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RESEARCH ARTICLE

3-BETA-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY CONGENITAL ADRENAL HYPERPLASIA: A RARE DISORDER IN SAUDI ARABIA

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ABSTRACT

Background: 3-beta-hydroxysteroid dehydrogenase deficiency is a rare type of congenital adrenal hyperplasia that impairs steroidegenesia. The clinical spectrum of this inherited disorder is heterogenous and ranges from the severe salt-wasting with or without ambiguous genitalia to the non-salt-wasting form.

Design and Setting: A retrospective-hospital based study, conducted at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, during the period January 1990 and December 2014.

Patients and Methods: During the period under review, 95 patients were diagnosed with congenital adrenal hyperplasia, of these; only 4 (4.2%) patients were diagnosed with 3-beta-hydroxysteroid dehydrogenase deficiency and constituted the subjects for the study. Their medical records were retrospectively reviewed. This included age, sex, clinical presentation and important chromosomal, radiological and biochemical investigations.

Results: Four Saudi patients, three from one family, were diagnosed with 3-β-hydroxysteroid dehydrogenase deficiency, among 95 (4.2%) patients with congenital adrenal hyperplasia. Their clinical and biochemical characteristics were presented.

Conclusion: Although rare, 3-beta-hydroxysteroid dehydrogenase deficiency congenital adrenal hyperplasia, should be considered in the 46XY individuals presenting with ambiguous genitalia, with or without salt-wasting, as well as a normal looking females with salt-wasting.

INTRODUCTION

3-β-hydroxysteroid dehydrogenase Type II deficient congenital adrenal hyperplasia (3β-HSD CAH) is an uncommon form of congenital adrenal hyperplasia (CAH) resulting from mutation in the gene for one of the key enzymes in cortisol synthesis by the adrenal gland, 3β-hydroxysteroid dehydrogenase (3β-HSD) type II (HSD3β2) figure 1. As a result, higher levels of 17 OH pregnenoloneand dehydroepiandosterone (DHEA) appear in the blood with adrenocorticotropic hormone (ACTH) that stimulates adrenal corticosteroid synthesis. (Pang, 2001; Simard *et al.,* 2002; Stewart, 2008; Zachmann, 1996; Krone *et al.,* 2009; Simard *et al.,* 2005; Subramanian *et al.,* 2010). There is a wide spectrum of clinical presentations of 3β-HSD CAH, from mild to severe forms that results from variable loss of enzymatic activity and manifests itself in infancy as a salt-wasting due to the loss of mineralocorticosteroids or ambiguous genitalia. Milder forms resulting from incomplete loss of 3β-HSD type II function that do not present with adrenal crisis, but can still produce virilization of genetically female infants and under virilization of genetically male infants. Figure 2, like the other forms of CAH, suspicion is usually raised by the appearance of the genitalia at birth, or the development of salt-wasting crisis.

The diagnosis is usually confirmed by the specific pattern of adrenal steroids; elevated pregnenolone, 17-hydroxy-prenenolone, dehydroepiandosterone and renin. (Subramanian *et al.,* 2010; Lachance *et al.,* 1990). We report here on our experience with patients diagnosed with 3β-hydroxysteroid dehydrogenase deficiency congenital adrenal hyperplasia over twenty-five years (January 1990 and December 2014).

Patients and Methods

One hundred and three patients were diagnosed to have congenital adrenal hyperplasia (CAH) in the period under review (January 1990 to December 2014). Eight patients were excluded from the study as they were from different

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nationalities. Of these, 4 (4.2%) patients were diagnosed withhormonally 3-beta-hydroxysteroid dehydrogenase deficiency and constituted the subjects for the study. The diagnosis of 3-beta-hydroxysteroid dehydrogenase deficiency (HSD3β2) congenital adrenal hyperplasia was based on increased ratio of dehydroandrosterone (DHEA) and adrostenedione with low androstenedione, therefore, in a clinically suspected individual. A salt wasting state was suspected by hyponatremia, hyperkalemia and natriuresis and confirmed by elevated serum concentration of renin activity with low or normal serum aldosterone concentration. Data were retrospectively reviewed and included age, sex, family history, clinical presentation and important radiological chromosomal and biochemical investigations.

RESULTS

Four (4.2%) patients among the 95 patients with congenital adrenal hyperplasia (CAH) were proved to have 3-beta-hydroxysteroid dehydrogenase deficiency. They were from two families. Three were siblings. Two brothers and one sister. Tables 1 and 2 show the clinical and biochemical characteristics of the patients. All male patients presented in the neonatal period with ambiguous genitalia, while one female patient presented at six months of age with salt-wasting. They were followed and maintained normal electrolytes on hydrocortisone 10-15 mg/m^2/day and fludrocortisones 0.1-0.2 mg/kg. They had surgical repair, of the external genitalia at 1-4 years and achieved normal puberty with normal development of secondary sexual characteristics.

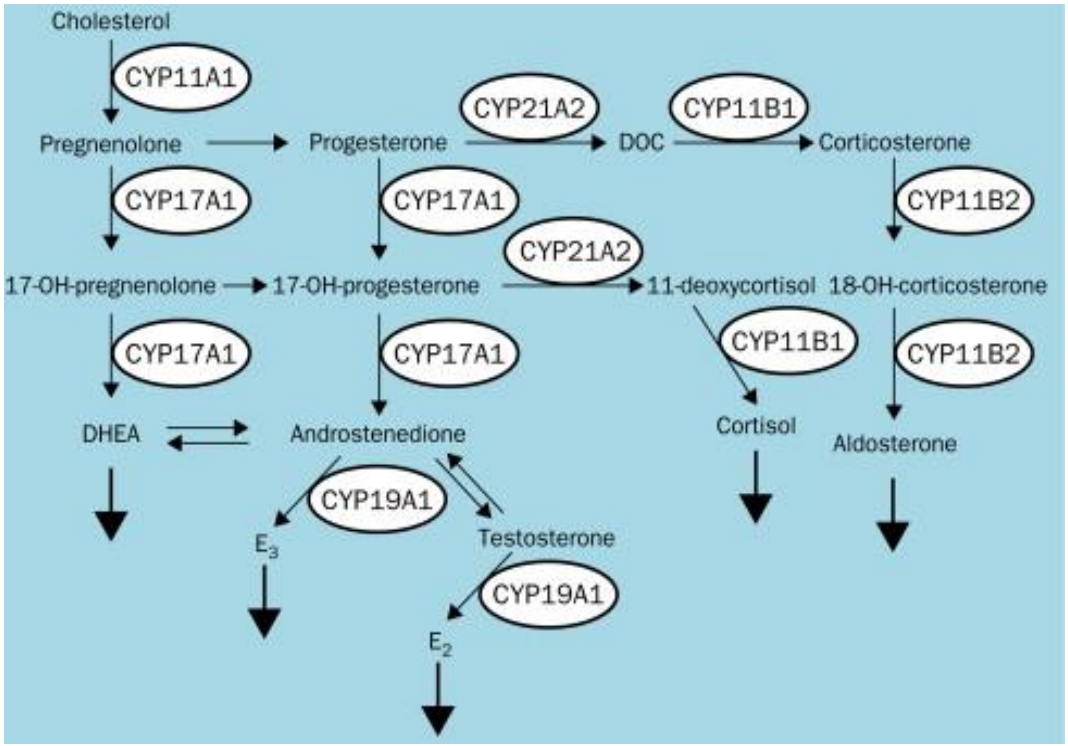

Figure 1. Simplified scheme of the adrenal steroidogenesis. Note that 3-beta-hydroxysteroid dehydrogenase (3βHSD) is required for the synthesis of all the three groups of adrenal steroids, (mineralcorticosteroids, glucocorticoids and sex steroid

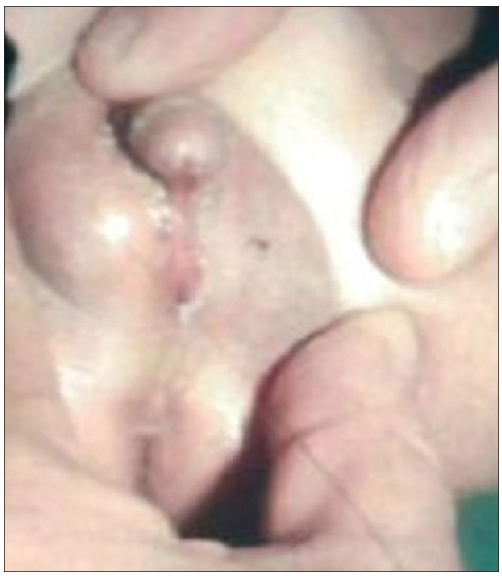

Figure 2. A patient with 46 XY disorder of sex development who proved to have 3-β-hydroxysteroid dehydrogenase deficiency congenital adrenal hyperplasia. Note the pigmented short curved phallus, central urogenital slit and separated labioscrotal testis

Table 1. Clinical characteristics in 4 patients with CAH due to (3βHSD)

Patients	Family	Family History	Clinical Presentation	Puberty
1	1	+ve family history (1st degree) Male sibling	Newborn ambiguous genitalia + salt-wasting	12 years
2		Female sibling 2	6 month, salt-wasting	11 years
3		Male sibling 3	Newborn ambiguous genitalia + salt-wasting	12 years
4	2	-ve family history (1st degree)	Newborn ambiguous genitalia + salt-wasting	11 years

Table 2. The biochemical profile, mean (range), in 4 patients with CAH due to 3-β hydroxysteroid dehydrogenase deficiency

Normal range	ACTH 5-18 Pmol/L	Cortisol 150-685 nmol/L	17-hydroxyprogesterone 0.6-4.2 nmol/L	DHEA 4-10 nmol	Androstenedione 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)

ACTH – Adrenocorticotropin Hormone
DHEA – Dehydroepiandosterone
*All patients were salt-waster with low to normal serum aldosterone concentration and high serum renin activity concentration.

DISCUSSION

3-β-hydroxysteroid dehydrogenase Type II deficient congenital adrenal hyperplasia (3-β HSD CAH) is an uncommon form of CAH resulting from mutation in the genes for one of the key enzymes in cortisol synthesis by the adrenal gland, 3-beta-hydroxysteroid dehydrogenase (3-β HSD) type II. As a result, higher levels of 17-OH-pregnenolone appear in the blood with adrenotrophic hormone (ACTH) challenge, which stimulates adrenal corticosteroid synthesis. There is a wide spectrum of clinical presentations of 3-β-HSD CAH, from mild to severe forms. The uncommon severe form results from complete loss of enzymatic activity and manifests itself in infancy as salt-wasting due to the loss of mineralcorticosteroids and ambiguous genitalia. Milder forms resulting from incomplete loss of 3-β HSD type II function do not present with adrenal crisis, but can still produce virilization of genetically female infants and under virilization of genetically male infants. As a result this form of primary hypoaldosteronism is the only form of CAH that can cause ambiguous genitalia in both genetic sexes.[1-3]Like the other forms of CAH, suspicion of 3-β HSD HSD is usually raised by the appearance of the genitalia at birth or by the development of a salt-wasting crisis in the first month of life. The diagnosis is usually confirmed by the distinctive pattern of adrenal steroids; elevated pregnenolone, 17 hydroxypregnenolone, Dehydroepiandrosterone (DHEA), and renin activity. The disease is caused by mutation in the HSD3β2 gene located on chromosome (p13). (Pang, 2001; Simard *et al.,* 2002; Stewart, 2008; Zachmann, 1996; Krone *et al.,* 2009; Simard *et al.,* 2005; Subramanian *et al.,* 2010; Lachance *et al.,* 1990). The hormonal criteria of HSD3β2 deficiency have been revised by Lutfallah et al which have more accurate prediction of HSD3β2 deficiency. (Lutfallah *et al.,* 2002). Our patients had neonatal ambiguous genitalia and salt-wasting secondary to HSD3β2 deficiency. However, at puberty, they had normal development of the secondary sex characters with an adequate testosterone and oestrogen levels. This is similar to the report of Bin Abbas et al. (Bin-Abbas *et al.,* 2004) from Saudi Arabia. It is believed that HSD3β1 activity, which is responsible for the extra-adrenal and gonadal conversion of △5-hydroxysteroid precursors into the corresponding △4-ketosteroid. The peripheral HSD3β activity could explain why some patients with HSD3β2 deficiency will have normal puberty. In conclusion, although 3 beta-hydroxysteroid dehydrogenase deficiency congenital adrenal hyperplasia is rare, it should be considered in 46XY individual presenting with ambiguous genitalia with or without salt-wasting, as well as normal looking females with salt-wasting.

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REFERENCES

Bin-Abbas, B. S., Al Sakati, N. A. and Al Ashwal, A. A. 2004. Congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase type II deficiency in 4 Saudi children. Long-term follow-up. *Saudi Med. J.,* 25(9): 1293-1295.

Krone, N. and Arlt, W. 2009. Genetics of congenital adrenal hyperplasia. *Best Pract. Res. Clin. Endocrinol. Med* 23(2):181-192.

Lachance, Y., Luu-The, V., Labrie, C., Simard, J., Dumont, M., de Launoit, Y., Guerin, S., Leblanc, G. and Labrie, F. 1990. Characterization of human 3-Beta-hydroxysteroid dehydrogenase / delta 5 – delta 4- isomerase gene and its expression in mammalian cells. *H. Biol. Chem.,* 265(33):20469-75.

Lutfallah, C., Wang, W., Mason, J. I., Chang, Y. T., Haider, A., Rich, B., *et al.* 2004. Newly proposed hormonal criteria via genotype proof for type 11 3-β-hydroxysteroid dehydrogenase deficiency. *J. Clin. Endocrinol.,* 87;2611-2622.

Pang, S. 2001. Congenital adrenal hyperplasia owing to 3-beta-hydroxysteroid dehydrogenase deficiency. *Endocrinol. Metab. Clin. North Am.,* 30; 81-99.

Simard, J., Moisan, A. M. and Morel, Y. 2002. Congenital adrenal hyperplasia due to 3-beta-hydroxysteroid dehydrogenase / Delta (5) – Delta (4) Isomerase deficiency. Semin *Reprod, Med.,* 20(3):255-76.

Simard, J., Ricketts, M.L., Gingras, S., Soucy, P., Feltus, F.A. and Meiner, M. H. 2005. Molecular biology of 3-beta-hydroxysteroid dehydrogenase / delta 5 – delta 4 isomerase gene family. *Endocr. Res.,* 26(4):525-82.

Stewart, P. 2008. Congenital Adrenal Hyperplasia In: Williams Textbook of Endocrinology Chapter 14, Section IV 11th Edition. *Elsevier,* p485-494.

Subramanian, P., Clayton, P. T., Portmann, B. C., Mieli-Vergani, G., Hadzic, N. 2010. Variable clinical spectrum of the most common inborn error of bile acid metabolism 3-beta-hydroxy-delta 5 – C27 steroid dehydrogenase deficiency. *J. Pediatr. Gastroenterol. Nutr.,* 50(1):61-6.

Zachmann, M. 1996. Congenital adrenal hyperplasia due to 3-β-hydroxysteroid dehydrogenase deficiency. *Eur. J. Pediatr.,* 155(4):259-261.

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