

PEARLS OF LABORATORY MEDICINE

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TITLE: Hypercortisolism

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Slide 1:

Hello, my name is Qing Meng. I am the Section Chief of Clinical Chemistry and Professor, in the Department of Laboratory Medicine, at The University of Texas MD Anderson Cancer Center. Welcome to this Pearl of Laboratory Medicine on “**Hypercortisolism.**”

Slide 2:

Here are the 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

Slide 3:

Cortisol is regulated through a hypothalamic-pituitary-adrenal axis. Corticotropin-releasing hormone or CRH is released by stress, exercise, and hypoglycemia. This elicits episodic and circadian secretion of Adrenocorticotropin Hormone or ACTH by pituitary. Secreted ACTH then stimulates the adrenal glands to produce cortisol, which provides negative feedback inhibition to the CRH-ACTH axis.

The secretion of cortisol is featured by pulsatile secretion and circadian rhythm.

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The disorders of adrenal cortex can be divided into Adrenocortical Hyperfunction and Adrenocortical Hypofunction. One of the adrenocortical hyperfunction disorders is hypercortisolism or Cushing syndrome.

Now Let's talk about Hypercortisolism or Cushing Syndrome.

Cushing syndrome is a group of clinical abnormalities including symptoms, physical signs, metabolic and biochemical changes due to chronic exposure to high levels of cortisol. The incidence of Cushing syndrome is 10-15 per million and mostly occur between the ages of 20 to 50 years.

Cushing syndrome was first described by Harvey Cushing, an American neurosurgeon in 1912. This is where the name came from.

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Based on the causes of cortisol hypersecretion, Cushing syndrome can be classified as ACTH-dependent or ACTH-independent.

Hypersecretion of ACTH by pituitary microadenoma is the primary defect leads to bilateral adrenal hyperplasia, cortisol over production, and then the characteristic clinical picture. This is called Cushing Disease. It accounts for 70% of the cases of Cushing Syndrome.

Some non-pituitary, non-endocrine tumors such as lung, ovarian, and carcinoid tumors can also secrete ACTH, resulting in adrenal hyperplasia and over production of cortisol. This is called ectopic or non-pituitary Cushing syndrome.

Patients with primary adrenal disease such as adrenal adenoma, adrenal carcinoma, or other type of tumors can increase the secretion of cortisol with phenotype as Cushing syndrome but they are independent of ACTH stimulation. Long term Exogenous or iatrogenic administration of glucocorticoid can also cause ACTH-independent Cushing syndrome.

A group of conditions such as alcoholism, depression, obesity, polycystic ovary syndrome (PCOS) associated with clinical and biochemical features of Cushing syndrome, is called Pseudo-Cushing syndrome but the hypercortisolemia is usually secondary to other factors.

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So, what's the difference between Cushing syndrome and Cushing disease?

Actually Both Cushing syndrome and Cushing disease are caused by over secretion of the adrenal cortisol. Cushing syndrome refers to the general state characterized by excessive production of cortisol and classic symptoms such as obesity, red face, moon face, buffalo hump, thin extremities, pink or purple striae, and thin skin etc.

Cushing disease is specifically meant for the pituitary-dependent form of Cushing syndrome caused by over secretion of ACTH by pituitary tumors primarily by microadenoma.

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What are the common causes for Ectopic ACTH Secretion?

In such cases, which means ACTH is secreted by tumors outside of pituitary and adrenal glands. These include:

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

Others are:

- Small cell carcinoma of the lung
- AND
- Pheochromocytoma

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The diagnosis of hypercortisolism mainly relies on clinical manifestations and laboratory findings. For lab testing, serum cortisol and 24 hour urinary free cortisol are useful primary screening tests.

Suppression or stimulation tests are needed in order to make the diagnosis while plasma ACTH is not the 1st line test.

Sometimes imaging study such as CT and MRI is used to localize the lesion.

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Overall, In Cushing syndrome, you would expect to see high serum cortisol.

Plasma ACTH levels maybe elevated in ACTH-dependent Cushing syndrome particularly in ectopic ACTH-secreting tumors while in pituitary tumor, ACTH could be normal or only moderately elevated.

24-hour urinary cortisol levels are elevated.

There is a Loss of diurnal variation in cortisol levels in Cushing syndrome.

Dexamethasone suppression test can be used for further investigation on confirmation and differentiation of ACTH dependent or independent.

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Let's look at the **Screening Tests for Cushing Syndrome**

There will undergo two steps of investigation for Cushing syndrome: the screening tests and the diagnostic tests.

Two simple screening tests are usually conducted for detecting Cushing syndrome. One is the Measurement of the 24-hour urinary free cortisol (UFC) and another reliable and convenient screening test is The overnight low-dose dexamethasone suppression test with measurement of cortisol at 8am the next morning.

A midnight cortisol measurement (plasma or salivary cortisol) is also used to examine the morning to night difference of cortisol or to determine the circadian rhythm.

Hypercortisolism is strongly suggested when any two out of three tests are abnormal. I'll explain a bit more in detail for each of the tests in the next a few slides.

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A 24-hour urine cortisol can eliminate the circadian variation and give an overall estimate of blood cortisol levels. In some studies, the diagnostic sensitivity and specificity of urinary free cortisol are 100 and 98% respectively.

Therefore, 24 hour urine free cortisol measurement is considered to be the best screening test for hypercortisolism.

A 24 hour urinary free cortisol concentration less than $<50 \mu\text{g}/\text{day}$ excludes the diagnosis of Cushing syndrome. A 24-hour urinary free cortisol concentration greater than $>120\mu\text{g}/\text{day}$ suggests the diagnosis of Cushing syndrome.

Keep in mind that Urine cortisol measurements do not establish the diagnosis and abnormal results need to be followed by further investigation.

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Let's talk about the Dexamethasone suppression test

Dexamethasone is an exogenous steroid that provides negative feedback to the pituitary gland to suppress the secretion of ACTH.

The dexamethasone suppression test is used to assess adrenal gland function by measuring how cortisol levels change in response to dexamethasone.

For The Overnight Low-Dose Dexamethasone Suppression Test:
1.0 mg dexamethasone is given orally at 11pm - Then Serum cortisol is measured at 8:00am next day;

If Serum cortisol is suppressed to less than $<2\mu\text{g/dL}$, it is considered Normal. Serum cortisol greater than $2\mu\text{g/dL}$ may be seen in cases of stress, obesity, infection, acute or chronic illness, alcohol abuse, severe depression, oral contraceptive use, pregnancy, estrogen therapy etc.

While in - Cushing Syndrome: Serum cortisol is not suppressed and the cortisol level greater than $>10\mu\text{g/dL}$ is suggestive of the diagnosis.

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A multiple low-dose dexamethasone suppression test is sometimes also used. In that, Urine is collected every 24h for 3 days for measurement of cortisol. 0.5 mg Dexamethasone is given orally every 6 hours starting at 8am on day 2 and continue on day 3 for 2 days.

In normal subjects, Urinary free cortisol is decreased to less than 25 µg/in 24h urine or less than 50% of the baseline level on day 3.

If Urinary free cortisol is **NOT** decreased compared to the baseline level, then it is suggestive of Cushing Syndrome

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Another screening test is the measurement of Midnight Serum Cortisol or Salivary Cortisol since Cortisol production is normally suppressed at night.

In patients with Cushing Syndrome, midnight cortisol levels are elevated. So you may see the Loss of diurnal variation in cortisol levels but this is not always the case and are thus less helpful and usually less recommended.

Here are a few useful points:

If a single cortisol measurement is to be taken, this should be done at midnight (2400) not the morning one.

Some endocrinologists favor Salivary cortisol measured at midnight but this test usually needs to be sent to a reference laboratory and requires high sensitivity assay because salivary cortisol concentration is much lower than serum cortisol concentration.

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The Diagnosis of Cushing Syndrome

When the findings of the above discussed screening tests are abnormal, more definitive testing should then be performed to determine the source of the overproduction of cortisol.

Plasma ACTH can be measured and is usually low in patients with adrenal tumor.

Plasma ACTH concentrations are normal or moderately elevated in patients with Cushing disease.

Plasma ACTH concentrations are often markedly elevated in patients with ectopic Cushing (ACTH) syndrome.

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High-dose dexamethasone suppression testing can be used to differentiate Cushing syndrome caused by adrenal tumors or nonendocrine ACTH-secreting tumors from pituitary Cushing disease.

Some patients with Cushing disease may fail to suppress cortisol with low-dose dexamethasone suppression test or giving false negative test results. Such test results can be assessed by administering 8 mg (high dose) of dexamethasone at midnight.

Serum is collected at 8am for the measurement of cortisol.

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

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More specifically, High-dose dexamethasone can be given in two ways: 4 mg taken orally at 11pm and midnight or Dexamethasone 2mg, orally, every 6 hours for 2 days. After that, the next day morning, if Serum or urinary free cortisol at 8am is reduced by more than >50%, then it is Cushing disease or Pituitary adenoma.

On the other hand, if Serum or urinary free cortisol is NOT reduced by more than >50% of the basal value, then it suggests Adrenal tumor, carcinoma, or ectopic ACTH syndrome.

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Corticotropin releasing hormone or CRH stimulates the secretion of ACTH and then cortisol. In this CRH Stimulation Test, Synthetic CRH, 1.0 µg/kg body weight, is given intravenously in bolus form at 9am or 8pm.

Serum cortisol and plasma ACTH are measured 15 min and immediately before and 5, 15, 30, 60, 120, and 180 min after CRH injection.

- An increase of serum cortisol by equal or greater than $\geq 20\%$ or ACTH by equal or greater than $\geq 50\%$ above basal level is seen in patients with Cushing disease.
- A Poor responses occur in patients with adrenal tumor and in most patients with nonendocrine ACTH-secreting tumor as those usually already having elevated baseline cortisol or ACTH concentrations.

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Sometimes additional examinations are needed to determine the cause and locate the disease. In addition to use CT scan and MRI for localization of the tumors.

Selective Inferior petrosal sinus sampling (**IPSS**) for ACTH measurements before and after CRH administration can be helpful:

- 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 (or ectopic).
- In Cushing disease, the ACTH level in the inferior petrosal sinus vein is much higher compared to the peripheral vein (usually higher than >2:1 ratio).

Slide 20: Here is the laboratory evaluation algorithm with suspicion of Cushing syndrome

Basically this diagram covers the screening process and tests we discussed and described earlier. If these tests are ABNORMAL, then move to confirmatory tests. If these tests are NORMAL, then Cushing syndrome is excluded.

Slide 21: Diagnosis and differential diagnosis of Cushing Syndrome

With positive findings from screening tests, you then move to diagnostic testing with over-night low dose dexamethasone suppression test and high dose dexamethasone suppression test which were also discussed earlier to determine the suppression of cortisol secretion. If there is lack of suppression, then you need CRH stimulation test, an increase of ACTH suggests Cushing disease or ectopic ACTH. And if there is no response of ACTH, then it is adrenal tumors.

Slide 22 References

Slide 23: Disclosures

Slide 24: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on
“Hypercortisolism”