Cushings Disease

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Learning objectives

• The anatomy and function of the adrenal and other endocrine glands
• The diagnosis and management of endocrine disorders
• The role of surgery in the management of endocrine disorders
HARVEY CUSHING (1932)

"Which has been found at autopsy in 6 out of 8 to be associated with pituitary adenoma, in 5 cases definitely composed of basophil elements."
Hypothalmus-Pituitary-Adrenal Axis

Trauma via nociceptive pathways

Emotion via limbic system

Afferents from NTS

Drive for circadian rhythm

CRH

Hypothalamus

Anterior pituitary

ACTH

Cortisol

Systemic effects

Adrenal cortex
Cortisol Circadian Rhythm

Daily ups and downs of body rhythms

- Body temperature (°F)
- Systolic blood pressure (mm Hg)
- Cortisol hormone secretion (μm/dl)

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• Cushing described patients with a peculiar fat deposition, amenorrhea, impotence (in men), hirsutism, purple striae, hypertension, diabetes, and other features that constitute the syndrome.

• He also recognized that several of these patients had basophilic tumors of the pituitary gland and concluded that these tumors produced hormones, which caused adrenocortical hyperplasia, thus resulting in the manifestations of the syndrome.
Cushing's Syndrome

- red cheeks
- moon face
- Osteoporosis; compressed (codfish) vertebrae
- bruisability ecchymoses
- high blood pressure
- pendulous abdomen
- red striae
- thin skin
- thin arms and legs
- poor wound healing

Excessive Cortisol

- fat pads (buffalo hump)
- pendulous abdomen
the term **Cushing's syndrome** refers to a complex of symptoms and signs resulting from hypersecretion of cortisol regardless of etiology.

In contrast, **Cushing's disease** refers to a pituitary tumor, usually an adenoma, which leads to bilateral adrenal hyperplasia and hypercortisolism.

Cushing's syndrome (endogenous) is a rare disease, affecting 10 in 1 million individuals. It is more common in adults but may occur in children. Women are more commonly affected (male:female ratio 1:8).
Cushing's syndrome may be classified as ACTH-dependent or ACTH-independent

**ACTH dependent**
- Pituitary adenoma or cushing disease 70%
- Ectopic ACTH production 10%
- Ectopic CRH production

**ACTH Independent**
- Adrenal adenoma (10-15%)
- Adrenal carcinoma (5-10%)
- Adrenal hyperplasia
The most common cause of hypercortisolism is ingestion of prescribed medication, usually for **Non-Endocrine disease**.

- Oral
- Injected
- Topical (intra-articular, epidural, nasal, & dermal)
- Inhaled glucocorticoids

**Cizza J Clin Endocrinol Metab. 1996**

**Raff H. The Endocrinologist. 1998**
Iatrogenic Cushing's Syndrome

CRH
(+)

Exogenous Hydrocortisone

ACTH
(-)

(-) Cortisol
ACTH-dependent Cushing’s disease

Autonomous ACTH secreting tumour

CRH (+)

ACTH (+) (−) Cortisol
Adrenocortical tumour

CRH

ACTH

Autonomous cortisol secreting tumour

Cortisol
Ectopic ACTH syndrome

Ectopic ACTH secreting tumour

ACTH (+)

CRH (+)

(+) Cortisol
Ectopic CRH producing tumour

ACTH (+) \rightarrow CRH (+) \rightarrow Ectopic CRH secreting tumour

(+)(+) Cortisol
Clinical features

- **General**
  - Weight gain, Obesity, fat deposition
- **Integumentary**
  - Hirsuitism, plethora, acne, striae, ecchymosis
- **Cardiovascular**
- **Musculoskeletal**
- **Neuropsychiatry**
- **Metabolic**
- **Renal**
- **Gonadal**
Striae in Cushing's disease

Axillary and lower abdominal striae in a 21-year-old man with Cushing's disease. Abdominal obesity is also present.  
*Courtesy of David N Orth, MD.*
Mnemonic
The word "cushingoid" is a useful way to consider the complications and symptoms of Cushing's.

- Cataracts
- Ulcers
- Skin: striae, thinning, bruising
- Hypertension/ Hirsutism/ Hyperglycemia
- Infections
- Necrosis, avascular necrosis of the femoral head
- Glycosuria
- Osteoporosis, obesity
- Immunosuppression
- Diabetes
Diagnosis
Diagnostic tests

**Steps in Diagnosis**

1. Confirm the diagnosis
2. Determine source of hypercortisolism
   - Decreased ACTH Lack of suppression
     - Adrenal source
       - CT scan adrenals
   - Increased ACTH Positive
     - Pituitary source
   - Increased ACTH Lack of suppression
     - Ectopic ACTH source
     - ACTH gradient?
   - Equivocal results
     - Further testing Bilateral petrosal vein sampling

**Diagnostic Studies**

1. Overnight DST
2. 24-hour urinary free cortisol
3. 11:00 pm salivary cortisol

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Cushing Syndrome Suspected

- 24-h Urine Free Cortisol Level
  - Filtered Load of Cortisol
  
- 11 p.m. Salivary Cortisol Level
  - Disrupted Circadian Rhythm
  
- Low-Dose Dexamethasone Suppression Test
  - Attenuated Negative Feedback

Normal Results

Equivocal Results

Abnormal Results

Dexamethasone CRH Test

Cushing Syndrome Excluded

(Repeat Testing if High Index of Suspicion)

Cushing Syndrome Established
Many studies have demonstrated great promise in the use of this test as a screening test for CS. More than 140 patients found an increased bedtime salivary cortisol levels yield both a

- Sensitivity of 93%
- Specificity of 100%

Papanicolaou J Clin Endocrinol Metab. 2002
Low-Dose Dexamethasone Suppression Test

- 1mg of dexamethasone at 2300 hours and measurement of plasma cortisol at 0800 or 0900 hours the next morning.
  - High diagnostic accuracy with a sensitivity of 98% using a post-dexamethasone serum cortisol value of less than 50nmol/l (1.8µg/l)
- Consensus opinion in the United Kingdom: value of less than 50nmol/l (1.8µg/l) effectively excludes the Cushing syndrome

Wood Ann Clin Biochem 1997
• False positive results can occur because:
  • Failure to take dexamethasone as prescribed.
  • Accelerated hepatic metabolism
    • Phenytoin, Carbamazepine, Barbiturates, Aminoglutethimide or Rifampicin), and ETOH.
  • Increased concentration of cortisol binding globulin (CBG)
    • Pregnancy or Estrogen treatment.
Dexamethasone-CRH Test

- Dexamethasone (0.5 mg Q 6 hours) is given X8, the first dose at noon and the last dose at 6:00 a.m.

- Corticotropin-releasing hormone CRH (1µg/kg) is then administered IV at 8:00 a.m., and plasma cortisol and ACTH levels are obtained at 15-minute intervals for 1 hour.

- Cortisol level greater than 39 nmol/L (1.4 g/dL) measured 15 minutes after the administration of CRH correctly identifies patients with the Cushing syndrome, and levels of 39 nmol/L or less (1.4 g/dL) are considered normal.

- ??Normal ACTH response.
  - Patients with the Cushing syndrome usually have a peak ACTH response exceeding 3.3 pmol/L (15 pg/mL) during the test.
The dexamethasone-CRH test is usually reserved for patients with equivocal results on other diagnostic tests and a high index of suspicion for the Cushing syndrome.
- CT
- MRI
Treatment

- Laparoscopic adrenalectomy
- Open adrenalectomy more than 6 cm
- Bilateral adrenalectomy
- Transsphenoidal excision of pituitary adenoma
- Pituitary irradiation