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Case Report

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Abstract

Case summary A 3-month-old intact male Somali cat was evaluated for a history of seizures, hypoglycaemia and mental dullness 4 weeks after being bitten in the head by a dog. The cat's body size and weight were approximately half that of his littermates and its haircoat was woolly, with fewer guard hairs. Multiple hypoglycaemic episodes were documented over a period of 4 weeks, which resolved rapidly after correction of the hypoglycaemia. Juvenile hyposomatotropism was presumptively diagnosed by demonstrating low circulating levels of insulin-like growth factor 1 and after exclusion of other endocrine and non-endocrine causes of small stature and hypoglycaemia. The cat's intermittent hypoglycaemia resolved spontaneously within 1 month and the cat never showed any more neurological signs. Nevertheless, the physical retardation and the coat abnormalities remained unchanged. A year later, the cat was diagnosed with chronic kidney disease IRIS stage 2.

Relevance and novel information Hyposomatotropism is an extremely rare feline endocrinopathy. This is the second case reported in the veterinary literature, and the only one to describe hypoglycaemic events associated with growth hormone deficiency. Although hypoglycaemia is one of the most common disease manifestations in children with pituitary dwarfism, this has not yet been reported in veterinary medicine.

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Introduction

Hyposomatotropism, or pituitary dwarfism, is a relatively uncommon endocrine disease caused by a primary deficiency of growth hormone (GH) and the secondary deficiency of insulin-like growth factor 1 (IGF-1).[1,2] Canine pituitary dwarfism is encountered most often in German Shepherd dogs as a recessively inherited disorder.[3] In cats, however, it is an extremely rare endocrinopathy.[4]

GH is produced in the adenohypophysis and its secretion is regulated by the hypothalamic hormones growth hormone-releasing hormone (GHRH) and somatostatin. Deficiency of GH can be due to a congenital defect in the differentiation of endocrine cells of the pituitary gland or to an acquired disorder of the pituitary gland, such as traumatic brain injury (TBI), or neoplasia, resulting in isolated GH deficiency or deficiency of multiple hormones, such as thyroid-stimulating hormone, prolactin, adrenocorticotropic hormone (ACTH), follicle-stimulating hormone and luteinising hormone.[1–3]

Deficiency of GH and secondary deficiency in IGF-1 at a young age result in impairment of linear growth.[1] The consequent proportional dwarfism may be associated with a wide range of other clinical manifestations, such as thin skeleton, changes in ossification centres, delayed closure of growth plates and delayed dental eruption (usually with normal dentition), muscle atrophy, soft, woolly haircoat, retention of secondary hair, lack of primary guard hairs, skin hyperpigmentation,

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bilateral symmetrical alopecia, scaling, comedones, papules, pyoderma, uni- or bilateral cryptorchidism, testicular atrophy, flaccid penile sheath, persistent anoestrus, puppy-like shrill bark, lethargy, listlessness, mental dullness and signs of secondary hypothyroidism.[1,5]

Affected animals are typically presented at 3–5 months of age owing to growth retardation and/or skin and haircoat abnormalities.[1,2,4] Owing to the rarity of reports in cats, no information is known regarding breed or sex predispositions in cats.

The present case describes a Somali cat diagnosed with juvenile pituitary dwarfism associated with hypoglycaemic events after a previous head trauma.

Case description

A 3-month-old male intact Somali cat weighing 0.63 kg presented to the Small Animal Hospital of the University of Bern for evaluation of seizures. Approximately 4 weeks previously, the cat had been bitten in the head by a dog. Immediately after, the cat had one generalised seizure and was ataxic for 24 h. Two weeks later, the cat began having intermittent tonic-clonic seizures on a daily basis. It also showed opisthotonus and tremors. Upon evaluation by its primary veterinarian, blood sampling revealed hypoglycaemia as the only abnormality. The cat received subcutaneous fluid therapy, including glucose supplementation, and was discharged with no additional treatment. The cat did not have any more seizures; however, its mental dullness persisted and, according to the owner, it was blind. The cat lived indoors in an apartment with one dog and 10 other cats, four of which were littermates. It was up to date on vaccinations and had been recently dewormed.

Upon evaluation at the University Hospital, 4 weeks after the dog bite, physical examination showed a small-statured cat with proportional appearance. It was moderately apathic. Apart from mild hypothermia (37.6°C), clinical parameters were all within normal limits. On neurological examination, the cat was severely obtunded and showed mild-to-moderate ataxia. Postural reactions were absent on all four limbs. Menace response and nasal sensation were absent bilaterally. The evaluation of the remaining cranial nerves proved normal. The neuroanatomical location was forebrain and cerebellum. At that time point, differential diagnoses included metabolic disorders such as portosystemic shunt or hypoglycaemia, viral encephalitis, TBI, storage disorders and congenital malformation of the brain or the heart.

Emergency blood work revealed normoglycaemia (4.2 mmol/l; reference interval [RI] 3.2–5.7 mmol/l). Complete blood count (CBC) was unremarkable. A serum biochemistry panel showed a slightly elevated urea (15.4 mmol/l; RI 6.5–12.2 mmol/l) with normal creatinine (112 µmol/l; RI 52–138 µmol/l) and mild hyperkalaemia (5.3 mmol/l; RI 3.1–4.9 mmol/l). Pre- and post-prandial bile acids were within the RI (1.7 µmol/l and 1.5 µmol/l, respectively; RI 0–15 µmol/l). A faecal examination, including direct examination and centrifugation flotation, was negative. Four hours after admission, repeat blood sampling revealed marked hypoglycaemia (<1.5 mmol/l) using a portable glucose meter (AlphaTRAK; Abbott Animal Health). Hypoglycaemia was confirmed in the laboratory using a biochemistry analyser.

An intravenous (IV) bolus of 50% glucose (0.5 ml diluted 1:3 in 0.9% sodium chloride solution) resulted in clinical improvement. The cat was more alert and ambulatory. An IV 5% glucose continuous rate infusion (sodium chloride 0.9% w/v and glucose 5% w/v solution for injection [G25; B Braun Medical]) was commenced.

Given the history of head trauma a few weeks prior, MRI of the brain and a cerebrospinal fluid analysis were undertaken, both of which were unremarkable. General anaesthesia was uneventful. However, 12 h later, the cat's general condition suddenly deteriorated and it was found in lateral recumbency, stuporous, hypothermic (36°C) and hypoglycaemic (<1.5 mmol/l). Following the administration of an IV bolus of 0.5 ml 50% glucose, the cat's stupor and hypothermia rapidly resolved. It was more alert and started eating. Frequent feedings every 2–3 h were instituted, and the cat's glycaemia was monitored every 4 h. Over the next 48 h, glucose substitution was slowly decreased and finally stopped. The cat's condition was good, with no neurological deficits, and its blood glucose remained stable, between 3.2 and 6.5 mmol/l. Four days after initial presentation, the cat was discharged with instructions to feed the cat frequent meals throughout the day, and to contact us if the cat showed any clinical signs.

Two weeks after discharge, the cat was presented again with stupor, hypothermia and with severe hypoglycaemia (<1.5 mmol/l). For the first time, the owner recognised that the cat was smaller and lighter than his littermates. Also, the cat was more lethargic and not as active as the others. On physical examination, it was noted that the cat's haircoat was woolly and contained fewer primary guard hairs.

CBC showed a mild anaemia (haematocrit 22%; RI 27–47%), mild leukopenia (3.8×10^9/l; RI 6.5–15.4 $\times 10^9$/l) with neutropenia (1.6×10^9/l; RI 2.5–12.5 $\times 10^9$/l) without left shift or toxic changes. Serum biochemistry panel revealed slightly elevated urea (14.1 mmol/l; RI 6.5–12.2 mmol/l) with normal creatinine (81 µmol/l; RI 52–138 µmol/l). Both fasting serum cortisol (2.18 µg/dl; RI 0.50–8.80 µg/dl) and post-ACTH stimulation (6.72 µg/dl; RI 0.50–8.80 µg/dl) were within the RIs. Total thyroxine concentration was also normal (19.8 mmol/l; RI 16–46 mmol/l). Insulin concentrations were unmeasurably low (<1 mU/l; RI 5–30 mU/l). As before, the cat's condition responded rapidly to IV glucose substitution

Figure 1 A 4-month-old Somali cat diagnosed with pituitary dwarfism

Figure 2 A kitten with pituitary dwarfism (in the middle), with two healthy litter mates. Note the proportionate growth retardation and the lack of guard hairs of the dwarf cat

and was discharged 3 days later. The serum IGF-I concentration was significantly low (<25 ng/ml; RI >50 ng/ml). Blood sampling and measurements were repeated twice and the results verified, confirming a presumptive diagnosis of juvenile pituitary hyposomatotropism. Concentrations of IGF-1 from four other Somali cats, (two littermates of the same age, one adult half-sister and one adult unrelated cat) were also determined and were all within normal limits: 394 ng/ml (sibling 1), 614 ng/ml (sibling 2), 406 ng/ml (half-sister) and 561 ng/ml (unrelated Somali cat). When the owner brought the other siblings for blood sampling, the small stature, mental dullness and haircoat abnormalities of the cat became obvious (Figures 1 and 2).

Given that porcine GH is not available in Europe, no hormonal replacement therapy was offered to the owner. The owner was recommended to check the cat's glycaemia at home, using a portable glucose meter, once daily for 1 week, and then once weekly for 4 weeks, and whenever the cat showed neurological signs. The glucose concentration was always normal and the cat did not show neurological signs. However, the cat's physical retardation and woolly haircoat with secondary hair retention persisted.

One year after initial presentation, the owner reported that the cat showed polyuria and polydipsia. The cat was found to be mildly azotaemic (creatinine 178 µmol/l [RI 52–138 µmol/l] and urea 19.6 mmol/l [RI 6.5–12.2 mmol/l]) and urinalysis showed isosthenuria Specific Gravity (SG 1.010) and alkalinuria (pH 7.9) without proteinuria. Arterial blood pressure was normal. An abdominal ultrasound showed normal renal size, shape and internal architecture. There was very mild bilateral pyelectasia (left renal pelvis: 2 mm; right renal pelvis: 1.7 mm; RI <1 mm). Urine culture was negative. Ten days later, alkalinuria and renal pyelectasia persisted. Given the suspicion of a pyelonephritis, treatment with amoxicillin-clavulanate (20 mg/kg orally q12h) was prescribed. Two weeks after starting antibiotic therapy, kidney values, urinalysis and ultrasound findings were re-checked, all of which remained unchanged. Antibiotic therapy was then discontinued. Kidney values stayed stable for the following 6 weeks. The cat was diagnosed with chronic kidney disease (CKD) IRIS stage 2 without proteinuria and hypertension.

Discussion

To our knowledge, this is the second case of feline dwarfism in a cat reported in the veterinary literature, and the first one to present with seizures associated with intermittent hypoglycaemia. Congenital dwarfism in Abyssinian cats caused by hypothyroidism has been described, but thyroid concentration was found to be within the normal range in this case.[5]

In human medicine, marked fasting hypoglycaemia has been described in conjunction with GH deficiency, especially in children.[6–10] Several theories on the pathomechanisms of hypoglycaemia due to GH deficiency have been proposed. In general, hypoglycaemia can result from decreased glucose production, increased glucose utilisation or a combination of both. GH has different effects on lipid, protein and glucose metabolism. GH leads to increased lipolysis and decreased proteolysis.[9] Both the increased lipolysis and the direct effects of GH can decrease muscle glucose uptake.[11] Growth hormone increases glycogenolysis, with no effect on gluconeogenesis.[6,9,12,13] Furthermore, GH is also an insulin antagonist, resulting in decreased muscle glucose uptake, as well as decreased utilisation of glucose, glycogen synthesis and glucose oxidation.[9,10,14–16] In cases of GH deficiency, there will be increased insulin sensitivity and up-regulation of insulin signalling in the liver, which has been shown in mice with dwarfism.[9] An increase in insulin receptors or improved affinity of binding in response to the low concentrations of GH might be responsible for the insulin hypersensitivity reported in humans with GH.[17]

Furthermore, it has been hypothesised that dwarfism may lead to hypoglycaemia due to decreased glycogenolysis caused by decreased hepatic glycogen stores,[18,19] and defective ketogenesis.[6] In fact, decreased serum ketones concentrations have been reported in children with GH deficiency.[6] Children have a greater brain size in relation to their body size, and thus they may have a higher glucose consumption.[20] This could explain why children with GH deficiency are more susceptible to developing fasting hypoglycaemia.

In the present case, given the diagnosis of GH deficiency and the exclusion of other diseases that could potentially lead to hypoglycaemia in a young cat (liver failure, portosystemic shunt, hypoadrenocorticism, sepsis, intoxication, insulinoma, extrapancreatic tumour, drugs), an association between GH and intermittent fasting hypoglycaemia was suspected. Although a mild degree of leukopenia was noted once, a septic process as the cause of hypoglycaemia is unlikely, given the fact that no infectious cause was found, and the cat's leukopenia and hypoglycaemia resolved without antibiotic treatment. Although IGF-2 levels were not determined, given the follow-up normoglycaemia, an extrapancreatic neoplasia is very unlikely. Interestingly, the cat was normoglycaemic at the first admission. The cat had received fluid therapy and glucose supplementation by its private veterinarian 2 days prior. It is possible that the cat had experienced a temporary rebound hyperglycaemia before developing hypoglycaemia 4 h after admission. Another possibility is that the activation of counter-regulatory hormones (eg, catecholamines) had led to a transient euglycaemia. The first time the hypoglycaemia was documented, a portable blood glucose meter (PBGM) was used to measure the cat's glucose concentrations. Although it has been shown that AlphaTRAK is more accurate than other PBGMs in cats, glucose concentrations can be underestimated in the presence of low and normal glucose levels.[21] However, given the fact that the cat showed clinical signs compatible with hypoglycaemia, and that it responded to glucose supplementation, true hypoglycaemia is likely.

In this case, an acquired GH deficiency was suspected, possibly due to TBI after a dog bite in the head. In humans, the incidence of anterior pituitary dysfunction following TBI is between 28% and 80%.[22] GH deficiency is the most common reported TBI pituitary disturbance and it comprises 0.7% of all cases of hypopituitarism.[22] The exact mechanism of pituitary dysfunction secondary to TBI is not well understood, and it may be associated with anterior lobe infarction and necrosis from direct trauma or vascular injury, posterior lobe haemorrhage and/or stalk laceration. In our case, the cat's neurological signs and hypoglycaemic events started soon after the head trauma. Also, the physical features and mental dullness had not been recognised by the owner until after the trauma. However, given the young age of the cat, a congenital GH deficiency cannot be excluded.

In cats, GH deficiency has only been described once before, in a 6-month-old female domestic shorthair cat with a history of failure to grow and bilateral corneal opacity due to corneal oedema.[4] This cat was euglycaemic.

In the cat presented herein, pituitary dwarfism was presumptively diagnosed based on the clinical features of the cat (small stature, haircoat abnormalities), markedly low serum IGF-1 concentrations and by excluding other causes of small stature, such as chronic malnutrition, hypothyroidism and portosystemic vascular anomalies. Although a radioimmunoassay for feline GH has been validated, determination of IGF-1 is a more reliable tool for the diagnosis of dwarfism, given its more constant secretion and longer half-life compared with basal GH.[1,3] In fact, the basal GH concentrations in dogs with pituitary dwarfism may overlap with those of healthy dogs.[1] A definitive diagnosis of hyposomatotropism requires evidence of lack of increase in GH concentrations after the administration of a GH secretalogue, such as human GHRH, clonidine or xylazine.[3]

In the present case, CKD was diagnosed 1 year after the initial examination, when the cat was 18 months old. At that time, it started showing polyuria and polydipsia, and was azotaemic. Although the cat did not show polyuria and polydipsia a year before, its initial blood work showed high serum urea and high–normal creatinine concentrations. As the kidney values were not monitored over time, it is possible that the cat had an earlier onset of CKD.

Whether the cat's CKD may have been a result of an untreated pituitary dwarfism remains unclear. In humans, azotaemia has been attributed to the lack of development of glomeruli due to GH deficiency.[23,24] GH and IGF-1 are important hormones for pre- and postnatal kidney development. IGFs affect renal haemodynamics both directly and indirectly by interacting with the renin–angiotensin system.[25] IGF-1 dilates the resistance-regulating renal microvasculature, increases glomerular filtration rate (GFR), and promotes tubular phosphate and possible sodium absorption.[23] Consequently, GH deficiency is associated with decreased GFR and renal plasma flow, along with low body sodium and water levels.[24] Dysregulation of the IGF system has been implicated in a number of kidney diseases, including CKD.[25]

In humans, recombinant human GH is the treatment of choice to treat children with GH deficiency. In dogs, porcine GH is considered to be the first line of treatment of congenital GH, because the amino acid sequences of porcine and canine GH are identical.[26] As an alternative treatment option, synthetic progestagens have been used to induce the synthesis of GH in the mammary glands.[1,27] In cats, the best treatment options for feline GH deficiency remain unknown. Progestagen-induced GH production in the mammary glands does not reach the systemic circulation.[28] Even though the amino acid sequences of feline GH differ only by a single amino acid residue from canine and porcine amino acid sequences,[29] the effectiveness and safety of porcine GH has not been reported in cats.

In this case, GH concentrations could not be measured and GHRH stimulation was not performed. Therefore, it is unclear whether our cat's hyposomatotropism was due to true GH deficiency or GH insensitivity, which would also result in low levels of IGF-I. If the cat suffered from GH insensitivity, hormonal therapy would not have been effective. Given the fact that the owners were not interested in hormonal treatment for their cat, and that porcine growth hormone is not available in Europe, no therapy was instituted. Therefore, it remains unknown whether the cat's physical appearance would have responded to hormonal therapy and if there would have been any side effects associated with it.

After discharge, the cat was regularly monitored by the referring veterinarian and never showed hypoglycaemia again. We hypothesise that by the time the cat was older than 5 months of age, its hepatic glycogen stores may have been adequate, and glycogenolysis may have normalised. It is possible that the maturation of the liver prevented any further episodes of hypoglycaemia.

Conclusions

Hyposomatotropism is a very rare endocrine disease in cats. In this case, hyposomatotropism was diagnosed in a kitten with generalised seizures associated with intermittent hypoglycaemia, a few weeks after a head trauma. It is unclear whether the cat's hyposomatotropism was congenital or acquired following TBI. GH deficiency should be considered in kittens with recurrent hypoglycaemia, when the classic physical features of pituitary dwarfism may not yet be evident.

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