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Acromegaly in humans and cats: Pathophysiological, clinical and management resemblances and differences

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ABSTRACT

Objective: Acromegaly is a disorder associated with excessive levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). In general, GH/IGF-1 excess leads to morphologic craniofacial and acral changes as well as cardiometabolic complications, but the phenotypic changes and clinical presentation of acromegaly differ across species. Here, we review the pathophysiology, clinical presentation and management of acromegaly in humans and cats, and we provide a systematic comparison between this disease across these different species.
Design: A comprehensive literature review of pathophysiology, clinical features, diagnosis and management of acromegaly in humans and in cats was performed.
Results: Acromegaly is associated with prominent craniofacial changes in both species: frontal bossing, enlarged nose, ears and lips, and protuberant cheekbones are typically encountered in humans, whereas increased width of the head and skull enlargement are commonly found in cats. Malocclusion, prognathism, dental diastema and upper airway obstruction by soft tissue enlargement are reported in both species, as well as continuous growth and widening of extremities resulting in osteoarticular compromise. Increase of articular joint cartilage thickness, vertebral fractures and spine malalignment is more evident in humans, while arthropathy and spondylosis deformans may also occur in cats. Generalized organomegaly is equally observed in both species. Other similarities between humans and cats with acromegaly include heart failure, ventricular hypertrophy, diabetes mellitus, and an overall increased cardiometabolic risk. In GH-secreting pituitary tumours, local compressive effects and behavioral changes are mostly observed in humans, but also present in cats. Cutis verticis gyrata and skin tags are exclusively found in humans, while palmigrade/plantigrade stance may occur in some acromegalic cats.
Serum IGF-1 is used for acromegaly diagnosis in both species, but an oral glucose tolerance test with GH measurement is only useful in humans, as glucose load does not inhibit GH secretion in cats. Imaging studies are regularly performed in both species after biochemical diagnosis of acromegaly. Hypophysectomy is the first line treatment for humans and cats, although not always available in veterinary medicine.
Conclusion: Acromegaly in humans and cats has substantial similarities, as a result of common pathophysiological mechanisms, however species-specific features may be found.

Abbreviations: AIP, Aryl hydrocarbon receptor interacting protein; cDNA, Complementary deoxyribonucleotidic acid; DNA, Deoxyribonucleotidic acid; CT, Computerized tomography; GH, Growth hormone; GHRH, Growth hormone releasing hormone; GNAS, Guanine nucleotide binding protein alpha stimulating activity polypeptide; GPR, G-protein coupled receptor; IGF-1, Insulin-like growth factor 1; MAX, Myc-associated factor X; MEN1, Multiple endocrine neoplasia type 1; MRI, Magnetic resonance imaging; PIIP, Type III procollagen propeptide; SDHx, Succinate dehydrogenase; SRT, Stereotactic radiation therapy; SSTR, Somatostatin receptor.

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1. Introduction

The word "acromegaly" was coined by Pierre Marie, in the late 19th century from the Greek "akron", meaning 'tip or extremity', and "megas", meaning 'great'. However, reports of clinical signs compatible with acromegaly have been made as early as 1567 [1]. In cats, the first report dates from 1976 [2]. Acromegaly, or hypersomatotropism, is an endocrine disease that can affect both humans and cats. Acromegaly is characterized by an excessive production of growth hormone (GH), usually by a GH-secreting pituitary tumour in both species. In cats, a clear distinction between hypersomatotropism and acromegaly is usually made. While hypersomatotropism implies only a state of excess GH, acromegaly refers to the syndrome and associated clinical signs that result from GH excess. Hypersomatotropism may or may not result in acromegaly in cats, especially in the earlier stages of the disease [3].

Chronic excessive GH levels lead to increased synthesis of insulin-like growth factor 1 (IGF-1) by the liver [4]. High IGF-1 concentrations promote somatic overgrowth, which culminates in a constellation of signs and symptoms, including several acromegaly-related morphologic features, as well as cardiometabolic and skeletal complications [5].

We aimed to review the pathophysiology and clinical features of acromegaly in humans and cats in a systematic comparative manner, highlighting the overlapping and distinctive features of the disease in both species. Additionally, by identifying important similarities, we aimed to assess the potential use of cats as the animal model *par excellence* for the study of acromegaly in human medicine and gain further insights into this complex disease. On the other hand, the current knowledge of the disease in humans, reviewed here, can also benefit the understanding and management of acromegaly in cats.

2. Epidemiology and pathophysiology

2.1. Humans

Acromegaly is a rare disease affecting humans, with an estimated annual incidence of 7.7–10 cases per million population per year, and with a prevalence ranging from 3.6 to 13 cases per 100,000 individuals [6–10]. Acromegaly is mostly diagnosed during the 5th decade of life, and is associated with an increased mortality risk when untreated, particularly in older patients and in women [11–15].

Over 95% of patients diagnosed with acromegaly harbour a GH-secreting pituitary tumour, which stimulates the synthesis of IGF-1 by the liver, leading to somatic overgrowth and several acromegaly-related manifestations, such as cardiometabolic and skeletal complications [6,9]. Such pituitary tumours commonly arise from somatotroph cells, and may display different granulation patterns: densely-granulated, sparsely-granulated or mixed pattern. Densely-granulated somatotroph tumours represent approximately 50% of the cases, and are typically smaller and respond better to somatostatin analogues, whereas sparsely-granulated somatotroph tumours are more common in younger individuals and are often associated with an invasive behaviour as well as with poorer response to medical therapy [6,9,15]. Somatic mutations in the guanine nucleotide binding protein alpha stimulating activity polypeptide gene (*GNAS)* are responsible for 40% of sporadic GH-secreting pituitary tumours [16,17]. Environmental factors may also contribute for the onset of this disease in humans, as suggested by data from an Italian study reporting increased prevalence of acromegaly in highly-polluted areas [18].

Acromegaly may also be caused by the ectopic hypersecretion of GH or Growth Hormone-Releasing Hormone (GHRH) by a hypothalamic tumour or by a neuroendocrine tumour [6,19].

Acromegaly may occur in a familial setting, as part of a syndrome or in isolation. The syndromic forms of acromegaly include: i) multiple endocrine neoplasia type 1 (MEN1), most typically due to GH-secreting or GH and prolactin-secreting pituitary tumours, concomitantly with primary hyperparathyroidism and pancreatic neuroendocrine tumours, but GH or GHRH excess may also derive from a MEN1-related neuroendocrine tumour [20,21]; ii) MEN type 4 iii) "3PAs syndrome" due to mutations in the genes for succinate dehydrogenase *(SDHx)* or Myc-associated factor X (*MAX);* iv) Carney complex, which is associated with pituitary hyperplasia, mucosal and atrial myxomas, adrenal hyperplasia and hyperpigmentation; and also, iv) McCune-Albright syndrome, a hypersecretory endocrinopathy which comprises pituitary hyperplasia or adenoma, hyperthyroidism, hypercortisolism, hyperprolactinemia, cafe-au-lait pigmentation and polyostotic fibrous dysplasia. In contrast, familial acromegaly or gigantism may occur in isolation due to mutations in the aryl hydrocarbon receptor-interacting protein (AIP) [22], or more rarely, in the setting of X-linked acrogigantism due to G-protein coupled receptor 101 gene *(GPR101)* microduplications [6,23–27].

2.2. Cats

Hypersomatotropism is thought to affect 1 in 800 cats in the United Kingdom, thus being about 10 times more prevalent than in humans [28,29]. Feline hypersomatotropism is closely related with diabetes mellitus, with about 15–25% of diabetic cats exhibiting excessive levels of IGF-1 [28,30]. Earlier studies reported that 100% of cats with hypersomatotropism had diabetes, however it is currently known that hypersomatotropism may also occur in non-diabetic cats [31,32]. Cats with hypersomatotropism tend to be older/geriatric (mean age at diagnosis 11.3 years, for a median lifespan of 14 years, with an interquartile range of 9–17 years [33]), with 70% being neutered males; this is similar to cats with diabetes without GH/IGF-1 excess [34].

Like in humans, feline hypersomatotropism usually results from a neoplastic or hyperplasic transformation of somatotroph cells in the anterior pituitary, predominantly in the form of a pituitary adenoma [35]. In cats, such pituitary tumours normally secrete only GH [36], contrasting with humans where prolactin co-secretion may occur in up to 30% of GH-secreting pituitary adenomas [34,37]. Plurihormonal tumours have also been reported in cats, with increased adrenocorticotropic hormone (ACTH) and α-melanocyte-stimulating hormone (α-MSH), as well as increased GH [36,38,39].

Some environmental causes of feline hypersomatotropism have been suggested. Higher levels of organohalogenated contaminants have been found in cats with hypersomatotropism in comparison with healthy cats or diabetic cats, suggesting a possible connection between these endocrine-disrupting chemicals and feline hypersomatotropism [40]. Hypersomatotropism may also decrease the capacity to metabolize persistent chemicals like polychlorinated biphenyls [34,37].

Like in humans, hypersomatotropism in cats may also have a genetic component. In one study, 2 out of 10 cats with hypersomatotropism had a single non-conservative single nucleotide polymorphism in exon 1 of the *AIP* gene, while no *AIP* mutation was present in 10 control cats [41]. MEN-1 like syndrome has also been identified in cats, although no GH excess was detected [42,43]. Thus, genetic causes of hypersomatotropism in cats are yet to be described. [42]

3. Clinical features in humans and cats with acromegaly

3.1. Facial features

3.1.1. Humans

Clinical features of acromegaly usually show an insidious course, and subtle physical changes may be traced back in up to a decade before the diagnosis [6]. The most common manifestations include facial dysmorphia and acral overgrowth, leading to a particular acromegaloid appearance. A coarse face with frontal bossing, enlarged nose and ears, fleshy lips, prognathism, protuberant cheekbones and wrinkles are typical facial features of acromegaly (Fig. 1a-d) [6,9]. Other features may be found, such as maxillary prominence with dental malocclusion, increased interdental space (i.e. diastema) and macroglossia (Fig. 1c-d).

Besides contributing to esthetical compromise, these changes may also result in partial obstruction of the respiratory tract, leading to obstructive sleep apnoea, excessive snoring and narcolepsy [6,9,44,45]. Progressive hoarse voice in acromegaly results from laryngeal and paranasal sinuses hypertrophy [46].

3.1.2. Cats

Like in humans, facial bone growth leads to broad and prominent facial features in cats (Fig. 1e-f), increased width of the head, enlargement of the skull, inferior prognathia (Fig. 1g) and dental diastema (Fig. 1h). In the upper airways, soft tissue growth leads to inspiratory stridor and/or increased reporting of "snoring" by owners in 38% of cats with acromegaly [34,37,47]. In one study from Buenos Aires, physical changes consistent with acromegaly were observed in 61% of diabetic cats with excess GH [30]. In other studies, however, physical changes were only observed in 5–24% of a similar population [48,49]. In a series of 68 diabetic cats with hypersomatotropism, frontal and parietal bones as well as the mandibular rami were thicker, and the distance between the zygomatic arches was greater than in control cats. The skin and subcutis dorsal to the frontal bone, lateral to the zygomatic arch and ventral to the mandibular rami were also thicker in cats with hypersomatotropism. Prognathia inferior and signs of temporo-mandibular joint malformation were more often observed in cats with hypersomatotropism [50].

Broad facial features have also been reported in up to 37% of cats with acromegaly and prognathism in 18% [47].

3.2. Extremities

3.2.1. Humans

The enlargement of the extremities is a key feature of acromegaly (Fig. 2a-b). Continuous growth and widening of hands and feet, often revealed by the increase in ring and shoe size, should raise suspicion of acromegaly [6,9,51], although there are also other conditions unrelated to GH/IGF-1 that may lead to acral enlargement and/or acromegaloid appearance (pseudoacromegaly) [52,53].

3.2.2. Cats

The enlargement of extremities may also occur in cats, with large and clubbed paws, with distal limbs exhibiting a clubbed appearance (Fig. 2c) [34]. Increase in joint space secondary to thickening of the articular cartilage and cortical thickening contribute to enlargement of extremities, as well as periarticular periosteal reaction and osteophyte proliferation [54]. Joint stiffness and pain has been reported in 10% of cats with acromegaly and clubbed extremities in 13% [47].

3.3. Skeletal manifestations

3.3.1. Humans

Humans with acromegaly often show osteoarticular compromise due to IGF-1 induced increased bone metabolism. Skeletal changes in patients with acromegaly are mainly induced by excessive levels of IGF-1, and typically include: mono or polyarticular arthropathy, with painful, swollen and stiff joints (in about 70% of cases), carpal tunnel syndrome, in response to local fluid retention and wrist swelling (in more than half of patients), generalized increase of articular joint cartilage thickness, ossification of ligaments and vertebral fractures which jeopardize patients' mobility and quality of life [55–58]. Skeletal deformities may be severe and ultimately change rib cage structure, and spine alignment with dorsal kyphosis scoliosis in response to anteroposterior vertebral growth, widened disc spaces, osteoporosis, and vertebral fractures; calvaria thickening have also been reported in patients with acromegaly (Fig. 3a-d) [55,57–60].

3.3.2. Cats

In acromegalic cats, increased bone and cartilage growth can lead to arthropathy and *spondylosis deformans*. Radiographic changes include periarticular periosteal reaction and osteophytes with soft tissue swelling and collapse of the joint spaces (Fig. 3h). Although these findings are compatible with osteoarthritis, lameness is not often described in affected cats [54]. In fact, the pathogenesis of acromegalic arthropathy in cats is thought to be noninflammatory, with cartilage hypertrophy and hyperplasia leading to the disruption of joint geometry and chondrocyte metabolism [54,61]. Thickened skull bone may also be found in acromegalic cats (Fig. 3f-g).

Fig. 1. Acromegalic facial appearance in humans (a-d) and cats (e-h). Acromegalic features in humans include large faces (a-b), frontal bossing (b), enlarged nose and ears (a-b), fleshy lips (a-c), prognathism (b), protuberant cheekbones (a-b), dental malocclusion, increased interdental space (c) and macroglossia (d). Acromegalic cats may exhibit similar characteristics, including broad facial features (e, f), prognathism (f,g) and increased interdental space (h). Pictures a-h are unpublished original images.

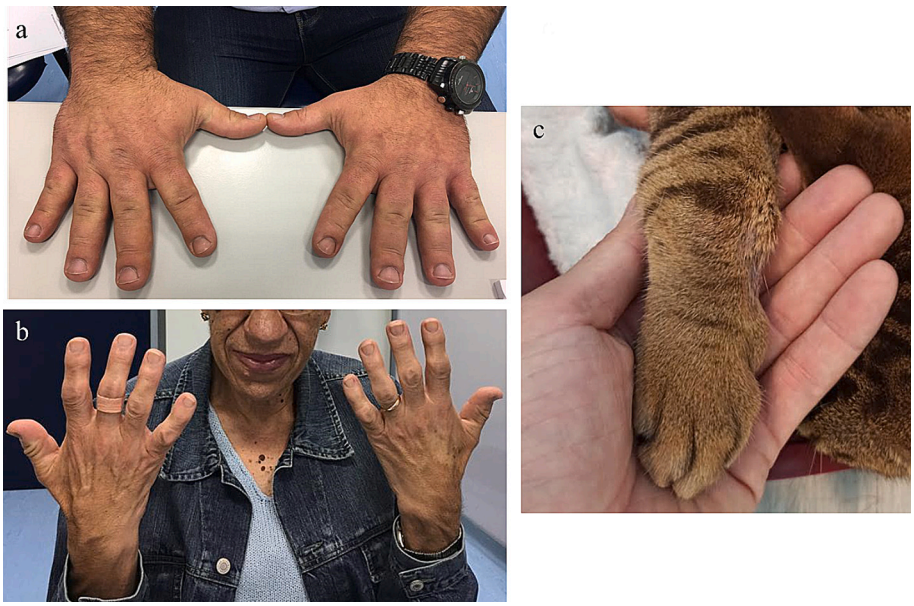

Fig. 2. Acral extremities enlargement in humans (a-b) and cats (c-d) with acromegaly. Patients with acromegaly may present with widened hands (a-b) and feet. Cats with acromegaly present with "clubbed paws" due to acral enlargement of extremities (c-d). The sources from the pictures are: a-c) unpublished original images.

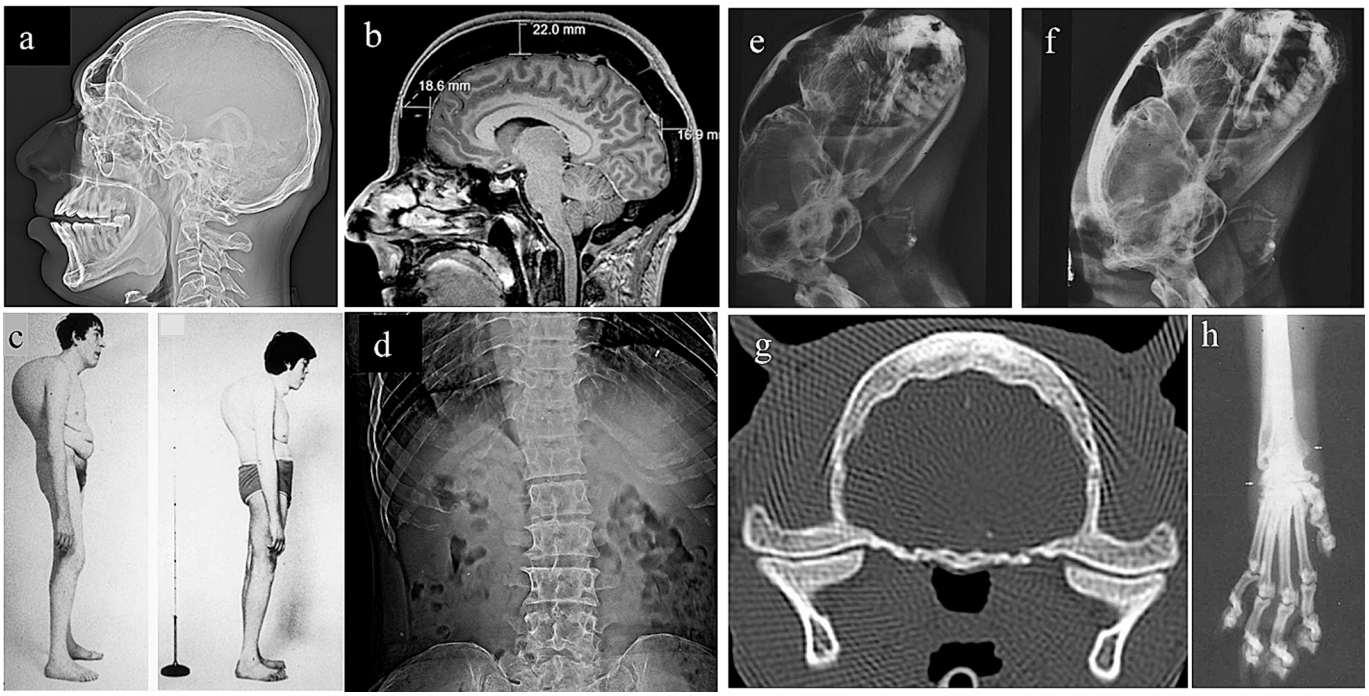

Fig. 3. Skeletal features of acromegaly in humans (a-d) and cats (e-h). Skull X-ray and Computed Tomography (CT) scan of patients with acromegaly may show increased calvaria thickness, frontal sinus overgrowth and malocclusion of teeth with prognathism (a-b). Spine alignment may be compromised and dorsal kyphosis scoliosis may occur (c) increased disc-facet and intervertebral joint space with mild kyphosis of lumbar vertebrae, hyperostosis of T11-L3 anterior vertebrae body and posterior scalloping of the lower lumbar vertebrae may be seen in frontal spine X-ray (d). Cats with acromegaly may also present with thickening of the skull, which can be seen on X-ray (skull of the same cat before (e) and after developing acromegaly (d)) or on CT scan (g). Osteoarthritis is also a common finding in acromegalic cats, with associated soft tissue swelling, collapse of joint spaces and periarticular periosteal reaction (h). The sources from the pictures are: a,d) Jones, Acromegaly. Reference article, Radiopaedia.org, https://doi.org/10.53347/rID-5748 (accessed on 19 Dec 2023); b) Cosme 2023 Med Clin (Barc) [PMID: 36456415]; c) Whitehead 1982 Clin Endocrinol (Oxf) [PMID: 7165969]; e-f) Greco 2012 Top Companion Anim Med [PMID: 22958795]; g) Fracassi 2016 JFMS Open Rep [PMID: 28491423]; h) Peterson 1990 J Vet Intern Med [PMID: 2401966].

3.4. Organomegaly

3.4.1. Humans

There is a tendency for generalized organomegaly in patients with acromegaly, often presenting with enlarged thyroid, salivary glands, tongue, liver, spleen, kidney, heart (Fig. 4b) and prostate. An abnormally long and large colon, termed dolicomegacolon, may also be present and carries the risk of abnormal intestinal rotation and volvulus (Fig. 4a) [62,63].

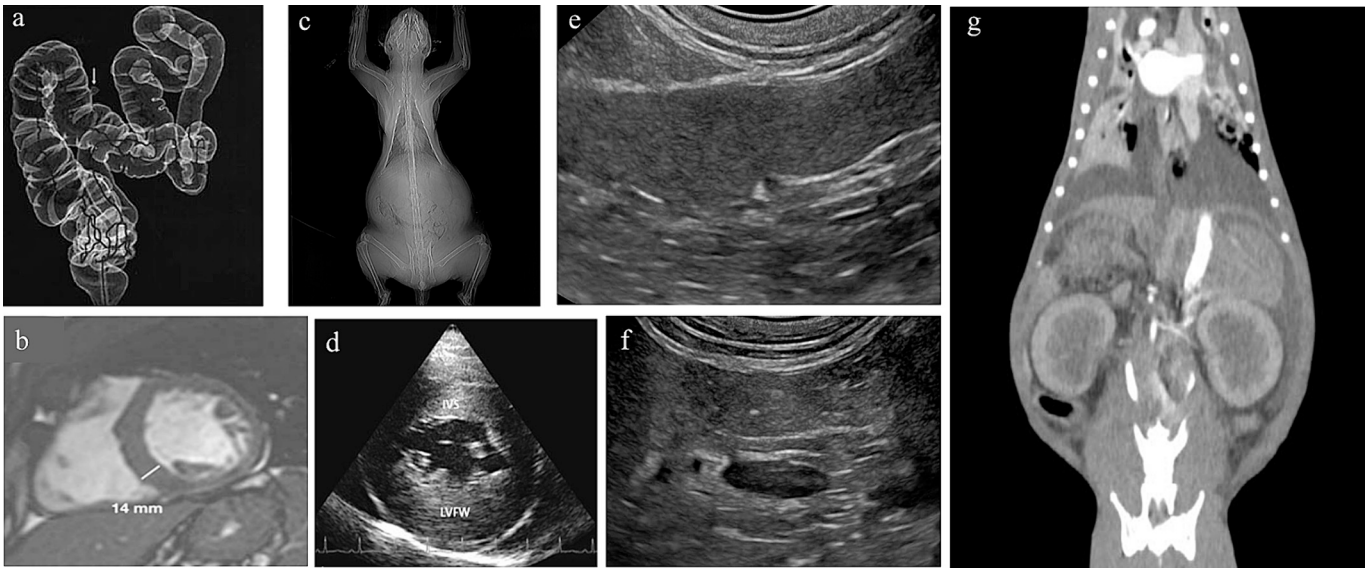

Fig. 4. Organomegaly examples in humans (a-b) and cats (c-g) with acromegaly. Computed tomography (CT) colonoscopy of a patient with acromegaly showed a large colon - dolicomegacolon (a); cardiac magnetic resonance imaging may identify marked left ventricular hypertrophy in acromegaly (b). Cats with acromegaly also present with organomegaly: generalized abdominal distension may be noted on X-ray (c); cardiac ultrasound may show signs of hypertrophic cardiomyopathy, with concentric thickening of the left ventricle (d); ultrasound may show enlarged spleen and adrenal glands (e-f); CT scan may show exuberant enlargement of the kidneys (g). The sources from the pictures are: a) Resmini 2009 J Clin Endocrinol Metab [PMID: 18957501]; b) Bogazzi 2010 J Endocrinol Invest [PMID: 31143230]; c) Niessen 2015 PLoS One [PMID: 26023776]; d) Ferasin 2012 In Practice, https://doi.org/10.1136/inp.e2271 (accessed on 19 Dec 2023); Pictures e-g are unpublished original images.

3.4.2. *Cats*

Abdominal enlargement may be noted in cats with acromegaly due to GH/IGF-1 excess-related organomegaly (Fig. 4c). Hepatomegaly, splenomegaly, renomegaly, as well as enlargement of the adrenal glands and pancreas have been reported (Fig. 4e-g) [37,64].

3.5. *Cardiovascular and metabolic comorbidities*

3.5.1. *Humans*

Cardiovascular disease represents a major cause of morbidity and mortality in patients with acromegaly [6]. Chronic excess of GH and IGF-1 lead to hypertension, left ventricular hypertrophy and diastolic dysfunction, which are often the first cardiovascular manifestations of acromegaly [65,66]. Heart failure, arrhythmia and valvular disease may also occur in acromegaly [67,68]. Metabolic comorbidities such as dyslipidaemia, insulin resistance, glucose intolerance or diabetes owing to the lipolytic and insulin-antagonistic effects of GH may also increase the cardiovascular risk [9,15,69]. Diabetes may be identified in 19–28% of patients with acromegaly [70].

3.5.2. *Cats*

Cardiovascular abnormalities in cats with hypersomatotropism include systolic murmur (present in 18% of cats with acromegaly [47]), cardiomegaly, cardiomiopathy and ventricular hypertrophy (Fig. 4d); congestive heart failure may also occur in some acromegalic cats [71]. Many of the metabolic complications seen in cats with hypersomatotropism may be attributed to diabetes rather than to GH/IGF-1 excess. Cats usually present with polyuria/polydipsia and polyphagia. However, polyphagia (and weight gain) independent of glycaemic control and extreme polyphagia (due to stimulation of the hunger centre by GH) are more indicative of hypersomatotropism than diabetes mellitus [34]. Insulin resistance or increased glycaemic variability, in the absence of other causes, is often the only clue pointing towards feline hypersomatotropism in diabetic cats [72]. GH, especially in carnivores, has a powerful diabetogenic activity and appears to provoke hyperglycaemia by inducing peripheral insulin resistance [34]. In one study involving 14 acromegalic cats, after prolonged illness, half of them developed azotemia and signs of renal disease [54]. Cats in general are prone to developing chronic kidney disease, with some studies reporting a prevalence that can reach close to 70% in geriatric cats [73]. However, diabetic nephropathy is not commonly reported and chronic kidney disease is usually linked to chronic interstitial glomerulonephritis. In feline acromegaly, however, the pathogenesis of kidney disease is not entirely clear. Inflammatory interstitial changes are mild or non-existent in acromegalic cats, and pathological changes have been characterized as diffuse thickening of the mesangium, resembling diabetic glomerulopathy or glomerulosclerosis lesions seen in humans [54].

3.6. *Local tumour effects*

3.6.1. *Humans*

The local growth of a pituitary tumour may be accompanied by severe headaches, which are particularly common in acromegaly [74], as well as visual field defects, and more rarely, cranial nerve palsies, diplopia, facial pain, and/or compression of the hypothalamus or the frontal lobe [9,65,75,76]. Pituitary stalk compression due to large pituitary tumours may contribute to hyperprolactinemia, which can lead to galactorrhoea and hypogonadotropic hypogonadism that can translate clinically as menstrual disturbances in women, and erectile dysfunction and low libido in male patients [6,77]. Hypopituitarism due to the mass effect on the normal pituitary gland may occur in up to 20% of patients [6,9,75].

3.6.2. *Cats*

Pituitary mass growth may have consequences in acromegalic cats such as peripheral blindness or mental dullness, but these might be difficult to recognise in early stages of the disease [34]. In cats with large pituitary masses, overt signs of central nervous system dysfunction may appear, such as seizures, circling, complete blindness, ataxia, tetraparesis and altered mentation [31].

3.7. Other clinical features

3.7.1. Humans

Patients with acromegaly are more prone to depression, anxiety, apathy and low self-esteem than healthy subjects [78–82]. Skin problems are also common in patients with acromegaly. Cutaneous thickening, acne, oily skin, hyperhidrosis, hirsutism, skin tags (Fig. 5a), acanthosis nigricans, may be seen in patients with acromegaly, and typically result from the trophic effects of GH/IGF-1 in the subcutaneous tissue and sebaceous glands [83,84]. Other skin lesions, such as cutis verticis gyrata, may also be found in patients with acromegaly (Fig. 5b) [85,86].

3.7.2. Cats

Changes in behaviour and demeanour are difficult to assess in cats, however, central nervous manifestations such as circling, blindness and seizures, may be seen in about 1.7% of acromegalic patients [31]. Lethargy, regardless of origin, may be present in 25% of these cats [47].

Some cats with hypersomatotropism (about 3% [47]) may display a palmigrade/plantigrade stance (Fig. 5c-d). This manifestation is however more common in uncomplicated diabetes, usually secondary to peripheral neuropathy, but it can still be found in non-diabetic cats with hypersomatotropism [34]. In one case study, a non-diabetic acromegalic cat which presented with posterior paraparesis and hypotonia, as well as plantigrade stance, broad facial features and respiratory stridor, was eventually diagnosed with sciatic nerve neuropathy [87].

4. Cancer

4.1.1. Humans

An increased incidence of cancer in patients with acromegaly has been suggested, however, this is not well established [88,89]. Recently, a modest increase in this risk has been shown in thyroid, colorectal, anal, central nervous system, gastric, urinary, haematological, pancreatic and small intestine tumours [88,89]. Despite the inconsistent evidence, patients with acromegaly should undergo a screening colonoscopy at diagnosis, considering the increased risk of colonic polyps. Further evaluation should be performed according to the general population, particularly when acromegaly is controlled or in remission [83].

4.1.2. Cats

To our knowledge, there is no data regarding the incidence (or risk) of cancer in cats with acromegaly.

5. Diagnosis of acromegaly

5.1. Humans

When acromegaly is suspected, a hormonal work-up should be performed, which can begin with assessing the serum levels of IGF-1 adjusted for age and gender [15,83]. High IGF-1 levels (1.3 times above the upper limit of the normal range), and lack of suppression of GH on an oral glucose tolerance test (GH nadir cutoff of <0.4 μg/L for non-obese patients and < 0.2 μg/L for obese patients) confirm the diagnosis of acromegaly [90]. However, IGF-1 and GH levels may be discordant in some situations, and elevated levels of IGF-1 or GH may not always be a synonym of acromegaly [91]. GH response to oral glucose load may also be abnormal in females, obese or older patients [6,15,68].

After biochemical confirmation of acromegaly, a pituitary magnetic resonance imaging (MRI) scan should be performed, which allows the detection and characterization of the pituitary tumour (Fig. 6a) [9,15,83]. In the rare cases of ectopic acromegaly, measurement of serum GHRH, functional somatostatin receptor imaging and/or whole-body cross-sectional imaging may be crucial [92,93].

5.2. Cats

The diagnosis of acromegaly in cats also relies on the measurement of serum IGF-1, which is typically lower than 600 ng/mL. In a study performed on diabetic cats from the United Kingdom, values >1000 ng/mL were shown to have a positive predictive value for the diagnosis of hypersomatotropism of 95% [34]. Values between 600 and 1000 ng/mL are considered abnormal but not diagnostic of hypersomatotropism. In these cases, vigilance regarding blood glucose and IGF-1 concentrations is recommended [34]. In contrast with humans, neither age nor sex appear to influence IGF-1 concentrations in cats [94,95]. It is important to note that, in cats, a diagnosis of acromegaly entails the presence of phenotypical changes. Otherwise, the preferred nomenclature is hypersomatotropism.

GH suppression tests are not routinely performed because there are no commercially available GH assays validated for cats [96]. Moreover, GH suppression test following a glucose load are not useful, since glucose does not inhibit GH secretion in cats [34,97].

Although not routinely performed in daily practice, serum type III procollagen propeptide (PIIP) also appears to have diagnostic value and indicates the presence of active acromegaly. PIIP correlates positively with serum IGF-1, and its concentration increases in the presence of abnormal tissue growth. PIIP is independent of portal insulin availability [34]. Portal insulin is required for hepatic IGF-1 production. In parallel

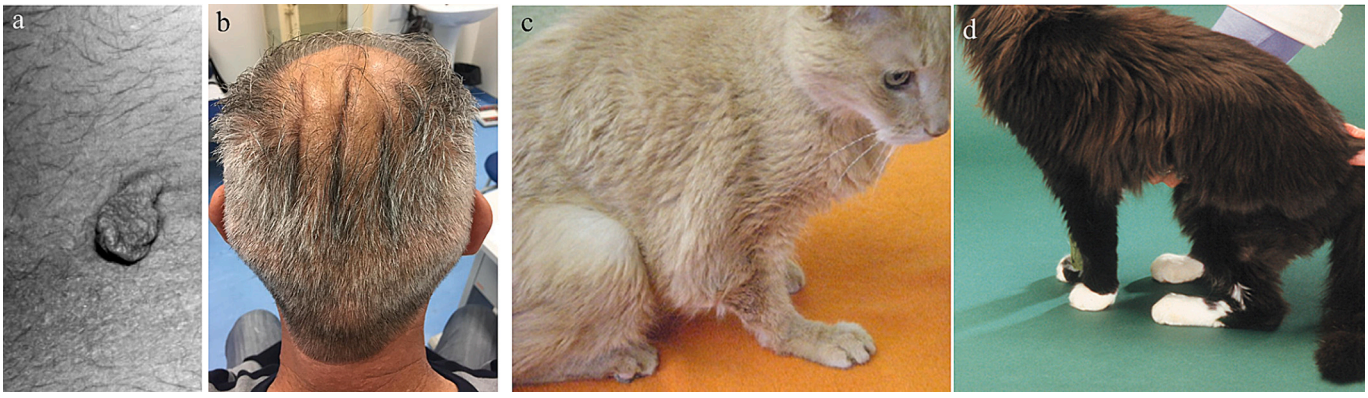

Fig. 5. Other clinical features of acromegaly in humans (a-b) and cats (c-d). Pigmented skin tags (a); convoluted folds and deep furrows of the scalp termed cutis verticis gyrata (b), and, may be found in patients with acromegaly (b). In cats, the most distinctive features from humans are palmigrade and plantigrade stance (c-d). The sources from the pictures are: a) Ben-Shlomo 2006 Clin Dermatol [PMID: 16828406]; b) unpublished original image; c) Romich 2014 ISBN 978-1133125761; d) Feline Medicine Q&A 15 Wikivet.net (accessed 5 Nov 2023).

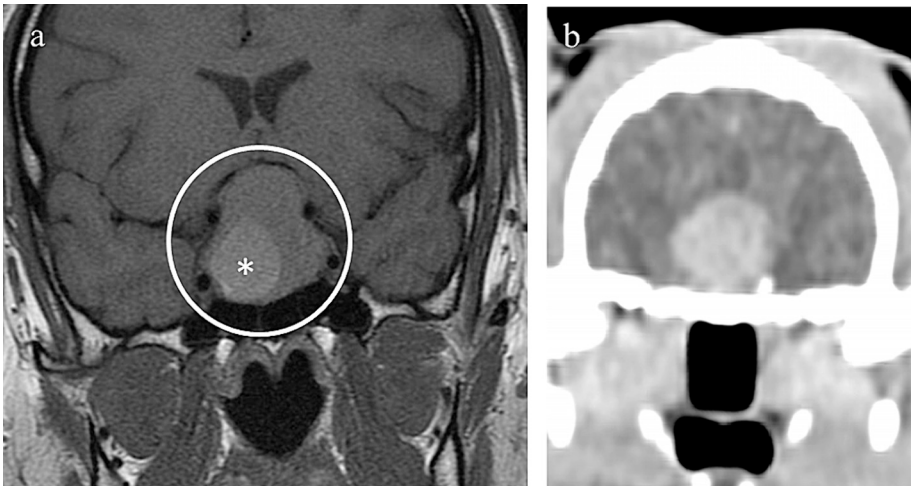

Fig. 6. Radiological appearance of growth hormone-secreting pituitary adenomas in humans (a) and in cats (b). Pituitary magnetic resonance imaging (MRI) scan reveals a large pituitary mass with suprasellar extension and optic chiasm compression (a), with an area corresponding to a probable subacute haemorrhage (*). Brain CT scan showing a pituitary tumour with a mass extending dorsally and to the right-hand side in an acromegalic cat (b). The sources from the pictures are: a) Weerakkody Y. Pituitary macroadenoma. Reference article, Radiopaedia.org, https://doi.org/10.53347/rID-9801 (accessed on 19 Dec 2023); b) Unpublished original image.

with people, endogenous insulin concentrations can be low in feline diabetes mellitus, a low IGF-1 reading could be obtained when sampling takes place prior to initiation of exogenous insulin treatment despite the presence of excess GH due to acromegaly [48]. In order to reduce the occurrence of false negatives, it is important to measure IGF-1 concentrations 2–4 weeks after initiating exogenous insulin therapy [34,98].

Other biochemical abnormalities that may also be found in acromegalic cats include hyperglycaemia (>120 mg/dL or 6.6 mmol/L), hypercholesterolaemia, mild increases in serum alanine aminotransaminase and in alkaline phosphatase, hyperproteinemia and elevated serum urea nitrogen [61]. Blood electrolytes may also be abnormal. Mild to moderate hyperphosphataemia without overt renal dysfunction (i.e., azotemia) has been described in almost a third of the reported acromegalic cats [54,61,99]. The most reported haematological change in feline acromegalics is erythrocytosis, which has been attributed to GH or IGF-1 effects on the bone marrow [61]. IGF-1 plays a key role in the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells, a type of stem cells in the bone marrow tissue with osteogenic differentiation potential [100]. An *in vitro* study has also showed that IGF-1 has a marked positive effect on the proliferative activity of stem cell cultures derived from the cat bone marrow [101]. None of these biochemical abnormalities are pathognomonic of acromegaly or hypersomatotropism and may appear in other endocrinopathies such as uncomplicated diabetes. Their stand-alone diagnostic ability is, therefore, quite limited.

After establishing the biochemical diagnosis of acromegaly in a cat, diagnostic imaging investigations should be performed. Most cats with serum IGF-1 >1000 ng/mL have a large (>4 mm) pituitary neoplasm extending beyond the dorsal rim of the sela turcica (Fig. 6b). MRI is more sensitive than computed tomography (CT) scan, but 95% of acromegalic cats will display abnormalities on the CT scan [34].

6. Management of acromegaly

6.1. Humans

The main treatment goals are achieving normal GH and IGF-1 serum levels, control tumour growth, prevent or ameliorate systemic comorbidities, improve the quality of life and reduce the mortality risk [102,103]. Acromegaly in humans is managed with transsphenoidal surgery to resect the GH-secreting pituitary tumour, medical therapy and radiotherapy [104]. A tendency for a "personalized" approach considering patient demographics, and tumour radiological and pathological characterization is emerging, favouring disease control over time [15,83,105].

Current recommendations favour transsphenoidal surgery as the first-line treatment approach for most cases [58,106]. Surgical remission is considered when normal IGF-1 and undetectable GH levels are obtained [9,15], but IGF-1 normalization and cure of acromegaly may be delayed [107]. If the disease persists after surgery or the patient is not suitable for an operation, medical treatment with somatostatin analogues, dopamine agonists or pegvisomant (GH receptor antagonist) may be used [9,15,104]. Biochemical control maybe achieved in 30–40% and tumour shrinkage can be observed in two thirds of patients treated with first generation somatostatin analogues; biochemical and structural responses to pasireotide may be found in 54% and 80% of cases [108]. Cabergoline may control IGF-1 levels in around 20% of cases, particularly those with mild elevations of IGF-1, and tumour shrinkage may be obtained in 33% of cases [108]. Pegvisomant is highly effective in blocking the action of GH, normalising IGF-1 levels in 90% of patients in clinical trials, and in about 73% of patients in real-life studies [109–113]. Stereotactic or conventional radiotherapy may also be employed to control the disease, particularly in cases refractory to surgery and medical therapy [114,115].

Acromegaly-related co-morbidities, including diabetes mellitus, hypertension, cardiovascular disease, obstructive sleep apnoea and osteoarthritis, should also be addressed and managed individually [15,116,117]. Acromegaly patients with hypopituitarism at diagnosis due to mass effect, or post-operative/post-radiotherapy hypopituitarism, should initiate adequate hormone replacement therapy [118].

6.2. Cats

Hypophysectomy is considered the gold-standard treatment, given its high success rates: insulin may be withdrawn in up to 85% of acromegalic cats with diabetes, and serum IGF-1 levels normalize in up to 90% of cats after surgery [34]. In one case series of 25 acromegalic cats undergoing hypophysectomy, 3 died within 8 weeks of surgery [119]. However, only one death was linked to the procedure. 96% of cats achieved normalization of serum IGF-1 and 92% achieved diabetic remission. Median survival time was 1347 days. Another study reported 15% of postoperative deaths, with 95% of the surviving cats having improved diabetic control and 71% achieving remission. Median survival time was 853 days [120]. Hypophysectomy, however, requires

lifelong glucocorticoid and thyroid supplementation [34]. The follow-up entails the measurement of IGF-1, and remission is considered in case of normal IGF-1 one year post-surgery [34,119]. Cryohypophysectomy, the destruction of the hypophysis through extreme cold, usually a liquid nitrogen cooled cryoprobe, has also been reported in two cats: one with a favorable outcome, with diminished insulin resistance, although with no IGF-1 measurements available; the other maintained peripheral insulin resistance with no significant reduction of plasma IGF-1 [121].

Medical therapy in acromegalic cats is widely unavailable and is associated with only modest success rates. Cats with acromegaly have higher expression of somatostatin receptor (SSTR) type 1 and SSTR type 5, and lower expression of SSTR type 2, which renders the first-generation somatotastin analogues (octreotide and lanreotide) rather ineffective, as they mainly act via SSTR type 2 [35]. Pasireotide inhibits SSTR types 1, 2, 3 and 5, and has shown modest success in treating cats with acromegaly [122]. While dopamine agonists such as cabergoline were initially considered ineffective [123], recent studies [124,125], including one case series of 3 cats that achieved remission following cabergoline treatment [125], have advocated its use as a promising option when other treatments are not available. Cabergoline and pasireotide appear to have similar efficacy regarding normalization of IGF-1 (25% vs 26%) [124,125]. Given that pasireotide has a higher rate of adverse effects, similar efficacy and an often-prohibitive cost for owners, cabergoline could be a treatment option for cats with hypersomatotropism and diabetes [122,124,125]. One study [124] has shown that, in cats undergoing treatment with cabergoline, median IGF-1 decreased significantly. However, the initial median pituitary height cats that experienced an IGF-1 reduction was significantly lower compared with those that did not experience an IGF-1 reduction [124]. This may indicate cabergoline is more suitable for treatment of "milder" cases of acromegaly, in cats with smaller pituitary tumours.

Conventional radiotherapy may also be an option if hypophysectomy is not available or the tumour is too large. Extent and timing of success are unpredictable, since improvement may take a more than a year. Stereotactic radiotherapy (SRT), however, appears to be more effective. In one study [126], 95% of cats exhibited a decrease in the required insulin dose. Studies regarding conventional radiotherapy show a more variable response, with 55 to 92% of cats being able to reduce insulin dose. The overall median survival time of cats undergoing SRT also appears to be better than those undergoing conventional radiotherapy (1072 vs 508–840 days) [126–130]. Diabetic remission can occur in some acromegalic cats following radiotherapy given as primary treatment (both SRT and conventional radiotherapy), but the efficacy rate is lower than in cats undergoing hypophysectomy. Hypophysectomy has been performed successfully in patients with post-radiation relapse. Radiation may also be a useful neoadjuvant treatment, allowing a pre-surgical reduction of large pituitary tumours in selected cases [34].

In countries where hypophysectomy or radiotherapy are not available, the treatment of acromegaly is purely symptomatic: exogenous insulin for diabetes, medication for hypertrophic cardiomyopathy, drugs for hypertension, and analgesia for joint pain [34,131].

7. Conclusions

Acromegaly in humans and cats share some key similarities summarised in Table 1. The metabolic effects of excess GH and IGF-1 in both species lead to complications such as hypertension, left ventricular hypertrophy, diastolic dysfunction, diabetes mellitus, arthropathy and

Table 1
Epidemiology, pathophysiology and clinical features of acromegaly in humans and cats.

		Humans		Cats	
General features	Epidemiology	3.6–13 cases per 100,000 individuals More common in older women		125 cases per 100,000 individuals (1 in 800 cats) More common in older neutered male cats (70%)	
	Pathophysiology	GH-secreting pituitary tumour (>95%) – May be plurihormonal (up to 30% also secrete prolactin) Genetic causes identified (e.g. *AIP*, *GNAS* and *GPR101* mutations) Environmental causes possible (pollution)		GH-secreting pituitary tumour – Very rarely plurihormonal. Prolactin secretion has not been documented No strong evidence for genetic causes Environmental causes possible (pollution)	
Clinical features	Facial features	Frontal bossing Prognathism Dental malocclusion	Diastema Macroglossia	Broad facial features (37%) Prognathism (18%) Dental malocclusion	Diastema
	Cardiovascular and metabolic	Hypertension (17–51%) Left ventricular hypertrophy Diastolic dysfunction Heart failure	Arrhythmia Valvular disease Diabetes (19–28%) Dyslipidaemia	Hypertension Left ventricular hypertrophy Diabetes (15–25%) Azotemia and kidney disease	Heart murmur (18%)
	Skeletal	Joint stiffness/pain (70%) Carpal tunnel syndrome (25–51%) Increased joint cartilage thickness Calvaria thickening	Ligament ossification Dorsal kyphosis scoliosis Osteoporosis and bone fractures	Joint stiffness/pain (10%) *Spondylosis deformans* Increased joint cartilage thickness	Calvaria thickening Enlarged extremities/clubbed paws (13%)
	Organomegaly	Thyroid enlargement/goiter Salivary glands Hepatomegaly Splenomegaly	Nephromegaly Cardiomegaly Dolicomegacolon Prostate hyperplasia	Hepatomegaly Splenomegaly Nephromegaly Cardiomegaly	Pancreas Adrenal glands Abdominal enlargement (40%)
	Local tumour effects	Headaches (32–87%) Visual field defects (4–62%) Cranial nerve palsies	Facial pain Hypothalamus or frontal lobe compression	CNS signs excluding lethargy (1.7%) Lethargy (25%)	
	Other notable features	Respiratory stridor/snoring Sleep apnoea (7–30%) Hirsutism	Hyperhydrosis (52–91%) Cutis verticis gyrata Skin tags and skin thickening	Respiratory stridor/snoring (38%) Palmigrade/plantigrade stance (3%)	
	Cancer	Modest increase in risk in certain cancers: Thyroid Gastrointestinal tract	Central nervous system Urinary tract Haematological Pancreatic	Not consistently reported	

AIP: Aryl hydrocarbon receptor interacting protein; CNS: Central nervous system; *GNAS*: Guanine nucleotide binding protein alpha stimulating activity polypeptide gene; *GPR101*: G-protein coupled receptor gene; HCM: hypertrophic cardiomyopathy.

nephropathy. Physical attributes are also similar in affected individuals, including enlarged/club-like extremities, broad facial features, dental diastema and inferior prognathia.

Some signs in humans, such as galactorrhoea, menstrual disturbances, erectile dysfunction and low libido are not observed in cats since most are spayed or neutered. Cats also do not usually have specific dermatological signs associated with acromegaly, while in humans skin manifestations, such as skin tags, oily skin or acne, are common. Unkempt coat can sometimes be observed but it is a universal sign of illness in cats. In affected cats, the typical acromegaloid phenotype is not always present. Cats can have very high serum IGF-1 concentrations and a normal appearance. Often, the only sign is insulin-resistant or increased glycaemia /diabetes in cats with diabetes mellitus. While not all acromegalic cats are diabetic, the overwhelming majority is.

Some studies suggest that the prevalence of acromegaly in humans may be vastly underestimated [102,103], since, like in cats, some patients with acromegaly may have very mild acromegalic features [132].

Given the overall similarities between the presentation of acromegaly in both species and the shorter lifespan of cats, feline acromegaly may be a useful model for studying this disease in human patients. On the other hand, since data regarding acromegaly in humans is significantly vaster, it may provide some insights and further knowledge about the disease in other species, including cats, especially given the same pathophysiological mechanisms underlying to the excess of GH and IGF-1, and the several similarities, as illustrated here.

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Declaration of competing interest

None.

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