Diagnosis and management of Addison disease

Thesis Submitted in fulfillment of the M.SC degree in pediatrics

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TO……

My parents, for all they did for me
My dear husband, for great efforts and support
And
My lovely children.

ABSTRACT

Addison disease is a rare endocrine disorder in which the body produces insufficient amounts of adrenal steroid hormones. In this study, Clinical and laboratory data of thirty Addisonian patients following up at the Diabetic Endocrine Metabolic Pediatric Unit (DEMPU) in Al Monira University Children Hospital & CSPM, are retrospectively studied in order to define the most common etiology, age of presentation, mode of presentation, and assess their treatment and growth pattern, with emphasis on; etiology, age of presentation, mode of presentation, relevant family history, laboratory investigations, imaging studies, anthropometric measures , type and dose of treatment along different visits. The results of the study showed that, the mean age of presentation was 6.722 years. Of the thirty patients; 20% were diagnosed as triple A syndrome and 10% were diagnosed as ALD. TB caused the adrenal insufficiency in 6.66% of the patients, while autoimmune adrenalitis was the cause of Addison disease in one patient. 60% of the patients remained of undiagnosed etiology. The mode of presentation included hyperpigmentation, vomiting, diarrhea, wt loss, failure to thrive, weakness, and drowsiness. Consanguinity was positive in 76.67% of the patients. Our results demonstrate that, inherited conditions were common causes of adrenal insufficiency in our study, high prevalence of positive consanguinity in Egypt is major contributing factor. Hyperpigmentation and vomiting were the most common clinical features at presentation, and after several years of treatment 40% of the patients are still below the 3rd percentile of growth while 60% are above it.

(Key Words): Addison disease - Primary adrenal insufficiency - Chronic adrenal insufficiency- Polyglandular autoimmune disease- Addisonian crises- Adrenal cortex.

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AD……Addison disease.

ACTH……..Adrenocorticotrophic hormone.

AHC…… Adrenal hypoplasia congenital.

AI ……...Adrenal insufficiency.

ALD ……Adrenoleukodystrophy.

AMN…….Adrenomyeloneuropathy.

APS ……..Autoimmune polyendocrine syndrome

CAH……..Congenital adrenal hyperplasia.

CT…….Computerized tomography.

DAX-1……... Dosage-sensitive sex reversal adrenal hypoplasea congenita critical region On the X chromosome gene.

DHEA……...Dehydroepiandrostendione.

FGD……...Familial glucocorticoid deficiency.

MRI……...Magnetic resonance imaging.

PRA……Plasma renin activity.

TB……...Tuberculosis.

VLCFA……...Very long chain fatty acids.

Introduction and Aim of the Work

Addison disease is a rare endocrine disorder in which the adrenal glands produce insufficient amounts of adrenal steroid hormones (glucocorticoids and often mineralocorticoids) (George and Judith, 2004). In 1855 the British physician Thomas Addison first described adrenal insufficiency which was subsequently named after him. The basis of Addison disease has dramatically changed since its initial description. Over the past decades, there have been important advances in elucidating the pathogenesis and underling genetics of the individual forms of the disease (Ten, et al, 2001) (Elizabeth and Alexander, 2007).

In Addison disease, with cortisol deficiency there is hypoglycemia and increased adrenocorticotropin(ACTH) level which leads to hyperpigmentation.The catecholamines have decreased inotropic and pressor effects in absence of cortisol leading to decreased cardiac output and vascular tone. These problems are initially manifested as orthostatic hypotension in older children and may progress to frank shock in patients of any age. The condition is exacerbated by aldosterone deficiency which leads to electrolyte disturbance; potassium is elevated in the blood and sodium is lost along with water in the urine. The end result of aldosterone deficiency is, dehydration, weight loss, low blood pressure and elevated plasma renin activity. (Lenore and Perrin, 2004) (Williams and Dluhy, 2001).

The symptoms of Addison disease are often non specific and occur gradually. These symptoms include; fatigue, weakness, anorexia, abdominal pain, vomiting, diarrhea, and failure to thrive. There is hyperpigmentation of the skin and mucous membranes. Oral

hyperpigmentation is pathognomonic for the disease. Addison disease may appear suddenly as acute adrenal failure (addisonian crisis) when the patient is subjected to stressful situations such as infections, or surgery (Nieman and Chanco, 2006).

The cause of adrenal insufficiency may originate from the gland itself (1ry adrenal insufficiency) or from the pituitary gland (2ry adrenal insufficiency). In primary adrenal insufficiency autoimmune destruction is the most common cause in developed countries. Tuberculosis was a common cause of adrenal destruction in the past, but now it is much less common. Other causes include tumors, hemorrhage, fungal infection and surgical removal of the adrenal gland. Causes of secondary adrenal insufficiency include sudden stoppage of glucocorticoids after long use, removal or destruction of pituitary gland (Erichsen et al, 2005) (Arlt, Allolio, 2003).

Addison disease is first suspected by history and clinical examination then evaluation of the disease involves diagnosis of insufficiency and then identification of the cause through the evaluation of blood levels of Na, K, cortisol and ACTH. ACTH stimulation test is an important dynamic test that confirms the diagnosis of adrenal insufficiency. Imaging studies such as, ultrasonography and CT are useful to check the size of adrenal gland, exclude the presence of calcifications or hemorrhage (Elizabeth, Alexander, 2007).

Additional testing could be done to reach the cause of adrenal insufficiency, such as antiadrenal antibodies in case of autoimmune pathogenesis (Lenore and Perrin, 2004),and very long chain fatty acids assay which is useful in early diagnosis of adrenoleukodystrophy, and

it is necessary to be measured in all males with idiopathic Addison disease (Dubey et al, 2005).

The treatment of Addison disease is by chronic replacement of the deficient hormones and control of acute adrenal crisis (Kyriazopoulou, 2007) (Lovas et al, 2004).

The aim of the present study is to review clinical and laboratory data of thirty cases of Addison disease patients following up at the Diabetic Endocrine and Metabolic Pediatric Unit (DEMPU), Al Monira University Children Hospital (Abou Alreesh), Cairo University, in order to define the most common etiology, age of presentation, mode of presentation, and assess their treatment and growth pattern.

ANATOMY OF THE ADRENAL GLANDS

Adrenal glands are small yellowish triangular endocrine glands 2cm wide, 5cm long, and 1cm thick located on top of the kidneys on its posteromedial surface (Stewart, 2003).

They receive their blood supply from the adrenal arteries while their venous drainage flows into the inferior vena cava on the right side and the left renal vein on the left side. Lymphatic drainage flows into the aortic nodes.

At one year of age, each gland weighs about one gram and the weight subsequently increases with age to the final adult weight of 4-5 grams (Lenore and Perrin, 2004).

Each gland is composed of two distinct parts, the adrenal cortex and the adrenal medulla. The former is divided into three zones. From exterior to interior they are zona glomerulosa, zona fasciculata, and zona reticularis (Bowen, 2002). The zona glomerulosa constitutes approximately 15% of the cortex, while the zona fasciculata makes up 75% of the cortex and the innermost zona reticularis is sharply demarcated from both zona fasciculata and adrenal medulla (Stewart, 2003).

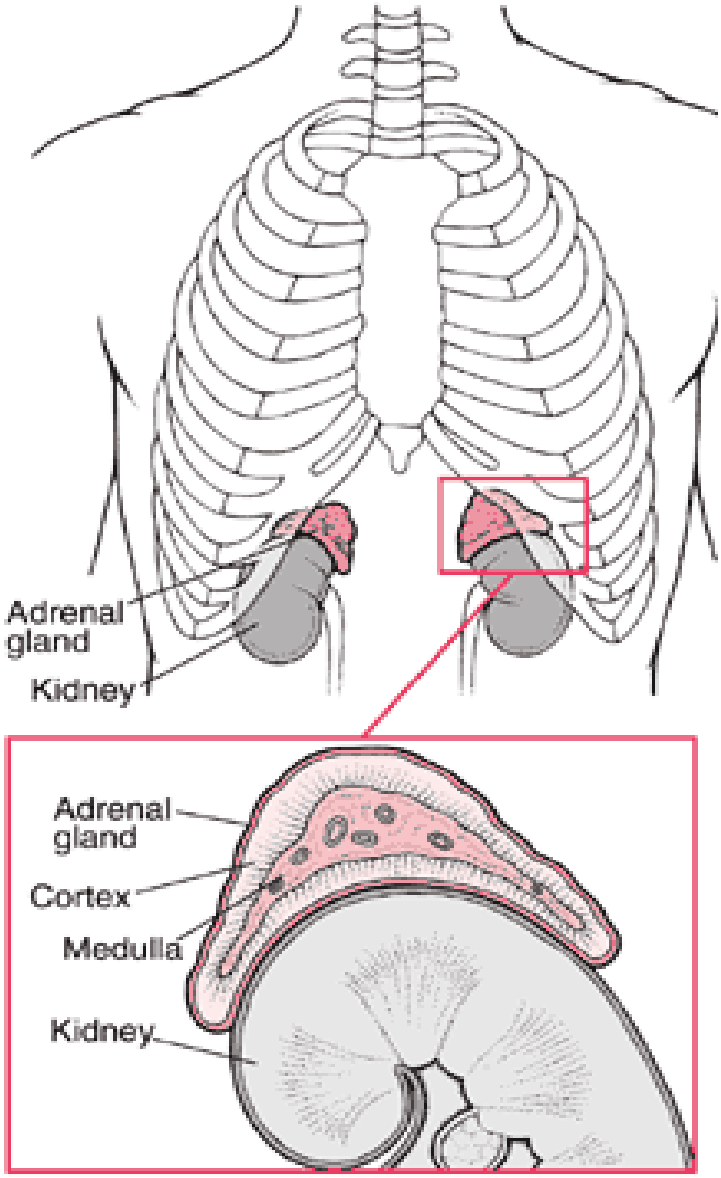

Figure (1): Anatomy of adrenal gland

Embryology of the adrenal gland

The two parts of the adrenal gland have different origins; the cells of the adrenal cortex are derived from the mesoderm and the chromaffin cells of the adrenal medulla are derived from neuroectoderm from neural crest cells that migrate to medial aspect of developing cortex (Lenore and Perrin, 2004) (Saundra and Helene, 2006).

Physiology of the adrenal gland

The two parts of the adrenal gland are functionally different endocrine organs. The hormones secreted from the adrenal medulla – epinephrine and norepinephrine – have the same effect on organs as the sympathetic nervous system. The most common stimuli for their secretion are exercise, hypoglycemia, hemorrhage and stress.

The cortex synthesizes and secretes three classes of hormones, mineralocorticoids, glucocorticoids and adrenal androgens.

The mineralocorticoids, the most important of which is aldosterone are secreted by zona glomerulosa, the glucocorticoids, predominantly cortisol secreted mainly by zona fasciculata and to a lesser extent zona reticularis, while adrenal androgens mainly dehydroepiandrostendione (DHEA) are secreted by zona reticularis (Bowen, 2002)(Lenore and Perrin, 2004)

Glucocorticoids are essential for survival as they have multiple effects on metabolism, where they increase glucose by stimulating gluconeogenesis and decreasing cellular glucose use. They also increase free fatty acids levels in the blood as they stimulate lipolysis and have catabolic effects on protein metabolism due to stimulation of

proteolysis in, skeletal muscles, bone, lymphoid and connective tissue. They also influence growth, bone metabolism and central nervous system activity in addition to their role in immune regulation where they exhibit anti-inflammatory effects. Glucocorticoids also elevate RBC and platelet levels. In stress situations, glucocorticoids increase cardiac contractility, cardiac output, and sensitivity to pressor effects of catecholamines in addition to increasing work capacity of skeletal muscles (Kevin et al, 2007).

Mineralocorticoids maintain extracellular fluid volume by conserving sodium and eliminating potassium and hydrogen ions. They exert these actions mainly in the kidneys, gut, salivary and sweat glands (Lenore and Perrin, 2004).

Adrenal androgens have weak effects which result from their extra adrenal conversion to active androgens or estrogens such as testosterone, dihydrotestosterone, estradiol and estrone. They are likely to play a role in early development of male sex organs in childhood and play an important role in women during pubarche. Adrenal androgens contribute to physiologic development of pubic and axillary hair during normal puberty (Parker et al, 2004) (Miller, 2001) (Lenore and Perrin, 2004).

Regulation of the adrenal cortex

The mineralocorticoids production is mainly regulated by the renin-angiotensin system and by potassium levels, with ACTH having a minor role. The glucocorticoid synthesis is regulated by adrenocorticotropin hormone (ACTH) secreted by anterior pituitary gland which is controlled by corticotrophin releasing hormone (CRH)