

CONGENITAL ADRENAL HYPERPLASIA IN NORTH-EAST OF IRAN: A REVIEW OF 47 PATIENTS AND THE ROLE OF PARENTAL CONSANGUINITY IN THE OCCURRENCE OF DISEASE

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ABSTRACT

In this study the clinical and epidemiological characteristics of congenital adrenal hyperplasia were evaluated prospectively in 47 patients admitted in Imam Reza Hospital in Mashhad during a 4 year period.

21-hydroxylase deficiency was present in 42 patients (89.3%), the simple virilizing form in 6 and the salt-losing form in 36 of them. 11 β -hydroxylase deficiency was present in 5 patients (10.7%). The median chronological age at diagnosis in the salt-losing form was 68 and 47 days in boys and girls respectively. 7 girls were considered to be male before the diagnosis was established. Parental consanguinity rate among families of patients was higher than the general population in Mashhad (82% vs. 35%). In 16.2% of patients the history of disease was positive in siblings.

This study showed that the incidence of congenital adrenal hyperplasia is expected to be high due to a high rate of consanguinity in our population, hence genetic counseling before marriage would definitely be beneficial in our population.

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by a defect in any of the five enzymatic steps required to synthesize cortisol from cholesterol. The deficiency of cortisol leads to adrenocortical hyperplasia and overproduction of intermediary metabolites. Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of mineralocorticoid deficiency or excess, incomplete virilization or premature androgenization of the affected male; and virilization or sexual infantilism in the affected female.

The most common form is 21-hydroxylase deficiency

which accounts for 90% of affected patients. A further 5-8% of cases are associated with a deficiency of 11 β -hydroxylase and all other enzymatic deficiencies together account for less than 1% of patients.¹

It is well known that early diagnosis and treatment is essential to avoid adrenal crisis, shock, and death. In this study, clinical and epidemiological characteristics of 47 patients admitted to Imam Reza Hospital of Mashhad University of Medical Sciences (MUMS) were evaluated.

MATERIAL AND METHODS

The clinical and laboratory characteristics of 47 pa-

tients with CAH who were managed in the Pediatric Endocrinology Unit of Imam Reza Hospital of MUMS during 4 years were recorded. The diagnosis was based on the presence of failure to thrive, weight loss, vomiting, dehydration, and virilization of the external genitalia in females in the salt-losing form of 21-hydroxylase deficiency and virilization and pseudoprecocious puberty in the simple virilizing form of 21-hydroxylase and 11 β -hydroxylase deficiency. Laboratory investigation including Na, K, venous blood gas, urea, creatinine, serum 17-hydroxyprogesterone, 17-ketosteroids in 24hr urine, DHEA-S, androstenedione and testosterone with commercial kits were done. We used Gruelich and Pyle's standard atlas for evaluation of bone age² and age-adjusted reference values for hormonal study.³ The chronological age, weight, height, sex at presentation, symptoms, family history for same problem and family relationship between parents were recorded.

Statistical significance was established at a *p* value <0.05. Data were analyzed with Chi-square test and common biostatistical methods.

RESULTS

21-hydroxylase deficiency was present in 42 patients (89.3%), 36 of them (23 female and 13 male) had the salt-losing form and 6 presented with simple virilization (Table I).

The median chronological age at diagnosis in the salt-losing form was 68 and 47 days in boys and girls respectively. In 5 patients (10.7%) 11 β -hydroxylase deficiency was diagnosed (Table II), who presented with signs of virilization and pseudoprecocious puberty, hypertension, hypokalemia and advanced stature and bone age. The median age at diagnosis in patients with 11 β -hydroxylase deficiency was 3.4 years. 7 girls with 21-hydroxylase deficiency were considered to be male before diagnosis was established.

Parental consanguinity was present in 82% of the patients, and in 6 families more than one offspring was affected, including a family with 3 affected children.

DISCUSSION

Congenital adrenal hyperplasia is an autosomal recessive disorder that refers to the histological alterations in the adrenal cortical tissue due to chronically elevated plasma levels of adrenocorticotrophic hormone (ACTH); ACTH elevations are secondary to low plasma cortisol arising biochemically from reduced or absent activity of one of the five enzymes of cortisol synthesis from cholesterol in the adrenal cortex. Each enzyme deficiency produces characteristic alterations in synthesized and secreted levels of the adrenal steroid hormones and their

precursors. The particular imbalances resulting in each case cause abnormalities of fetal genital development and accompanying specific recognizable metabolic disturbances.⁴

Although any of the enzymatic steps required for cortisol synthesis may be defective in CAH, steroid 21-hydroxylase deficiency accounts for more than 90% of all cases of CAH, while deficiency of 11 β -hydroxylase accounts for 5-8% of cases of adrenal hyperplasia.^{1,5}

In our study 89.3% of patients had 21-hydroxylase deficiency, 36 (79%) of them presented with the salt-losing form and 6 (21%) presented with simple virilization, not differing significantly with that reported in the literature (75% salt-losing and 25% simple virilizing form).¹ The median chronological age at diagnosis in the salt losing form was 68 and 47 days in boys and girls respectively and only 10 of them were diagnosed during the newborn period. The median age at diagnosis in our study is much higher than other studies especially for boys. For example in Kandemir et al's study⁶ the median age at diagnosis for the salt-losing form of CAH was 17 days. Many authors have concluded that newborn screening programs for CAH should be done.⁷ The worldwide incidence of classical CAH in Pang et al's study was taken from newborn screening programs in France, Italy, Japan, Scotland and the United States, in which 1,093,310 newborns were screened between 1980-1988, and 77 had CAH. Thus the worldwide incidence of this disorder was estimated at 1: 14,199 live births for homozygous patients, and 1:60 for heterozygous subjects, with a gene frequency of 0.0083.⁸

11 β -hydroxylase deficiency was present in 5 of our patients (10.7%). The median age at diagnosis was 3.4 years, and the main clinical signs were advanced height and weight for age, virilizing of genitalia, pseudoprecocious puberty, and hypertension. Hypertension with hypokalemic alkalosis is the one clinical feature distinguishing 11 β -hydroxylase from 21 hydroxylase deficiency.⁴ A retrospective study (1968-1986) in Tehran by Razzaghy-Azar and coworkers revealed that 19% of the CAH population was made up of 11 β -hydroxylase deficiency patients.⁹ In another relatively large series of patients with CAH studied by Karamizadeh and Amirhakimi from the southeast of Iran (Shiraz) the frequency of 11 β -hydroxylase was reportedly 13%.¹⁰ Similarly Kandemir et al. reported a high frequency of 11 β -hydroxylase deficiency from Turkey.⁶

Other enzymatic deficiencies (3 β -hydroxysteroid dehydrogenase, 17-hydroxylase, and lipoid adrenal hyperplasia) together account for less than 1% of reported cases of CAH. Only one case of lipoid adrenal hyperplasia was reported from Iran.¹¹

Parental consanguinity was present in 82% of our patients, higher than the general population in Mashhad

Table I. Clinical and laboratory characteristics of 6 patients with the simple virilizing form of 21-hydroxylase deficiency in Imam Reza Hospital.

No.	Sex	Age of presentation (years)	Age at diagnosis (years)	Weight (Kg)	Height (cm)	Blood Pressure (mmHg)	Bone age (years)	Tanner stage (Pubic hair)	17-OH Progesterone (ng/mL)	Na (mEq/L)	K (mEq/L)
1	M	4	7.5	29	133	100/80	9	IV	>50	137	4
2	M	6	7	34	140	105/70	11	IV	75	140	4.1
3*	F	5	6	28	130	95/65	9	III	50	138	3.9
4*	F	4.5	6	27	131	100/65	8	III	45	142	4.1
5**	M	2.3	3	16	100	95/60	5	III	>30	137	4.2
6**	M	2	3	14	91	90/60	5	II	45	136	4.5

*The two patients were sisters.

**The two patients were members of one family.

Table II. Clinical and laboratory characteristics of 5 patients with 11β-hydroxylase deficiency in Imam Reza Hospital, Mashhad.

No.	Sex	Age of presentation	Age at diagnosis (years)	Weight (Kg)	Height (cm)	Blood Pressure	Bone age (years) (mmHg)	Tanner stage	Na (mEq/L) (Pubic hair)	K (mEq/L)	Testosterone (ng/dL)	17-ketosteroid (mg/24h)
1	M	8 months	2.5	13.5	102	118/70	5-6	III	149	2.8	531	16
2	M	12 months	2.5	15	95.5	140/100	6-7	III	143	2.6	3.3	14
3	M	2 years	3.5	16	104	150/100	---	IV	139	2.1	340	13
4	M	9 months	4.5	14	103	125/75	5-6	III	148	2.7	420	15
5	M	18 months	4	16.5	105	145/95	5-6	III	145	2.3	520	15

(35%),¹² it's difference statistically significant ($p < 0.001$). In 18% of our patients there is a positive family history for the same problem and in 6 families more than one offspring was affected including a family with 3 affected children.

Since introduced as a therapy for CAH nearly 5 decades ago, cortisone and hydrocortisone have been the most widely used glucocorticoids in the treatment of CAH.¹³ Although successful treatment with achievement of normal height, puberty, sexual function and fertility has been reported,¹⁴ short stature, disordered puberty, menstrual irregularity, infertility, inadequate vaginal reconstruction, and lack of sexual function are frequent.¹ The results of Rivkees et al's study show that carefully adjusted doses of dexamethasone are at least as effective as hydrocortisone, and children treated with dexamethasone grow normally, have normal rates of skeletal maturation, undergo puberty at a normal age and reach acceptable adult stature with the convenience of once-a-day dosing in most cases.¹³

Although survival of patients with CAH has greatly improved since steroid therapy has been used, this dis-

ease can still have fatal consequences. The results of Serdlow et al's study shows that mortality in patients with CAH was higher than the general population and mortality was significantly increased at ages 1 to 4 years and

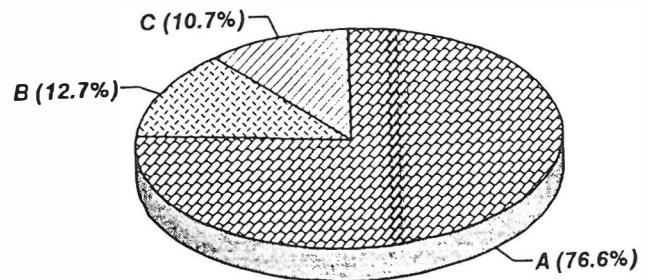


Fig. 1. Frequency of enzyme deficiency in 47 patients with C.A.H.

A= Salt-losing form of 21-hydroxylase deficiency
 B= Simple virilizing form of 21-hydroxylase deficiency
 C= 11β-hydroxylase deficiency

in patients of Indian-subcontinent ethnicity, particularly in girls. This may reflect the lack of parental acceptance and understanding of the disease as well as lack of the action required when their child becomes acutely ill.¹⁵

The results of this study emphasize that genetic counseling before marriage is beneficial in our population and newborn screening programs should be considered for early diagnosis and appropriate treatment.

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