropin-releasing hormone (TRH) stimulation. Simultaneously, the ACTH stimulation test was repeated (Table 2).[6] Hypoadrenocorticism was excluded and so was secondary hypothyroidism based on the 416% increase in TSH concentration after TRH stimulation. Clinical findings, a persistently low IGF-1 value and the non-responsive GH values post-GHRH stimulation test led to the diagnosis of congenital hyposomatotropism. Porcine GH is unavailable in Europe and progestins fail to increase circulating GH or IGF-1 concentration in cats. Recombinant human GH has been used in a hyposomatotropic cat, but concerns about antibody development were the main reason no specific treatment was started.[5,9,10]

Three months later, when the cat presented for ovariohysterectomy, renal values were normal (creatinine 107 µmol/l [RI 52–138]; urea 10.4 mmol/l [RI 6.5–12.2]), but urinalysis could not be performed. The cat weighed 3.1 kg (+600 g) but still had a subjectively small stature and a mildly broad skull. On histopathological examination, the ovaries were immature, consistent with a lack of hormonal stimulation. A brain MRI was performed to document pituitary changes such as pituitary cysts as described in dogs with hyposomatotropism.[11,12] The sella turcica was empty, filled with cerebrospinal-like fluid, which was interpreted as primary cyst and pituitary gland atrophy/hypoplasia (Figure 2).

Three months later, the cat was presented to the emergency service of the university hospital for tachypnoea and lethargy of 2 days' duration. Heart rate was 160 bpm and resting respiratory rate was 40 breaths/min. Dyspnoea developed rapidly upon manipulation. No heart murmur or arrhythmia was detected on auscultation and pulse palpation. Lung sounds were mildly muffled. Thoracic radiographs from the referring vet showed bilateral pleural effusion and suspicion of pulmonary oedema. Changes are reported in Figure 3. Owing to its fractious nature and stress-induced dyspnoea, the cat

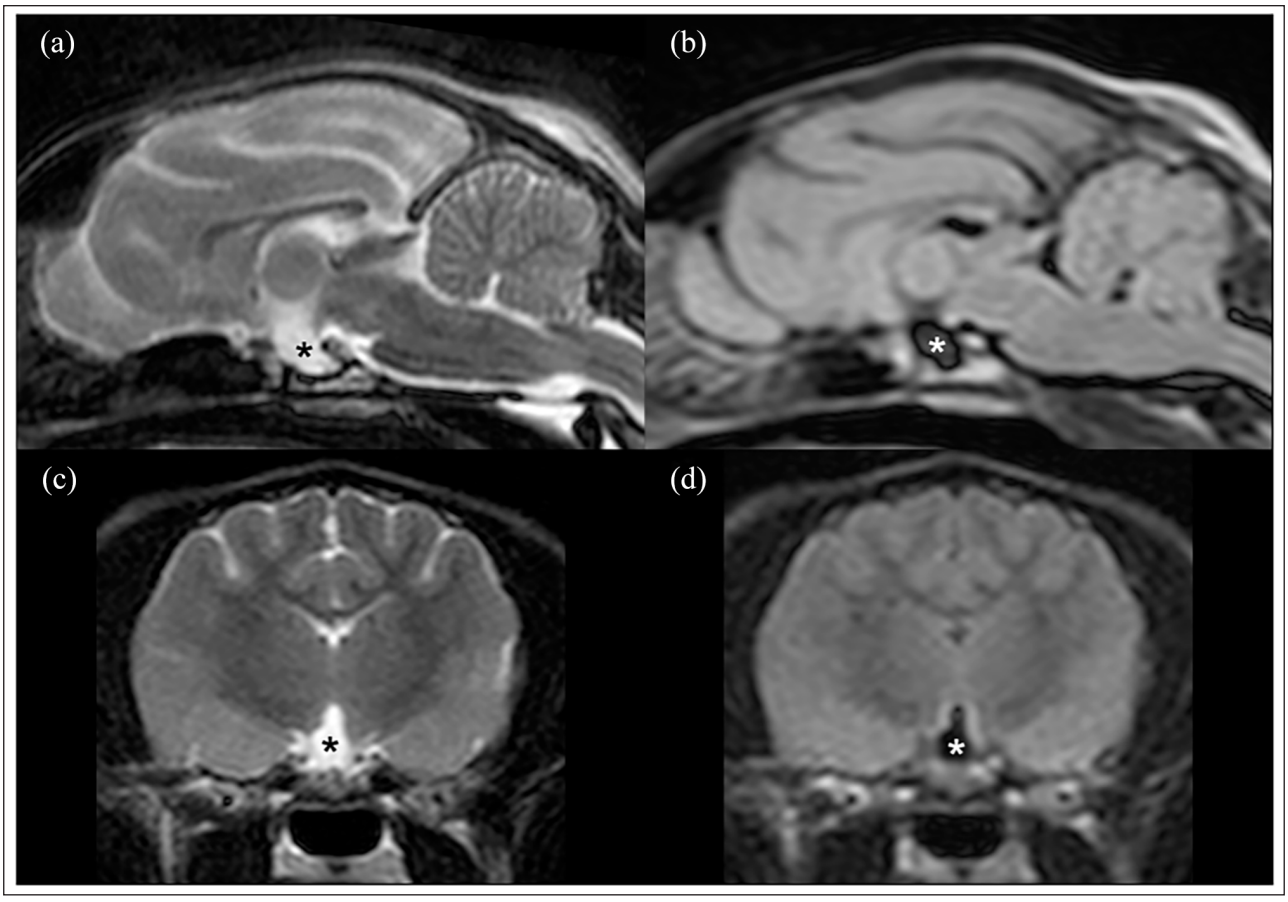

Figure 2 Mid-sagittal (a) T2-weighted (T2W) and (b) fluid-attenuated inversion recovery (FLAIR), and transverse (c) T2W and (d) FLAIR MRI of the cat's brain at the level of the sella turcica. The sella turcica is completely filled with fluid, which shows the same MRI signal characteristics as cerebrospinal fluid – being T2W hyperintense (black asterisks), T1-weighted hypointense (not shown) and suppressing in FLAIR sequences (white asterisks)

only tolerated unilateral (right) thoracocentesis. Twenty-five millilitres of straw-coloured effusion were removed and the cat was started on diuretics (furosemide 2 mg/kg q12h) and oxygen therapy. Later, echocardiographic findings were compatible with a DCM phenotype and a very mild amount of pleural effusion (Figure 4). Changes between the two echocardiographic examinations are described in Table 1. The cardiomyopathy was decompensated and led to cardiogenic pulmonary oedema. A positive inotrope was added empirically (pimobendan 0.25 mg/kg q12h), as well as taurine (250 mg q12h). The respiratory rate and effort showed partial improvement and the cat was discharged, against medical advice, with the same therapy.

Unfortunately, the cat developed dyspnoea again and died at home 4 days later. Necropsy revealed severe and diffuse atrophy of the adenohypophysis with acute and chronic haemorrhages. Histopathology revealed the number and size of the cells in the adenohypophysis to be reduced (Figure 5). There were several small cavities covered by a single layer of cuboidal epithelium. This was most likely the delineation of multiples cysts. There was mild cardiomegaly with moderate multifocal fibrosis of the left ventricle, a moderate hydropericardium, and mild, multifocal and chronic lymphoplasmacytic epicarditis. Lung changes were compatible with a severe pulmonary oedema.

Discussion

This report describes a young cat with congenital hyposomatotropism, based on clinical findings, persistently low circulating IGF-1 concentration, failure of GH response in a GHRH stimulation test, brain MRI and histopathological findings. Concurrent pituitary dysfunctions, such as secondary hypothyroidism and hypoadrenocorticism, could be excluded. Concurrent luteinising and follicle-stimulating hormone deficiencies were possible as the ovaries were hypoplastic on histopathology.

To our knowledge, this is the first report of congenital feline hyposomatotropism diagnosed with concurrent pituitary cysts and pituitary atrophy. Whether pituitary cysts caused hyposomatotropism by pressure atrophy of the anterior pituitary, or were a consequence of

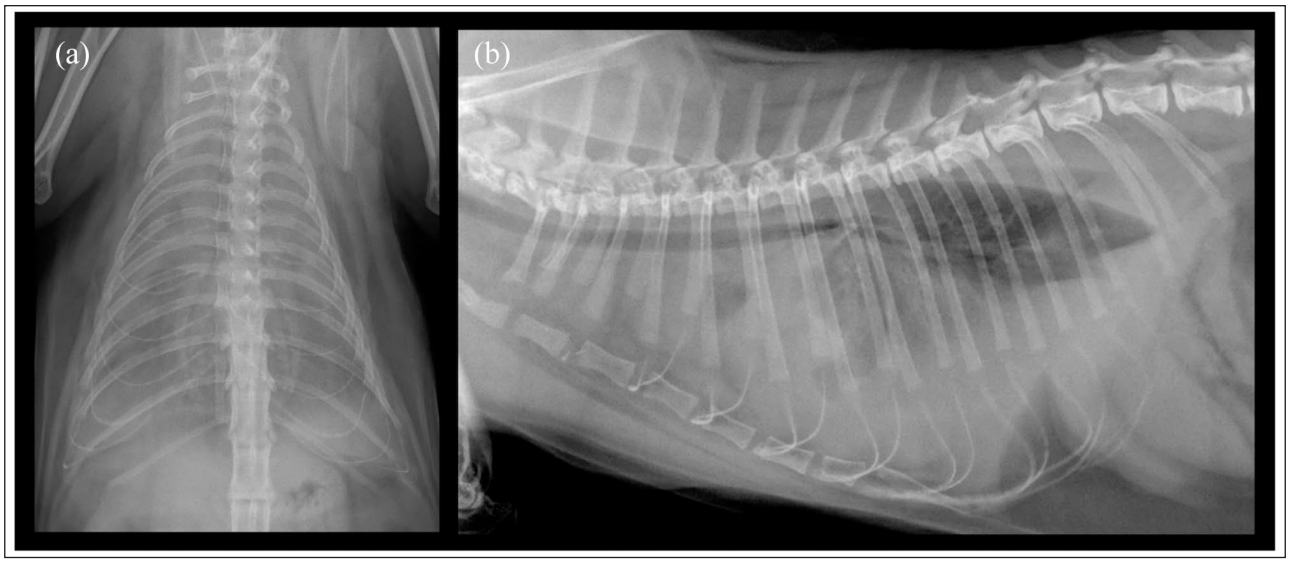

Figure 3 (a) Ventrodorsal and (b) left lateral views of the thorax, showing moderate-to-marked bilateral pleural effusion associated with lung lobe retraction, dorsal displacement of the trachea and a diffuse patchy interstitial-to-alveolar lung pattern. The cardiac silhouette is border effaced by the pleural and pulmonary changes. The main caudal pulmonary arteries and veins are enlarged

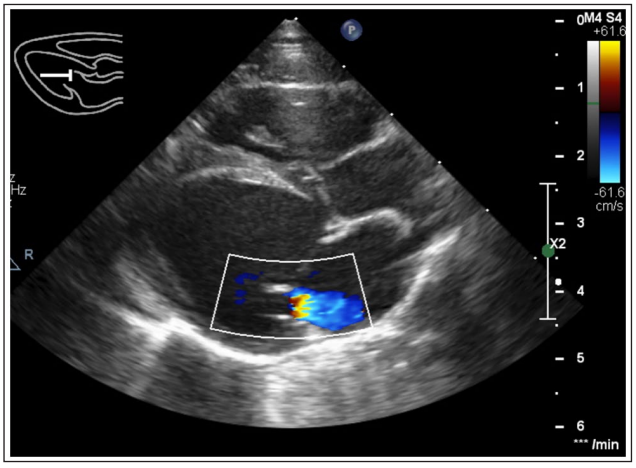

Figure 4 Right parasternal four-chamber view of the heart showing a dilated left ventricle and mitral regurgitation

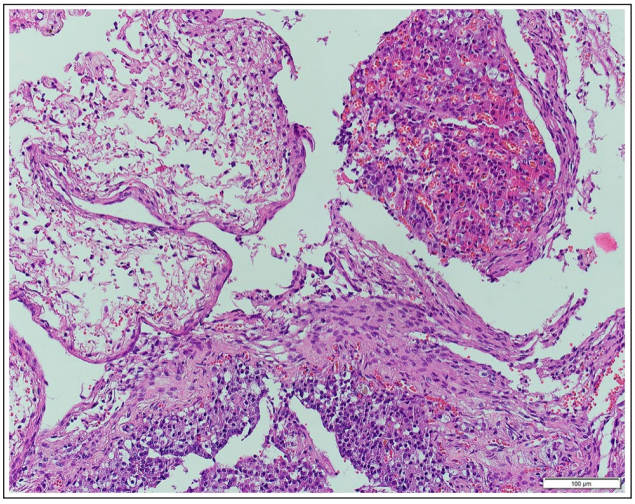

Figure 5 Cells in the adenohypophysis are atrophied and reduced in number (haematoxylin and eosin)

accumulation of proteinaceous material associated with spontaneous pituitary atrophy/failure of development, remains uncertain.[6,12] German shepherd dog dwarfs with very small or no cysts support the latter.[11] Brain imaging has not been previously reported in feline hyposomatotropism, so the prevalence of cysts is unknown. Preservation of ACTH and TSH secretion argues against pressure-induced atrophy.[11,12]

Three months after the diagnosis, the cat developed severe systolic dysfunction compatible with a DCM phenotype and secondary congestive heart failure. DCM in cats is described as 'left ventricle systolic dysfunction characterised by progressive increase in ventricular dimensions, normal or reduced LV wall thickness, and atrial dilatation'.[13] Given this definition and the norms for measurement in healthy cats,[14] our findings were compatible with a DCM phenotype. The main differentials for DCM were primary vs secondary due to myocarditis or GH deficiency. Considering the kitten had a normal appetite and was fed several balanced commercial diets, taurine deficiency was unlikely.[15] A serum taurine concentration would have helped to exclude this differential. Given the previous echocardiography at 7 months of age, primary DCM was considered very unlikely, although it was not ruled out. Chronic

volume overload-induced dilation, due to congenital abnormalities such as patent ductus arteriosus or valve dysplasia, were excluded on the first echocardiography.[16] Myocardial histopathology is the gold standard for the diagnosis of myocarditis,[17] and revealed no inflammation, excluding an acute myocarditis. A chronic myocarditis causing end-stage multifocal myocardial fibrosis without signs of inflammation is highly unlikely. Additional blood sampling for troponin I measurement was not performed.

Despite the partial improvement during hospitalisation, the cat most likely died at home due to congestive heart failure. This could partially be due to inadequate uptake of the oral medication, considering its fractious nature, and/or inappropriate improvement of cardiac output despite pimobendan treatment. Evidence that pimobendan can improve systolic dysfunction in cats is weak.[13] A retrospective study reported its use in non-taurine-responsive DCM phenotypes, but it does not cover the whole spectrum of feline DCM phenotypes.[18] Its use is also controversial in cats with outflow tract obstruction and has been associated with side effects.[19]

Cardiovascular effects of the GH–IGF-1 axis such as stimulation of cardiomyocytes replication, growth, strengthening and improvement of calcium signalling and sensitivity to enhanced contractility have been documented in human medicine.[20,21] In people, GH deficiency can lead to systolic dysfunction and reduction of cardiac mass.[7] Improvement of this condition has been shown with adequate GH supplementation.[7,22] A child with hypopituitarism (GH, TSH and prolactin deficiency) was reported to have concurrent DCM, possibly associated with GH deficiency.[23] There are also several reports of DCM in women affected by Sheehan's syndrome, who also all had GH deficiencies.[24–26] Sheehan's syndrome is an ischaemic pituitary necrosis due to severe postpartum haemorrhage causing varying degrees of anterior pituitary hormone deficiency. Although GH deficiency-induced cardiomyopathy has not been documented in veterinary medicine, IGF-1 excess-associated hypertrophic cardiomyopathy has been reported.[27,28] The scarcity of veterinary hyposomatotropism in combination with difficulty of screening for subclinical DCM phenotypes may be a reason why an association of both has not yet been reported.[13] Although primary DCM cannot be excluded in this case, an association with GH deficiency is likely. The histological changes are somewhat difficult to interpret given the paucity of histological analysis in GH-deficient humans and animals. Fibrosis is a common feature in feline DCM, presenting itself as mild and interstitial, but depending on the loss of myofibres there can also be foci of fibrosis.[29] The epicarditis is most likely due to the chronically increased pericardial effusion. An infectious cause is very unlikely considering the mild nature of the inflammation and lack of indication on histopathology, but, without a bacterial culture, it cannot be fully excluded.

The cat's fractious behaviour could be a purely behavioural trait, although hand-reared, bottle-fed kittens tend to be more sociable towards humans. Hyposomatotropism has been reported to cause depression and emotional lability in people.[30,31] In children with GH deficiency, mental immaturity, inattentiveness and increasing mental health issues have been reported.[32,33] Although not described in veterinary medicine, hyposomatotropism-induced behavioural changes cannot be excluded in this case.

The initial recurrent hypoglycaemic episodes of the cat could have been age-related or secondary to hyposomatotropism, as previously reported.[3] The cat was regularly bottle-fed with an adequate amount of balanced commercial cat milk, eliminating inadequate intake as a cause for the hypoglycaemic events. GH has a lipolytic effect, acts on protein synthesis, displays anti-insulin effects and influences hepatic glycogen storage.[34–36] GH deficiency can therefore lead to decreased glucose production, hepatic storage and/or increased consumption, potentially causing clinical hypoglycaemia.[37,38]

It is possible that the cat also had reduced renal function, considering the mildly increased creatinine in a young cat with reduced muscle mass and the concurrent isosthenuria. The isosthenuria could be age-related, although kittens have an increase in urine osmolality up to the age of 19 weeks.[39] At the age of 10 months, creatinine normalised but was still in the upper-normal range, despite reduced muscle condition. The lack of follow-up USG is an important limitation in this case and would have allowed a more precise evaluation of the renal function. The potential reduction in glomerular filtration rate (GFR) may be influenced by GH deficiency as GH and IGF-1 play important roles in glomeruli development, renal homeostasis, absorption and secretions.[40,41] Humans with GH deficiency commonly have a reduced GFR.[42] Chronic kidney disease has also been described in German shepherd dog dwarfs and cats suffering from juvenile hyposomatotropism.[3,12,43]

Conclusions

Congenital hyposomatotropism is a rare endocrine disorder in cats with only a few previous case reports, including one also presenting recurrent hypoglycaemia. This is the first case report to document a pituitary cyst in conjunction with histological atrophy of the pituitary gland. Moreover, the cat developed DCM, which was probably associated with hyposomatotropism. This disease could be a differential for DCM, especially if other signs such as recurrent hypoglycaemia or stunted growth are reported.

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Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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