Case Report

The Bite that Rewrote the Past and Changed the Future: A Case Report on Congenital Adrenal Hyperplasia

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ABSTRACT

15-year-old phenotypic male who presented with weakness that was initially attributed to centipede bite. Physical examination and hormone profile suggested 11-beta hydroxylase deficiency. Weakness improved with potassium supplementation. Hypertension was managed by using spironolactone, prednisolone and amlodipine, with advice of lifelong prednisolone. Hysterectomy was done and it was advised to rear the individual as male.
Introduction

Congenital Adrenal Hyperplasia (CAH) disorder of cortisol synthesis, characterised clinically by signs of androgen excess that is, masculinization of the female external genitalia. In some individuals, signs and symptoms of aldosterone deficiency such as hyponatremia, hyperkalemia and hypovolemia that could be life threatening within few weeks of life are observed. A small percentage of these subpopulation develop hypertension that responds to glucocorticoid therapy have been found to have 11-ß hydroxylase deficiency.¹

Case Report

15 year 3 months old adolescent, first issue to non consanguineous parents, presented with weakness of both legs of one day duration following a centipede bite within 24 hours of bite. He had episodic leg pains that exaggerated on walking long distances and relieved on rest for 6 months preceding the weakness. Pulse rate was 48 beats/min, regular, Blood Pressure - 134/79 mmHg (>95th percentile for the age), respiratory rate -12 breaths/min. height-142.3 cm. Local swelling, redness and tenderness were present at the bite (left lower limb). There was a generalized dark complexion, muscular build with gynaecomastia, androgenic pattern of body hair distribution over the chest and legs (Figure 2A), empty scrotum, Tanner stage 4 and stretched penile length (phallus): 9.5cm/girth 2.5cm (Figure 2B). There was hypotonia and decreased power, with lower limbs being more affected. Deep tendon reflexes were sluggish with babinsky reflex being flexor response. Serum potassium was 1.8 mEq/L. Arterial gas analysis was suggestive of metabolic alkalosis with base excess of 11 mEq/L. Bone age was accelerated by 1 year 9 months (>17 years). Renal arteries and parenchyma were normal on renal ultrasound and Doppler evaluation.

Both supra renal glands were bulky with each measuring 2cms. Uterus was normal in size and echo texture (adult type) and endometrium was 6mm in thickness. Plasma renin assay was <= 0.02ng/ml/hr. Base line concentrations of dehydroepiandrosterone sulfate (DHEAS) were elevated (726 µgm/dL). On adrenocorticotropic hormone (ACTH) stimulation test, 17 α (OH) progesterone was 15.7ng/ml, 17.5ng/ml, 17.29ng/ml at 0min, 60min and 120min respectively. Cortisol was 5.47µg/dl, 5.12µg/dl, 5.38µg/dl at 0min, 30min, and 60min respectively.

Failure of cortisol to rise in ACTH stimulation test confirmed diagnosis of CAH. On leuprolide stimulation test, base line, 60min and 120min following administration values were 5.51 U/L, 52.92 and 115.67U/L for LH, 3.82 IU/L, 10.89 IU/L and 22.29 IU/L for FSH. Base line and 60min post administration values were 38 pg/mL and 132 38 pg/mL respectively for estradiol (E2). Testosterone levels were 217.25ng/dl and 269.75ng/dl at 00hr and 24 hrs respectively. On CT pelvis, uterus and cervix were seen and ovaries looked normal. Ovaries were measured about 2.8cms.. Karyotyping revealed 46XX chromosomes. Finally, diagnosis was CAH-Non Salt losing type with pseudo precocious puberty with hypertension due to 11 beta hydroxylase deficiency.

The child was managed with intravenous potassium at 0.15mEq/kg/hr monitoring electrocardiogram and serum potassium levels followed by oral administration of potassium chloride, amlodipine at 0.3mg/kg/day, spironolactone 25mg twice a day. Prednisolone was started at 0.1mg/kg/day with an advice of lifelong treatment. His muscle weakness improved within 24hours. Blood pressure and serum potassium concentration returned to normal levels with treatment The family was counselled about the condition and
importance of regular monitoring and medication. Hysterectomy was done subsequently to prevent hormone induced excess uterine bleeding. Parents were counselled to rear the individual as a male and importance of regular follow up.

Discussion

CAH is a family of inherited disorders with defects in one of the enzymes involved in cortisol synthesis from cholesterol. Result of decreased cortisol secretion is removal of negative feedback on ACTH secretion leading to hyperplasia of adrenal cortex. Prevalence of CAH is 1/1, 00,000 live births with 21-hydroxylase deficiency and 11-β-hydroxylase deficiency accounting for 90% and 5-8% respectively.² Both 21α hydroxylase and 11β hydroxylase deficiency result in accumulation of cortisol precursors that are converted to androgens. End result is in utero virilisation of female fetus.

Biochemistry of adrenal steroid biosynthesis

Cortisol is synthesized from cholesterol in the zona fasciculata of the supra renal gland. Detailed pathway of hormone synthesis has been shown in flow chart 1. Conversion of 11-deoxycortisol to cortisol involves 11-β-hydroxylase. This enzyme has two isoforms: CYP11B1 and CYP11B2. These enzymes are located on the inner surface of the mitochondrial membrane. The isoenzyme CYP11B1 is responsible for this process.³ Accumulation of progesterone, 17α-OH-progesterone and their precursors are converted in to androgens. Androgens results in virilisation of the external genitalia in females or early puberty in males. (See figure 1.)

The first cases of this isoenzyme deficiency were reported in the 1950’s.⁴,⁵ The reduced production of glucocorticoids removes negative feedback to hypothalamo-pituitary-adrenal axis and thereby increasing ACTH secretion. ACTH stimulation of adrenal cortex sets in vicious cycle of stimulation and overproduction of precursors, worsening the clinical scenario.

Hypertension is seen in two thirds of the affected persons.⁶ Hypertension is mild to moderate in the majority of cases, with end organ damage in the one third. Hypertension induced stroke, sometimes culminates in death. Muscle weakness is caused by hypokalemia, result of mineralocorticoid excess. Hypokalemia and hypertension may not correlate. Excess of deoxycorticosterone in serum could be culprit for hypertension.⁷ Occasionally, some patients can present as salt losers with hypokalemia, hyponatremia and hypovolemia.

High DHEA levels in these patients could explain virilisation. Starting from the sixth week of gestation, Virilisation is mild to severe with some degree is being evident at birth. Severe clitoromegaly may be mistaken for a penis.⁶,⁸,⁹ In extreme cases, the labia may be fused presenting no differences from a masculine scrotum. But unlike the external genitalia, ovaries, ovarian tubes, uterus and cervix are present. Other signs of androgen overproduction include rapid somatic growth during childhood and early epiphyseal closure. This condition is to be suspected when serum ACTH levels are three or more times higher than the 95th percentile predicted for the patient’s age. The specific 11-β-hydroxylase deficiency is considered when high basal levels of DHEA and/or 11-deoxy cortisol or by the increased 24 hour urinary tetra-hydro metabolites.

There are only two reports on heterozygotes for 11β-hydroxylase
deficiency. Pang et al. reported that hormonal measurements, including ACTH stimulated serum levels of 11-deoxycorticosterone and 11-deoxycortisol are not useful for detecting heterozygotes for 11β-hydroxylase deficiency. R448H mutation in exon 8 of CYP11B1 gene has been detected commonly in 11β-hydroxylase deficiency among 3 families Jews studied in one report.

Restoring cortisol deficit, glucocorticoid therapy imposes negative feedback on ACTH. Growth, bone age, pseudo precocious puberty, cortisol and androstenedione concentrations are monitored. Hypertension is managed by using aldosterone antagonist like Spirinolactone that corrects hypokalemia as well. Laparoscopic bilateral adrenalectomy is a safe and effective procedure in patients with resistant hypertension, persistent and refractory hypokalaemia and steroid-unresponsive androgen excess. The association of myelolipoma with 11β-hydroxylase deficiency is also reported and they are looked for. Ambiguous genitalia are corrected surgically by removing uterus, fallopian tubes and ovaries.

Antenatal diagnosis and treatment

As labial fusion occurs before the eighth week of gestation, women at risk for having a fetus with classical CAH are treated immediately with dexamethasone (20μg/kg/day in three divided doses), blind to the status of the foetus when the pregnancy is confirmed. DNA analysis and karyotyping is done by taking Chorionic villus sampling at 10 weeks or amniocentesis at 14 weeks gestation. The dexamethasone therapy is discontinued in case of male karyotype or heterozygous state. Thus, only affected female foetuses are treated until term and the others are treated only until the sex or unaffected diagnosis has been established. Diagnosis is confirmed postnatally by clinical evaluation, measurement of serum deoxycorticosterone (DOC) and 11-deoxycortisol and DNA analysis.

Conclusion

CAH is a complex condition to deal with. A holistic approach, a quick and complete investigation profile to come to an early gender assignment, treatment of hypertension, electrolyte disturbance and long term psychological support to the patient and their families will improve the way we manage CAH.

References

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**Figure 1.** Flow chart showing biochemical pathway of hormone synthesis.
Figure 2A. 15-year-old phenotypic male with short stature, gynaecomastia, hirsutism and ambiguous genitalia

Figure 2B. Showing enlarged phallus and empty scrotum