

Hypersomatotropism without concurrent diabetes mellitus in cats: 28 cases (2014-2024)

Diego Miceli^{1,2}, Stijn J. M. Niessen^{3,4,5}, Juan P. Rey Amunategui⁶, Florian K. Zeugswetter⁷, Gustavo Pompili⁶, Flavia Tavares⁸, Estela Molina⁶, Rodolfo Leal^{9,10}, Ignacio Espiñeira⁶, Doroteia Bota¹¹, Andrea Corsini¹², Federico Fracassi^{13,*}

¹Laboratory of Molecular Endocrinology and Signal Transduction, Institute of Experimental Biology and Medicine (CONICET), Buenos Aires C1428ADN, Argentina

²Veterinary Science Center, Maimonides University, Buenos Aires C1405, Argentina

³Royal Veterinary College, University of London, Hertfordshire AL9 7TA, United Kingdom

⁴Veterinary Specialist Consultations & VIN Europe, Hilversum 1215 JX, The Netherlands

⁵Michigan State University, Lansing 48823, United States

⁶Faculty of Veterinary Sciences, University of Buenos Aires, Buenos Aires C1427CWO, Argentina

⁷Department for Companion Animals and Horses, University Clinic for Small Animals, University of Veterinary Medicine, Vienna 1210, Austria

⁸E + VET Clinic, Rio de Janeiro 22640-000, Brazil

⁹CIISA—Centre for Interdisciplinary Research in Animal Health, Faculty of Veterinary Medicine, University of Lisbon, Lisbon 1300-477, Portugal

¹⁰Associate Laboratory for Animal and Veterinary Sciences (AL4AnimalS), Vila Real 5000-801, Portugal

¹¹AniCura Restelo Veterinary Hospital, Lisbon 1400-195, Portugal

¹²Department of Veterinary Medical Sciences, University of Parma, Parma 43126, Italy

¹³Department of Veterinary Medical Science, University of Bologna, Bologna 40064, Italy

*Corresponding author: Federico Fracassi, Department of Veterinary Medical Science, Faculty of Veterinary Medicine, University of Bologna, via Tolara di Sopra, 50, Ozzano dell'Emilia, Bologna 40064, Italy (federico.fracassi@unibo.it).

Abstract

Background: Hypersomatotropism (HST) in cats has predominantly been associated with diabetes mellitus (DM) and HST in nondiabetic cats is poorly described.

Hypothesis/Objectives: To describe the clinical presentation, clinicopathologic findings, and outcome of nondiabetic cats with presumed HST.

Animals: Twenty-eight client-owned cats.

Methods: Multi-site retrospective study based on medical records of nondiabetic cats seen at 10 institutions between 2014 and 2024 with presumed HST (elevated serum insulin-like growth factor-1 [IGF-1] $\pm$ clinical signs compatible with acromegaly $\pm$ documented pituitary enlargement). Clinical presentation, diagnostic findings, and survival times were reviewed.

Results: Twenty-eight cats with HST were included. Twenty-six cats were males, and 2 cats were females; mean age was 9.5 years ($\pm$ SD 3.5 years); mean body weight was 7.1 kg ($\pm$ SD 2.1 kg). The median serum IGF-1 concentration was 1236 ng/mL (range 704-2455 ng/mL). Nineteen of 28 cats (68%) had clinical signs possibly related to acromegaly: prognathia inferior (13/28), weight gain (12/28), broad facial features (10/28), abdominal enlargement (10/28), respiratory stridor (9/28), polyphagia (9/28), and signs of neurological disease (3/28). The most common clinicopathological abnormalities were hyperproteinemia (12/28), serum creatinine above the reference interval (RI) (10/28), and urinary specific gravity below the RI (9/28). Hypertrophic cardiomyopathy phenotype was identified in 8/17 cases. The most common comorbidity was chronic kidney disease (10/28). The median survival time after diagnosis was 24 months (range 1-103 months).

Conclusions and clinical importance: Hypersomatotropism can present without DM and should be considered in cats with signs suggestive of growth hormone excess or a pituitary tumor.

Keywords acromegaly, cats, GH excess, nondiabetic

Abbreviations ALIVE, Agreeing Language in Veterinary Endocrinology; BCS, body condition score; CKD, chronic kidney disease; CLIA, chemiluminescence; CT, computed tomography; DM, diabetes mellitus; GH, growth hormone; HCM, hypertrophic cardiomyopathy; HST, hypersomatotropism; IGF-1, insulin-like growth factor 1; MRI, magnetic resonance imaging; RI, reference interval; RIA, radioimmunoassay

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Introduction

Hypersomatotropism (HST) is a chronic metabolic disorder caused by hypersecretion of growth hormone (GH) and occurs in both humans and companion animals.¹ In the domestic cat (*Felis catus*), it is caused by a functioning pituitary adenoma (somatotropinoma) or hyperplasia of the *pars distalis* of the anterior pituitary gland.² The clinical presentation is the result of the combined action of the catabolic and diabetogenic effects of GH, the synergistic anabolic effects of insulin-like growth factor 1 (IGF-1) and GH, and potentially the space-occupying effect of the somatotropinoma.^{1,2} Hypersomatotropism is predominantly described in cats with concurrent diabetes mellitus (DM), being one of the most prevalent underlying causes of DM, with prevalence rates ranging from 12.5% to 25% among diabetic cats depending on the geographical area.^{3–5} In humans, acromegaly is most often associated with impaired glucose tolerance without DM and, in long-standing cases, with overt DM. The prevalence of DM in humans with acromegaly ranges from 12% to 38%, and when cases with impaired fasting glucose and impaired glucose tolerance are included, this prevalence increases from 16% to 54%.⁶ Therefore, most humans with acromegaly do not develop overt DM.⁶

Several case reports and studies describe HST in cats without concurrent DM, and it could be hypothesized that this condition is currently underdiagnosed.^{7–14} The prevalence rate in the general feline population without DM is unknown. Measurement of serum GH and IGF-1 concentrations is useful for diagnosis of cats with HST. A validated method for measurement of feline GH was not widely and commercially available. Human assays for feline IGF-1 are validated, readily available, and useful for screening because IGF-1 reflects 24-hour GH secretion and is a sensitive marker for GH excess.^{3,15,16} In addition, IGF-1 is not secreted in a pulsatile fashion like GH; therefore, a single sample collected at any time of the day might have diagnostic value.^{3,15,16} In a retrospective study, 6.7% of nondiabetic cats with previously assumed hypertrophic cardiomyopathy (HCM) had a serum IGF-1 concentration (>1000 ng/mL, radioimmunoassay [RIA]) in a range that is consistent with HST in diabetic cats from the United Kingdom.^{3,10} Likewise, a similar proportion of nondiabetic cats previously diagnosed with overweight/obesity (8.75%) or chronic kidney disease (CKD) (5.8%) had serum IGF-1 concentrations above this same cut-off value.^{11,12}

The pathogenesis, comorbidities, treatment, and short- and long-term prognosis of nondiabetic cats with HST are currently poorly described. Hence, the aim of this study was to describe a cohort of nondiabetic cats with presumed HST.

Materials and methods

Cases were retrospectively recruited based on a review of medical records from 2014 to 2024 at 10 veterinary institutions (referral centers): 6 from Europe, 3 from South America, and 1 from the United Kingdom.

Inclusion criteria

The diagnosis of *presumed* HST was based on a serum IGF-1 concentration above the upper limit of the reference interval (RI)

(ie, >700 ng/mL for RIA and >670 ng/mL for chemiluminescence [CLIA]),^{3,16} plus a combination of clinical signs or phenotypic changes consistent with acromegaly (eg, prognathia inferior, broad facial features, abdominal enlargement, weight gain, broadening of paws, polyphagia, respiratory stridor, and signs of neurological disease possibly due to space-occupying effect). If performed, the presence of pituitary enlargement on computed tomography (CT) or magnetic resonance imaging (MRI) was also considered. Total serum IGF-1 was measured by commercially available RIA or CLIA developed for humans and previously validated for cats.^{15,16} A cut-off of total IGF-1 >1000 ng/mL measured by RIA results in a 95% positive predictive value for HST in a population of diabetic cats from the United Kingdom.³ Similarly, the best cut-off value for IGF-1 measured by CLIA for the diagnosis of HST is 746 ng/mL (sensitivity, 84.4%; specificity, 97.2%).¹⁶

Only cats without DM were included. The absence of DM was confirmed by the lack of clinical signs of DM and lack of hyperglycemia/glucosuria, according to the Agreeing Language in Veterinary Endocrinology (ALIVE) criteria for the diagnosis of DM in cats (random blood glucose ≥ 15 mmol/L [270 mg/dL]).¹⁷ Cats with a history of overt DM were excluded.

Data recorded for each cat were signalment (age, breed, sex, neuter status, body weight, and body condition score [BCS]), history, clinical findings, complete blood count, serum biochemistry, urinalysis, and serum IGF-1 concentration. Body condition score was defined using a scale from 1 to 9, where 1 was emaciated, 5 was ideal, and 9 was extremely fat.¹⁸ Presence of comorbidities was also evaluated. The diagnosis of CKD and staging was based on history, physical examination, systolic arterial pressure, clinicopathological findings, and renal ultrasonography, according to the International Renal Interest Society guidelines.¹⁹ If performed, the results of abdominal ultrasonography and echocardiography were recorded (8 out of 10 were board-certified veterinary radiologists/cardiologists).^{20–23} Adrenomegaly was defined as short-axis height >4.8 mm.²⁰ Hypertrophic cardiomyopathy phenotype was defined as left ventricular wall thickness ≥ 6 mm.²³ If recorded, the systolic blood pressure was measured with oscillometric or Doppler devices, according to ACVIM consensus statement.²⁴ Treatments used for HST and survival time after diagnosis were assessed.

Pituitary height was measured on transverse images showing the largest cross-section of the hypophysis. Pituitary enlargement was defined as a dorsoventral height >4 mm on CT,^{25,26} or >3.3 mm transverse height on MRI.²⁷ Spin-echo T1-weighted MRI images were acquired before and immediately after the intravenous administration of a 0.1 mmol/kg bolus of gadoterate meglumine. Masses extending dorsal to the rim of the sella turcica were classified as pituitary macroadenoma.²⁸ Images were evaluated by a veterinary radiologist at each institution (8 out of 10 were board-certified veterinary radiologists).

Data analysis

Collected data were managed with an electronic spreadsheet (Microsoft Excel) and analyzed using a commercial statistical data analysis software program (Graph Pad Prism 8, GraphPad Software, Inc, San Diego, California). Continuous data were analyzed for normal distribution (Shapiro–Wilk test). Data were reported using median (range), mean (SD), or absolute and percentage frequencies, as appropriate. A Kaplan–Meier curve

Table 1 Signalment and clinical signs of nondiabetic cats with presumed HST ($n = 28$).

Signalment	
Age, years	9.5 (± 3.5)
Sex: Male	26
Female	2
Breed	23 DSH, 2 DLH, 1 Norwegian Forest, 1 Ragdoll, and 1 Bengal
Body weight, kg	7.1 (± 2.1)
BCS	6.6 (± 1.5)
Clinical signs	Number of cats in which this was present (percentage)
- Prognathia inferior	13 (46%)
- Weight gain	12 (43%)
- Broad facial features	10 (36%)
- Abdominal enlargement	10 (36%)
- Respiratory stridor	9 (32%)
- Polyphagia	9 (32%)
- Increased paw size	7 (25%)
- Degenerative arthropathy	4 (14%)
- Signs of neurological disease	3 (11%)

All values are expressed as mean and SD. Abbreviations: BCS = body condition score; DLH = domestic long-hair; DSH = domestic short-hair.

was generated to display survival from the time that HST was diagnosed. Data were censored if the animal was still alive or lost to follow-up at the end of the study period and survival time was reported as median (range).

Results

Cats

Thirty-nine cases were identified and evaluated. Eleven cats with IGF-1 values above the cut-off were excluded because they did not show clinical signs of acromegaly and the owners did not agree to perform intracranial imaging; 28 met the inclusion criteria. Thirteen were diagnosed at the Institute of Experimental Biology and Medicine (CONICET, Argentina), 6 by Veterinary Specialist Consultations (The Netherlands), 3 at the E + VET Clinic of Rio de Janeiro (Brazil), 2 at the University of Bologna (Italy), 2 at the University of Vienna (Austria), 1 at the University of Lisbon (Portugal), and 1 at the AniCura Restelo Lisbon (Portugal). Data on age, sex, breed, body weight, and BCS are summarized in Table 1.

Clinical signs

Nineteen out of 28 (68%) cats had phenotypic changes possibly consistent with acromegaly (Figure 1 and Table 1). Three out of 28 (11%) cats had signs of neurological disease, such as central blindness and head tremor. In 2/3 of these cases, polydipsia and polyuria were also reported. Two out of 28 (7%) cats had behavioral changes, such as aggression.

The main reasons for considering HST were an evident acromegalic phenotype (11/28, 39%) and overweight/obesity (8/28, 29%). Other reasons for referral were signs of neurological disease (3/28, 11%), respiratory stridor (2/28, 7%), and bilateral adrenal hyperplasia detected on ultrasonographic examination of 2 cats with

CKD (2/28, 7%). The remaining 2 cases were referred due to polydipsia and polyuria, and the presence of a pituitary enlargement; both cats were exposed to CT to investigate the possibility of diabetes insipidus.

Serum IGF-1 concentrations

The median serum IGF-1 concentration of the 28 cats was 1185 ng/mL (704–2455 ng/mL). Twenty-two samples were evaluated using RIA, while 6 samples were evaluated using CLIA. Of the samples evaluated by RIA, 19/22 (86%) of cats had serum IGF-1 concentrations > 1000 ng/mL and 3/22 (14%) of cats had serum IGF-1 concentrations between 700 and 1000 ng/mL. One of them (IGF-1: 941 ng/mL) did not present phenotypic changes compatible with acromegaly, but did present pituitary enlargement (pituitary height: 4 mm) (Figure 2). The other 2 cases (IGF-1: 963 and 983 ng/mL) were not examined by intracranial imaging, but did present acromegalic features. Of the samples evaluated by CLIA, 5/6 (83%) of cats had serum IGF-1 concentrations > 746 ng/mL and 1/6 (17%) of cats had serum IGF-1 concentrations between 670 and 746 ng/mL (Figure 2; IGF-1: 704 ng/mL and pituitary height: 6.3 mm).

Pituitary imaging

Intracranial imaging was performed in 20 cats (17 by contrast-enhanced CT and 3 by contrast-enhanced MRI) and pituitary abnormalities were detected in 18/20 (90%) cases (Figure 3). In the thin T1-weighted MRI series of 1 cat (pituitary height: 3.3 mm), there was a small (1.2 mm) hypointense focus before and after contrast, which was considered abnormal. In the 2 cases in which no obvious pituitary alteration was observed by CT, both cats showed mandibular prognathism, thickening of the frontal and parietal bones, and increased thickness of subcutis. In addition, both cats had serum IGF-1 concentrations > 1000 ng/mL (RIA) and phenotypic changes compatible with acromegaly (one case presented with prognathia inferior, broad facial features, and abdominal enlargement, while the other case presented with prognathia inferior, broad facial features, and increased paw size). More details of pituitary imaging and serum IGF-1 concentrations for each case are shown in Figure 2.

Clinicopathological, ultrasonographic, and echocardiographic findings

The most relevant clinicopathological abnormalities were hyperproteinemia (12/28), serum creatinine above the RI (10/28), urinary specific gravity below the RI (9/28), serum alanine aminotransferase activity above the RI (6/28), hypertriglyceridemia (4/28), and hypercholesterolemia (2/28). Further details of the clinicopathological findings are summarized in Table 2.

Serum fructosamine measurement was performed in 19/28 cases (median 320 μ mol/L range 183–426 μ mol/L) and results within the RI were observed in 14/19. In the remaining 5/19 cases, slight elevations above the upper limit of the RI were recorded, but in none of the repeated assessments were classic clinical signs of DM, hyperglycemia, or glucosuria observed or documented, respectively. The cases therefore did not meet the ALIVE criteria for a diagnosis of DM.¹⁷



Figure 1 Phenotypic changes consistent with acromegaly. (A) Prognathia inferior, (B) broad facial features, (C) increased paw size, (D) broad facial features and abdominal enlargement, and (E) abdominal enlargement.

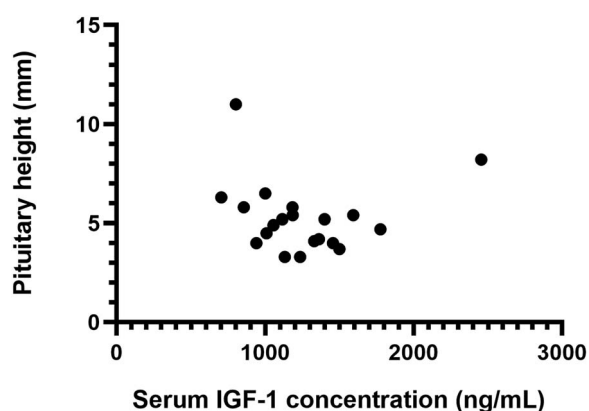


Figure 2 Serum IGF-1 concentration and pituitary dorsoventral height of the 20 nondiabetic cats with presumed HST.

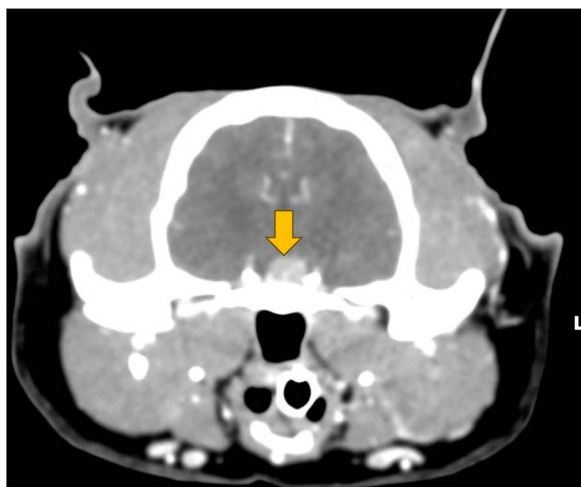


Figure 3 Suprasellar contrast-enhancing mass (arrow), highly suggestive of a pituitary gland neoplasia, likely a macroadenoma.

Abdominal ultrasonographic examination was performed in 17/28 cases and signs of possible bilateral chronic nephropathy (10/17, 59%), bilateral adrenomegaly (9/17, 53%), hepatomegaly

Table 2 Clinicopathological findings of nondiabetic cats with presumed HST ($n = 28$).

Clinicopathological finding	Number of cats in which this abnormality was present (percentage)
- Hyperproteinemia	12 (43%)
- Hyperalbuminemia	2 (7%)
- Serum creatinine above the RI	10 (36%)
- Urinary specific gravity below the RI	9 (32%)
- ALT activity above the RI	6 (21%)
- Hypertriglyceridemia	4 (14%)
- Anemia	3 (10%)
- Hypercholesterolemia	2 (7%)
- Hypercalcemia	2 (7%)

Abbreviations: ALT = alanine aminotransferase; RI = reference interval.

(6/17, 35%), and splenomegaly (6/17, 35%) were observed. Echocardiography was performed in 17/28 cats and a HCM phenotype was identified in 8/17 cases (47%).

Concurrent diseases

The most common comorbidity was CKD (10/28, 36%), with 8 cats classified as CKD IRIS stage 2, and 2 cats as CKD IRIS stage 3. Three cats (11%) had concurrent neoplasia (thyroid neoplasia, ACTH-producing pituitary tumor, and soft tissue sarcoma) and 4 cats (14%) had a recent history of neoplasia (2 soft tissue sarcoma, 1 mast cell tumor, and 1 colon carcinoma), which had been surgically removed within 1 year before the diagnosis of HST. The cat with HST and concurrent Cushing's syndrome had clinical signs compatible with hypercortisolism (alopecia, thin and inelastic skin, and abdominal distention), increased urinary cortisol creatinine ratio, and no suppression to the low-dose dexamethasone suppression test (0.1 mg/kg EV). Other concurrent diseases were: 2 cats had central diabetes insipidus (1 with history of head trauma and 1 possibly due to compression by a large pituitary

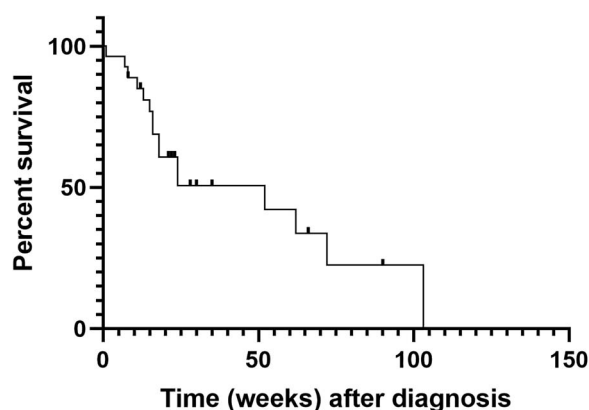


Figure 4 Kaplan–Meier curve to show overall survival of nondiabetic cats with presumed HST.

macroadenoma), 2 cats had lower airway diseases (exact type undetermined), 1 cat had rhinitis, and 1 cat had possible cholangitis (exact type undetermined). Systemic hypertension with moderate risk of target-organ damage (160–179 mmHg) was reported in 8/18 cases (44%), using Doppler (2/8) and oscillometric (6/8) devices.

Clinical outcome, development of DM, and survival

Two cats received radiotherapy and 1 cat underwent hypophysectomy. Two cats developed overt DM, 1 after 6 weeks of prednisolone administration post-radiotherapy (initial dose: 1.1 mg/kg q24h, with subsequent dose reduction) and the other after 6 months receiving prednisolone (0.4 mg/kg q24h) for suspected respiratory disease. At the time of writing, 13 cats were still alive, while 15 cats had died, resulting in a censored median survival time of 24 months (1–103) after diagnosis (Figure 4). Of those 15 cats, the probable immediate cause of death was identified in 11 cases: 4 due to cardiorespiratory complications, 3 due to worsening of CKD, 2 due to suspected pulmonary thromboembolism, 1 from invasion of regional lymph nodes (history of colon carcinoma), and 1 euthanized due to inability to drink and eat, blindness, and lethargy. Cause of death or euthanasia was not recorded for 4 cats.

Discussion

In this case series, 28 nondiabetic cats with presumed HST were identified from case summaries submitted by different secondary and tertiary care institutions across the world over an 11-year study period. This highlights that such a population exists and should be considered in a wide range of presentation types. If more cats with a similar phenotype or presentation had been proactively screened, more cases might have been uncovered, as is reported in nondiabetic cats with HCM, obesity, and CKD.^{10–12} This is supported by developments in human endocrinology, where initial estimates of the prevalence of acromegaly were 60/10⁶ persons.²⁹ After adjustment of the criteria to consider screening for this condition in a wider population, more incidental findings on CT/MRI and improved disease awareness, more recent studies suggest a prevalence rate of 122/10⁶ persons.³⁰

Hypersomatotropism in cats has previously been characterized by the presence of concurrent DM, with prevalence rates in diabetic cats varying across geographical areas (UK [24.8%], Netherlands [21.3%], Germany [17.5%], Argentina [14.9%], and Switzerland [12.5%]).^{3–5,31} Hypersomatotropism can be present without DM; however, the prevalence rate in the general cat population remains unknown. A study from North America among 4620 cats with presumed HST showed that only 44% had a history of DM on the submission form. Although the erroneous omission of such details could be suspected in at least a proportion, it further suggests the possible existence of a relevant nondiabetic HST population.³²

Hypersomatotropism implies a state of excessive production and secretion of GH, whereas acromegaly is the syndrome that results from this state of excessive GH production.³³ Clinical signs of acromegaly might not be present in HST, especially in mild or early stages of this progressive disease process.^{3,34,35} In both cases, GH excess in cats is described as the result of an acidophilic adenoma, carcinoma, or hyperplasia of the pituitary gland.² In this case series, most cases (68%) had phenotypic changes consistent with GH excess. The remaining 32% of cases had no evident clinical signs compatible with acromegaly.

The current clinicopathological diagnostic criteria for HST in diabetic cats could be controversial in some cases. This is because the IGF-1 cut-off values might be too high to detect milder or early stages of HST, and there is the difficulty in identifying an enlarged pituitary on CT in cases with a small pituitary tumor or hyperplasia. In the present case series, the diagnosis of presumed HST was supported by increased serum IGF-1 concentration above the cut-off established for diabetic cats (>1000 ng/mL [RIA] or > 746 ng/mL [CLIA]) in 24 cases (86%). Of the 4 cases with IGF-1 in the “gray zone” (700–1000 ng/mL [RIA] or 670–746 ng/mL [CLIA]),^{3,16} 2 had evidence of pituitary enlargement/mass, while the other 2 did not undergo intracranial imaging but did have evidence of physical changes compatible with acromegaly. It is important to emphasize that there is currently no IGF-1 cut-off to diagnose HST in cats without concurrent DM.^{10–12} Finally, in 2 cases with IGF-1 > 1000 ng/mL (RIA) and acromegalic features, interestingly, no pituitary enlargement was observed. Although historically intracranial imaging (CT and MRI) has been recommended as part of the diagnostic process for HST/acromegaly in cats, it is also recognized that pituitary imaging does not confirm or exclude hormonal dysfunction. Arguably, the assessment of the hormones themselves, in this case, serum IGF-1 as an indicator of GH excess, is a more direct means of establishing such a diagnosis. Another possibility is that these cases involved false positive IGF-1 elevation, but the presence of obvious clinical signs of acromegaly makes this scenario less likely. Indeed, it is crucial to consider that not all cats with HST are described as having evident pituitary enlargement on CT, or even MRI, making the diagnosis in these cases reliant on hormone/IGF-1 assessment.^{3,36,37} Cases of HST without evidence of pituitary alterations on CT/MRI have been confirmed by postmortem examination, showing histopathology consistent with acidophilic hyperplasia, not with well-demarcated adenoma.^{3,36} The presence of HST in 2 cats with IGF-1 < 1000 ng/mL (RIA) and acromegalic features, but without pituitary imaging, as well as in 2 cats with IGF-1 > 1000 ng/mL (RIA) and acromegalic features, but without pituitary enlargement, warrants additional tests with contrast-enhanced CT, MRI, GH measurement, or examination of the pituitary gland

(post-hypophysectomy/postmortem) to strongly support the diagnosis of HST.

It could also be argued that the reported cats were not diabetic because they had incidental or nonfunctional pituitary enlargement; however, the abnormally high serum IGF-1 concentrations and the low incidence of incidental pituitary enlargement in cats argue against such a hypothesis. In a cohort of cats undergoing CT imaging for reasons other than pituitary visualization, only 1.6% (1/62 cases) had an incidental pituitary enlargement.³

Hypersomatotropism/acromegaly in cats is assumed to have a gradual onset and development, with a period during which GH and IGF-1 concentrations are increased but DM has not yet developed; perhaps it will never develop within the lifetime of a cat. Likewise, a strong and long-standing clinical association exists between DM and the recognizable physical features of acromegaly.^{3,34,35} In the present case series, both these assumptions could be questioned. On the one hand, long-term follow-up (median 22 months, range 1-103 months) was performed in the current study and none developed overt DM, apart from the 2 cases that became diabetic after corticosteroid administration (both had initially presented with signs of neurological disease, and one of them also had aggression). Therefore, the development of DM in cats with HST appears to be related to factors that have yet to be elucidated and not necessarily to the duration of the increase in IGF-1 or GH. In fact, 3 of the cats with an obvious pituitary macroadenoma, implying a possible long duration of tumor growth, were included in this study. Indeed, pituitary tumors are understood to grow slowly in nature. On the other hand, 68% of the cases in this study had phenotypic changes compatible with acromegaly syndrome. Therefore, phenotypic changes of GH and IGF-1 excess would not necessarily correlate with the development of DM over time. It could be concluded that these cats with presumed HST have an adequate pancreatic β -cell reserve, enabling them to recover from or adapt to the diabetogenic effects of GH excess.^{3,38} Serum fructosamine concentrations were above the upper limit of the RI in 5/19 cats, but without meeting the diagnostic criteria for DM in any of these cases.¹⁷ Fructosamine concentrations are higher in male cats.³⁹ Likewise, cats with hypoproteinemia have low concentrations of fructosamine.⁴⁰ In this scenario, it could be hypothesized that hyperproteinemia would be correlated with serum fructosamine concentration above the RI; however, no significant changes in serum fructosamine were detected in cats with hyperproteinemia in one study.⁴⁰ Another possible explanation is a change in protein composition, with an increased presence of proteins that are more easily glycosylated. The 5 cats of this case series were males and 4 had hyperproteinemia, which is a common clinicopathologic finding in diabetic cats with HST, possibly reflecting increased protein synthesis induced by the GH/IGF-1 excess and dehydration associated with DM.^{34,35} On the other hand, it is possible that the average blood glucose concentration of these cats was slightly higher than that of the other cats, even though their blood glucose concentration was normal and they did not have glucosuria. Clinical signs of DM are evidenced when the cat presents blood glucose concentrations above the renal threshold for glucose reabsorption.⁴¹

In total, 93% of the cats in the present case series were males, as were the 5 nondiabetic cats with HST described in case reports, confirming the likely sexual predisposition in HST/acromegaly.⁷⁻⁹

Regarding the comorbidities associated with HST in the non-diabetic cats in this study, it is important to highlight that the most common concurrent disease was CKD, observed in 36% of cases. Diabetic cats with IGF-1 > 1000 ng/mL have higher serum creatinine concentrations than diabetic cats with lower IGF-1 concentrations.⁴ Likewise, CKD develops late in the course of the HST in 7/14 (50%) diabetic cats.³⁴ On the other hand, none of the 17 diabetic cats with HST included in a previous study and none of the reported cases of nondiabetic cats with HST describe concurrent CKD.^{7-9,36} In humans, one of the comorbidities of acromegaly is renal disease, the most common of which are glomerular hypertrophy, renal cysts, and nephrolithiasis.^{42,43} Further studies are needed to better understand this comorbidity in HST in cats, especially considering that CKD is a common condition in older cats.

Three cats had concurrent neoplasia at the time of diagnosis of GH excess. A report describes the pituitary gland of 2 nondiabetic cats with HST and strong positive labeling for ACTH, FSH, and MSH, consistent with a plurihormonal adenoma, but neither cat had characteristic features associated with hypercortisolism.⁸ Likewise, the cat with HST and hyperthyroidism could be classified as having concurrent endocrine neoplasia, and would be the first reported case with this combination of diseases.^{44,45} On the other hand, in the present case series it was observed that 4/28 cats had a recent history of neoplasia. In humans with acromegaly, long-term exposure to growth factors leads to complications such as the development of benign or malignant tumors.⁴⁶ One of the cats in the present study had a diagnosis of colon carcinoma, a tumor with a high incidence in humans with acromegaly.⁴⁶

A total of 44% of the nondiabetic cats with presumed HST had systemic hypertension (>160 mmHg).²⁸ The pathogenesis has not been elucidated and probably involves multiple factors.⁴⁷ For example, in this study, 36% of the cats had concurrent CKD. On the contrary, in a previous study including 17 diabetic cats with HST, evidence of hypertension was not observed in any cat.³⁶ In humans, hypertension is one of the most important and frequent complications of acromegaly, with a median frequency of 33.6% (ranging from 11% to 55%). It is associated with greater risk of cardiovascular disease, higher rate of hospitalization, and more relevant costs for disease management.⁴⁷

One of the cats in this study was 1 year old (IGF-1: 1851 ng/mL [RIA]), representing a case of presumed HST in a domestic kitten. This finding could resemble early-onset acromegaly in young humans, where excessive GH secretion before epiphyseal closure results in gigantism rather than classic acromegaly.^{48,49} Similar cases in humans demonstrate that early disease onset can manifest differently in terms of clinical phenotype, biochemical profile, and tumor behavior.^{48,49} Accordingly, the present observation raises the possibility that gigantism could occur in domestic cats. However, further studies are required to confirm this phenomenon and elucidate its underlying pathophysiology.

The present study has several limitations. First, its retrospective and multicenter nature precluded access to some data, and involved case records from different centers with different methods of measuring IGF-1. In addition, the recorded clinical signs were not standardized beforehand. Secondly, we note the lack of validated serum IGF-1 cut-off values in the nondiabetic population. Thirdly, there is a need to introduce a cohort named "presumed HST." Nonetheless, the authors deem it justified to include this group, since excluding it would potentially leave this cohort of cats "under the radar." It was also not possible to perform specific

tests to study the insulin sensitivity of these nondiabetic cats in detail. Finally, the lack of postmortem examination to evaluate pituitary abnormalities was a limitation.

In conclusion, this case series describes nondiabetic cats with presumed HST. It highlights that HST should be considered in cats without concurrent DM. Most cases were males (93%) and presented with phenotypic changes compatible with acromegaly (68%); therefore, the diagnosis of HST should not be ruled out in cats with obvious physical changes but without DM. Prognathia inferior, broad facial features, and weight gain were the most common clinical signs; the most common concurrent disease was CKD. Given the increasing evidence over the last few decades that the relatively high prevalence of HST in diabetic cats is unquestionable in parts of the world, making it one of the most common endocrinopathies in the species, and the lack of evidence regarding HST in nondiabetic cats, further studies should be undertaken to properly define the relevance of this condition in the general cat population. A focus on screening a wider range of presentation types (eg, HCM, obesity, and CKD) could uncover a larger nondiabetic HST group among cats. Increased awareness of suspected cases would make early diagnosis, prevention of comorbidities and treatment more effective and appropriate, as has been the case in humans.

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Author contributions

Diego Daniel Miceli (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing), Stijn Johannes Maria Niessen (Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing—review & editing), Juan P. Rey Amunategui (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing), Florian Karl Zeugswetter (Conceptualization, Investigation, Methodology, Supervision, Validation, Writing—review & editing), Gustavo Pompili (Investigation, Methodology, Supervision, Visualization, Writing—review & editing), Flavia Tavares (Investigation, Methodology), Estela Molina (Investigation, Methodology), Rodolfo Oliveira Leal (Investigation, Methodology, Supervision, Writing—review & editing), Ignacio Espiñeira (Investigation, Methodology), Doroteia Isabel Bota (Investigation, Methodology), Andrea Corsini (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing—original draft, Writing—review & editing), and Federico Fracassi (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing)

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The authors declare no off-label use of antimicrobials.

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The authors declare human ethics approval was not needed for this study.

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