Adrenal Disorders

Done by: 429 Medicine Team

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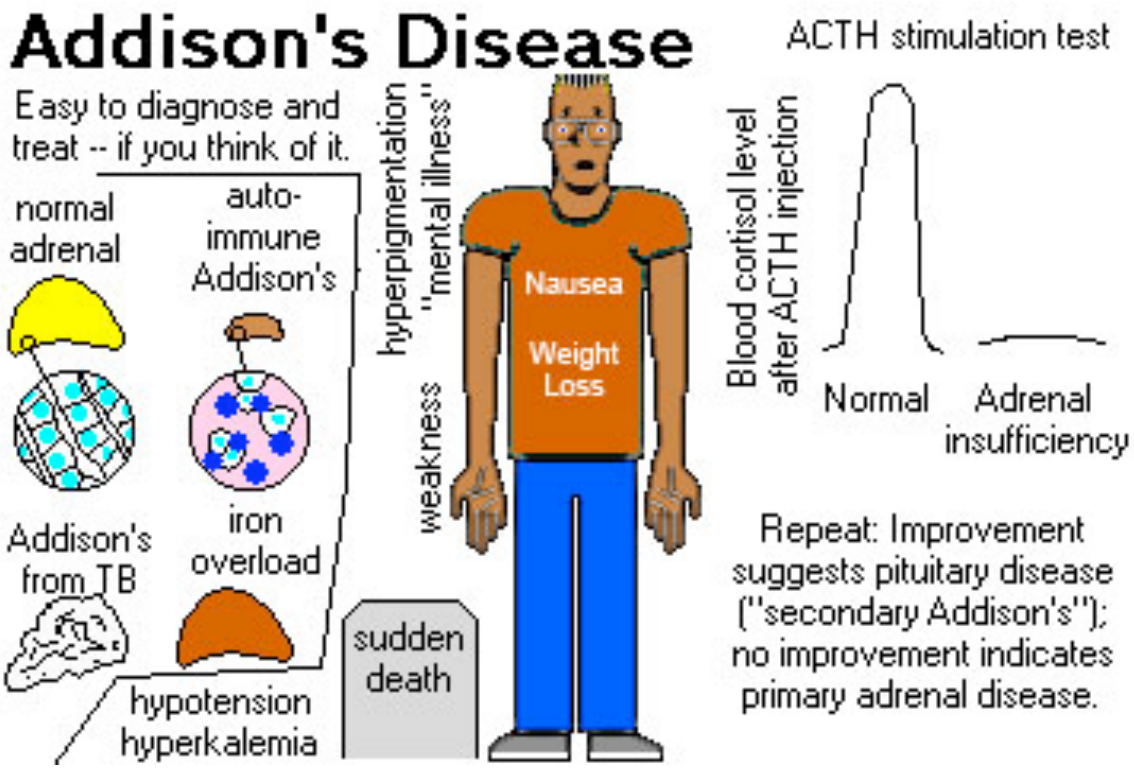
• April 27, 2012



Adult Adrenal Glands:

- Each gland weighs 4-5 g, very vascular organ.
- Location: In the retroperitoneum above or medial to the upper poles of the kidneys.
- Surrounded by a fibrous capsule.
- The yellowish outer cortex comprises 90% of adrenal weight.
- The inner medulla 10% of adrenal weight.

Note That:

1- The Cortex and medulla are totally different in Embryo and physiological function, Although they are connected to each other.

2- The Medulla is not a true endocrine gland its : a modified Sympathetic Ganglion.

Arterial Supply:

Main arterial supply from branches of:
Inferior phrenic artery.
Renal arteries.
Aorta.

Venous Drainage:

Rt. adrenal vein drains directly in the posterior aspect of I.V.C.
Lt. adrenal vein into Lt. Renal vein.

Embryology of Adrenal Cortex:

- Adrenal Cortex is of mesodermal origin.
- Identifiable as a separate organ at the 2 month-old-fetus.
- At this stage, composed of:

1- Fetal zone:
Additional zone in fetus.
Makes up the main bulk of weight at this time.
Lost in the 1st year (usually within 3 months after birth).

2- Definitive zone :

- The origin of the adrenal cortex.
- Fetal adrenal increases rapidly in size (Larger than the kidney at mid gestation & much larger than adult gland in relation to total body mass).
- Fetal adrenal produces mainly DHEA & DHEA-S (precursors of maternal-placental estrogen).

- Definitive zone synthesizes many steroids mainly cortisol.
- The anatomic relationship of fetal and definitive zones is maintained until birth.
- Adrenocortical weight decreases gradually until the fetal zone disappears 3 months after delivery.

During the first 3 years, the adult adrenal cortex develops and differentiates into 3 adult zones :

1- Zona Glomerulosa.
2- Zona Fasciculata.
3- Zona Reticularis.

Embryology of Adrenal Medulla:

- Medullary chromaffin cells (the principal cells of adrenal medulla) are from the neural crest.
- During development the medullary cells migrate and lie surrounded by the cortex.

Adrenal gland is composed of 2 distinct compartments :

Adrenal cortex :

produces many steroid hormones; the most important of which are :

A- Cortisol.
B- Aldosterone.
C- Adrenal androgens.

Adrenal Medulla :

Produces Catecholamines :

A- Adrenaline (Epinephrine).

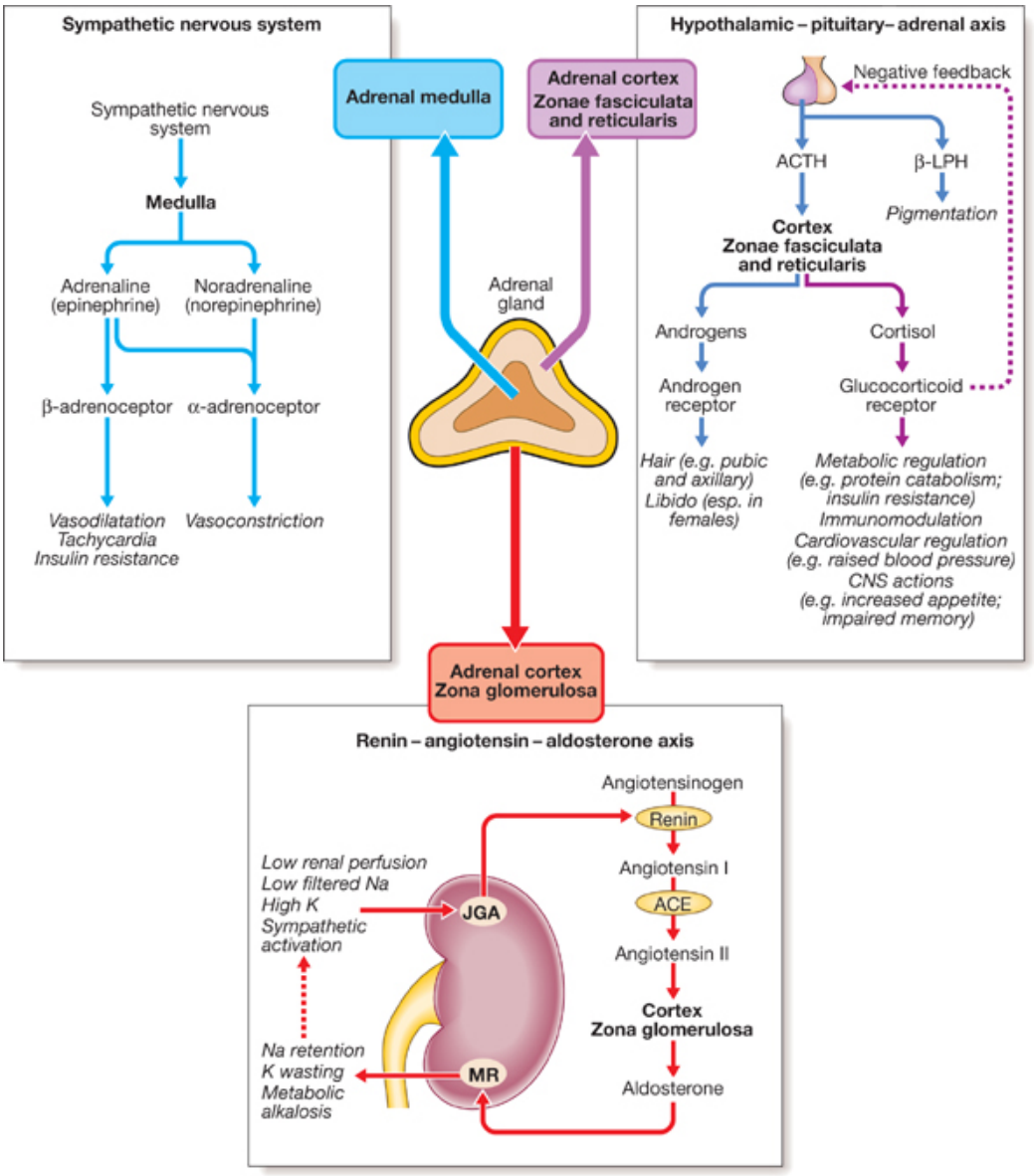
B- Noradrenaline (Norepinephrine).

Note That:

1- The Adrenal Gland may take variable shapes.

2- In the second month of the fetus the size is enlarged more than adult size, then after year of birth it takes it adult size.

3-Dopamine also could be secreted from the medulla of the adrenals.



Zones of Adrenal Cortex :

Zona Glomerulosa	Zona Fasciculata	Zona Reticularis
	Functionally considered as one unit.	
The outermost.	the thickest	The innermost
Cells are small & lipid-poor & scattered beneath the adrenal capsule.	Cells are larger, contain more lipid & termed "clear cells"	"Compact" lipid-poor cells but contain lipofuscin granules.
Aldosterone (Cannot produce cortisol & Androgens)	Cortisol & Androgens	Cortisol & Androgens
Regulated by Renin-Angiotensin System & K	Both structure and function are regulated by ACTH	Both structure and function are regulated by ACTH

The Figure:

Zona Fasciculata and Zona Reticularis: (Structurally and Functionally Considered to be one unit).

Q: How the structure is Regulated by ACTH in The Zona Fasciculata and Zona Reticularis?

If there is deficiency in ACTH secretion, the adrenal gland will shrink in size ! so it regulate the size in structure.

Classification of Adrenal Steroids :

Classified into 3 groups based on their predominant functions:

1. Glucocorticoids.
2. Mineralocorticoids.
3. Androgens.

Major Classes of Adrenal Steroids :

Steroid Class	Androgens (C19)	Glucocorticoids (C21)	Mineralocorticoids (C21)
Main Hormones	DHEA, DHEA-S Androstenidione	Cortisol Corticosterone	Aldosterone
Predominant action	Androgenic activity	metabolism of: • carbohydrates • and proteins	• metabolism of: Na & K •Maintain the ECV
Main Zone of production	Z. Fasciculata Z. Reticularis (functionally as one unit)		Z. Glomerulosa

Disorders of Adrenal glands :

(The Doctor Covered The Most Important Things As He Said it will be in Blue)

- Adrenal Cortex:

Cushing's syndrome, Addison's disease, Hyperaldoteronism, Syndomes of congenital adrenal hyperplasia (CAH), Hirsutism, Virilization, Cancer.

- Adrenal Medulla:

Pheochromocytoma.

Adrenal Insufficiency:

Adrenocortical insufficiency (hypofunction of the adrenal cortex) includes all conditions in which there is deficient production of :
Adrenal glucocorticoid, and Mineralocorticoid hormones.

Types of adrenal insufficiency:

These conditions are divided into 2 general groups according to the level of hypofunction:

1. Primary adrenal insufficiency (Addison's diease) : due to primary hypofunction of the adrenal cortex.

2. Secondary adrenal insufficiency : adrenocortical failure secondary to a primary deficient secretion of
ACTH from the pituitary gland.

Etiology of adrenal insufficiency:

Primary Adrenal Insufficiency :
A. Anatomic destruction of gland (chronic & acute).
1. "Idiopathic" atrophy (autoimmune). (antibodies produced against adrenal Gland).
2. Surgical removal.
3. Infection (TB, fungal, viral-esp. AIDS).
4. Adrenal Hemorrhage.
5. Invasion: metasteses, amyloidosis, sarcoidosis.

B. Metabolic failure in hormone production :
1. Congenital adrenal hyperplasia (CAH).
2. Enzyme inhibitors : (metyrapone, ketoconazole, aminoglutethemide).
3. Cytotoxic agents : (mitotane).

C. ACTH-blocking Antibodies.

Secondary Adrenal Insufficiency :
A. Hypopituitarism due to hypothalamic-pituitary disease.

B. Suppression of hypothalamic-pituitary axis.
1. Exogenous steroids (Iatrogenic). (using high dose of steroids .. Drugs)
2. Endogenous steroids (from tumors).

Incidence:

1- Primary adrenal insufficiency:
Relatively rare, Occurs at any age, Affects both sexes equally.

2- Secondary adrenal insufficiency:
Relatively common (because of common therapeutic use of steroids).

Addison's Disease:

Etiology and Pathogenesis:

Addison's disease results from progressive destruction of adrenal cortex.
At least 90% of gland is destroyed before signs of insufficiency appear.

1- 50% of patients have +ve circulating adrenal Abs.
2- Some Abs destroy the adrenal glands, others
3- block the binding of ACTH to its receptors.
4- Some patients have +ve Abs to thyroid,
5- parathyroid and/or gonadal tissues.
6- Polyglandular Autoimmune (PGA) syndromes

Associated Autoimmune Disorders :

- Endocrine Disorders :
1- Chronic lymphocytic thyroiditis, 2- Premature ovarian failure, 3- DM type 1,
4- Primary hypothyroidism, 5- Hyperthyroidism.

- **Nonendocrine Disorders** :
1- Pernicious anemia. 2- Vitiligo. 3- Alopecia. 3- Chronic active hepatitis 4-Nontropical sprue. 5- Myasthenia gravis.

Note That:

1- When the disease is evident clinically it means that u lost already 90% of the Gland.
2- Poly glandular Autoimmune: Multiple Endocrine glands are affected by antibodies.
3- Associated Autoimmune Disorders it means if the patient have one of them you should look for the others coz they usually come together.

Common Symptoms in chronic primary adrenal insufficiency

Symptoms	Frequency
Asthenia (weakness, tiredness, fatigue)	100
Anorexia	100
Gastrointestinal symptoms	90
•Nausea	85
•Vomiting	75
•Constipation	30
•Abdominal pain	30
•Diarrhea	15
•Salt craving	15
•Postural dizziness	10
•Muscular or joint pains	10

Common Signs in chronic primary adrenal insufficiency

Signs	Frequency
Weight loss	100
Hyperpigmentation of skin	95
Pigmentation of mucous membrane	80
Decreased axillary and pubic hair (in women only)	60
Hypotention (systolic BP <110 mm Hg) with postural accentuation	15
Vitiligo (with autoimmune)	10

Common Laboratory findings in chronic primary adrenal insufficiency

Laboratory Findings	Frequency
Electrolytes disturbances	**90**
• **Hyponatremia**	**90**
• **Hyperkalemia**	**65**
• **Hypercalcemia**	**5**
Azotemia	**55**
Anemia	**40**
Eosinophilia	**15**

Note That:

In the Symptoms:

- Salt Craving Coz the patient is looking to compensates for the loss of salt.

- Loss of hair In axillary and pubic is found only in women .. Why ?
Coz the men have other sources of androgens but women No (they don't have testis)

In the electrolytes:
Hyponatremia and Hyperkalemia (opposite in Cushing's)

Azotemia --> electrolytes increase in urine

Skin Pigmentations comes before Buccal Pigmentation !

Hyperpigmentation:

1- Generalized hyperpigmentation of skin & mucous membrane (the classical physical finding).
2- Along with other features, suggests primary adrenocortical insufficiency.
3- One of earliest manifestations of Addison's disease.
4- Increased at exposed areas and accentuated at pressure areas (knuckles, toes, elbows, knees).
5- Associated with black or dark brown freckles.
6- Hperpigmentation of buccal mucosa & gum is preceded by generalized hyperpigmentation of skin.
7- Other areas : palmar creases, nail beds, nipples, areolae, perivaginal, perianal mucosa & scars that formed after onset of ACTH excess (but not older scars).

Adrenal Imaging:

Abdominal x-rays: (They Used to do it in the past nowadays)

o Adrenal calcification : in 50% tuberculous cases & some other invasive or hemorrhagic causes.

CT Scan:
more sensitive for adrenal calcification & enlargement.
Causes of bilateral adrenal enlargement :
o TB.
o Fungal infection.
o CMV infection.
o Infiltrative diseases (malignant or nonmalignant).
o Adrenal hemorrhage

Note:
CT and MRI:
Are the best imaging and we look for Calcifications and Enlargements.
If you have Bilateral Enlargement the look for TB etc..
other causes than the previous will cause Atrophy rather than Enlargements.

Acute Adrenal Crisis

A state of acute adrenal insufficiency occurring in patients with Addison's disease who are exposed to any form of stress.

Precipitating stress factors :

1. Infection.
2. Trauma.
3. Surgery.
4. Dehydration (Salt deprivation, vomiting, diarrhea).
5. Discontinuation of steroids replacement therapy.

- Common Clinical Features :

1- Hypotension & shock.
2- Fever (due to infection or hypoadrenalism)
3- Dehydration, volume depletion.
4- Nausea, vomiting, anorexia.
5- Abdominal pain (may mimic acute abdomen).
6- Weakness, apathy, depressed mentation.
7- Hypoglycemia (more in children).
8- Shock and coma may rapidly lead to death in untreated patients.

Laboratory Findings Suggestive of Diagnosis:

1- Hyponatremia & Hyperkalemia (In a small number of acute cases).
2- Azotemia (usual).
3- Lymphocytosis.
4- Eosinophilia.
5- Hypoglycemia.

Acute Adrenal Hemorrhage:

A progressively deteriorating condition resulting from bilateral adrenal hemorrhage and acute adrenal
destruction in an already compromised patient with major illness.

Manifestations :

1- Abdominal, flank or back pain & abdominal tenderness.
2- (Less frequently, abdominal distention, rigidity & rebound tenderness).
3- Hypotension & shock.
4- Fever.
5- Nausea & Vomiting.
6- Confusion & disorientation.

7- Tachycardia.

With progression, the following manifestations may ensue :

1- Severe hypotention.

2- Volume depletion.

3- Dehydration.

4- Hyperpyrexia.

5- Cynosis.

6- Hypoglycemia.

7- Coma.

8- Death.

Secondary Adrenal Insufficiency

Causes :

- ACTH deficiency most commonly due to exogenous glucocorticoid therapy.
- Pituitary & Hypothalamus tumors the most common causes of naturally occuring pituitary ACTH hyposecretion.

Pathphysiology :

- ACTH deficiency is the primary event.
- This leads to :
- decreased cortisol & androgen secretion.
- But aldosterone secretion remains normal except in few cases.

In early stages :

- Basal ACTH & cortisol levels may be normal.
- ACTH reserve is impaired. Response of ACTH & cortisol to stress is subnormal.
- With further loss of basal ACTH secretion :
- There is atrophy of Z. Fasciculata & Z. Reticularis.
- Basal cortisol secretion is decreased.
- The entire pituitary adrenal axis is impaired (i.e. Decreased ACTH responsiveness to stress & decreased adrenal responsiveness to stimulation with exogenous ACTH).
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Note That:

Q: what is the most common cause of Secondary Adrenal Insufficincy ?
ACTH due to exogenous glucocorticoids Therapy

- Zona glomerulosa -> which secrets Aldosterone it will be normal due to it is not regulated from the Pituitary.

Q: What is the difference in clinical Features between Primary and Secondary Adrenal ?

Primary: you may find hyper pigmentation (due to increase ACTH)
secondary: you dont have it ! coz of lack of ACTH

Zona glumerosa is not dependent of Pituitary so you don't find Hypotention etc ..

Clinical Features

- Usually chronic nonspecific manifestations.
- Acute crisis occurs in :

1- Undiagnosed patients.

2- Patients who do not receive increased steroid dosage during periods of stress.

Clinical features differ from primary in that:

1. **Hyperpigmentation does not occur (Because of ACTH deficiency).**
2. **Manifestations of mineralocorticoid deficiency are usually absent (Because Aldosterone secretion by Z. G. is usually preserved). Therefore :**

A- Volume depletion, dehydration & hyperkalemia usually absent.
B- Hypotention is usually absent except in acute presentations.
C- Hyponatremia may occur as a result of water retention.

Prominent features (due to glucocorticoid deficiency) are nonspecific & include :

1- Weakness, lethargy & easy fatigability.
2- Anorexia, nausea & occasionally vomiting.
3- Arthralgias & myalgias.
4- Hypoglycemia.
5- Acute decompensation with severe hypotention or shock unresponsive to vasopressors.

Associated Features :

The following additional features may be present :

1- History of glucocorticoid therapy or Cushingoid features.
2- Features of loss of other pituitary hormones (hypogonadism & hypothyroidism).
3- Features of hypersecretion of GH or PRL from pituitary adenoma.
4- Pressure symptoms from pituitary tumors.

Diagnosis of Adrenal Insufficiency

- Basal levels of adrenocortical steroids in plasma or urine may be normal in partial adrenal insufficiency.
- Tests for adrenocortical reserve are necessary to establish the diagnosis.

1- Rapid ACTH Stimulation Test.
2- Plasma ACTH Levels.
3- Metyrapone Test.
4- Insulin-induced Hypoglycemia.
5- CRH Stimulation.

Other indirect clues :

1- Features of hypersecretion of GH or PRL from pituitary adenoma.
2- Pressure symptoms from pituitary tumors.

Evaluation of Suspected Adrenal Insufficiency

- Rapid ACTH Stimulation Test.

A. Abnormal ACTH Stimulation Test:
- Adrenocortical insufficiency +ve. Which type?
- Plasma ACTH level :
1- Elevated: Primary Adrenal Insufficiency +ve.
2- Normal or Low: Secondary Adrenal Insufficiency +ve.

B. Normal ACTH Stimulation Test:
- This excludes Primary Adrenal Insufficiency & Adrenal atrophy.
- But does not exclude “Decreased ACTH Reserve”
- Metyrapone Test OR Insulin-hypoglycemia Test OR CRH stimulation Test :
1- Normal: Exclude Adrenal Insufficiency.
2- Abnormal: Secondary Adrenal Insufficiency +ve.

Note That:

- If you stress the adrenal .. it might fail to increase the steroids secretion .. how ?

Reserve -- in order to test for the reserve by a stimulant or Stress ?

ACTH - Stimulating test:

you inject ACTH and you see if it can stimulate the cortisol secretion or not .. If not there is a problem with the adrenal Cortex.

- Plasma ACTH level : if high it means primary and cortisol low
- Metyrapone : used in the past now a days not
- Insulin:

you induce Hypoglycemia to the patient then you give insulin

and the adrenal did not increase cortisol it means there is deficiency

- CRH:

injection -- then you measure the Cortisol .. Normally should increase.

- Pressure symptoms is like: change or blurred vision
- When there is a tumor it makes proliferation of some tumor and expansion of the tumor destroys the other cells
- Note that: IF ACTH is Normal it is not Primary (it must Be high)

- early stage of secondary adrenal insufficiency -- If normal or low ACTH Test

Treatment of Adrenal Insufficiency :

Acute Addisonian Crisis :

Glucocorticoid Replacement :

1- Cortisol (Hyrdocortisone succinate or phosphate) 100 mg every 6 hrs. for 24 hrs.

2- When stable, reduce to 50 mg 6 hrs.

3- Taper to maintenance therapy by day 4 or 5 & add mineralocorticoid as required.

4- If complications persist or occur, maintain or increase the dose to 200-400 mg/d.

General or Supportive Measures :

1- Correct volume depletion, dehydration, & hypoglycemia with I.V. saline and glucose.

2- Evaluate and treat infection or other precipitating factors.

Maintenance Therapy :

Life-long replacement therapy with glucocorticoid and mineralocorticoid.

Preparations :

1-Cortisol (hydrocortisone) tablets :

- First choice.
- Maintenance dose: 15-30 mg/d.
- Usually, divided into 2 doses (2/3 AM & 1/3 PM).

2- Cortisone acetate (37.5mg/d) :

- Absorbed rapidly from GIT.
- Converted in the liver to cortisol.

3- Synthetic Steroids :

Prednisone or Prednisolone :

- 5 mg of prednisone tab is equivalent to 20 mg of hydrocortisone.

4- Fludrocortisone (9-alpha fludrocortisol) :

- Used for mineralocorticoid therapy.
- Usual dose : 0.05-0.1 mg/d PO AM.

- Regimen Therapy :

- Cortisol 15-20 mg AM & 10 mg at 4-5 pm.
- Or prednisone 5.0-7.5 mg AM.
- Fludrocortisone (Fluranif) 0.05 0.1 mg PO AM.
- Clinical Follow up :

Maintenance of normal body weight, BP & electrolytes.

Regression of clinical features.

- Patient education & identification card or bracelet.
- Increased cortisol dosage during stress.

NOTE

TTT: do not Stop the treatment.

IF Stress .. then double the dose Temporarily

Done !