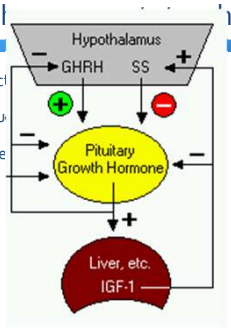
Feline acromegaly: How to diagnose it and treat it

Yaiza Forcada DVM PhD DECVIM PGCertVetEd FHEA MRCVS

1

Acromegaly: l ism

- Excess of GH produc
- GH stimulates produ
- Growth of soft tissue
- Insulin resistance
- Diabetes



2

Feline acromegaly: Causes

3

AIP gene mutations?

- In humans most tumours are spontaneous
- 20-40% familiar (Primary genetic cause)
- Feline acromegaly is similar to human familiar acromegaly
  - Male gender
  - Macroadenoma somatotrophs
  - Resistant to octreotide
- Feline AIP gene: 6 exons - 330 AA
- 98% homology with human AIP protein
- DNA cats with acromegaly and controls

4

AIP in feline acromegaly?

- Mutation in Exon 1
- Glutamic-Aspartic aminoacid change

20%

0%

5

6

Environment International 57-58 (2013) 60–67

Contents lists available at SciVerse ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Organohalogenated contaminants in domestic cats' plasma in relation to spontaneous acromegaly and type 2 diabetes mellitus: A clue for endocrine disruption in humans?

Alin C. Dirtu [a], Stijn J.M. Niessen [b], Philippe G. Jorens [c], Adrian Covaci [a,*]

[a] Toxicological Centre, University of Antwerp, Wilrijk, Antwerp, Belgium
[b] Department of Veterinary Clinical Sciences, The Royal Veterinary College, University of London, Hatfield, Herts, United Kingdom
[c] Department of Clinical Pharmacology, University of Antwerp and Antwerp University Hospital, Edegem, Antwerp, Belgium

ARTICLE INFO ABSTRACT

Group 1: Acromegalic cats
Group 2: Diabetic cats
Group 3: Non-endocrine matched controls

assess human exposure to chemicals present in indoor dust.

7

Table 2. Overview of the concentrations (mean, median, 10th, 25th, 75th and 90th percentile expressed in pg/mL) of persistent organic pollutants measured in serum samples collected from three groups of cats from the UK sampled in 2010-2011.

	Group 1 (G1) (acromegaly induced diabetes)	Group 2 (G2) (type 2 diabetes)	Group 3 (G3) (age matched controls)

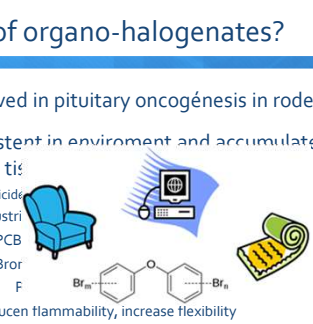
- All OHCs↑ in acromegalic cats
- ↑↑ PBDE in brominated fire retardants
- ↑↑ Metabolites OHCs
- Can explain geographical differences

Dirtu, Niessen, Jorens, Covaci, Env Int 2013

8

Role of organo-halogenates?

- Involved in pituitary oncogénesis in rodents
- + Persistent in enviroment and accumulate in living tis
  - + Pesticide
  - + Industri
    - PCB
    - Bror
      - F
- + Reducen flammability, increase flexibility



9

Role of organo-halogenates?

- Animals and humans are exposed through different routes
  - Food
  - Interior of houses
    - Dust ingestion
    - Cats washing themselves
- Comparable to feline hyperthyroidism

Dye 2007, Olczak 2005, Scarlett 1988

10

Clinical features

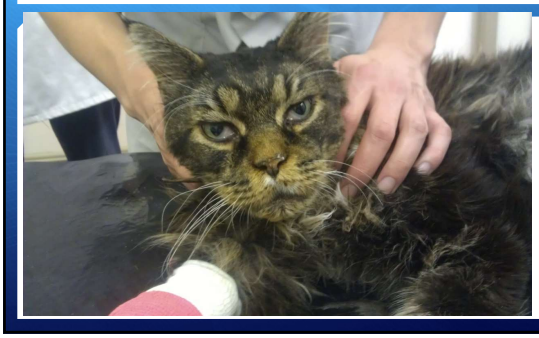
Prevalence

Feline acromegaly: In which patients to I need to look for it?

Causes

11

Acromegaly: clinical features



12

Acromegaly: epidemiology

- More common in male cats
- Average 11 years old
- Breeds: DSH, Maine Coon, Burmese

13

Acromegaly: Clinical signs(2007)

14

Acromegaly: clinical signs

2007

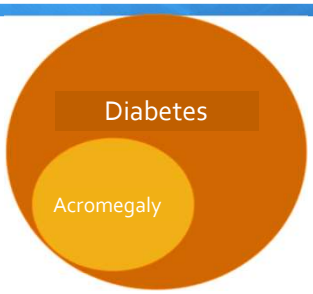
Diabetes with severe insulin resistance
- Weight gain
- Respiratory stridor
- Organomegaly
- Broad paws
- Broad facial features
- HCM

2021

- Younger
- Non-diabetic
  - Weight gain
  - Respiratory stridor
  - Normal facial features
  - No broad paws
  - HCM
  - Epilepsy

15

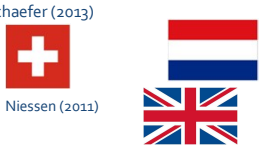
Feline acromegaly



16

Feline acromegaly: Prevalence

- 2007: Feline acromegaly has a relatively high prevalence in diabetic patients
  - 26-32% prevalence Niessen 2007, Berg 2007
- Recently: several other prevalence studies
- Schaefer (2013)



  - Niessen (2011)

17

Prevalence

- Schaefer abstract ECVIM Congress, JVIM, 2013
  - First opinion vets (Switzerland and Netherlands)
  - Se
  - T
  - [I
  - I
- N= 2
- [IGF-1
  - median 584
  - 17.8% IGF-1 > 1000 ng/ml

1 in 5

18

Prevalence

- Free fructosamine measurement of diabetic cats
- Leftover serum: IGF-
  - Different assay
- Cats had a free CT if
- N=1222
-
-

Different methodology
Different population

1 in 4

19

Evaluation of four methods used to measure plasma insulin-like growth factor 1 concentrations in healthy cats and cats with diabetes mellitus or other diseases

AJVR, 2012

Flurin Tschuor, Dr med vet; Eric Zini, Dr med vet; Stefan Schellenberg, Dr med vet; Monique Wenger, Dr med vet; Felicitas S. Boretti, Dr med vet; Claudia E. Reusch, Prof Dr med vet

Objective—To evaluate 4 methods used to measure plasma insulin-like growth factor (IGF) 1 concentrations in healthy cats and cats with diabetes mellitus or other diseases.

Animals—39 healthy cats, 7 cats with diabetes mellitus, and 33 cats with other diseases.

Procedures—4 assays preceded by different sample preparation methods were evaluated, including acid chromatography followed by radioimmunoassay (AC-RIA), acid-ethanol extraction followed by immunoradiometry assay (AEE-IRMA), acidification followed by immunochemiluminescence assay (A-ICMA), and IGF-2 excess followed by RIA (IE-RIA). Validation of the methods included determination of precision, accuracy, and recovery. The concentration of IGF-1 was measured with all methods, and results were compared among cat groups.

Results—The intra-assay coefficient of variation was < 10% for AC-RIA, A-ICMA, and AEE-IRMA and 14% to 22% for IE-RIA. The linearity of dilution was close to 1 for each method. Recovery rates ranged from 69% to 119%. Five healthy cats had IGF-1 concentrations > 1,000 ng/mL with the AEE-IRMA, but < 1,000 ng/mL with the other methods. Compared with healthy cats, hyperthyroid cats had significantly higher concentrations of IGF-1 with the A-ICMA method, but lower concentrations with the IE-RIA method. Cats with lymphoma had lower IGF-1 concentrations than did healthy cats regardless of the method used.

Conclusions and Clinical Relevance—Differences in the methodologies of assays for IGF-1 may explain, at least in part, the conflicting results previously reported in diabetic cats. Disorders such as hyperthyroidism and lymphoma affected IGF-1 concentrations, making interpretation of results more difficult if these conditions are present in cats with diabetes

20

Geographical differences

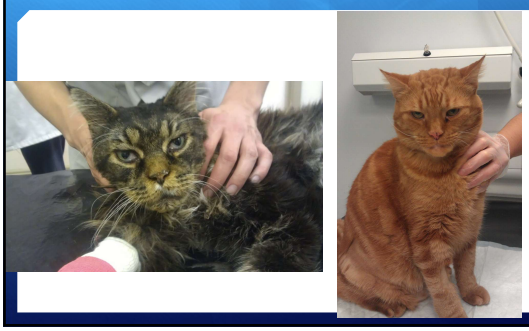
21

Prevalence

- Exact prevalence remains unknown
- But the message is the same:
- Acromegaly is still a common cause of DM in cats

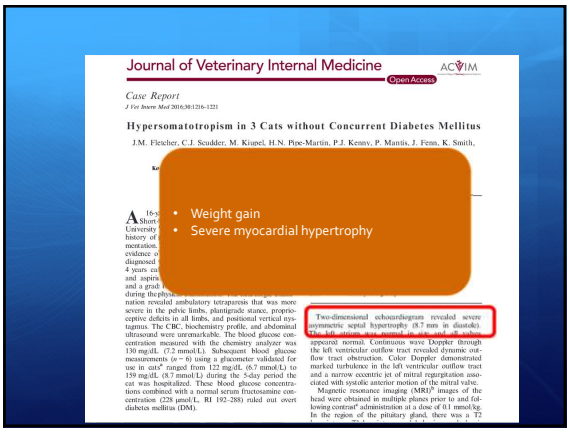
22

Boots (2007)

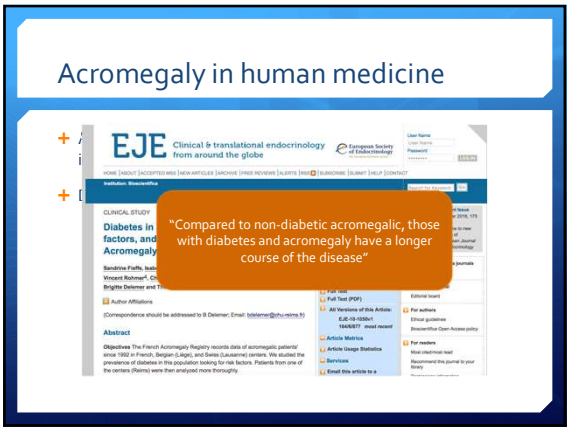


23

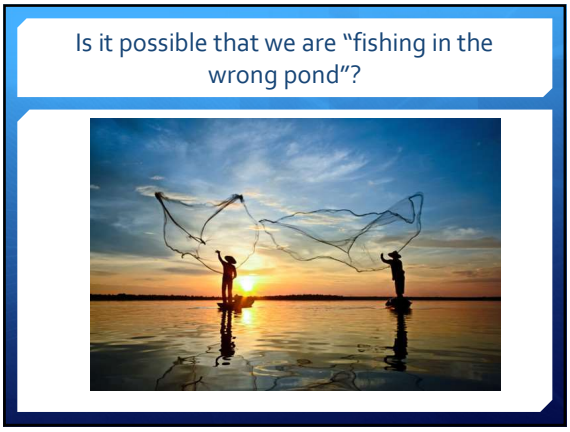
24


Journal of Veterinary Internal Medicine
ACVIM
Open Access
Case Report
Hypersomatotropism in 3 Cats without Concurrent Diabetes Mellitus
• Weight gain
• Severe myocardial hypertrophy

25


Acromegaly in human medicine
EJE
Clinical & translational endocrinology from around the globe
"Compared to non-diabetic acromegalic, those with diabetes and acromegaly have a longer course of the disease"

26


Is it possible that we are "fishing in the wrong pond"?

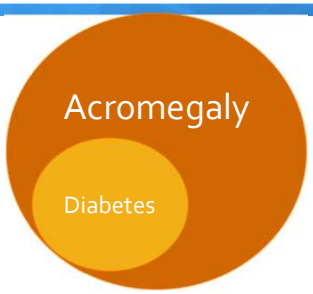
27

Acromegaly in human medicine

- 2004: American Association of Clinical Endocrinologists – acromegaly "rarely diagnosed disease"
  - Estimated anual incidence 3-4 casos/ million
- 2011 recommendations were changed:
  - New studies suggest higher incidence
  - Belgium: 130 / million
  - Germany: 1,034 / million
  - Reasons: adjusting diagnostic criteria and higher awareness/knowledge about the disease
- **"Most acromegalic patients are not diagnosed early on"**

28

Feline acromegaly



29

Prevalence in non-diabetics

D.J. Connolly; J.R. Payne; K. Borgeat; D.B. Church; M. Steele; P. Coss; S.J.M. Niessen. **Prevalence of Hypersomatotropism in Non-Diabetic Cats with Left Ventricular Hypertrophy - A Silent and Curable Phenocopy for Hypertrophic Cardiomyopathy** 28th ECVIM-CA Congress, 2018

- N= 66 cats
- Diagnosed with HCM
- 6% IGF-1 >1000ng/ml

30

31

Can we use the phenotype?

- **Most extensive case series** Niessen 2011
  - N=323 cats suspected of having acromegaly
  - Mostly male neutered (70%)
  - Mean age: 11.3+/-2.7 years (range: 4-19)
  - Mostly (87%), Maine Coon (2%)
  - Very similar to the average diabetic population
  - Diferences:
    - Weight
    - Fructosamine
    - Average insulin dose: 15 iu/day vs 6 iu/day

32

33

>300 veterinarians sent samples

24% suspected acromegaly

Conclusion:
Phenotype and clinical history are useful, but not all

34

Can we trust IGF-1?

- Problems
  - false + in diabetics
  - false – in newly diagnosed diabetics
  - Diferences in methodology
- It is a good test in general
  - 94% specificity if > 1000 ng/ml Niessen et al. 2013

35

Can we trust IGF-1?

	Fruct	Insulin	BW	IGF-1
Month 0	680	1	3.95	212

36

False negative in newly diagnosed diabetics?

- Why?
- Duration of insulin administration plays an important role

37

False negative in newly diagnosed diabetics?

- Why?
- Duration of insulin administration plays an important role

38

Falso negativo en nuevos diabéticos?

- Nuevos diabéticos (<6semanas desde el diagnóstico)
- Múltiple IGF-1s
  - N=413

39

Can we trust IGF-1?

- Sensitivity 90% & specificity 94-95% a 1000 ng/ml

Best available diagnostic test
Careful in newly diagnosed diabetics
Careful in choice of lab

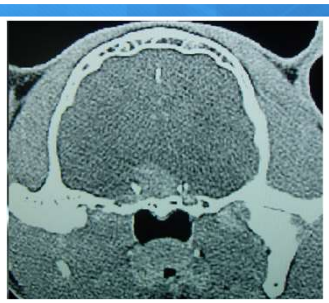
40

GH and Glucose GH suppression test

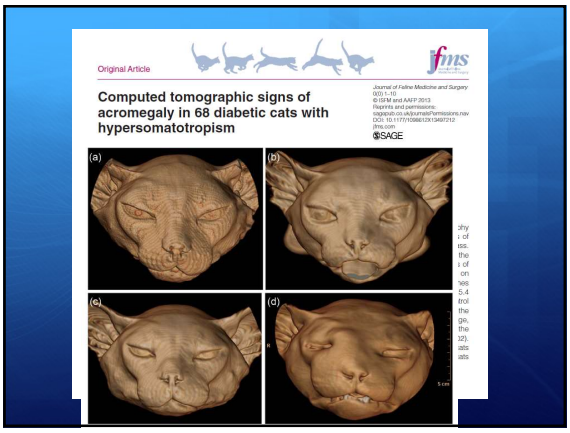
- GH
  - Pulsatile secretion (less reliable?)
  - No acromegalic cat had a normal GH on a previous study
    Niessen et al 2007a/b
  - Glucose infusion reduces pulsatile secretion of basal GH secretion
    - Little evidence in cats
    - 1 paper describes this in acromegalic cats (Eigenmann et al., 1984)
    - No supression in 4 healthy cats (Kokka et al., 1971)

41

Diagnostic imaging



42


Original Article
Computed tomographic signs of acromegaly in 68 diabetic cats with hypersomatotropism
SAGE

43


Diagnostic imaging
The presence of physical changes can help us, but their absence does not exclude the disease

44


Feline acromegaly, how should I treat it?

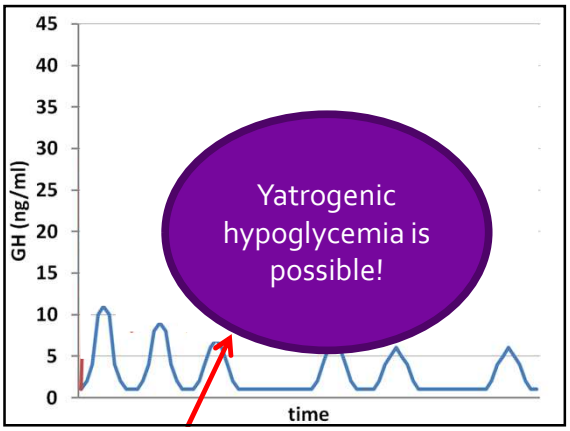
45

Non-invasive treatment

Conservative:

- Insulin
  - Unlikely to achieve good glycemic control
  - Risk hypoglycemia
  - Quality of life is important
- Treatment of additional signs
  - Polyphagia (Fluoxetine)
  - HCM
  - Arthritis, etc.

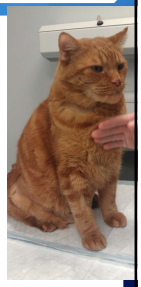
46



47

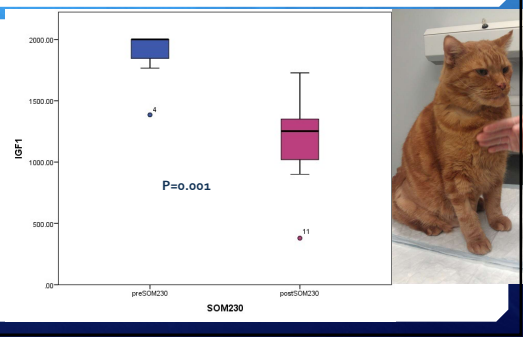
Non-invasive: Pasireotide

- **SOM230 (Signifor®, Novartis, Basel, Switzerland)**
  - Non-specific somatostatin analogue
  - High affinity somatostatin receptors 1, 2, 3 & 5
  - Supresses GH, IGF-1 & ACTH in mice and humans with acromegaly



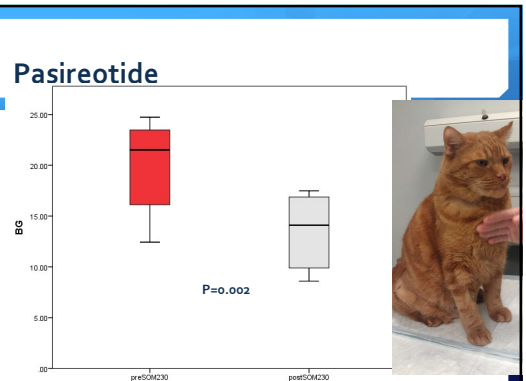
48

Pasireotide



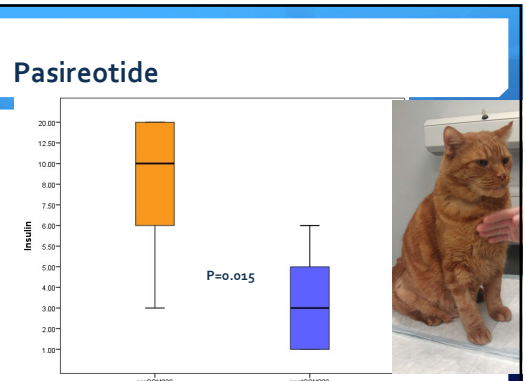
49

Pasireotide

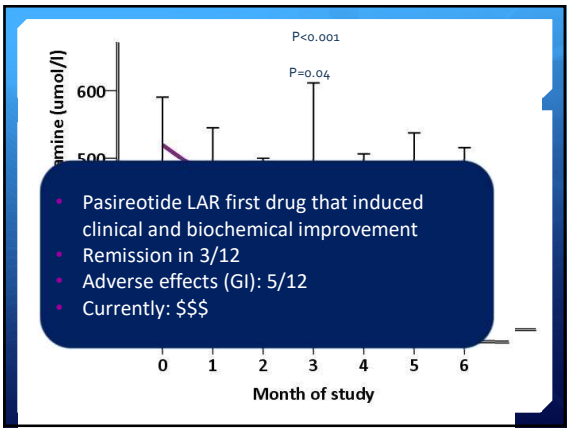


50

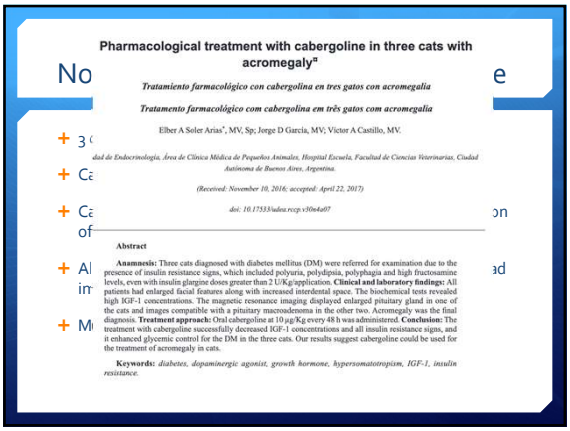
Pasireotide



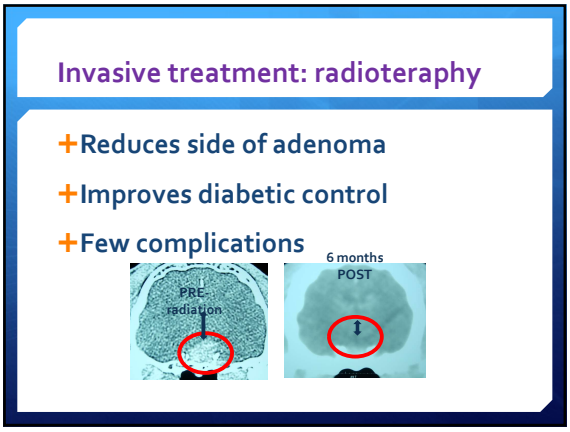
51


P<0.001
P=0.04
600
500
0
1
2
3
4
5
6
Month of study
Pasireotide LAR first drug that induced clinical and biochemical improvement
Remission in 3/12
Adverse effects (GI): 5/12
Currently: $$$

52


Pharmacological treatment with cabergoline in three cats with acromegaly*
Tratamiento farmacológico con cabergolina en tres gatos con acromegalia
Tratamento farmacológico com cabergolina em três gatos com acromegalia
Elber A Soler Arias*, MV, Sp; Jorge D García, MV; Victor A Castillo, MV.
Abstract

53


Invasive treatment: radioteraphy
+Reduces side of adenoma
+Improves diabetic control
+Few complications
PRE radiation
6 months POST

54

Invasive treatment: Radiation

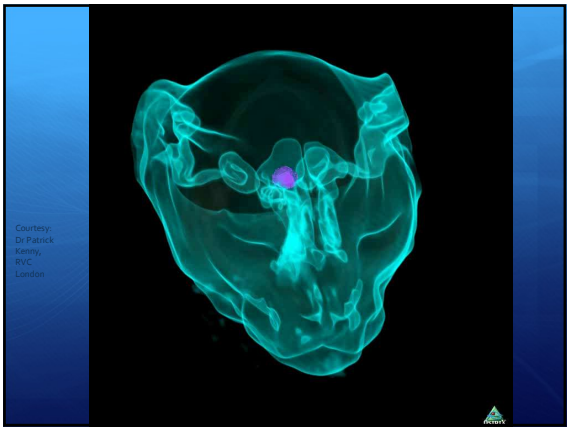
- Takes some time to work
- Difficult to predict how long
- Requires anesthesia
- Improves DM but does not reduce IGF-1
  - HCM persists
  - Other disease features progress

55

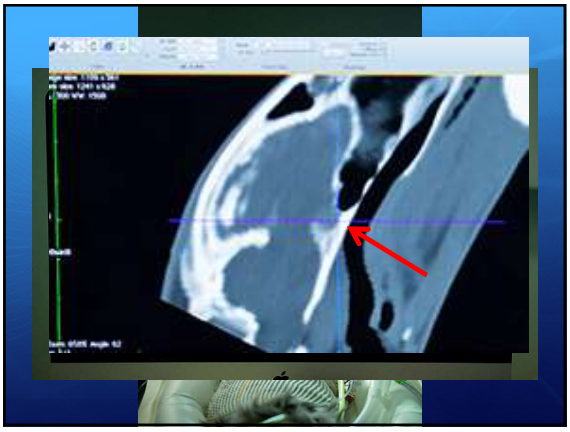
Hypophysectomy

- Probably best treatment option
- Removes the tumour
- GH concentration normalises within hours
- High chance of remission

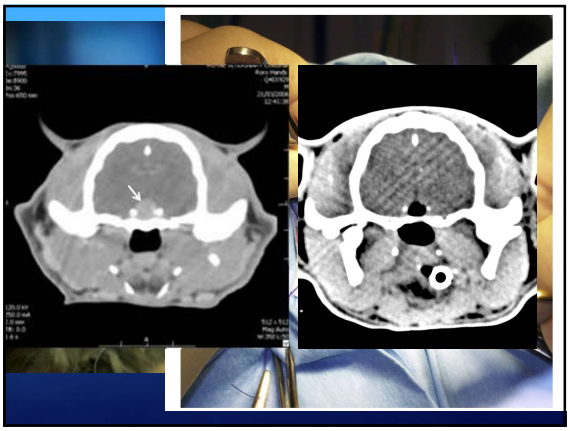
56



57



58



59

Hypophysectomy

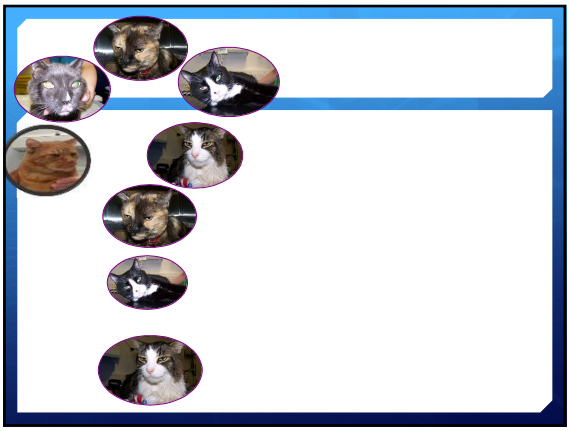
- Post-surgical period:
  - Hydrocortisone q24h
  - Thyroid hormone q24h
  - First three weeks: DDAVP drops q 8h
  - 20%: DDAVP a long term
    - Q8-24h
- Insulin requirements go down progressively

60

Conclusions

- Acromegaly is common in diabetic cats
- Starting to see it in non-diabetic cats
- Clinical signs can be subtile
- Important to be aware of diagnostic tolos and their limitations
  - IGF-1
  - False negatives in newly diagnosed cats

61



62