International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Original Research Article

Congenital Adrenal Hyperplasia in Saudi Arabia: The Biochemical Characteristics

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Received: 25/03/2015 *Revised: 14/04/2015* *Accepted: 17/04/2015*

ABSTRACT

Background: Congenital Adrenal Hyperplasia (CAH), is a group of autosomal recessive disorders resulting from the deficiency of one of the enzymes required to synthesis cortisol, and hence, increased production of adrenocorticotropin releasing home (ACTH) which leads to adrenal hyperplasia.
Design and Setting: A retrospective, hospital based study were conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia during the period January 1989 and December 2014.
Patients and Methods: Medical records of children with the diagnosis of congenital adrenal hyperplasia were retrospectively reviewed. Data included age, sex, and results of the relevant laboratory investigations.
Results: During the period under review, 95 patients with CAH were reviewed. Of these, 76 (80%) were due to 21-α-hydroxylase deficiency, 15 (15.8%) patients with 11β-hydroxylase deficiency and 4 (4.2%) patients were due to 3-β-hydroxysteroid dehydrogenase deficiency. Serum concentrations of 17-hydroxyprogesterone, 11 deoxycortisol and the ratio of dehydroepiandrosterone, androstenedione were diagnostic for the appropriate diseases.
Conclusions: Although, genetic testing would assist accurate diagnosis of the affected individuals, biochemical (hormonal) concentrations of 17-hydroxyprogesterone, 11-deoxycortisol and dehydroepiandrosterone / androstenedione ratio can be of a help in diagnosis

Keywords: Biochemical, congenital adrenal hyperplasia, profile, Saudi Arabia

INTRODUCTION

Congenital adrenal hyperplasia CAH, the so called Adrenogenital syndrome, is a group of autosomal recessive disorders resulting from the deficiency of one of the enzymes required to synthesize cortisol, figure. As a result increased production of adrenocorticotropin-releasing hormone (ACTH), leads to adrenal hyperplasia. [1,2] Ninety to ninety-five percent of cases of CAH are due to a deficiency in the enzyme 21-α-hydroxylase which is also associated with the production of excess adrenal androgens. Aldosterone deficiency may or may not be involved, depending on the severity of the enzyme deficiency. [3,4] 11-β-hydroxylase deficiency is the second most common which accounts for 5-10 percent of patients depending on the geographic location and ethnic background. Although somatic virilization and hypertension are considered the main

features of the disease, great variability in the clinical expression has been reported [5,6] with complete dissociation between the degree of enzyme deficiency and the severity of the clinical, manifestations. The other three enzymes deficiencies, 3-β-hydroxysteroid dehydrogenase, 17-α-hydroxylase and 20,22 desemolase are quite rare. [7-10] A significant difference in the pattern of the disease has been reported in different regions of the world. [11-14]
The aim of this study was an attempt to report of the biochemical characteristics of the disease in this part of the world.

MATERIALS AND METHODS

During the period January 1989 to December 2014, 103 (95 Saudi and 8 non-Saudi) children with CAH were evaluated at the Pediatric Endocrine Unit at the KKUH, Riyadh, Saudi Arabia. Only Saudi children were included in this study. Diagnosis of CAH was suspected in clinical grounds and confirmed in all patients by detailed chromosomal, hormonal and radiological investigations. [12,15]

Diagnosis of classical 21-α-hydroxylase deficiency was confirmed by high plasma concentration of 17-hydroxy progesterone while elevated plasma concentration of 11-deoxycortisol with suppressed plasma renin activity are confirming the diagnosis of 11-β-hydroxylase deficiency CAH in the presence of a normal or slightly high 17-hydroxyprogesterone. The diagnosis of 3-β-hydroxysteroid dehydrogenase deficiency was based on elevated dehydroepiandrosterone (DHEA) level associated with low concentration of androstenedione and testosterone is clinically suspected subjects. The salt depleting state was confirmed by the presence of hyponatremia, hyperkalemia, and natriuria with high serum renin activity and low serum aldosterone concentration. All the hormones were measured commercially by Bioscienti Laboratory, Germany. Chromosomal analysis, abdominal ultrasound, genitography or magnetic resonance imaging (MRI) was performed when appropriate. Data were retrospectively reviewed and included age, sex, and results of the relevant laboratory investigations.

RESULTS

There were 95 patients, 44 males and 51 females with CAH aged between newborns to 13 year of age. Of these, 76 (80%), (34 males and 42 females) were having CAH due to 21α-hydroxylase deficiency, with salt wasting in 71 (93.4%) patients, 15 (7 males and 8 females) (15.8%) patients with 11-β-hydroxylase deficiency, while only 4 patients (3 males and 1 female) (4.2%) were due to 3-β-hydroxysteroid dehydrogenase deficiency, also all were salt-waster, Table 1.

Table 1: Distribution of 95 patients with CAH and enzyme deficiency.

Enzyme deficient	No. of patients	%
21-α-hydroxylase	76*	80%
11-β-hydroxylase	15	15.8%
3-β-HSD	4**	4.2%
Total no. of patients	95	100%

3-β-HSD - 3-β-hydroxysteroid dehydrogenase
CAH - congenital adrenal hyperplasia
* 71 patients were salt-waster
** All patients were salt-waste

Table 2: The biochemical profile, mean (range) in 76 patients with CAH due to 21α hydroxylase deficiency*

	ACTH	Cortisol	17-OH progesterone	Testosterone
Normal range	5-18 Pmol/L	150-685 nmol/L	0.6-4.2 nmol/L	0.1-0.4 nmol
Mean (range)	41.7 (9-102)	112 (60-250)	194 (44-920)	1.43 (0.2-2.3)

ACTH - Adrenocorticotropic hormone
* 71 patients were salt-waster with low aldosterone and high plasma renin activity
5 patients were non-salt-waster with normal aldosterone

Table 3: The biochemical profile, mean (range), in 15 patients with CAH due to 11β hydroxylase deficiency

	ACTH	Cortisol	17-OH progesterone	11-deoxycortisol	Aldosterone	Plasma renin activity
Normal range	5-18 Pmol/L	150-635 nmol/L	0.6-4.2nmol/L	<30nmol/L	0.14-1.7nmol/L	μg/h (<2.0)
Mean(range)	52.8 (5.3-81)	282 (<50 – 773)	13.4 (4.8 – 30.3)	2.16 (0.13 – 201)	0.64 (0.13 – 1.2)	<0.2 <0.2

Table 4: The biochemical profile, mean (range), in 4 patients with CAH due to 3-β hydroxysteroiddehydrogenase deficiency

	ACTH	Cortisol	17-hydroxyprogesterone	DHEA	Androstenedione
Normal range	5-18 Pmol/L	150-685 nmol/L	0.6-4.2 nmol/L	4-10 nmol	0.5-1.7 nmol/L
Mean (range)	39 (5.6 – 90)	80 (60 – 350)	10 (6-12)	15.6 (10-31.4)	0.8 (0.6-1.5)

Tables 2, 3 and 4 show the biochemical (hormonal) data of the various patients with CAH at the time of presentation and diagnosis. Serum concentrations of 17 hydroxyprogesterone, 11 deoxycortisol and the ratio of dehydroepiandrosterone and androsteridine were diagnostic to the appropriate disorders.

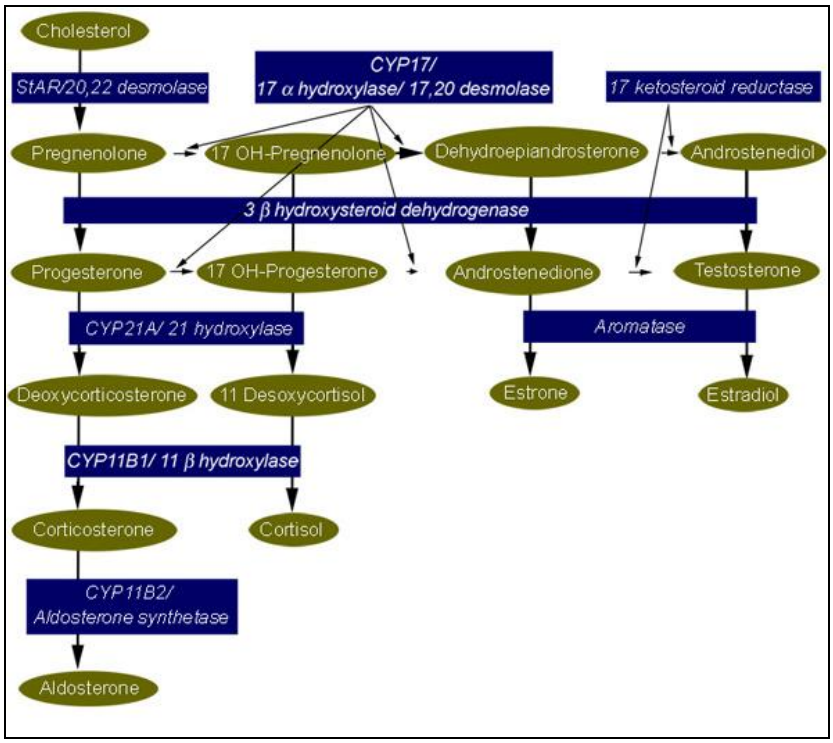

Figure 1: Schematic structure for biosynthesis of adrenal cortex hormones (glucocorticoids, mineral-corticoids and sex steroid hormone.

DISCUSSION

Congenital adrenal hyperplasia (CAH), is one of the common endocrine disorders, encountered by the practitioner, in this part of the world due to increased prevalence of consanguinity. [16,17] It is caused by reduced or complete absence of the enzymatic activities of steroid biosynthesis pathway. Based on the phenotypic expression of the disorder, it is categorized into two major forms. Severe or classic forms, consists of salt-wasting and simple virilizing type, and late onset or non-classic form. The variable clinical phenotypes depend on the reduced enzymatic activity due to different combination of gene mutations which may lead to mortality and morbidity.

Congenital adrenal hyperplasia occurs due to mutations in gene including

CYP21A2, S (tAR), CYP 11 A1, HSD3 B2, CYP 17 A1 and CYP 11 B1 which encode the following enzymes: 21 hydroxylase, steroidogenic regulatory protein S(tAR), lipoid adrenal hyperplasia, cholesterol 20-22 desmolase, 3β-hydroxysteroid dehydrogenase (3β-HSD) 17α-hydroxylase (17α-OH) and 11β hydroxylase (11β-OH), respectively. [18,19]

All reported CAH mutations are inherited recessively, thus the recurrence risk of 25% is suspected for patients with a previous affected child, although de novo mutations may occur. Genetic testing would assist accurate diagnosis. [19] However, CAH can be diagnosed on the basis of biochemical assessment of hormonal concentrations such as 17-α-hydroxyprogesterone (17-OHD), 11 deoxdycortisol, androstenedione, dehydroepiandrosterone (DHEA), cortisol, adrenocorticotropin-releasing hormone (ACTH) and testosterone which accumulate before the block with the expectation of lipoid adrenal hyperplasia that no steroid is produced in this form of the disorder. Normally, high concentration of serum 17 hydroxyprogesterone is observed in classic 21 hydroxylase deficiency, as in our series. However, to differentiate the salt-waster from the non-salt-waster, we need to perform aldosterone which is usually low and renin activity which is usually high. [4] Elevated concentrations of 11-deoxycortisol with suppressed plasma renin activity are confirming the diagnosis of 11-β-hydroxylase deficiency CAH, while the plasma 17 OHP concentration is normal or slightly high. [5] The diagnosis of 3-β-hydroxysteroid dehydrogenase enzyme deficiency CAH is usually associated with an elevated, concentration of dehydroepiandrosterone (DHA) with low concentrations of androstenedione and testosterone in clinically suspected subject.

CONCLUSION

A variety of enzyme deficiency can lead to CAH, with 21-hydroxylase being the commonest, followed by 11-β-hydroxylase deficiency. Other forms, 3-β-hydroxysteroid, 17-hydroxylase and 20,22 desmolase are quite rare. Genetic testing would assist accurate diagnosis of the affected individuals. However, biochemical (Hormonal) profiles can be of help in the diagnosis.

ACKNOWLEDGEMENT

The author would like to thank Ms. Loida M. Sese for typing the manuscript and Mr. Moaath N. Al Jurayyan for the technical support.

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How to cite this article: Al Jurayyan NAM. Congenital adrenal hyperplasia in Saudi Arabia: the biochemical characteristics. Int J Health Sci Res. 2015; 5(5):98-102.

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