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Evaluation of hypophysectomy for treatment of hypersomatotropism in 25 cats

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Abstract

Background: Successful treatment of cats with hypersomatotropism by transsphenoidal hypophysectomy is described in small numbers of cats.

Objectives: To describe the endocrine profile, survival, and remission rates of hypersomatotropism and diabetes mellitus in a cohort of cats with hypersomatotropism that underwent hypophysectomy between 2008 and 2020.

Animals: Twenty-five client-owned cats with spontaneous hypersomatotropism.

Methods: Retrospective study. Diagnosis of hypersomatotropism was based on clinical signs, plasma insulin-like growth factor-1 (IGF-1) concentration, and imaging of the pituitary gland. Growth hormone (GH) and IGF-1 concentrations were measured repeatedly after surgery. Survival times were calculated based on follow-up information from owners and referring veterinarians.

Results: Median postoperative hospital stay was 7 days (range, 3-18 days). One cat died within 4 weeks of surgery. Median plasma GH concentration decreased significantly from 51.0 ng/mL (range, 5.0-101.0 ng/mL) before surgery to 3.8 ng/mL (range, 0.6-13.0 ng/mL) at 5 hours after surgery. Remission of hypersomatotropism, defined as normalization of plasma IGF-1 concentration, occurred in 23/24 cats (median, 34 ng/mL; range, 14-240 ng/mL) and 22/24 cats entered diabetic remission. Median survival time was 1347 days (95% confidence interval, 900-1794 days; range, 11-3180 days) and the overall 1-, 2-, and 3-year all-cause survival rates were 76%, 76%, and 52%, respectively.

Conclusions and Clinical Importance: This study shows the beneficial outcome of hypophysectomy in cats with hypersomatotropism, marked by low death rate and a high percentage of diabetic remission and definitive cure.

KEYWORDS

acromegaly, diabetes mellitus, feline, pituitary adenoma, remission

Abbreviations: CT, computed tomography; DM, diabetes mellitus; GH, growth hormone; IGF-1, insulin-like growth factor-1; MR, magnetic resonance; P/B value, pituitary height/brain area value; STT, Schirmer tear test.

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1 | INTRODUCTION

Hypersomatotropism in cats is caused by a growth hormone (GH)-secreting pituitary adenoma.[1,2] Hypersomatotropism is increasingly recognized, with prevalence rates of 18% to 32% in cats with diabetes mellitus (DM).[3-6] Clinical signs are dominated by the direct catabolic effects of GH and indirect anabolic effects via insulin-like growth factor-1 (IGF-1). The profound hormonal effects on carbohydrate metabolism and insulin action result in DM in the majority of cats with hypersomatotropism.[2,7-9] Other manifestations of GH and IGF-1 excess include soft tissue growth, organomegaly, and acral enlargement. In addition, expansion of the pituitary tumor can lead to signs of neurological disease.[2] Because of acral enlargement, the syndrome is often described as "acromegaly"; however, as cats are diagnosed without profound physical changes, hypersomatotropism is the preferred terminology for this disease.[7]

Treatment is aimed at the hypersomatotropism itself and treatment of concurrent DM. Treatment of DM by exogenous insulin is often unrewarding as long as the primary hypersomatotropism remains untreated; insulin resistance is common and high doses of insulin may be required.[1,2,10] Described treatment modalities for hypersomatotropism include medical treatment, radiation therapy, cryotherapy, and surgery.[2,11-21] In humans, surgery is the definitive treatment of choice for hypersomatotropism.[22] In 2010, successful treatment by transsphenoidal hypophysectomy of a cat with hypersomatotropism and insulin-resistant DM was reported. The cat went into full remission as evidenced by normalization of IGF-1 levels and diabetic remission was achieved by disappearance of exogenous insulin requirements.[21] Larger cohort studies on hypophysectomy as a treatment of hypersomatotropism in cats are lacking. Therefore, the aim of this study is to report on the results of hypophysectomy in a large cohort of 25 cats with hypersomatotropism, including description of the hormone profile, the percentages of cats with remission of DM and hypersomatotropism, and discussion of the complications of hypophysectomy.

2 | MATERIALS AND METHODS

2.1 | Animals and diagnosis

Over a period of 12 years (January 2008 to January 2020), 25 cats were referred to the Department of Clinical Sciences, Faculty of Veterinary Medicine, Utrecht University, the Netherlands, for treatment of hypersomatotropism. Diagnosis of hypersomatotropism was based on clinical signs (most commonly polyuria/polydipsia because of uncontrolled DM, polyphagia, weight gain, acral, and facial growth) and measurement of elevated plasma IGF-1 concentration.

2.2 | Imaging

Pituitary imaging was performed in all cats using contrast-enhanced computed tomography (CT) or high-field magnetic resonance (MR) imaging.[2,23-26] Pituitary dimensions were measured in millimeter on CT or MR images using Agfa Impax computer software (Agfa-Gevaert, Mortsel, Belgium) or Radiant DICOM viewer (Medixant 2019, version 5.5.1, Poznan, Poland) tools. Pituitary height was measured on transverse images showing the largest cross section of the pituitary mass. The brain area was measured in mm^2 on the same transverse image, and the pituitary height/brain area (P/B) value was calculated. A pituitary height of >4 mm was considered enlarged.[26-29] Pituitary images were also used to plan the surgery, especially the assessment of the bone landmarks on transverse images (hamular processes and the sphenoid ridge) in relation to the pituitary mass. On the midline sagittal view, the air-filled sphenoid sinus, typical for cats, just rostral to the pituitary fossa, was another feature that was used to plan the burr hole.[30,31]

2.3 | Preoperative preparation

Cats were typically hospitalized in the intensive care unit 2 days before surgery. A jugular catheter was placed on the first day, hydration status was optimized via IV fluid therapy and in the diabetic cats short-acting insulin therapy (Actrapid, Novo Nordisk, Denmark) via continuous rate infusion was initiated to regulate blood glucose concentrations. The cat had free access to water with regular feeding during the day. An esophageal feeding tube was placed to enable postoperative feeding. In the first 10 cats, this was done postoperatively and only if the cat did not eat sufficient amounts itself. This occurred in multiple cats and was considered to be related to the long travel to the clinic, the unknown environment, influence of anesthesia and surgery, or both. Based on these insights, an esophageal feeding tube was placed preoperatively in all cats thereafter, in the same procedure and sedation as jugular catheter placement.

2.4 | Transsphenoidal hypophysectomy and aftercare

Transsphenoidal hypophysectomy was performed according to a technique described previously.[23,32] Briefly, the soft palate was incised in the midline and retracted laterally with a self-retaining Gelpi retractor. The mucoperiosteum was separated from the sphenoid bone and the hamular processes and the sphenoid ridge were identified to determine the position of the burr hole. During burring, the air-filled sphenoid sinus was usually opened in the rostral part of the burr hole which supported the approach to the pituitary fossa. After exposure of the pituitary gland, the dura was coagulated using bipolar electrocautery and incised. Next, the pituitary mass was circumferentially detached and carefully retracted from the pituitary fossa. The pituitary tissue was collected for routine histopathology and immunocytochemistry, and whenever possible, specimens were identified as normal pituitary tissue or affected adenomatous pituitary tissue. After hypophysectomy, the empty fossa was filled with a piece of gel foam and the sphenoid slot was closed with bone wax. The soft palate was closed in 2 layers.

As soon as the cats were awake, free water was provided. Postoperative IV fluid therapy was continued at maintenance rate and correction

was administered to minimize dehydration and correct electrolyte imbalances. In diabetic cats a glucose-free isotonic crystalloid (Sterofundin ISO, B. Braun Vet Care GmbH, Tuttlingen, Germany) fluid was used. Electrolyte and fluid balance were monitored meticulously to enable titration of fluids when indicated. This was initially done every 4 hours or as deemed necessary by the attending critical care specialist or endocrinologist and monitoring frequency was tapered down when the electrolytes and fluid balance stabilized. Hormone substitution was initiated postoperatively as described previously.[21,23,32] Briefly, substitution consisted of hydrocortisone 1 mg/kg q6h IV (Solu-Cortef, Pfizer, the Netherlands) and desmopressin (Minrin; Ferring, the Netherlands) 1 drop q8h topically in the conjunctival sac, alternating the left and right eye. When excessive free water loss occurred with q8h desmopressin administration, as evidenced by markedly negative fluid balances and increasing plasma sodium concentrations, the interval between desmopressin administrations was decreased to every 6 hours. When the cat started eating, levothyroxine (Forthyron, Eurovet Animal Health, the Netherlands) 15 μg/kg PO q12h was added and glucocorticoid treatment was changed to oral cortisone acetate (Pharmachemie Ltd, the Netherlands) 1 mg/kg q12h. Insulin treatment via continuous rate infusion was continued postoperatively and blood glucose levels were measured by a hand-held glucometer using microsamples collected from the jugular catheter. This was done initially every 2 hours with the interval increasing to every 4 hours in accordance with stabilization of glucose concentrations and only if deemed safe by the clinician in charge. CRI insulin dose was adjusted based on the changing plasma glucose concentrations, as expected with decreasing insulin resistance after removal of the GH-producing pituitary tumor. Usually a few days after surgery, with the stabilization of hydration and electrolytes, and supported by return of voluntary food intake, CRI insulin treatment was changed to subcutaneous administration of the insulin type the cat had received preoperatively q12h. Monitoring of the cats' blood glucose concentrations was continued with the interval of measurements adjusted based on the individual cat's condition including demeanor and previous blood glucose course. Subcutaneous insulin treatment was stopped if the glucose concentrations normalized throughout the day. The cats' glycemic states were continued to be monitored as their blood glucose could decrease further, resulting in hypoglycemia. Specific treatment for possible hypoglycemic episodes with IV glucose supplementation was initiated as indicated on an individual basis. Cats were offered soft food but if hyporexia occurred, they were fed via the esophageal feeding tube every 6 hours to prevent inadequate or inconsistent food intake as a factor contributing to blood glucose derangements. The day after surgery, a Schirmer tear test (STT) was performed. If tear production appeared reduced (<10 mm in 1 minute), eye lubricating ointment was applied q6h, and the STT repeated before discharge to determine whether treatment and evaluation of tear production should be continued.

2.5 | Histopathology

Histologic examination of the surgically removed pituitary specimens included hematoxylin and eosin staining. Immunohistochemical staining was performed by the avidin-biotin technique using a monoclonal mouse antibody to synthetic $ACTH_{1\text{-}24}$ (Department of Infectious Diseases and Immunology, Faculty of Veterinary Medicine, Utrecht University, the Netherlands), a polyclonal rabbit antibody to synthetic human α-MSH (PU060-UP, Biogenex Laboratories, San Remon, California), and a polyclonal rabbit antibody to porcine GH (source 4750-3959, Biogenesis Ltd, Poole, UK).[33] Normal canine pituitary tissue served as control tissue. The dilution factor for the antibodies was 1:100 for ACTH, 1:5000 for GH, and 1:600 for α-MSH.

2.6 | Perioperative hormone analysis

Growth hormone concentrations were measured in preoperative plasma samples and in samples taken 1, 3, and 5 hours postoperatively. Plasma IGF-1 concentrations were measured at diagnosis and repeated perioperatively. From the first 10 cats, this was done at the day of surgery and at variable times during follow-up by the referring veterinarian. In the following cats, additional IGF-1 concentrations were measured on several days during the hospitalization period. Assays were performed as described elsewhere.[11,34] Remission of hypersomatotropism was defined by normalization of plasma concentrations of IGF-I (reference range, 39-590 μg/L).[11,21]

2.7 | Follow-up

Follow-up information was collected from the medical files and by contacting owners and referring veterinarians. Postoperative death rate was defined as death within 4 weeks after surgery irrespective of the cause. Major complications were defined as complications which necessitated treatment, whereas minor complications were defined as physical or clinicopathologic abnormalities which improved without specific treatment.

2.8 | Data analysis

Descriptive analysis was performed using commercial statistical software (SPSS 13.1 for Windows, SPSS). The Q-Q plots and Shapiro–Wilk W-test were used to assess the normality of the data. Results are expressed as median and range. The Wilcoxon signed-rank test was used to compare pre- and postoperative GH values.

Two survival analyses were performed; 1 evaluating hypersomatotropism- and hypophysectomy-related deaths and 1 evaluating all-cause mortality. In the hypersomatotropism- and hypophysectomy-related survival analysis, censored cases were cats that died because of unrelated causes. In the all-cause mortality analysis, censored cases were cats that were alive at the last known date of follow-up. Survival time and rates were calculated from this Kaplan–Meier survival analysis.

3 | RESULTS

3.1 | Animals and diagnosis

The majority of the 25 cats included in this analysis were neutered males (n = 21); the remaining cats were neutered females (n = 4). Median age at presentation was 9.7 years (range, 4.6-12.5 years) and median body weight 5.7 kg (range, 4.4-9.4 kg). Breeds represented were domestic shorthair (n = 21), Maine Coon (n = 2), Siamese (n = 1), and Sphynx (n = 1). The cats originated from 7 countries: the Netherlands (n = 8), France (n = 5), Italy (n = 4), Germany (n = 4), Switzerland (n = 2), Norway (n = 1), and Spain (n = 1).

All cats except 1 were diagnosed with DM by referring veterinarians through repeated measurements of elevated plasma glucose and fructosamine concentrations. In these 24 cats, insulin treatment was initiated before referral; however, insufficient glycemic control was obtained despite relatively high insulin doses (median dose, 1.9 IU/kg SC BID; range, 0.9-3.9 IU/kg). In the 1 cat without overt DM, further diagnostics, including plasma IGF-1 (>1000 ng/mL) and CT (pituitary height 5 mm), were performed because of polyphagia, weight gain, and a nasal stridor.

3.2 | Imaging

Pituitary glands were visualized using CT (n = 20) and high-field MR imaging (n = 5) scans. Pituitary enlargement was present in 24/25 cats (median height, 5.2 mm; range, 4.3-13.3 mm; Figure 1). The median P/B value in these cats was 0.58 (range, 0.49-1.41). In the 1 cat with a nonenlarged pituitary, the height was 3.6 mm and the P/B value 0.40.

3.3 | Transsphenoidal hypophysectomy and histology

Surgery and recovery were uncomplicated in all cats. Within the pituitary height range of the enlarged tumors in 24/25 cats (4.3-13.3 mm), the larger tumors were not particularly more difficult to remove than the mild-to-moderately enlarged pituitary glands. Completeness of hypophysectomy was assessed by a clear view on the hypothalamus and the entrance to the third ventricle, careful exploration of the empty pituitary fossa with a fine ball-tipped neurosurgical probe, and visualization and palpation of the dorsum sellae. Histology revealed a somatotroph adenoma in 24/25 cats. In 2 of these cats, a double adenoma was found, consisting of GH- and ACTH-positive cells. In these cats, the clinical picture was dominated by hypersomatotropism and DM; based on the clinical signs (weight gain, no hair coat or skin abnormalities), there was no suspicion of hypercortisolism secondary to an ACTH-producing pituitary adenoma. In 1 cat, the pituitary specimen was nondiagnostic.

3.4 | Perioperative hormone analysis

At the time of diagnosis, the median plasma IGF-1 concentration was 1600 ng/mL (range, 780-4387 ng/mL). The cat with an initial plasma IGF-1 concentration of 780 ng/mL showed a marked elevation (2895 ng/mL) at the day of surgery. Plasma GH concentrations were available from 23 cats and decreased significantly ($P < .001$) with a preoperative median value of 51 ng/mL (range, 5.0-101.0 ng/mL) and a median value of 3.8 ng/mL at 5 hours postsurgery (range, 0.6-13.0; Figure 2). Marked IGF-1 decrease was noted in the postoperative period and remission of hypersomatotropism was demonstrated in 23/24 cats surviving ≥4 weeks after surgery (median plasma IGF-1, 34 ng/mL; range, 14-240 ng/mL). In 15 cats, plasma IGF-1 was measured repeatedly during the hospitalization period and revealed remission in 14/15 cats after a median of 3.5 days (range, 1-7 days; Figure 3). In the remaining cats, plasma IGF-1 concentrations were not measured repeatedly during the postoperative hospitalization period. In these cats, IGF-1 normalization was demonstrated during revisits in the months after discharge. In the 1 cat in which the plasma IGF-1 concentration decreased from 3185 to 1200 ng/mL 9 days postoperatively (Figure 3), no IGF-1 levels were determined after

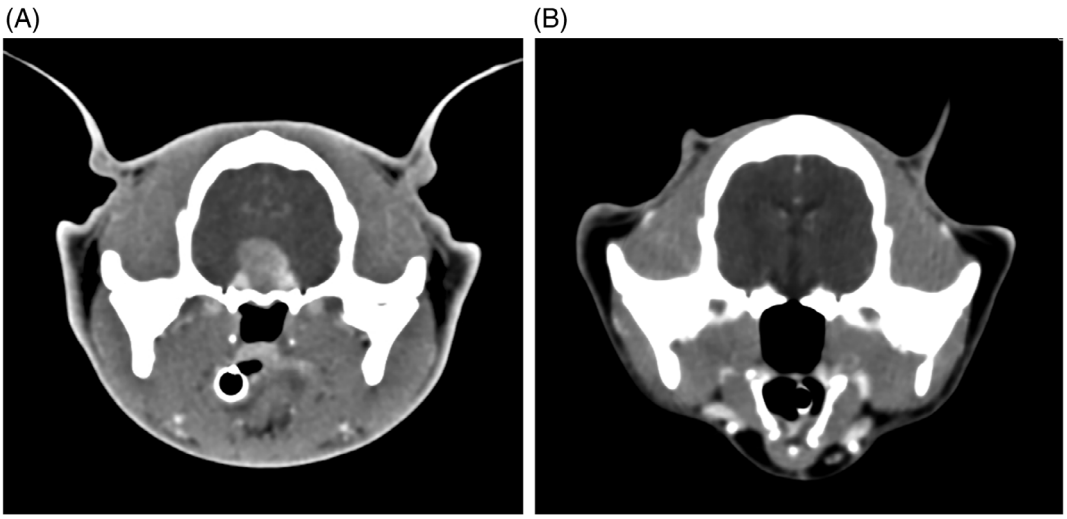

FIGURE 1 Transverse contrast-enhanced computed tomography of a 10-year-old male castrated domestic shorthair cat (no. 2 in the cohort) with diabetes mellitus and hypersomatotropism (plasma growth hormone [GH] >100 ng/mL and plasma insulin-like growth factor-1 [IGF-1] > 1100 ng/mL) because of a pituitary adenoma (A) before and (B) 3 months after transsphenoidal hypophysectomy

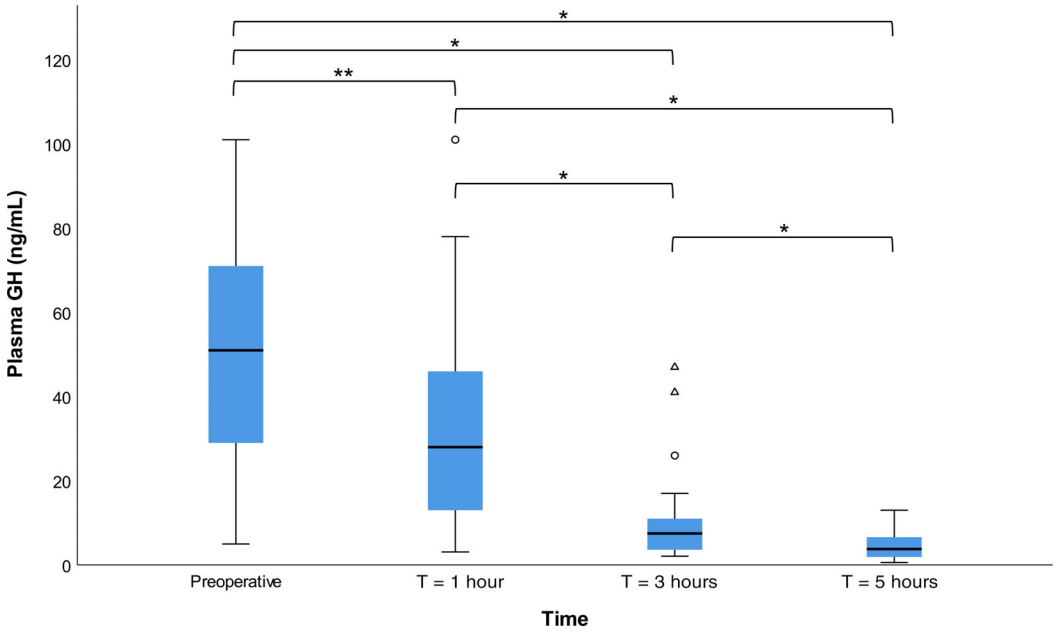

FIGURE 2 Plasma growth hormone (GH) concentrations before and 1, 3, and 5 hours after hypophysectomy in 23 diabetic cats with hypersomatotropism. *P < .001, **P = .006

discharge. The follow-up data for this cat showed survival of 822 days without the need for exogenous insulin. Two of the cats with elevated IGF-1 concentrations at the time of diagnosis (1192 and 1063 ng/mL), showed relatively normal IGF-1 and GH concentrations at the day of surgery (IGF-1:174 and 369 ng/mL, GH: 7.8 and 5.0 ng/mL, respectively). Somatotroph adenomas were confirmed with histopathology, and IGF-1 concentration decreased to <25 ng/mL in both cats at 14 days and 3 months after surgery.

3.5 | Follow-up

Major complications consisted of decreased tear production (n = 11), clinical signs of hypoglycemia after discontinuation of exogenous insulin (n = 4), and palate wound dehiscence (n = 3). In all cats with decreased tear production, eye lubricant treatment could be discontinued in the weeks postoperatively as tear production normalized. Cats with clinical hypoglycemia were treated with increased dosages of cortisone acetate, frequent small meals and IV glucose supplementation in case of severe clinical signs of hypoglycemia. Two of these cats belonged to the cohort in which plasma IGF-1 concentrations were measured repeatedly during the postoperative hospitalization period and these values confirmed rapid remission of hypersomatotropism. Rapid IGF-1 decline was demonstrated in the 2 weeks after surgery and the majority of the cats recovered without hypoglycemic events (Figure 3). Dehisced palate wounds were reoperated successfully. Based on advancing insights, electrocautery to incise the soft palate was replaced by incision of the oral mucosa using a scalpel blade no. 10 and from the 6th cat onward, major palate wound dehiscence was not seen anymore. Minor complications consisted of hypoglycemia without clinical signs (n = 5), self-limiting epistaxis within 24 hours after surgery (n = 2), and minor palate wound dehiscence which healed without specific treatment (n = 2). In 3 of the hypoglycemic cats (with plasma glucose concentrations of 3.1, 3.5 and 2.7 mmol/L, respectively), an inappropriately elevated or normal (within reference interval) endogenous serum insulin concentration was found (242, 12, and 4.1 mIU/L, respectively, reference interval 3.7-11.4 mIU/L). The esophageal feeding tube could be removed in all cats within the first weeks after hypophysectomy as they all demonstrated sufficient voluntary food intake. In all but 1 cat, voluntary water intake was seen within days after surgery. In the remaining cat, water was administered via the feeding tube and normal electrolyte and fluid balances were achieved and maintained when water intake was stimulated after discharge by adding water to its food.

After tapering insulin dosages postoperatively, 22/24 (92%) cats entered diabetic remission as demonstrated by normal blood glucose levels without exogenous insulin treatment. The 2 cats that remained diabetic improved to excellent glycemic control with lower exogenous insulin requirements (preoperatively: 1.2 and 0.9 IU/kg SC BID, postoperatively: 0.4 and 0.6 IU/kg SC BID, respectively). Based on advancing insights, treatment with oral diazoxide was initiated in 3 cats (2 temporarily) because of hypoglycemia after discontinuation of exogenous insulin. This treatment increased the plasma glucose concentration and resulted in markedly less clinical signs of hypoglycemia. All cats were treated with cortisone acetate and levothyroxine for the remainder of their lives. The majority of cats achieved normal fluid balances and plasma electrolyte concentrations with TID desmopressin administration. Of the cats with >6 months follow-up available, 11/19 (58%) needed desmopressin treatment permanently TID or BID as further tapering resulted in excessive urinary free water loss leading to polyuria. Advanced diagnostic imaging was repeated for follow-up evaluation in 1 cat, which entered diabetic remission

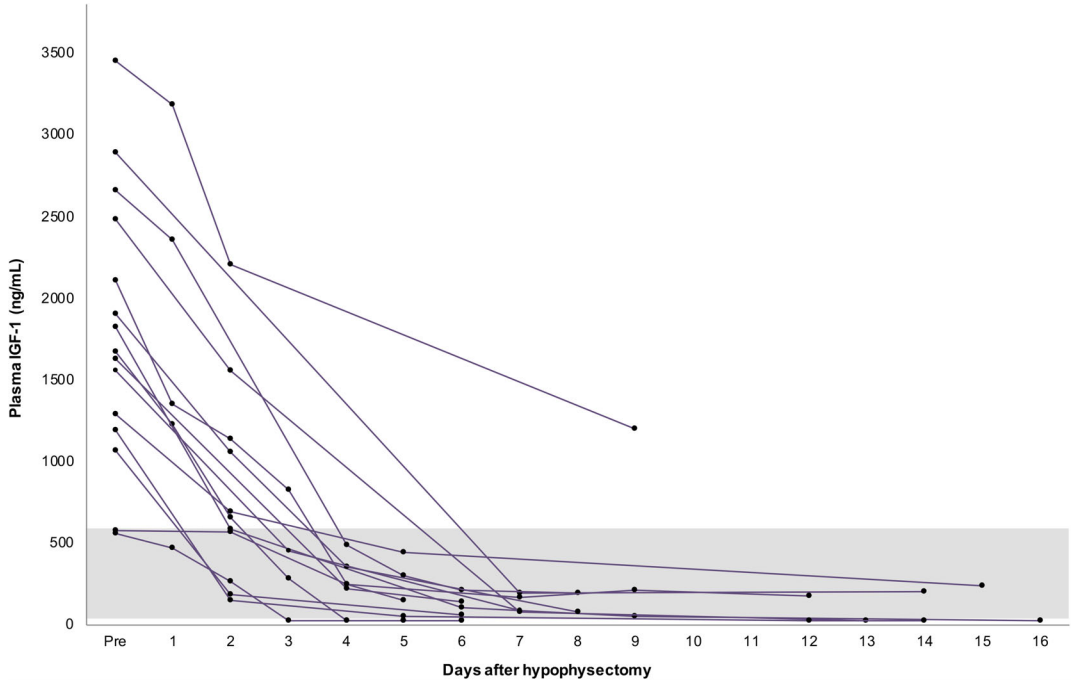

FIGURE 3 Plasma insulin-like growth factor-1 (IGF-1) concentrations before hypophysectomy and postoperatively in 15 cats with hypersomatotropism. The gray shaded area represents the plasma IGF-1 reference interval

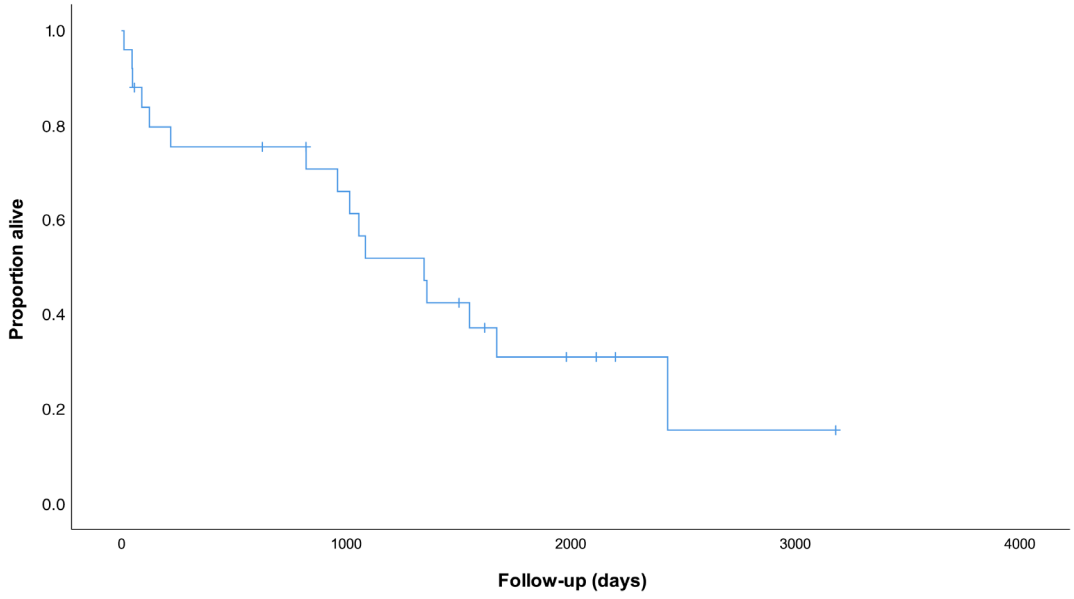

FIGURE 4 Kaplan-Meier survival analysis in 25 cats with hypersomatotropism that underwent hypophysectomy with all causes of death included. Vertical bars represent cats that were alive at the last point of follow-up

and showed no clinical signs. The contrast-enhanced CT scan revealed no signs of contrast enhancing tissue in the area of the pituitary fossa at 12 months postoperatively (Figure 1).

Cats were discharged from the hospital at a median of 7 days (range, 3-18 days) after hypophysectomy. Postoperative death within 4 weeks was restricted to 1 cat (4%). This cat (pituitary height 3.6 mm, P/B value 0.40; preoperative IGF-11840 ng/mL) died 11 days after uneventful hypophysectomy but was initially discharged after 5 days and already in diabetic remission. Despite careful monitoring and high initial (stress-dose) cortisone acetate doses at home, the cat was readmitted to the hospital 5 days after discharge because of seizures and hypoglycemia. Low plasma glucose concentration was corrected via IV supplementation; however, the cat's neurological condition did not improve, and it died the next day. Postoperative hypersomatotropism-related death was considered possible, but not confirmed, in 2 other cats (pituitary height 4.9 and 6.7 mm, P/B value

0.49 and 0.78, preoperative IGF-11900 and 1630 ng/mL, respectively) which were found dead 6 to 7 weeks after hypophysectomy because of unknown cause; these 2 cats were classified as treatment-related deaths in the survival analysis for hypersomatotropism- and hypophysectomy-related mortality. No other disease- or treatment-related deaths were reported thereafter, resulting in a censored survival of 88% for year 1, 2, and 3. Unrelated causes of death at later follow-up included kidney disease (2 cats), gastrointestinal disease (chronic enteropathy, obstipation, anorexia; 2 cats), neoplastic disease (2 cats), respiratory disease (lung edema, dyspnea; 2 cats), cholecystitis (1 cat), feline infectious peritonitis (1 cat), and severe anemia of unknown cause (1 cat). In 2 cats, the cause of death could not be confirmed definitely. Nine cats are still alive by the time of writing. Overall, median calculated survival time was 1347 days (95% confidence interval, 900-1794 days; range, 11-3180 days). With all causes of death included, overall 1-, 2-, and 3-year calculated survival rates were 76%, 76%, and 52%, respectively (Figure 4).

4 | DISCUSSION

This study demonstrates the beneficial outcome of hypophysectomy in cats with hypersomatotropism. When cats survived the critical postoperative period of 2 to 3 months, prognosis was excellent. The high percentage of diabetic remission and definitive cure exceeds outcomes of previously reported medical treatment and radiation therapy.[2,13,14,16-18] The most consistent effect of radiotherapy is the improvement or resolution of signs of neurological disease because of tumor size reduction; however, remission of hypersomatotropism and DM is often not achieved. In a recent publication on radiotherapy as treatment of hypersomatotropism in cats, stereotactic radiation therapy resulted in diabetic remission in 32% of the cats and in more than one third of these cats remission was only temporarily. Furthermore, a substantial proportion of the cats died of causes related to effects of the GH-producing pituitary tumor or treatment, for example, heart failure or neurologic disease.[18] The permanent diabetic remission rate of 92% and low disease- or treatment-related mortality in our cohort of cats indicate clear advantages of hypophysectomy as treatment of hypersomatotropism in cats.

The median age at presentation, breeds, and male predilection observed in this study are comparable to previous findings.[2] Besides hypersomatotropism as inclusion criteria, cats were also selected by referring vets as "able to be supplemented by mouth" with glucocorticoids and levothyroxine after hypophysectomy. The selection of good candidates for this definitive treatment should be kept in mind by clinicians interested in hypophysectomy for cats with hypersomatotropism.

Perioperative death rate in our cohort of cats was low (4%) and the observed complications generally mild. Decreased tear production is commonly seen in dogs and cats after hypophysectomy and was temporary in all cases in this study. Hypersomatotropism in cats often leads to thickening of the soft palate and covering of the sphenoid bone by thick folds of mucoperiosteum.[31] Based on the experience gained in this study with dehiscence of the soft palate, it is advised to refrain from using electrocautery to incise the soft palate in cats like is commonly done in dogs.

The cause of death of the cat that died within 4 weeks after surgery was related to hypoglycemia. Two other cats in which remission of hypersomatotropism was demonstrated died a relatively short time (6-7 weeks) after surgery at home where they were found dead without preexisting signs. No recent blood glucose measurements or postmortal examinations were available in these cases. It is therefore not definitive whether these mortalities were related to, for example, hypoglycemia or unrelated to the hypersomatotropism and treatment. However, these events were interpreted as the direct consequence of surgical intervention and rapid remission of hypersomatotropism leading to a possible state of hyperinsulinemia. Hypoglycemia has been found in multiple cats of this cohort after discontinuation of exogenous insulin. It is hypothesized that this is because of hyperinsulinemia, secondary to hyperplasia of the pancreatic beta-cells as a compensatory mechanism for the previous hypersomatotropic state associated with insulin resistance. This hypothesis is supported by the relative hyperinsulinemia found in 3 cats with hypoglycemia. Cortisone acetate supplementation can be increased to stimulate hepatic gluconeogenesis. If this effect is insufficient, administration of diazoxide can help to inhibit pancreatic insulin secretion, stimulate hepatic gluconeogenesis and glycogenolysis, and inhibit tissue use of glucose.[35] This drug has been used successfully in 3 cats in this study. Despite the possible gastrointestinal adverse effects, it is advised to have this drug available for treatment of hypoglycemic events after hypophysectomy in cats with hypersomatotropism. In many cats, remission of hypersomatotropism already occurred within the first week postoperatively. As the majority of these cats recovered uneventfully, it seems unlikely that the development of signs of hypoglycemia or even hypoglycemic crises can be predicted by determining the plasma IGF-1 concentration.

Diabetic remission is an important goal of hypophysectomy in cats with hypersomatotropism. Hypoglycemia seems to be the toll for surgical success and the described cases of hypoglycemia demonstrate the importance of thorough monitoring of the patient's demeanor and blood glucose levels in the postoperative period. However, the cat's demeanor can be affected by other factors including recovery from surgery, long travel homewards by plane or car, and the success of thyroid hormone and glucocorticoid supplementation. Finding the balance among these factors remains the most important challenge in an animal posthypophysectomy.

The high percentage of diabetic remission in this study shows the ability of the feline pancreatic beta-cells to recover, even after prolonged periods of poor glycemic control despite high exogenous insulin dosages. Hypersomatotropism, responsible for the development of DM, appears to rarely cause permanent, irreversible damage to the pancreatic endocrine cells, and insulin-responsive peripheral tissues. This is in sharp contrast with DM caused by spontaneous hypercortisolism in dogs, which is usually irreversible.[36]

Growth hormone concentrations are elevated in cats with hypersomatotropism; however, the GH assay is performed in only a few

specialized laboratories and not on a weekly basis. The plasma IGF-1 concentration reflects the GH secretion over the past 24 hours and has been shown to be diagnostic in cats with hypersomatotropism.[2,37,38] Reference ranges differ among laboratories in Europe but as a general rule, plasma IGF-1 >1000 ng/mL is considered consistent with hypersomatotropism. Previous investigations have however shown that IGF-1 values within the reference range do not exclude hypersomatotropism.[38,39] Also in the 1 cat in this study with an initial plasma IGF-1 concentration <1000 ng/mL, histopathology confirmed a somatotroph adenoma, the cat went into diabetic remission within a few weeks after surgery and was still alive by the time of writing of this manuscript. In addition, 2 cats with IGF-1 concentrations >1000 ng/mL at the time of diagnosis showed relatively normal IGF-1 and GH concentrations on the day of surgery. These fluctuations might reflect variations in time and support repeated evaluation of hormone levels in case of equivocal results. With respect to monitoring of remission of hypersomatotropism after hypophysectomy using plasma GH and plasma IGF-1 concentrations, the half-life of these hormones must be considered. The half-life of GH, which has a pulsatile secretion, is 10 to 20 minutes in humans, whereas protein bound IGF-1 has a relatively long half-life (hours).[2,12] It is therefore useful to monitor plasma GH concentration within hours after surgery, whereas the decline of plasma IGF-1 concentration only becomes apparent several days after surgery. This is in line with the observations in the cohort of cats in our study.

Based on pituitary height, 1 cat had a nonenlarged pituitary and the other cats had mild to severely enlarged pituitaries (ie, >4 mm). High-field MR imaging and contrast-enhanced CT allow for calculation of the pituitary height/brain area (P/B) value. Previously, the reference range for nonenlarged (P/B ≤ 0.31) versus enlarged (P/B > 0.31) pituitaries was established for canines.[40] This value enables correction for the size of the dog's skull, which is generally less indicated in felines with more consistent skull sizes. Nevertheless, the P/B value also gives additional information on the pituitary size in cats which is important for the pituitary surgeon. Based on previous experiences, it has been suggested that the upper normal P/B value for cats is most likely higher (closer to 0.40) compared to the value in dogs.[31] Indeed, the calculated P/B value of the cats in this cohort which had enlarged pituitaries based on pituitary height measurements ranged from 0.49 to 1.41, confirming that a P/B value reference value >0.40 can be used for assessment of enlargement in cats.

In the cats described in this study, the pituitary glands and associated adenomas were removed successfully resulting in confirmed remission of hypersomatotropism in 23/24 surviving cats. By the time of writing of this manuscript, recurrence as evidenced by an elevated plasma IGF-1 concentration was noted in none of the cats. Histopathology confirmed a somatotroph adenoma in all but 1 cats. In the latter cat, with a normal-sized pituitary gland (3.6 mm height), histopathology was nondiagnostic. Apart from a small tumor that may have been missed microscopically, it may also have been lost in surgery during controlled suction at the surgical site and, less likely, it cannot be excluded that no pituitary lesion was present and hypersomatotropism was because of a different etiology. GH-releasing hormone excess from a hypothalamic or peripheral tumor as a cause of hypersomatotropism is incidentally seen in humans and might have been present in 1 cat described previously.[2,3,5] In 2 cats, double adenomas with GH and ACTH positive cells were found on histopathology. Double adenomas have been described before.[11,41,42] No adrenocortical function test was performed in these cats before hypophysectomy, as the clinical picture was dominated by hypersomatotropism and DM.

In conclusion, hypophysectomy is an intensive treatment, both regarding the surgical procedure and the perioperative stabilization. However, when the investigations and procedure is performed in a setting with an experienced team consisting of an endocrinologist, neurosurgeon, and critical care specialist, hypophysectomy can provide an excellent prognosis with a high rate of complete remission for cats with hypersomatotropism and secondary insulin-resistant DM.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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