Hypercortisolism

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Learning Objectives

After participating in this presentation, you will be able to:

• Understand the different etiologies and pathophysiologies of hypercortisolism

• Discuss the screening tests for Cushing syndrome

• Establish diagnostic approach and differential diagnosis of Cushing syndrome
Regulation of Cortisol Secretion

Hypothalamic-Pituitary-Adrenal Axis

- Pulsatile Secretion
- Circadian Rhythm

Hypercortisolism (Cushing Syndrome)

- A group of clinical abnormalities due to chronic exposure to excess of cortisol.

- The incidence of Cushing’s syndrome is 10-15 per million and mostly occur between the ages of 20 and 50 years.

- First described by Harvey Cushing, an American neurosurgeon in 1912.
Causes of Cushing Syndrome

• ACTH-dependent causes
  - ACTH-secreting pituitary tumor (Cushing disease)(70% cases)
  - Ectopic ACTH-secreting tumors (non-pituitary)(15%)

• ACTH-independent causes
  - Adrenal adenoma: benign (5%)
  - Adrenal carcinoma: malignant (3%)
  - Nodular adrenal hyperplasia (9%)
  - Adrenal rest tumor (<1%)
  - Iatrogenic and factitious glucocorticoid administration (exogenous)

• Pseudo-Cushing Syndrome
  Associated in patients with alcoholism, depression, obesity, PCOS
Cushing Disease vs. Cushing Syndrome

• Cushing disease and Cushing syndrome are caused by an oversecretion of the adrenal cortex.

• Cushing syndrome refers to the general state characterized by excessive production of cortisol leading to classic symptoms.

• Cushing disease is the pituitary-dependent form of Cushing syndrome caused by hypersecretion of ACTH by pituitary tumors primarily microadenoma.
Hypercortisolism

Common Causes of Ectopic ACTH Secretion

• Neuroendocrine tumors:
  - Carcinoid tumors of the lung (bronchi)
  - Carcinoid tumors of pancreas
  - Carcinoid tumors of thymus
  - Medullary thyroid cancer

• Small cell carcinoma of the lung

• Pheochromocytoma
Diagnosis of Hypercortisolism

• Clinical manifestations
• Lab findings
  - Serum cortisol
  - Plasma ACTH (not the 1st line test)
  - 24 hour urinary cortisol
  - Suppression or stimulation tests
• Imaging: CT, MRI
Laboratory Evaluations of Cushing Syndrome

- Serum cortisol levels elevated
- Plasma ACTH levels maybe elevated (ACTH-dependent)
- 24-hour urinary cortisol levels elevated
- Loss of diurnal variation in cortisol levels
- Dexamethasone suppression test
Screening Tests for Cushing Syndrome

Three screening tests are commonly applied:

• Measurement of the 24-hour urinary free cortisol (UFC)
• The overnight low-dose dexamethasone suppression test
• A midnight cortisol measurement (plasma or salivary cortisol)

Hypercortisolism is strongly suggested when any two out of three tests are abnormal.
Screening Tests for Cushing Syndrome

- **Measurement of the 24 hour urinary free cortisol (UFC)**

  A 24 hour urinary free cortisol concentration <50 μg/day excludes the diagnosis of Cushing syndrome.

  A 24-hour urinary free cortisol concentration >120 μg/day suggests the diagnosis of Cushing syndrome.

  Urine cortisol measurements do not establish the diagnosis and abnormal results need to be followed by further investigation or testing.
Screening Tests for Cushing Syndrome

• The Overnight Low-Dose Dexamethasone Suppression Test
  - 1.0 mg dexamethasone given orally at 2300h
  - Serum cortisol measured at 8:00am next day
  - Normal: Serum cortisol suppressed to <2µg/dL
  - Cushing Syndrome: Serum cortisol not suppressed. >10µg/dL suggestive of the diagnosis.
Screening Tests for Cushing Syndrome

- **Multiple Low-Dose Dexamethasone Suppression Test**
  - Urine is collected every 24h for 3 days for measurement of cortisol.
  - Dexamethasone, 0.5 mg q6h P.O on day 2 for 2 days
  - Urinary free cortisol decreased: Normal
  - Urinary free cortisol NOT decreased: Cushing Syndrome
Screening Tests for Cushing Syndrome

• Midnight Serum Cortisol and Salivary Cortisol Measurements
  - Serum (or salivary) cortisol measurement taken at 2400 hours
  - Cushing Syndrome
    • Elevated midnight cortisol levels
    • Loss of diurnal variation in cortisol levels (less helpful).
Diagnosis of Cushing Syndrome

Plasma ACTH

- Plasma ACTH concentrations are low in patients with adrenal tumor
- Plasma ACTH concentrations are normal or moderately elevated in patients with Cushing disease
- Plasma concentrations of ACTH are very often markedly elevated in patients with ectopic Cushing (ACTH) syndrome
Diagnosis of Cushing Syndrome

High-Dose Dexamethasone Suppression Test

- High-dose dexamethasone suppression test can be used to differentiate Cushing syndrome from Cushing disease.

- Serum is collected at 0800 hours for the measurement of cortisol.

- In patients with adrenal tumor and in most of the patients with nonendocrine ACTH-secreting tumor, suppression does not occur after the high-dose 8 mg dexamethasone administration.
Diagnosis of Cushing Syndrome

High-Dose Dexamethasone Suppression Test

- High-Dose Overnight Dexamethasone Suppression Test: DX 4mg, P.O at 2300 and 2400 hours
- Multiple High-Dose Overnight Dexamethasone Suppression Test: DX 2mg, P.O, q6h for 2 days.

- Serum or urinary free cortisol at 0800 hours reduced >50%: Cushing disease (Pituitary adenoma)
- Serum or urinary free cortisol NOT reduced >50%: Adrenal tumor, carcinoma, ectopic ACTH syndrome
Diagnosis of Cushing Syndrome

CRH Stimulation Test

• Exogenous CRH, 1.0 μg/kg b.w, is given intravenously in bolus form at 0900 or 2000 hours.
• Serum cortisol and plasma ACTH are measured 15 min and immediately before and 5, 15, 30, 60, 120, and 180 min after CRH injection.

• Interpretation:
  - An increase of serum cortisol by ≥20% or ACTH by ≥ 50% above basal level is seen in patients with Cushing disease.
  - Poor responses occur in patients with adrenal tumor and in most patients with nonendocrine ACTH-secreting tumor.
Tests for Localization of Cushing Syndrome

• Computed tomography (CT) and magnetic resonance imaging (MRI) are helpful in localizing the tumors.

• Selective Inferior petrosal sinus sampling (IPSS) for ACTH measurements before and after CRH administration:
  - Blood samples are taken from each sinus vein and from a peripheral vein.
  - If the ACTH level in the inferior petrosal sinus vein is similar to the peripheral vein, this suggests a non-pituitary source of the ACTH (ectopic).
  - In Cushing disease, the ACTH level in the inferior petrosal sinus vein is much higher compared to the peripheral vein (>2:1).
Laboratory Evaluation of Cushing Syndrome

Cushing syndrome suspected

Exclude exogenous glucocorticoid exposure

UFC/ON DST/
Mid night salivary or serum cortisol (days 1&2)

Abnormal

Confirmatory tests

Normal

Cushing syndrome excluded

UFC: 24-hour urinary free cortisol
ON DST: overnight 1mg dexamethasone suppression test

Tietz Text Book (5th edition)
Differential Diagnosis of Cushing Syndrome

Biochemical evidence of Cushing syndrome

LDDST (days 2&3)

Lack of suppression (UFC≥50% of baseline) → Cushing syndrome confirmed → High-dose DS suppression test

Suppression (UFC<50% of baseline) → Cushing syndrome ruled out

High-dose DS suppression test

Suppression (UFC<50% of baseline) → CRH stimulation test

Lack of suppression (UFC≥50% of baseline) → ↑ACTH (>50pg/mL) → Ectopic ACTH or CRH → ↓ACTH(<10 pg/mL) → Adrenal cortical tumor

LDDST: overnight low-dose dexamethasone suppression test

IPSS: inferior petrosal venous sinus sampling ACTH vs. peripheral venous ACTH

Tietz Text Book (5th edition)
References

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