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Congenital Adrenal Hyperplasia and Complete Masculinization Masquarading as Sexual Precocity and Cryptorchidism

C.V. Harinarayan
A.C. Ammini
M.G. Karmarkar
Ved Prakash
R. Gupta
N. Taneja
I. Mohapatra
K. Kucheria
M.M.S. Ahuja

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

From the Departments of Endocrinology and Metabolism, Radiology and Anatomy, All India Institute of Medical Sciences, New Delhi 110 029.

Reprint requests: Dr. A.C. Ammini, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi 110 029.

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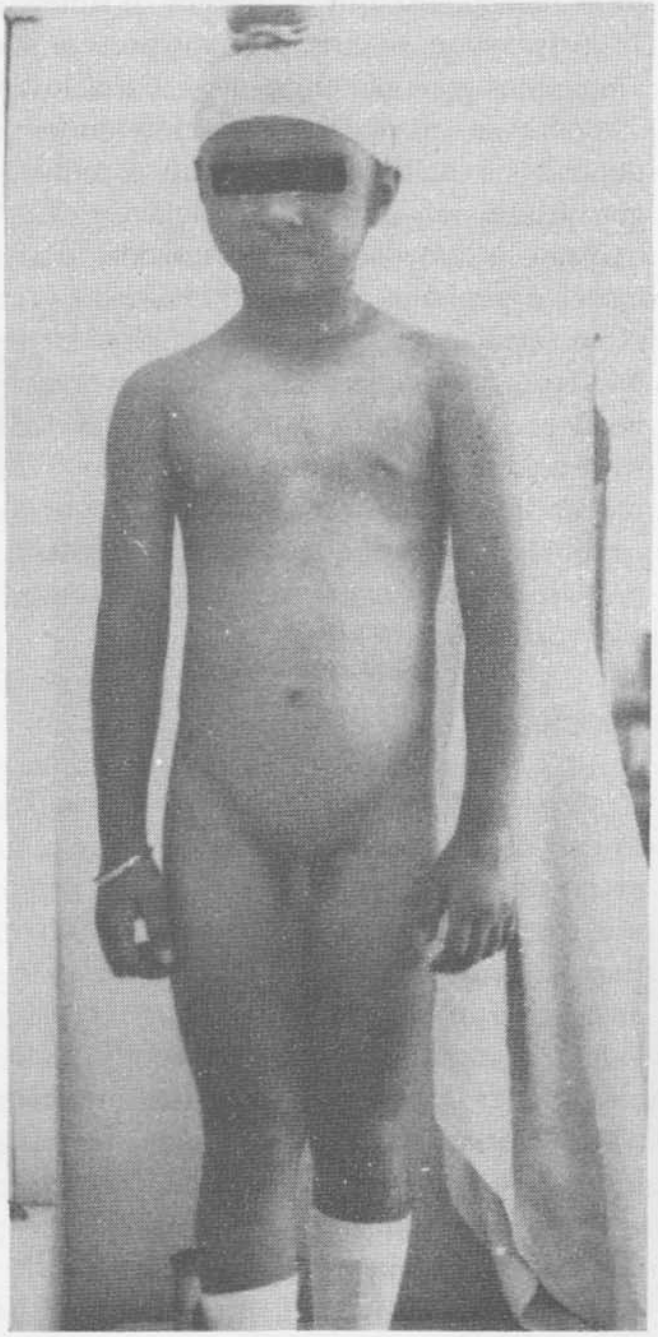

Fig. 1. Patient at age 5 years.

developed precocious puberty, his parents (III-3 and III-4) are also first cousins.

On physical examination, the child was 98 cm tall (95th percentile of ICMR with pubic hair Stage II (Tanner) and stretched phallus length of 6 cm. Scrotal sacs were well formed, fused and rugose. Testes could not be felt on either side. Axillary hair were present. No other obvious abnormality was seen.

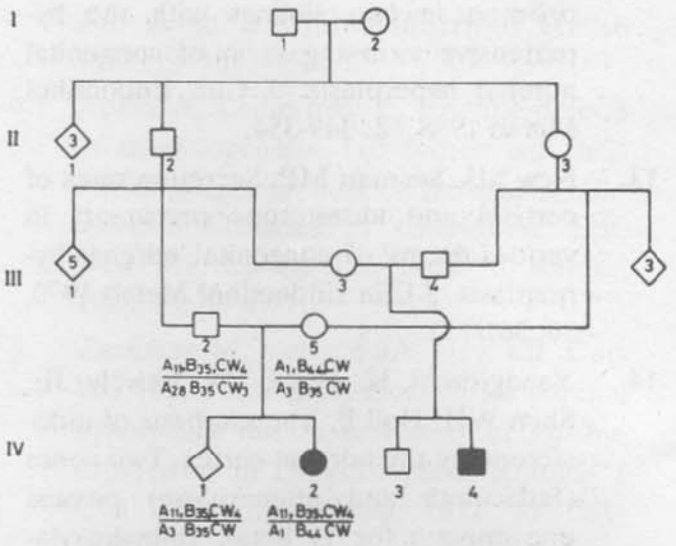

Fig. 2. Pedigree chart with HLA typing for family.

Buccal smear was positive for X-chromatin. Chromosomal studies showed 46, XX karyotype. Bone age was eight years. Ultrasound of abdomen revealed presence of uterus and ovaries while normal adrenals were visualised on CT abdomen. Serum testosterone level was 1.5 ng/ml (normal 0.1-0.9 ng/ml). Basal 24 hours ketosteroids were 16.0 mg (normal 4-8 mg); after one week of dexamethasone (0.5 mg/qid) levels came down to 5.1 mg/24h. On ACTH stimulation there was a rise in the level of serum 17-hydroxyprogesterone (17-OHP) to more than 2000 ng/dl (normal >350 ng/dl) at one hour. Both 17-OHP and testosterone suppressed to normal with dexamethasone.

A diagnosis of CAH with 21-hydroxylase deficiency was made and patient put on cortisol supplements. The child perceived himself to be a male as he was reared as a boy by the family. The behavioral pattern and activities conformed to that of boys. After the condition of the child was explained to the parents, they preferred to continue his male identity, therefore surgical removal of uterus and ovaries is planned.

Discussion

CAH is a common genetic disorder due to lack of one or more of the enzymes involved in cortisol synthesis. The commonest form being due to deficiency of steroid 21-hydroxylase. The prevalence of this has been reported to vary from 1/500 to 1/14,000 in different populations. New born screening for 21 OH deficiency identified 77 cases in 1,093,310 cases screened in 6 countries(4).

Deficiency of cortisol and thus of negative feedback leads to excess ACTH production which causes increased adrenal steroidogenesis and adrenal hyperplasia. Accumulation of steroid precursors prior to the site of block leads to increased androgen production.

There is considerable controversy regarding when does the pituitary adrenal axis becomes functional during intrauterine development. The definitive zone of the human fetal adrenal (the site of cortisol production during fetal life) is considered to be quiescent till the third trimester of pregnancy by biochemical and electron microscopic criteria(5). However, invitro studies have documented increased cortisol production in response to ACTH and fetal pitutary homogenates by adrenals of 10-20 weeks fetuses(6). Amniotic fluid 17 OHP and 44 androstenidione are significantly elevated by 14-20 weeks of gestation in fetuses with CAH(7). Morphogenesis of external genetalia into male phenotype is dependent on androgen exposure during the critical period of development, thought to be 8-13th week in human embryos(8). Excess androgen during and subsequent to this period produces varying degree of labial fusion and clitoromegaly. Cases of complete masculinisation and phallic urethra such as this one suggest that the fetal pituitary adrenal axis probably becomes functional before this critical period.

Complete virilization can occur in cases of CAH due to 21OH and 11 OH deficiency(9). Virilization was thought to be more severe in cases with salt losing defects. However, there have been reports of male phenotype in genetic females with non salt losing variety(10-14), presenting with sexual precocity.

The consequences of delayed diagnosis of congenital virilising adrenal hyperplasia in genotypic females are serious. Late attempts to change gender identity generally have not produced socially and sexually well adapted adult women(15). Preservation of male gender identity requires surgical removal of female internal genitalia with resulting infertility, and androgen supplements at puberty. Once the male gender identity is established, the decision to continue or change the identity should be taken only after careful evaluation and detailed discussion with the family.

It is, therefore, important that children without identifiable tests should be subjected to chromosome analysis early enough, so as to avoid gender identity problems later.

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Transient Nephrogenic Diabetes Insipidus in a Neonate

K.S. Gautham
V. Bhandari
A. Shenoi
M. Singh
O.N. Bhakoo

Nephrogenic diabetes inspidus (NDI) is a rare disorder which manifests with polyuria, passage of dilute urine concomitant with serum hyperosmolality, with no response to exogenously administered vasopressin. The disease can be inherited or can be secondary to various insults to

From the Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012.

Reprint requests: Dr. Meenu Singh, Assistant Professor, Department of Pediatrics, PGIMER, Chandigarh 160 012.

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