ADRENAL FAILURE (INSUFFICIENCY) – DIAGNOSTIC TESTS

UNIVERSITY OF PAPUA NEW GUINEA
SCHOOL OF MEDICINE AND HEALTH SCIENCES
DISCIPLINE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY
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VJT
What is the basic classification of Adrenal Failure?

• Basic classification of Adrenal failure (Adreno-Cortical Hypo-function) depends on location of lesion: (Fig. 1)

• **Primary Adrenal Failure** or Primary Adrenal Insufficiency (Addison's Disease) is due to:
  • Failure of Adrenal Gland due to destruction of Gland;
  • Cortisol and Aldosterone production may be affected,

• **Secondary Adrenal Failure** or Secondary Adrenal Insufficiency:
  • Hypothalamic or Pituitary disease leading to deficiency of ACTH (Corticotrophin) production;
Fig. 1: HPA-Axis showing location of lesions

HYPOTHALAMUS

Corticotrophin-Releasing Hormone (CRH)

ANTEROIOR PITUITARY

Adrenocorticotropic Hormone (ACTH)

ADRENAL CORTEX

CORTISOL

GABA, Serotonin, Acetylcholine, Norepinephrine

(Non-Steroidal illness)

Secondary Adrenal Failure

Primary Adrenal Failure

Target cells
What are some causes of Primary Adrenal Failure?

• Several causes including:
• Infective (Tuberculosis, Meningococcal, HIV, etc)
• Autoimmune Adrenalitis,
• Metastasis (from Lung and Breast Carcinomas),
• Hemorrhage,
• Metabolic failure, insufficient hormone production, caused by:
  • Congenital Adrenal Hyperplasia (CAH),
  • Enzyme inhibitors, such as Metyrapone,
  • Cytotoxic agents (e.g. Etomidate),
What are some signs and symptoms of Primary Adrenal Failure?

• Some **non-specific signs** and symptoms include:
  • Weakness, Abdominal Pain, Nausea, Weight Loss, Shock, Hypotension, Acid-Base Disturbance, Lack of Libido, Loss of body hair in women, Psychiatric changes;

• Some specific signs and symptoms include:
  • Hypoglycemia with Hyponatraemia,
  • Hyperkalemia,
  • Raised Serum Urea levels,
  • Hyper-pigmentation (affecting Buccal mucosa),
  • Scars, Skin creases

• These conditions are life threatening and requires urgent investigation if suspected;
What are some signs and symptoms of Secondary Adrenal Insufficiency?

• Some signs and symptoms of Secondary Adrenal Insufficiency may be identical to Primary Adrenal Insufficiency,

• **Hyper-pigmentation** does not occur in Secondary Adrenal Insufficiency *(WHY?)*
  
  • Because of Insufficient production of ACTH and other products of Proopiomelanocortin (POMC) metabolism {i.e., Melanocyte Stimulating Hormones (MSH)};}
What lab results are indicative of Primary Adrenal Insufficiency?

- Biochemical results indicative of Primary Adrenal Insufficiency include:
  - Hyponatraemia,
  - Hyperkalemia,
  - Elevated Serum Urea,
  - Hyper-pigmentation;
What is the Biochemical basis for Hyponatraemia, Hyperkalemia, Elevated Serum Urea and Hyper-pigmentation in patients with Primary Adrenal Insufficiency?

- Lack of Aldosterone leads to pathological Sodium loss via Kidneys,
  - Resulting in contraction of Extracellular Fluid Volume (Hypovolaemia), causing Hypotension & Pre-renal Uremia,
  - Patient may develop Sodium depletion and Potassium Retention due to Aldosterone Deficiency,
- Hypovolaemia and Hypotension stimulate AVP Secretion, thus causing Water Retention,
- Absence of Cortisol impairs ability of Kidneys to excrete water, which leads to Hyponatraemia,
• Overall effect causes reduction in Total Body Water, (dehydration) reflected by increase in Serum Urea,

• Absent of Cortisol causes failure in Negative Feedback control, resulting in excessive secretion of ACTH from Anterior Pituitary,

• ACTH structure contains part of Amino Acid sequence of Melanocyte-stimulating hormone (MSH),

• Excessive secretion ACTH causes darkening of skin and mucus membranes, resulting from the action of MSH;
Screening and Diagnostic Tests for Adrenocortical Insufficiency (Adrenal Failure)

What basal lab tests are done on a patient suspected of having Adrenal Insufficiency?

• Before the patient is given any medication (Cortisol), blood must be collected for Basal measurements of:
  • Plasma Urea,
  • Electrolytes,
  • Glucose,
  • Serum Cortisol,
  • Plasma ACTH concentration;
• Patient intake of Sodium must be monitored to ensure adequate intake, whilst investigations proceed,
Important points with respect to Cortisol and ACTH measurements

• Normal Serum [Cortisol] at 8a.m., or Normal 24-hour Urinary Free Cortisol, does not exclude Primary Adrenocortical Insufficiency (Why?)
  • Because patient may be able to maintain Normal Basal output of Cortisol but is unable to secrete adequate amounts of Cortisol in response to Stress;

• Serum [Cortisol] below 50nmol/L at 8 a.m. is strong presumptive evidence for Primary Adrenal Failure;
• Diagnosis of Primary Adrenal Failure is unlikely, if Serum [Cortisol] is 550nmol/L or more at 8 a.m. (in absence of Steroid Therapy),

• Diagnostic accuracy for Primary Adrenal Failure is greatly improved when Serum [Cortisol] and [ACTH] are measured at the same time; Why?
  • Because Low Serum [Cortisol] < 200nmol/L, and Raised Serum [ACTH] > 200nmol/L may be diagnostic of Primary Adrenal Failure,
List some Biochemical tests used for Screening and Diagnosis of Adrenal Failure

- Biochemical tests for diagnosis of Adrenal failure:
  - Short Cosyntropin (Synacthen, Cortrosyn or Tetracosactrin) Test,
  - Depot (Long) Synacthen test,
  - Prolonged Cosyntropin Stimulation (Rose) test,
  - Corticotrophin Releasing Hormone (CRH) stimulation test,
  - Rapid Synacthen stimulation test,
What is the procedure for Short Cosytropin test?

- Short Cosytropin (Synacthen, Cortrosyn or Tetracosactrin) test indicates ability of Adrenal Cortex to respond to ACTH,
  - *Cosytropin is Synthetic 1 – 24 analogue of ACTH*,
  - *Trade name for Cosytropin is Synacthen or Cortrosyn,*
Procedure for Short Cosyntropin test includes the sequence:

- Measure Baseline Plasma [Cortisol], [Aldosterone]
- Patient is given 0.25mg Synacthen as Intravenous bolus or as Intra-muscular Injection,
- Measure Plasma [Cortisol] & [Aldosterone] again after 30 minutes,
- Blood samples for Aldosterone can be held until results of Cortisol response are known,
IMPORTANT TO NOTE

• Normally, Baseline Plasma [Cortisol] should be within Reference Range,
  • 280 – 720nmol/L at 08.00 am to 10.00 am
  • Acceptable Baseline Plasma [Cortisol] > 225nmol/L
• There should be an increment of more than 200nmol/L Plasma [Cortisol] after Synacthen,
• Final Plasma [Cortisol] should be greater than 500nmol/L,
• Aldosterone response in Synacthen test may be blunted or absent in patients with Primary Adrenal Failure;

• In Secondary Adrenal Failure, Aldosterone response is normal (an increase of about twice the baseline value) in Synacthen test (WHY?),
  • Because the RAA-axis is not affected by decreased production of ACTH,
How are the results of Short Cosyntropin test interpreted?

• Criteria for interpretation of Short Cosyntropin test:
  
  • Three criteria should be met for normal response, these criteria are:
  
  • Baseline Plasma [Cortisol] should be > 225nmol/L
  • Final Plasma [Cortisol] should be > 500nmol/L,
  • Increment in [Cortisol] should be at least 200nmol/L,

  • For a patient to be declared as normal all Three Criteria must be satisfied;
• Normal response to Short Synacthen test excludes Primary Adrenocortical Insufficiency;
• Failure to meet any of the criteria indicates Adrenocortical Inadequacy;
• **Elevated Plasma [ACTH]** can be used to **confirm diagnosis** of Primary Adrenal Insufficiency in a patient with abnormal response to Short Synacthen test,
What addition test should be carried out if the results from the Short Synacthen test are equivocal (unclear)?

- Patients with equivocal responses to Short Synacthen test may be re-tested after Stimulation of Adrenal Cortex with **depot-Synacthen**,  
- This longer acting material (1.0 mg) should be given IM daily for three days;  
- On fourth day, Short Synacthen test should be repeated,  
  - If normal criteria for Short Synacthen test are fulfilled on the second testing, then Adrenal Insufficiency is not of Primary origin,  
  - Such a result points towards Secondary Adrenocortical Insufficiency,
What are some factors that can affect Short Synacthen test?

• Some factors that can affect Short Synacthen test to the point of invalidating the tests include:
  • Severe Emotional Stress,
  • Treatment with Glucocorticoids within 12-hours prior to Synacthen test,
  • Taking of Estrogen-containing Oral Contraceptives,
What is the use and procedures for Prolonged Cosyntropin Stimulation (Rose) test?

• Prolonged Cosyntropin-Stimulation (Rose) test is used to differentiate Primary from Secondary Adrenal Failure;

• **Procedure for the test:**
  • Measure Baseline Plasma [Cortisol],
  • Measure 24-hr Urinary [17-Hydroxycorticosteroids] (17-OHCS),
  • Patient is given infusion of 0.25mg Cosyntropin for 48hrs, after the first 24hrs measurements are repeated;
  • Measure Plasma [Cortisol],
  • Measure 24-hr Urinary [17-OHCS],
  • At the end of infusion repeat the measurements,
How are results of the Prolonged Cosyntropin Stimulation (Rose) test interpreted?

• In **Primary** Adrenal Insufficiency, no change is seen in Plasma [Cortisol] or 24-hr Urinary [17-OHCS] *WHY??*
  • Because Cortisol is not produced,

• In **Secondary** Adrenal Insufficiency, Incremental Increase occurs over the course of the Infusion *WHY??*
  • Because the problem is **not Primary**, Cosyntropin action stimulates Adrenal Cortex, which then produces Cortisol,
  • Results indicate that **Adrenal Cortex has undergone Atrophy** because of **Insufficient ACTH stimulation**; however, with **longer stimulation**, the Adrenal Cortex is capable of functioning,
Diagnosis of Secondary Adrenocortical Insufficiency

How can Secondary Adrenocortical Failure be diagnosed?

• **Low Plasma [Cortisol] and Low Plasma [ACTH]** indicate diagnosis of Adrenocortical Insufficiency **Secondary** to Hypothalamic or Pituitary disease,

• In such cases, whilst the Atrophied Adrenocortical cells may fail to respond in Short Synacthen test, the Adrenal Cortex can become responsive over a longer period of stimulation using **Depot (long) Synacthen test**, 
Procedure for the Depot (Long) Synacthen Test

• Measure Baseline Serum [Cortisol],

• Patient is administered Depot Synacthen (1.0 mg) Intramuscularly on three successive days,

• On each of the Three days Serum [Cortisol] must be measured between Five to Eight hours after administration of Depot Synacthen,

• (In each instance [ACTH] can also be measured)
How are the results interpreted?

• In **Primary** Adrenocortical Insufficiency, Serum [Cortisol] will NOT INCREASE above 600nmol/L at 5 to 8 hours after the Third injection,

• In **Secondary** Adrenocortical Insufficiency, Stepwise increase in Serum [Cortisol] will be apparent after successive administration of the Depot Synacthen,
IMPORTANT TO NOTE

• Poor responses to Prolonged Synacthen tests may occur in patients with Hypothyroidism (both Primary and Secondary),

• In patients with Hypothyroidism, Adrenal Function cannot be satisfactorily assessed until the Thyroid Deficiency has been corrected,

• Once a decision has been made as to whether Adrenal Insufficiency is Primary, or Secondary, the appropriate Imaging Technique should be used to rule out other treatable causes,