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Diagnosis and management of diabetes mellitus in five cats with somatotrophic abnormalities

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The clinical findings and management of five cats with abnormalities consistent with acromegaly were examined retrospectively. Growth hormone (GH) concentrations were elevated in four cats. In one, a minimal elevation of GH was accompanied by a marked elevation in insulin-like growth factor-1 (IGF-1). Insulin-like growth factor-1 concentrations supported the diagnosis in three of four cats measured, but was not elevated initially in one cat, despite a markedly elevated GH concentration. These findings suggest that elevated IGF-1 concentrations are a reliable indicator of acromegaly, but that values within the reference range do not exclude such a diagnosis. Clinical signs of acromegaly were similar to those previously reported, although upper respiratory stridor occurred in one cat, and insulin-resistant diabetes mellitus was not a consistent feature. Despite the lack of a widely available definitive treatment for acromegaly, good control of the clinical signs of diabetes mellitus can be achieved for long periods despite high doses of insulin often being required.

Acromegaly (hypersomatotrophism) is a syndrome of excessive growth hormone (GH) production by the pituitary gland. It is a rare disease in the cat, caused by a functional somatotroph adenoma in the pars distalis (Feldman & Nelson 1996b). Growth hormone exerts an anabolic effect mediated by insulin-like growth factor-1 (IGF-1), leading to bony enlargement and organomegaly (Feldman & Nelson 1996b). Direct catabolic effects of GH include the development of insulin resistance, possibly due to a post-receptor defect in insulin action (Rosenfeld et al 1982). The resultant hyperinsulinaemia and hyperglycaemia leads to downregulation of insulin receptors and carbohydrate intolerance (Feldman & Nelson 1996b).

Although a rare disease, acromegaly is an important cause of insulin-resistant diabetes mellitus in the cat. All cats with acromegaly described to date have carbohydrate intolerance and most have concurrent insulin-resistant diabetes mellitus (Eigenmann et al 1984b, Middleton et al 1985, Lichtensteiger et al 1986, Heinrichs et al 1989, Kittleson et al 1989, Morrison et al 1989, Peterson et al 1990, Abrams-Ogg 1993, Goossens et al 1998). Doses of insulin required to control signs of diabetes mellitus are commonly as high as 30 units twice daily in these cats (Peterson et al 1990) and the diagnosis of acromegaly is usually made during investigation of insulin resistance (Feldman & Nelson 1996b). Basal GH concentrations are elevated in cats with acromegaly (Eigenmann et al 1984b, Lichtensteiger et al 1986, Kittleson et al 1989, Morrison et al 1989, Peterson et al 1990, Goossens et al 1998) but the assay is performed in only a few specialised laboratories. Insulin-like growth factor-1 concentrations reflect the GH secretion over the past 24 hours and have been shown to be increased in dogs with acromegaly (Eigenmann et al 1984a). This assay is non-species specific and recently has become commercially available. The use of IGF-1 for diagnosis of feline acromegaly has been previously reported in two cats (Middleton et al 1985, Abrams-Ogg et al 1993), but in which simultaneous GH measurement was not performed.

Definitive treatment of feline acromegaly is of limited availability. Successful treatment in small

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numbers of cats has been reported using pituitary cobalt irradiation (Goossens et al 1998) and transphenoidal cryotherapy (Abrams-Ogg et al 1993). Reports of successful medical treatment with octreotide or dopamine agonists are lacking. Hence, at present, treatment of acromegaly is usually confined to management of clinical signs of diabetes mellitus, hypertrophic cardiomyopathy and renal failure. The management of diabetes mellitus is usually complicated by insulin resistance.

In this study, the diagnosis of acromegaly in five naturally occurring cases using GH and IGF-1 assays, and their management is examined. These cases represent the first reports of this disease in the UK.

Materials and methods

An antemortem diagnosis of acromegaly was made in five cats at the University of Glasgow Veterinary School between 1992 and 1997. In all cases the diagnosis was suspected on the basis of history, clinical signs and the results of routine laboratory testing, and supported by the finding of an elevated basal GH concentration and/or IGF-1 concentration. Commercially available radioimmunoassays were used for GH and IGF-1* measurements. The reference range for GH was 2–5 ug/l, and concentrations greater than 6 ug/l were considered to be consistent with acromegaly. The reference range for IGF-1 was 200–800 ng/ml, and concentrations greater than 1000 ng/ml in the adult animal were considered to be consistent with acromegaly.

All the cats were treated with insulin. Assessment of glycaemic control was made by the evaluation of the presence or absence of clinical signs of diabetes mellitus (polyuria, polydipsia, polyphagia), blood glucose concentration 6 h after insulin administration, and serum fructosamine concentration. Fructosamine analysis was performed on a Cobas Mira (Roche) discrete analyser using commercial reagent (Unimate Fructosamine; Roche) calibrated on glycated polylysine brand specific calibrator (Fructosamine Calibrator; Roche), previously validated for use in cats (Graham et al 1999). The reference range for fructosamine was 216–387 µmol/l. A fructosamine concentration of less than 450 µmol/l was considered to indicate excellent control of diabetes mellitus and less than 550 µmol, good control of diabetes mellitus.

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Results

This case series comprised five domestic shorthaired cats—four neutered males and one neutered female. Their ages at initial diagnosis ranged from 8 to 13 years and body weight ranged from 4.8 to 6.8 kg. All had clinical signs of diabetes mellitus. Palpable hepatic enlargement was detected in three cats. Upper respiratory noise was present in one cat at rest. Continuing weight gain was a feature in all cats. Other changes included enlargement of the head, progressive prognathism, gradually noticeable ventral bowing of the hard palate and thickening of the skin. Increased tooth spacing was only noted in one cat.

In two cats both urea and creatinine concentrations were above the reference range at initial presentation (Table 1). All other cats had a mildly elevated urea concentration without a concomitant creatinine elevation. Total hyperproteinaemia was not a feature, but in three cats the albumin fraction was mildly increased (mean 41 g/l). Hyperphosphataemia was only present in one cat with uncompensated renal failure. Mild hypercalcaemia was present in three cats (mean 2.73 mmol/l). A mild increase in ALT (mean 57.4 U/l) was present in all cats and in three this was the only hepatic enzyme elevation. Cholesterol was mildly and occasionally increased. Leucocytosis was detected on initial presentation in three cats. Erythrocytosis was not detected. Serum total thyroxine assay was within the reference range in all five cats. Radiographically, hepatomegaly was detected in one further cat which did not have palpable hepatomegaly. Renal enlargement was detected on abdominal ultrasound examination in one cat, and in two cats echocardiography was performed which revealed changes consistent with hypertrophic cardiomyopathy.

In four cats a diagnosis of acromegaly was made following investigation of insulin-resistant diabetes mellitus. In one cat (cat 2) the diagnosis was made during investigation of concurrent diabetes mellitus, hypertrophic cardiomyopathy and compensated renal failure. In this cat insulin-resistance was not a feature. Results of GH and IGF-1 testing are presented in Table 2. In cat 2, IGF-1 concentration was not elevated when first sampled, despite an elevated GH concentration. When retested one year later,

Table 1. Results of haematological and biochemical screening tests on first presentation in five cats with acromegaly

Case	1	2*	3	4	5	Units	Reference range
RBC	6.49	7.09	8.43	7.65	8.65	10^{12}/l	(5.0–10)
Haemoglobin	9.7	10	12.2	10.4	11.1	g/dl	(10–15)
Haematocrit	26	39.7	35.6	30.5	33	%	(30–45)
MCV	40	42	42	40	38	fl	(39–59)
MCH	14.9	14.1	14.4	13.5	12.8	pg	(12.5–17.5)
MCHC	37.3	33.6	34.2	34	33.6	g/dl	(30–36)
Platelets	134	531		264	248	10^9/l	(300–800)
WBC	15.3	11.4	23.2	28.6	15.6	10^9/l	(5.5–15.5)
Bands			0.232			10^9/l	
Neutrophils	10.1	10.1	17.2	21.7	11.1	10^9/l	(2.5–12.5)
Lymphocytes	3.0	0.9	1.9	5.7	3.6	10^9/l	(1.5–7.0)
Monocytes	1.0	0.1	0.5	0.6	0.6	10^9/l	(0–0.85)
Eosinophils	1.1	0.2	3.0	0.6	0.3	10^9/l	(0–1.5)
Basophils	0.2	0	0.2	0	0	10^9/l	(0)
Urea	13.9	15.5	11.4	12.8	11.7	mmol/l	(2.7–9.2)
Creatinine	125	208	116	135	205	µmol/l	(91–180)
Glucose	21.1	21.7	18.5	19.8	16.6	mmol/l	(2.7–5.5)
Cholesterol	4.2	2.79	6.04	6.2	5.18	mmol/l	(1.8–5.2)
Bilirubin	2	1	1	1	1	µmol/l	(<10)
ALP	92	271	93	107	74	µg/l	(<100)
ALT	56	51	71	66	43	µg/l	(<35)
AST		61	25	22	11	µg/l	(<30)
Na	151	148	149	152	145	mmol/l	(145–160)
K	4.4	3.7	4.2	5	4.2	mmol/l	(2.6–5.2)
Cl	117	121	112	112	113	mmol/l	(94–113)
Ca	2.8	2.3	2.7	2.6	2.7	mmol/l	(1.6–2.56)
Phosphorus	1.9	1.9	1.4	1.8	1.4	mmol/l	(1.29–2.84)
Total protein	84	82	79	74	76	g/l	(60–85)
Albumin	43	39	38	42	33	g/l	(26–36)
Globulin	41	33	41	32	43	g/l	(27–45)

*Cat 2 was collapsed and severely dehydrated on first presentation, so results presented are from 3 weeks later when the cat was clinically well and on insulin.
RBC, red blood cells; MCV, mean cell volume; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; WBC, white blood cells; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

the IGF-1 concentration was consistent with acromegaly.

All cats were treated with twice daily injections of bovine lente insulin (Insuvet; Schering-Plough Animal Health and Hypurin; CP Pharmaceuticals). In cats 1, 3, 4 and 5, doses of insulin required to control clinical signs gradually increased over the follow-up period to reach those shown in Table 3. Despite the gradual increase in doses, long periods in which clinical signs of diabetes were well controlled occurred in cats 3, 4 and 5, ranging from 2 to 6 months. Fructosamine concentrations ranged between 229 and 399 µmol/l during these times.

A special diet was not prescribed and cats were fed 2–4 times daily on commercial cat foods except cat 5 which had been on Prescription diet

Table 2. Results of GH and IGF-1 measurements in five cats with acromegaly

Case	GH (µg/l)	IGF-1 (ng/ml)
1	158	nd
2	>18	451 (>1000 1 year later)
3	>17	1259
4	9.5	1466
5	nd	1987

The reference range for GH concentration in cats is 2–5 µg/l with concentrations >6 µg/l consistent with acromegaly. The reference range for IGF-1 concentrations in cats is 200–800 ng/ml with concentrations >1000 ng/ml consistent with acromegaly. nd=not done.

Table 3. Peak doses of insulin achieved in five cats with diabetes mellitus and acromegaly and corresponding fructosamine concentrations on this dose

Case	Fructosamine (µmol/l)	Time after diagnosis (months)	Insulin dose (lente) (units/day)
1	nd	6	30
2	287	23.5	3
3	352	22	34
4	229	19	28
5	278	6	26

nd=not done.

k/d (Hill's Pet Products) for some years, prescribed by the referring veterinarian. Other medications prescribed were diltiazem (diltiazem hydrochloride; Bioglan Laboratories) 7.5 mg 8 hourly for hypertrophic cardiomyopathy (cat 2) and carprofen (Zenecarp; C-Vet Veterinary Products) 5 mg daily for control of joint pain (cats 3 and 4).

Euthanasia was performed on cats 1 and 2 because of uncompensated renal failure after 6 and 25 months and no necropsy was performed. Cat 3 developed lymphosarcoma and euthanasia was performed at 26 months. Necropsy confirmed acidophil hyperplasia of the pituitary. Cat 4 developed uncompensated renal failure due to renal adenocarcinoma after 18 months and euthanasia was performed. An acidophil adenoma of the pituitary was found at necropsy. Cat 5 had stable clinical signs at last follow-up, 8 months after diagnosis.

Discussion

The normal pattern of GH secretion, which involves large, brief secretory pulses (Hartman et al 1990, Feldman & Nelson 1996b), means that a single elevated GH is not proof of acromegaly (Mol & Rijnberk 1997). In 54 healthy cats, mean GH concentration was 1.21±1.0 µg/l but ranged up to 8.5 µg/l (Peterson et al 1990). In another study, 18% of 38 healthy cats had a single GH concentration between 12 and 17 µg/l (Kittleson et al 1992). In healthy humans, GH secretory peaks may reach concentrations of 29 µg/l (Barkan et al 1989). For this reason it has been proposed that a GH suppression test is a more appropriate diagnostic test for acromegaly (Mol & Rijnberk 1997). Evaluation of the response to an intravenous glucose load is a commonly performed suppression test in humans, with GH concentrations failing to fall to appropriately low concentrations in acromegalic patients (Chang-DeMoranvill & Jackson 1992). Resistance to suppression of GH concentrations following intravenous administration of glucose has been demonstrated in acromegalic dogs (Eigenmann & Venker-van Haagen 1981), and in one acromegalic cat (Eigenmann et al 1984b). However, glucose infusion in four healthy cats did not result in decreased GH secretion (Kokka et al 1971), and hence this is unlikely to be a useful test in the cat. Other dynamic endocrine tests, such as the thyrotropin releasing hormone (TRH) stimulation test, growth hormone releasing hormone (GHRH) stimulation test, and paradoxical suppression with L-dopa or bromocriptine have limited use in the diagnosis of human acromegaly (Chang-DeMoranville & Jackson 1992) and have not been evaluated in acromegalic cats.

Despite this difficulty, in acromegaly there is an increased frequency of secretory pulses and higher than normal basal or interpulse GH concentrations (Barkan et al 1989, Hartman et al 1990) and a high probability of acromegaly exists when single GH values are above 10 µg/l in humans (Chang-DeMoranville & Jackson 1992). In the presence of appropriate clinical features, a single elevated GH concentration has been suggested to be adequate for diagnosis in the cat (Peterson et al 1990, Feldman & Nelson 1996b). In all 14 cats with acromegaly in a study by Peterson et al (1990), GH concentrations were greater than 22 µg/l. In all four cases in which it was measured in this study, GH concentration was elevated; however, in one case the concentration did not approach values previously reported in acromegalic cats. In this case assessment of plasma IGF-1 concentration was of more use than a single GH concentration.

Insulin-like growth factor-1 assay has become a useful test for acromegaly in humans

(Chang-DeMoranville & Jackson 1992). In both healthy and acromegalic humans, IGF-1 concentrations are strongly correlated with non-pulsatile integrated 24 h GH concentration (Hartman et al 1990). A single elevated IGF-1 concentration is therefore a more reliable indicator of human acromegaly than a single GH determination (Rieu et al 1982, Barkan et al 1988). Elevated IGF-1 concentrations have been found in untreated acromegalics despite normal mean and total integrated 24 h GH concentrations (Hartman et al 1990), and normal basal and/or post-glucose GH concentrations (Rieu et al 1982). Insulin-like growth factor-1 concentrations were increased in dogs with acromegaly (Eigenmann et al 1984a), and in two cats with acromegaly confirmed at necropsy (Middleton et al 1985, Abrams-Ogg et al 1993).

In the four cats in this study in which IGF-1 was assessed, elevations supported the diagnosis of acromegaly in three cases. The finding of an IGF-1 concentration well within the reference range in one cat in which GH was markedly elevated is unexpected given the evidence of GH as the primary regulator of IGF-1 (Chang-DeMoranville & Jackson 1992). The probability of finding a normal plasma IGF-1 concentration in a human patient with any degree of elevation of GH secretion as measured by mean daily GH concentration has been calculated to be as low as 2.5^{-10} (Barkan et al 1988). Following treatment, however, human patients occasionally have normal IGF-1 concentrations associated with elevated basal GH concentrations (Rieu et al 1982). Species differences have been suggested in the relationship between GH secretory patterns and IGF-1 concentrations (Hartman et al 1990). Other possible reasons for this discrepancy include an incorrect diagnosis of acromegaly and the effects of nutritional status and other diseases on IGF-1 and GH concentrations.

An incorrect diagnosis of acromegaly may be made if a secretory pulse of GH which exceeds the reference range is detected in a non-acromegalic animal. In the absence of acromegaly, sub-optimally controlled diabetes mellitus in humans is associated with elevations in 24 h GH secretion, and GH pulse frequency (Asplin et al 1989). These changes are accompanied by significantly lowered IGF-1 concentrations and mimic those produced by fasting in normal human subjects (Asplin et al 1989). Mild reductions in IGF-1 have also been associated with decreased energy intake in dogs (Maxwell et al 1996). The effects of diabetes mellitus and fasting on GH and IGF-1 secretion remain to be studied in the cat; however, although significant, the changes in human subjects are small compared to those accompanying acromegaly, suggesting that these factors alone would not account for the elevated GH and normal IGF-1 concentration in this cat. Elevated GH concentrations have been demonstrated in cats with hypertrophic cardiomyopathy and without clinical signs of acromegaly (Kittleson et al 1992). In 19 of 31 cats the GH concentration was greater than 11 µg/l; however, IGF-1 concentrations were not evaluated (Kittleson et al 1992). Hypertrophic cardiomyopathy-associated elevation in GH may account for the increased GH in this cat, leading to a false diagnosis of acromegaly. The pathogenesis of GH elevations in hypertrophic cardiomyopathy is unknown. The lack of necropsy confirmation of acromegaly in this cat makes it impossible to resolve this issue, and further study comparing GH and IGF-1 concentrations in cats with necropsy-confirmed acromegaly and other diseases is necessary. However, elevated IGF-1 concentrations were later demonstrated in this cat, and combined with appropriate clinical signs, suggest that the initial diagnosis of acromegaly was indeed correct.

Clinical signs in our cats were similar to those previously reported (Peterson et al 1990) including diabetes mellitus, progressive increase in body size and organomegaly, hypertrophic cardiomyopathy, arthropathy, and renal failure. Inspiratory stridor is often seen in dogs with acromegaly associated with diffuse increase in oropharyngeal soft tissue mass (Eigenmann & Venker-van Haagen 1981); however, this finding in one of the cats in this study represents the first report of its occurrence associated with acromegaly in this species.

Azotaemia was thought to reflect renal failure in both cases in which it occurred. Uncompensated renal failure attributed to glomerulonephropathy has been reported to develop in 50% of cats with acromegaly (Peterson et al 1990). Its pathogenesis has not been determined but may be the result of poorly controlled diabetes mellitus or an uncharacterised direct result of GH excess (Peterson et al 1990). In one cat renal neoplasia was the likely cause of the terminal development of azotaemia and renal failure. Subclinical dehydration may have resulted in the mild elevations in urea and albumin found in three cats. Volume contraction may lead to increased tubular resorption of urea

in the absence of decreased glomerular filtration rate (DiBartola 1995). Other causes of elevation of urea in the absence of creatinine elevation were not evident, such as gastrointestinal bleeding and consumption of high protein diets. However, if renal function was marginal in these cats, post-prandial rises in urea concentration may have been greater than otherwise expected (Finco & Duncan 1976). Although diabetes mellitus results in increased protein catabolism and urea production, this is offset by the anabolic actions of GH. The absence of total hyperproteinaemia is in contrast to the findings of Peterson et al (1990), in which it was found in more than half of the cats with acromegly. Hyperphosphataemia is found in approximately half of human patients with acromegaly (Thorner et al 1998). Although the elevation in phosphate concentration found by Peterson et al (1990) in six of 14 acromegalic cats was slight or mild (range, 2.0–2.4 mmol/l), values were not above 2.1 mmol/l in any of the five cats in this study except during the terminal stages of renal failure. Hypercalcaemia does not occur in human patients with acromegaly except in the presence of concurrent primary hyperparathyroidism (Thorner et al 1998). The mild total hypercalcaemia found in these cats is likely to be a result of the increased blood albumin concentration. Ionised calcium concentrations were not measured. Hepatic enzyme changes found in these cats are typical of those seen in diabetic cats (Crenshaw & Peterson 1996). Mild increases in cholesterol are also seen in diabetes mellitus. Erythrocytosis is reported in human patients with acromegaly (Casanueva 1992), and has been recorded in some cats with acromegaly (Peterson et al 1990) but was not detected in any cat in this study. Leucocytosis is found in almost one-third of non-ketoacidotic diabetic cats (Crenshaw & Peterson 1996) and its occurrence reflects the presence of secondary infections or stress.

Insulin-resistant diabetes mellitus is a feature of almost all cats with acromegaly (Eigenmann et al 1984b, Lichtensteiger et al 1986, Heinrichs et al 1989, Morrison et al 1989, Peterson et al 1990, Abrams-Ogg et al 1993, Goossens et al 1998). Waxing and waning, non-insulin-resistant diabetes mellitus has been reported in one cat, however (Middleton et al 1985), and hypersomatotrophism was associated with hypertrophic cardiomyopathy and hyperinsulinaemia in one other cat but there were no clinical signs of diabetes mellitus (Kittleson et al 1989). In humans, 25–60% of acromegalics have glucose intolerance but overt diabetes mellitus is present in only 10–25% (Barkan 1989, Molitch, 1992), and when present it is frequently insulin-resistant (Barkan 1989). The degree of carbohydrate intolerance correlates well with GH concentrations in some studies but not in others (Molitch 1992). Although four of the five cats in this series demonstrated marked insulin resistance, this was not a feature in one cat over a 23.5 month follow-up period. Although it appears that insulin-resistant diabetes mellitus is a common diagnostic feature of acromegaly in the cat, evaluation of the somatotrophic axis should not be restricted to those cats in which it is present.

Insulin resistance is also a frequent feature of hyperadrenocorticism in cats. None of the cats exhibited typical clinical signs, however (Nelson et al 1988) and the prolonged follow-up without their development suggests that this was not a complicating cause or contributor to insulin resistance in these cats.

Good control of diabetes mellitus was obtained with twice daily administration of lente insulin in three cats with insulin resistance as judged by clinical signs and fructosamine assay. In these cats a mean dose of insulin required at last follow-up was 29.3 units per day, reached after a mean of 15.6 months. This is lower than the mean dose of 58 units per day after a mean of 14 months noted by Peterson et al (1990) in which PZI was the most commonly used insulin type and lente was used rarely. While this difference may reflect a difference in insulin potency (Feldman & Nelson 1996a), it may also be due to the small numbers reported here. There was a tendency in all three cats for insulin requirements to increase and it is likely that, given time, insulin requirements would approach those previously reported. In addition, an increased level of suspicion may have led to the diagnosis of acromegaly being made earlier in the course of disease in these cases.

Difficulties in availability and interpretation of GH assay have led to increased interest in the use of IGF-1 assay for the diagnosis of acromegaly. In this study, the first in which IGF-1 and GH concentrations have been compared in acromegalic cats, IGF-1 elevations supported the diagnosis in three cats. In a fourth cat, IGF-1 rose with time, suggesting that an IGF-1 concentration within the reference range does not rule out acromegaly. However, further characterisation of the response of IGF-1 and GH concentrations in cats with acromegaly, poor nutritional status, diabetes mellitus and

hypertrophic cardiomyopathy is needed. Clinical signs of acromegaly in this series of cats are similar to those previously reported, although it is noted that upper respiratory stridor occurs in some acromegalic cats, and insulin-resistant diabetes mellitus is not always a feature. Despite the lack of a widely available definitive treatment for acromegaly, good control of the clinical signs of diabetes mellitus can be achieved for long periods despite high doses of insulin being required.

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