Case Report

An interesting case of masculine voice in a girl: A case report of 11 beta hydroxylase deficiency

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ABSTRACT

A 7-year-old girl presented to our outpatient department (OPD) with masculine voice, hyperpigmentation of skin, and genital ambiguity. On clinical examination, she had hypertension, hyperpigmentation of skin, pubarche, clitoromegaly, and low-pitched voice. Karyotype was 46 XX and ultrasound showed bilateral enlarged adrenals, uterus, and ovaries. Hormonal workup revealed elevated levels of 17-α-hydroxyprogesterone, testosterone, 11-deoxycortisol, and deoxycorticosterone. Due to the presence of hypertension, genital ambiguity and elevated 11-deoxycortisol, a diagnosis of 11-β-hydroxylase deficiency variant of Congenital Adrenal Hyperplasia was made. The child was started on hydrocortisone and amlodipine after which her symptoms such as hyperpigmentation improved.

Key words: Ambiguous genitalia, Hypertension, Voice change

11-β-Hydroxylase deficiency accounts for 7% of all cases of congenital adrenal hyperplasia (CAH), with an incidence of 1 in 100,000 live births [1]. It occurs due to mutation in the 11-β-hydroxylase (CYP11B1) gene that results in loss of enzyme activity and a block in the conversion of 11-deoxycortisol to cortisol, leading to cortisol deficiency. The loss of negative feedback on adrenocorticotrophic hormone (ACTH) secretion leads to enhanced ACTH mediated adrenal androgen synthesis. Clinical features in a female baby, therefore, consist of virilization of the external genitalia and genital ambiguity. Milder cases can manifest later in childhood or in young adults. The principal differentiating feature from 21-hydroxylase deficiency is hypertension, which is thought to be secondary to the mineralocorticoid effect of excess deoxycorticosterone (DOC).

CASE REPORT

We report a 7-year-old girl, who was brought by her mother, with the chief complaint of change in the girl's voice to adult male voice. The child was a product of a non-consanguineous marriage and the only child to her parents and there was no history of miscarriages or intrauterine deaths. She was born of normal vaginal delivery at term gestation. There was no history of neonatal seizures, hypoglycemia, sepsis, or salt wasting crisis. Developmental history was normal. Her mother noticed change in her voice that progressed to a male voice, over a period of 2 months. On probing, mother revealed the presence of phallus like structure noticed in infancy, which progressively increased in its size. There was history of increased skin pigmentation from infancy. The girl developed axillary and pubic hair at an age of 4 years. There was no history of weight loss, loss of appetite, pain abdomen, or vomiting.

The general physical examination revealed hyperpigmentation over face, palmar creases, knuckles, and gums. Her skin was greasy with acne (Fig. 1). The girl had a low-pitched voice similar to that of a pubertal boy. Her pulse rate was 93/min, blood pressure (BP) was 130/80 mm Hg. Hypertension was confirmed after checking blood pressure three times on different days. Her height was 127 cm (75th–90th centile), weight was 23 kg (50th centile), and sexual maturity rating was B1 A2 P3. External genital examination revealed clitoromegaly (2.6 cm in length), single urogenital orifice and partially fused labioscrotal swellings (Prader's stage-3). Other systems were found normal on examination.

The base line investigations such as complete blood count, serum creatinine, electrolytes, and blood glucose were normal. Bone age was advanced (11 years). Ultrasound abdomen revealed bilateral prominent suprarenal glands measuring 10 mm × 7.9 mm on the right side and 10 mm × 9 mm on the left side. Karyotype was 46 XX. Basal 17-α-hydroxyprogesterone level was 14.6 ng/ml and post Synacthen stimulation, the

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value was 34.23 ng/dl. Testosterone was 4.42 ng/ml. In view of hypertension and virilization, 11-β-hydroxylase deficiency was suspected. Serum 11-deoxycortisol levels and 11-DOC levels were obtained which were 1019 ng/dl and 4222 ng/dl, respectively. Significant elevations of 11-deoxycortisol and DOC confirmed the diagnosis of 11-β-hydroxylase deficiency in the child.

She was started on hydrocortisone at a dose of 15 mg/m^2/day and amlodipine 2.5 mg once daily (0.1 mg/kg). We are planning further follow up based on growth velocity, weight, clitororal length regression, control of BP, 17-α-hydroxy progesterone levels, and testosterone levels every 4th monthly. Bone age assessment has been planned after 1 year. The child is under follow-up with well controlled BP, decrease in skin pigmentation, arrest of puberty, and testosterone levels came to 10 ng/ml.

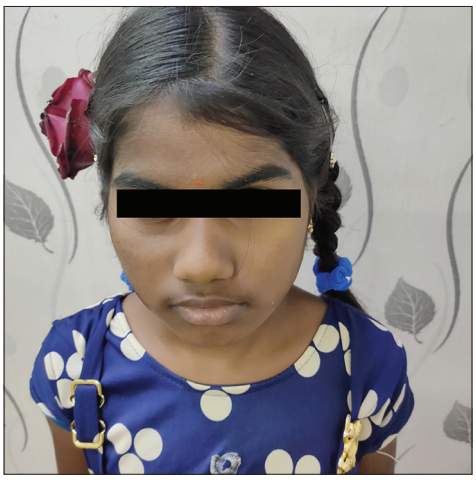

Figure 1: Image of the child

DISCUSSION

The most common adrenal steroidogenic defects are deficiencies of enzymes involved in cortisol production, collectively referred to as CAH. They are transmitted as autosomal recessive traits. Impaired cortisol synthesis leads to chronic elevation of ACTH due to the loss of the negative feedback inhibition of the hypothalamic-pituitary-adrenal axis. Excess ACTH results in adrenal hyperplasia and androgen excess. Specific types of CAH are identified by the various abnormal patterns of glucocorticoid (GC), mineralocorticoid, and sex steroid secretion, and by associated clinical manifestations, including genital ambiguity, disturbances in sodium homeostasis and BP regulation, and the postnatal consequences of sex steroid imbalance affecting somatic growth and fertility.

11-β-hydroxylase deficiency, second most common form of CAH, was first described by Eberlein and Bongiovanni in 1955 [2,3]. 11-deoxysteroids (11-deoxycortisol and 11-DOC) accumulate when conversion of 11-deoxycortisol to cortisol is reduced [4]. Hyperandrogenism results from shunting of cortisol precursors similar to that of 21-hydroxylase deficiency. Females with 11-β-hydroxylase deficiency exhibit a higher degree of virilization than those with 21-hydroxylase deficiency. The principal difference from 21-hydroxylase deficiency is hypertension, which is secondary to the mineralocorticoid effect of excess DOC. However, there is a poor correlation between DOC secretion and the presence of hypertension, and unexplained salt wasting has been reported in few patients during early life [5]. Elevated serum 11-deoxycortisol (compound S) and DOC are diagnostic of 11-β-hydroxylase deficiency [6].

The mainstay of therapy is GCs which causes suppression of ACTH secretion which, in turn, suppresses adrenal DOC and androgen secretion. In general, higher suppressive doses of GCs are needed to be compared with 21-hydroxylase deficiency, and add-on antihypertensive therapy may be necessary in some cases. During childhood, the preferred GC is hydrocortisone because its short half-life minimizes the adverse side effects typical of longer-acting, more potent GCs; especially, growth suppression [7]. Amlodipine provides effective BP control without significant adverse effects in children with hypertension [8].

The 11-β-hydroxylase deficiency has varied presentations. So far, few cases have been reported, worldwide with hypertension in childhood, precocious puberty in boys, genital ambiguity in girls, steroid responsive hypertension, Addisonian crisis, testicular adrenal rest tumor, and hypokalemic weakness. Our patient presented with genital ambiguity, low pitched masculine voice, hyperpigmentation, and hypertension. The virilization in our case is very severe to the extent of change in the pitch of the voice, which is a rare clinical presentation in CAH.

CONCLUSION

Although included in neonatal screening programs in various countries, the diagnosis of CAH is missed because of lack of awareness and financial constraints in many developing countries. 11-β-hydroxylase deficiency sub-type has the additional feature of hypertension, along with genital ambiguity. Early diagnosis and treatment can help to prevent many complications including adrenal crisis, precocious puberty, and growth failure. Our case presented late; still, clinical, and biochemical parameters improved after treatment.

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