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RESEARCH ARTICLE

HYPERTENSION ASSOCIATED WITH CONGENITAL ADRENAL HYPERPLASIA

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ABSTRACT

Background: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from the deficiency of one of the five enzymes required to synthesis cortisol, and hence, increased production of adrenocorticotrophin releasing hormone (ACTH) which leads to adrenal hyperplasia. In 11-β-hydroxylase and 17-α-hydroxylase deficiencies, the accumulation of the mineralocorticosteroids or 11-deoxy-cortisol can lead to hypertension.
Design and settings: A retrospective, hospital based study, was conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, during the period January 1989 and December 2014.
Methods: Medical records of children who were diagnosed to have congenital adrenal hyperplasia were retrospectively reviewed. Data included age, sex, clinical presentation and results of the relevant laboratory and radiological investigations.
Results: During the period under review, 95 Saudi patients with CAH were diagnosed. Of these 76 (80%) were due to 21-α-hydroxylase deficiency, 15 (15.8%) patients with 11-β-hydroxylase deficiency, and 4 (4.2%) patients were due to 3-β-hydroxysteroid dehydrogenase deficiency. Six (40%) patients with 11-β-hydroxylase deficiency developed persistent hypertension during the course of follow-up.
Conclusion: Hypertension is common occurrence in congenital adrenal hyperplasia due to 11-β-hydroxylase deficiency and should be considered in the differential diagnosis of hypertension.

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from the deficiency of one of the five enzymes required to synthesize cortisol, figure 1. As a result increase production of adrenocorticotrophin-releasing hormone (ACTH) leads to adrenal hyperplasia. (Al Jurayyan 2015, Speicer & White 2003, Merke & Borstein 2005) More than ninety-percent of patients of CAH are due to a deficiency in the enzyme 21-α-hydroxylase which is also associated with the production of excess androgen. Aldosterone deficiency may or may not be involved depending in the severity of the enzyme deficiency. 11-β-hydroxylase deficiency is the second most common, accounts for about 10 percent of patients depending on the ethnic group and the geographic locations. Although somatic virilization and hypertension are considered the main feature of the disease, great variability in the clinical expression has been reported, with complete dissociation between the degree of enzyme deficiency and severity of the clinical manifestation. The other three enzyme deficiencies: 3-β-hydroxysteroid dehydrogenase, 17-α-hydroxylase, and 20, 22 desmolase are rare. 17-α-hydroxylase usually presents with hypertension. (Levine *et al.,* 1980, Al Jurayyan 1995, Rosa *et al.,* 2007, Simard *et al.,* 2002, Metherel, 2009) Hypertension as a clinical problem in children has recently advances in our ability to identify, evaluate, and care for hypertension. These have led to an increase awareness of hypertension in modern management (Guideline, the Fourth Report on high BP, 2004). This report presents our experience over 25 years (January 1989 and December 2014) in a major teaching hospital in Riyadh, Saudi Arabia.

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METHODS

During the period January 1989 and December 2014, 103 (95 Saudi and 8 non-Saudi) children with the diagnosis of congenital adrenal hyperplasia were seen in the Pediatric Endocrine Unit of the King Khalid University Hospital (KKUH) of the King Saud University, Riyadh, Saudi Arabia.

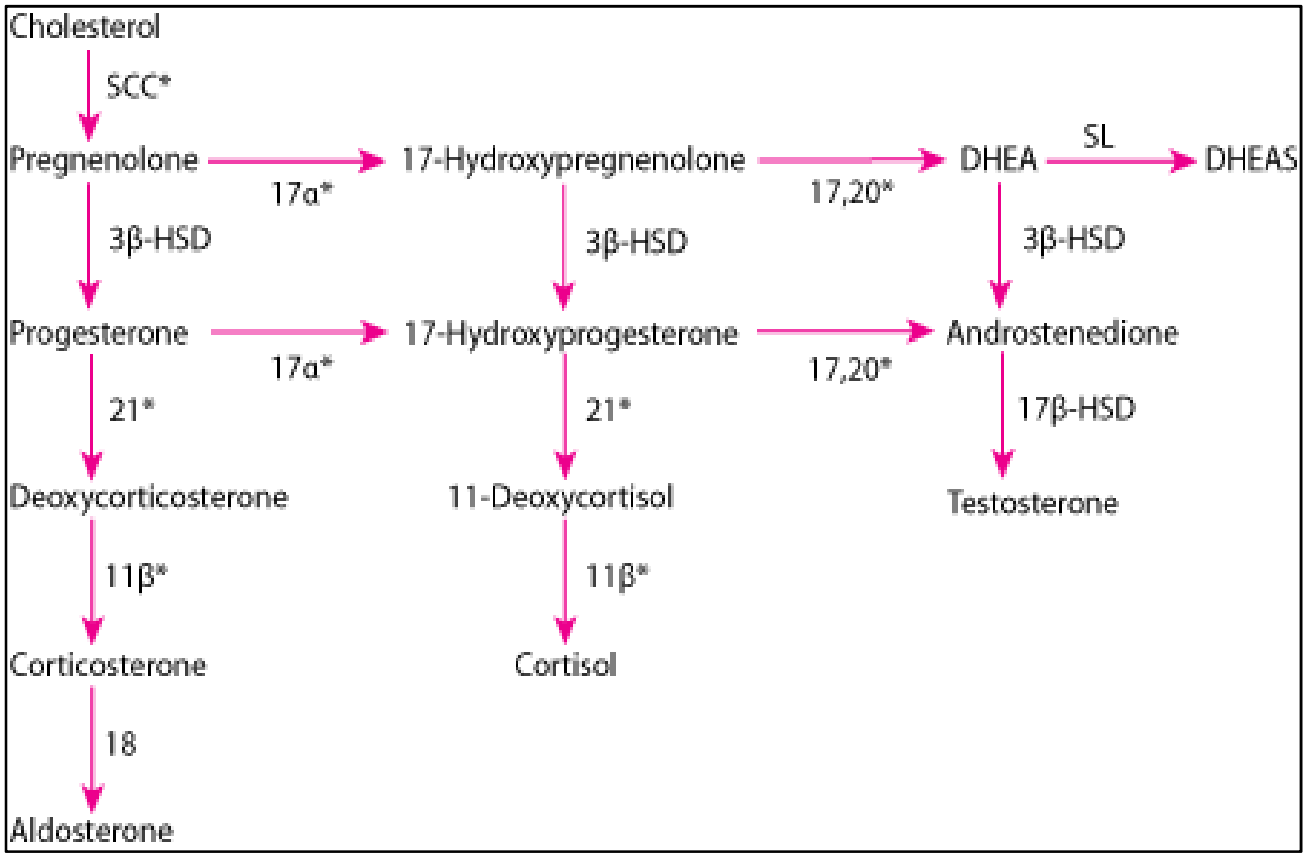

Figure 1. Schematic structure for biosynthesis of adrenal cortex hormones (glucocorticosteroids, mineralocorticosteroids and sex steroid hormones)

The diagnosis was suspected on clinical grounds and confirmed in all patients by demonstrating the appropriate biochemical findings. (Al Jurayyan, 2015). Records of all patients were retrospectively reviewed, and data extracted for analysis included, age, sex, clinical manifestations, relevant family history and results of all laboratory, and ancillary investigations performed. Details of management as well as outcome were also reviewed. For blood pressure, the normal value of task force on blood pressure control in children was used. The severity of the virilization of external female genitalia was rated according to Prader's classification. (Prader, 1954)

RESULTS

There were 95 patients, 44 males and 51 females, with congenital adrenal hyperplasia (CAH), aged between newborns to 13 year of age. Of these, 76 (80%), 34 males and 42 females, were having CAH due to 21-α-hydroxylase deficiency, with salt-wasting in 71 (93.4%) patients, 15 (7 males and 8 females) (15.8%) patients with 11-β-hydroxylase deficiency, and only 4 (4.2%), three males and one female, were due to 3-β-hydroxysteroid dehydrogenase deficiency, all salt-wasters. None of our patients were noted to have 17-α-hydroxylase or 20, 22 desmolase deficiency, Table 1. Overt hypertension of various degrees of severity associated with hypokalemia was observed in six (40%) patients from two families, Table 2. In four, hypertension persisted inspite of adequate hydrocortisone therapy. Patients were controlled on hydrochlorothiazide and amlodipine. There was clear dissociation between the clinical picture and severity of hypertension.

DISCUSSION

Congenital adrenal hyperplasia (CAH) is one of the common endocrine problems, encountered by the practitioner, in this part of the world due to increased prevalence of consanguineous mating. (Saedi-Wong *et al.,* 1989) It is caused by reduced or complete absence of any of the enzymatic activity of the steroid biosynthesis pathway. The commonest enzyme deficiency is 21-α-hydroxylase, followed by 11-β-hydroxylase. Other rare enzyme deficiency may be due 3-β-hydroxysteroid dehydrogenase or 17-α-hydroxylase and 20, 22 desmolase. (Rosa, 2007, Simard *et al.,* 2002, Metherel, 2009)
Hypertension (HT) in children is usually defined as blood pressure consistently above the 95th percentile for age, sex and height of the child. Blood pressure should be measured with an appropriate sized pediatric cuff, with the child supine or sitting down. Renal or vascular causes are the commonest, but hypertension in younger children is almost always secondary unless otherwise proved. Endocrine hypertension per se is often asymptomatic in children, but signs of the underlying diseases may be evident, like features of Cushing's syndrome, growth failure and pubertal abnormalities. Sustained severe hypertension in children can represent with headache, seizures, epistaxis, visual disturbance, unexplained cardiac and renal failure.

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

Enzyme deficiency	No. of patients	%
21-α-hydroxylase	76	80
11-β-hydroxylase	15	5.8
3-β HSD	4	.2
Total of patients	95	100%

CAH – congenital adrenal hyperplasia
3βHSD – 3-β-hydroxysteroid dehydrogenase
** 71 patients were salt-wasters*
*** All patients were salt-wasters*

Table 2. Clinical data of 15 patients with 11-β-hydroxylase deficiency congenital adrenal hyperplasia

Patient No.	Age	Sex	Clinical manifestation			
			Genitalia	Hypertension	Hypokalemia	11-deoxycortisol <30nmol/L
1	2.8 y	M	Precocious puberty	-	-	30
2	1 w	F	Ambiguous genitalia	-	-	120
3	4 w	M	Normal genitalia	-	-	70
4	12 y	F	Ambiguous genitalia P_5	+	+ +	33
5	4 y	M	Precocious puberty	+	+	42
6	3 y	M	Precocious puberty	+	+ +	58
7	Newborn	F	Ambiguous genitalia P_4	+	+	160
8	7 y	F	Mild virilization P_2	-	-	34
9	5 y	F	Mild virilization P_2	-	-	181
10	Newborn	M	Normal genitalia	-	-	123
11	1 m	F	Ambiguous genitalia P_3	-	-	78
12	1 m	F	Moderate virilization P_3	-	-	58
13	3 y	F	Mild virilization P_2	+	+	164
14	1 y	F	Mild virilization P_2	+	+	81
15	2 y	M	Precocious puberty	-	-	38

w – week; m – month; y – year; m – male; f – female
Prader classification for virilization of the external female genitalia; P = potassium level > 3.5, < 3 mmol/L +, < 3 mmol/L ++

(Bhvani, 2011) Biglieri and associate have described a syndrome were defective 17-α-hydroxylase is present in the adrenal and gonads. The resultant low levels of cortisol, acting via the negative feedback mechanism, stimulate ACTH i.e. ease with subsequent bilateral hyperplasia and excessive secretion of corticosterone and deoxycorticosterone. These in turn CAH due to 17-hydroxylase deficiency is associated with hypertension and excess of deoxycorticoasterone (DOC) which is the second most common naturally occurring mineralocorticosteroid after aldosterone. DOC excess typically is associated with hypertension, hypokalemia and renin and aldosterone suppression. Cause sodium retention, potassium loss and as a result hypertension and hypokalaemicalkalosis. Renin levels are also suppressed. (Cerame & New, 2000, Wranock 2000) In the presence of 11-β-hydroxylase deficiency, defective cortisol secretion lead to a secondary elevation of ACTH and to bilateral adrenal hyperplasia. In addition, there are high circulating levels of 11-deoxycortisol and deoxycorticosterone. (White, 2001)

The variability in the clinical and biochemical findings, however, could be due to different genetic mutations. Also, it is tempting to say that increased tissue sensitivity to DOC, or the presence of the metabolites such as 18-OH DOC with none marked mineralocosticoid activity is responsible for hypertension. (Al Jurayyan, 1995) Although, we do not have any patient with 17-α-hydroxylase deficiency, it is rare and accounts to less than one percent of all cases of CAH. The gene for this enzyme has been mapped to chromosome 10 and mutations, are common in Duch Mennonites.

17-α-hydroxylase is the enzyme which converts pregnenolone and progesterone to 17-hydroxy pregnenolone and 17-hydroxy progesterone, respectively. When this enzyme is deficient, 17 deoxy steroids are produced in excess leading to increased serum concentrations of DOC and corticosterone which have mineralocorticoid activity. So renin is suppressed and aldosterone levels are decreased and patients have hypotension and hypokalaemia. But since the precursors cannot enter the androgenic pathway as well, the males with 46 XY chromosomes have under virilization in utero, leading to genital ambiguity, at puberty they develop gynaecomastia due to unknown reasons. Females with 46XX constitution have no ambiguity, but have sexual infantilism at puberty. Elevated levels of 17-deoxysteroids such as progesterone, pregnenolone, DOC and corticosterone in the plasma establish the diagnosis. (Bhavani, 2011, Cerame and New 2009, Scaroni et al, 1994)

Conclusion

Although, endocrine causes of hypertension are still rare in children, excess levels and/or action of mineralocorticosteroids associated with low renin levels inCAH can lead to the right diagnosis.

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REFERENCES

Al Jurayyan, N.A.M. 2015. Congenital adrenal hyperplasia in Saudi Arabia: The biochemical characteristics. *International J. Health Sci. and Res.,* 5(5):98-102.

Al Jurayyan, N.A.M. 1995. Congenital adrenal hyperplasia : due to 11-β-hydroxylase deficiency in Saudi Arabia. Clinical and biochemical characteristics. *Acta Paediatr.,* 84:651-4.

Bhvani, N. 2011. Pediatric endocrine hypertension. *Indian J. Endocrinol. Metab.,* 15(8);361-366.

Cerame, B. New MI, 2000. Hormonal hypertension in children: 11-beta-hydroxylase deficiency and apparent mineralocorticosteroid excess. *J . Pediatr. Endocrinol. Metab.,* 13 (9):1537-47.

Guideline, 2004. The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and adolescents. Pediatrics 114(5); 555-576.

Kater, C.E. and Biglieri, E.G. 1994. Disorders of steroid 17-α-hydroxylase deficiency. *Endocrinol. Metab. Clin. North. Am.,* 23:341-357.

Levine, L.S., Rauth, W., Gottesdiener, K., Chow, D., Gunczler, P. and Rapaport, R., *et al.,* 1980. New studies in 11-β-hydroxylation of 18-hydroxylase enzymes in hypertensive forms of congenital adrenal hyperplasia. *J. Clin. Endocrinol. Metab.,* 50:258-63.

Merke, D.P. and Borstein, S.R. 2005. Congenital adrenal hyperplasia. Lancet 365(2):25-36.

Metherel, L.A. 2009. Non-classic lipoid congenital adrenal hyperplasia masquerading as familial glucocorticoid deficiency. *J. Clin. Endocrinol. Metab.,* 94:3865-71.

Prader, A. 1954. Der Genitalbefundbeim Pseudohermaphroditismfeminimus des Kongenitenadrenogenitalen syndromes. Helv Paediatr Acta 9:231-48.

Rosa, S., Duffe, C., Meyer, M., *et al.* 2007. P450e 17 hydroxylase: clinical and molecular characteristic of six patients. *J. Clin. Endocrinol. Metab.,* 92(3);1000-1007.

Saedi-Wong, S., Al Frayh, A.R. and Wong, H.Y. 1989. Socio-economic, epidemiology of consanguineous matings in the Saudi Arabian population. *J. Asian Afr. Stud.,* 24:247-52.

Scaroni C, Biason A, Carpene G, Opocher G, Mantero F, 1991. 17-alpha-hydroxylase deficiency in three siblings : short and long-term studies. *J. Endocr. Invest.,* 14:99-108.

Simard, J., Moisan, A.M. and Morel, Y. 2002. Congenital adrenal hyperplasia due to 3-α-hydroxysteroid dehydrogenase 1 Delta (5)- Delta (4). Isomerase deficiency. Semin Reprod Med 20(3):225-76.

Speicer, P.W. and White, P.C. 2003. Congenital adrenal hyperplasia. *N. Engl. J. M.,* 349(8):770-788.

White, P.C. 2001. Steroid 11-beta-hydroxylase deficiency and related disorders. EndocrinolMetabClin North Am 30:61-79.

Wranock, D.J. 2000. Aldosterone related genetic effects in hypertension. *Curr. Hypertens. Rep.,* 2:295-301.

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