TITLE: Hypocortisolism
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Slide 1:
Hello, my name is Qing Meng. I am the Section Chief of Clinical Chemistry Laboratories and Professor, in the Department of Laboratory Medicine, The University of Texas MD Anderson Cancer Center. Welcome to this Pearl of Laboratory Medicine on "Hypocortisolism."

Slide 2:
After participating in this presentation, you will be able to:
• Understand the etiologies and laboratory abnormalities of hypocortisolism
• Discuss the stimulation tests
• Establish diagnostic approach of Addison disease

Slide 3:
Adrenocortical Hypofunction or hypocortisolism is called Adrenal Insufficiency also known as Addison disease.
Based on the causes, Adrenal Insufficiency can be classified as:
• Primary adrenal insufficiency, which is commonly referred as Addison disease
• Secondary adrenal insufficiency (means pituitary) and
• Tertiary adrenal insufficiency (means hypothalamic or due to exogenous glucocorticoid administration).
Addison disease, also known as primary adrenal Insufficiency or hypocortisolism, is a chronic endocrine disorder in which the adrenal glands fail to produce adequate levels of steroid hormones, mostly cortisol and to a certain degree aldosterone. Addison disease is named after renowned English physician and scientist: Thomas Addison, who was the first to describe the condition in 1855. Addison disease is adrenocortical insufficiency due to the destruction or dysfunction of the entire adrenal cortex. It affects both glucocorticoid and mineralocorticoid function.

Addison disease is primarily caused by autoimmune disease or adrenalitis due to inherited genetic disorders, which accounts for 80% of the cases. It includes Autoimmune polyglandular syndrome type 1 and type 2. All are involved in multiendocrine dysfunction. Type 1 is mostly associated with candidiasis, hypoparathyroidism, and primary gonadal failure. Type 2 is associated with primary hypothyroidism, primary hypogonadism, type 1 diabetes, and pernicious anemia.

Other causes which make about 20% of the cases include:
- Granulomatous disease such as Tuberculosis, histoplasmosis, sarcoidosis
  – Infectious disease such as HIV, cytomegalovirus, fungus.
- Metastatic infiltration: carcinoma of the lung or breast.
- Systemic amyloidosis.
  – Hemochromatosis.
- Congenital adrenal hyperplasia and rarely seen in congenital adrenal hypoplasia
- Hemorrhage (Waterhouse-Friderichsen syndrome associated with Warfarin and leukemia etc.)
Slide 7:

The pathogenesis of Addison Disease is due to the adrenal gland autoimmune-destruction by various reasons just described in previous slides and Failure to produce adequate levels of cortisol and/or Aldosterone by adrenal glands. Inadequate secretion of cortisol and/or aldosterone affect body physiological functions characterized with the deficiency of the corresponding hormone.

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The onset of clinical manifestations is usually gradual but progressive. The degree and severity of symptoms depend on the extent of adrenal failure. Patients with Addison disease may start with fatigue, weakness and other non-specific symptoms such as anorexia and nausea and other GI symptoms. Patients usually experienced with weight loss and hyperpigmentation due to increased ACTH secretion.

The Biochemical changes include: - Hyperkalemia, hyponatremia, hypoglycemia, and hypercalcemia.

Patients usually have Hypotension due to volume depletion & dehydration.

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Laboratory findings of Addison Disease usually include:

- High plasma ACTH
- Hyperkalemia
- Hyponatremia
- Hypoglycemia
- Low serum cortisol
- Low serum aldosterone
- Other laboratory Abnormalities such as - elevated BUN and creatinine, hypercalcemia,
  And - normocytic normochromic anemia
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The Diagnosis of Addison Disease can be made based on Early morning basal serum cortisol and plasma ACTH concentrations along with ACTH stimulation test. Patients with Addison Disease usually show High Basal ACTH levels and ACTH is usually greater than > 150 pg/mL and low serum Cortisol, which is usually less than <10 µg/dL. Other laboratory tests such as - Plasma aldosterone and renin activity, - Salivary cortisol and - Urinary free cortisol can also be performed to help to make the diagnosis.

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In some cases of Addison Disease, Baseline cortisol may be normal. Thus, ACTH stimulation test or other challenge test is needed to support the diagnosis. ACTH Stimulation Test is also called Cosyntropin test, Corticotropin test or Synacthen test. ACTH test is usually performed by injecting a small amount of synthetic ACTH with 24 amino acids(1-24AA), and the amount of cortisol that the adrenals produce in response to ACTH is measured to determine the adrenal function or insufficiency.

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There are several types of ACTH stimulation tests. For Rapid ACTH Stimulation Test, a baseline serum sample for cortisol is collected first, and then 250µg ACTH is given intramuscularly or intravenously (1h) and • Samples for serum cortisol are collected 30 and 60 min after injection. • For Normal response: we would see a rapid rise in serum cortisol with peak concentration greater than >20µg/dL. Please keep in mind that the Peak value is more important than the incremental change. Please note the cutoff set may be too high and recent study suggests>13 µg/dL. • For Subnormal response: no or slight change in serum cortisol suggests the diagnosis of adrenal insufficiency. However, This subnormal ACTH stimulation test result cannot identify the cause of adrenal insufficiency or mild to moderate dysfunction of ACTH secretion as it remains sufficient function to prevent adrenal atrophy. In these cases, further tests are needed such as metyrapone or insulin-induced hypoglycemia test if secondary or tertiary adrenal insufficiency is suspected but should never be used for primary adrenal insufficiency.
Slide 13:

Investigators have found some patients have normal responses to 250 μg of ACTH yet inadequate responses to 1 μg of ACTH. This means 1 μg of ACTH stimulation test might be more sensitive for the detection of adrenal insufficiency compared to the 250 μg of ACTH. Please be aware of that This remains a point of controversy, and the 1 μg ACTH dose has not been universally accepted as superior to the 250 μg dose in detecting glucocorticoid deficiency. This test is only specifically used for investigation of central causes of adrenal insufficiency.

Slide 14:

When the response to the Rapid ACTH test is abnormal, a “prolong” or multi-day ACTH stimulation test is required to determine the cause of adrenal insufficiency. The multi-day ACTH stimulation test is used to distinguish between primary and secondary or tertiary adrenal insufficiency, particularly useful for patients receiving glucocorticoids. For this test, 250μg ACTH, is injected for 3 days followed by a standard 8-hour infusion of 250μg ACTH.

• Serum and urinary cortisol are measured daily.

For Normal subjects, serum cortisol is greater than >20µg/dL

If patients with- Primary adrenal insufficiency, there is little or no increase in cortisol
If patients with -Secondary or tertiary adrenal insufficiency, a delayed or staircase rise is seen over 2 to 3 days.

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Sometimes Insulin is given to induce hypoglycemia and stimulates the release of CRH in suspected hypothalamic or pituitary disease.

Regular insulin 0.1 U/kg b.w. is injected intravenously at morning

• Blood samples for glucose and cortisol are measured at 30, 60, 90, and 120 min after insulin injection
• For Normal response: blood glucose levels are less than <40 mg/dL and cortisol levels are greater than >20 µg/dL.

- No response or inadequate responses may be due to pituitary or hypothalamic hormone insufficiency.
*This **Test is to Confirm Secondary Adrenal Insufficiency**
*This test is not recommended in cases of suspected Addison disease for fear that suppression of cortisol production might precipitate an Addison crisis.

**Slide 16: References**

**Slide 17: Disclosures**

**Slide 18: Thank You from** [www.TraineeCouncil.org](http://www.TraineeCouncil.org)

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