

A Child with Increased Skin Darkening

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Abstract

Addison Disease is one of the causes of primary adrenal insufficiency, and the most common cause of Addison Disease is an autoimmune destruction of the adrenal gland. Usually, the medulla is not destroyed and there is a marked lymphocytic infiltration in the area of the former cortex.

In advanced disease, all adrenocortical function is lost, but early in the clinical course, isolated cortisol deficiency can occur.

Most patients have anti-adrenal cytoplasmic antibodies in their plasma 21-hydroxylase (CYP21), the most commonly occurring biochemically defined autoantigen

Keywords: *Primary Adrenal Insufficiency; Addison Disease; Adrenal Cortex*

Introduction

Primary adrenal insufficiency, mostly encountered in pediatric practices in neonatal periods as ambiguous genitalia in female with or without salt wasting crisis which could be a life threatening one and is usually due to a congenital adrenal hyperplasia, with a 95% of cases due to 21- α -Hydroxylase deficiency and become part of the routine neonatal screening test (by measuring 17-hydroxy-Progesteron).

Addison disease is one of the rare causes of acquired primary adrenal insufficiency due to autoimmune destruction of the adrenal cortex which could be an isolated event of part of either type I autoimmune polyendocrinopathy (AR), which consist of chronic mucocutaneous candidiasis, hypoparathyroidism, thyroiditis, and Addison disease, or type II autoimmune polyendocrinopathy which consist of thyroiditis, type I diabetes mellitus and Addison disease [1-3].

Case Presentation

A 5 years old boy came with his father complaining of generalized darkening of the skin color over a period of around one year (see photo below). This is also associated with body weakness and low appetite, without any significant family or personal history.

Clinical examination only revealed Hypotension with a BP - 60/50. Other investigations were within normal limits including a normal Brain Computed Tomography Scan (CT-Scan).

One month later, the patient came to our hospital ER lethargic and with abdominal pain. RBS was 22 mg/dL treated with IV Dextrose 0.5 g/kg IV push. Shortly after that the [patient becomes conscious, serum biochemistry showed marked salt wasting with an ABG result of Moderate Metabolic Acidosis and Urinary Ketones is negative (sample taken after treatment).

Upon collection of all data pertaining to the patient showing that this 5 years old boy patient with a complaints of generalized skin darkening with long history of weakness and fatigue and now came with Hypoglycemia, Acidosis and Salt-wasting, we infer that this is an Acute Adrenal Crisis related to Chronic Adrenal Insufficiency.

With the diagnosis mentioned above, we requested for Cortisol and ACTH. The result showed Cortisol level of 0.2 µg/dL (Normal Value: 2.3 - 11.9 µg/dL) and ACTH level of 943.4 pg/dL (Normal Value: 0 - 30 pg/dL) which confirm our diagnosis of Primary Adrenal Insufficiency (Addison Disease) and this gives us the explanation of the generalized darkening of the skin. ACTH, which is highly elevated is a 39 aminoacids peptide (single chain) that is derived by proteolytic cleavage from a Large Molecular Weight Precursor Peptide known as Pro-Opiomelanocortin (POMC) 240 Aminoacid. POMC is cleaved to ACTH and β-lipoprotein in which both are further cleaved to yield α and β Melanocyte stimulating hormone, which increases the melanin secretion form Melanocyte of the patient skin which in turn causes the gradual generalized skin darkening.



Figure 1

Discussion

what is the adrenal gland?

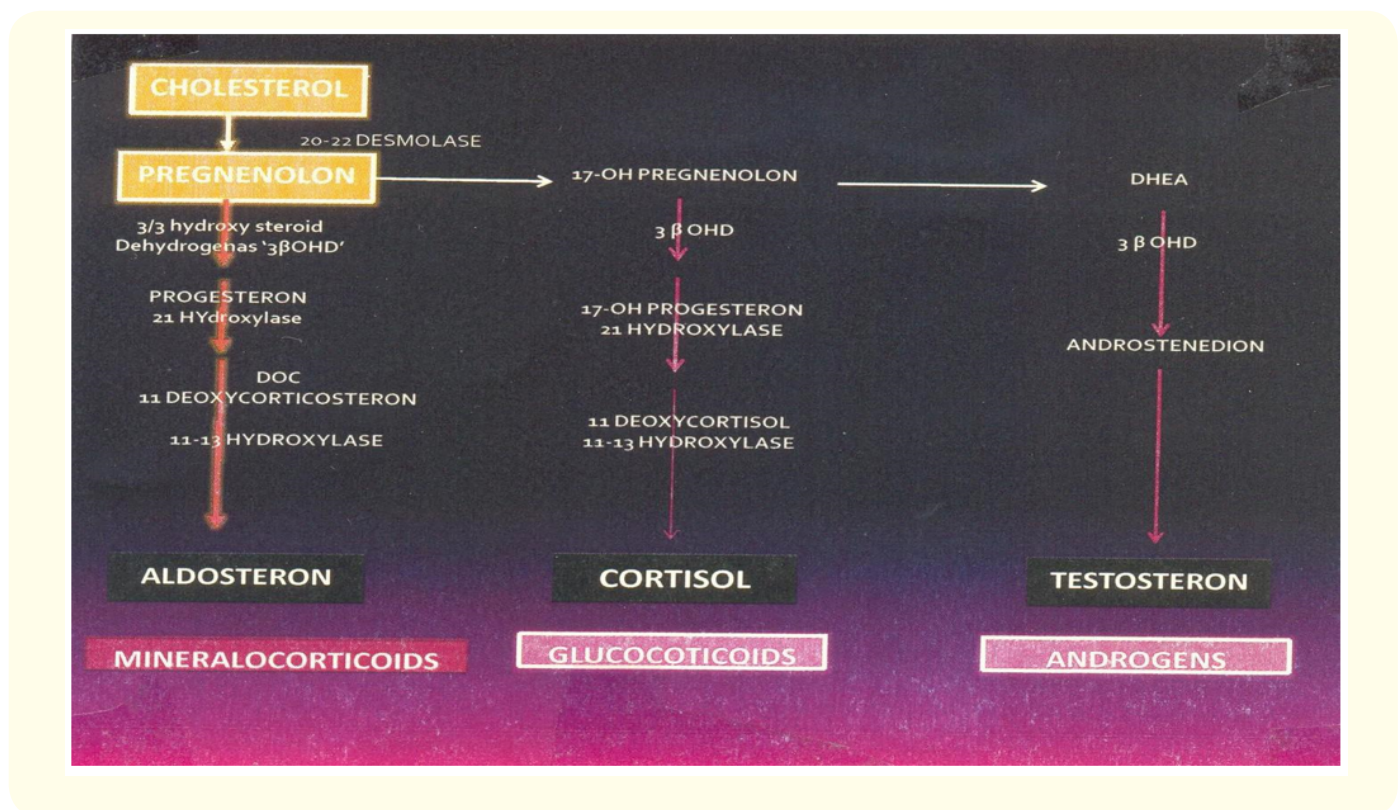
There are two (2) glands on the upper pole of each kidney measuring 4 x 3 x 3 cm that consist of two main regions known as the Adrenal Cortex and Adrenal Medulla.

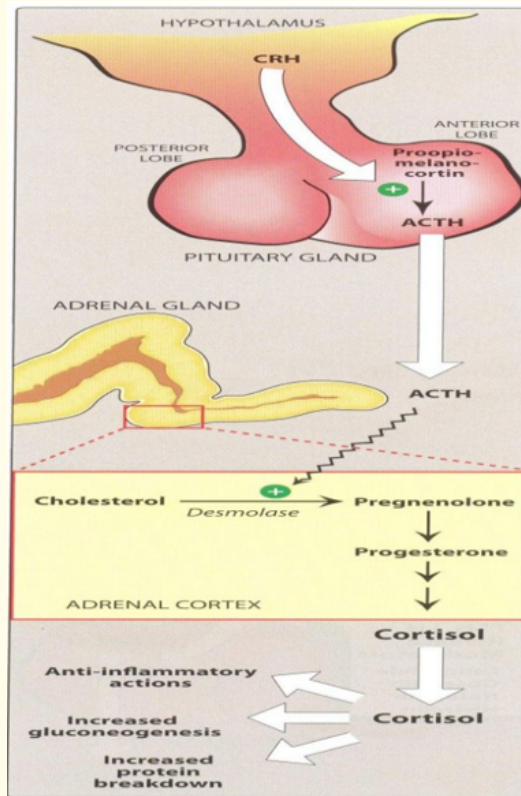
The adrenal cortex consists of the following three main areas:

1. **Zona Glomerulosa:** The outer most layer of the adrenal cortex which secretes mineralocorticoid "Aldosterone" that acts on the distal convoluted tubule to cause sodium and water reabsorption in exchange with potassium and hydrogen secretion.
2. **Zona Fasciculata:** The middle layer of the adrenal cortex which secretes glucocorticoid "Cortisol".
3. **Zona Reticularis:** The innermost layer of the adrenal cortex which secretes Androgen.

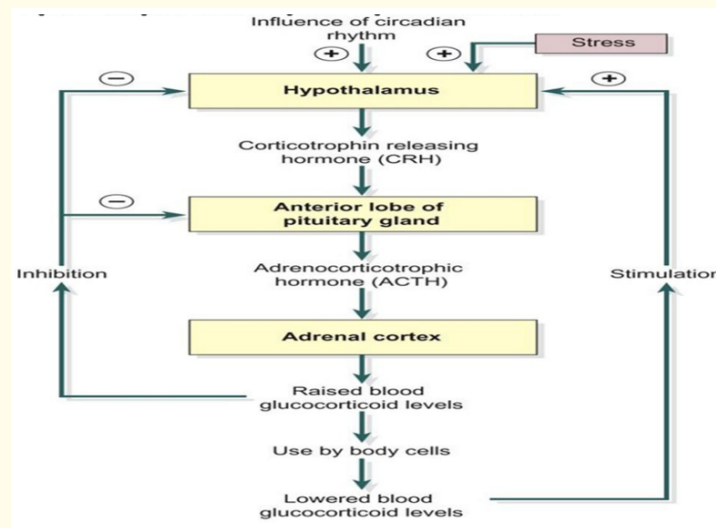
The adrenal medulla secretes adrenalin and noradrenalin (short term response "Fight or Flight").

How it is regulated?





Secretion and actions of adrenocorticotropic hormone (ACTH). CRH: Corticotropin-releasing hormone.



Negative feedback regulation of glucocorticoid secretion.

Figure 2

What are the causes of Primary Adrenal Insufficiency?

1. Congenital cause
 - The most common one is congenital adrenal hyperplasia.
2. Acquired causes
 - Autoimmune Addison disease.
 - Infection (ex: Tuberculosis, etc).
 - Drugs (ex: Ketoconazole, phenytoin, phenobarbital and etomidate).
 - Or hemorrhage into the adrenal gland (in neonate, it is due to difficult labor with or without breech presentation, or due to anticoagulant use or children abuse).

What are the clinical manifestations?

1. Corticosteroid deficiency
 - Hypoglycemia
 - Hypotension
 - Decreased cardiac output and vascular tone.
2. Mineralocorticoid deficiency
 - Salt wasting
 - Hyponatremia (S.Na < 135 mEq/L)
 - Hyperkalemia (S.K > 5.5 mEq/L)
 - Increased plasma renin activity.
3. Hyperpigmentation
 - Localized hyperpigmentation (Nipple, genitalia, palmar creases and buccal mucosa)
 - Generalized hyperpigmentation.
4. Other
 - Muscle Weakness
 - Malaise
 - Anorexia
 - Weight loss.

How to differentiate primary and secondary adrenal insufficiency?

We should measure the basic Serum Cortisol level, then we give ACTH (Synacthen or Cosyntropin) 0.250 mg, then after one hour we measure the S.Cortisol level. In Primary Adrenal Insufficiency, there will be an increment of S.Cortisol less than 200 nmol/L (7.2 mcg/dL).

What are the treatments?

1. Glucocorticoid replacement
 - Hydrocortisone 10 - 15 mg/m²/day in three divided doses or we can give Prednisolone (20-25%) of Hydrocortisone dose.
 - And we use ACTH level for treatment monitoring (should be in normal level or up to 2-3 times higher is satisfactory).
2. Stress dosing of corticosteroid in children.

	Setting	Hydrocortisone	Fludrocortisones
Mild	Low grade fever, Viral	No stress dose	Same Dose
Moderate	Vomiting, Diarrhea	30 mg/m ²	
Severe	Pneumonia, Meningitis	50 mg/m ²	Skip Dose
Very Severe	Surgery, Shock	100 mg/m ²	

3. Mineralocorticoid replacement

- Given as fludrocortisone, the dose is 0.05 - 0.2 mg daily. Maximum is 0.3 mg daily and the treatment is monitored by plasma renin activity.
- For infants, salt supplement is given (2 - 4 mEq/kg/day in three divided doses).
- Remember: 58.3 mg of salt = 1 mEq Na.

4. Treatment of acute adrenal crisis which is manifested by shock, hyponatremia, hyperkalemia, hypoglycemia and acidosis.

- Normal saline 20 mL/kg IV Bolus repeated as required then 1.5 - 2 times the maintenance fluid.
- Treat hypoglycemia with 4 mL/kg of 10% dextrose
- Give hydrocortisone 100 mg/m² (10 mg for infant, 25 mg for toddlers, 50 mg for children, 100 mg for adolescent) as IV Bolus, then we can give the same dose as continuous IV Infusion over 24 to 48 hours
- With suitable treatment of hyperkalemia (Calcium gluconate to stabilize the heart, NAHCO₃, glucose and insulin infusion, salbutamol nebulizer or infusion, diuretics, kayexalate or dialysis).

Conclusion

- Addison disease (an acquired primary adrenal insufficiency) is a rare but serious disease that needs early recognition and proper treatment.
- One of the most early sign is the hyperpigmentation of the skin, mucous membranes (either localized or generalized) and is accompanied by chronic fatigue malaise, and orthostatic hypotension.
- Once diagnosed, you have to look for the presence of other autoimmune disorder. In children, hypoparathyroidism is the most common which is suspected by low s. calcium and high alkaline phosphatase (ALP).

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