CONGENITAL ADRENAL HYPERPLASIA AMONG PERIPUBERTAL GIRLS WITH HYPERANDROGENISM

A.C. Ammini
P.G. Sunderaraman
R. Gupta
M.G. Karmarkar
K. Buckshee
M.M.S. Ahuja

ABSTRACT

Fifteen girls with severe hyperandrogenism were investigated by us during the last 6 years. Thirteen of these were cases of untreated congenital adrenal hyperplasia (CAH) and 2 were cases of tumoral (one sertoli leydig cell tumor of the ovary and one adrenal adenoma) hyperandrogenism. Here we present the clinical profile and laboratory data of those with congenital adrenal hyperplasia.

All the girls had masculinization of genitalia (clitoromegaly alone 5, clitoromegaly with varying degree of posterior labial fusion 8). Eleven cases had hirsutism and 9 had short stature. Two patients underwent unilateral adrenelectomy with diagnosis of adrenal adenoma. Hormonal profile confirmed the diagnosis of CAH with 21 hydroxylase deficiency (elevated 17 OHP levels with exaggerated 17 OHP response to ACTH) in 12 cases and 3 beta hydroxy steroid dehydrogenase deficiency (elevated DHEAS and 17 pregnenelone levels and exaggerated DHEAS and 17 pregnenelone response to ACTH) in one case.

Key words: *Congenital adrenal hyperplasia, 21 Hydroxylase deficiency, Hyperandrogenism.*

Hirsutism is a cause for considerable psychological embarrasment for young girls. In addition to being a cosmetic problem this could rarely be an indication of a life threatening physical illness like an androgen producing tumor. Progressive virilization with significant elevation of plasma testosterone or DHEAS suggests presence of an androgen producing tumor(1-3). These guidelines may not be true for our population as many cases with classical congenital adrenal hyperplasia remain undiagnosed or untreated as is evident from this study. Here, we present the clinical profile and diagnostic problems of peri pubertal girls and young women with untreated congenital adrenal hyperplasia attending a general endocrine clinic.

Methods

Fifteen cases of female hyperandrogenism presenting with hirsutism, virilization and elevated androgen levels were investigated by us during the last six years. Based on laboratory data, 13 of these patients were diagnosed to be cases of congenital adrenal hyperplasia. Clinical details of these 13 patients are given in *Table 1* & *Fig.* Ten cases sought medical attention for hirsutism, 2 for ambiguous genitalia and one (case 5) was detected during family survey.

Case 9 had clitorectomy done during infancy, but discontinued steroid therapy

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

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

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TABLE I–*Clinical Features*

No.	Age	Menstruation	Hirsutism (Ferriman gallaway score)	Posterior labial fusion	Breast development	Height	Masculine body
1.	23	Regular	27	–	Poor	Short	+
2.	13	Amenorrhea	20	+	Poor	Short	+
3.	16	Regular	22	+	Poor	Short	+
4.	13	Amenorrhea	20	+	Poor	Short	+
5*.	9	Prepubertal	4	+	Nil	Normal	–
6[a].	13	Amenorrhea	22	+	Poor	Short	+
7	7	Prepubertal	4	+	Nil	Normal	–
8.	22	Amenorrhea	22	+	Poor	Short	+
9	18	Irregular periods	16	–	Poor	Short	–
10.	23	Irregular periods	30	–	Normal	Normal	–
11	14	Amenorrhea	16	–	Poor	Short	–
12[a].	16	Amenorrhea	22	+	Poor	Short	+
13[b].	18	Irregular periods	20	–	Normal	Normal	–

* Sister of Case No. 4.

a. Younger brother has sexual precocity secondary to CAH.

b. Operated elsewhere as virilizing adrenal adenoma. Histopathology revealed adrenal hyperplasia.

after age of one year. She presented with hypertrophy of the amputated stump of clitoris, menstrual irregularity and hirsutism. Case 13 was operated outside as adrenal adenoma based on CT findings. Histopathology revealed hyperplasia of the resected adrenal. The others were undiagnosed cases.

Plasma testosterone, DHEAS and 17 hydroxy progesterone (17 OHP) after ACTH stimulation (one hour after 40 units of ACTH intramuscular between 8 and 10 a.m. after tab dexamethasone 1 mg at 11 p.m. the previous night and an over night fast) were done for all cases. Plasma testosterone and DHEAS levels were estimated after dexamethasone 0.5 mg 6 hourly for 7 days in those cases where basal values were elevated (except case 10 where a diagnosis of adrenal adenoma was made on CT evaluation). All subsequent cases had CT done to evaluate adrenal morphology. All hormonal assays were done using RIA. For DHEAS and 17 OHP, commercially available RIA kits from Wien laboratories, USA were used.

Results

Cinical and laboratory data are given in *Tables I and II,* respectively.

Case 10, a 23-old-year lady, complained of hirsutism and irregular periods. Physical examination revealed clitoromegaly in addition to significant hirsutism. DHEAS levels were very high (>800 μg/dl, normal 174.9 + 79.8 μg/dl). Testostrone and 17 OHP were only marginally elevated. CT

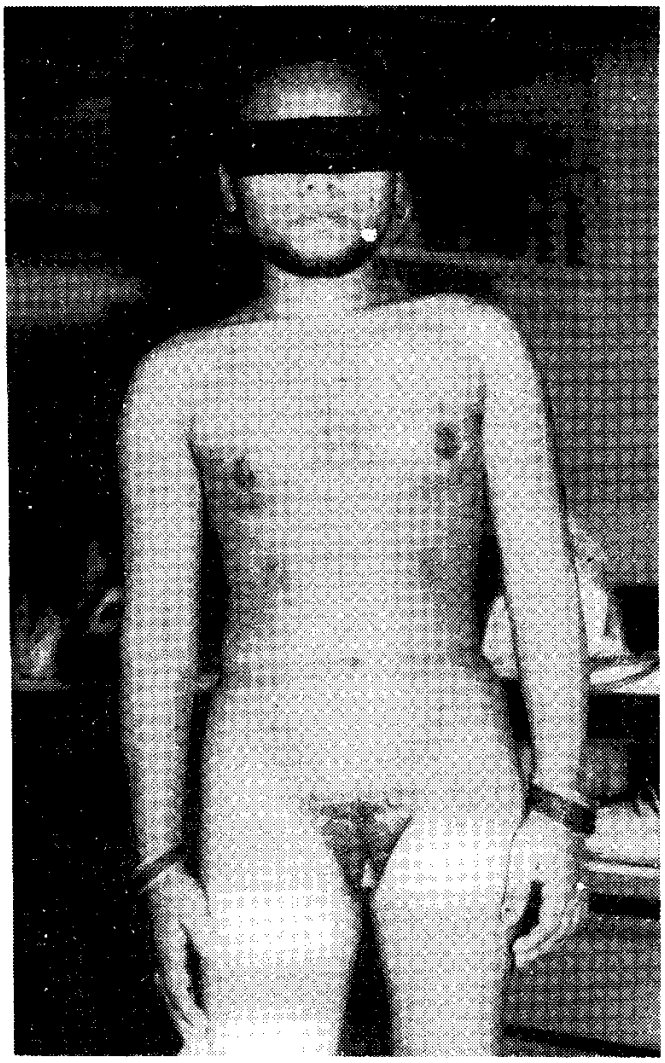

Fig. Clinical photograph of case 8; a 22-year-old lady with hirsutism, short stature, masculine body, habitus, poor breast development and clitoromegaly.

revealed an adrenal nodule 1 × 1 cm in the left adrenal. She underwent left adrenelectomy. Histopathology of the resected adrenal revealed adrenal hyperplasia. Subsequent investigations revealed this to be a case of 3 beta hydroxysteroid dehydrogenase defect (DHEAS levels came down to normal with dexamethasone, DHEAS and plasma 17 pregnen showed exaggerated response to ACTH stimulation).

Eight patients had varying degree of posterior labial fusion indicating androgen excess *in utero*, case 9 had been operated for clitoromegaly during infancy. In the other 4 cases we do not know if there was genital ambiguity at birth.

Discussion

Congenital adrenal hyperplasia refers to a family of genetic disorders resulting from deficiency of one or more of the enzymes involved in cortisol biosynthesis. Total or near total blocks in the activity of these enzymes result in genital ambiguity and abnormalities of salt retention (in 3/4 cases), or genital ambiguity alone (1/4 cases)(4). In infants the salt wasting symptoms and even crisis may not appear till the 7th to 10th day of life. In girls, the diagnosis is often made before symptoms of salt wasting appear because of genital ambiguity which ranges from mild clitoral enlargement through varying degree of labio scrotal fusion to the profound morphological anomaly of a penile urethra. Untreated they may present later with progressive virilism and advanced somatic development. These comprise the classical forms of CAH(4).

The incidence of classical 21 hydroxylase has been extensively investigated. The incidence varies in different populations from 1 in 700 to 1 in 20,000(4). There are no reported studies on prevalence of CAH in our population.

Improved biochemical assessment of adrenal functions allows identification of lesser enzyme defects which cause milder endocrine dysfunctions like hirsutism, acne, infertility, *etc.* with no genital ambiguity. Such partial defects, known as non classical forms, have been confirmed for steroid 21 hydroxylase(5), 11 beta hydroxylase(6) and 3 beta hydroxysteroid dehydrogenase defects(7) and the prevalence of

TABLE II—*Laboratory Data*

No.	Testosterone (nmol/L)	DHEAS (μg/dl)	170 HP (ng/dl)	Remarks
1.	6.8	240	1000	–
2.	4.5	320	1000	–
3.	6.2	180	1000	–
4.	3.6	800	1000	–
5.	6.4	320	1000	–
6.	5.6	180	1000	–
7.	3.1	280	1000	–
8.	5.0	75	1000	–
9.	2.4	120	1000	–
10.	3.1	800	270	Left adrenal adenoma on CT, left adrenelectomy done.
11.	3.6	200	1000	Bilateral diffuse adrenal enlargement on CT.
12.	5.0	560	1000	Bilateral adrenal enlargement with nodular transformation of the left adrenal.
13.	1.3	320	1000	Adrenelectomy, adrenal hyperplasia histologically.

Normal range for controls.
Serum testosterone 1.3 ± 0.438 nmol/L.
Serum DHEAS 179.4 ± 79.8 μg/dl.
Serum 170 HP 65.5 ± 45.3 ng/dl.

these defects among hirsute women varies from 0 to 30% in different populations(8). Screening for nonclassical CAH among north Indian hirsute women revealed a prevalence rate of 8.4%(9,10).

Nine of the 15 cases of severe hyperandrogenism in this series are cases of classical 21 hydroxylase deficiency. In the other 5 cases of CAH we do not have sufficient data to group them into classical or nonclassical variety. Girls with classical CAH diagnosis is often made during infancy or early childhood. Surprisingly, only one of these girls received treatment during infancy. Almost all our patients sought medical attention for hirsutism. It is difficult to say if it is lack of awareness or fear of these children being labelled Hijras that delayed/prevented the parents form seeking medical help for the genital ambiguity.

Glucocorticoid therapy alone (in doses of 0.25 to 0.5 mg of dexamethasone late in the night) was sufficient for initiating breast development and menarche and also normalizing serum testosterone levels. There was considerable reduction in clitoris size also with glucocorticoid therapy. But prolonged anti-androgen therapy was required in addition to glucocorticoids for controlling hirsutism.

Adrenal tumors are known to occur in cases of untreated congenital adrenal hyperplasia(11-13). Two cases in the present series had unilateral adrenelectomy done

with diagnosis of adrenal adenoma. CT scanning for adrenals was done for all subsequent cases (after case 10) which revealed nodular transformation of the adrenals in another(14).

To conclude, undiagnosed classical CAH is not rare among young females with severe hyperandrogenism in our country. A careful physical examination to exclude genital ambiguity and screening for CAH (17 OHP assay) should be done in all cases of peripubertal girls with hyperandrogenism before initiating investigations for androgen producing tumors.

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