11β hydroxylase deficiency in children: the first case reported from Bahrain

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ABSTRACT

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder commonly caused by 21-hydroxylase deficiency. It accounts for 90-95% of cases. The second most common cause is 11β hydroxylase deficiency. We report on the first case of 11β hydroxylase deficiency in Bahrain with a review of the literature.

Keywords: 11β hydroxylase deficiency; congenital adrenal hyperplasia (CAH)

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by a defect in any of the five enzymatic steps required to synthesize cortisol from cholesterol. 21-hydroxylase deficiency accounts for 90-95% of cases with CAH, and is considered the most common cause.[1] The second most common cause of CAH is 11β hydroxylase deficiency which accounts for 5-8% of cases.[2]

A high prevalence of 11β hydroxylase deficiency has been reported in different ethnic groups in Saudi Arabia (25.6%),[3] while in Turkey a lower incidence has been reported (11.5%).[4] In Moroccan Jews in Israel the disease incidence is 1 in 5,000 live births.[5] Subsequent studies in the Jewish populations have shown that this type of congenital adrenal hyperplasia occurs less frequently[6] but it remains more common than in other ethnic groups. Great variability in clinical expression has been reported.[5, 7, 8] There are two types of 11β hydroxylase deficiency, classical and non-classical. The classical form is associated with ambiguous genitalia in genetically female infants, while in males it presents at 2-4 years of age with signs and symptoms of androgen excess, including increased growth velocity, advanced bone age, pubic hair, increased penile length, and aggressive behavior. The non-classical form presents in girls or women with symptoms of androgen excess, such as hirsutism, cystic acne, or oligomenorrhea.

To our knowledge this is the first case to be reported in Bahrain with 11β hydroxylase being the cause of CAH in children.

THE CASE

A three-and-one-half-year-old Bahraini male presented at the age of 2 years and 6 months with an early development of pubic and axillary hair of 4 months' duration. This was associated with a rapid increase in height, bowing of both legs and darkly pigmented acne over the face. During this period the parents also noticed increased activity and physical aggressiveness. There was no history of abdominal pain or vomiting. The patient had no history of change in body odor. The pregnancy was uneventful and the mother was not on any medication. The patient was born at term with normal genitalia with no history of neonatal hypoglycemia and no history of electrolyte imbalance. Medication history was not significant. The parents are cousins with no family history of early pubertal development, neonatal death or ambiguous genitalia.

Examination revealed hyper-pigmented acne over the cheeks, forehead, nose, skin and gums (See Figure 1). There were no dysmorphic features. Height was 102 cm (>98th centile), weight was 16.6 kg (>90th centile) and blood pressure was 173/84 mmHg. His genital examination revealed pigmented skin, pubic hair stage II, axillary hair stage II, penile length 9 cm (>98th centile for age) with significant increase in width, the testicular volume was 2ml (normal prepubertal testicular volume is <4ml). His systemic examination was unremarkable.

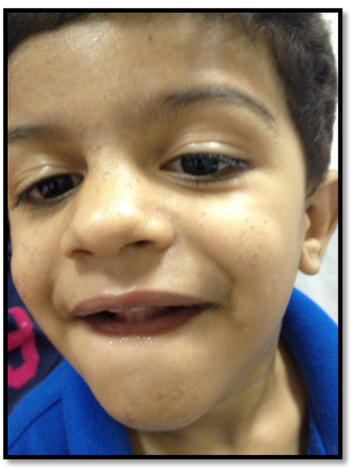

Figure 1. Hyperpigmentation and acne in patient with 11β hydroxylase deficiency

At this stage the patient was diagnosed to have precocious puberty most likely secondary to congenital adrenal hyperplasia. The patient was investigated and found to have an advanced bone age of six years at the chronological age of two years and seven months. Abdominal ultrasound showed normal adrenals. MRI of the brain was normal. Results of blood test showed an elevated ACTH, 11-deoxycortisol, deoxycorticosterone, testosterone, DHEAS and 17-OHP, with suboptimal response to Synacthen stimulation test.

This led to the diagnosis of 11β hydroxylase deficiency. The results of blood investigation are shown in Table 1. Synacthen test results are shown in Figure 2.

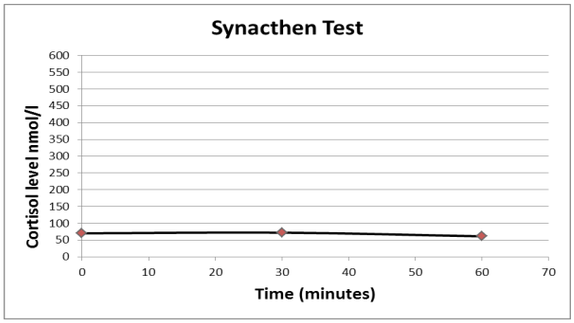

Figure 2. Synacthen stimulation test showing suboptimal response at 30 and 60 minutes (normal response cortisol level >550nmol/l)

Laboratory test	Normal value	At presentation	After treatment
ACTH* (pmol/L)	0-10	156.3	36.4
LH† (IU/L)	0.0-0.9	0.5	-
FSH‡ (IU/L)	0.2-3.8	<0.1	-
11-Deoxycortisol (micrograms/ml)	0.02-0.025	33.2	-
Deoxycorticosterone (ng/100 ml)	2-34	1170	677
Testosterone (nmol/L)	<3.5	5.6	1.7
S. Calcium (mmol/l)	2.12-2.65	2.27	-
S. Sodium (mmol/L)	137-148	137	140
S. Potassium (mmol/L)	3.9-5	4.2	5.1
S. Chloride (mmol/L)	100-107	103	104
S. Bicarbonate (mmol/L)	24-30	20	19
FBG§ (mmol/l)	3.6-5.6	4.7	-
DHEAS** (umol/L)	0.27-1.63	5.3	4.1
17- OHP†† (mmol/L)	2.12-7.6	>30.3	15.9
PRA‡‡ (ng/L)	0.2-2.8	0.3	1.6
Aldosterone (nmol/L)	0.02-0.42	0.067	-
TSH§§ (uIU/ml)	5	(0.025-5)	-
T4*** (pmol/L)	15.4	(10-24)	-

*Adrenocorticotrophic hormone, Luteinizing hormone, ‡Follicle stimulating hormone, §Fasting blood glucose level, **Dehydroepiandrosterone sulfate, ††17-Hydroxyprogesterone, ‡‡Plasma renin activity, §§Thyroid stimulating hormone, ***Thyroxine.

Table 1. Results of laboratory tests done at presentation

At this stage the patient was treated with oral hydrocortisone at a dose of 19 mg per m^2 per day. The patient was evaluated clinically after one week of starting treatment and found to have normal blood pressure. Repeated blood test four weeks after starting treatment showed suppression of deoxycorticsosterone and 17-OHP with normalization of testosterone. In addition, there was improvement in his behavior and non-progression of puberty.

DISCUSSION

Deficiency of 11β hydroxylase is by far the second most common cause of CAH, corresponding to 5-8% of all cases in most ethnic groups.[2] It occurs in 1 in 100,000 live births.[9, 10] However, it is more common in some populations, like in Saudia Arabia where it is estimated that there are up to 25.6% of cases diagnosed with CAH.[3] The clinical features of 11β hydroxylase deficiency consist of virilization, hypertension and hypokalemia. Up to 35% of cases are normotensive and normokalemic.[11, 12]

Genetic:

Two 11β hydroxylase genes have been identified, located at chromosome number 8q.[12, 14] The first, termed CYP11B1, encodes for the P450c11B1 enzyme, and is located in the zona fasciculata. CYP11B1 is involved in the production of cortisol. The second, CYP11B2, encodes for the P450c11B2 enzyme, which predominantly synthesizes aldosterone in the zona glomerulosa.[12, 14, 22]

Prenatal diagnosis and treatment:

Due to recent advances in the mutation identification in CYP11B1 and CYP11B2, molecular prenatal diagnosis is possible through DNA analysis that requires chorionic villus sampling in the ninth to eleventh week of gestation, or sampling of amniotic fluid cells obtained by amniocentesis in the second trimester.[15-21] This is shown to be safe with no major side effects to the mother or the fetus. Administration of dexamethasone to pregnant mothers is shown to be effective as prenatal treatment if done before 9 weeks gestation.[15-21]

Pathophysiology:

11β hydroxylase enzyme is responsible for the conversion of 11-deoxycorticosterone (DOC) to corticosterone and 11-deoxycortisol to cortisol. The reduction in the cortisol leads to overproduction of adrenocorticotropin (ACTH), which in turn leads to overproduction of precursors proximal to the enzyme blockage, increasing the production of androgen. These non-11β-hydroxylated products include 11-deoxycortisol and DOC, plus upstream precursors such as 17α-hydroxyprogesterone (17-OHP) and D4-androstenedione (D4-A) which is the product of conversion of 17-OHP to D4. Similarly, our patient had an elevated ACTH, 11-deoxycortisol, deoxycorticsosterone, testosterone, DHEAS and 17-OHP.

In female infants with ambiguous genitalia elevations of serum 11-deoxycortisol and DOC indicate 11β-OHD. Tetrahydro-11-deoxycortisol (THS) and tetrahydrodeoxycorticosterone (THDOC), the principal metabolites of serum 11-deoxycortisol (S) and DOC, are significantly increased in the urine. Urinary 17-ketosteroids are elevated, reflecting the raised serum levels of adrenal androgens.

Due to excess fetal adrenal androgens, the affected female fetus will develop ambiguous genitalia (female pseudohermaphroditism) in all cases, while the internal genital organs are normal female.

It is not uncommon to misassign an 11β-OHD-affected female as male at birth.[3, 5] This excess of fetal adrenal androgens overproduction results in premature and inappropriate secondary sexual characteristics in both boys and girls, which may include progressive penile and clitoral enlargement, appearance of axillary pubic and facial hair, acne, deepening of voice, and rapid skeletal growth. If left untreated it may lead to early epiphyseal maturation resulting in short adult stature.

Additionally, patients may have premature development of sexual and body hair (premature adrenarche) and acne. Androgens may affect the hypothalamic-pituitary-gonadal axis, leading to amenorrhea or oligomenorrhea in females and true precocious puberty or, conversely, poor spermatogenesis in males.[5, 23]

In our patient, the child presented at the age of two years and six months with premature development of pubic and axillary hair, acne, accelerated growth, skin hyperpigmentation and large phallus.

High level of DOC and failure of aldosterone production cause salt retention and hypertension.

Approximately two-thirds of patients with the severe "classic" form of 11β hydroxylase deficiency have high blood pressure,[5] often beginning within the first few years of life, though it may present as early as three months of life. Although the hypertension is usually of mild to moderate severity, left ventricular hypertrophy, retinopathy, or both have been observed in up to one-third of patients, and deaths from cerebrovascular accidents have been reported.[3, 5, 23] Our patient had hypertension at presentation which normalized after starting hydrocortisone. In addition, hypertension correlates variably with biochemical values, and clinical signs of mineralocorticoid excess and the degree of virilization are not well correlated. Some severely virilized females are normotensive, whereas mildly virilized patients might experience severe hypertension leading to fatal vascular accidents.[3, 5, 23]

Other signs of mineralocorticoid excess such as hypokalemia and muscle weakness or cramping occur in a minority of patients and are not well correlated with blood pressure. Plasma renin activity is usually suppressed in older children, and aldosterone levels are consequently low even though the ability to synthesize aldosterone is actually unimpaired.[23] Aldosterone production is low secondary to low serum potassium and low plasma renin.

A mild non-classical form of 11β-OHD CAH has been detected among normotensive children with mild virilization or precocious pubarche[25] and in an adult female with primary infertility and mild hirsutism.[24] This mild form seems to be rare compared to non-classical 21OHD CAH which is common.

CONCLUSION

11β hydroxylase deficiency is the second most common cause of CAH in Bahrain. It is very rare and to our knowledge this is the first case to be reported. Clinical presentations are variable and may consist of virilization, hypertension and hypokalemia. It is an autosomal recessive condition. Prenatal diagnosis should be considered in mothers with previously affected children.

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