Cushing's Syndrome

Done By: 429 Medicine Team

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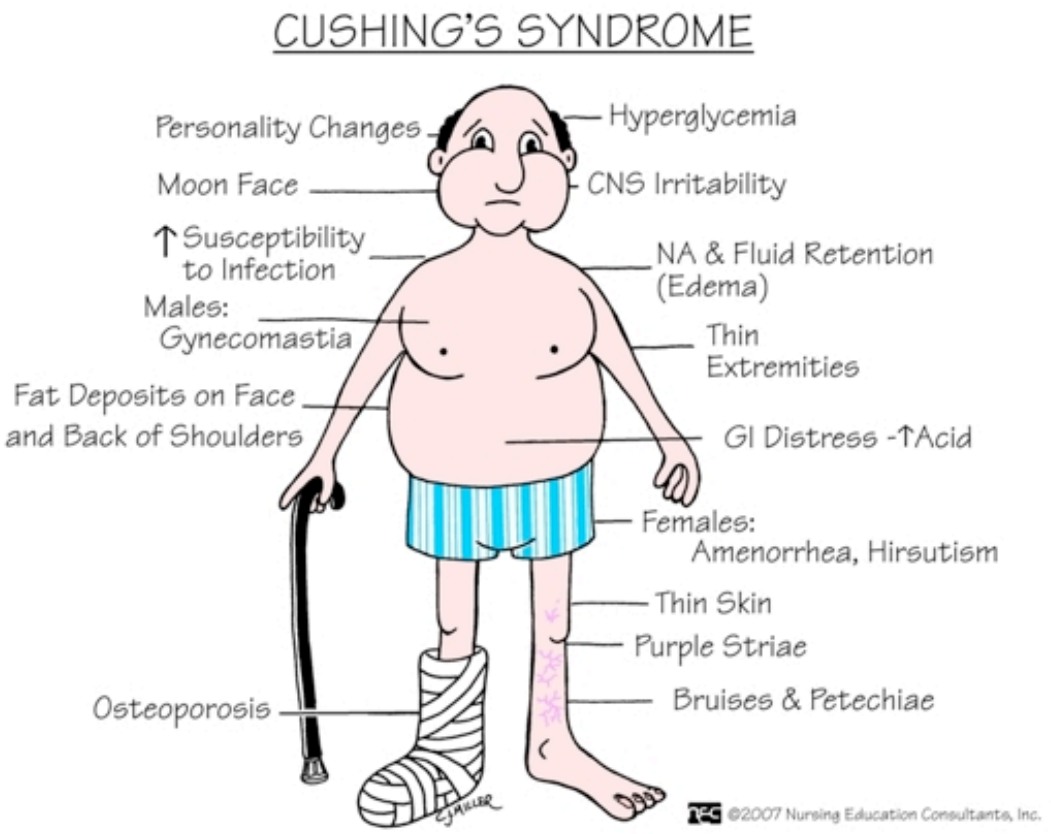
• April 27, 2012



Cushing's Syndrome

Introduction & Definitions:

Glucocorticoids

Cortisol is the major glucocorticoid in humans. Levels are highest in the morning on waking and lowest in the middle of the night. Cortisol rises dramatically during stress, including any illness. This elevation protects key metabolic functions (such as the maintenance of cerebral glucose supply during starvation) and inhibits potentially damaging inflammatory responses to infection and injury. The clinical importance of cortisol deficiency is, therefore, most obvious at times of stress.

More than 95% of circulating cortisol is bound to protein, principally cortisol-binding globulin. It is the free fraction which is biologically active. Cortisol regulates cell function by binding to glucocorticoid receptors which regulate the transcription of many genes. It can also activate mineralocorticoid receptors, but it does not normally do so because most cells containing mineralocorticoid receptors also express an enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which converts cortisol to its inactive metabolite, cortisone. Loss of the protection of mineralocorticoid receptors by inhibition of 11β-HSD2 (e.g. by liquorice or as a result of an inherited enzyme defect) results in cortisol acting like aldosterone as a potent sodium-retaining steroid

Definitions

Cushing' Syndrome:
A state of chronic glucocorticoid excess leading to constellation of symptoms and signs of hypercortisolism regardless of the cause.

Cushing's Disease:
The specific type of Cushing's syndrome due to excessive ACTH secretion from a pituitary tumor.

Ectopic ACTH syndrome:
Type of Cushing's syndrome due to ACTH secretion by nonpituitary tumor.

In another words:

Cushing Syndrome: any condition with hypercortislosiom - General Increase,other source than pituitary.

Cushing Disease: Increase ACTH Secretion from Pituitary - So the problem is from the Pituitary.

Ectopic ACTH Syndrome: Small cell carcinoma can produce ACTH -- Non pituitary source.

Cushing's Syndrome:

- The most common cause is iatrogenic due to chronic use of glucocorticoid.
- Regardless of etiology, all cases of endogenous or spontaneous Cushing's syndrome are due to overproduction of cortisol by the adrenal glands.
- Most endogenous types are due to ***Bilateral Adrenal Hyperplasia*** due to ACTH secretion by pituitary adenoma.
- Incidence of pituitary-dependent adrenal hyperplasia in women is 3 times that in men.
- The most frequent age of onset is 3rd to 4th decade.

Note That:

- The difference from ectopic and pituitary is much higher levels than pituitary sources.

Cushing's syndrome – Differential Diagnosis:

1- ***ACTH-dependent :***

o Pituitary adenoma (Cushing's disease).

o Non-pituitary neoplasm (ectopic ACTH).

2- ***ACTH-independent*** :

- Iatrogenic (glucocorticoid, megestrol acetate).
- Adrenal neoplasm (adenoma, carcinoma).
- Nodular adrenal hyperplasia :

A- Primary pigmented nodular adrenal disease.

B- Massive macronodular adrenonodular hyperplasia.

C- Food-dependent (GIP-mediated).

- Factitious.

<u>Tumors causing ectopic ACTH syndrome:</u>

1- Small cell carcinoma of the lung (50% of ectopic ACTH cases). -- Most Common

2- Pancreatic islet cell tumors.

3- Carcinoid tumors (lung, thymus, gut, pancreas, ovary).

4- Medullary carcinoma of the thyroid.

5- Pheochromocytoma and related tumors.

<u>Pathology of Cushing's Syndrome:</u>

1- **Anterior Pituitary Gland.**

A- **Pituitary adenoma (> 90% of Cushing's disease) :**

- Microadenoma (< 10 mm in diameter) 80-90%. More COmmon
- Macroadenoma (> 10 mm in diameter) & could be invasive.
- Mostly benign adenoma; rarely malignant.

B- **Pituitary Hyperplasia :**

- Diffuse hyperplasia of corticotrophs cells are rare.
- Due to excessive stimulation of pituitary by CRH.

2- Adrenocortical Hyperplasia:

- Bilateral hyperplasia of adrenal cortex.
- Results from chronic ACTH hypersecretion.
- **There are 3 types of adrenocortical hyperplasia:**

A- Simple Adrenocortical Hyperplasia (Cushing's disease)

B- Ectopic ACTH syndrome.

C- Bilateral Nodular Hyperplasia.

- Nodular enlargement of adrenal glands resulting from long-standing ACTH hypersecretion (pituitary or nonpituitary).

- **There are 2 types of Bilateral Nodular Hyperplasia :**
- Primary Pigmented Nodular Adrenocortical Disease, PPNAD).
- Massive Macronodular Adrenal Hyperplasia).

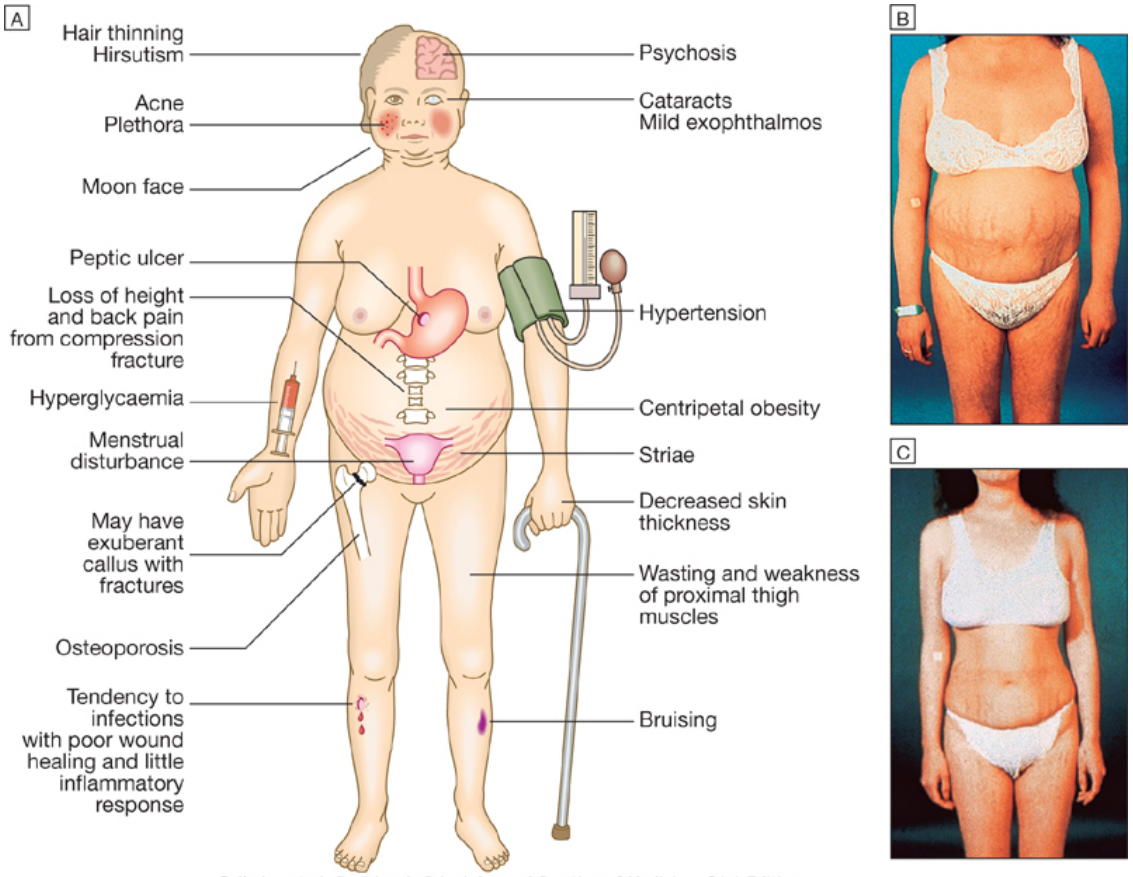
3- Adrenal Tumors:

A- **Adrenal Adenomas :**

- Glucocorticoids-secreting adenomas.
- Encapsulated.
- Weigh 10 – 70 gr.
- Size : 1- 6 cm.

B- **Adrenal Carcinomas :**

- Usually weigh over 100 gr.; commonly palpable mass.
- Encapsulated.
- May invade local structures.



Clinical Symptoms and Signs of Cushing's Syndrome

1- **General :**

o Central obesity.
o Proximal muscle weakness.
o Hypertension.
o Headaches.
o Psychiatric disorders.

2- **Skin :**

o Wide(>1cm), purple striae.
o Spontaneous echymoses.
o Facial plethora.
o Hyperpigmentation.
o Acne.
o Hirsutism.
o Fungal skin infections.

3- Endocrine and Metabolic Derangements :

o Hypokalemic alkalosis.
o Osteopenia.
o Delayed bone age in children.
o Menstrual disorders, decreased libido, impotence.
o Glucose intolerance, diabetes mellitus.
o Kidney stones.
o Polyurea.

Clinical Features of Cushing's Syndrome (Percentages)

1- ***General :***

o Obesity 90%.
o Hypertension 85%.

2- ***Skin :***

o Plethora (70%).
o Hirsutism (75%).
o Striae (50%).
o Acne (35%).
o Bruising (35%).

3- Metabolic :

o Glucose intolerance(75%).
o Diabetes (20%).
o Hyperlipidemia (70%).
o Polyuria (30%).
o Kidney stones (15%).

4- Musculoskeletal :

o Osteopenia (80%).
o Weakness (65%).

5- ***Neuropsychiatric (85%) :***

o Emotional lability.
o Euphoria.
o Depression.
o Psychosis.

6- ***Gonadal dysfunction*** **:**

o Menstrual disorders (70%).
o Impotence, decreased libido(85%).

Cushing' Disease

The most common type of endogenous Cushing's syndrome (70%).
Female : Male Ratio about 8 : 1
Incidence age ranges from childhood to 70 years.

Ectopic ACTH Hypersecretion

15-20% of ACTH-dependent Cushing' syndrome.
Very high ACTH may result in severe hypercortisolism with lack of classical features of Cushing's syndrome.
More common in men.
Age incidence : 40-60 years.

Primary Adrenal Tumors

10% of cases of Cushing's syndrome.
Most are benign adrenocortical adenomas.
Adrenocortical carcinomas are uncommon.
Both adenomas & carcinomas are more common in women.

Childhood Cushing's Syndrome

Adrenal carcinoma is the commonest (51%) & Adrenal adenoma (14%).
More common in girls than in boys.
Most in age 1 – 8 years.
Cushing's disease more common in adolescents (35%); most at age over 10 years.

Routine Laboratory Findings

High normal Hb, Htc & RBC.
WBC usually normal but lymphoctytes may be subnormal.
Eosinophils may be reduced.
Electrolytes : Hypokalemia & alkalosis in marked steroid hypersecretion (ectopic ACTH).
Impaired glucose tolerance or hyperglycemia.
Serum Calcium normal but hypercalciuria in 40%.

Features suggesting specific causes

1. Cushing's Disease :

o Typifies classic clinical picture:
o Female predominance
o Onset age: 20 – 40 years.
o Slow progression over several years.
o Hyperpigmentation & hypokalemic alkalosis are rare.
o Androgenic manifestations are limited to acne & hirsutism.
o Moderately increased cortisol & adrenal androgens.

2. Ectopic ACTH Syndrome (Carcinoma) :

o Predominantly in males.

o Highest incidence at age 40 – 60 years.

o Clinical manifestations are frequently limited to: weakness, hyperpigmentation & glucose intolerance.

o Primary tumor is usually apparent.

o Hyperpigmentation, hypokalemia & alkalosis are common.

o Weight loss & anemia are common.

o Hypercortisolism is of rapid onset.

o Steroid hypersecretion is frequently severe with equally elevated levels of glucocorticoids,
androgens & DOC.

3- Ectopic ACTH Syndrome (Benign Tumor) :

o Slowly progressive course with typical features of Cushing's syndrome.

o Presentation may be identical to pituitary-dependent Cushing's disease & the responsible tumor may not be apparent.

o Hyperpigmentation, hypokalemic alkalosis & anemia are variably present.

4. Adrenal Adenomas :

o Usually the clinical picture of glucocorticoid excess alone.

o Androgenic effects usually absent.

o Gradual onset.

o Mild to moderate hypercortisolism.

5. Adrenal Carcinomas :

o Rapid onset & rapid progression.

o Clinical picture of excessive glucocorticoids, androgens & mineralocorticoids secretion.

o Marked elevation of cortisol & androgens.

o Abdominal pain, palpable masses & metasteses in liver & lungs.

o Hypokalemia is common.

- If the cause of Cushing is CA, the progression is fast, all hormones are elevated, the primary tumor is
identifiable and hypokalemic alkalosis is seen.

- Less of these Sym, Signs with adenomas.

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Diagnosis of Cushing's Syndrome

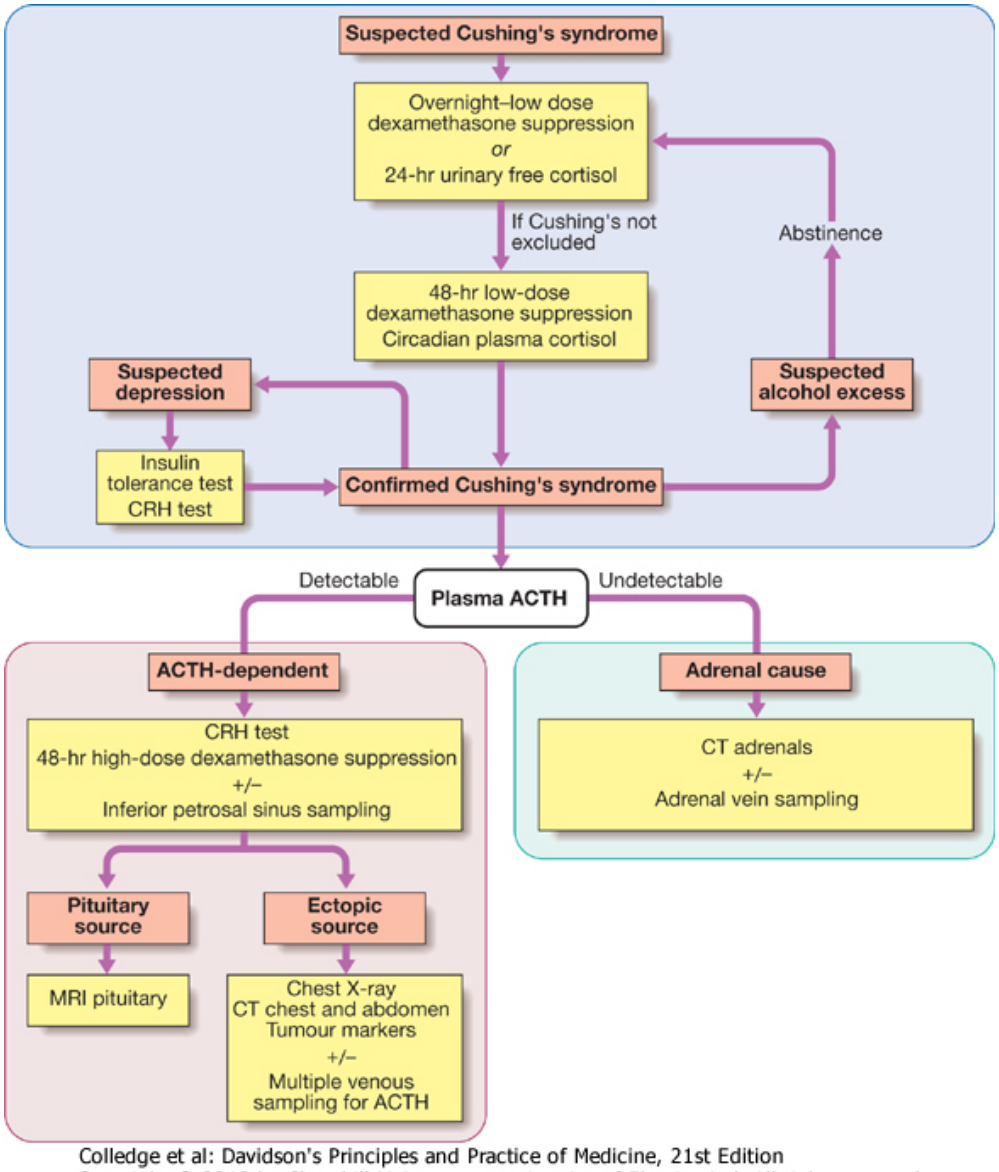
- **Stages of Evaluation :**
- Clinical suspicion.
- Biochemical diagnosis of hypercortisolism status.
- Differential diagnosis for etiology of hypercortisolism (Biochemical & Imaging Tests).

Biochemical diagnosis of hypercortisolism status :

1. Dexamethasone suppression test.
2. 24 hr Urine free cortisol.
3. Diurnal rhythm of cortisol secretion.

- Differential diagnosis of etiology of hypercortisolism (Biochemical & Imaging Tests).

1. Plasma ACTH.
2- Pituitary MRI.
3. High-dose Dexamethasone suppression test.
4. Inferior Petrosal Sinus Sampling with CRH stimulation.
5. Localizing occult ectopic ACTH.
6. Adrenal localizing procedures.



Colledge et al: Davidson's Principles and Practice of Medicine, 21st Edition

Non-Cushing Causes of Hypercortisolemia

1- Physical stress :

- Operations, trauma.
- Chronic exercise.
- Malnutrition.

2- Mental stress and psychiatric disorders :

- Hospitalization.
- Drug and alcohol abuse and withdrawal.
- Chronic depression (unipolar, bipolar).
- Panic disorder.
- Anorexia nervosa.

3- Metabolic abnormalities :

- Hypothalamic amenorrhea.
- Elevated cortisol-binding globulin (estrogen therapy, pregnancy, hyperthyroidism).
- Glucocorticoid resistance.
- Complicated diabetes mellitus.

Pitfalls in the interpretation of the 1-MG Overnight Dexamethasone Suppression Test

1- **False-positive tests (I.e., lack of suppression) because of pseudo-cushing :**

o Non-Cushing hypercortisolemia.
o Obesity.
o Stress.
o Alcoholism.
o Psychiatric illness (anorexia nervosa, depression, mania).
o Elevated cortisol binding globulin (estrogen, pregnancy, hyperthyroidism).
o Glucocorticoid resistance.

2- **Test-related artifacts :**

o Laboratory error, assay interference.
o insufficient dexamethasone delivery into the circulation.
o Noncompliance.
o Decreased absorption.
o Increased metabolism (drugs).

3- **False-negative tests :**

o Chronic renal failure (creatinine clearance < 15 mL/min).

o Hypometabolism of dexamethasone (e.g., liver failure).

Problems in Diagnosis of Cushing's Syndrome

A- **Pseudo-Cushing's syndromes :**

Conditions :

1. Depression.

2. **Alcoholism** & withdrawal from alcohol intoxication.

3. **Eating disorders** (anorexia nervosa & bulimia).

Similarities in biochemical features of Cushing's syndrome :

1. Elevation of urine free cortisol.

2. Disruption of the normal diurnal pattern of cortisol secretion.

3. Lack of suppression of cortisol after overnight 1 mg dexamethasone suppression test.

Distinguishing Tools :

1. History & physical examination.

2. Repeating screening tests.

3- Dexamethasone suppression test followed by CRH stimulation & measurement of plasma cortisol.

Treatment of Cushing's Syndrome

1. Pituitary microsurgery :

- Transphenoidal hypophysectomy.
- Transfrontal hypophysectomy.

2. Radiotherapy :

- Conventional irradiation (not recommended).
- Heavy particles irradiation.
- Gamma-knife radiosurgery.
- Implantation of radioactive seeds (gold & yttrium).

3. Medical Therapy :

- Ketoconanzole.
- **Aminoglutethimide.**
- **Mitotane (adrenolytic drug).**

- Other types of Cushing's syndromes :

1. Ectopic ACTH syndromes.
2. Adrenal Adenomas.
3. Adrenal Carcinomas.
4. Nodular Adrenal Hyperplasia.

Prognosis of Cushing's Syndrome :

1. Cushing's Disease.
2. Ectopic ACTH syndromes.
3. Adrenal Adenomas.
4. Adrenal Carcinomas.
5. Nodular Adrenal Hyperplasia.

- Additional Explanations for The treatment:

Management

Untreated Cushing's syndrome has a 50% 5-year mortality. Most patients are treated surgically with medical therapy given for a few weeks prior to operation. A number of drugs are used to inhibit corticosteroid biosynthesis, including metyrapone and ketoconazole. The dose of these agents is best titrated against 24-hour urine free cortisol.

Cushing's disease

Trans-sphenoidal surgery with selective removal of the adenoma is the treatment of choice. Experienced surgeons can identify microadenomas which were not detected by MRI and cure about 80% of patients. If the operation is unsuccessful, then bilateral adrenalectomy is an alternative.

If bilateral adrenalectomy is used in patients with pituitary-dependent Cushing's syndrome, then there is a risk that the pituitary tumour will grow in the absence of the negative feedback suppression previously provided by elevated cortisol levels. This can result in Nelson's syndrome, with an aggressive pituitary macroadenoma and very high ACTH levels causing pigmentation. Nelson's syndrome can be prevented by pituitary irradiation.

Adrenal tumours

Adrenal adenomas are removed by laparoscopy or a loin incision. Surgery offers the only prospect of cure for adrenocortical carcinomas, but in general prognosis is poor with high rates of recurrence even in patients with localised disease at presentation. Although often used, there is little evidence that radiotherapy, chemotherapy or the adrenolytic drug mitotane improves recurrence rates or survival.

Ectopic ACTH syndrome

Localised tumours such as bronchial carcinoid should be removed surgically. In patients with incurable malignancy it is important to reduce the severity of the Cushing's syndrome using medical therapy (see above) or, if appropriate, bilateral adrenalectomy.

Done !