INSULIN RESISTANCE

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.

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INSULIN RESISTANCE

What is the definition ?

Greater than 1.5 units/kg of insulin BID

Greater than 3 units of glargine BID

Glucoses > 300 mg/dl during BG curve

Glycemic control is erratic

Insulin requirements fluctuate

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Resulting from Insulin Therapy

Inactive insulin
Diluted insulin
Improper administration
Inadequate dose
Somogyi

INSULIN RESISTANCE

Resulting from Insulin Therapy

Inadequate frequency of administration

Impaired insulin absorption

Anti-insulin antibodies

Act of God

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Resulting from Concurrent Disorder

Diabetogenic drugs
Hyperadrenocorticism
Diestrus (canine)
Acromegaly (feline)
Infections (skin, urinary, oral cavity)

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Resulting from Concurrent Disorder

Hypo and hyperthyroidism
Renal insufficiency
Hepatic insufficiency
Heart disease
Glucagonoma (canine)

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Resulting from Concurrent Disorder

Pheochromocytoma

IBD

Pancreatitis/triaditis

EPI

Obesity

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Resulting from Concurrent Disorder

Hyperlipidemia
Neoplasia
Act of God

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Diagnostic Approach

History

- Presence of obesity ?
- Concurrent medications ?
- Is the pet spayed ? When was last estrus ?
- Signs of infection ?

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Diagnostic Approach

Physical Examination

- Obesity (BCS)
- Rectal examination, thyroid evaluation
- Abdominal palpation
- Thoracic auscultation

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Diagnostic Approach

Laboratory testing

- CBC, chemistry panel, UA, UMIC
- Serum progesterone
- Abdominal US
- Thoracic radiographs

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Diagnostic Approach

Laboratory testing

- Hormonal Evaluation
  - TT4, fT4ED
  - ACTH stimulation/LDDS
  - IGF-1

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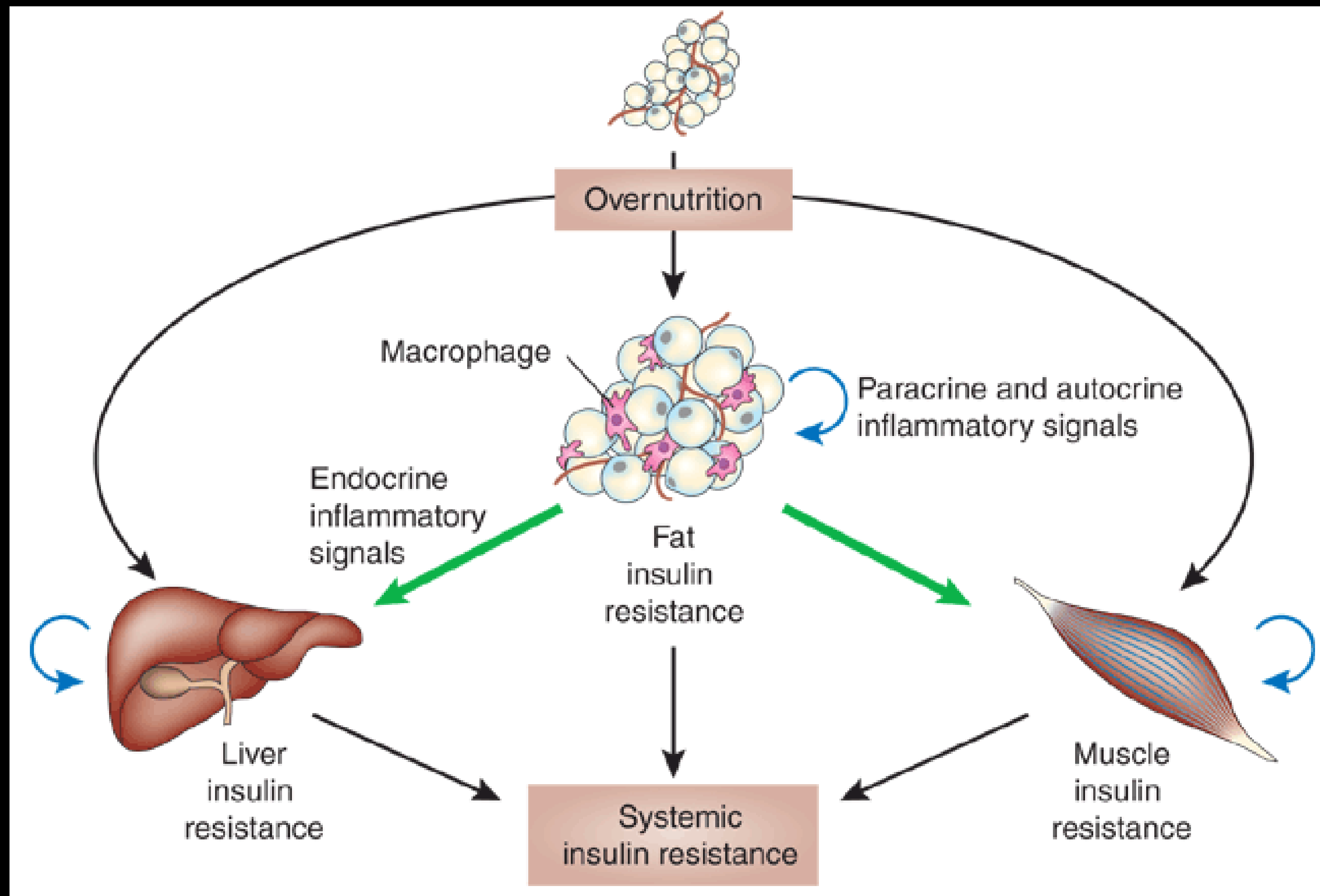
Diagnostic Approach

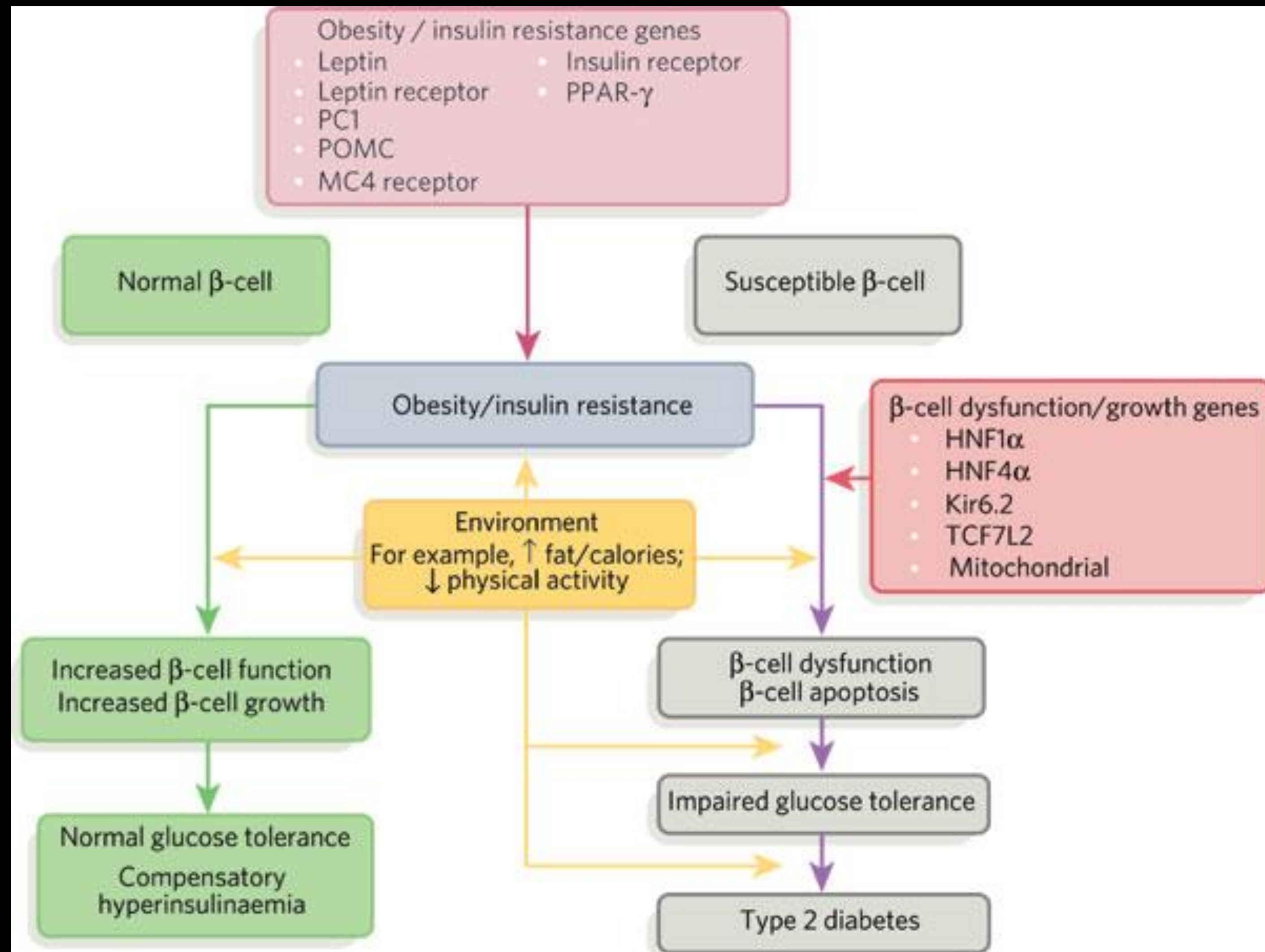
Laboratory testing

- PLI
- TLI
- CT/MRI of pituitary

OBESITY



OBESITY



DIABETES MELLITUS

Progesterone and Insulin Resistance

Pregnancy, diestrus (dog) or adrenal neoplasia (dog, cat)
- Reduces insulin binding
- Reduced glucose transport in tissue

Increased mammary production of GH
- Decreased number of insulin receptors
- Decreased expression of glucose transporter genes

Rapid decrease in GH and resistance following OHE

DIABETES MELLITUS

Hyperadrenocorticism and Insulin Resistance

Most common cause in dogs – 38 %
2nd most common cause in cats – 17 %

Antagonize insulin in liver and muscle cells
Decrease number and/or efficacy of glucose transporters
Increase glucagon and fatty acids

Which came first the diabetes or the Cushing's syndrome ?

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Bacterial Infections

2nd most common cause in dogs – 16 %

4th most common cause in cats – 9 %

Skin, urinary and oral cavity

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Bacterial Infections

Diabetics pre-disposed to infections:

- Decreased blood supply
- Impaired humoral immunity
- Abnormal chemotaxis of neutrophils
- Defects in phagocytosis

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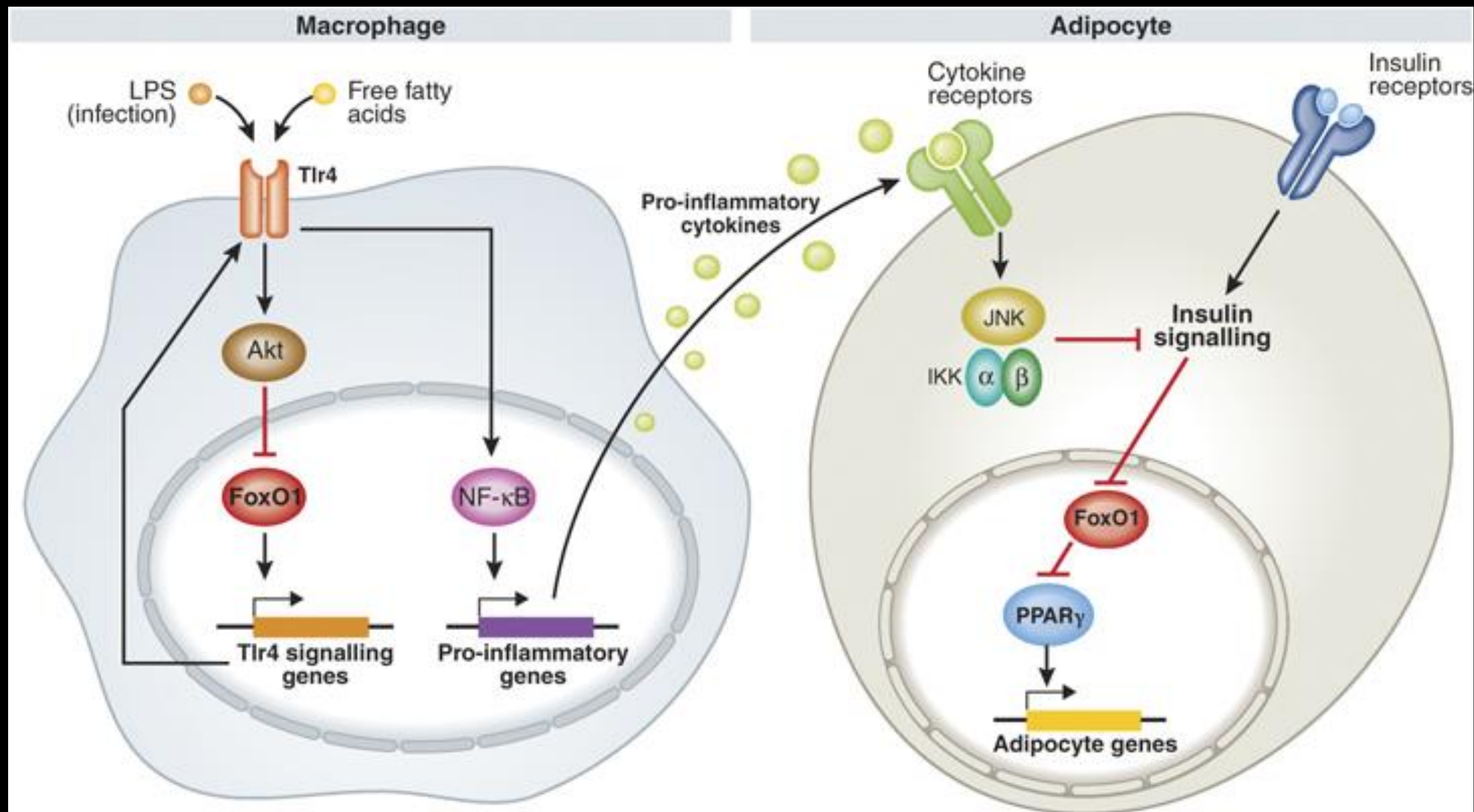

The EMBO Journal (2010) ***29, 4068 - 4069***

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Renal Insufficiency

3rd most common cause in cats – 15 %

- Poor and/or erratic glycemic control
- Increased insulin sensitivity
- Decreased insulin clearance
- Decreased renal glucose production
  - Normally up to 40%

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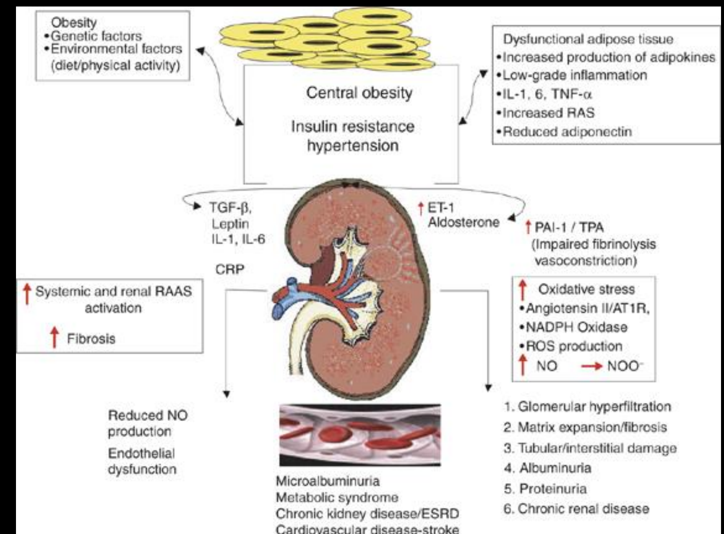
Renal Insufficiency

Decreased insulin sensitivity
Common clinical signs
Primary focus is on
managing the renal disease



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Chronic Pancreatitis

Identified at necropsy in 35 % of diabetic dogs and 50 % of diabetic cats

Poor glycemic control and persistent hyperglycemia
Fluctuating insulin requirements
Lethargy and inappetence (ADR)

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Exocrine Pancreatic Insufficiency

EPI with diabetes in juvenile patients

- pancreatic atrophy

As a result of chronic pancreatitis

- Signs of EPI become more pronounced

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Hypothyroidism

4th most common cause in dogs – 9 %

- Post receptor defect in glucose transport
- Obesity
- Hypertriglyceridemia
- Insulin requirement decreased by 50-60% after
  2 weeks of supplementation

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Neoplasia

Insulin resistance is 5 – 10 % of dogs

- Pheochromocytoma, glucagonoma, LSA, mast cell

- Excess secretion of catecholamines and glucagon
  - Inc hepatic gluconeogenesis
  - Inhibit glucose uptake in muscle

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Hypertriglyceridemia

Impairs insulin binding to receptors
Post-receptor defects
Increased hepatic gluconeogenesis
Down regulates insulin receptors
- Schanauzers and hypothyroidism

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Hypertriglyceridemia

Which came first ?

In general, triglycerides < 500 mg/dl
> 800 raises suspicion for an underlying disorder

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Feline Acromegaly

1 cause in cats –

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

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

- Most commonly present for 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, adrenaomegaly, pancreatic enlargement
- 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 abnormalities
- 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

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Feline Acromegaly

"Chairman Meow" 14 yr MC DSH
Diabetes mellitus x 6 months
Increased insulin dose from 2 – 15 units glargine BID
Persistent pu/pd

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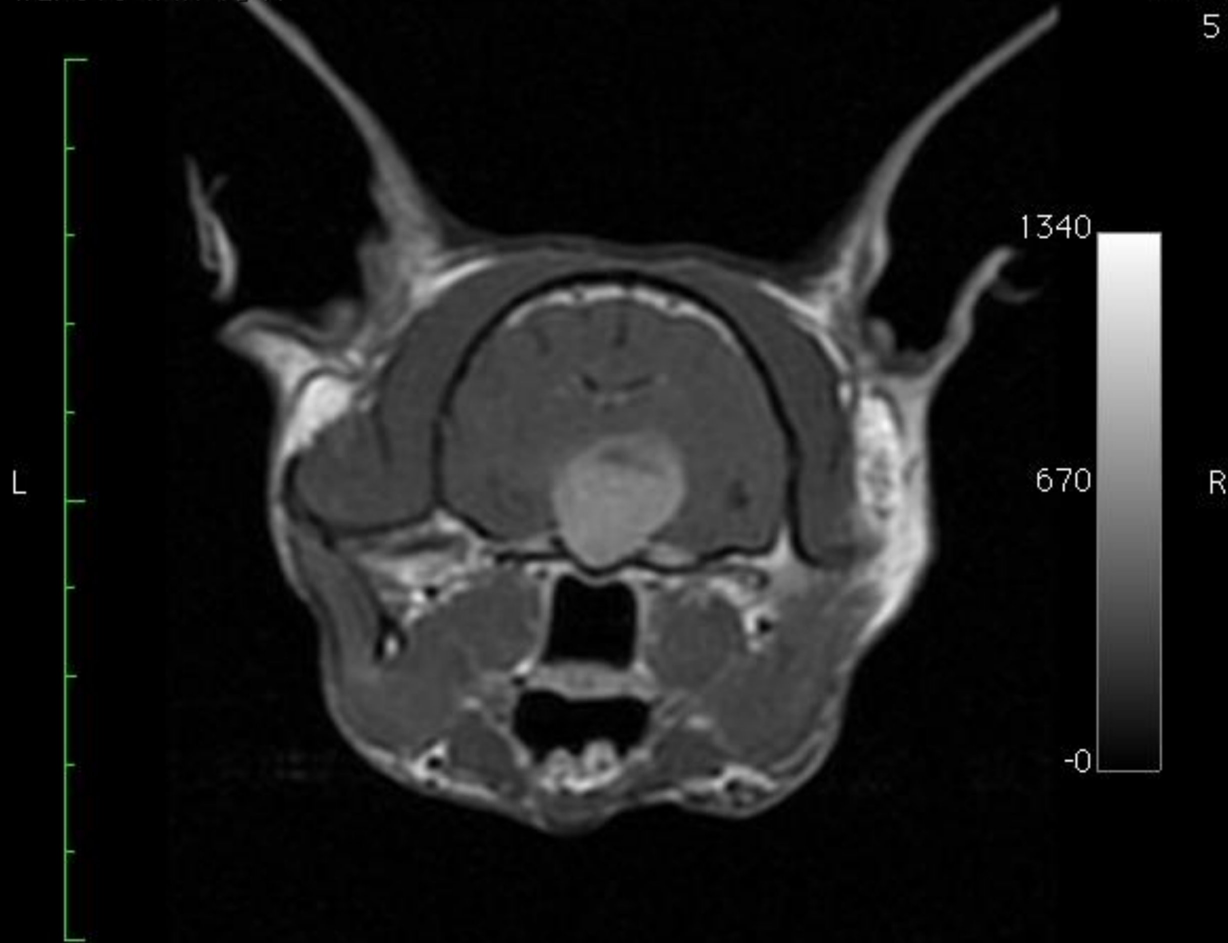
Feline Acromegaly

CBC, chemistry panel,TT4, UA, UMIC
Thoracic radiographs
Serum IGF-1
    > 560 nmol/L (12 – 92)
MRI

NCE



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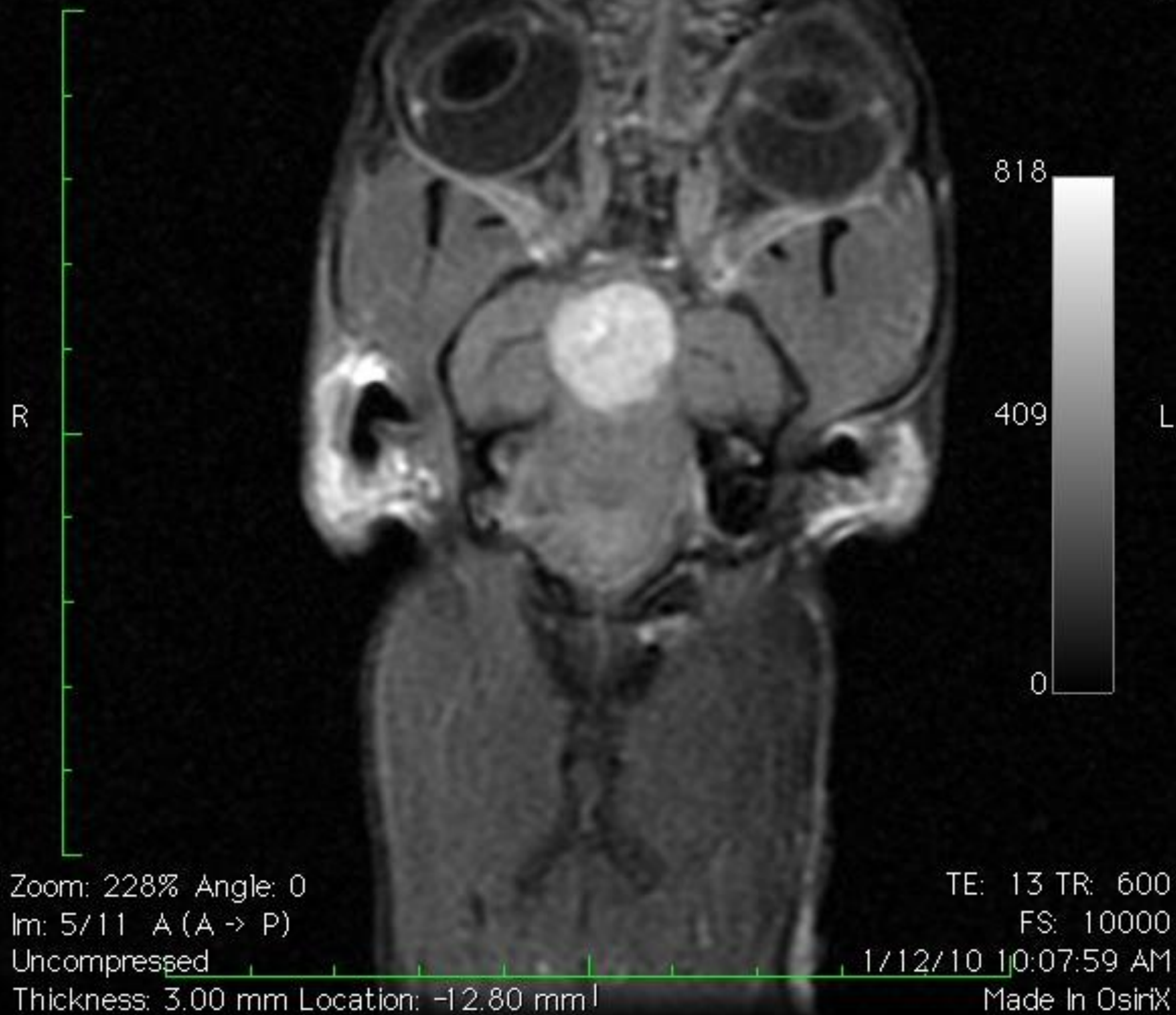

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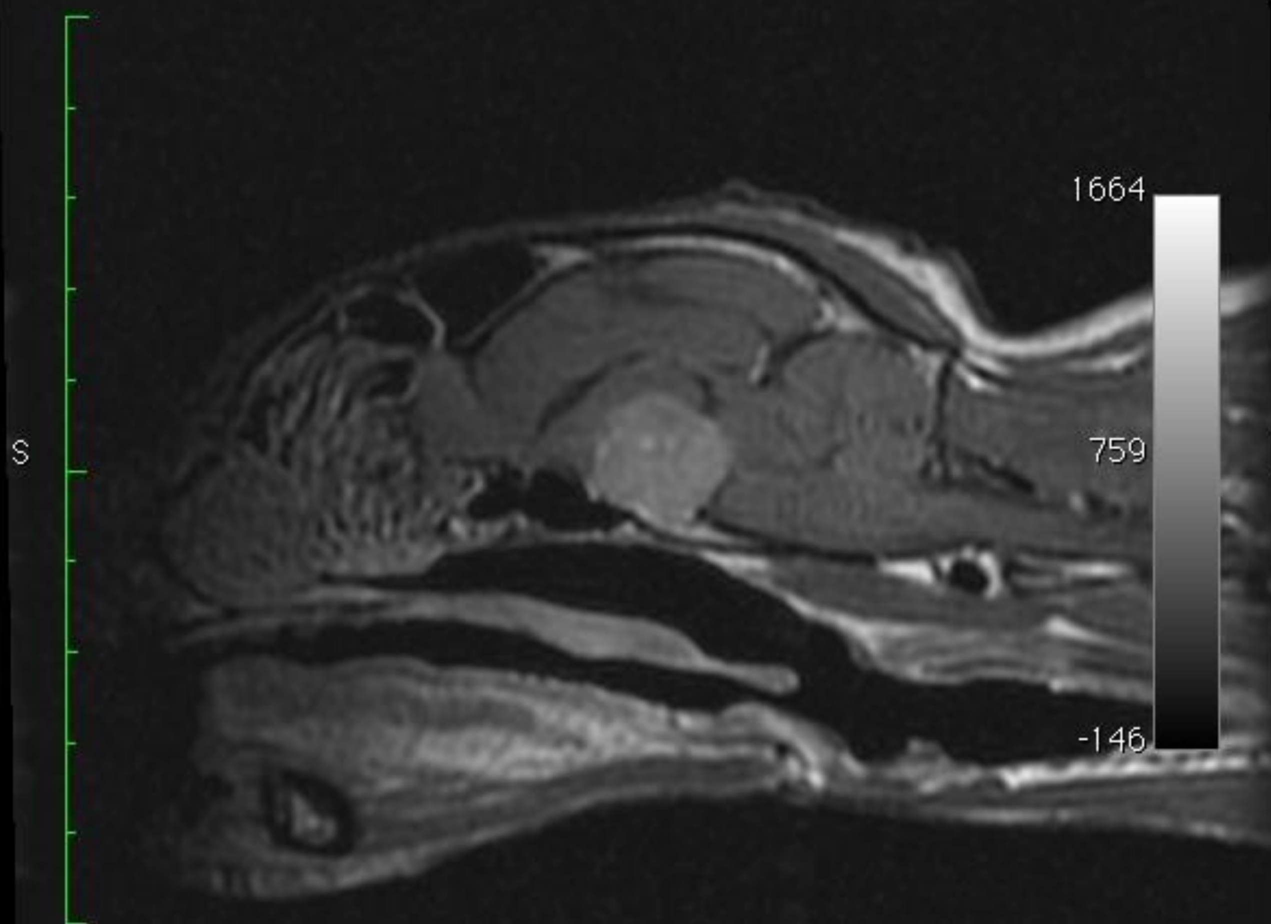

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Feline Acromegaly

Transsphenoidal surgery

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Feline Acromegaly

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

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Feline Acromegaly

Studies on pathogenesis
Role of somatostatin analogues
GH receptor antagonists
Dopaminergic therapy

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Most common complication of insulin therapy

Logical diagnostic approach

Good clinical outcome

Rewarding cases to work-up