

responsible for an increase in LHRH production and thus secretion of FSH and LH(7). Evers *et al.*(8) while agreeing with the overlap theory, felt that an overlap of glycoprotein synthesis may be the real cause of rise in FSH and LH rather than a non specific hormonal feedback overlap. FSH, LH and TSH are all glycoproteins with a common alpha subunit.

Hyperprolactinemia in primary juvenile hypothyroidism has been attributed to several factors; decreased hypothalamic dopamine leading to uninhibited action of TRH on lactotrophs; lactotroph hyperplasia due to lack of negative feedback by thyroid hormones, leading to increased sensitivity to existing TRH; and perhaps decreased degradation of prolactin. There may be associated galactorrhea.

With institution of thyroxine replacement, most evidence, clinical and hormonal, of precocity regresses completely, and spontaneously puberty has been reported to occur at the normal time and sequence. It is important to think of this condition in the differential diagnosis of precocity as treatment is simple and results gratifying.

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### Congenital Adrenal Hyperplasia Due to 11 $\beta$ -Hydroxylase Deficiency

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Congenital adrenal hyperplasia (CAH) due to deficient 21-hydroxylase usually

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manifests with symptoms of androgen excess and adrenal insufficiency. A defect in  $11\beta$ -hydroxylase causes the "hypertensive" form of CAH. In general,  $11\beta$ -hydroxylase deficiency ( $11\beta$ -OHD) is rarer than  $21$ -hydroxylase deficiency ( $21$ -OHD) and results in decreased cortisol synthesis which induces increased ACTH secretion with resultant overproduction of androgens and cortisol precursors such as deoxycorticosterone (DOC) and  $11$ -deoxycortisol (compound S). Their urinary metabolites such as  $17$ -ketosteroids and  $11$ -tetrahydro- $11$ -deoxycorticosterone (THS) are markedly increased. Elevated serum levels of  $11$ -deoxycortisol and DOC which further increase with ACTH administration distinguish  $11\beta$ -OHD from  $21$ -OHD. Diagnosis of  $11\beta$ -OHD is often suspected but seldom confirmed. In this paper we present the first proven case of  $11\beta$ -OHD from India and a review of the salient features of this disorder.

### Case Report

A child was brought to the All India Institute of Medical Sciences Hospital at the age of 3 years with appearance of secondary sexual characteristics and enlarged penis. Pubic and axillary hair were noticed along with progressive enlargement of penis at 1 year 6 months and facial hair at 3 years of age. Facial acne started appearing at 2 years and increasing thereafter. Adult like voice change was present at 6 years. Darkening of skin and increase in muscle mass with an athletic build was evident at the same time. He was born full term to unaffected non-consanguineous parents whose two earlier children were normal and had normal onset of puberty.

At 3 years of age he had a height of 108 cm (>95 percentile-ICMR), span 108 cm and upper : lower segment ratio of 59 : 49.

His height age was 6 years and he had facial acne, axillary hair, and pubic hair Stage III, with penile length of 6 cm and testicular volume of 2 ml each. His blood pressure was 100/60 mm Hg. He had generalized hyperpigmentation more marked on genitalia and nipples and systemic examination was normal.

Investigations were as follows: bone age 12 years, skull X-ray normal pituitary fossa, serum sodium 130 mEq/L, potassium 2.6 mEq/L, plasma cortisol 8 a.m. 30  $\mu$ g/dl, 4 p.m. 24  $\mu$ g/dl 24 h urinary  $17$ -ketosteroids 21.8 mg,  $17$ -hydroxysteroids 10.75 mg and  $17$ -ketogenic steroids 14.5 mg. He was presumed to have CAH secondary to  $21$ -OHD and put on steroid replacement. He grew at a velocity of 4 cm/year in the first 6 years. Testis size increased to 4 ml each and there was no further progress in precocity. He was normotensive and asymptomatic during this period. But at the age of 9 years he discontinued treatment on his own and thereafter was taking steroids irregularly.

At the age of 18 years he presented with episodic weakness of proximal muscles of all limbs. On examination he had a height of 145 cm (<5 percentile-ICMR), height age of 13 years, span of 143 cm and upper to lower segment ratio of 1 : 1. He had severe facial acne, and Stage IV pubertal development with a penile length of 12 cm and testis volume of 15 ml each. Hyperpigmentation was marked (Fig.). His investigations were as follows: serum sodium 130 mEq/L and potassium 2.6 mEq/L; 24 h urinary ketosteroids 14.5 mg which fell to 0.5 mg on dexamethasone suppression (2 mg/day for 7 days). ACTH stimulation tests showed plasma cortisol at 0, 1 and 4 hours of 26, 32, and 28  $\mu$ g/dl,  $17$ -hydroxyprogesterone 110, 140 and 160 ng/dl and dehy-

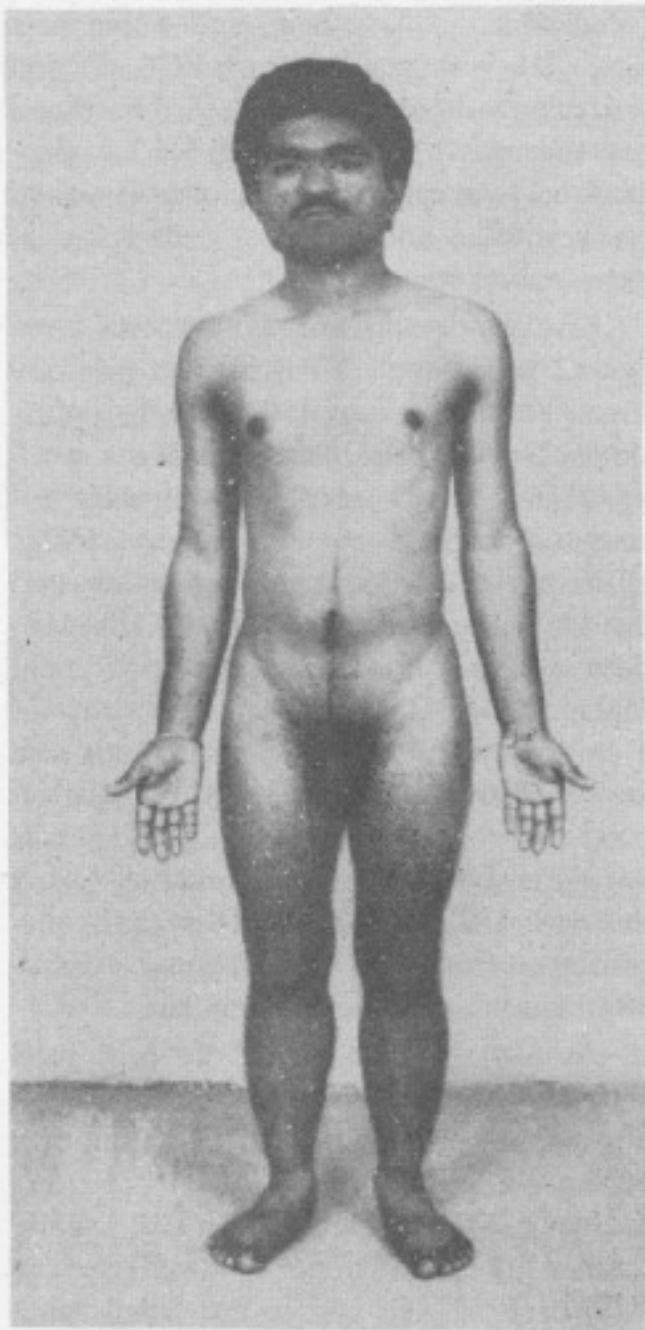


Fig. Photograph of the patient at 19 years of age. Short stature and facial acne are evident, with Stage V sexual development.

drocpiandrosterone 106, 136 and 136 ng/dl, respectively. Plasma renin activity was 6.8 ng/ml/min ( $n = 0.4-5.0$ ). Bone age was more than 18 years and CT scan and ultrasound of abdomen did not show any abnormality of adrenals. He did not improve on therapy with potassium supplements and became worse and developed episodic pal-

pitations. At this time he was detected to be hypertensive with a BP of 140/100 mm Hg. He was suspected to have CAH due to  $11\beta$ -OHD and further investigated (Table). His blood pressure was controlled with antihypertensives ( $\beta$ -blockers) and he is on hydrocortisone replacement and is asymptomatic now.

### Discussion

CAH due to  $11\beta$ -OHD is a rare disorder compared to 21-OHD and accounts for 5% or less of all cases of CAH(1). The presence of hypertension along with virilization was observed in early 1950s(2), but the defect in  $11\beta$ -hydroxylation was confirmed only a couple of years later(3). Most published reports of this disease are individual case reports and detailed account of the spectrum of the disease is available in the two reviews(1,4).

Even though hypertension is considered to be the hallmark of this disorder, its presentation appears to be widely variable. Zachman *et al.*(1) observed persistent hypertension in only 3 out of 25 children with  $11\beta$ -OHD even while on cortisol replacement. Overt hypertension was present only in 14 out of 22 children in the series by Rosler *et al.* and was unrelated to the degree of virilization(4). Also, cases of  $11\beta$ -OHD with hypertension first manifesting in adult life and normotensive patients have been described(1,4,5).

Hypertension in  $11\beta$ -OHD is generally attributed to the increased accumulation of DOC. Normotensive patients with elevated DOC(5) as well as hypertensive patients with normal DOC have been reported(6). It has been suggested that 18OH-DOC a metabolite of DOC with marked mineralocorticoid activity may be responsible for hypertension rather than DOC itself(7).

CAH due to  $11\beta$ -OHD appears to be a

TABLE—Hormone Evaluation (ACTH Test)\*

Hormones (ng/dl)	0 h	1 h	4 h	Normal **
Progesterone	<5	<5	<5	15 - 25
17-OH pregnenolone	90.4	58.5	65.5	50 - 130
17-OH progesterone	73.9	68.3	90.6	118 ± 34
Δ4 androstenedione	388.3	278.9	410.7	112 ± 30
Testosterone	181.8	156.2	217.9	587 ± 135
Corticosterone	88.0	72.0	31.0	< 1000
Compound S	2680.0	3239.0	3205.0	< 500
Cortisol	181.0	130.0	199.0	14000 ± 5000

\* A single injection of 40 IU of 1-24ACTH.

\*\*Basal values in young adult male in early morning.

heterogeneous disorder with different clinical expression. This is an autosomal recessive defect and genetic studies have not shown any specific HLA association(8). The gene encoding 11β-hydroxylase is located to the middle of the long arm of chromosome 8(9). Also, unlike 21-OHD, studies of basal and ACTH stimulated cortisol precursors in family members are not useful for heterozygote detection in 11β-OHD(10).

In this disorder, there is a complete dissociation between the degree of virilization, the impairment of cortisol and corticosterone and aldosterone biosynthesis, the cardiovascular manifestations and hypokalemia(4). Metabolic studies have led to the suggestions that there are two types of 11β-hydroxylase, one affecting 17-hydroxylated steroids alone and the other affecting the conversion of both compound S and DOC to cortisol and corticosterone, respectively(1). Our patient apparently belongs to the first type, the severe hypertension suggesting an overproduction of the DOC, which, however, was not enough to suppress plasma renin activity (being high normal). It has also been proposed that

there may be two separate enzyme systems in the adrenals with severe disease manifesting enzyme deficiency in both fasciculata and glomerulosa while the mild disease would affect only the zonal fasciculata(11,12). That the glomerulosa and fasciculata function as two separate glands is also suggested by previous studies showing the return to normalcy of aldosterone levels on treatment with dexamethasone in some cases(11,13). However, it has been recently shown that a single cytochrome P450c11 catalyzes not only the 11β-hydroxylation but also the 18-hydroxylation and aldehyde synthesis of steroid precursors in both the glomerulosa and the fasciculata zones(14). Finally, in an attempt to explain the clinical and biochemical heterogeneity in this disorder it has been suggested that 11β- and 18-hydroxylating activities, while strongly linked in the zonal fasciculata, may be less so in the zonal glomerulosa(12).

Androgen excess produces somatic abnormalities usually after the age of 1 year which progressively increase, but prenatal virilization can occur in genetic females. These children are taller at a younger age but as adults tend to be

shorter than peers as observed in this patient. Even with adequate glucocorticoid replacement beginning at an early age, the growth can be expected to be only in the low normal range(15).

Missed diagnosis and late diagnosis of  $11\beta$ -OHD, common before specific tests for various steroid metabolites were available are still observed nowadays(6,12). In our patient hypertension was not present at initial presentation at the age of 3 years, but developed subsequently. Thus it appears that the presentation of  $11\beta$ -OHD is clinically indistinguishable from 21-OHD in early infancy and childhood. Hypertension responsive to glucocorticoids is a helpful diagnostic feature(5,10).

Similar to the variation seen in clinical presentations, the biochemical profile also vary in  $11\beta$ -OHD. Overt hypokalemia is common and seen in association with both normal and elevated blood pressure. Occasionally normokalemia is seen with hypertension(4) as was seen in our cases. Urinary 17-ketosteroids are elevated in all as are serum testosterone and  $\Delta 4$  androstenedione. The low testosterone in our patient could be because of the effect of treatment, or suppression of LH by testosterone of adrenal origin.

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## Congenital Adrenal Hyperplasia and Complete Masculinization Masquerading as Sexual Precocity and Cryptorchidism

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Congenital adrenal hyperplasia (CAH) is a family of inherited disorders caused by deficiency or defective functioning of one or more of the enzymes involved in adrenal steroid biosynthesis, the most common

form being caused by deficiency of steroid 21-hydroxylase. In girls, this may present as ambiguous genitalia alone or with salt loss. The degree of virilization and ambiguity depends on the time and quantity of androgen production during intrauterine development. Complete masculinization of external genitalia is rare: these cases are often misdiagnosed as cryptorchid at birth and reared as males(1,2). Available world literature has reports of 45 cases of CAH with complete virilization till 1989(3). We report from India the first such case of complete virilization of external genitalia presenting with sexual precocity at the age of 3 years.

### Case Report

A 3-year-old child (*Fig. 1*) was brought to the Endocrine Clinic because of sexual precocity and cryptorchidism. The child was considered a cryptorchid male at birth. Parents noticed appearance of pubic hair and increasing phallus size during the previous six months in this apparently male child. Developmental milestones were within normal limits. There was no past history of vomiting, dehydration or salt craving. Family history (*Fig. 2*) shows two first cousin marriages including that of the parents (III-2 and III-5) of the index case (IV-2). IV-4 was also detected to have CAH at the age of 4 years when he

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