Feline acromegaly: the ultimate advanced update

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Update on the Morphology of the Somatotrophinoma

Most cases of hypersomatotropism (HS) suffer from a benign acidophilic pituitary adenoma. Until recently little was known about whether the adenomatous change is associated with a change in receptor expression. This has been especially pertinent since medical inhibition of the feline somatotrophinoma using traditional somatostatins like octreotide has proven challenging. This question has now been answered (unpublished data). Hypersomatotropic cats were demonstrated to display increased somatostatin receptor (SSTR) 1, 2 and 5 expression compared to healthy controls. Additionally, a higher expression of SSTR1 and SSTR5 vs. SSTR2 than in most humans may also explain the greater biochemical response to pasireotide (multireceptor agonist) than octreotide (SSTR2 agonist) in cats. Decreased dopamine receptor 2 expression in larger feline tumours was also shown and this may hint towards a mechanism which allows unchecked adenoma growth, as well as likely confirms the cause behind previous disappointing treatment results with dopamine agonists like cabergoline.

Update on the Possible Causes of Feline Hypersomatotropism

The exact cause of human and feline hypersomatotropism remains to be elucidated, though both genetic and environmental factors are thought to be involved. Previously, human pituitary adenomas were widely considered to be monoclonal in origin, supporting a hypothesis of an acquired single cell, somatic, mutation and subsequent formation of a neoplasm. However, it was subsequently demonstrated that an additional mechanism of somatotropinoma formation involved germline mutations causing inactivation of tumour suppressor genes. Particularly, mutations of the human aryl hydrocarbon receptor interacting protein (AIP) gene have been strongly associated with up to 40% of isolated familial and spontaneous human somatotropinomas. AIP is involved in activation of sensitive genes including xenobiotic metabolising enzymes. The author's research group has sequenced the feline AIP gene and found that 20% of cats with hypersomatotropism show polymorphism of that AIP gene, rendering AIP variation also as a possible part of the etiology of hypersomatotropism in a minority of cats (though likely not the majority). Organohalogenated contaminants (OHCs) have been implicated as an environmental cause for pituitary oncogenesis in rodent models. OHCs are persistent and bioaccumulative chemicals and include organochlorine pesticides, industrial chemicals, such as polychlorinated biphenyls (PCBs) and brominated flame retardants (BFRs) added to various materials to reduce flammability, such as polybrominated diphenyl ethers (PBDEs). Both cats and humans are exposed to such chemicals via a multitude of routes including food and indoor contamination, mainly through dust ingestion which is especially relevant in light of cats' grooming behaviour. It has therefore been hypothesised that companion animals may serve as sentinels to assess the relationship between human exposure to chemicals via indoor environments and adverse health effects. Comparison can therefore be drawn with feline hyperthyroidism where a similar link has been previously suggested between its emergence and the presence of OHCs in domestic materials and/or food. In light of this, the author and colleagues compared OHCs levels in the plasma of a group of elderly cats without identifiable endocrinopathy, with those with primary diabetes mellitus and those with secondary diabetes mellitus as a consequence of hypersomatotropism. Significantly higher levels for all contaminants were observed in cats suffering from hypersomatotropism. Particularly, total PBDE levels, brominated flame retardants, were significantly higher in the plasma of acromegalic cats. When additionally looking at the metabolites of these OHCs, data suggested that cats with hypersomatotropism have a lower capacity to metabolise persistent chemicals like PCBs than other cats.

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Update on Prevalence in the Diabetic Cat Population

After initial studies published in 2007 proposed feline acromegaly to be a relatively common underlying cause for feline diabetes mellitus, reporting a 26–32% prevalence rate, two further prevalence studies have been conducted recently.

One study was conducted among first-opinion veterinarians in Switzerland and the Netherlands who were asked to provide blood samples from diabetic cats treated with insulin for at least 4 weeks. Serum IGF-1 was analysed by IGFBP blocked radioimmunoassay (RIA) and like the author's 2007 study, who used a different RIA, an IGF-1 > 1000 ng/dl was considered suggestive of acromegaly. Blood samples were collected from 225 cats and IGF-1 concentrations ranged from 15–2471 ng/ml (median 584); interestingly, 17.8% of the cats had a serum IGF-1 > 1000 ng/ml. These data therefore once again confirm that it is likely that feline acromegaly represents a frequently encountered underlying etiology for the diabetes mellitus in cats seen in primary practice. Absence of a pituitary tumour in some of these cats could be explained by a false elevation in IGF-1 or absence of a macroscopically identifiable pituitary structural abnormality. The latter is especially relevant when screening newly diagnosed diabetic cats, given that the pituitary somatotropinomas tend to be slow growing and therefore will be very small at such early stage of the disease process.

The second prevalence study estimated the prevalence of hypersomatotropism or acromegaly in the largest cohort of diabetic cats to date. Diabetic cats were once again screened for hypersomatotropism using serum total insulin-like growth factor-1 (RIA), followed by further evaluation of a subset of cases with suggestive IGF-1 (>1000 ng/ml) through pituitary imaging and/or histopathology. Clinicians indicated pre-test suspicion for hypersomatotropism. In total 1221 diabetic cats were screened; 319 (26.1%) demonstrated a serum IGF-1 > 1000 ng/ml (95% confidence interval: 23.6–28.6%). Of these cats, a subset of 63 (20%) underwent pituitary imaging and 56/63 (89%) had a pituitary tumour on computed tomography; an additional three on magnetic resonance imaging and one on necropsy. These data suggest a positive predictive value of serum IGF-1 for hypersomatotropism of 95% (95% confidence interval: 90–100%), thus suggesting the overall hypersomatotropism prevalence among UK diabetic cats to be 24.8% (95% confidence interval: 21.2–28.6%). Most interestingly, only 24% of clinicians indicated a strong pre-test suspicion; most hypersomatotropism cats did not display typical phenotypical acromegaly signs.

The scientific debate about the exact prevalence of feline hypersomatotropism/acromegaly is currently ongoing and remains interesting. Differences might relate to the use of differing IGF-1 assays, recruitment methods, as well as geographical influences. Nevertheless, from a clinical point of view, the outcome of such debate will not change the overall message coming from all studies conducted in the last decade: feline hypersomatotropism/acromegaly should be considered as a possible cause of diabetes mellitus in the cat. Since it is generally accepted to screen for urinary tract infections (UTI) in feline diabetics (UTI prevalence estimate 12%) and it is also recommended to differentiate adrenal-dependent (ADH) from pituitary-dependent hyperadrenocorticism in dogs (ADH prevalence estimate 15%), it therefore seems only logical to also recommend screening newly diagnosed diabetic cats for the presence of hypersomatotropism/acromegaly (prevalence estimate 18–32%), especially given the tremendous implications on optimal treatment method, potential for diabetic remission and prognosis.

Update on Prevalence in the Non-Diabetic Cat Population

Thus far, all peer-reviewed reports of hypersomatotropic/acromegalic cats have included diabetes mellitus in their presentation. This is at odds with the situation in humans where most reports document only a minority of acromegalic humans (approximately 1 in 3) to be suffering from diabetes mellitus. Nevertheless, this has resulted in the "dogma" that all hypersomatotropic cats are diabetics. It is this dogma and the idea of a "typical" acromegalic phenotype that has likely resulted in very few cats being screened for hypersomatotropism prior to the development of insulin-resistant diabetes mellitus and an acromegalic phenotype. As a result, the true prevalence in non-diabetic cats remains unknown. As in humans, feline hypersomatotropism likely has a gradual onset and a period during which the GH and IGF-1 concentrations are increased, though diabetes and signs constituting the syndrome of acromegaly have yet to occur. If the cat does not have dysfunctional pancreatic beta cells, as is suggested to be the case in type 2 diabetes mellitus, it is likely able to withstand a period of increasing insulin resistance without developing overt diabetes. This is further substantiated by the fact that most diabetic cats with hypersomatotropism will enter diabetic remission once the somatotrophinoma is removed. Therefore, by focusing only on the diabetic population, we could be missing hypersomatotropic cats prior to the development of overt diabetes mellitus as well as those that may never become diabetic. To illustrate this, the author and colleagues have now documented the details of three hypersomatotropic cats, which presented with weight gain (n = 1), ataxia (n = 1) and seizures (n = 1), though not diabetes mellitus (manuscript accepted, JVIM).

Update on Diagnostic Tools

Serum GH and IGF-1

For most veterinarians, serum total insulin-like growth factor-1 (IGF-1) assessment still represents the most feasible and accessible means of performing screening for hypersomatotropism in the (diabetic) cat. The positive predictive value of elevated IGF-1 (>1000 ng/ml, RIA) was shown to be a respectable 95%, rendering it very useful clinically. It should be born in mind though that hepatic IGF-1 production is dependent on the presence of sufficient portal insulin, which can be deficient in newly diagnosed diabetic cats, resulting in false-negative results. Additionally, elevation of IGF-1 has been reported in non-acromegalic diabetic cats. Finally, differences in the performance of IGF-1 assays exist. Growth hormone assays remain difficult to access commercially, despite their potential value. Alternative or additional diagnostic tests for hypersomatotropism, as well as to evaluate the success of treatment of hypersomatotropism, are therefore desirable.

Serum Procollagen Propeptide

Since feline HS is associated with tissue growth, serum type III procollagen propeptide (PIIIP), a peripheral indicator of collagen turnover, was recently shown to be a useful indicator of active disease or growth hormone bioactivity in the cat. Median serum PIIIP was five times higher in hypersomatotropism-induced diabetic cats compared to cats with primary diabetes mellitus. There was also a significant correlation between serum IGF-1 and PIIIP. Given that PIIIP is not dependent on portal insulin availability, this parameter could prove useful, perhaps as part of a panel, to increase the possibility of reliably diagnosing feline hypersomatotropism without the explicit need for intracranial imaging.

Serum Ghrelin

The orexigenic peptide ghrelin is a growth hormone secretagogue and has been shown to be down-regulated in humans with hypersomatotropism, whilst it increases following successful therapy. Serum ghrelin was shown to be significantly higher in control cats compared to cats with hypersomatotropism-induced diabetes mellitus. However, the latter group had similar concentrations as those with regular diabetes mellitus, rendering this test not useful in the initial diagnostic phase. However, it has also been shown that post-radiotherapy serum ghrelin increases significantly in cats with hypersomatotropism-induced diabetes mellitus, whilst IGF-1 changes prove not significant. This suggests a possible role for serum ghrelin as a marker of treatment effect.

Update on Most Effective Treatment

Hypophysectomy

With increasing experience of using hypophysectomy to definitively treat feline hypersomatotropism/acromegaly, it also becomes increasingly clear that this constitutes the gold-standard treatment option, provided there is no contraindication. Contraindications can include excessive tumour size, significant comorbidities that prevent a safe anaesthetic and post-operative recovery (particularly significant renal and cardiovascular disease) or an owner who is completely risk-averse. The initial financial commitment forms another obstacle although it is important to realise that a year of ineffective insulin treatment or radiotherapy could have similar cost implications. The hypophysectomy experience in acromegalic cats is therefore in line with the human acromegaly experience. In the author's Hypophysectomy Clinic, 36 feline acromegalics have been treated since April 2012, and approximately 85% of cases have entered diabetic remission within 1 month after surgery. This demonstrates the enormous resilience of the cats' pancreatic beta-cells which seem unaffected by, often, more than a year of severe insulin resistance. The peri- and post-operative mortality rate in this clinic is currently 14%, which is acceptable to most cat owners given the paucity of equally effective alternative treatment modalities. Post-operatively, cats are treated with a low dose of hydrocortisone and levothyroxine (both lifelong) and DDAVP, which can be discontinued in most cats.

Medical Inhibition

Pasireotide (SOM230), a novel multireceptor ligand sst analogue with high binding affinity for sst receptor subtypes 1, 2, 3 and 5 has been the only drug shown to consistently suppress growth hormone (GH) and insulin-like growth factor-1 (IGF-1) in diabetic cats with hypersomatotropism. All eight cats treated with BID injections of a short-acting form showed a significant decrease in serum IGF-1, average 12-hour blood glucose and insulin requirements. A once-monthly formulation proved effective when 12 cats were treated for 6 months, making the treatment less intense for the owners and cats involved. Unfortunately, the cost of the short-acting form of this drug (trade name Signifor®, Novartis, Basel, Switzerland) is considerable and some cats suffer from loose stools or diarrhoea, which can necessitate the cessation of the drug.