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CONGENITAL ADRENAL HYPERPLASIA: 11B-HYDROXYLASE DEFICIENCY AFFECTING BOTH SIBLINGS: A RARE CASE REPORT.

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ABSTRACT **BACKGROUND:** Congenital adrenal hyperplasia (CAH) is family of autosomal recessive disorder of steroid biosynthesis. The incidence of 11β-hydroxylase deficiency is 1 in 1,00,000 to 2,00,000 newborns and less than 5% of CAH cases. Hypertension is present in two-third of the such cases at time of diagnosis [2]. As CAH due to 11β hydroxylase deficiency is very rare and hence we would like to publish this case affecting 2 siblings, who presented with hypertension and features of androgen excess. **CLINICAL DESCRIPTION:** Two brothers of same family aged 5 year 4 months and 2 year 5 months, presented with features suggestive of precocious puberty and tall for their age. On examination both siblings had features of androgen excess, hypertension and advanced SMR Staging for their age. Also, elder brother had enlarged right testicle probably suggestive of testicular adrenal rest tumors (TARTs). Systemic examination was normal in both. After ruling out other causes of precocious puberty and hypertension, CAH due 11β-hydroxylase deficiency was suspected. **MANAGEMENT:** Increased levels of 11-deoxycortisol levels along with the clinical presentation confirmed the diagnosis of CAH due to 11β-hydroxylase deficiency. Both the children were started with oral hydrocortisone and antihypertensives. They are under follow up for regular monitoring of growth and hypertension and to assess need for GnRH (Gonadotropin Releasing Hormone) analogues. **CONCLUSION:** Though the most common cause of CAH is 21-hydroxylase deficiency, 11β-hydroxylase deficiency should be suspected when present with features of androgen excess along with hypertension. High index of suspicion is required for diagnosis and early initiation of treatment which helps in better outcome in terms of final height achieved and prevention of complications of long-standing hypertension.

KEYWORDS : Hypertension, precocious puberty, GnRH analogues, 11-deoxycortisol, TARTs

Congenital adrenal hyperplasia (CAH) is family of autosomal recessive disorder of steroid biosynthesis, which takes place in adrenal cortex of adrenal gland. Eberlein and Bongiovanni in 1956 were the first to propose a deficiency of 11β-hydroxylase enzyme based on plasma and urinary corticosteroid profile in a case of CAH with hypertension [2]. CAH can be caused by deficiency of any enzymes involved in the cortisol synthesis namely 21-hydroxylase, 11β-hydroxylase, 3β-hydroxysteroid or 17α-hydroxylase. Among these commonest being 21-hydroxylase deficiency which accounts for 90% of the cases. CAH due to 11β-hydroxylase deficiency accounts approximately 5% of cases. Two cytochrome P450 isoenzymes with 11-hydroxylase activity, catalysing the biosynthesis of cortisol and aldosterone, are present in the adrenal cortex [1]. CYP11B1, the gene encoding 11-hydroxylase (P450c11), is expressed in high levels in the zona fasciculata and is regulated by adrenocorticotropic hormone (ACTH) [1]. The substrate for P450c11 is 11-deoxycortisol. Mutations in CYP11B1 cause CAH due to 11-hydroxylase deficiency [1]. This disorder is characterised by androgen excess and hypertension [1]. Hypertension is present in two-third of such cases at the time of diagnosis [2]. Classical and nonclassical forms of 11β-hydroxylase deficiency can be distinguished [1]. 11β-hydroxylase deficiency is considered to occur in a classic form that is apparent at birth and a non-classic form that is present with signs of androgen excess during childhood, puberty, or adulthood [1]. The incidence of 11β-hydroxylase deficiency being 1 in 1,00,000 to 2,00,000 newborns and less than 5% of CAH cases, hence we would like to publish this rare case of siblings with CAH due to 11β-hydroxylase deficiency who presented with hypertension and features of androgen excess.

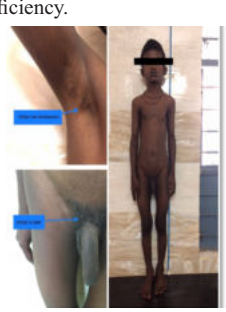
Clinical Description:

5years 4month old boy who was 1st issue of second-degree consanguineous marriage, brought by mother with complains of increased height as compared to children of same age group, and hoarseness of voice noticed by the mother for the last 2 years. There was no history of headache, blurring of vision, vomiting, convulsion, severe head trauma, intolerance to cold, weight gain. No history of previous hospitalisation. Child was developmentally normal for his age. There was no history suggestive of attainment of precocious puberty in either of the parents. On examination, height for age was >99th percentile according to IAP growth charts. Child had acne form eruptions on face, there was development of axillary and pubic hairs. Stretched penile length was 12 cm and corresponded to stage-IV SMR (Sexual Maturity Rating) [Fig. No 1]. Right testis was uniformly enlarged compare to left side. BP was more than 99th percentile consistently. Rest of the systemic examination was within normal limits.

As the child's younger brother also accompanied to hospital who is 2 years-5month old, we noticed that he also had acne form eruption on his face. On further evaluation and examination, it was surprised to notice that development of pubic hair in this child and genitals corresponding to stage-II SMR which was advanced for his age [Fig. No 2]. His blood pressure was between 90-95th percentile consistently. Height for age corresponded to 3rd and 50th percentile.

Both children were admitted and evaluated in terms of causes for precocious puberty and hypertension.

Child with clinical features of excess androgen secretion along with hypertension was evaluated and approached in line with precocious puberty and hypertension. Initially inherited causes of precocious puberty and hypertension was thought as both the siblings had similar presentation. To rule out central cause of precocious puberty, MRI brain was done which was normal. After ruling out other causes of precocious puberty and hypertension, CAH due to 11β-hydroxylase deficiency was thought as child presented with both features of excess androgen secretions and hypertension. 11-deoxycortisol levels were sent for both. The values were 218.61 ng/ml and 284.07 ng/mL in index case and younger sibling respectively which were abnormally high and hence confirms the diagnosis of CAH due to 11β-hydroxylase deficiency.



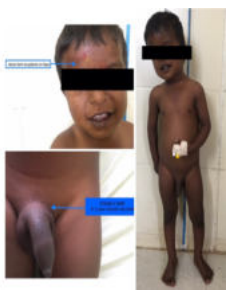


Figure 1: Clinical pictures highlighting features of excessive androgen secretion in 5 year 4 month old male child (elder child)

Figure 2: Clinical pictures showing features of excessive androgen secretion in 2 year 5month old male child (younger child

Management:
In elder child, initial routine blood investigations were normal. Bone age (BA) was between 12 to 18 years which is remarkably high compared to his chronologic age (CA) which indicated accelerated skeletal maturation (HA=BA>CA) [Fig. No 3]. Similarly, younger sibling was also evaluated individually. Bone age was 6 years (HA=BA>CA) [Fig. No 4]. 11-deoxycortisol levels were also increased in this child. While awaiting the results of 11-deoxycortisol levels, secondary causes of hypertension such renal and cardiac causes were ruled out by renal ultrasonography and echocardiography. USG Abdomen showed bilateral adrenal hyperplasia, right enlarged testicular volume, enlarged seminal vesicles. 2-D echocardiography was normal. MRI brain was normal which was done to rule out the central cause of precocious puberty. Hypertension along with features of androgen excess along with raised 11-deoxycortisol levels in both siblings confirmed the diagnosis of CAH due to 11β-hydroxylase deficiency.

Both the children were started with oral hydrocortisone 15mg/m2/day in 3 divided doses and calcium channel blockers (CCBs) for control of hypertension in elder child. Both children are under follow up for regular monitoring of growth and hypertension and to assess need for GnRH (Gonadotropin Releasing Hormone) analogues.

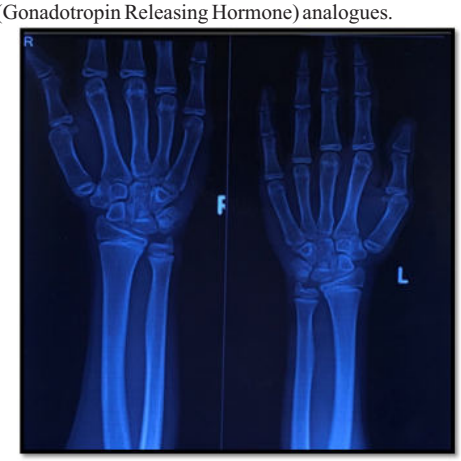


Figure 3. X-ray Wrist Suggestive Of Advanced Bone Age In Elder Child

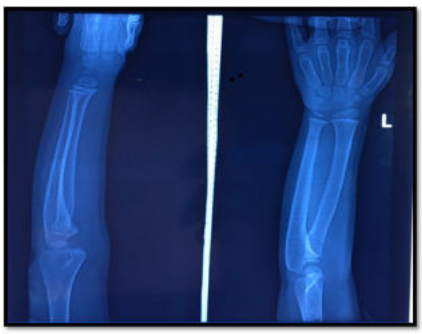


Figure 4: X-ray Wrist Suggestive Of Advanced Bone Age In Younger Child

DESCRIPTION:
Clinical features of 11β-hydroxylase deficiency can be early growth spurt initially, then short adult stature, advanced bone age, premature adrenarche, acne, precocious puberty in males, amenorrhea/ hirsutism/ virilism in females [5]. Other differential diagnosis for mineralocorticoid excess which present are CAH due to 17α-hydroxylase deficiency where there will be no features of androgen excess, Liddle syndrome who present with severe hypertension, hypokalaemia, metabolic alkalosis and muscle weakness, Geller syndrome with early onset hypertension presenting before age 20 years.

In one case report [5] reported by E. Melcescu et all, 3-year-old African American boy presented with precocious puberty. The examination revealed a BP of 150/114 mm Hg, fully developed male phallus, 3–4 ml testes descended, SMR stage-III, minimal acne with increased oily secretions and increased muscle mass. He was 90th percentile for age height, weight, and head circumference. 11-deoxycortisol and 17α-hydroxyprogesterone were elevated at presentation, and he was diagnosed with 11β-hydroxylase deficiency. Bone age was read as markedly advanced to 11 years while at 3 years chronologic age[5].

In our case both siblings featured hypertension, features of androgen excess and advanced bone age with increased 11-deoxycortisol levels due to 11β hydroxylase deficiency. In this condition, though the end product of mineralocorticoid- the aldosterone is not synthesised due to particular enzyme deficiency, its precursor deoxycorticosterone levels are elevated which is responsible for hypertension due to its mineralocorticoid action. Simultaneously it leads to increased sex steroids and its precursors responsible for precocious puberty. As the elder sibling had increased right testicular mass, there is possibility of having testicular adrenal rest tumour TARTs in this child. TARTs are benign testicular masses, present in the rete testes Based on histological studies, TARTs have close resemblance to adrenocortical tissue which is more common associated with 21-hydroxylase deficiency [2]. But in our case tissue diagnosis could not be done because of parental denial. Prevalence of TARTs is variable and up to 86–94%, but most studies have looked at frequency rates only in patients with 21-hydroxylase deficiency. Two case series and one case report describe patients with 11β-hydroxylase deficiency and TARTs [2]. One of these series was a follow-up study of 60 boys and adolescent males with CAH of which five had 11β-hydroxylase deficiency. Three of five boys (60%) were identified to have TARTs based on ultrasonography. All three cases had poor biochemical control and were diagnosed with TARTs at ages 14, 16 and 17 years[2]. Though hypokalaemia as a result of excess mineralocorticoid activity is found in a minority of patients [2], in this case both siblings had normal electrolyte regulation.

Clinical management of CAH due to 11β-hydroxylase deficiency can pose a challenge to maintain adequate glucocorticoid dosing to suppress adrenal androgen excess while avoiding glucocorticoid-induced side effects [2]. Hydrocortisone is frequently used in such patients to maximise their growth potential while minimising their risk for developing Cushing's syndrome from overuse of glucocorticoid therapy (i.e., dexamethasone with its longer half-life and higher affinity for the glucocorticoid receptor). In addition, appropriate therapy with hydrocortisone will reduce concentrations of adrenal androgens and thereby signs and symptoms of androgen excess[5].

Although height seems to be more for their present age, final adult height attained with be short stature in untreated condition. Hypertension should be addressed at the earliest as it leads to serious adverse complications and becomes uncontrolled later if not managed properly. Monitoring should include measurements of blood pressure every 3 months and levels of 11-deoxycortisol, aldosterone, plasma renin, androstenedione, cortisol, serum sodium and potassium. Follow-up of such patients is important to monitor for the somatic growth, progression of bone age and hypertension.

The few case series in 11β-hydroxylase deficiency patients looking at glucocorticoid treatment and TARTs size showed responses from complete disappearance to no response at all on high dose glucocorticoid therapy [2]. Elder child should also be monitored this aspect.

There is need for screening programme which includes CAH profile for 11β-hydroxylase enzyme deficiency along with 21-hydroxylase enzyme deficiency should be made universal for early detection of CAH and its treatment to prevent adverse outcomes of the disease.

CONCLUSION:
Suspect CAH due to 11β-hydroxylase deficiency when patients present with features of androgen excess and hypertension.

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