

FELINE ACROMEGALY



Our mission is to redefine and elevate your pet's health through collaborative, minimally-invasive, and compassionate care that supports the well-being of your pet and peace of mind for your family.

David Bruyette, DVM, DACVIM, FNAP

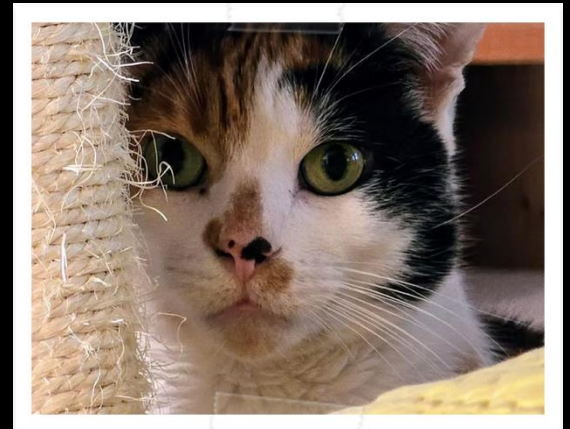
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FELINE ACROMEGALY

Introduction

History, signalment, and clinical signs

Diagnostics

Laboratory tests

Imaging

Treatment

Medical

Surgical

Radiation

Areas for future research

GROWTH HORMONE

Growth hormone is produced in the pars distalis of the anterior pituitary – produced by acidophilic cells (somatotrophs)

Rhythmic release

Release stimulated by hypothalamic growth hormone releasing hormone (GHRH)

Release also stimulated by ghrelin produced by the stomach

GROWTH HORMONE

Ghrelin release stimulated by meal initiation

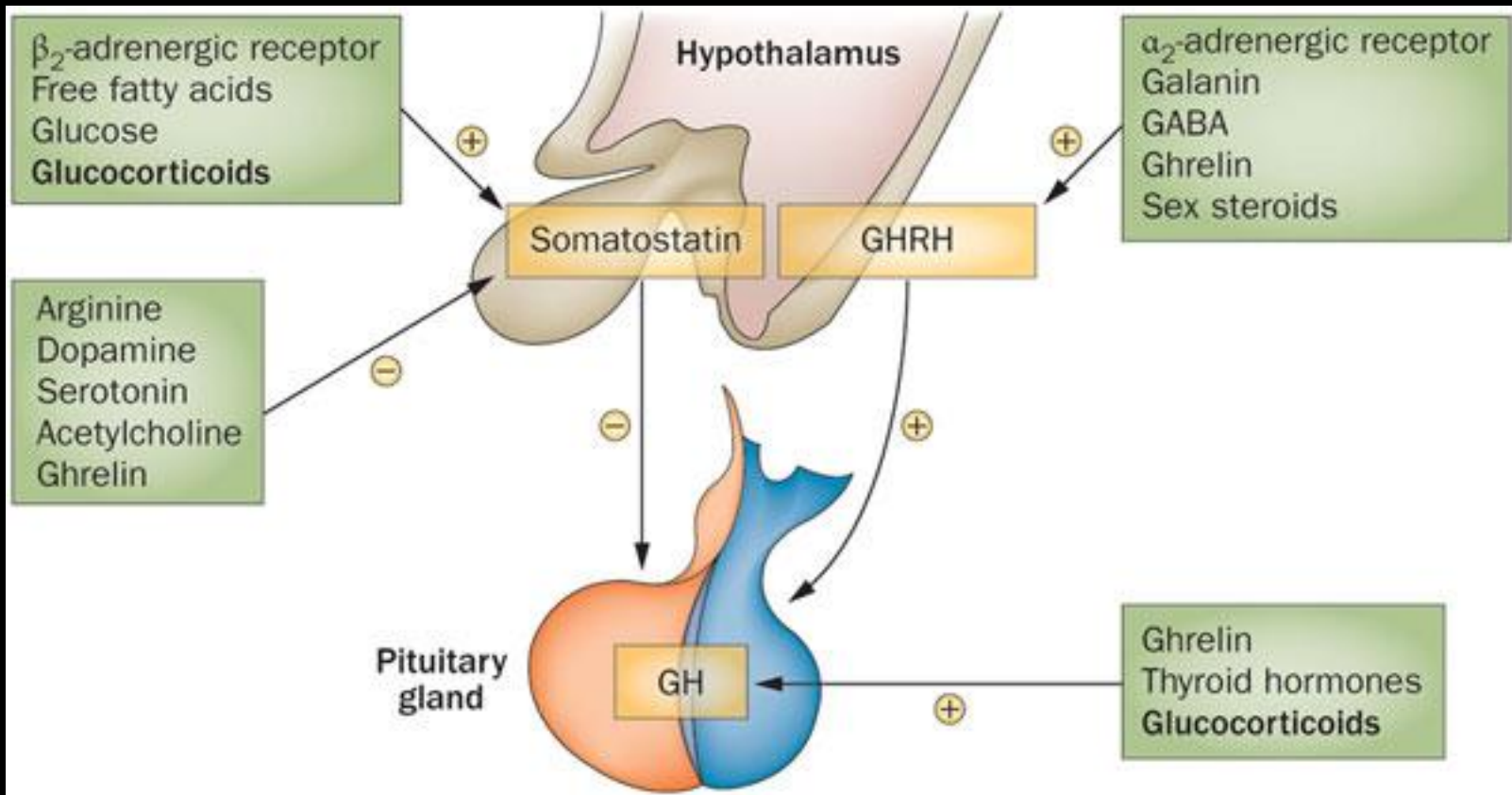
Ghrelin is a potent stimulator of the release of GH, especially in young dogs

Release inhibited by hypothalamic somatostatin

GH exhibits negative feed back at the level of the hypothalamus

Insulin like growth factor-1 (IGF-1) acts to inhibit GH release at the level of the hypothalamus and pituitary

GROWTH HORMONE REGULATION



ACTIONS OF GROWTH HORMONE

Rapid catabolic actions of GH

Due to insulin antagonism

Enhance lipolysis, gluconeogenesis, and restrict glucose transport across cell membranes

Net effect of GH is hyperglycemia

ACTIONS OF GROWTH HORMONE

Slow anabolic (hypertrophic) actions of GH

Mediated by insulin like growth factors (IGF' s)

IGF' s are produced in many different tissues

Have local (paraendocrine and autoendocrine) effects
mainly stimulation of growth

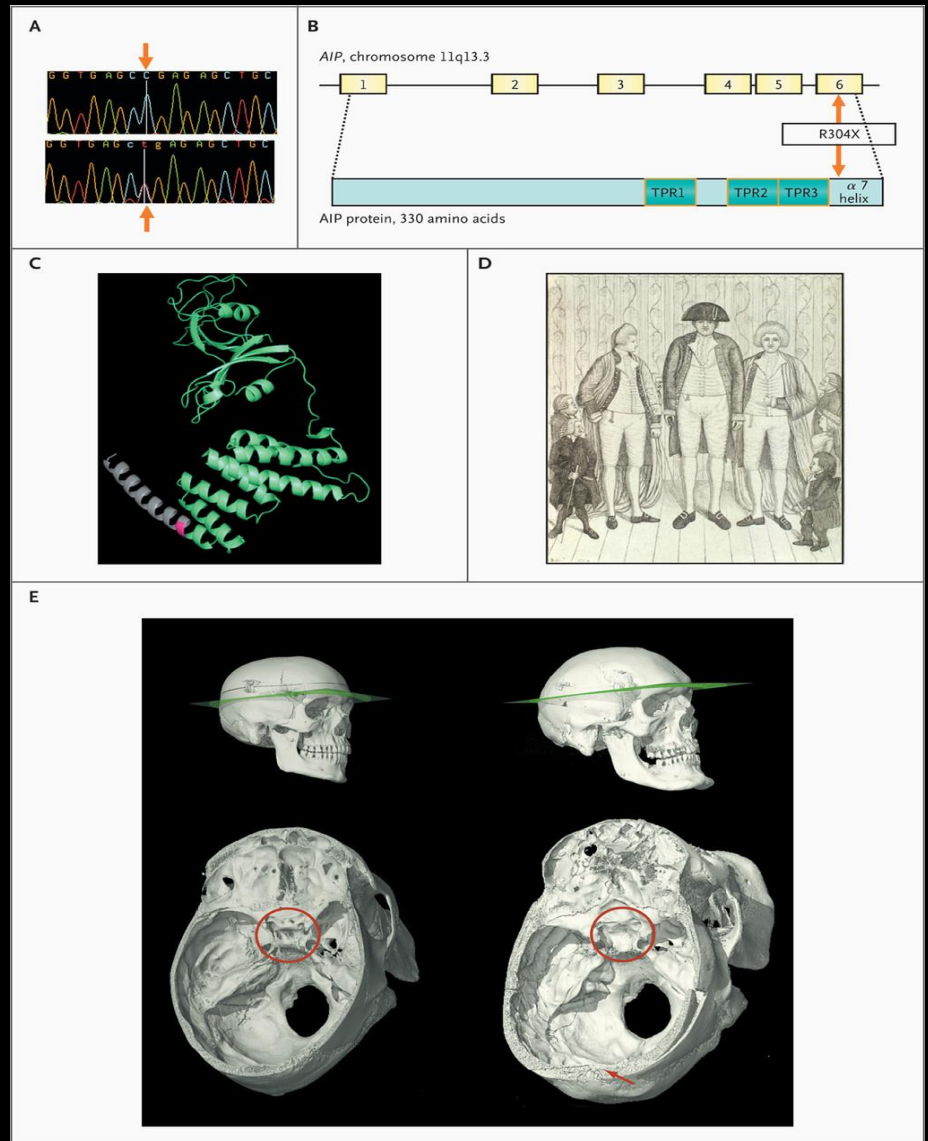
ETIOLOGY

Functional adenoma of the pars distalis of the pituitary gland releases GH in the face of negative feedback

Insulin resistance – GH induced post-receptor defect in the action of insulin in target cells

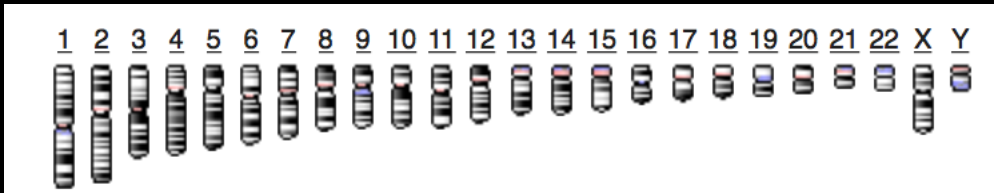
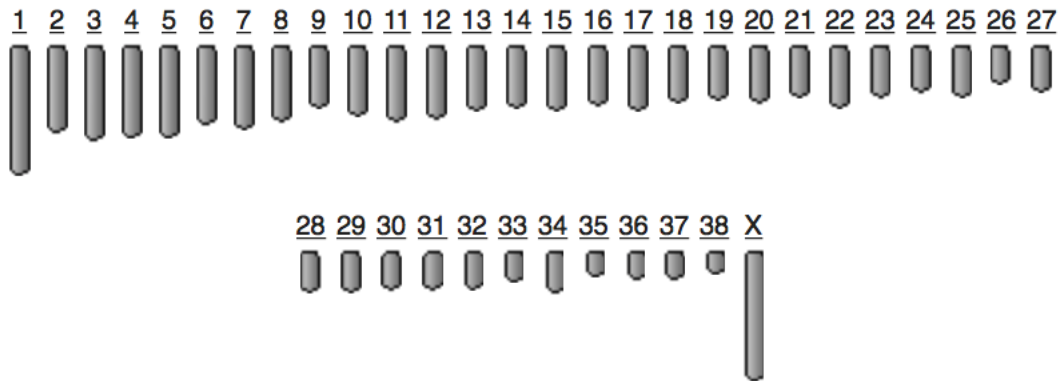
Anabolic effects of GH are responsible for characteristic signs of acromegaly

Images of the Index Patient and the Structure and Specific Mutation of *AIP*.





Coalescent analysis estimated that the mutant allele was carried by an ancestor around 57 to 66 generations ago (1425 to 1650 years ago)



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HUMAN      MADIIARLREDGIQKRVIQEGRGELPDFQDGTKATFHVRTLHSDDEGTVLDDSRARGKPM
CAT        MADLIARLREDGIQKRVIQEGRGELPDFQDGTKATFHVRTLHSDKEGTVLDDSRVRGKPM
***:*****.*****.*****

HUMAN      ELIIGKKFKLPVWETIVCTMREGEIAQFLCDIKHVLYPLVAKSLRNIAVGKDPLEGQRH
CAT        ELIIGKKFKLPVWETIVCTMREGEIAQFCCDVKHVLYPLVAKSLRNIAAGKDPLEGQRH
*****.*****.*****

HUMAN      CCGVAQMREHSSLGHADLDALQQNPQPLIFHMEMLKVESPGTYQQDPWAMTDEEKAKAVP
CAT        CCGIAQMREHSSLGHADLDALQQNPQPLIFDIEMMLKVESPGTYQQDPWAMTDEEKAKAVP
***:***.*****.*****

HUMAN      LIHQEGNRLYREGHVKEAAAKYYDAIACLKNLQMKEQPGSPEWIQLDQQITPLLLNYCQC
CAT        VIHQEGNRLYREGHVREAAAKYYDAIACLKNLQMKEQPGSPDWIQLDQQITPLLLNYCQC
:*****.*****.*****

HUMAN      KLVVEEYEVLDHCSSILNKYDDNVKAYFKRGKAHAAVWNAQEAQADFAKVLELDPALAP
CAT        KLVAQEYEVLDHCSSILNKYDDNVKAYFKRGKAHAAVWNAQEAQADFAKVLELDPALAP
***:*****

HUMAN      VVSRELQALEARIRQKDEEDKARFRGIFSH
CAT        IVSRELRALRARIRQKDEEDKARFRGIFSH
:*****.*****

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Fig. 1. Comparison of the homology of the human and feline AIP amino acid sequence using CLUSTAL multiple sequence alignment by MUSCLE (3.8) (<http://www.ebi.ac.uk/Tools/msa/muscle>). The feline AIP protein was 96% homologous to the human AIP protein. AIP, aryl-hydrocarbon-receptor interacting protein.

NCBI Gene ID: 101092293

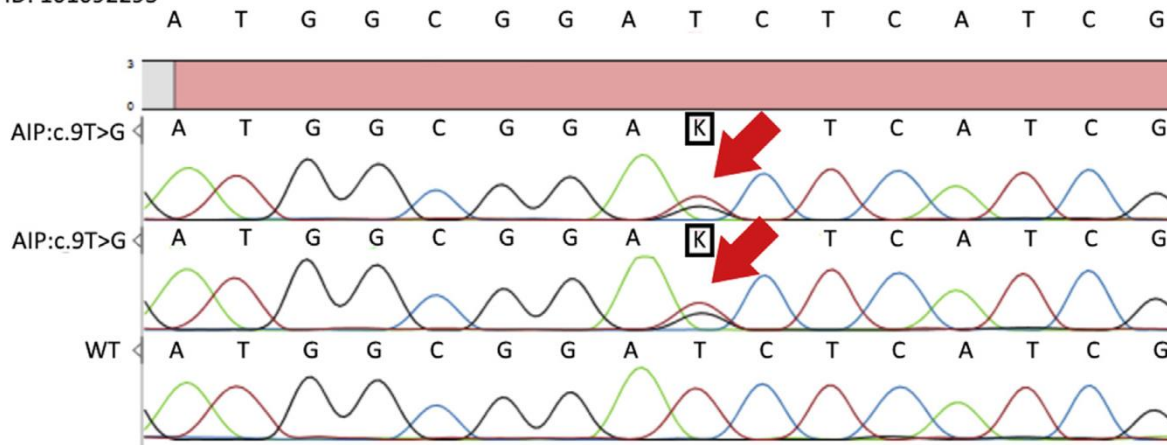


Fig. 2. Sanger sequencing chromatographs from 3 cats. The nucleotides shown represent the first 16 nucleotides of exon 1 of the feline *AIP* gene. The top 2 chromatographs contain the AIP:c.9T > G SNP (highlighted by red arrows) and the third chromatograph is the wild-type (WT) feline *AIP* sequence. The AIP:c.9T > G SNP is heterozygous at nucleotide 9 and labeled K as denoted by the IUPAC nucleotide ambiguity code nomenclature. AIP, aryl-hydrocarbon-receptor interacting protein. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

ETIOLOGY

Genetic Mutations

AIP gene

Involved with xenobiotic metabolizing enzymes

Environmental Factors

Organohalogenated Contaminants (OHC)

PCB, PDBE

Together they may lead to tumorigenesis

INCIDENCE

184 cats with variably controlled diabetes

59 (32.1%) had markedly high IGF-1 concentrations

18 were subsequently examined, and acromegaly was confirmed by demonstration of a pituitary mass on CT imaging in 17/18

INCIDENCE

225 cats with variably controlled diabetes

40 (17.8 %) had markedly high IGF-1 concentrations

1222 cats with diabetes

323 (26.4 %) had IGF-1 suggesting acromegaly

90% had a pituitary mass

SIGNALMENT

Middle-aged to older cats

Male castrated

No breed predilection (Maine Coon)

May be biased as most diabetic cats are middle-aged to older, male castrated cats and most acromegalics are diagnosed because they are poorly controlled diabetics

HISTORY AND CLINICAL SIGNS

Insulin resistant diabetes mellitus

Insulin dose > 1.5-2.2 U/kg SQ BID

BG persistently > 300 mg/dl

Persistent pu/pd, polyphagic, **with weight gain**

Organ enlargement

Hepatomegaly, renomegaly, adrenomegaly, pancreatic enlargement

HISTORY AND CLINICAL SIGNS

Increased body size and weight

Enlarged feet

Broad face

Protrusion of mandible

Increase interdental spacing

Stertorous breathing, stridor

HISTORY AND CLINICAL SIGNS



HISTORY AND CLINICAL SIGNS

Heart murmur, arrhythmia, gallop rhythm

HCM

Hypertension

Ocular hemorrhage, papilledema, blindness

Neurologic disease (uncommon)

Often macroadenoma (>1 cm)

Extends dorsally and compressing hypothalamus

Dullness, lethargy, abnormal behavior, circling,
impaired vision

Peripheral (diabetic) neuropathy

Weakness, plantigrade stance

HISTORY AND CLINICAL SIGNS

Renal failure secondary to glomerulopathy

Thickening of the glomerular basement membrane
and Bowman's capsule

Periglomerular fibrosis

Degeneration of renal tubules

Protein-losing nephropathy

Secondary to DM or Acromegaly?

Arthropathy

Periarticular periosteal reaction, osteophytes, cartilage
abnormalities

DIAGNOSIS

Clinical suspicion: History, clinical signs, signalment

CBC

Erythrocytosis (mild) – due to anabolic effects GH/IGF-1

Serum chemistry

Hyperglycemia

Increased ALP, ALT

Hypercholesterolemia

Hyperphosphatemia

GH induced renal retention of phosphorus

Hyperglobulinemia

Normal distribution on electrophoresis

Azotemia

DIAGNOSIS

Urinalysis

Glucosuria

Ketonuria

Proteinuria

Isosthenuria

GROWTH HORMONE

Assay not widely available (ovine test can be used – available in Europe)

May not be reliable as sole diagnostic

GH may be elevated in non-acromegalic diabetic cats

Portal insulin is needed for the production on IGF-1 in the liver

Only intraperitoneal insulin administration can increase portal insulin

IGF-1 is an important negative feedback inhibitor of GH

GH production is cyclic

GROWTH HORMONE

GH level usually less than 5 ng/ml

Some non-acromegalic diabetics may have elevated GH levels (6%) but depends on cutoff's

In early stages of disease may not be elevated outside of reference range

In later stages (anabolic clinical signs apparent) GH levels typically significantly elevated 10-25 ng/ml

INSULIN-LIKE GROWTH FACTOR-1

IGF-1 increases when GH chronically elevated

IGF-1 concentration elevations reflect GH levels over last 24 hours

IGF-1 protein bound

- Levels are less likely to fluctuate

- Longer half-life

Widely available (MSU)

Normal range 5-70 nmol/L

Cats with acromegaly > 100 nmol/L

INSULIN-LIKE GROWTH FACTOR-1

Some non-acromegalic diabetics may have elevated IGF-1 levels

Starkey et al. found that diabetic cats with long-term insulin treatment (> 14 months) had higher IGF-1 levels than non-diabetics

Hypothesis: Insulin treatment and resolution of hyperglycemia may allow for beta cell regeneration (resolution of glucose toxicity). Subsequent return of beta cell function allows for increased portal insulin and the production of IGF-1 by the liver

INSULIN-LIKE GROWTH FACTOR-1

Berg et al. evaluated the medical records of 74 diabetic cats that had IGF-1 quantified.

Results: IGF-1 levels were significantly elevated in acromegalic diabetic cats when compared to diabetic and healthy cats. No correlation between IGF-1 levels and duration of insulin treatment was found. Concluded IGF-1 was 84% sensitive and 92% specific for acromegaly.

However, diagnosis of acromegaly in this study was made by history and clinical signs. Acromegaly was not confirmed by identifying a pituitary mass by advance imaging or necropsy.

IMAGING: RADIOGRAPHS

Radiologic findings

Hyperostosis of the calvarium

Spondylosis deformans of the spine

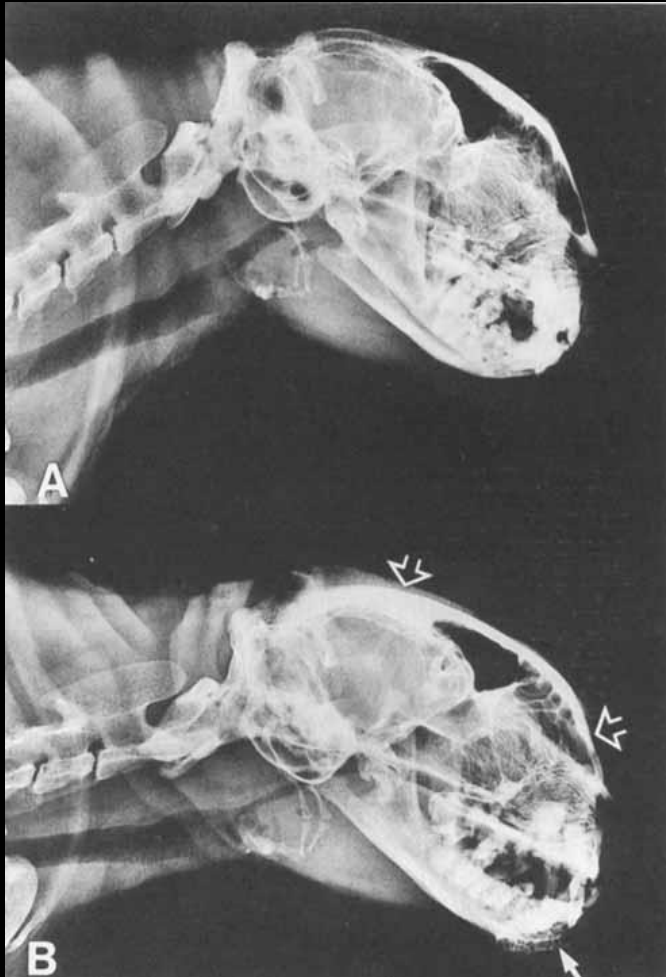
Protrusion of the mandible

Degenerative joint changes – periosteal reaction, osteophytes, soft tissue swelling, collapse of joints spaces

Thoracic radiographs may be consistent with CHF/
HCM

Abdominal radiographs may reveal organomegaly

IMAGING: RADIOGRAPHS



IMAGING: ULTRASOUND

Abdominal ultrasound

Hepatomegaly

Renomegaly

Adrenomegaly

ADVANCED IMAGING

Detection of pituitary mass

CT

MRI

Some pituitary masses were only identified by
MRI

Lack of mass does not rule out acromegaly

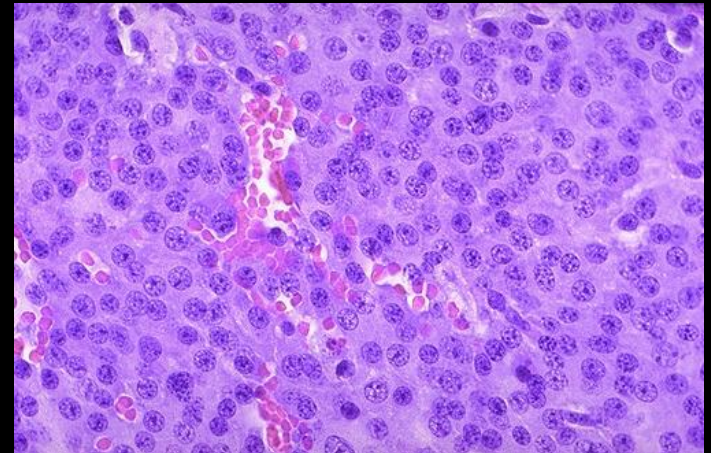
Early in the disease a mass may not be detected

HISTOPATHOLOGY

Histopathology

Acidophil proliferation

Reported in suspected acromegalics with negative CT and MRI



ADRENOCORTICAL TESTING

Hyperadrenocorticism and acromegaly are 2 main causes for insulin resistance in cats

Both can be associated with a pituitary mass

Both can cause bilateral adrenomegaly

Acromegaly can cause nodular hyperplasia of the adrenals

PDH can cause bilateral adrenal hyperplasia as well

Acromegalics should respond normally to ACTH stimulation and LDDS tests

MEDICAL MANAGEMENT

Somatostatin analogs

Octreotide, lanreotide, lasireotide, paseriotide

Bind to somatostatin receptors and suppress release of GH from pituitary 90% effective in humans

Singerland et al. – 5 cats with acromegaly – A single dose of octreotide caused a significant decrease in plasma GH (up to 90 minutes after injection)

MEDICAL MANAGEMENT

Seven 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.

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.

MEDICAL MANAGEMENT

Eight diabetic cats with acromegaly. On day 1 and 5, serum IGF-1 concentration was established and glycemic control assessed using a 12-hour blood glucose (BG) curve, measuring BG every 2 hours. On day 2, 3 and 4, the cats were injected with 0.03 mg/kg SOM230 s.c. BID.

All eight cats showed a significant decrease in serum IGF-1 (mean 1884 ng/ml; day 5: 1169 ng/ml) and average 12-hour BG (day 1: 20 mmol/l; day 5: 13 mmol/l). A significant insulin dose reduction was necessary in all cats (day 1: 10.8 iu/injection; day 5: 3.1 iu/injection). No side effects were noticed during or after the 3-day treatment period, apart from hypoglycemia in one cat.

Twelve diabetic cats with acromegaly. Cats received 8 mg/kg SC pasireotide LAR once monthly for 6 months. Fructosamine concentration, IGF-1 concentration and a 12-hour blood glucose curve (BGC) were performed at baseline and once monthly thereafter to monitor treatment response. A repeat CT-scan was performed at the end of the trial.

Seven of 12 cats completed the trial; 3 of 12 cats entered diabetic remission. Trial withdrawal occurred after a median of 2 months (range 1–4.5 months) due to persistence of uncontrolled diabetes mellitus (n = 1), diarrhea (n = 2), a hypoglycemic event (n = 1) and an episode of diabetic ketoacidosis (n = 1). A significant decrease in IGF-1, insulin dose, fructosamine, though not MBG was documented. Adverse events included soft stools (9/12), worsening polyphagia (3/12), hypoglycemia (4/12). Maximum pituitary mass height had increased in 2/7, decreased in 4/7 and remained the same in 1/7 cats.

MEDICAL MANAGEMENT

GH receptor antagonist

Pegvisomant – human medication

Use not reported in cats

Dopamine agonists

Bromocriptine, cabergoline

Used in humans – 70% effective (decreased GH levels), especially in conjunction with other medications

Single reported case study: No effect on reducing insulin requirement or clinical signs of disease

Insulin

Insulin sensitivity – may cause sudden precipitous drop in blood glucose

RADIATION THERAPY

Multiple fraction and single fraction treatments have been used

Reported doses range from 1,500 – 5,400 cGy

Efficacy in cats

Difficult to assess due to small samples size

Time to remission/clinical improvement: 1-10 months

Insulin resistance improved

Reductions in tumor size

Disadvantages: cost, availability, repeated anesthesia

RADIATION THERAPY

Acute effects: hair loss, skin pigmentation, otitis externa

Early-delayed brain effects: dullness, ataxia, stiffening of limbs, hypermetria

Late effects: blindness, hearing impairment, brain necrosis

Clinically hard to distinguish late effects on the nervous system from tumor regrowth -

Survival times: 5-28 months

RADIATION THERAPY

Mayer et al. – 8 cats with pituitary tumors – 3 suspected acromegaly, 4 hyperadrenocorticism. 4,500-5,400 cGy doses in fractions of 270-300 cGy fractions (6-MV linear accelerator). 2/4 that had follow up imaging showed decreased tumor size. All 6 cats that were insulin resistant became more insulin responsive – MST 17.4 months

Sellon et al. – 11 cats with pituitary tumors – Linear accelerator – single large dose 15-20 Gy – 8 cats treated once, 2 cats treated twice, 3 cats treated 3 times – 7/11 had improvement of clinical signs – 5/9 cats with insulin resistance had improved responses to insulin – 2/2 cats with neurologic signs improved – MST 25 months

RADIATION THERAPY

Brearily et al. – 12 cats with pituitary tumors – 4 with neurologic signs – 8 with insulin resistance due to acromegaly – Linear accelerator 3700 cGy in 5 once weekly doses

Of the cats with neurologic signs, 1 died before finishing its course, the other 3 showed complete or partial improvement

Of the cats with insulin resistant diabetes mellitus, 5 no longer required insulin, one less insulin, and 2 stabilized – MST 72.6 weeks

RADIATION THERAPY

Kaser-Hotz et al. – 5 cats with pituitary tumors – 3 presented with neurologic signs – presented with insulin resistant diabetes mellitus secondary to acromegaly – 10-12 fractions of 3.5-4.0 Gy 3x/week with a mean dose of 39 Gy – 4 cats had follow up CT, 1 tumor disappeared, the 3 others decreased in size or remained stable – 1 cat with insulin resistant diabetes mellitus had a mild dose reduction, the other cat had its insulin dose cut in half

RADIATION THERAPY

Peterson et al. (early paper) – 2 cats with acromegaly – treated with cobalt therapy – 4,800 cGy total dose – one cat had decreased GH concentration – remission of insulin resistance and neurologic signs

SURGICAL MANAGEMENT

Transsphenoidal hypophysectomy or adenoma removal

Increasing availability

Procedure also used to treat pituitary dependent hyperadrenocorticism in cats and dogs

Hypopituitarism

Patients may require life long treatment with cortisone and L-thyroxine, +/- desmopressin

Cryohypophysectomy

Reported in 2 cats – not effective in resolving insulin resistant diabetes mellitus in either case, more complications

TRANSSPHENOIDAL HYPOPHYSECTOMY

“Chairman Meow”

13 yr MC DSH, 6.5 kg

Hx: Insulin resistant diabetes mellitus

14 u glargine insulin BID

Diagnosed with acromegaly

IGF-1 = 477 nmol/L (12-97)

MRI: Pituitary mass

TRANSSPHEOIDAL HYPOPHYSECTOMY

Image size: 256 x 256
View size: 584 x 584
WL: 670 WW: 1341

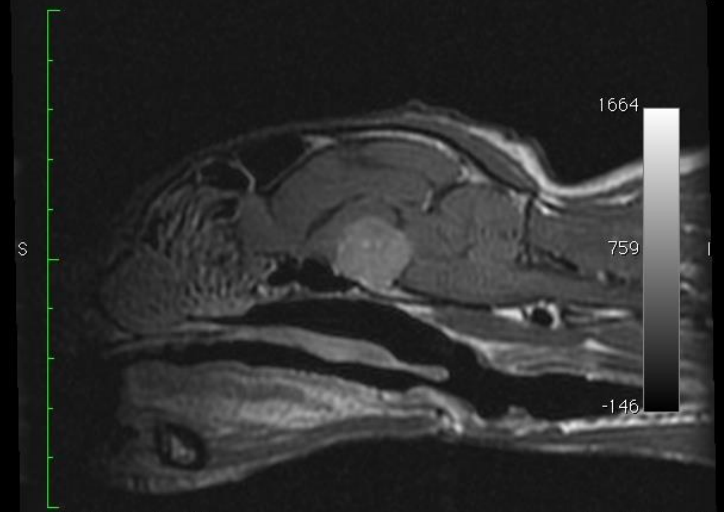
DeBoto,Chairman Meow 4976 (14 y , 13 y)
3 KG Dog Knee-- 0-Ax T1 SE H 3mm
1673
5



Zoom: 228% Angle: 0
Im: 10/20 (I -> S)
Uncompressed
Thickness: 3.00 mm Location: 45.30 mm A
TE: 13 TR: 500
FS: 10000
1/12/10 9:58:53 AM
Made In OsiriX

Image size: 256 x 256
View size: 595 x 584
WL: 759 WW: 1810

DeBoto,Chairman Meow 4976 (14 y , 13 y)
Thin slice Pituitary(1mm-- 0-Sag T1 SE S unilateral
1673
8



Zoom: 228% Angle: 268
Im: 9/16 (L -> R)
Uncompressed
Thickness: 1.00 mm Location: 9.44 mm A
TE: 16 TR: 500
FS: 10000
1/12/10 10:26:25 AM
Made In OsiriX

TRANSSPHENOIDAL HYPOPHYSECTOMY

Transsphenoidal surgery

4 weeks post-op off insulin

8 weeks post off all hormone replacement therapy

MRI and repeat IGF-1 at 6 and 12 months

ACROMEGALY: PROGNOSIS

Guarded

Reported survival times ranges from 4-60 months

Most die or are euthanized for heart failure, renal failure, respiratory distress, neurologic signs, hypoglycemic coma

FELINE ACROMEGALY

Studies on pathogenesis

Role of somatostatin analogues

GH receptor antagonists

Dopaminergic therapy