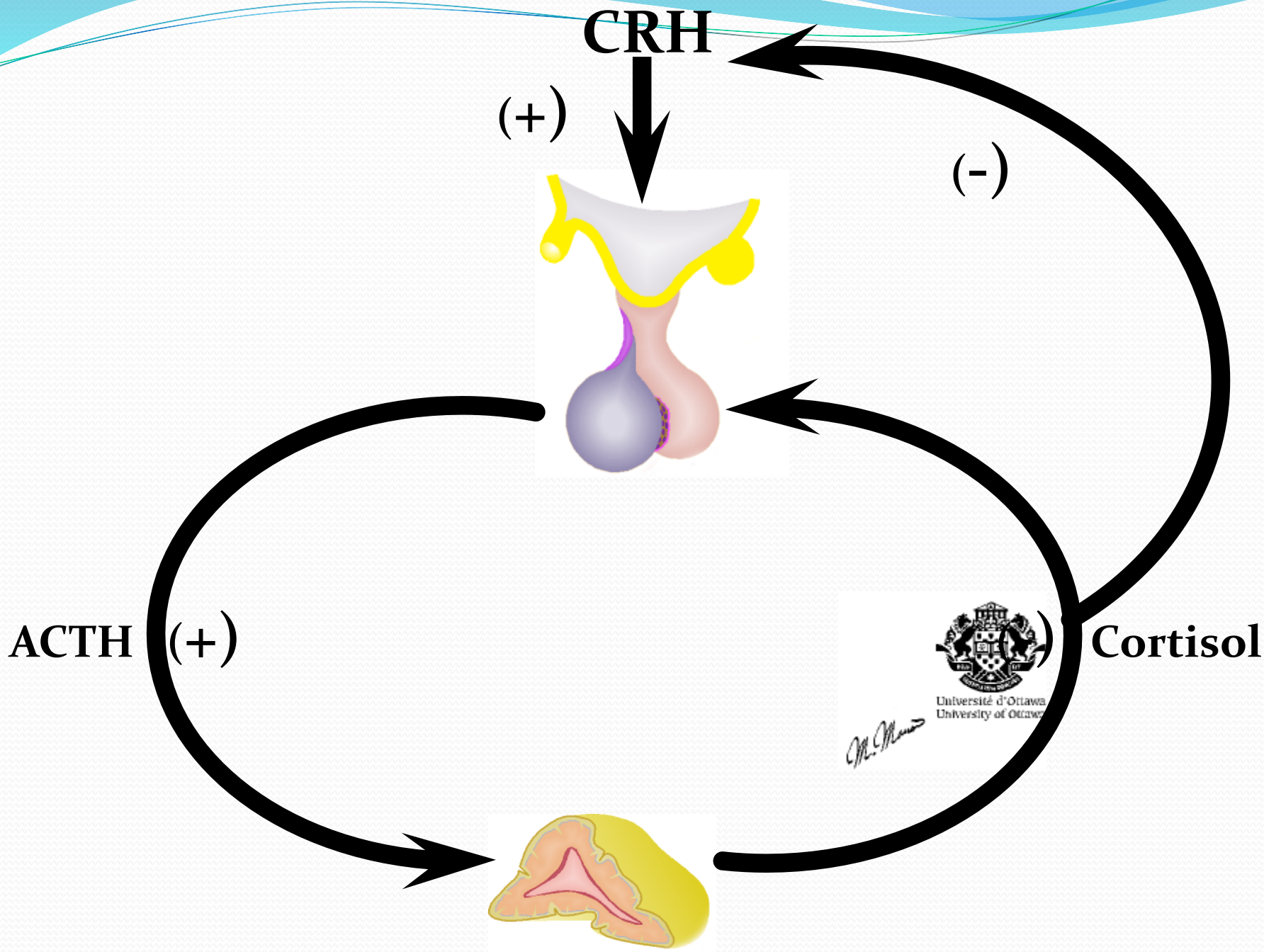
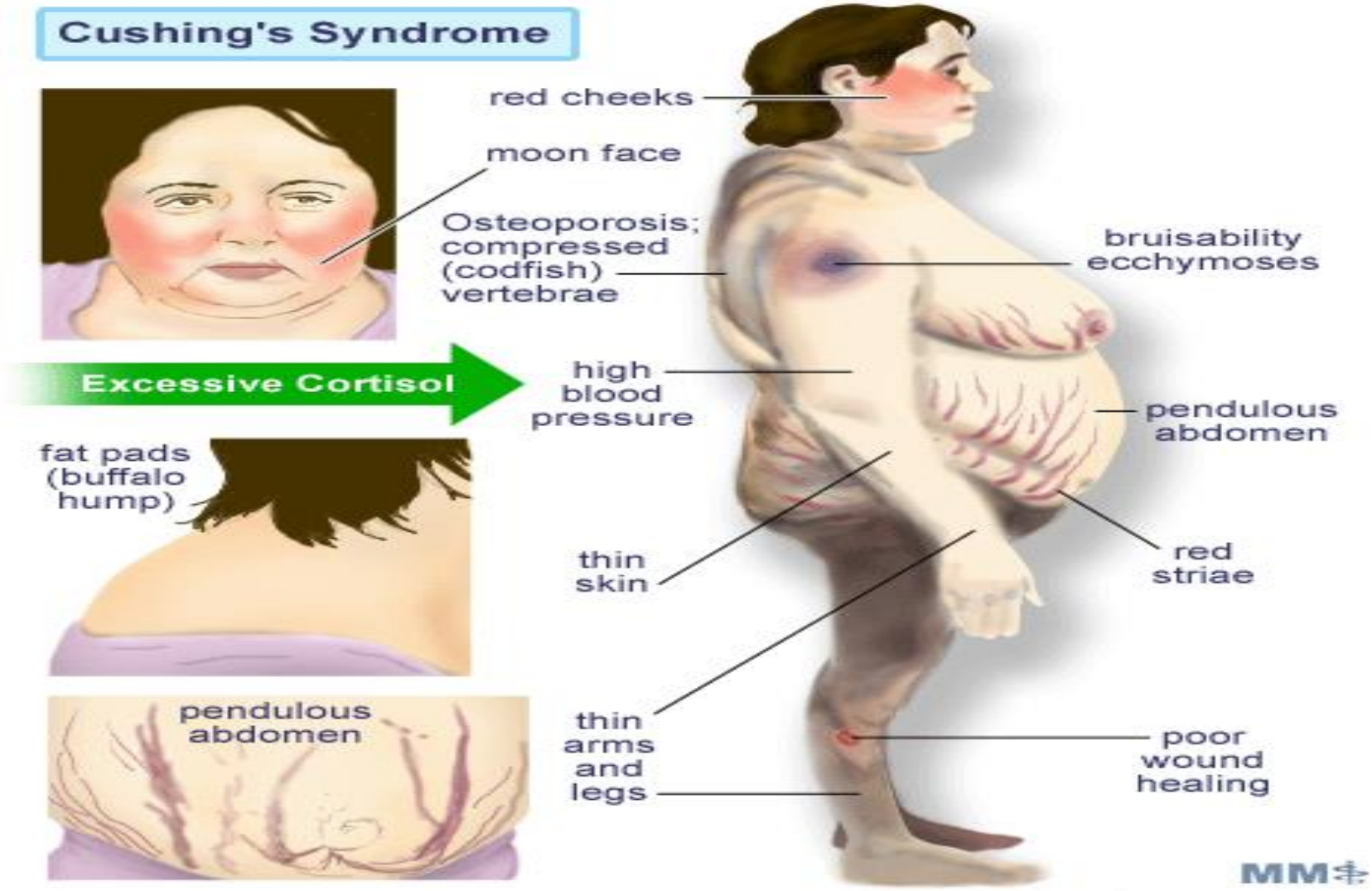
Cushing's syndrome

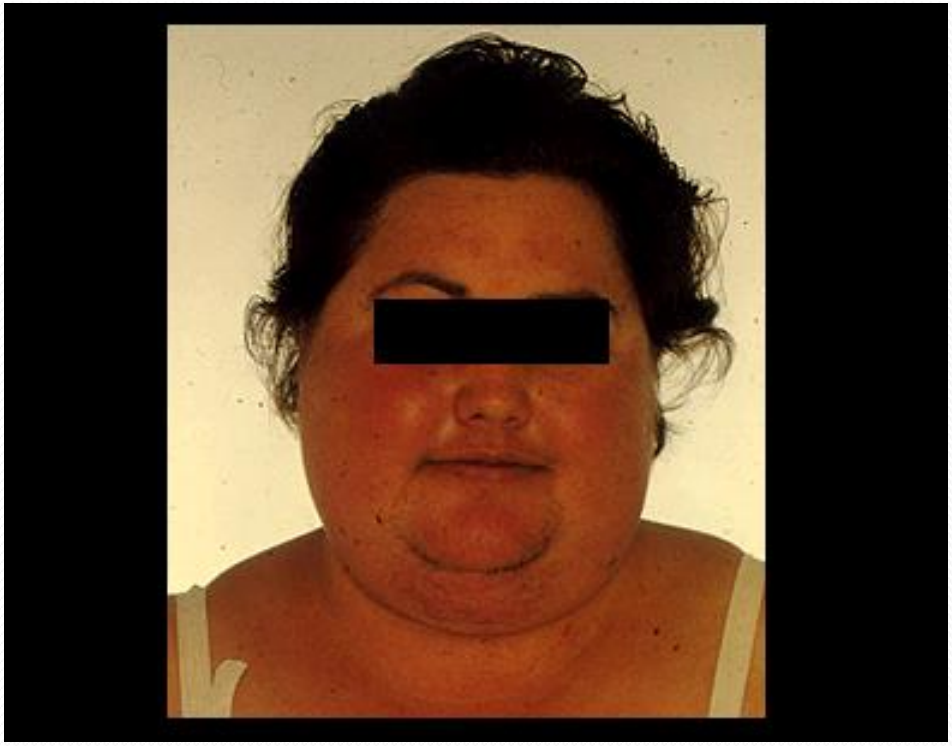
Introduction

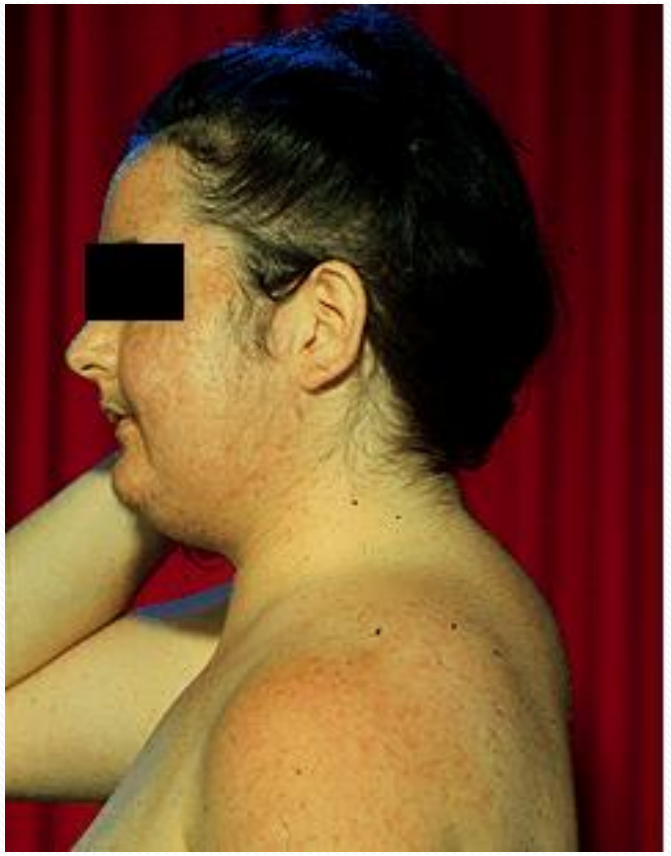
- **Cushing's syndrome (hypercortisolism)** is a hormonal disorder caused by prolonged exposure to high levels of steroid hormones called glucocorticoids.
- **Exogenous Cushing's syndrome:** caused by taking excessive amounts of medications e.g. prednisone, dexamethasone → for chronic asthma, rheumatoid arthritis, lupus, to suppress immune system after transplant to prevent rejection, other inflammatory diseases.
- **Endogenous Cushing's syndrome**: excess cortisol produced by the adrenal glands. This is far rarer, but if left undiagnosed & untreated it can result in a shorter lifespan.


CRH
(+)
(-)
ACTH
(+)
(-)
Cortisol
Université d'Ottawa
University of Ottawa

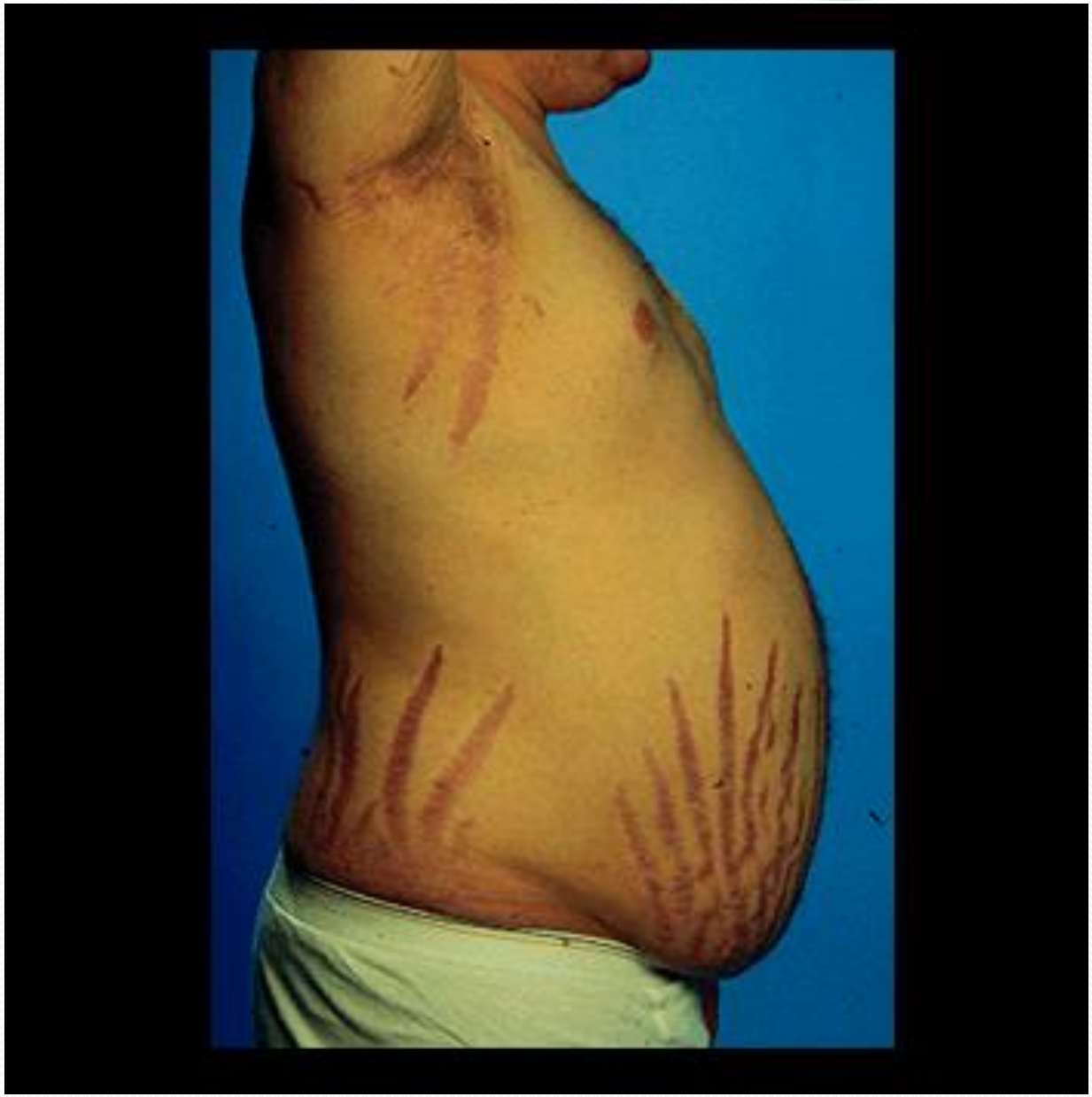

Cushing's Syndrome
red cheeks
moon face
Osteoporosis; compressed (codfish) vertebrae
bruisability ecchymoses
Excessive Cortisol
high blood pressure
pendulous abdomen
fat pads (buffalo hump)
thin skin
red striae
pendulous abdomen
thin arms and legs
poor wound healing
MM

Facial Plethora & Centripetal Obesity

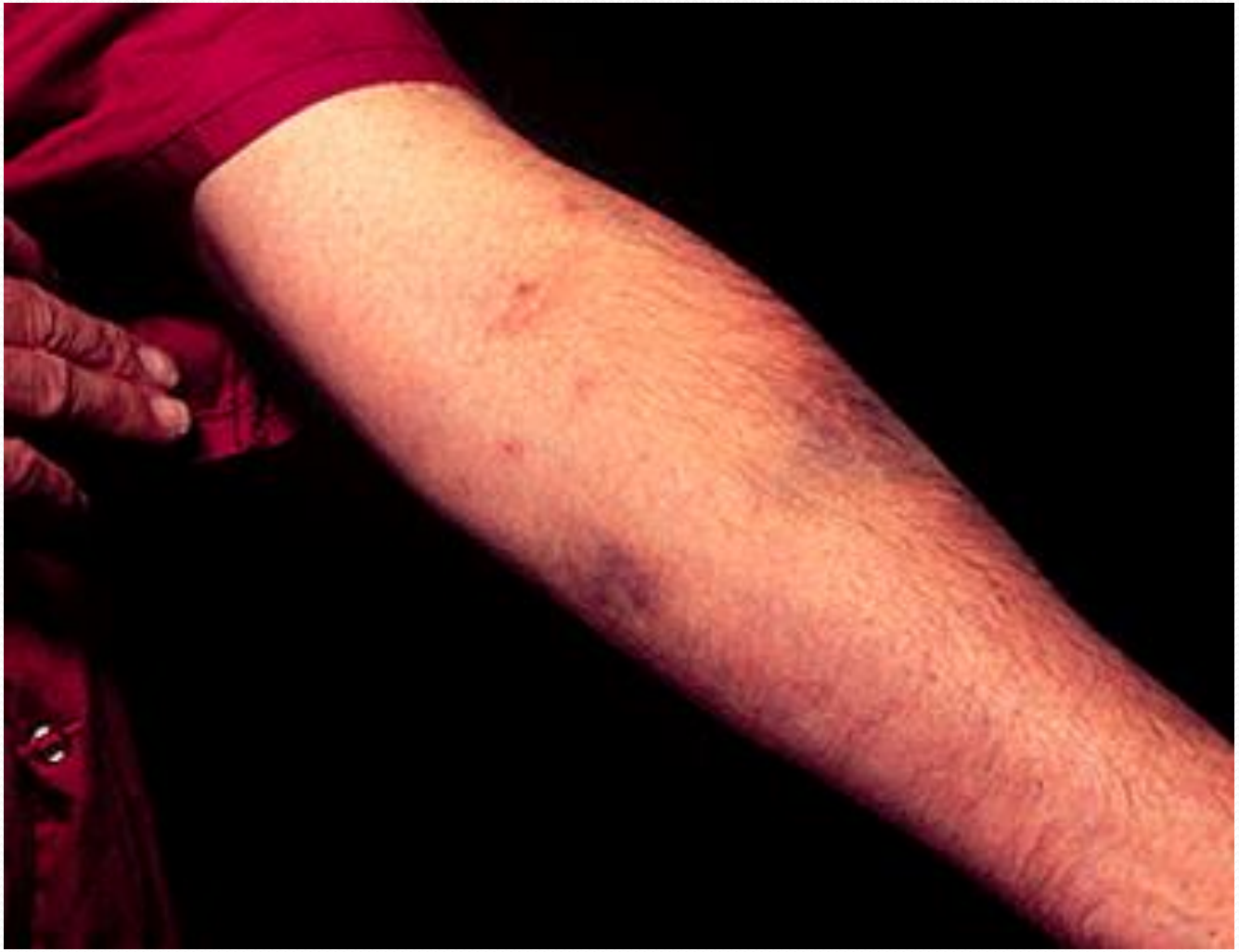




Wide (>1cm) Purple Striae



Spontaneous Ecchymoses



Neuropsychological changes

Emotional lability

- **Agitated depression**
- **Anxiety**
- **Irritability**
- **Panic attacks**
- **Mild paranoia**

Causes of Cushing's Syndrome

- **ACTH-dependent**
  - **Pituitary ACTH-dependent Cushing's syndrome (Cushing's disease)**
  - **Ectopic ACTH syndrome**
  - **Ectopic CRH syndrome**
- **ACTH-independent**
  - **Adrenal Adenoma or Carcinoma**
  - **Adrenal hyperplasia (Micro- and macro-)**
  - **Glucocorticoids administration**

Causes cont…

- **The most common cause of hypercortisolism is ingestion of STEROIDS usually for Non-Endocrine disease.**
  - **Oral**
  - **Injected**
  - **Topical (intra-articular, epidural, nasal, & dermal)**
  - **Inhaled glucocorticoids**

Ectopic ACTH

- SCLC >50%
- Thymic carcinoid 15%
- Islet cell tumors 10%
- Bronchial carcinoid 10%
- Other carcinoids 5%
- Pheochromocytomas 2%

Differential Diagnosis

- Alcoholism
- Anorexia nervosa (high urine free cortisol)
- Familial cortisol resistance

Cushing's Syndrome
Diagnostic approach

1. Establishing the diagnosis of CS

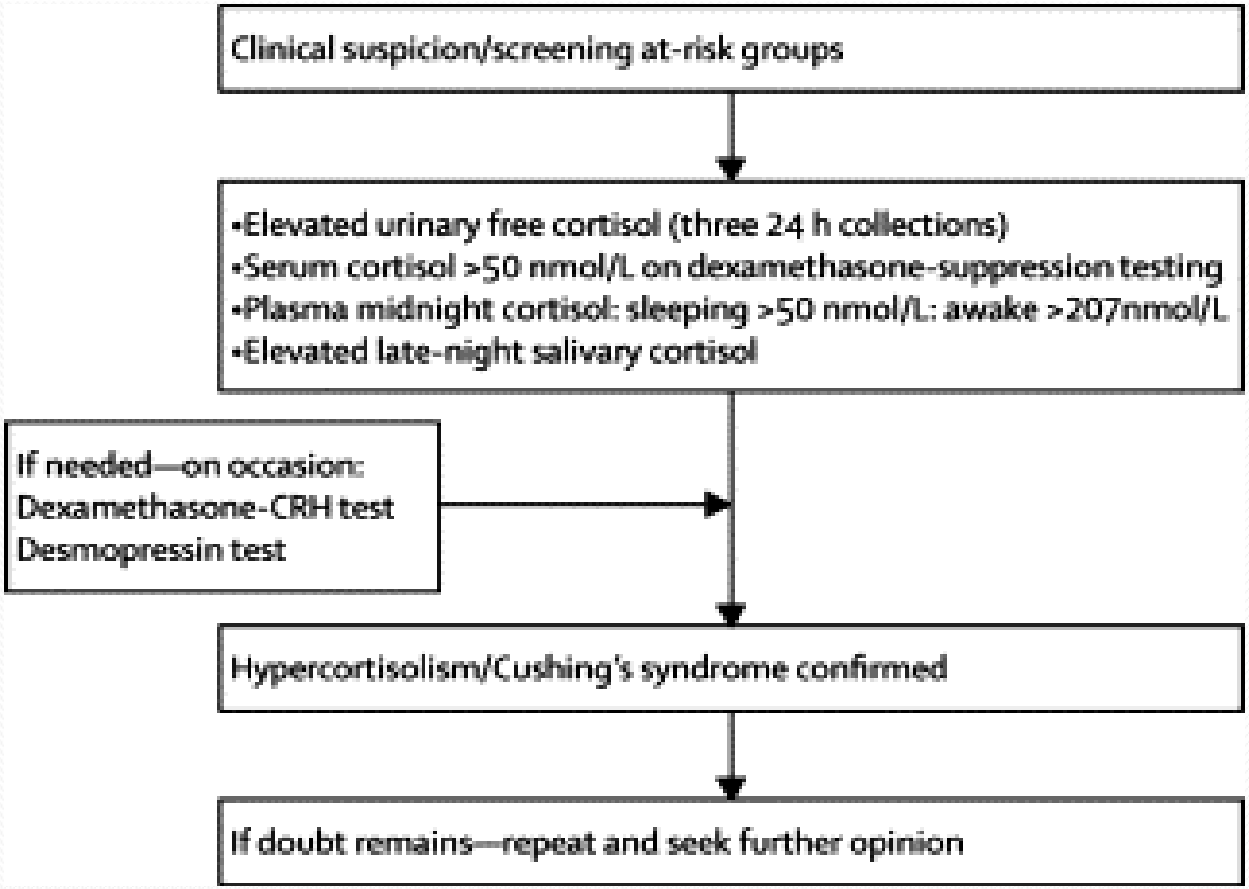
↓

2. Establishing the cause of CS
   a. ACTH-dependent vs independent
   b. Identifying the source in ACTH-dependent

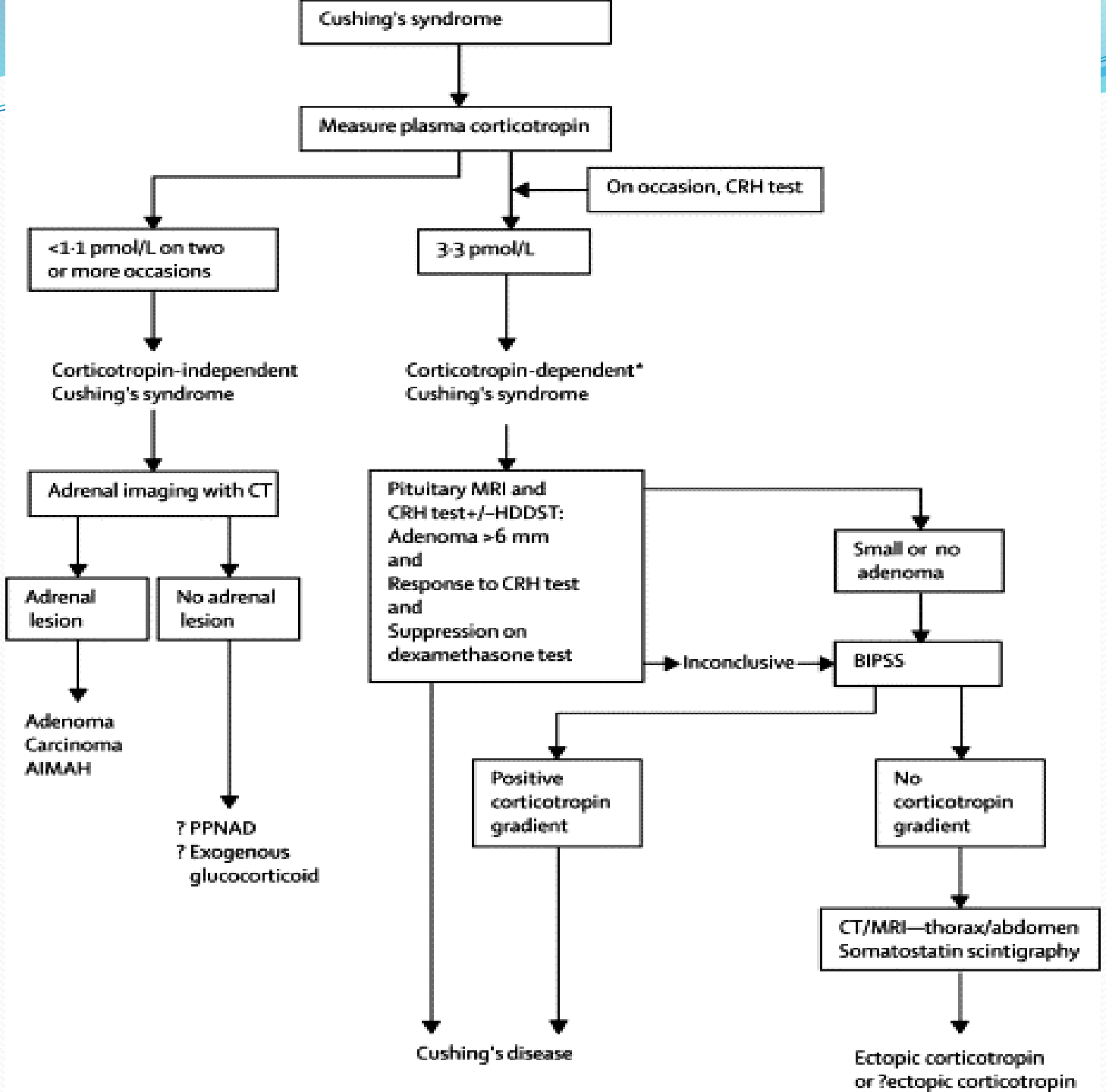
↓

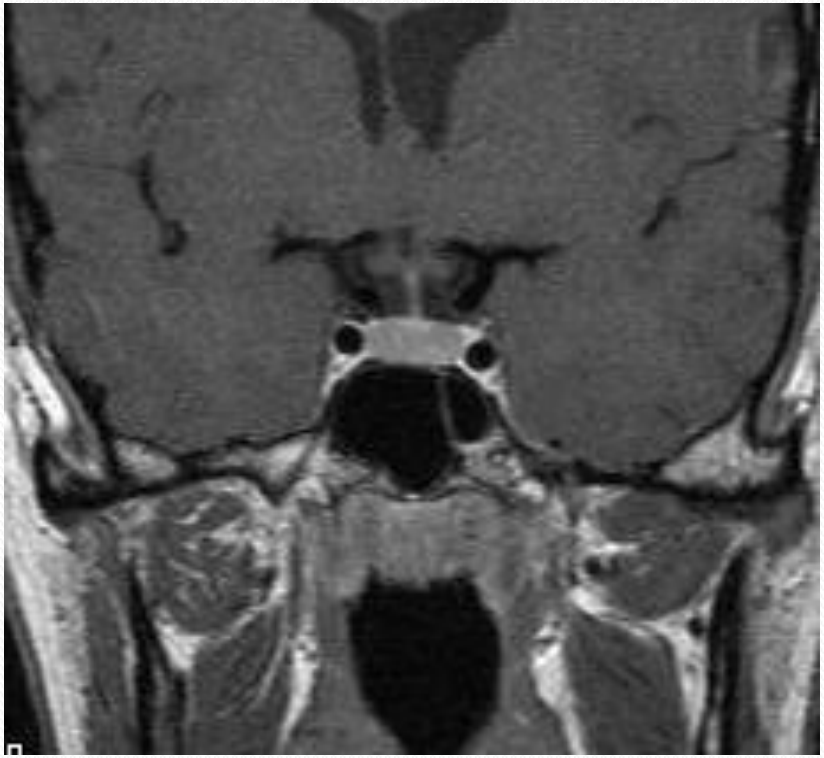
3. Imaging

Cushing's Syndrome
Establishing the diagnosis

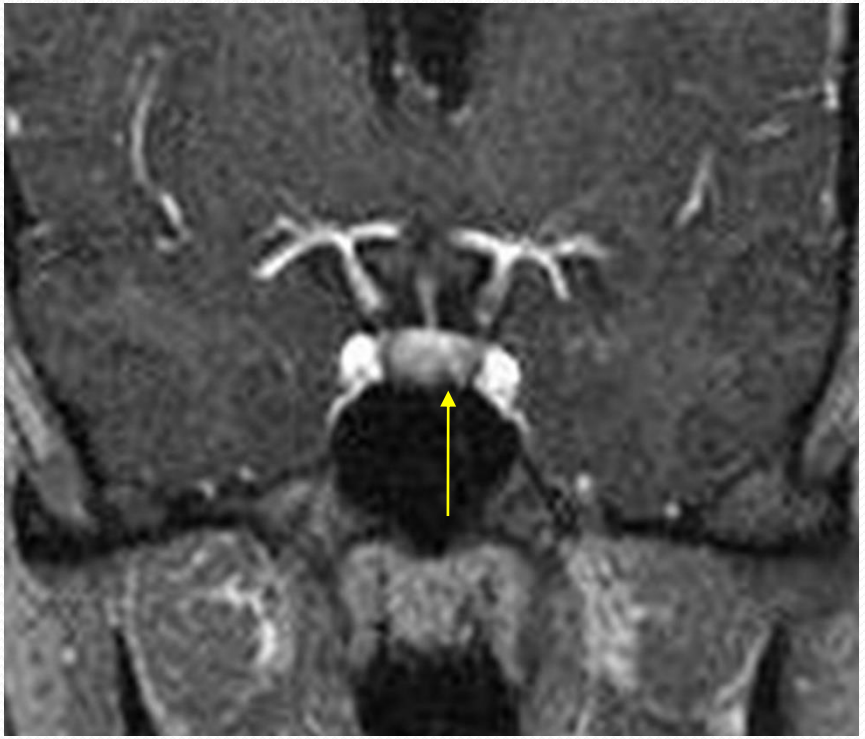


Source: Newell-Price et al. *Lancet*


Cushing's syndrome
Measure plasma corticotropin
On occasion, CRH test
<1·1 pmol/L on two or more occasions
3·3 pmol/L
Corticotropin-independent Cushing's syndrome
Corticotropin-dependent* Cushing's syndrome
Adrenal imaging with CT
Adrenal lesion
No adrenal lesion
Adenoma
Carcinoma
AIMAH
? PPNAD
? Exogenous glucocorticoid
Pituitary MRI and CRH test+/–HDDST:
Adenoma >6 mm
and
Response to CRH test
and
Suppression on dexamethasone test
Small or no adenoma
Inconclusive
BIPSS
Positive corticotropin gradient
No corticotropin gradient
CT/MRI—thorax/abdomen
Somatostatin scintigraphy
Cushing's disease
Ectopic corticotropin
or ?ectopic corticotropin



Coronal T1-weighted
Static MRI (Contrasted)



Coronal T1-weighted
Dynamic MRI (Contrasted)

Treatment

- Cushing's Disease: Transphenoidal resection of pituitary adenoma
- Adrenal neoplasms: resection
- Ectopic ACTH: resection if possible
- Bilateral adrenal hyperplasia: may need adrenalectomies (lifelong glucocorticoid and mineralcorticoid replacement

Cushing's Syndrome
Surgical Treatment

- **Transphenoidal adenomectomy**
  - Done by neurosurgeons who perform pituitary surgery frequently
  - **Remission rate of 80-90%--**Most common surgical failures with macroadenomas
  - Cure is confirmed by demonstrating profound hypoadrenalism post-op (8am cortisol <50 nmol/L)

Cushing's Syndrome
Surgical Treatment cont…

- **Adrenal Surgery**
  - Laparoscopic surgery is the treatment of choice for unilateral adrenal adenomas.
  - Pitfalls
    - Permanent need for GC and MC
    - **10% risk of recurrent CS**

Cushing's Syndrome
Pituitary Irradiation

- Conventional irradiation induces remission in only 20-83% of adults
- Onset of remission: 6mo-5 years
- Disadvantages:
  - Delayed effectiveness
  - Significant risk of hypopituitarism
  - Risk of neurologic and cognitive damage
- The role of newer stereotactic radiosurgery remains to be determined

Medical Therapy for Cushing's Disease

- No effective drug lowers ACTH production and shrinks the pituitary tumor.
- There are medications that inhibit the adrenal glands production of cortisol.
- There are 4 main indications of medical treatment: in case of contra-indication or refusal of surgery, in the lack of adenoma image on pituitary MRI, waiting for radiation techniques to be effective, as multimodality approach in the rare cases of pituitary carcinomas

Steroidogenesis inhibitors

- **Mitotane** inhibits side chain cleavage of cholesterol and also other cytochrome P450 enzymes (11-alpha and 18-hydroxylase)
- **Ketoconazole** is an antifungal agent which causes inhibition of cytochrome P450 enzymes. It was reported to normalize cortisol levels in Cushing's disease in about 50% of cases.

- **Metyrapone** is a pyridine derivative that blocks cortisol synthesis by mainly inhibition of 11 beta hydroxylase..
- In a small series of 13 patients with CD, Jeffcoate et al demonstrated a rapid clinical improvement in combination with a fall in plasma cortisol level after treatment with metyrapone in all patients..
- **Etomidate** is an intravenous anaesthetic agent. It inhibits cortisol synthesis by inhibiting CYP11B1 with 11-beta hydroxylase activity, and cytochrome P450 at high concentrations.

- **Glucocorticoid receptor antagonist** **Mifepristone** is currently the only available glucocorticoid receptor antagonist. Only rare cases have been reported to date.

Novel therapies

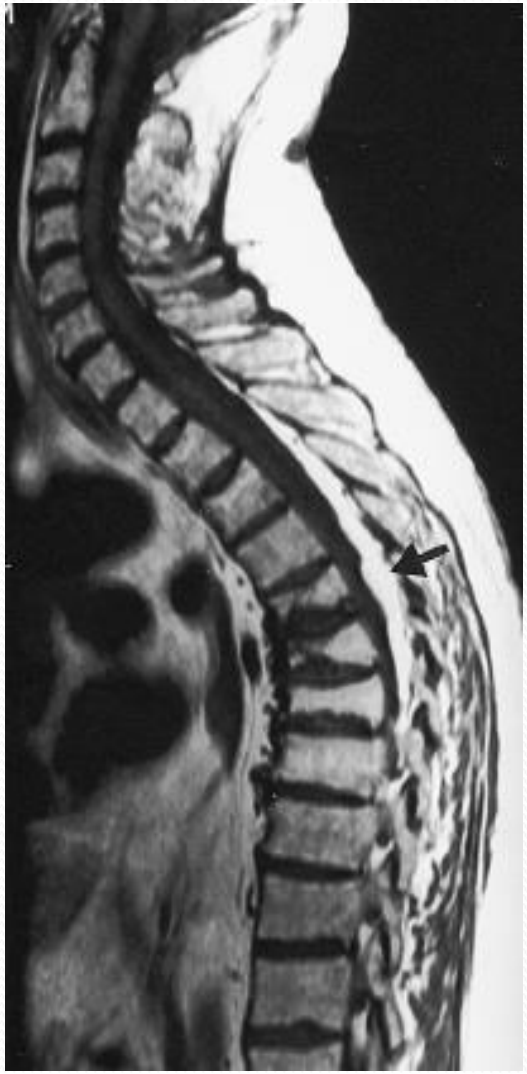
- **Pasireotide** is a novel somatostatin agonist with a particular binding affinity for somatostatin receptor (sstr) isoforms 1, 2, 3 and 5..

Potential novel adrenal-blocking drugs

- **LCI699** is a potent inhibitor of 11_-hydroxylase and 18-hydroxylase . The drug is currently under investigation for its efficacy in patients with CD.

- Finally, the **serotonin antagonist cyproheptadine**, as an inhibitor of hypothalamic CRH and vasopressin secretion, as well as the amino butyric acid uptake inhibitor.
- **sodium valproate** have been tested with limited success in CD to lower ACTH and cortisol levels.

STUDIES



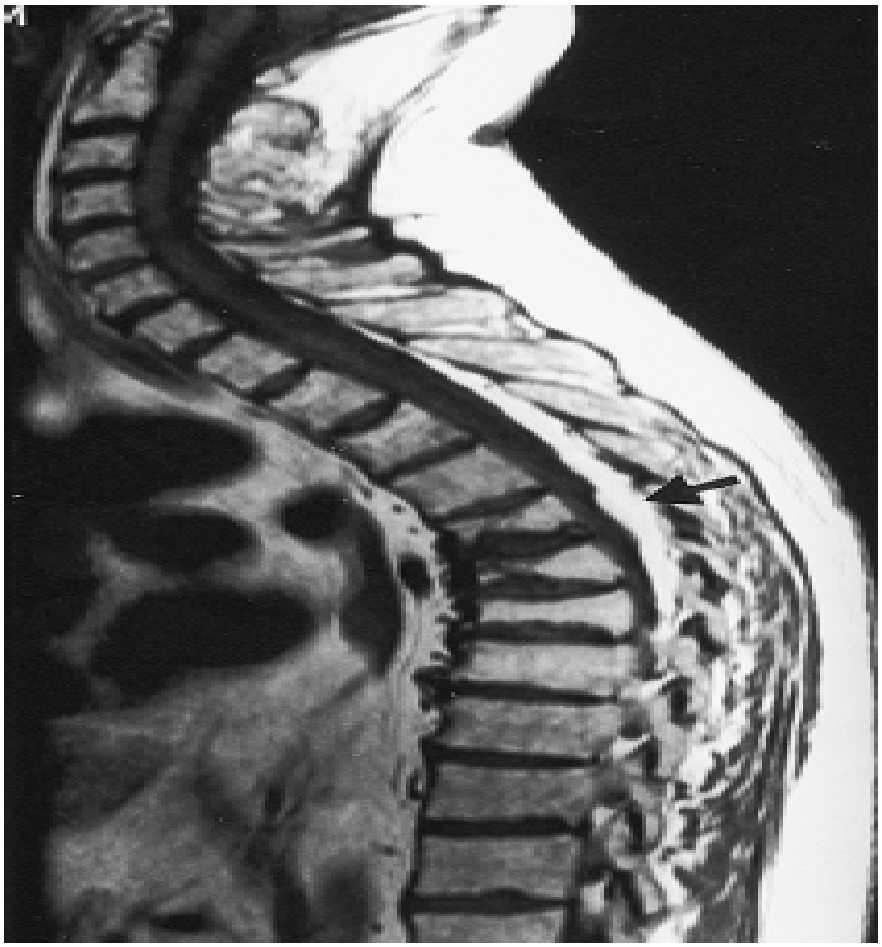
- 63y.o M admitted with muscle weakness and a T6 sensory level
- Diagnosis?

Cushings syndrome presenting as epidural lipomatosis

Clinical picture: Epidural lipomatosis

Stavroula Christopoulos, Jeffrey Minuk, Peter Assimakopoulos, Susan R Kahn

A 63-year-old male with diabetes mellitus and hypertension was admitted to the hospital with a 1-year history of weakness and symptoms typical of Cushing's syndrome. On examination he had proximal muscle weakness and a sensory level at T6. Magnetic resonance imaging of the spine showed multiple vertebral fractures and posterior thoracic epidural lipomatosis with cord compression at T6 (figure). He had increased urinary and plasma cortisol concentrations, with lack of suppression after 1 mg of dexamethasone. Magnetic resonance imaging of the sella turcica showed an enlarged pituitary gland, and we resected a pituitary adenoma. Postoperatively, the patient developed pulmonary emboli, hepatic steatotis, and sepsis. 3 months later, he suffered a sudden cardiac arrest and died. Epidural lipomatosis can be caused by exogenous steroid use and obesity, or endogenous hypercortisolaemia. Treatment choices include surgical debulking, or medical correction of hypercortisolaemia, and should be based on the severity of neurological signs, the reversibility of the causative factor, and estimated operative morbidity.



Case presentation

- 41 y.o woman referred by her family doctor with fatigue and weight gain

- History significant for DM (1year), hypercholesterolemia, and HTN resistant to 2 medications

Case presentation….

- **Physical examination**
- wt gain over 1 year
- Severe insomnia, depression and difficulty concentrating
- Round, plethoric face
- proximal muscle weakness
- Abdominal striae and hyperpigmentation

Cushing's Syndrome

Diagnostic approach

1. Establishing the diagnosis of CS

↓

2. Establishing the cause of CS
   a. ACTH-dependent vs independent
   b. Identifying the source in ACTH-dependent

↓

3. Imaging

Case presentation

ACTH dependent cushing syndrome

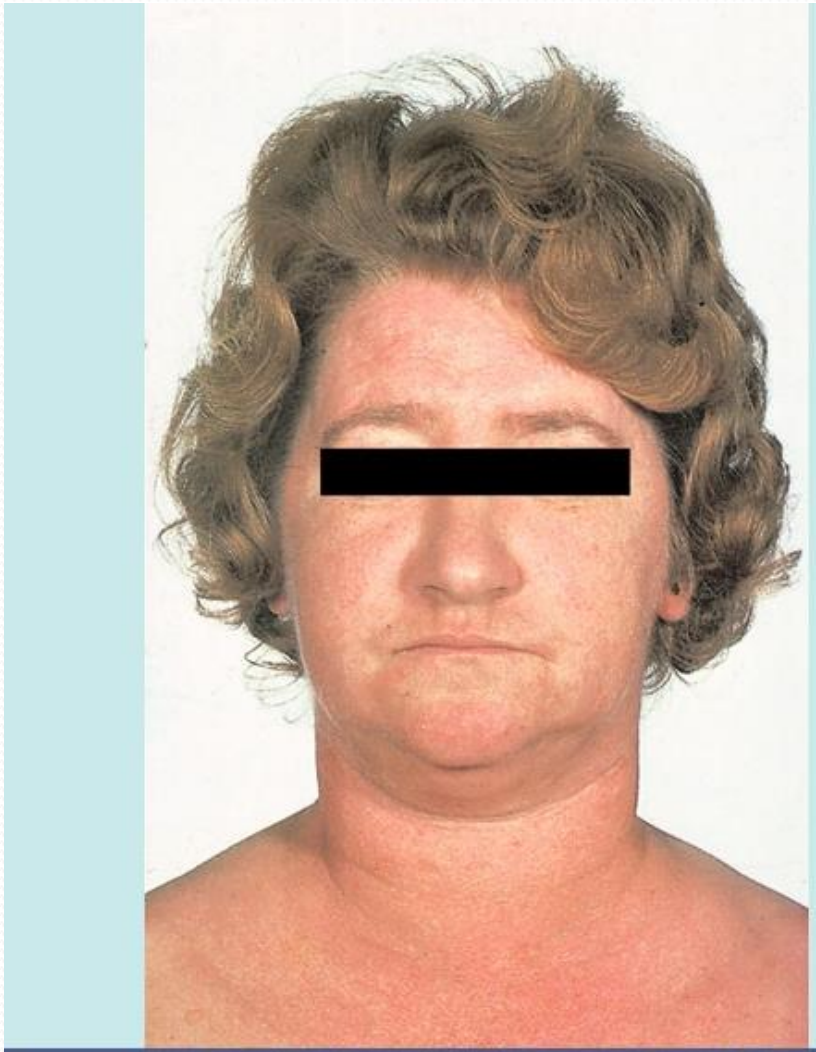
MRI pit; bulge on right lobe of pitutary gland

CXR, CT chest: normal

Case presentation

Patient underwent a transphenoidal surgery to resect the right lobe of the pituitary

- Pathology: 2 mm corticotroph adenoma



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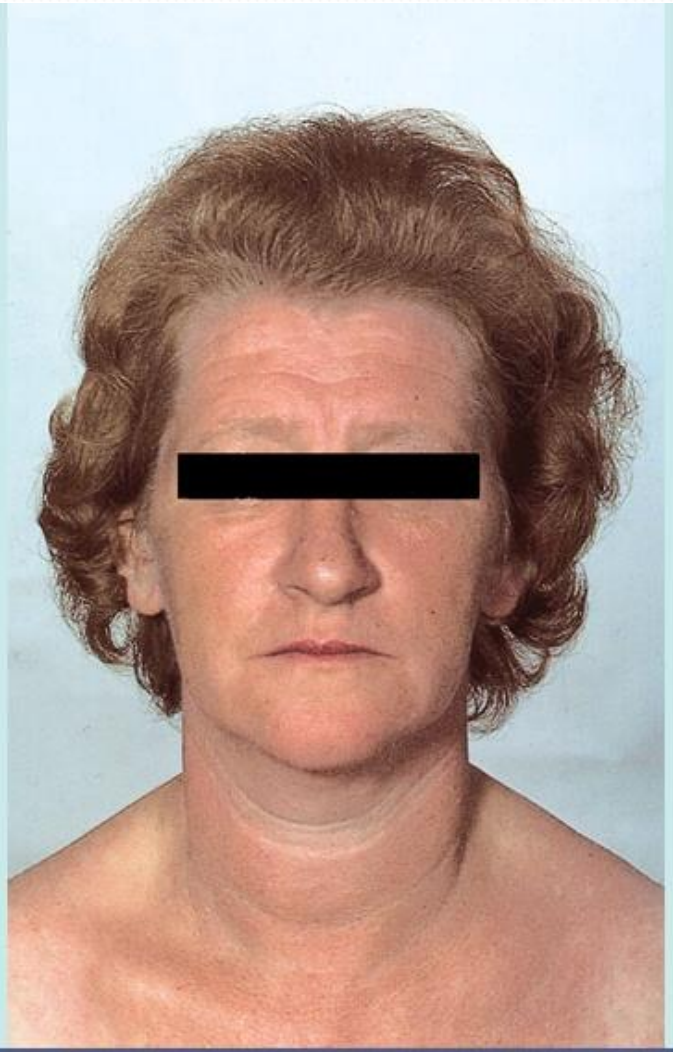

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Conclusion

- Diagnosis and management of CS remains a considerable challenge.
- Diagnostic algorithm (biochemical confirmation followed by localisation) should be closely followed to avoid major pitfalls and misdiagnosis.
- Tumour-specific surgery is the mainstay of treatment followed by radiotherapy and/or medical treatment.


UP