FELINE ACROMEGALY

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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

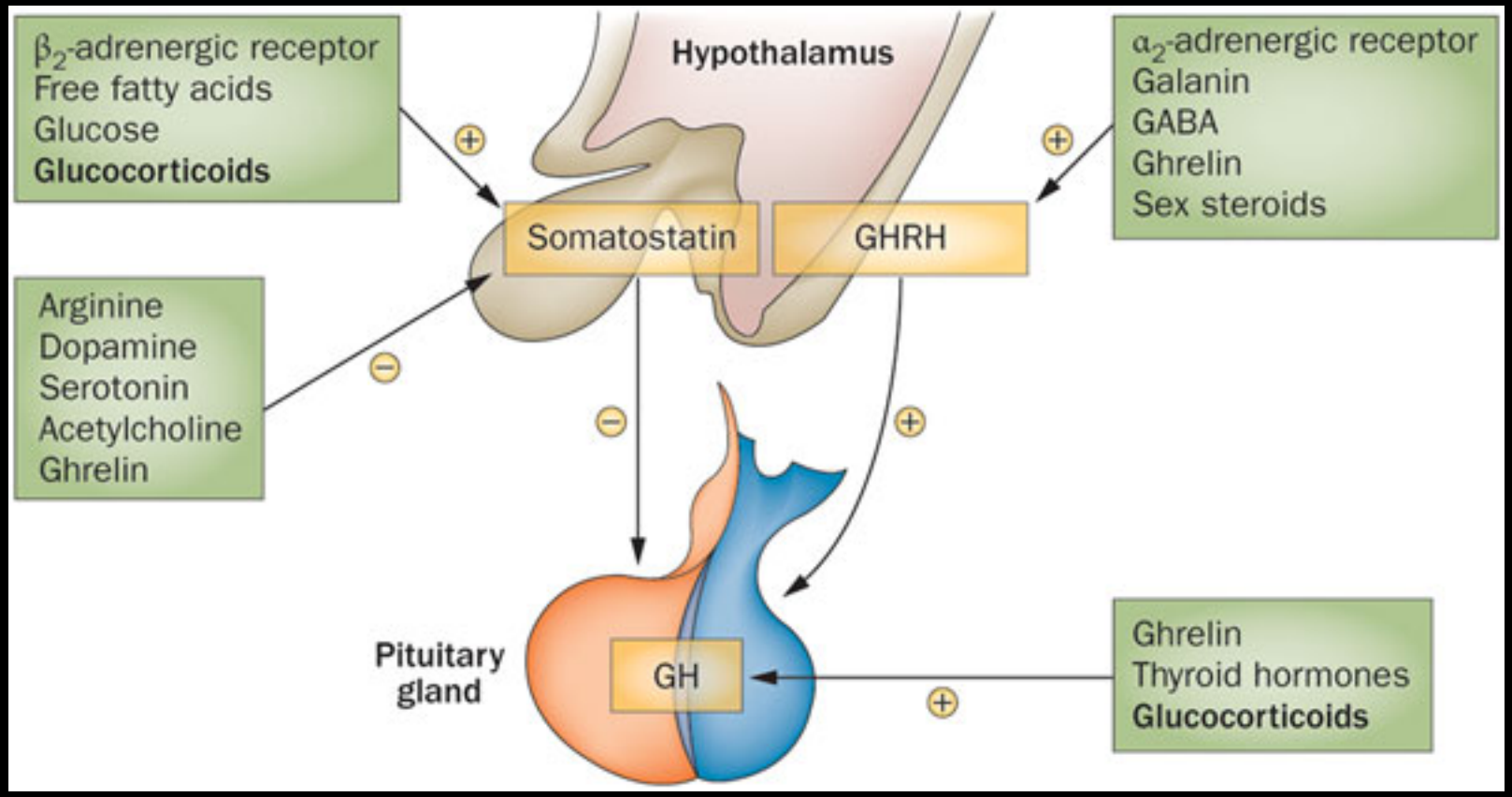
Ghrelin is a potent stimulator of the release of GH, especially in young dogs

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

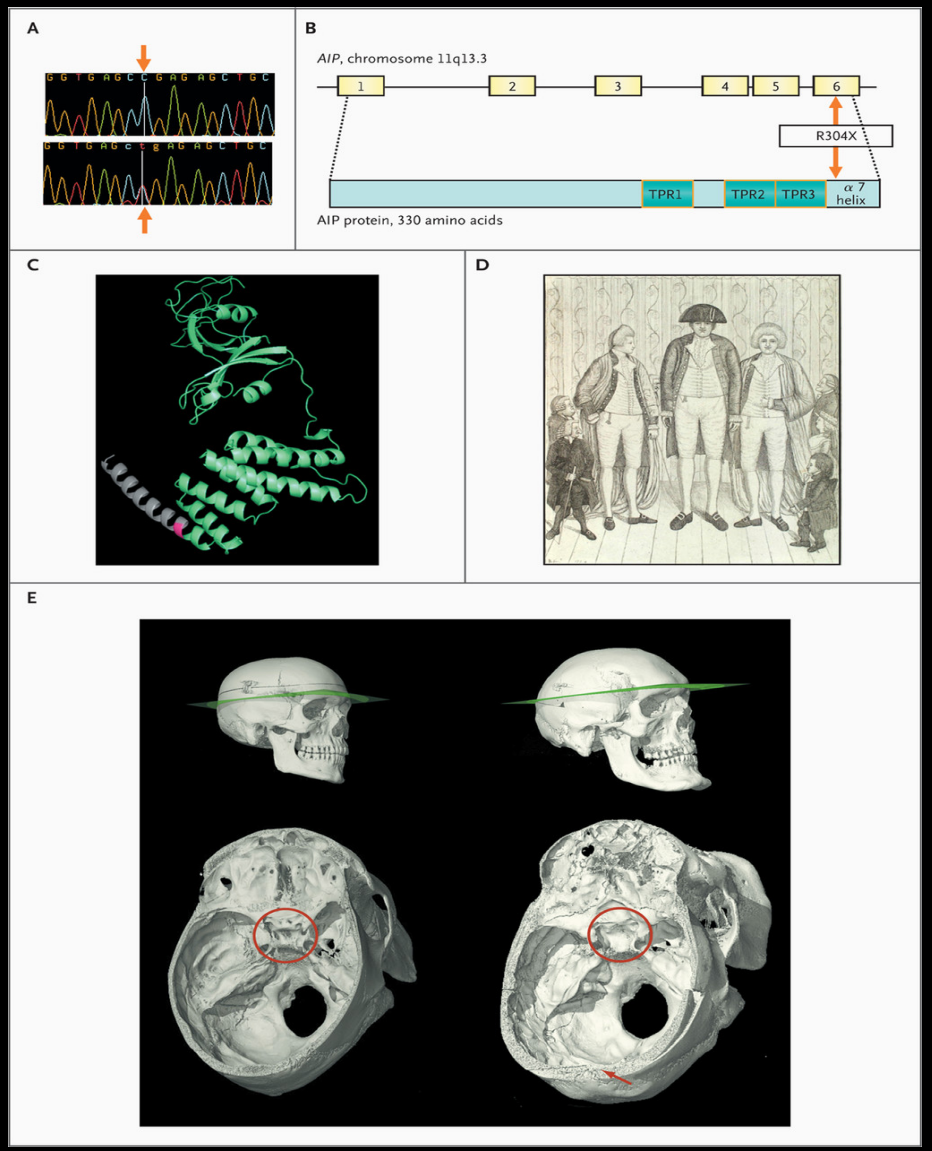
ETIOLOGY

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

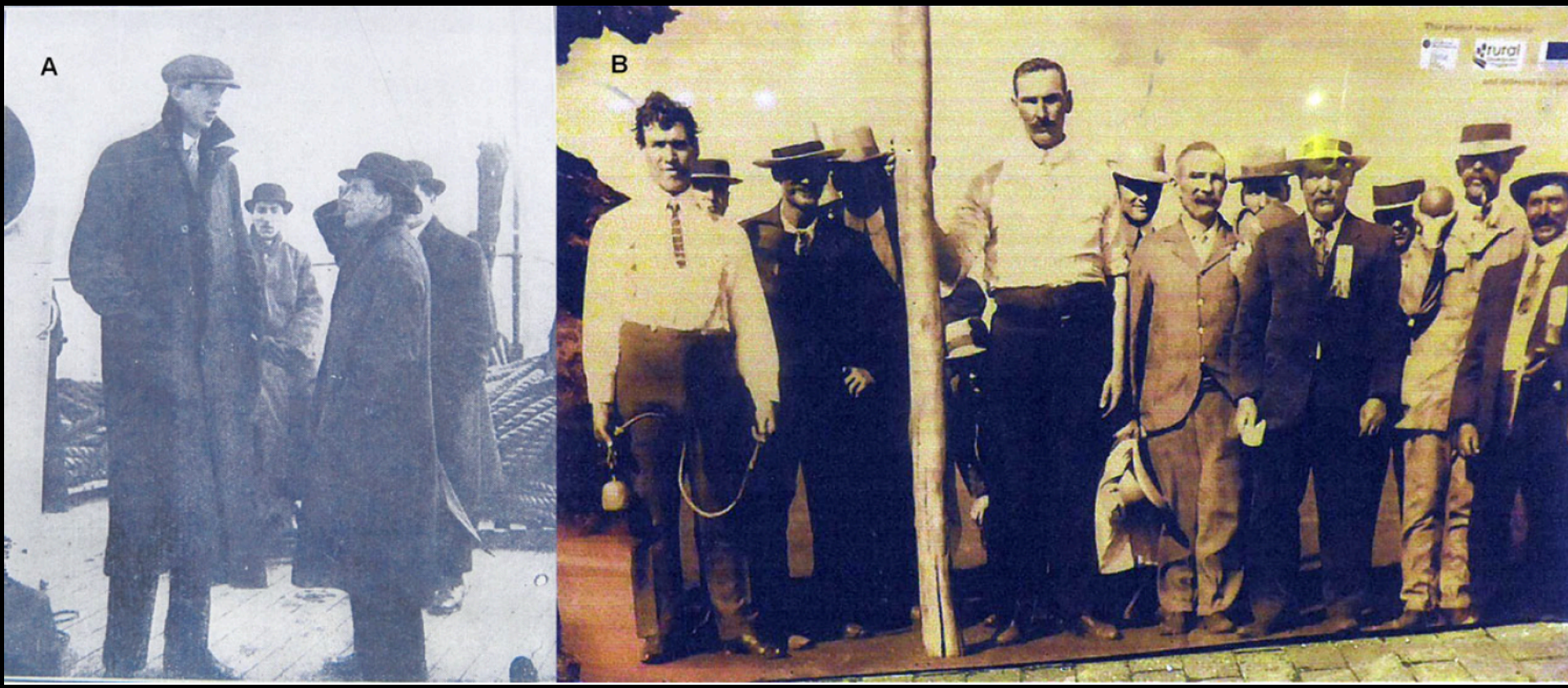
Insulin resistance – GH induced post-receptor defect in the action of insulin in target cells

Anabolic effects of GH are responsible for characteristic signs of acromegaly

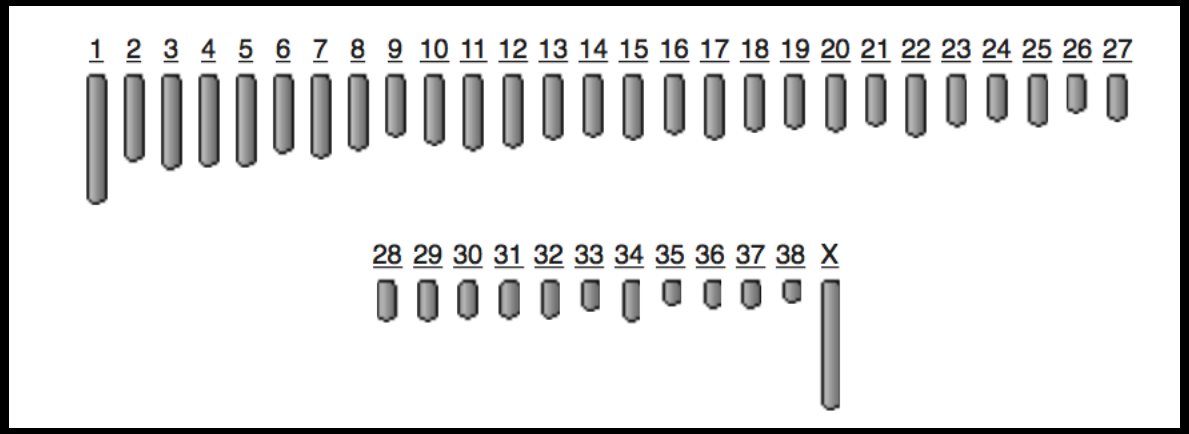
Images of the Index Patient and the Structure and Specific Mutation of *AIP.*



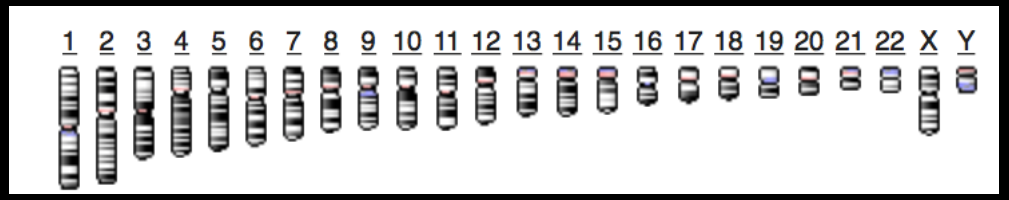
CHAHAL HS ET AL. N ENGL J MED 2011;364:43-50.



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


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27
28 29 30 31 32 33 34 35 36 37 38 X


A1 A2 A3 B1 B2 B3 B4 C1 C2 D1 D2 D3 D4 E1 E2 E3 F1 F2 X


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X Y

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HUMAN          MADIIARLREDGIQKRVIQEGRGELPDFQDGTKATFHYRTLHSDDEGTVLDDSRARGKPM
CAT            MADLIARLREDGIQKRVIQEGRGELPDFQDGTKATFHYRTLHSDKEGTVLDDSRVRGKPM
               ***:*************************************.*********.*****

HUMAN          ELIIGKKFKLPVWETIVCTMREGEIAQFLCDIKHVVLYPLVAKSLRNIAVGKDPLEGQRH
CAT            ELIIGKKFKLPVWETIVCTMREGEIAQFCCDVKHVVLYPLVAKSLRNIAAGKDPLEGQRH
               *************************** **:*****************.**********

HUMAN          CCGVAQMREHSSLGHADLDALQQNPQPLIFHMEMLKVESPGTYQQDPWAMTDEEKAKAVP
CAT            CCGIAQMHEHSSLGHADLDALQQNPQPLIFDIEMLKVESPGTYQQDPWAMTDEEKAKAVP
               ***:***.********************** :****************************

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

HUMAN          KLVVEEYYEVLDHCSSILNKYDDNVKAYFKRGKAHAAVWNAQEAQADFAKVLELDPALAP
CAT            KLVAQEYYEVLDHCSSILNKYDDNVKAYFKRGKAHAAVWNAQEAQADFAKVLELDPALAP
               ***.:*****************************************************

HUMAN          VVSRELQALEARIRQKDEEDKARFRGIFSH
CAT            IVSRELRALEARIRQKDEEDKARFRGIFSH
               :*****.**********************
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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.

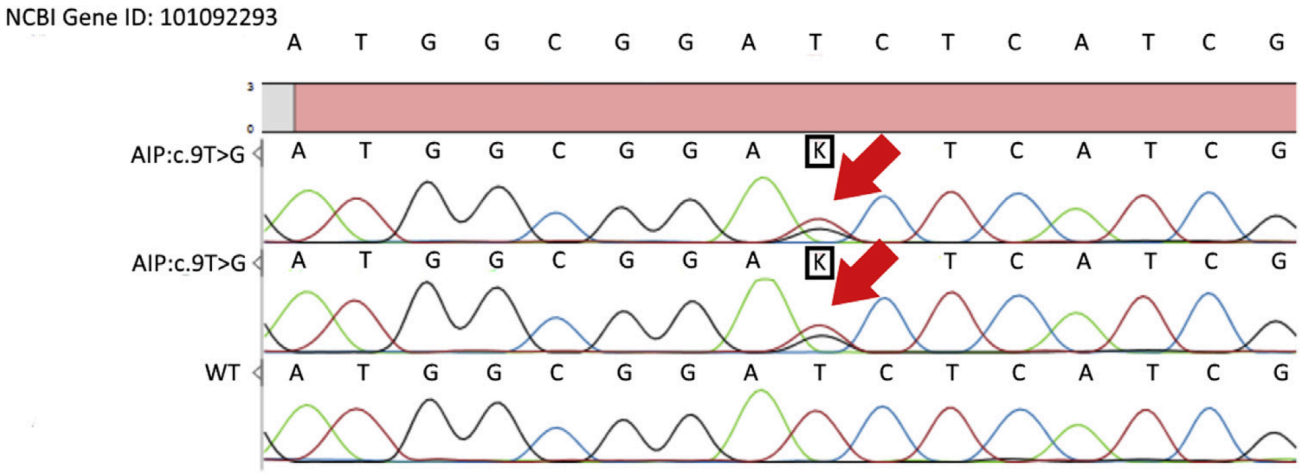


Fig. 2. Sanger sequencing chromatographs from 3 cats. The nucleotides shown represent the first 16 nucleotides of exon 1 of the feline *AIP* gene. The top 2 chromatographs contain the AIP:c.9T > G SNP (highlighted by red arrows) and the third chromatograph is the wild-type (WT) feline AIP sequence. The 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

Niessen SJM, Forcada Y, Mantis P, Lamb CR, Harrington N, Fowkes R, et al. (2015) Studying Cat (Felis catus) Diabetes: Beware of the Acromegalic Imposter. PLoS ONE 10(5): e0127794. doi:10.1371/journal.pone.0127794

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.

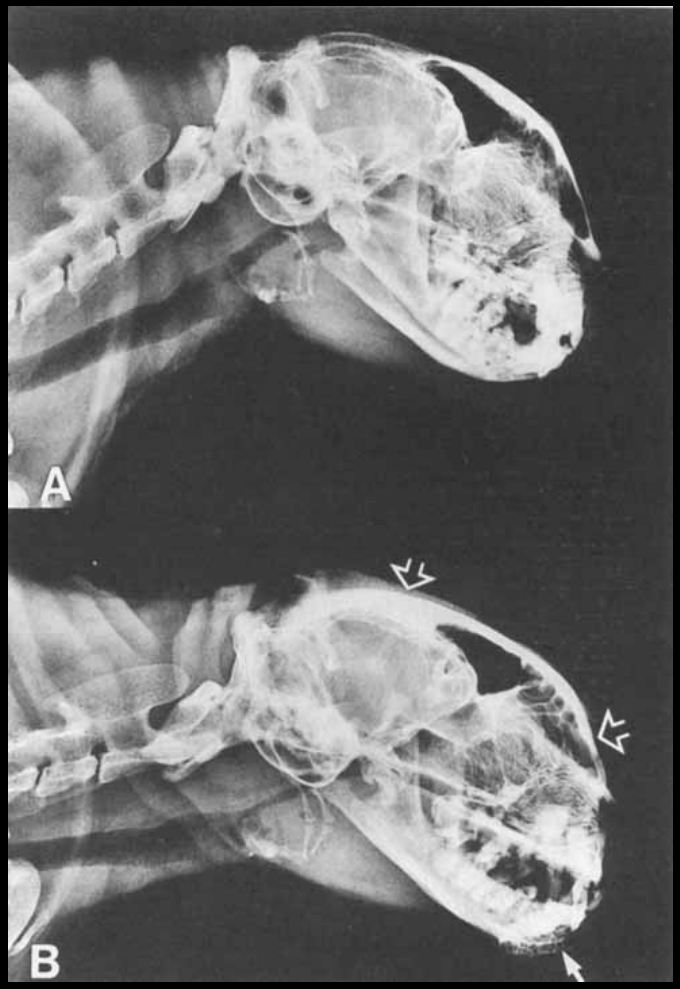
Results: IGF-1 levels were significantly elevated in acromegalic diabetic cats when compared to diabetic and healthy cats. No correlation between IGF-1 levels and duration of insulin treatment was found. Concluded IGF-1 was 84% sensitive and 92% specific for acromegaly.

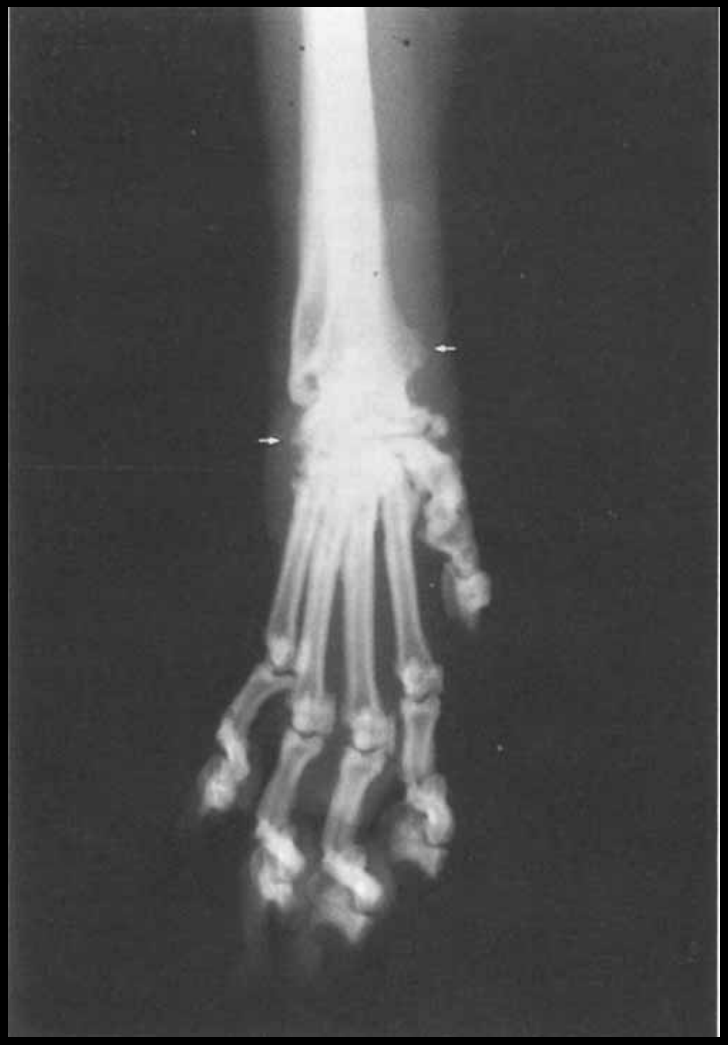
However, diagnosis of acromegaly in this study was made by history and clinical signs. Acromegaly was not confirmed by identifying a pituitary mass by advance imaging or necropsy.

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

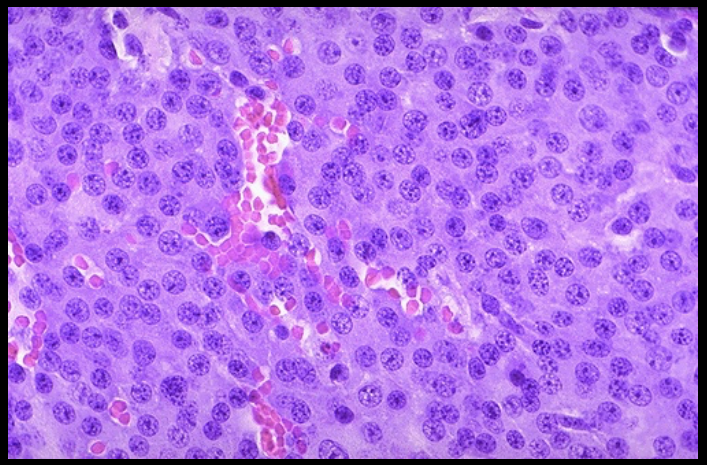
Early in the disease a mass may not be detected

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

Brearly 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 coarse, 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

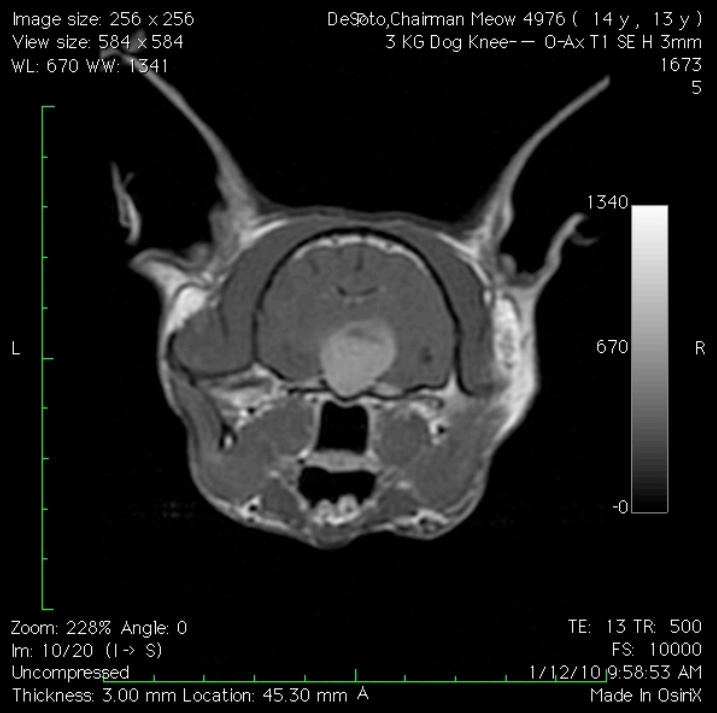
14 u glargine insulin BID

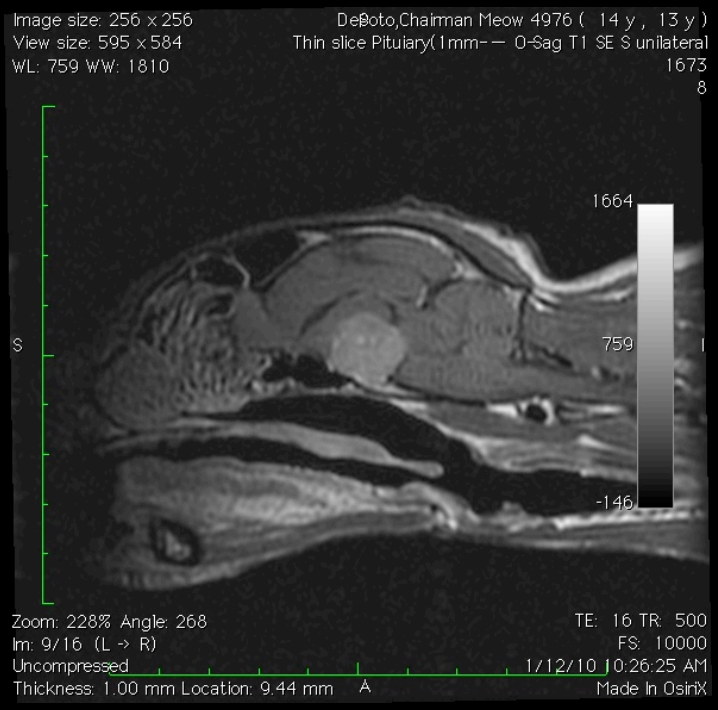
Diagnosed with acromegaly

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

MRI: Pituitary mass

TRANSSPHENOIDAL HYPOPHYSECTOMY





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