REPORT OF 285 PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA AND EVALUATION OF APPROXIMATE PREVALENCE OF THE DISEASE IN IRAN

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Abstract - In this study, 285 cases of congenital adrenal hyperplasia who were followed in the Tehran University Hospitals and Institute of Endocrinology and Metabolism are reported. Among these cases, 165 (57.9%) were female and 120 (42.1%), male. The most common type of congenital adrenal hyperplasia in these patients was the salt-losing type of 21-hydroxylase deficiency (57.9%); 11-hydroxylase deficiency was present in 13.68% of patients. There were only 3 cases with 3-beta hydroxysteroid dehydrogenase deficiency, 2 cases with 17-alphahydroxylase deficiency and one with 20, 22-desmolase deficiency. Presenting complaints were in decreasing order of frequency: ambiguous genitalia, vomiting and dehydration, precocious puberty, hypertension, failure to thrive, hirsutism and primary amenorrhea. The age of patients at the time of diagnosis was between 2 days to 17 years and the most common age was in the first two years of life especially in the neonatal period.

A positive family history of the same disease was present in 17 siblings of our patients. (21-OHD=14 H-OHD=3). There were 27 cases of death among these patients (23 male and 4 female that 24 cases had 21-OHD and 2 cases had 3 beta HSD deficiency and one case had 20,22-desmolase deficiency)
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Key words: Congenital adrenal hyperplasia 21-hydroxylase deficiency (21-OHD), 11-hydroxylase deficiency (H-OHD), 3-beta hydroxysteroid dehydrogenase (3-beta HSD)

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is the term applied to a family of inherited disorders of steroidogenesis caused be a deficiency of any of the five enzymes necessary for the conversion of cholesterol to cortisol (1).

The presenting complaints in CAH are ambiguous genitalia, vomiting and dehydration, precocious puberty, failure to thrive, hypertension, hirsutism and menstrual irregularity (4).

In the vast majority of CAH cases, 21- hydroxylation is impaired (21-OHD). Based on case surveys and neonatal screening, the frequency of the homozygous affected state for classical 21-hydroxylase deficiency ranges from 1/5000 to 1/23000 in most populations. Incidence of the disease varies in different geographic areas for example in the Alaskan Eskimo, the incidence is markedly higher and the condition occurs in approximately 1.700 live births (1,6). The incidence of classical 21-OHD in the Causasian population is more common than phenylke - tonuria (PKU), a disorder in which newborn screening is mandated. 21-OHD is certainly more common than all the disorders for which newborn screening is mandatory, with the exception of congenital hypothyroidism (7). At the present time, newborn screening for 21-OHD (CAH) is performed in some parts of the world. We believe that the incidence of CAH in Iran is higher than some other parts of the world, perhaps because of the high occurrence of family marriage in Iran. In this survey, CAH patients were followed in the endocrine clinics of Tehran University Hospitals and the Institute of Endocrinology and Metabolism from 1976 to 1996 (during a 20 year period) in order to determine the approximate prevalence of the disease in Iran, the frequency of the types of CAH, clinical presentation, male to female ratio, recurrence rate of the disease in the family, mortality rate and the age of patients at the time of diagnosis.

PATIENTS AND METHODS

In the past 20 years, 285, patients with CAH have been seen in endocrine clinics. Patients

with the salt-losing form of the disease were seen in infancy because of vomiting and dehydration, failure to thrive and ambiguous genitalia.

The diagnosis was made somewhat later, especially in boys with the simple virilizing form which presented with clitoromegaly and ambiguous genitalia in females, rapid growth and pseudoprecocious puberty in males. In patients with 21-hydroxylase deficiency, the diagnosis was first confirmed by elevated urinary, 17-ketosteroids and then by elevated plasma 17-hydroxyprogesterone level (17 OHP).

Eight girls with late-onset 21-hydroxylase deficiency presented with hirsutism, menstrual irregularity at puberty, and elevated levels of 17-hydroxyprogesterone after an intravenous bolus of ACTH. Thirty-nine patients with 11-hydroxylase deficiency presented with pseudoprecocious puberty and hypertension.

Three incompletely virilized boys with hypospadias, cryptorchidism, and XX genotype presented with a salt-wasting syndrome in their neonatal period. These cases had 3-beta-hydroxysteroid dehydrogenase (3-beta HSD) deficiency. Two phenotypic females with hypertension, absence of secondary sex characteristics, and primary amenorrhea in the pubertal age had 17-alpha hydroxylase deficiency.

One XY phenotypic female patient who had developed adrenal crisis in his neonatal period was diagnosed as a case of 20,22-desmolase deficiency.

Cortisol and 17 hydroxyprogesterone, testosterone, dehydroepiandrosterone sulfate (DHEAS) and ACTH (in some cases) were made on blood samples obtained between 8 to 10 a.m. and 17-ketosteroids on 24 hour urine collection (this measurement was done in the first years of our study). In salt-wasting patients, serum sodium potassium levels were determined.

In cases of ambiguous genitalia, buccal smear and often karyotype study were done.

RESULTS

Of the 285 CAH patients who were studied, 165 were female and the remaining 120 were male. They were from 2 days to 17 years. Of the 240 patients with 21 hydroxylase deficiency, 165 (57.9%) had the salt-losing syndrome, 67 (23.5%) had simple virlizing CAH and 8 (2.8%) had late onset manifestations. Thirty-nine patients (13.68%) had 11-hydroxylase deficiency. Three incompletely virilized boys (1.05%) with 46 XY karyotype who presented with the salt-losing syndrome had 3-beta hydroxysteroid dehydrogenase deficiency. Two XX phenotypic females (0.7%) who presented with hypergonadotropic hypogonadism (absence of secondary sex characteristics and primary amenorrhea) and hypertension at puberty had 17-alphahydroxylase deficiency. Only 1 boy (0.35%) with a female phenotype had 20, 22 desmolase deficiency.

Table 1. Incidence of different types of CAH in 285 cases.

Types	Sex		Total
	Male NO.	Female NO.	NO.(%)of all cases
21-OH deficiency			240(84.2)
Salt-Loser	65	100	165(57.9)
Simple Virilizing	29	38	67(23.5)
Late-Onset	--	8	8(2.8)
11-hydroxylase deficiency	22	17	39(13.68)
3-beta hydroxysteroid dehydrogenase deficiency	3	--	3(1.05)
17-alpha hydroxylase dificiency	–	2	2(0.7)
20,22 desmolase deficiency	1	--	1(0.35)
Total	120(42.1%)	165(57..9%)	285(100%)

Distribution of the different types of CAH are shown in Table 1. Presenting complaints in decreasing order of frequency include: ambiguous genitalia (28.77), vomiting and dehydration (25.61%), precocious puberty (15.08%), hypertension (14.38%), failure to thrive (12.63%), hirsutism (2.8%) and primary amenorrhea (0.7%). Clinical presentations are shown in Table 2. There was a family history of the same disease in siblings of 17 cases (5.9%) of whom 14 had

Table 2. Clinical manifestations of 285 cases with CAH.

Clinical Manifestations	No.(%)
Ambiguous genitalia	82(28.77)
Vomiting, dehydration	73(25.61)
Precocious puberty	43(15.08)
Hypertension	41(14.38)
Failure to thrive	36(12.63)
Hirsutism	8(2.80)
Primary amenorrhea	2(0.7)

Table 3. Positive family history of the CAH in 285 cases.

Type	No
21-OH deficiency	14
11-OH deficiency	3
Other type	0
Total	17

Table 4. Incidence of mortality in 285 cases with CAH

Types	Sex		Total No
	Male NO.	Female NO.	
21-hydroxylase deficiency salt-loser	20	4	24
3-beta hydroxysteroid dehydrogenase	2	--	2
20,22 desmolase	1	--	1
Total	23	4	27

Table 5. Distribution of the age of 285 cases with CAH at the time of diagnosis.

Age (yr)	No.	Percent(%)
≤2	203	71.22
3-5	38	13.33
6-8	21	7.36
9-11	10	3.50
12-14	11	3.85
15-17	2	0.7
Total	285	100%

21-hydroxylase deficiency and 3 had 11-hydroxylase deficiency (Table 3). Mortality (Table 4) occurred in 27 cases, more commonly in males with the salt-wasting type of CAH (24 cases of 21-OHD, 2 cases of 3-beta HSD deficiency and one 20,22 desmolase deficiency. The age at the time of diagnosis was between 2 days to 17 years, most commonly in the first two years of life, especially in the neonatal period (Table 5).

DISCUSSION

CAH is a group of autosomal recessive disorders of steroidogenesis caused by a deficiency of one of five enzymes necessary for the conversion of cholesterol to cortisol. The pathophysiology of clinically recognized 21-OHD is attributable to impaired synthesis of cortisol and consequent lack of negative feedback to the pituitary resulting in excessive secretion of ACTH. This in turn leads to hyperplasia of the adrenal cortex with accumulation of steroid precursors proximal to the blocked step and the by-products of these precursors, including androgens which cause prenatal and postnatal virilization (2,5,6). The pathophsiology of virilization of females in 11 hydroxylase and 3-beta hydroxysteroid dehydrogenase is similar. CAH is the cause in most cases of female pseudohermaphroditism and approximately one half of all the patients with ambiguous genitalia (most cases are 21-OHD) (2). No genital abnormalities are discerned in the newborn male with 21-OHD. The simple virilizing form of 21-OHD and 11-hydroxylase deficiency in males presents by rapid growth and pseudoprecocious puberty, and also hypertension in most cases of 11-hydroxylase deficiency after infancy (5,6,10). The genitalia of newborn males with 20,22 desmolase dificiency, 3-beta hydroxysteroid dihydrogenase deficiency and 17-alphahydroxylase enzyme defect are incompletely masculinized because of insufficient testosterone and dihydrotestostrone production (male pseudohermaphroditism) (2,5). In females, 17-alpha hydroxylase deficiency presents with primary amenorrhea, lack of development of secondary sex characteristics and hypertension (5,7). Most the cases (95%) are due to 21-Hdyroxylase deficiency (2,6). In our study the incidence of the latter type was less than in other

reports (84.2%) but it was still the most common type. Classic 11-hydroxylase deficiency accounts for 5 to 8 percent of cases with CAH (3,7). In our study the incidence of 11-hydroxylase deficiency was 13.8% that was more common compared to that reported previously. In our study the incidence of other types of CAH was less than 5%, that was similar to other studies. The incidence of the disease was higher in females than males (female=165, male=120, female/male ratio=1.37). A large number of affected males developed salt wasting crisis and died without any specific diagnosis, because the most common type of disease, i.e. 21-OHD does not present with genital abnormalities in the males. In our cases, the mortality rate was higher in males with the salt-wasting syndrome, and the most common age at the time of diagnosis was during the first two years of life, especially in the neonatal period. During a period of 20 years (from 1976 to 1996), we report 285 cases. In comparison, in a study from Birmingham, England from 1958 to 1985 (27 years), 117 cases of CAH were reported (9). The incidence of disease may be higher in Iran than other parts of the world. Therefore, we recommend that in addition to newborn screening for congenital hypothyroidism in Iran, newborn screening for 21-OHD, (the most common cause of CAH) be performed in our country, because early diagnosis can protect or reduce many of the physical and psychological problems associated with the disease.

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