Acromegaly in a cat: Diagnosis by magnetic resonance imaging and treatment by cryohypophysectomy

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An eight-year-old, male neutered, domestic longhair cat weighing 6.5 kg was presented with a two-month history of polyphagia. The owners reported that the cat had always had a generous appetite but was now becoming destructive when seeking food. Three episodes of hyperglycemia (12.3 mmol/L–18.1 mmol/L, reference values 3.5 mmol/L–9.0 mmol/L) and glucosuria (56-111 mmol/L), and on one occasion ketonuria (0.5 mmol/L), had occurred in association with constipation during the previous ten months, but had been resolved without insulin therapy.

No abnormalities other than obesity were noted on physical examination. Results of a complete blood count, serum chemistry profile, and urinalysis were unremarkable. Hyperthyroidism and hyperadrenocorticism were considered to be possible causes of the cat's polyphagia. The serum thyroxine level was 10 nmol/L (reference values 9.3 nmol/L–57.9 nmol/L). An adrenocorticotropic hormone (ACTH) stimulation test (1) was performed. Serum cortisol levels assayed before, and at 30 and 60 minutes after, intramuscular (IM) administration of a total dose of 0.125 mg cosyntropin (Cortrosyn, Organon Canada, West Hill, Ontario) were 229 nmol/L, 270 nmol/L, and 276 nmol/L, respectively. These results were considered to be normal and no treatment was instituted.

Six weeks later the cat was presented for evaluation of polyuria/polydipsia (PU/PD) and an increasing polyphagia of two weeks' duration. No abnormalities were noted on physical examination other than obesity and mild muscle wasting (body weight [BW] 5.8 kg). Glucosuria (111 mmol/L) and fasting hyperglycemia (18.1 mmol/L) were present. Diabetes mellitus was diagnosed. The cat was treated with protamine zinc (PZ) insulin (Iletin Protamine Zinc Insulin, Eli Lilly Canada, Scarborough, Ontario), beginning with a dose of two units given subcutaneously (SC), q24h, and gradually increased over a one-month period to five units administered q12h. This resulted in a mild reduction in PU/PD and glucosuria (random urine glucose values ranged from 56 nmol/L–111 mmol/L), but extreme polyphagia persisted. Serial blood glucose determinations ruled out that the poor insulin effect was due to Somogyi effect, rapid insulin metabolism, or delayed insulin absorption.

Additional diagnostic testing was performed to rule out causes of insulin resistance. Feline leukemia virus and feline immunodeficiency virus tests were negative. The serum thyroxine level was normal (10 nmol/L). Urine culture was negative. A dexamethasone suppression test (1) was performed with normal results; the resting serum cortisol level was 90 nmol/L and eight hours following the intravenous (IV) administration of 0.01 mg/kg BW dexamethasone sodium phosphate (Dexasone, ICN Canada, Montreal, Quebec), it was 30 nmol/L.

No improvement in regulation was achieved over the next five months by gradually increasing the dose of PZ insulin to 13 units q24h. To investigate if a more rapid acting insulin would be more efficacious, NPH insulin (NPH Insulin, Connaught Novo Nordisk, Mississauga, Ontario) was administered, up to five units, SC, q12h, with no improvement in regulation. Regardless of the insulin treatment regime, the blood glucose level remained above 18 mmol/L during a twenty-four hour period with the cat being fed its daily ration in four feedings. Because of the poor diabetic regulation and the absence of other diseases causing insulin resistance, acromegaly was suspected. Plasma insulin-like growth factor-I (IGF-I, somatomedin C) level determined by radioimmunoassay (Animal Health Diagnostic Laboratory, Michigan State University, Lansing, Michigan) was 1251 U/L. Two months later the level had increased to 2181 U/L. Plasma levels of IGF-I determined for five clinically normal, three to six-year-old, male neutered, cats ranged from 170–438 U/L. The plasma IGF-I level in a well-regulated 11-year-old, male neutered, diabetic cat was 286 U/L.

A tentative diagnosis of acromegaly was made. Radiographs of the skull and extremities were interpreted to be normal. Mild cardiomegaly, seen on thoracic radiographs, was determined echocardiographically to be due to mild left ventricular hypertrophy. An electrocardiogram was normal. Magnetic resonance image (MRI) studies of the cat's brain were obtained using a SISCO 85/310 (Spectroscopy Imaging Systems Corporation, Fremont, California, USA) animal imaging system, as previously described (2). A large pituitary mass was identified, which unlike normal pituitary tissue, did not enhance following administration of the contrast agent gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) (Magnevist, Berlex Canada, Montreal, Quebec) (Figure 1b), 0.1 mmol/kg BW, IV. This mass was suspected of being a tumor, secreting either growth hormone or ACTH. An ACTH stimulation test and dexamethasone suppression test were repeated. Serum cortisol levels measured before, and at 30 and 60 minutes following, ACTH administration were <30 nmol/L, 164 nmol/L, and 223 nmol/L, respectively. The serum cortisol level measured eight hours following the administration of 0.01 mg/kg BW dexamethasone was <30 nmol/L. The endogenous ACTH level was 11.6 pmol/L (reference

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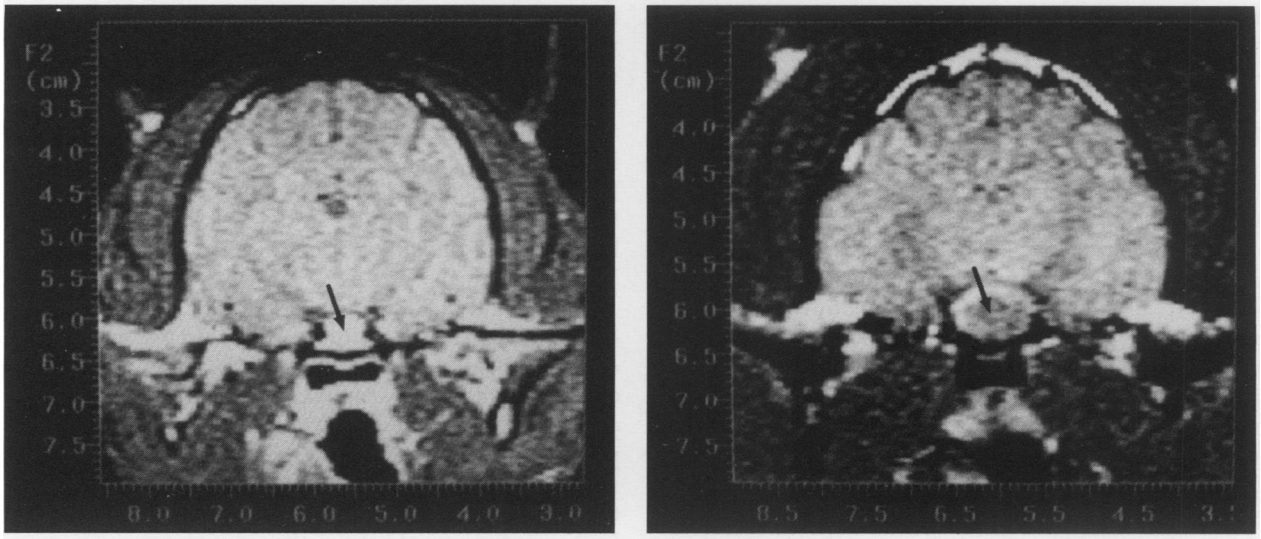

Figure 1. Transverse oriented, contrast-enhanced T_1-weighted (echo time = 25 ms, repetition time = 500–700 ms) magnetic resonance images of the heads of a normal cat (Figure 1a, left) and a cat with acromegaly (Figure 1b, right). Images were obtained following administration of the contrast agent gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) (Magnevist, Berlex Canada, Montreal, Quebec) 0.1 mmol/kg body weight IV. The normal pituitary gland (arrow) measured 4 × 3 × 3 mm^3 and had a homogeneous increase in intensity, indicating normal uptake of contrast. The pituitary of the acromegalic cat was enlarged (measuring approximately 8 × 6 × 8 mm^3) and only partially enhanced after administration of Gd-DTPA. The region of poor enhancement (arrow) represents the pituitary tumor.

values 6.7 pmol/L–25 pmol/L). These results were normal and ruled out hyperadrenocorticism.

Cryosurgical ablation of the pituitary gland (cryohypophysectomy) was performed. The cat was premedicated for anesthesia with meperidine (Meperidine, Abbott Laboratories, Montreal, Quebec), 4 mg/kg BW, IM, and anesthesia was induced and maintained with isoflurane (Aerrane, Anaquest, Mississauga, Ontario). A transsphenoidal approach to the pituitary gland was employed, as described for the dog (3). A large (estimated 1 cm diameter) pituitary mass was visualized and biopsied. A cryoprobe was applied to the mass and two freeze-thaw cycles performed. Histopathologically, the mass was an acidophil adenoma, consistent with a growth hormone secreting tumor.

Amoxicillin/clavulanate (Clavamox, Ayerst Laboratories, St. Laurent, Quebec), 125 mg combined dose was given postoperatively PO, q12h, for two weeks. Desmopressin (DDAVP Nasal Solution 0.1 mg/mL, Richmond Pharmaceuticals, Richmond Hill, Ontario), 0.1 mL, was placed into the conjunctival sac, q12h, for three days, as prophylaxis in the event that diabetes insipidus developed. No electrolyte abnormalities occurred. Therapy with PZ insulin was continued with 10 units given q24h.

Insulin requirements dropped during the second postoperative week and the PZ insulin dose was reduced to five units given each evening. Over the next five days, with the cat being fed in three divided feedings, blood glucose levels were 20.2 mmol/L–20.4 mmol/L prior to insulin injection and 3.6 mmol/L–9.2 mmol/L at the time of peak insulin effects (sixteen to seventeen hours after injection). Randomly determined urine glucose levels varied from negative to 28 mmol/L. Although fairly well regulated, the cat remained ravenous.

During the next six weeks, the cat's PU/PD worsened and random urine glucose levels increased to 28 mmol/L–56 mmol/L. The PZ insulin dose was gradually increased to 10 units, q24h; but there was no improvement in clinical signs nor reduction in urine glucose levels. Results of serial blood glucose determinations were similar to those obtained prior to cryohypophysectomy, and plasma IGF-I was 6212 U/L. Tumor regrowth was considered, and an MRI study was obtained. The tumor margins were difficult to define, but the size of the pituitary had decreased in comparison to that in the previous study, and a larger area of the gland enhanced with Gd-DTPA. It was suspected, therefore, that the pituitary tumor had decreased in size. It was also noted that the hippocampus enhanced with Gd-DTPA. These regions do not normally enhance following administration of Gd-DTPA, because this agent does not cross the blood-brain barrier (4). The enhancement of the hippocampus indicated, therefore, breakdown of the blood-brain barrier in these regions.

Two months postoperatively, following a 10 unit PZ insulin dose the previous evening, the cat was presented in status epilepticus. It was hypothermic (<35.0°C) and comatose between seizures, with constricted and non-responsive pupils. Blood glucose was 2.2 mmol/L. Treatment was given with diazepam (Valium 10 Roche Injection, Hoffman-La Roche Ltd., Mississauga, Ontario), 5 mg total dose, IV; 50% dextrose (Dextrose 50%, MTC Pharmaceuticals, Cambridge, Ontario) 7.5 mL total dose, IV; dexamethasone sodium phosphate 2 mg/kg BW, IV; and 25% mannitol (Mannitol 25%, Abbot Laboratories), 1.5 g/kg BW, IV. Insulin therapy was withdrawn. The cat's condition stabilized over 24 h. During the next three days, pupillary light reflexes became normal, but the cat had become blind. Diazepam therapy (2.5 mg total dose, IV, q12h) was required to control seizures. Fasting blood glucose levels remained normal. Two days later, neurological examination revealed poor proprioceptive positioning, poor physiological nystagmus, and absent menace response. The cat was responsive, especially to sound. No abnormalities were

noted on ophthalmological examination, and the cat would turn his head away from bright light. Visual impairment was attributed to acute cortical necrosis. The deficits in proprioception and poor physiological nystagmus indicated that brainstem injury had also occurred.

Sporadic seizure activity continued. Phenobarbital (Phenobarbital, Parke-Davis Canada, Scarborough, Ontario) 2 mg/kg BW, PO, q12h, was substituted for diazepam, and no further seizures occurred. The cat's appetite returned to normal, and during the next two weeks its blood glucose level dropped from mild persistent hyperglycemia (11.5 mmol/L–14.9 mmol/L) to normoglycemia, without insulin treatment. One month later, phenobarbital therapy was withdrawn. Seizures did not occur, but a change in personality was noted. The cat, which was normally very affectionate and easy to handle, began to growl and hiss with minimal stimulation. Two weeks later, pupillary dilation and sluggish pupillary light reflexes were noted, and tapetal hypereflectivity and retinal vessel attenuation were observed on ophthalmological examination. No activity was present on an electroretinogram. These findings indicated that retinal degeneration had occurred. An MRI study was performed (six months following cryohypophysectomy) to rule out an expanding pituitary mass as the cause of the behavioral changes and visual deficits. Results were similar to those of the previous study. Plasma IGF-I level was 893 U/L.

No improvement in vision occurred during the next nine months; the cat's behavior remained abnormally aggressive, and there was no improvement during therapeutic trials with phenobarbital, 2 mg/kg BW, PO, q12h, diazepam (Novo-Diazepam, Novopharm Ltd., Scarborough, Ontario), 2 mg/kg BW, PO, q12h, or hydroxyzine (Atarax, Pfizer Canada, Kirkland, Quebec), 10 mg total dose, PO, q12h. Polyphagia persisted and body weight increased to 9.3 kg. Urine glucose was monitored daily; glucosuria did not occur. Fifteen months following cryohypophysectomy, the results of a laboratory evaluation were as follows: A complete blood count, serum chemistry profile and urinalysis were unremarkable. The serum thyroxine level was 30 nmol/L (reference values 10–50 nmol/L). The serum cortisol levels obtained before and 30 minutes after ACTH administration were 60 nmol/L and 132 nmol/L, respectively. The endogenous plasma ACTH level was 5 pmol/L. The original radioimmunoassay procedure used for determining plasma IGF-I level was not available at the time. Using a different radioimmunoassay procedure, the plasma IGF-I level was 109 nmol/L (tentative reference values 5 nmol/L–112 nmol/L). The procedure used for this measurement differed from the former procedure in that IGF-I was extracted from binding proteins.

The cat was euthanized because of its aggressive behavior and necropsied. No pituitary remnants were observed either grossly or histologically. Histologically, there was a well-demarcated zone of vacuolation in the basal regions of the hypothalamus. Widespread vacuolation of the optic tracts and optic chiasm was also present, with widely scattered axonal necrosis. The optic nerves and the nerve fiber and ganglion cell layers of the eyes were histologically normal. However, complete photoreceptor atrophy and loss of outer nuclear layers of the retina were noted. Areas of microgliosis and astrocytosis of varying severity were present within cortical laminae. In the areas of greatest severity, which were observed within the temporal cortex and hippocampus, there was endothelial swelling, low numbers of perivascular plasma cells, and a marked increase in the presence of microglia. Other significant histological findings included diffuse mild nonseptic lymphocytic-plasmacytic meningitis and pancreatic islet amyloidosis.

Acromegaly is a well-documented cause of insulin-resistant diabetes mellitus in the cat (5–8). The disease has been reported in cats six years of age and older, and with one exception, only in males. All reported cases have presented with polyuria, polydipsia, and polyphagia, associated with the diabetic state. Cardiomegaly has been present in most cases; other acromegalic features have been reported with varying frequency. In the case reported herein, the signalment and history of insulin-resistant diabetes mellitus were typical. The striking feature of this cat's history was the intense polyphagia that preceded the development of overt diabetes mellitus. The polyphagia was attributed to exacerbation of a primary behavioral disturbance by carbohydrate intolerance. There were no acromegalic features apart from the mild cardiomegaly. It is possible, however, that subtle changes were not recognized due to the cat's normally large physique.

Definitive diagnosis of acromegaly has relied upon the demonstration of elevated plasma growth hormone levels (6–8). This assay is currently not available. Presumptive diagnosis in this case was based on the exclusion of other diseases that could cause insulin resistance, elevated plasma IGF-I levels, the demonstration of a pituitary mass by MRI, and pituitary biopsy. An elevated plasma IGF-I level is generally diagnostic of acromegaly in humans, and levels fall following successful tumor excision (9). Little data are available for cats (10). In a previous report (5), a cat with acromegaly had a serum IGF-I level that was elevated by comparison with those of two clinically normal cats. The plasma IGF-I level of our cat was markedly elevated in comparison to those of five clinically normal and one diabetic control cat, and the levels reported herein were similar to those reported previously (5). Reduced plasma IGF-I levels were measured at six and fifteen months after surgery, although the latter level is not directly comparable to the former plasma IGF-I levels because of the change in assay procedure. The elevation in plasma IGF-I level measured two months after surgery is unexplained.

The histopathological diagnosis of the pituitary tumor was an acidophil adenoma. Definitive diagnosis of a somatotroph adenoma requires demonstration of growth hormone in the neoplastic tissue. This can be achieved with an immunoperoxidase reaction (5), but this test was not available. However, at necropsy, all acromegalic cats have had an acidophil adenoma (5–8, 11–12).

Options for treating acromegaly in humans include adenectomy, radiation therapy, and pharmacotherapy with dopaminergic and somatostatin analogs (13). To the authors' knowledge, only radiation therapy (beneficial in one case) and somatostatin analog therapy (not beneficial in four cases) have been reported in cats (10).

Therapy in cats has usually consisted of regulation of the diabetic state with high doses of insulin (5–8,10). This report demonstrates the feasibility of a transsphenoidal approach to the pituitary gland in the cat and the benefit of cryosurgery. Cryohypophysectomy was chosen over excisional hypophysectomy in this study because of familiarity with the procedure in experimental dogs (DLH, unpublished observations), potential for killing neoplastic tissue while sparing normal pituitary function, and potential for killing neoplastic tissue extending outside the sella turcica that may remain following curettage. The procedure was successful in that all neoplastic tissue was apparently killed and diabetes mellitus resolved for up to fifteen months. Although normal pituitary tissue was not identified at necropsy, functional pituitary failure did not occur. The postoperative MRI changes in the hippocampus and histopathological changes in the hypothalamus and optic tracts suggest that cryoinjury occurred to nervous tissue immediately surrounding the pituitary. However, the behavioral change that occurred fifteen weeks postoperatively resulted probably from hypoglycemia-induced brain damage and possibly from inability to adjust to blindness, but not from cryoinjury to the limbic system, which would have resulted in earlier behavior change. Similarly, if cryoinjury to the optic tracts had been sufficient to cause blindness, there would have been earlier evidence of visual impairment. Blindness was attributed initially to acute cortical necrosis and later to retinal degeneration. The cause of the latter is not known. To the authors' knowledge, retinal degeneration following seizures and coma has not been described in humans or animals. The retinal degeneration seen in this cat is similar to the sudden acquired retinal degeneration syndrome in dogs that has been associated with disturbances in carbohydrate metabolism (14).

The principal management complication in this cat was insulin overdose. It is not known why insulin resistance transiently increased prior to abrupt cessation of the diabetic state. Regardless of the cause, because acromegalic cats are not disposed to ketoacidosis (8) and because hypophysectomy may mitigate counterregulatory hormone response to insulin overdose, continued reduction of insulin dosage following hypophysectomy is advisable to prevent a hypoglycemic crisis, such as the one that occurred in this case.

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