

## EXPERIENCE WITH 115 PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA AND EVALUATION OF GROWTH PATTERNS IN 24 PATIENTS WITH THE SALT-LOSING TYPE

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### ABSTRACT

In this study the data on 115 cases of congenital adrenal hyperplasia (CAH) who were followed in the Pediatric Endocrine Clinic at Nemazee Hospital, Shiraz will be reported.

Among these cases 51 were male and 64 female. The most common type of CAH in these patients was the salt-losing type of 21-hydroxylase deficiency (85.2%). 11-hydroxylase deficiency was present in 13.04% of patients. There was only one case with 20,22-desmolase deficiency and one also with 3-beta-hydroxysteroid dehydrogenase deficiency.

Presenting complaints were ambiguous genitalia, vomiting, failure to thrive, precocious puberty and hypertension.

The analysis of data on 24 patients with the salt-losing type of 21-hydroxylase deficiency who were followed for at least 2 years showed that these patients suffered from abnormal growth patterns. Growth failure was maximal during the first year of life.

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### INTRODUCTION

Congenital adrenal hyperplasia results from an inherited defect in any of the five enzymatic steps required to synthesize cortisol from cholesterol. The presenting complaints in CAH are ambiguous external genitalia, failure to thrive, hypertension, precocious puberty and hirsutism. A deficiency of 21-hydroxylase accounts for 90 to 95 percent of cases with congenital adrenal hyperplasia.<sup>1,2</sup>

Growth velocity provides a valuable guide for the adequacy of control during infancy and childhood, and attaining normal adult height is one of the principles of treatment.<sup>3</sup> Nevertheless, short stature is common even with proper therapy. This may result from mild hyperandrogenemia associated with inadequate adrenal suppression<sup>4,5</sup> or from the direct growth suppressive effect of excessive treatment.<sup>6,9</sup> In this report our experience with

115 patients with CAH with special emphasis on growth velocity will be reviewed.

### PATIENTS AND METHODS

115 patients with CAH were seen in the Pediatric Endocrine Clinic in the past 15 years. Patients with the salt-losing form of the syndrome were seen in infancy because of vomiting and failure to thrive. The diagnosis was made somewhat later in patients with the simple virilizing form when they presented because of rapid growth or virilism. In patients with 21-hydroxylase deficiency, the diagnosis was confirmed by elevated urinary 17-ketosteroids. Salt loss was determined by clinical status and serum electrolytes. Two girls with late-onset 21-hydroxylase deficiency presented with hirsutism at puberty. Both had elevated levels of 17-

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hydroxyprogesterone after an intravenous bolus of ACTH. The patients with 11-hydroxylase deficiency presented with premature pseudopuberty and hypertension.

One XY phenotypic female patient who developed adrenal crisis in her neonatal period was diagnosed as a case of 20,22-desmolase deficiency. An incompletely virilized boy with hypospadias who presented with salt-wasting syndrome in his neonatal period had 3-beta-hydroxysteroid dehydrogenase deficiency.

Cortisol determinations were made on blood samples obtained between 8 and 10 a.m. and 17-ketosteroids on 24-hour urine collections.

Following the diagnosis, emergency therapy was initiated with hydrocortisone intravenously in all infants, and if mineralocorticoids were required deoxycorticosterone acetate (DOCA) was given intramuscularly. Prednisolone and fluorocortisone were used for long-term management.

Steroids were taken in two or three divided doses. The dose for each patient was determined by body surface area. Growth patterns were evaluated every 3 months and urinary excretion of 17-ketosteroids once yearly. Bone maturation was determined at 12 and 18 months of age and once a year thereafter using the method of Greulich and Pyle. The daily dosage of replacement prednisolone therapy was 5 mg/m<sup>2</sup> and that of fluorocortisone was 0.05 to 0.2 mg depending on clinical findings, blood pressure and serum electrolyte levels.

Growth velocities of 24 children (14 boys and 10 girls) with the salt-losing variety of 21-hydroxylase deficiency during the first 5 years of life were studied. These patients were followed for a duration of at least 2 years.

Steroid therapy was started within the first 2 months of life. Medical evaluation of these children included determination of length or height and linear growth velocity.

The National Center of Health Statistics (NCHS) whole year velocity standards (50th percentile) for height in boys and girls were used for comparison.

### RESULTS

115 patients (64 girls and 51 boys) aged 1 month to 13 years with CAH were studied. Of 98 patients with 21-hydroxylase deficiency, 67 (68.5%) had the salt-losing syndrome, 29 (29.5%) had simple virilizing CAH and 2 (2%) had late-onset manifestations.

15 patients (13.04%) had 11-hydroxylase deficiency. Only 1 boy with a female phenotype had 20,22-desmolase deficiency and one undervirilized boy had 3-beta-hydroxysteroid dehydrogenase deficiency. Distribution of different types of CAH are shown in Table I.

Presenting complaints in order of frequency were ambiguous genitalia (26.9%), vomiting and dehydration (22.6%), failure to thrive (17.3%), precocious puberty (18.2%), hypertension (13%) and hirsutism (1.73%). Clinical

**Table I. Incidence of different types of CAH in 115 cases.**

Types	Sex		Total No. (%) of all cases
	Male No.	Female No.	
21-OH deficiency	39	59	98 (85.2)
salt-loser	25	42	67 (58.26)
non salt-loser	14	15	29 (25.22)
late-onset	—	2	2 (1.74)
11-hydroxylase	10	5	15 (13.04)
3-beta-OH steroid dehydrogenase	1	—	1 (0.87)
20,22-desmolase	1	—	1 (0.87)
Total	51 (44.3%)	64 (55.6%)	115 (100%)

**Table II. Clinical presentation of 115 cases with CAH.**

Clinical manifestations	No(%)
Ambiguous genitalia	31 (26.9)
Vomiting, dehydration	26 (22.6)
Precocious puberty	21 (18.2)
Failure to thrive	20 (17.3)
Hypertension	15 (13)
Hirsutism	2 (1.73)

**Table III. Growth velocity during the first 5 years of life in 24 cases of 21-OH deficiency with salt wasting (14 males, 10 females).**

Age	Growth velocity (mean + SD)	
	Male	Female
1st year	17.22+3.03	16.4 + 2.7
2nd year	9+4.7	6.8+1.6
3rd year	6.3+1.19	6.5+0.98
4th year	4.5+1.06	5.4+1.54
5th year	5+0.73	5.1+2.19

signs and symptoms are shown in Table II.

Growth velocities of 24 patients with salt-losing syndrome who were followed for at least 2 years revealed that the growth of these patients was significantly lower than that of normal children of the same age range ( $P < 0.005$ ). Table III and Figs. 1 and 2 show the growth velocities of these boys and girls.

It must be noted that growth failure is more pronounced

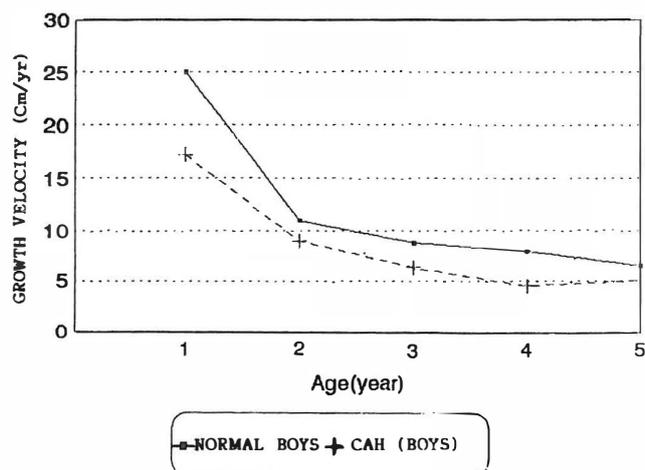


Fig. 1. Yearly gain in height in normal boys and male patients with congenital adrenal hyperplasia.

during the first year of life in these patients.

There was also a delay in bone maturation of less than 2 months in 20 of 24 patients at one year of age, while bone age advanced by about 6 months at the end of the second year. During follow-up, none of these patients developed moon face, truncal obesity, hypertrichosis or high blood pressure. The daily 17-ketosteroid excretion in these patients was less than 0.5 mg.

## DISCUSSION

CAH is caused by a family of autosomal recessive disorders of adrenal steroidogenesis which lead to cortisol deficiency.

21-hydroxylase deficiency accounts for 95% of affected patients.<sup>1,2</sup> Classic 11-hydroxylase deficiency accounts for 5 to 8 percent of cases with CAH.<sup>1,8</sup> In the present study the incidence of these enzymatic defects was 85.2% and 13.04%, respectively. In our study 11-hydroxylase deficiency was more common compared to that reported in the literature.

CAH accounts for most cases of female pseudohermaphroditism and approximately one-half of all patients with ambiguous external genitalia. Ambiguous genitalia was the most common clinical finding in the present report.

Growth is extremely sensitive to exogenous steroid administration, and even a small amount of steroids given in excess of the physiological dose may have a significant effect on growth.<sup>10</sup>

Glucocorticoids can affect the spontaneous secretion of growth hormone and its response to provocative stimulation; steroids also inhibit growth by direct action on the epiphyseal cartilage.<sup>10,13</sup> Stunted linear growth, particularly during infancy may be attributed to overtreatment with steroids, but none of the patients showed any evidence of steroid

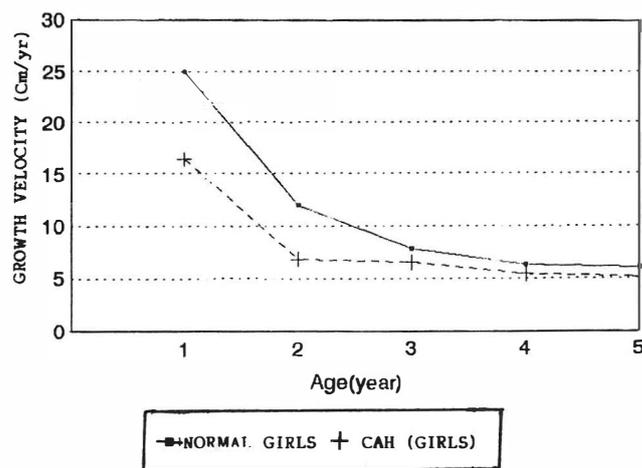


Fig. 2. Yearly gain in height in normal girls and female patients with congenital adrenal hyperplasia.

overdose during follow-up. The question arises whether or not there are other factors besides treatment that influence growth patterns. It must be noted that all patients who were begun on treatment before one year of age had the salt-losing type of congenital adrenal hyperplasia, this more severe form of the disease perhaps making optimal treatment more difficult.<sup>13</sup>

In our cases during the first two years of life, increases in hydrocortisone dosage were frequently necessary for episodes of stress, such as infection or acute dehydration. This increased dosage was prolonged in most cases beyond the acute phase of infection. Thus, growth retardation could possibly be due to this period of overtreatment.

Recommended glucocorticoid preparations include hydrocortisone, prednisolone or prednisone. In spite of the fact that hydrocortisone has less growth-suppressing effects compared to other synthetic corticoids, severe growth retardation was observed during the first 2 years of life in patients with the salt-losing form of congenital adrenal hyperplasia who were treated orally with this agent.<sup>6</sup> Perhaps some loss of height is inevitable in patients with congenital adrenal hyperplasia, even with the smallest possible dose of glucocorticoids.

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