CUSHING SYNDROME

* Please check out this link to know if there are any changes or additions.
OBJECTIVES:

✔ To identify different causes of Cushing’s syndrome

✔ To understand the diagnostic algorithm for Cushing’s syndrome

✔ To understand the interpretation of laboratory and radiological tests of Cushing’s syndrome
### Introduction to the adrenal gland:

**ANATOMICALLY:**
- The adrenal gland is situated on: the anteriosuperior aspect of the kidney.
- It receives its blood supply from: the adrenal arteries.

**Histologically:**

The adrenal gland consists of two distinct tissues of different embryological origin, the outer cortex and inner medulla.

<table>
<thead>
<tr>
<th>The adrenal cortex comprises three zones based on cell type and function:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The outermost zone</td>
</tr>
<tr>
<td><strong>Zona glomerulosa</strong></td>
</tr>
<tr>
<td>Aldosterone (the principal mineralocorticoid).</td>
</tr>
</tbody>
</table>

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اقروهم على السريع..تخيلوا سؤال بايو ويسأل عن الزونا فسكيولاتا؟ وش بيخلون للهستو؟

435 Biochemistry Team
Steroid Hormone Synthesis

Cholesterol (27C)

Pregnenolone (21C)

Progesterone (21C)

17-α-Hydroxylase

3-β-Hydroxysteroid dehydrogenase

17-α-Hydroxyprogesterone (21C)

17-α-Hydroxylase

11-Deoxycorticosterone (21C)

11-Deoxycortisol (21C)

Corticosterone

11-β-Hydroxylase

Aldosterone (21C)

Androstenedione (19C)

Testosterone (19C)

Cortisol (21C)

Estradiol (18C)

Peripheral tissues

Cholesterol is the precursor. حفظوه من الفزيو...
Hypothalamic-Pituitary-Adrenal (HPA) Axis

The hypothalamus secretes corticotrophin-releasing hormone (CRH) which stimulates the anterior pituitary gland to release ACTH. ACTH acts on the zona fasiculata cells releasing glucocorticoids (Cortisol).

**Regulation of ACTH and Cortisol Secretion**

<table>
<thead>
<tr>
<th>Negative feedback control</th>
<th>Stress</th>
<th>The diurnal rhythm of plasma cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACTH</strong> release from the anterior pituitary is stimulated by hypothalamic secretion of corticotrophin releasing hormone (CRH).**</td>
<td>e.g. major surgery, emotional stress</td>
<td>➢ <strong>Highest</strong> Cortisol level in the <strong>morning</strong> (8 - 9 AM). ➢ <strong>Lowest</strong> Cortisol level in the late afternoon and evening (8 - 9 PM).</td>
</tr>
<tr>
<td>CRH → ↑ACTH → ↑[Cortisol] → ↑[Cortisol] or synthetic steroid suppress CRH &amp; ACTH secretion</td>
<td>Stress → ↑↑CRH &amp; ACTH → ↑↑Cortisol</td>
<td></td>
</tr>
</tbody>
</table>
In the circulation, glucocorticoids are mainly protein-bound (about 90%), chiefly to cortisol-binding globulin (CBG or transcortin).

- ↑↑ in pregnancy and with estrogen treatment (e.g. oral contraceptives).
- ↓↓ in hypoproteinemic states (e.g. nephrotic syndrome).
- The biologically active fraction of cortisol in plasma is the free (unbound) component.

CORTISOL AND ACTH MEASUREMENTS

Serum measurement is preferred for cortisol and Plasma for ACTH.

Samples must be collected between 8 a.m. and 9 a.m. and between 10 p.m. and 12 p.m. because of the diurnal rhythm.

Temporary ↑↑ in these hormones may be observed as a response to emotional stress.

Diurnal rhythm: increase of cortisol in early morning, and decrease in the night.

The diurnal rhythm of cortisol secretion; the area between the curves represents values that lie within the reference range.
**URINARY CORTISOL EXCRETION**

- **Cortisol** is removed from plasma by the **liver**
- Metabolically **inactive** compounds
- Excreted in urine mainly as **conjugated metabolites** (e.g. glucuronides).
- A small amount of **cortisol** is excreted unchanged in the urine (UFC).

**Notes:**
- The early morning specimen in case of babies or old people who cannot obtain the 24 sample.
- We use the ratio to differentiate between the diluted or concentrated urine, and as more diluted as more accurate results.

**In normal individuals:**
- Urinary **free cortisol (UFC)** is < 250 nmol/24 h.
- **Cortisol / Creatinine ratio** in an early morning specimen of urine is < 25 μmol cortisol / mol creatinine.

**Used in cushing test**
CAUSES OF elevated serum cortisol concentrations:

Increased cortisol secretion:
- Exercise
- Alcohol abuse
- Obesity
- Chronic renal failure
- Stress, Anxiety, Depression
- Congenital
- Estrogen therapy
- Pregnancy

Increased cortisol binding globulin (CBG):

ACTH – dependent
1. Pituitary ACTH 70% (Cushing’s disease).
2. Ectopic ACTH by neoplasms 10%. (Example: Bronchial cancer) “Not from the pituitary – Lung cancers”
3. ACTH therapy.

ACTH – independent
1. Adrenal tumor 20% (adenoma or carcinoma)
2. Glucocorticoid therapy.

CUSHING’S SYNDROME

من بداية المحاضرة لازم نتفق على شيء:
الكوشينق مرض هرموني نطلق عليه "فرز الكورتيزول بكميات كبيرة". الكوشينق ديزيز هو مرض يندرج تحت السندروم "أفرز كميات كبيرة من الكورتيزول" وسببه هالزيادة في الادينوما. هالائيتاري "بالرئة على سبيل المثال" وومن يكون الشخص باخذ كعلاج وإذاء يسبب للهالائيتاري.
Glucocorticoid Functions

- Glucocorticoids have **widespread** metabolic effects on **carbohydrate**, **fat** and **protein** metabolism.
- **Conserving glucose**: by **inhibiting** uptake into **muscle** and **fat** cells.

**CORTISOL enhances metabolism in several ways**

- **In the muscles**:
  - Cortisol $\rightarrow$ $\uparrow\uparrow$ proteolysis and amino acid release

- **In the adipose tissue**:
  - Cortisol $\rightarrow$ $\uparrow\uparrow$ Lipolysis through breakdown of **fat**

- **In the liver**
  - Cortisol is an insulin antagonist and has a weak mineralocorticoid action $\rightarrow$
    1. $\uparrow\uparrow$ Gluconeogenesis $\rightarrow$ production of **glucose** from newly-released amino acids and **lipids**
    2. $\uparrow\uparrow$ Amino acid uptake and degradation
    3. $\uparrow\uparrow$ Ketogenesis.
### Cushing’s Syndrome signs & symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1- Weight gain:</strong> trunk and face with sparing of the limbs (central obesity)</td>
</tr>
<tr>
<td><strong>2- Buffalo’s hump.</strong></td>
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<tr>
<td><strong>3- Moon face.</strong></td>
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<tr>
<td><strong>4- Excessive sweating.</strong></td>
</tr>
<tr>
<td><strong>5- Atrophy</strong> of the skin and mucous membranes.</td>
</tr>
<tr>
<td><strong>6- Purple striae</strong> on the trunk and legs.</td>
</tr>
<tr>
<td><strong>7- Proximal muscle weakness (hips, shoulders).</strong></td>
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<tr>
<td><strong>8- Hirsuitism</strong></td>
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<tr>
<td><strong>9- The excess cortisol may also affect other endocrine systems → ↓ libido, amenorrhea and infertility</strong></td>
</tr>
<tr>
<td><strong>10- Patients frequently suffer various psychological disturbances ranging from euphoria to frank psychosis.</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
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<tr>
<td><strong>1- Loss of diurnal rhythm of cortisol and ACTH.</strong></td>
</tr>
<tr>
<td><strong>2- Hypertension</strong> (due to the aldosterone - like effects)</td>
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<tr>
<td><strong>3- Hyperglycemia or diabetes due to insulin resistance.</strong></td>
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<td><strong>4- Hypokalemic alkalosis</strong></td>
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<tr>
<td><strong>5- ↑ protein metabolism.</strong></td>
</tr>
<tr>
<td><strong>6- Impaired immunity.</strong></td>
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Moon face
Indications of Suspected Adrenocortical Hyperfunction

A. Screening Tests (out-patient)
   - To assess the **clinical diagnosis** of adrenocortical hyperfunction

B. Confirmatory tests (in-patient)
   - To **confirm** or **exclude** the provisional diagnosis

C. Tests used to determine the cause
   - To ascertain:
     1. The **site** of the pathological lesion (adrenal cortex, pituitary or **lungs**).
     2. The **nature** of the lesion.

- **Other blood tests** commonly performed for patients suspected to have Cushing’s syndrome are:
  - Full blood count
  - Blood glucose
  - Blood electrolytes and pH
  - Renal function tests
  - Liver function tests

USMLE ALGORITHMS: Cushing Syndrome
We use them to: assess the clinical diagnosis of adrenocortical hyperfunction.

- Effective screening tests need to be sensitive but do not have to be highly specific.

Interpretation of screening tests:

- The screening tests serve to: distinguish simple non-endocrine obesity from obesity due to Cushing's syndrome.
- Confirmatory tests (in-patient basis) are required to rule out pseudo-Cushing's syndrome. Thus we can't judge if the patient has Cushing's or not from the screening tests only.

Pseudo-Cushing's syndrome: it's a condition in which patients shows the symptoms and the signs of Cushing's syndrome (especially the elevated hormones).

- Examples of pseudo-Cushing's syndrome include:
  - Depressed or extremely anxious patients.
  - Severe intercurrent illness.
  - Alcoholism.
A. Screening Tests (out-patient)

C. Tests used to determine the cause

1- Low-dose dexamethasone (DXM) suppression test (DST):

- Also called Overnight suppression test.

DXM will mimic the cortisol, thus it’ll act as an exogenous cortisol and send a negative feedback, thus:

\[
\text{Dexamethasone } \rightarrow \downarrow \text{CRH } \rightarrow \downarrow \text{ACTH } \rightarrow \downarrow \text{cortisol}
\]

So after the test we measure the cortisol level, if it’s suppressed (lower than 50 nmol/L) then we can exclude Cushing syndrome and look for other reasons, but if it’s not suppressed, then we think of Cushing and do more investigations.

2- 24- hour urinary free cortisol:

bișnent في هذا التس بِيفا يجميع البسرين إلى يطعه لمدة ٢٤ ساعة، لكن المشكلة هنا أنه احتمال ما يجمع العينة مرة أو ثنتين لأي سبب - يمكن مشغول، ناسي، مستعجل، أو متعجج و يظن إن "مرة ما تضر :) - وعلى كذا ممكن يؤدي هذا إلى False-negative result.
Investigations Of Suspected Adrenocortical Hyperfunction

A. Screening Tests (out-patient)

1- Low-dose dexamethasone (DXM) suppression test:

**Procedure:**
1 mg DXM administered at **11-12 PM** the night before attending the clinic.
serum cortisol is measured at **8-9 AM**.

**Result:**
Cortisol < 50 nmol/L (**suppression**) → exclude Cushing’s disease.

**Precautions:**
Drugs that induce hepatic microsomal enzymes (Phenobarbitone & phenytoin) → ↑ DXM metabolism and ↓ DXM blood level to achieve CRH suppression (**false diagnosis of Cushing**)
These drugs increase the metabolism of DXM → no or little CRH suppression → which means the test result is wrong, but you will think it’s because of Cushing, so the diagnosis will be wrong.

B. Confirmatory tests

2- 24- hour urinary free cortisol:

**Result:**
Cortisol < 250 nmol/day → exclude Cushing’s disease.

**Disadvantage:**
incomplete collection of urine → a false-negative result

- An alternative is to determine the urinary cortisol : creatinine ratio on an early morning specimen.

Because I’m a normal individual my cortisol levels after the suppression test will be low, diseased people will have high level due to the absence or impairment of the negative feed-back mechanism.
Insulin-induced hypoglycemia: (Hypoglycemia $\rightarrow$ CRH $\rightarrow$ ACTH $\rightarrow$ cortisol) (DXM عكس)

- **Goals of the test:**
  1. To test the integrity of the hypothalamic-pituitary-adrenal (HPA) axis.
  2. To distinguish true Cushing's syndrome from pseudo-Cushing’s syndrome.

- **Contraindicated in:** epilepsy or heart disease.

- **Procedure:**
  1. **Insulin I.V.** (0.15 U/kg) to lower blood glucose to 2.2 mmol/L or less.
  2. Samples for simultaneous measurement of serum glucose and cortisol levels are taken basally (before insulin injection) and at 30, 45, 60 and 90 min after I.V. insulin injection.

- Failure to achieve a glucose level of 2.2 mmol/L invalidates the test and should be repeated with increment in step of 0.05U/kg.
Investigations Of Suspected Adrenocortical Hyperfunction

A. Screening Tests

B. Confirmatory tests (in-patient)

C. Tests used to determine the cause

Insulin-induced hypoglycemia

- **Interpretation of the results:**
  - **In normal people:**
    - Basal serum cortisol ≥ at least 145 nmol/L.
    - At 60 - 90 minutes: the serum cortisol level is > 425 nmol/L.
  - **In Pseudo-Cushing patients:**
    - they show abnormal diurnal rhythm of Serum cortisol, but with Insulin-induced hypoglycemia → ↑ CRH, ACTH and cortisol blood levels.
  - **In Patients with Cushing's syndrome:**
    - Whatever the cause, they don’t respond normally to insulin-induced hypoglycemia.
    - High basal serum cortisol than normal (much higher than 145nmol/L, usually higher than 400 nmol/L).
    - At 60 - 90 minutes: no increase in Serum cortisol, despite the production of an adequate degree of hypoglycemia.

When we induce the hypoglycemia by insulin in normal people the cortisol level will increase to compensate and increase the glucose level in the blood, diseased patient will have high cortisol all the time but there will be no further increase in cortisol in response to the the hypoglycemia induced by insulin.
A. Screening Tests

B. Confirmatory Tests

C. Tests used to determine the cause

1- Plasma [ACTH]

- Plasma [ACTH] should be measured on blood specimens collected at 8-9 a.m. and 8-9 p.m.

- Undetectable amount
  - Functional adrenal tumor
  - Confirmed by an abdominal CT scan to detect an adrenal mass

- \( \uparrow \uparrow \) ACTH
  - Cushing's disease (pituitary-dependent)

- \( \uparrow \uparrow \uparrow \uparrow \) ACTH
  - Ectopic origin of ACTH (non-endocrine origin)
  - Ectopic could be a small cell carcinoma or bronchial carcinoma (lung is the source).

The ACTH is extremely high, although the cortisol is also high (remember that the cortisol down-regulates the ACTH by negative feedback, but here it didn’t, which means that the ACTH is not secreted from the pituitary gland, but from somewhere else, usually the lung)
Investigations Of Suspected Adrenocortical Hyperfunction

A. Screening Tests

B. Confirmatory tests

C. Tests used to determine the cause

2- High-dose dexamethasone suppression test:

- **Goal:** It is used to distinguish Cushing's disease from ectopic ACTH secretion.

- **Procedure:**
  - 2 mg dexamethasone six-hourly for 48 hours to suppress cortisol secretion.
  - Basal serum cortisol (pre-dexamethasone S. cortisol) or 24-hour urine free cortisol is compared with the results at the end of the 48-hour period.

- **Interpretations:**
  - About 90% of patients with Cushing's disease show suppression of cortisol output.
  - In contrast, only 10% of patients with ectopic ACTH production (or with adrenal tumors) also show suppression. Because of these 10%, we do the CRH stimulation test with this test to exclude the adrenal tumor & ectopic ACTH origin.

  - **Suppression:** a fall to less than 50% of basal value.
3- CRH stimulation test

Procedure:
- Measures the ACTH and cortisol levels **basally** and **60 minutes after** injection of 100 µg CRH.

Interpretation:
- **Cushing's disease**
  - ↑↑ ACTH & cortisol above basal at 60 min.
  - 10% of patients fail to respond.

- **Ectopic ACTH & adrenal tumors**
  - No response.
  - (False-positive responses are unusual).

In Cushing's disease: High-dose dexamethasone suppression test + the CRH test → 100% specificity and sensitivity.
A. Screening Tests

B. Confirmatory tests

C. Tests used to determine the cause

4- Radiological tests

- 1- MRI of pituitary gland: Coronal contrast-enhanced MRI of the sella turcica in a patient with recurrent Cushing’s disease.

- 2- CT scanning of the adrenal glands or lungs.

Dr. Rana: I don’t want you to go through it
Cushing?

Low DXM/UFC

Pesudo-Cushing  True Cushing

Insulin hypoglycemia

Normal response  No response

ACTH/High DXM

ACTH-dependent

CRH Test

Pituitary  Ectopic

MRI pituitary  CT chest

Adrenal

Screening

Confirmatory

Cause

Alcoholism  Depression  Severe illness

ACTH-dependent

Pituitary  Ectopic

MRI pituitary  CT chest

ULS/CT adrenals

Summary :)
# Adrenal Hyperfunction

## Summary of Biochemical Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Cushing’s disease</th>
<th>Adrenal tumor</th>
<th>Ectopic ACTH secreting tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. cortisol</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Dexamethasone Low dose test</td>
<td>Not suppressed</td>
<td>Not suppressed</td>
<td>Not suppressed</td>
</tr>
<tr>
<td>Urinary cortisol</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Diurnal rhythm</td>
<td>Lost</td>
<td>Lost</td>
<td>Lost</td>
</tr>
<tr>
<td>Insulin-induced hypoglycemia</td>
<td>No response</td>
<td>No response</td>
<td>No response</td>
</tr>
<tr>
<td>Plasma [ACTH]</td>
<td>Normal or ↑</td>
<td>Not detectable</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>Dexamethasone High dose test</td>
<td>suppressed</td>
<td>Not suppressed</td>
<td>Not suppressed</td>
</tr>
<tr>
<td>CRH test</td>
<td>↑</td>
<td>No response</td>
<td>No response</td>
</tr>
</tbody>
</table>
Cushing syndrome?

Overnight dexamethasone suppression test or 24-hr urinary free cortisol level

Abnormal

Measure ACTH level

Low

Adrenal tumor or hyperplasia

Adrenal imaging

High

Goal is to determine source of ACTH

>50% suppression

High-dose dexamethasone suppression test

Cushing disease (pituitary)

Pituitary MRI

<50% suppression

CRH stimulation test

No response

Ectopic ACTH-producing tumor

• Chest CT
• Abdominal CT
• Octreotide scan

Normal

Stop workup (no Cushing syndrome)
Q1: Which one of the following zones release cortisol by the action of ACTH:
A. Zona glomerulosa.
B. Zona fasciculata.
C. Zona reticularis.
D. A & B.

Q2: The cortisol gets removed from the plasma by:
A. Kidney.
B. Pancrease.
C. Liver.
D. None of the above.

Q3: In normal individuals urinary free cortisol is:
A. <250 nmol/24 h.
B. <100 nmol/24 h.
C. <200 nmol/24 h.
D. <50 nmol/24 h.

Q4: Which one of the following is a cause of elevated serum cortisol concentration:
A. Exercise.
B. Stress.
C. Cushing’s syndrome.
D. All of them.

Q5: Which one of the following is a function of cortisol:
A. Decrease gluconeogenesis.
B. Increase lipolysis.
C. Decrease proteolysis.
D. Increase lipogenesis.
Q6: Which one of the following is a sign for Cushing’s syndrome:
A. Moon face.
B. Hypotension.
C. Buffalo’s hump.
D. Weight gain.

Q7: Which one of the following causes of Cushing’s syndrome is ACTH-independent:
A. Pituitary adenoma.
B. ACTH therapy.
C. Adrenal tumor.
D. Small cell carcinoma of the lung.

Q8: Which one of the following is used to distinguish Cushing’s disease from ectopic ACTH secretion:
A. High-dose dexamethasone suppression test.
B. Plasma ACTH.
C. Blood test.
D. Short ACTH stimulation test.

Q9: Insulin-induced hypoglycemia test is contraindication in:
A. Patients with kidney stones.
B. Patients with epilepsy.
C. Patients with heart disease.
D. B & C.

Q10: Which one of the following radiological technologists is used to look at the adrenal gland:
A. X-ray.
B. MRI.
C. CT scan.
D. Ultrasound.
You will meet selfish people, and you will meet who will disappoint you at the end, who will be thankless...
Life will slap you on your face with people who you have trusted to teach you how to rise again and rely only on yourself.

Done by:

- عبد الله الغزي.
- شهد العنزي.
- ثاني معاق.
- نورة المريح.
- عبدالله الشنيفي.
- لينا الشهري.
- عبدالله الطويل.
- أحمد الرويلي.

Revised by:

- فراس المؤمن.

Resources:

- 435’s slides and notes.