Feline Acromegaly

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Introduction

Feline acromegaly is a disease characterized by excessive growth hormone secretion leading to a wide array of clinical signs caused by the hormones effects on multiple organ systems. These effects can be divided into two major classes. The first are the catabolic actions of growth hormone that include: insulin antagonism, lipolysis, and gluconeogenesis with the net effect of promoting hyperglycemia. The second are the slow anabolic (or hypertrophic) effects of growth hormone, which are mediated by insulin like growth factors. Growth hormone stimulates production of insulin like growth factors in several different tissues. Insulin like growth factor-1 (IGF-1) which is produced in the liver is thought to be the key factor that facilitates the anabolic effects of growth hormone that are responsible for the characteristic appearance of acromegalic people, dogs, and cats.

Growth hormone is produced in the pars distalis (anterior pituitary), specifically by acidophilic cells, called somatotrophs. The release of growth hormone is regulated by many factors, the most important of which is growth hormone releasing hormone (GHRH) produced by the hypothalamus. Recently, another hormone, ghrelin, has also been identified as a potent stimulator of growth hormone release. Ghrelin is a hormone produced by the stomach and released following ingestion of a meal.

Release of growth hormone is inhibited by the hypothalamic hormone somatostatin as well as by growth hormone and IGF-1 via negative feedback. Feline acromegaly is typically the result of a functional adenoma of the pituitary that releases growth hormone despite negative feedback resulting in excessive growth hormone production and release[1].

Signalment, History, Clinical Signs

Feline acromegaly is an uncommon disease although it may be under diagnosed. A recent study in the United Kingdom measured IGF-1 levels in variably controlled diabetic cats. Of the 184 cases, 59 (32%) had markedly increased IGF-1 concentrations. Eighteen of these 59 cats underwent pituitary imaging confirming a diagnosis of acromegaly in 17/18 (94%)[2].

Feline acromegaly most commonly affects middle aged to older, male castrated cats. In one study 13 of 14 cats with acromegaly were males with an average age of 10.2 years[3]. This association may be biased, however, as most cats that are diagnosed with acromegaly present for insulin resistant diabetes mellitus, which is also more common in older, male castrated cats. Based on available data there is no known breed association for acromegaly.

Most patients with acromegaly present for insulin resistant diabetes mellitus (insulin doses greater than 1.5-2.2 units/kg BID) with concurrent weight gain rather than weight loss[3]. Growth hormone has effects on all of the tissues in the body and therefore the disease has a range of clinical signs. Physical characteristics of acromegaly include increased body weight, a broadened face, enlarged feet, protrusion of the mandible (prognathia inferior), increased interdental spacing, stertorous breathing, organomegaly, and a poor haircoat (see images 1-3). Cardiovascular signs include the presence of a heart murmur, hypertension, arrhythmia, and is associated with hypertrophic cardiomyopathy[4]. Neurologic disease associated with feline acromegaly is uncommon but can occur with a pituitary macroadenoma. Neurologic signs that have been observed with acromegaly include dullness, lethargy, abnormal behavior, circling, and blindness. Glomerulopathy and secondary renal failure has also been associated with feline acromegaly. Histopathologic evaluation of the kidneys from acromegalic cats has revealed thickening of the glomerular basement membrane and Bowman's capsule, periglomerular fibrosis, and degeneration of the renal tubules[3]. Arthropathy and peripheral (diabetic) neuropathy have been shown to cause lameness in acromegalics cats.

Diagnosis

Diagnosis of feline acromegaly starts with clinical suspicion, using a thorough history, signalment, and clinical signs. Many of the abnormalities in the minimum database of affected cats reflect concurrent diabetes mellitus and include erythrocytosis, hyperglycemia, increased liver enzymes (ALT, ALP), hypercholesterolemia, hyperphosphatemia, hyperglobulinemia, azotemia, glucosuria, ketonuria, proteinuria, and isosthenuria[1,3,5].

Growth hormone concentration is a common diagnostic used to diagnose acromegaly in humans, however, assays specifically for feline growth hormone are not widely available. An assay using ovine GH as the antigen, has been validated for use in cats, but is only available in Europe[6]. However, even if an assay was available, growth hormone concentrations alone may not be a reliable diagnostic for acromegaly. Growth hormone production is cyclic and levels may vary throughout the day. A single high value may not necessarily be diagnostic for acromegaly. Additionally, it has been shown that growth hormone may be elevated in non-acromegalic diabetic cats. This elevation in growth hormone may be due to the fact that portal insulin is required for the liver to produce IGF-1. In diabetics that are being treated with insulin subcutaneously, portal insulin concentrations will remain low resulting in decreased IGF-1 production and theoretically decreased inhibition of GH release. In addition, growth hormone levels may also not be elevated early in the course of the disease, but later typically increase significantly.

Insulin like growth factor-1 is the most commonly used endocrine assay used to diagnose feline acromegaly and it is widely available through the Michigan State University Diagnostic Center for Population and Animal Health (http://animalhealth.msu.edu/Submittal%5FForms/AD.ADM.FORM.007.pdf). Unlike growth hormone, IGF-1 concentrations are less likely to fluctuate over the course of the

day as the majority of IGF-1 is protein bound giving it a longer half-life in the body. In addition, insulin like growth factor-1 increases in response to chronically elevated growth hormone concentrations and is thought to be a reflection of growth hormone levels over the last 24 hours. However, just as with growth hormone, elevations in IGF-1 concentration alone may not be diagnostic for acromegaly. One study found that IGF-1 levels in non-acromegalic cats on long-term insulin treatment (>14 months) had higher levels of IGF-1 than non-diabetics[7]. It was proposed that insulin treatment allowed for beta cell regeneration and increased portal insulin leading to elevations in IGF-1. A subsequent study evaluating IGF-1 levels in confirmed acromegalics diabetics, diabetics, and healthy cats found that acromegalic diabetics had significantly higher levels of IGF-1 than diabetics and non-diabetics[8]. This study concluded that IGF-1 was 84% sensitive and 92% specific for diagnosing feline acromegaly. No correlation between long-term insulin use and elevations in IGF-1 concentrations were found in this study.

Diagnostic Imaging

Radiographic findings associated with feline acromegaly are related to the hypertrophic effects of excessive growth hormone. Hyperostosis of the calvarium, spondylosis of the spine, and protrusion of the mandible are common findings. Periosteal reaction, osteophyte production, soft tissue swelling, and collapse of joint spaces are signs associated with the degenerative arthropathy linked to feline acromegaly. Thoracic radiographs may reveal cardiomegaly (hypertrophic cardiomyopathy) and/or congestive heart failure. Non-specific signs such as abdominal organomegaly (hepatic, renal, and adrenal) may be revealed by abdominal ultrasound.

Advanced imaging is needed to document the presence of a pituitary macroadenoma. Computed tomography (CT) and magnetic resonance imaging (MRI) are both useful for identifying pituitary masses[9,10]. However one study found MRI to be the more sensitive imaging modality[10]. The presence of a pituitary tumor alone is not diagnostic for feline acromegaly as other functional tumors of the pituitary may also result in insulin resistant diabetes such as ACTH producing tumors in patients with Cushing's disease. Conversely, the absence of a pituitary mass does not rule out acromegaly as there have been reported cases where a patient had a negative MRI but a pituitary mass was identified at necropsy and histopathology confirmed a growth hormone secreting adenoma.

Histopathology

Histopathology is needed for definitive diagnosis which makes ante-mortem diagnosis challenging. However, with advancements in surgical procedures such as the transsphenoidal hypophysectomy, surgical excisional biopsy is possible. The main histopathologic change associated with acromegaly is acidophil proliferation in pituitary tumors[3].

Adrenocortical Testing

There is no single test for the diagnosis of feline acromegaly. Clinical suspicion based on a thorough history and physical exam are essential. As earlier stated the most common presenting complaint for patients with acromegaly is insulin resistance with weight gain. The 2 most common causes of insulin resistance in cats are hyperadrenocorticism and acromegaly. Both of these diseases can be associated with a pituitary mass and bilateral adrenomegaly. As such, all suspected acromegalics should undergo adrenocortical testing via the ACTH stimulation test and/or low dose dexamethasone suppression test. Normal results on these tests would then be an indication to screen for acromegaly.

Medical Management

Somatostatin is a hypothalamic hormone that acts on the pituitary to inhibit growth hormone release. Somatostatin analogs are commonly used in human medicine for the treatment of acromegaly and have efficacy rates 50-60%[11]. The somatostatin analog, octreotide, has been evaluated in a small number of feline acromegalics with limited success. One study in 4 cats, found no change in growth hormone following treatment[3]. Another study measured the short-term effects of octreotide in 5 feline acromegalics and found a decrease in growth hormone concentrations for up to 90 minutes[12]. However a recent study evaluating a long acting somatostatin analogue (Sandostatin LAR) showed no benefit in cats treated for 3-6 months[13]. Failure of these dugs may be related to difference in somatostatin receptor subtypes. Future studies are required to identify the somatostatin receptor subtypes in GH secreting feline pituitary tumors to determine if they are similar to the ones found in humans.

Dopamine agonists and more recently growth hormone receptor antagonists are also used in human medicine for the treatment of acromegaly. The use of growth hormone receptor antagonists has not been reported in cats, but in humans response rates have been reported to be as high as 90%[11]. However, it has been noted that the medication has no effect on tumor size and thus would be of no benefit in patients with neurologic signs. A single case study using a dopamine agonist (L-deprenyl) for the treatment of feline acromegaly showed no effect on reducing insulin requirements or clinical signs of disease[13]. In humans dopamine agonists are typically only 10-20% effective, but are often used in combination with other medications[11].

Increasing the dosage of insulin to improve glycemic control and clinical signs of diabetes, is the most conservative choice for treating insulin resistant diabetic acromegalics. However, there have been reports that some patients suddenly and inexplicably become sensitized to insulin resulting in hypoglycemic crises[1,3]. In one study, several acromegalic cats were euthanized after experiencing hypoglycemic coma[3].

Surgical Treatment

Surgical removal of the pituitary tumor (adenectomy) is the treatment of choice for acromegaly in human medicine. The procedure can be performed in cats and dogs usually employing complete removal of the entire pituitary (hypophysectomy). Availability of this procedure is limited in the United States and as of this writing the

procedure is only available at the VCA West Los Angeles Animal Hospital, although other institutions may soon be able to offer this option.

In veterinary medicine a transsphenoidal approach is used involving only a small incision through the soft palate and then approaching the pituitary gland through the basisphenoid bone. Complications associated with the surgery include hemorrhage and incision dehiscence. Post surgery patients are treated with cortisone, L-thyroxine, and desmopressin. The same surgical procedure is also used to treat pituitary dependant hyperadrenocorticism in both dogs and cats. A study in which 7 cats with pituitary dependant hyperadrenocorticism were treated with transsphenoidal hypophysectomy resulted in 5 cats showing complete resolution of the disease. Four of these cats had concurrent diabetes mellitus, 2 of which showed increased insulin responsiveness after surgery[14]. A single case report exists for the treatment of feline acromegaly with transsphenoidal hyposphysectomy. Prior to surgery the patient was an insulin resistant diabetic that was still exhibiting clinical signs despite receiving 25 U of insulin (Levemir; Novo Nordisk) 4 times per day. Three weeks after surgery the patient no longer required insulin therapy and up to one year later the patient's IGF-1 and GH concentrations were within normal limits[15].

In another single case report from VCA West Los Angeles Animal hospital a 13 year old male-castrated domestic short hair was treated for acromegaly with transsphenoidal hyposphysectomy. The patient had a history of insulin resistant diabetes mellitus (15 units of glargine BID) and was diagnosed with acromegaly via elevated IGF-1 (447 nmol/L) and visualization of a pituitary mass on MRI. The diabetes resolved 2 weeks post-operatively and remained in remission for 8 months at which time the patient was euthanized as a result of FIP.

An alternative procedure, cryohypophysectomy, has been reported in a small number of cats but the procedure has shown to be less effective and results in a higher complication rate[16, 17].

Radiation

Radiation therapy is another option for the treatment feline acromegaly especially if the tumor is inoperable, the patient is not a suitable candidate for anesthesia, or if surgical treatment is not available in the area. In human medicine radiation therapy is regarded as a second line treatment as beneficial effects may take years to develop and the patient typically experience undesired late-term CNS radiation effects.

The majority of studies that have been performed in veterinary medicine focus on radiation treatment of pituitary masses regardless of functional status. There is no standard treatment protocol for pituitary masses in veterinary medicine and varying methods have been used including both single and multiple dose fractions administering total dosages ranging from 1,500 – 4,0 cGY. The majority of the cats included in these studies had insulin resistant diabetes (suspected acromegaly or Cushing's disease) and/or neurologic signs. Radiation therapy was shown to be successful in improving insulin

resistance and neurologic signs. Neurologic improvement was generally seen within weeks to months and an improved insulin response was seen within the first month, however, most patients still required insulin therapy. In cases where repeat imaging was available a decrease in tumor size was also noted. Disadvantages of radiation therapy are the early and delayed effects of radiation, repeated anesthesia, and expense. Early effects from radiation therapy include hair loss, skin pigmentation and otitis externa. Reported late term side effects include brain necrosis, tumor regrowth, and visual and hearing impairment. In one study, 12 cats with pituitary tumors were treated with a coarse fractionated radiation protocol delivering a total dose of 37 Gy in 5 once weekly doses. Eight of these cats had insulin resistant diabetes mellitus secondary to acromegaly. Of these 8 cats, 5 no longer required insulin therapy, 2 became stable diabetics, and 1 required less insulin. In addition, 3 of 4 cats had improved neurologic signs. The mean survival time of cats in this study was approximately 18 months[19]. In another study, 14 cats with confirmed acromegaly and insulin resistant diabetes were treated with a total dose of 3,700 cGy divided into 10 fractions (3 per week). Thirteen of the 14 cats had improved insulin responses. The average insulin dosage reduction was approximately 75%. Six of the cats went into complete diabetic remission and at the time the article was written 3 of the 6 remained in remission. The median survival time of cats in this study was 28 months[20].

Conclusion

Feline acromegaly is likely an under diagnosed disease in older male cats, especially in patients with insulin-resistant diabetes. There is no single diagnostic test for acromegaly. The diagnostician should use history, clinical signs, laboratory tests (GH and IGF-1), and advanced imaging to arrive at a diagnosis. There are several treatments options, however, clinical studies on long-term safety and efficacy are limited and often lack controls. Until more work is done evaluating medical treatments such as somatostatin analogues and growth hormone antagonists, most patients are best treated with either surgery or radiation therapy to control GH levels, improve glycemic control, and improve or prevent the development of neurologic signs.

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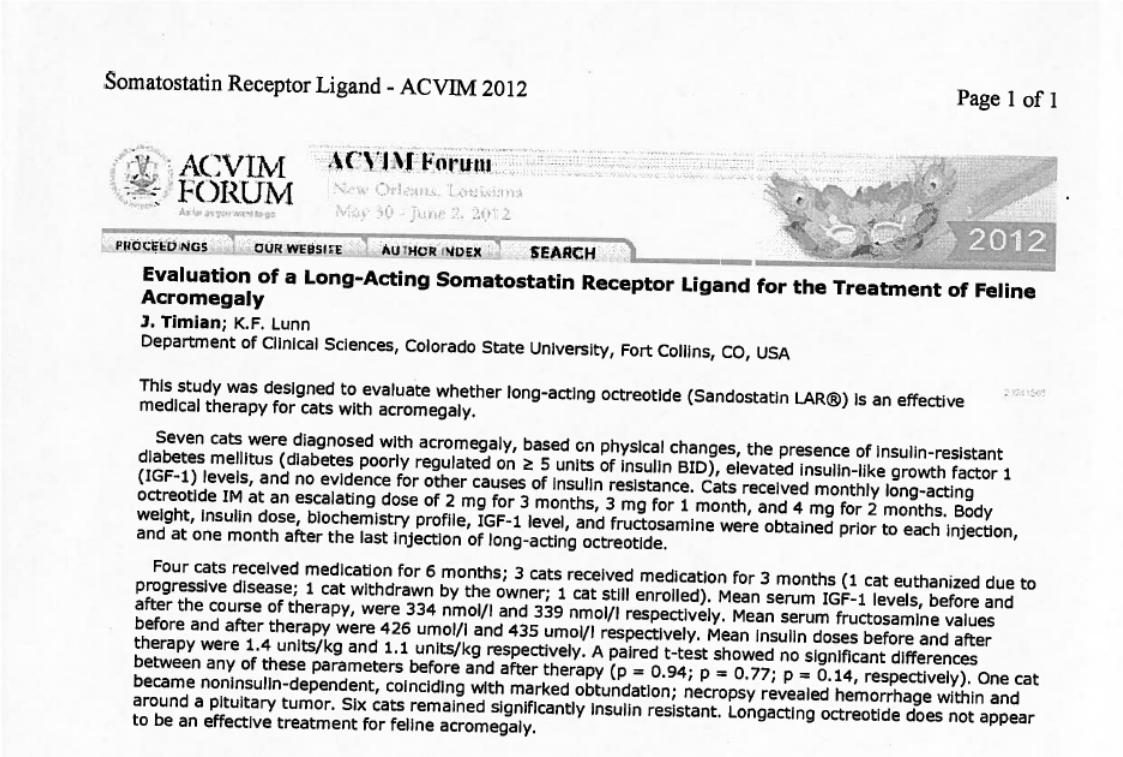

Somatostatin Receptor Ligand - ACVIM 2012

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Evaluation of a Long-Acting Somatostatin Receptor Ligand for the Treatment of Feline Acromegaly

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This study was designed to evaluate whether long-acting octreotide (Sandostatin LAR®) is an effective medical therapy for cats with acromegaly.

Seven cats were diagnosed with acromegaly, based on physical changes, the presence of insulin-resistant diabetes mellitus (diabetes poorly regulated on ≥ 5 units of insulin BID), elevated insulin-like growth factor 1 (IGF-1) levels, and no evidence for other causes of insulin resistance. Cats received monthly long-acting octreotide IM at an escalating dose of 2 mg for 3 months, 3 mg for 1 month, and 4 mg for 2 months. Body weight, insulin dose, biochemistry profile, IGF-1 level, and fructosamine were obtained prior to each injection, and at one month after the last injection of long-acting octreotide.

Four cats received medication for 6 months; 3 cats received medication for 3 months (1 cat euthanized due to progressive disease; 1 cat withdrawn by the owner; 1 cat still enrolled). Mean serum IGF-1 levels, before and after the course of therapy, were 334 nmol/l and 339 nmol/l respectively. Mean serum fructosamine values before and after therapy were 426 umol/l and 435 umol/l respectively. Mean insulin doses before and after therapy were 1.4 units/kg and 1.1 units/kg respectively. A paired t-test showed no significant differences between any of these parameters before and after therapy ($p = 0.94$; $p = 0.77$; $p = 0.14$, respectively). One cat became noninsulin-dependent, coinciding with marked obtundation; necropsy revealed hemorrhage within and around a pituitary tumor. Six cats remained significantly insulin resistant. Longacting octreotide does not appear to be an effective treatment for feline acromegaly.