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Congenital Adrenal Hyperplasia: Experience in Iranian Patients

Maryam Razzaghy Azar [1, 2*], Mona Nourbakhsh [2], Mitra Nourbakhsh [3]

[1] Inborn Error of Metabolism, Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, IR Iran
[2] Department of Pediatrics, H. Aliasghar Hospital, Tehran University of Medical Sciences, Tehran, IR Iran
[3] Department of Biochemistry, School of Medicine, Tehran University of Medical Sciences, Tehran, IR Iran

* *Corresponding author:* Maryam Razzaghy Azar, Inborn Error of Metabolism, Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, IR Iran.Tel: +98-21 66942903, Fax: +98-21 66421054, E-mail: mrazar_md@yahoo.com

ABSTRACT

Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder stemming from one of the enzymatic defects in the biosynthesis of cortisol from cholesterol. In the majority of instances the disorder comprises deficiency of 21-hydroxylase (21-OHD). This defect causes excessive androgen production from adrenal source, which leads to virilization with varying degrees of severity (Prader grade 1-5) in female fetuses.
Objectives: To determine the frequency of different types of congenital adrenal hyperplasia, rate of consanguinity, family occurrence, birth weight, and final height and weight.
Patients and Methods: Medical records of patients with CAH between 1968 and 2011 were reviewed.
Results: Out of 617 patients, 79.6% had 21-hydroxylase deficiency (21-OHD). In 21-OHD group 94.5% had classical type and 5.5% were non-classic. Among the classic type 78% had salt-wasting form (SW) and 22% simple virilizing (SV). Both 21-OHD-SV and SW were diagnosed more frequently in females. Frequency of other types were as follow: 11-hydroxylase deficiency (11-OHD), 13.3%; 3ß-hydroxysteroid dehydrogenase deficiency (3ß –OHD), 4.1%; lipoid adrenal hyperplasia, 1.1%; 17-hydroxylase deficiency, 1%; hypoaldostronism, 0.6% and Antley-Bixler, 0.3%. Parental consanguinity was present in 62.6% and familial occurrence was reported in 42.6% of the patients. Sixteen girls had grade 5 virilization of Prader staging (SW, 10; SV, 2; 11-OHD, 4). The most prevalent Prader stage was 4 in 21-OHD-SW and 11-OHD. In 21-OHD-SV, 9 patients had Prader grade 4 and 5 virilization. The difference between mid-parental height and final height was highest in 21-OHD-SV; its SDS was (-1.2 ± 1.1). Birth weight of all patients was normal except for 5 patients. The frequency of low and very low birth weight was not significantly different from the general population. All patients were assigned as their genetic gender except for 5 patients with delayed diagnosis or parental opposition.
Conclusions: The prevalence of different types of CAH, grade of virilization, final weight, height and birth weight, were recorded from the referral patients.

Keywords: Congenital Adrenal Hyperplasia, Height, Weight, Grade of Virilism, Birth Weight

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Implication for health policy/practice/research/medical education:
Clinical experience on a large series of CAH patients in a tertiary care hospital.

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1. Background

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that is due to one of the enzymatic defects which occur in cortisol biosynthesis from cholesterol. The most prevalent type is 21-hydroxylase deficiency (21-OHD). This defect causes excessive androgen production from adrenal source, which leads to virilization of varying severity (Prader grade 1- 5) in female fetuses (1). Moreover, in some types of this disorder there is undervirilization of males. Management of this condition consists of medical treatment with glucocorticoids, mineralocorticoids (in salt-wasters) and surgical repair of the external genitalia. There is general agreement about the need for primary surgical intervention before 2 years of age (2, 3).

2. Objectives

The aim of this study is to present the clinical experience accumulated over 43 years on a large series of CAH patients in a tertiary care hospital. Frequency of different types, degree of virilization, final height and weight, birth weight and unusual cases are reported.

3. Patients and Methods

Medical records of 617 patients with CAH from 1968 to 2011 were reviewed. Diagnoses were based on clinical manifestations and measurement of 24 hour urinary 17-ketosteroids (17-KS), pregnanetriol and 17-hydroxycorticosteroids (17-OHCS) (using the Porter-Silber method) until 1985 and the assessment of serum 17-hydroxyprogesterone (17-OHP) and serum cortisol at 8 AM, ACTH, aldosterone, plasma renin activity (PRA), dehydroepiandrosterone (DHEA) and androstenedione by radio immunoassay thereafter. Clinical manifestations in salt-wasting types were; dehydration, poor feeding, failure to thrive, vomiting, lethargy, sometimes cyanosis and shock, and diagnostic laboratory tests included; low serum sodium, high serum potassium and high PRA. Patients with 21-OHD were detected by the presence of high 24 hour urinary 17-KS and pregnanetriol (before 1985) and high serum 17-OHP (after 1985). Simple virilizing type of 21-hydroxylase deficiency (21-OHD-SV) was diagnosed in girls who had ambiguous genitalia, without salt-wasting manifestations. This condition was also diagnosed in boys who presented with pseudoprecocious puberty, without hypertension. The patients with non-classical form of 21-hydroxylase deficiency (NC21-OHD) had normal genitalia. They had normal blood pressure, and manifested with premature adrenarche in childhood or adrenarche that precedes testicular enlargement during puberty in males, or was manifested by hirsutism during or after adolescence in females. They had high levels of 17-OHP at 8 AM and in suspicious cases a provocative test with short-acting ACTH was conducted. The patients, who had high levels of 24 hour urinary 17-OHCS and pregnanetriol or high serum levels of 17-OHP and hypertension, were diagnosed as having 11-OHD. A 3ß-hydroxysteroid dehydrogenase deficiency (3ß-OHD) was the diagnosis when the 17-OHP level was high (due to peripheral conversion of 17-hydroxypregnenolone to 17-OHP), in boys who presented with salt-wasting and ambiguous genitalia and in girls who had salt-wasting with no or low grade ambiguity, high DHEA-S and low androstenedione. Patients who had 17-hydroxylase deficiencies (17-OHD) presented due to the absence of secondary sexual characteristics at the age of puberty. They had hypertension, high progesterone, low estradiol, high follicle stimulating hormone (FSH) and luteinizing hormone (LH), low cortisol, high ACTH, low PRA and normal aldosterone. Patients with hypoaldostronism (Hypoaldo) had salt-wasting crisis, low sodium, high potassium with high PRA, but frequent measurements of 17-OHP, cortisol and ACTH were normal initially and during the follow-up period. Boys were diagnosed as having lipoid adrenal hyperplasia (Lipoid) if they presented with; a female phenotype, salt-wasting manifestations, low cortisol, low 17-OHP and high ACTH levels, and girls who had the same manifestations, were relatives of these boys and documented by genetic study. Height and weight of the patients were considered final when growth had stopped for more than 6 months with bone age > 16 years in girls and > 17 years in boys. Mid-parental height (target height) was calculated as mean of parental heights plus 6.5 cm for males and minus 6.5 cm for females. The difference of the patient's height with mid-parental height (MPH) was determined. Standard deviation scores (SDS) of height were calculated for the final height and MPH of the patients using these formulas according to CDC2000:

Height SDS =(patient height-height 50% for age)/(SD for age)

and

MPH SDS =(MPH-height 50% for 20 yr)/(SD for 20 yr)

The difference between the patient's height SDS and mid-parental height SDS (final H- MPH SDS) was also determined. Final body mass index (BMI) was calculated by the formula, weight (kg)/height (m^2). Weight status was considered; underweight when BMI was < 18.5, normal weight 18.5–24.9, overweight 25.0–29.9, and obese 30 or higher. Bone age was determined according to the atlas of Greulich and Pyle. The gender of the patients was detected by karyotyping with a banding method.

4. Results

Among 617 patients with congenital adrenal hyperplasia, 260 patients (42%) were male and 356 cases (58%) were female and one patient with Antley-Bixler syndrome had a karyotype of 45, XO. The most prevalent type of CAH was 21-OHD (79.6%). The prevalence of different types of CAH according to gender is shown in (Table 1 , 2) and (Figure 1).

Table 1. Frequency of Different Types of CAH

Type	Gender No. (%)[a]		Total No. (%) [b]
	Female	Male	
21-OHD	300 (61)	191 (39)	491 (79.6)
11-OHD	39 (48)	43 (52)	82 (13.3)
3-βOHD	6 (24)	19 (76)	25 (4.1)
Lipoid	3 (43)	4 (57)	7 (1.1)
17-OHD	5 (83)	1 (17)	6 (1)
Hypoaldo	2 (50)	2 (50)	4 (0.6)
Antley-Bixler	1T + 1	No one	2 (0.3)
Total	356 (58) + 1T	260 (42)	617 (100)

Abbreviations: 3-βOHD, 3-β hydroxysteroid dehydrogenase deficiency; 11-OHD, 11 hydroxylase deficiency; 17-OHD, 17 hydroxylase deficiency; 21-OHD, 21 hydroxylase deficiency; Hypoaldo, hypoaldostronism; Lipoid, lipoid adrenal hyperplasia; T, Turner syndrome; 45, XO
[a] Percent is horizontal
[b] Percent is vertical

In our study of the 491 cases with 21-OHD, 94.5% had classic and 5.5% had a non-classic type of this disorder; 78% of all classic types had salt-wasting and 22% had a simple virilizing form. Salt-wasting and simple virilizing forms were more common in girls, and NC21-OHD was diag

nosed in 24 girls and 3 boys. (Figure 2). In all of the patients with NC21-OHD, 0800 hr serum 17-OHP levels were > 25 ng/mL and an ACTH test was not necessary. In this category, premature adrenarche without testicular and phallus enlargement presented in two boys at the age of 4 and 6 years and adrenarche preceded testicular enlargement in an 11 year old boy with signs of puberty. Age at entry differed according to the type of CAH (Table 3 , 4).

Genital ambiguity resulted in referral after birth and salt-wasting usually presented after 10 to 14 days of age, however, some of these patients came later so the mean age ± SD of presentation in 21-OHD-SW was 32 ± 40 days (range, 7 to 270 days). The longest period was in a girl whose treatment was not approved by the parents after diagnosis in the neonatal period.

Table 2. Frequency of Different Types of 21 hydroxylase Deficiency (21-OHD) According to Gender

Gender	Types of 21-OHD (%)[a]				
	Classic (C)			Non Classic (NC)	Total NC & C
	SW	SV	Total C		
Female	211 (58)	65 (64)	276 (59.5)	24 (89)	300 (61)
Male	151 (42)	37 (36)	188 (40.5)	3 (11)	191 (39)
Total, No. (% of C)[b]	362 (78)	102 (22)	464 (100)		
(% of C + NC)[b]	(73.7)	(20.8)	464 (94.5)	27 (5.5)	491 (100)

Abbreviations: SV, simple virilizing; SW, salt-wasting
[a] Percent is vertical
[b] Percent is horizontal

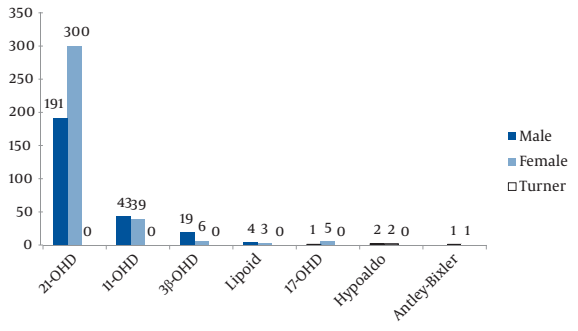

Figure 1. Frequency of Different Types of CAH According to Gender

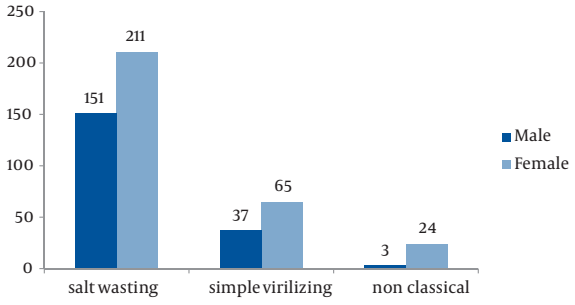

Figure 2. Sex Distribution in Patients With 21 Hydroxylase Deficiency

At the second presentation she was 9 months of age with Prader 5 virilization, weight of 5.35 kg and height of 62.5 cm. Serum sodium was 90 mEq/L and potassium 8 mEq/L. Treatment was commenced and she is now 18 years old, with a height of 157 cm midparental height of 161.5 and good intelligence.

Parental consanguinity was reported in 241 (62.2%) out of 387 cases (187 first cousins, 54 second cousins).

Table 3. Age Entry in Different Types of Congenital Adrenal Hyperplasia

Type	Minimum	Maximum	Mean ± SD
21-OHD	At birth	27 y	1.7 ± 4.2 y
11-OHD	11 d	11 y	2.1 ± 2.5 y
3-bOHD	At birth	3, 9/12 y	4 ± 11.8 m
Lipoid	15 d	1,1/12 y	3.6 ± 4.4 m
17-OHD	13 y	20 y	15.7 y
Hypoaldo	22 d	2 y	7 ± 2.3 y
Antley-Bixler	15 d	18 d	16.5 ± 2 d

Abbreviations: d, day; m, month; y, year

Table 4. Age Entry in Different Forms of 21-Hydroxylase Deficiency

Forms of 21-OHD	Minimum	Maximum	Mean ± SD
Salt-wasting	At birth[a]	9 m	32 ± 40 d
Simple virilizing	12 d	26 y	4.5 ± 5.4 y
Non-classical	4 y	27 y	10 ± 6.6 y

Abbreviations: m, month; d, day; y, year
[a] entry at birth was due to a disorder of sex development

A history of family occurrence was noted in 136 (42.8%) out of 318 patients, of these 104 (76.5%) were among siblings. Birth weight of the patients was reported in 151 patients and it was not found to be significantly different between the different types of CAH. Very low birthweight (VLBW) (≤ 1.5 kg) was seen in one girl with 21-OHD-SW (0.7% of 151 cases) and low birthweight (LBW) (>1.5 and ≤2.5 kg) was seen in 16 patients (10.6% of 151 cases) (21-OHD SW, 8 patients; SV, 1; NC, 2; 11-OHD, 1; 3β-OHD, 1; lipoid, 1 and Antley-Bixler, 1) (*Table 5*).

Table 5. Birth Weight of Patients With Different Types of Congenital Adrenal Hyperplasia.

Type	Minimum	Maximum	Mean ± SD
21-OHD			
SW	1.20	4.90	3.20 ± 0.6
SV	2.50	3.95	3.30 ± 0.4
NC	2.10	3.40	2.97 ± 0.4
11-OHD	2.50	4.20	3.4 ± 0.5
3-OHD	1.60	3.80	2.9 ±1
Lipoid	2.50	3.75	3 ± 0.4
17-OHD	3.00	3.50	3.2 ± 0.2
Hypoaldo	3.40	3.40	3.4 ± 0
Antley-Bixler	2.35	2.70	2.5 ± 0.3

Frequency of different grades of virilization is shown in (Table 6). The most frequent grade of virilization was Prader grade 4 in 21-OHD-SW and 11-OHD. Out of the 24 patients with 21-OHD-SV, seven girls had Prader 4 and two had Prader 5 virilization.

4.1. Gender Assignment

Our patients, including Prader 5 virilized females underwent combined correction of clitoro-vaginoplasty between one to two years of age in one session, with preservation of the glans and associated nerves and vessels and these patients did not have any problem in their sexual identity. Exceptions occurred in three patients. One of the girls with 11-OHD who had Prader 5 virilization had been reared as a boy. Her medical treatment had started when she was one year old and she had good medical control, so her clitoris was like the phallus of a prepubertal boy.

Table 6. Grade of Virilization in Different Types of Congenital Adrenal Hyperplasia

Type of CAH	Stage of Virilization	Count	Percent
21-OHD -SW	1	10	11.9
	2	3	3.6
	3	18	21.4
	4	43	51.2
	5	10	11.9
	Total	84	100
21-OHD -SV	1	11	45.8
	2	1	4.2
	3	3	12.5
	4	7	29.2
	5	2	8.3
	Total	2	100
21-OHD -NC	0	14	82.4
	1	3	17.6
	Total	17	100
11-OHD	1	2	13.3
	3	1	6.7
	4	8	53.3
	5	4	26.7
	Total	15	100.0
3-βOHD	No	5	33.3
	3	1	6.7
	4	9	60.0
	Total	15	100.0

When she was referred to a surgeon after one year of age, the surgeon made a mistake, and instead of removal of the uterus and ovaries, he explored for undescended testes and ended the operation with a diagnosis of anorchia. At 12 years of age, when she was a student at a boy's school, breast development appeared and menarche occurred, following consultation with a

psychologist, the patient and her family accepted the change of gender. She underwent genitoplasty, married later on, and now has a healthy child. She expressed no sexual desire towards girls. However, two boys who had 21-OHD-SW had desire on boys and acted female before they understood about their misdeed. Two girls with 11-OHD and Prader 4 virilization were reared as boys and they did not receive treatment until 6 and 17 years of age, respectively. They had phallus enlargement and secondary sexual characteristics at pubertal stage 5 of the Tanner scale. They did not agree to change their gender and underwent removal of their uterus and ovaries. The complications of surgery in all of the patients were clitoral atrophy, vaginal stenosis, and fistula in the urethra, each in one patient.

4.2. Final Height

Final heights of the patients and their differences with mid-parental height (MPH) are illustrated in *Table 7* . The lowest height SDS occurred in males with 21-OHD-SV and the highest were for the 17-OHD group. The tallest boy was in the 21-OHD-SW group. His height was 186 cm which was 7 cm more than his mid-parental height. The maximum height in females (excluding 17-OHD patients) was 169 cm (3 cm > MPH) and 165 cm (5.5 cm > MPH) in 21-OHD-SV and 21-OHD-SW patients, respectively. Final BMI and weight status are shown in Tables 8 , 9 . Overall 23.5% of males and 20.8% of females were overweight, while 11.8% of males and 19.4% of females were obese. Obesity and overweight were seen more frequently in patients who were treated with high doses of cortisone acetate and hydrocortisone in the early years of the study. Short stature was seen more frequently in patients who came to treatment late, or those who were treated with high doses of corticosteroids, including those who received prednisolone or dexamethasone.

Table 7. Final Height and the Difference Between Final Height and Mid-Parental Height and the Difference Between Final Height SDS and Mid-Parental Height SDS In Different Types of CAH According to Gender

Type	Final Height, cm	Final Height, cm, Mean ± SD	Final Height–MPH, Cm			Final H SDS–MPH SDS		
			Minimum	Maximum	Mean ± SD	Minimum	Maximum	Mean ± SD
Male								
21-OHD								
SW	148-186	165 ± 9	-18	+ 7	-6.3 ± 6.7	-2.5	+ 0.97	-0.87 ± 0.9
SV	158-169	165 ± 5	-21	+ 0.75	-8.6 ± 7.9	-2.9	+ 0.1	-1.2 ± 1.1
11OHD	153-173	164 ± 8	-14	+ 9.5	-3.5 ± 7.3	-1.95	+ 1.3	-0.5 ± 1
Female								
21-OHD								
SW	143-165	152 ± 6	-19	+ 5.5	-5 ± 5.5	-2.9	+ 0.85	-0.8 ± 0.9
SV	145-169	155 ± 9	17.5	+ 5.5	-4.8 ± 7.2	-2.7	+ 0.85	-0.7 ± 1.1
NC	145-162	157 ± 5	14.5	+ 5	-3.6 ± 7	-2.3	+ 0.77	-0.5 ± 1
11OHD	138-160	153 ± 7	-21	+ 1.5	-4.6 (7.8)	-3.2	+ 0.23	-0.7 ± 1.2
3βOHD	155-157	157 ± 0.8	-4.5	-0.8	-2.3 ± 2	-0.7	-0.12	-0.3 ± 0.3
Lipoid	164	164	2.5	+ 2.5	2.5	0.34	+ 0.34	0.34
17-OHD	152-174	162 ± 8	-3.3	+ 12	2.6 ± 8	-0.5	+ 1.9	0.39 ± 1.3

Abbreviations: 3β-OHD, 3β hydroxysteroid dehydrogenase deficiency; 11-OHD, 11-hydroxylase deficiency; 17-OHD, 17-hydroxylase deficiency; 21-OHD, 21-hydroxylase deficiency; Final H – MPH, final height minus MPH; H, height; Max, maximum; Min, minimum; MPH, mid-parental height; NC, non-classic; SD, standard deviation; SDS, standard deviation score; SV, simple virilizing; SW, salt-wasting

4.3. Unusual Cases

Two girls with 11-OHD had salt wasting in the neonatal period with a serum sodium of 128 mEq/L and serum potassium levels of 5.8 and 6 mEq/L before the start of treatment. Two sisters with lipoid adrenal hyperplasia had cryptogenic infantile spasm in the neonatal period that disappeared without any residual neurodeficits.

Two boys with a salt-wasting type of CAH and normal male genitalia, who also had some salt-wasting crises during the follow-up period, had a spontaneousl remission at the age of 2.6 and 9.6 years, respectively. Their initial laboratory parameters were as follow: First boy; serum sodium = 125 mEq/L, serum potassium = 5.7 mEq/L, 17-OHP = 19.3 ng /mL. Second boy; serum sodium = 119 mEq/L, serum potassium = 6.1, 17-OHP = 17.55 ng/mL. Hydrocortisone and 9α-fluorocortisol were administered to the boys. Trying to reach the lowesr dosage for control of disease resulted in discontinuation of drugs and they did not need any further treatment during the 10 year follow-up period.

Table 8. Final Weight and BMI of Patients With Different Types of Congenital Adrenal Hyperplasia According to Gender.

Type	Male				Female			
	Final Age, y	Last Weight, kg	BMI Range	BMI	Final Age, y	Last Weight	BMI Range	BMI
21-OHD								
SW	23 ± 4	69 ± 19	18.7 - 46.9	25 ± 7.5	19 ± 5	61 ± 16	16.2- 42.6	26 ± 6
SV	24 ± 6	63 ± 7	18.6 - 28	23 ± 3.4	24 ± 6	59 ± 17	17.4 - 34.7	24 ± 5
NC	No	No	No	No	32 ± 10	56 ± 8	19.5 - 27.7	23 ± 2.5
11OHD	21 ± 4	76 ± 27	17.5 - 66.4	29 ± 13	22 ± 4	62 ± 12.5	18.8 - 33.7	26 ± 4
3β-OHD	18	63	24.2 - 24.2	24	22 ± 1	56 ± 10	18.8 - 27.5	23 ± 4
Lipoid	No	No	No	No	17.5	60	22.3	22.3
17-OHD	22	59	20.2	20	24 ± 3	53 ± 6.6	14.9 - 23.6	20 ± 4

Abbreviations: 3β-OHD, 3β hydroxysteroid dehydrogenase deficiency; 11-OHD, 11-hydroxylase deficiency; 17-OHD, 17-hydroxylase deficiency; 21-OHD, 21-hydroxylase deficiency; Final H – MPH, final height minus MPH; H, height; Max, maximum; Min, minimum; MPH, mid-parental height; NC, non-classic; SD, standard deviation; SDS, standard deviation score; SV, simple virilizing; SW, salt-wasting

5. Discussion

Classical CAH due to 21-OHD was present in 80% of our patients compared to 90% of CAH cases reported in the literature (4). This may be due to a higher prevalence of 11-OHD and the diagnosis of rare forms of CAH among our patients. Salt-wasting is reported (4) in 75% of all cases of classical 21-OHD, and that is compatible with the 78% found in our study. Although 58% of the salt-wasting form of 21-OHD was detected in females and it might be due to the death of undiagnosed males, but 64% of the simple virilizing form was also seen in females, assuming that 21-OHD is more common in females than males.

Table 9. Final Weight Status in Patients With Congenital Adrenal Hyperplasia

BMI Classification	Male (%)	Female (%)
Underweight	2.9	6.9
Healthy weight	61.8	52.8
Overweight	23.5	20.8
Obese	11.8	19.4

Abbreviations: BMI, BIO MASS Index

Deficiency of 11-OHD accounts for 5–8 % of cases of CAH in persons of European ancestry, but it comprised 13.3% of cases in our study, which is nearer to the 15% reported in Moslem and Jewish, Middle Eastern populations (5). Deficiency of 3 β;OHD occurs in fewer than 5% of patients with CAH (6). It was diagnosed in 4.1% of our patients. Lipoid adrenal hyperplasia is a rare disorder, reported in fewer than 100 patients worldwide; the majority of them are Japanese (6). Seven patients in our study had this type of CAH, while 17-OHD has been described in more than 125 patients (6). Six of our patients had this disorder and all of them came in during the adolescent period. Two patients with 17-OHD had received sex hormone replacement therapy by gynecologists without any definite diagnosis, so there might be more patients with this enzyme deficiency who have not been properly diagnosed. Hypertension should be considered to be a clinical clue for the diagnosis of this disorder in girls with delayed puberty. It is estimated that 0.1% of White North Americans have NC21-OHD, with the highest frequency occurring in Ashkenazi Jews (6), 4.4% of our patients had a non-classical form of 21-OHD. They did not have ambiguous genitalia, but came for treatment because of hirsutism during or after adolescence, or premature adrenarche.

Two boys had premature adrenarche at four and six years of age without testicular and phallus enlargement, and adrenarche preceded by testicular enlargement in an 11 year boy. They had NC21-OHD with a high level of 8 AM 17-OHP. So the appearance of adrenarche before testicular enlargement may necessitate the evaluation of 17-OHP even at the age of puberty. It is likely that all patients with biochemical manifestations of NC21-OHD manifest signs of androgen excess at some time (7). In our patients, 0800 hr serum 17-OHP levels were > 25 ng/mL and an ACTH test was not necessary. In NC21-OHD, basal 17-OHP hormonal levels may not differ from normal values when measured randomly, but they are elevated during the diurnal peak of cortisol production, so early morning serum values are informative (8-10). Early morning 17-OHP should be measured in any girl or boy who has adrenarche or if it precedes breast development and testicular enlargement even at the age of puberty.

Parental consanguinity was seen in 62.2% of the patients. Family occurrence was reported in 42.8% of cases, with 76.5% among siblings. It is assumed that a low incidence among relatives, other than siblings, is due to concealment. Nine patients with the SV type of 21-OHD had Prader 4 and 5 virilization. Severe virilization is an unexpected event in a milder form of the disease. Characterization of the P450c21 protein (11), and gene cloning show

that there is only one 21-hydroxylase enzyme encoded by a single functional gene on chromosome 6p2 (12, 13). Perhaps other factors such as, 21-hydroxylase activity in extra-adrenal tissues (14) that are not mediated by the P450c21 enzyme of the adrenal (15), or changes in androgen sensitivity, or the action of separation glomerulosa and fasciculata zones under different gene control (as suggested by New and Seaman) (16), could be the cause of this discrepancy between severity of virilization and salt-wasting.

Some surgeons prefer to perform a reduction of the clitoris within the first three months of life, in order to give the child a firmer identity with the female gender, and a vaginoplasty is performed later during the teenage years (17). In our patients the operation was performed between one to two years of age in one session without deleterious effects on the child's sexual identity. We saw easy acceptance of the female gender by one girl who was in good medical control and experienced female puberty in spite of severe fetal virilization (Prader 5), and a rejection of the sexual changes occurred in two girls with delay in their therapy, and their secondary sexual characteristics were progressed. There were also two boys with good medical control who had a desire for homosexual relationships., These observations indicate that the embryonic hormonal milieu may not have impact on sexual desire, and extra-uterine factors and hormones may be more important in this matter, although further psychological investigations are needed. These observations show that the sex assignment of CAH patients should be made according to their karyotype, rather than their phenotype as soon as practicable after birth, and the disease should be suitably controlled. Two patients with 11-OHD had mild transient salt loss that had been reported earlier (5), presumably this is the result of the normal newborn's resistance to mineralocorticoids and that desoxycorticosterone acts as a weak mineralocorticoid (5, 18). Two patients, who were diagnosed as having CAH, were cured at an older age. They had a mild elevation of 17-OH progesterone, but perhaps they had a deficiency of the end enzymes for aldosterone synthesis and not 21-OHD-SW. The final heights of 186 cm in a male and 169 cm in a female, show that good control of the disorder plays a critical role in preserving the final height and that this is possible in these patients. Very low birth weight (VLBW) was seen in one case (0.7%) and low birth weight (LBW) in 16 cases (10.6%); this was not significantly different from reports in the general population, which was 1.47% and 8.1% of live births, respectively, in 2004 (19). The occurrence of cryptogenic infantile spasms in patients with lipoid adrenal hyperplasia in the neonatal period reveals the role of high CRH in the pathogenesis of this form of seizure which has been explained previously (20).

The present study describes the prevalence of different types of CAH. Discrepancies between the severity of virilization and salt-wasting were seen in the simple virilizing forms of 21-OHD. Salt-wasting was also observed in two patients with 11-OHD in the neonatal period. Two patients had a complete remission in childhood. CAH girls even those having Prader 5 virilization should be reared as females, surgical management is possible and this should be performed early in life. Appropriate therapy and good control of the disease prevents obesity and short stature in these patients.

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