Brief Reports

Audit of Care of Patients with Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency in a Referral Hospital in South India

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We carried out an audit of management of patients with 21-Hydroxylase deficiency CAH who presented to the Department of Endocrinology OPD from 1999 till 2004 and had a minimum follow up of 6 months. Of the 30 patients analysed 24 were girls and 6 were boys. The majority belonged to the Christian community. One third had a history of consanguinity or family history of similar illness. Sex assignment was appropriate in most. Karyotyping was done in half. Half the patients had adequate follow up and 17 OHP measurements. Only 7 out of 30 children had normal height for age. Bone age was done in 16 patients only. Most were on hydrocortisone. The average age of genital surgery was 31 months.

Key words: *Ambiguous genitalia, Congenital adrenal hyperplasia.*

CONGENITAL adrenal hyperplasia (CAH) is an inherited disorder of adrenal steroido-genesis. 90% of cases are due to 21 hydroxylase deficiency(1). 75% of classical CAH are salt wasters with both cortisol and mineralocorticoid deficiency and 25% simple virilisers with only cortisol deficiency(2). The Endocrinology Department in our tertiary care hospital has been managing children with CAH since 1999 and the audit was done to assess the adequacy of management and make appropriate changes.

Subjects and Methods

Patients with classical 21 hydroxylase CAH attending the Endocrinology OPD from 1999 till 2004 with a minimum follow up of 6 months were included. Diagnosis was based on elevated basal or ACTH stimulated 17 OHP levels(3). Salt Wasting (SW) form was considered if a salt wasting episode occurred during the first month of life(4) and Simple Virilizing form (SV) if clinical symptoms of CAH without SW were present before puberty *i.e.*, before 8 years of age(5). Case records were retrospectively analysed for the following points based on published guidelines and review of literature(2,6,7): (*i*) sex distribution and type of CAH–Simple virilisers or salt losers; (*ii*) religion; (*iii*) sex assignment whether done correctly in the neonatal period and if not the age of reassignment; (*iv*) karyotyping whether it had been done in children with ambiguous genitalia; (*v*) frequency of follow-up: The recommendation is once in 3-4 months. Patients were categorized

into those with follow up every 3 months, 3-6 months, 6 months or more; (*vi*) clinical parameters–height, weight, growth velocity, blood pressure; (*vii*) biochemical testing: Treatment efficacy is best monitored by measuring 17OHP levels at a consistent time in relation to medication. Levels should be partially suppressed to between 1-10 ng/mL. Hormonal assessment should be done at 0800 h at the peak of ACTH secretion, or at the nadir of hydrocortisone blood levels just before the next dose(2). Monitoring should be done every 3 months in infancy and 4-12 monthly thereafter(7). Frequency of monitoring of 17OHP, timing and levels were noted; (*viii*) bone age: It was noted whether this had been done annually and whether it was normal or not using the Greulich and Pyle method by a single observer(8); (*ix*) choice of glucocorticoid and optimal dosage: Deficient steroids should be replaced and adrenal androgens minimized without producing glucocorticoid excess(6). Hydrocortisone (10-20 mg/m^2) given orally in two or three daily divided doses is the glucocorticoid of choice(2). Long acting glucocorticoids like prednisolone or dexamethasone can be given when linear growth ceases. Prednisolone has to be given twice daily in a dose of 2-4 mg/m^2/day. The type of glucocorticoid, average dose in mg/m^2 and dosing frequency were ascertained; (*x*) mineralocorticoid therapy: All salt wasters should be treated with fludrocortisone in the newborn period. Typical maintenance doses are 0.05-0.2 mg/d. The dose of mineralocorticoid was noted; (*xi*) genital surgery: Surgery is recommended between 2 and 6 months of age. Timing of surgery was noted; and (*xii*) pubertal status.

Results

Thirty patients, six males and 24 females were analysed. Twenty two were salt wasters (16 female and 6 male) and 8 simple virilisers (all female). All except 2 had been diagnosed elsewhere. Nine patients were currently aged 3 years or less, fourteen between 3 and 10 years of age and seven patients were above 10 years.

Average age at diagnosis was 4.07 months. Among salt losers it was 1 month in males and 9 days in females and in girls who were simple virilisers it was 14 months. Some of the parameters are shown in *Table I*.

Majority were Christians, 18 (60%), followed by 8 Hindu (26.7%) and 4 Muslims

TABLE I– *Characteristics of Patients with CAH*

Variable	Mean	Minimum	Maximum
Current age (years)	7.516	0.08	22
Age at diagnosis (months)	4.070	0	48
Age at first visit (months)	22.539	0	180
Follow up period (months)	22.60	3	50
Mean 17OHP at diagnosis (ng/mL)	40.08	5	200
Mean 17 OHP at follow up (ng/mL)	18.716	0.50	72.00
Mean dose of HC (mg/m^2)	18.097	2.34	30.20
Mean dose of Prednisolone (mg/m^2)	4.22	1.84	7.94
Average age of first genital surgery (months)	31.2	4	72

(13.3%). Since 1998 of the 3,20,000 patients who have visited our hospital, 55% were Hindu, 35% were Muslim and 10% were Christian.

Ambiguous genitalia was diagnosed at birth in 23 of 24 girls and at 2 years in one girl. Six girls had been wrongly assigned male sex at birth. In 5 it was correctly reassigned by one month of age and in one at 6 years. Karyotyping had been done in only 16 of the 23 patients with ambiguous genitalia and it was 46,XX in all.

Frequency of follow up was every 3 months in 7, 3-6 months in 9 and more than 6 months in 13 patients. One patient was lost to follow up.

All patients had height, weight and blood pressure measured on most visits. Seven patients had 17OHP done once a year, 10 twice a year, 12 thrice a year and one patient 4 times a year. Only 7 out of 30 children had normal height. In 17 patients height was below the 5th centile and in 6 children it was above the 95th centile. Age-wise break up of height is shown in *Table II*.

Bone age was assessed in 16 patients only. It was normal in 2, delayed in 1 and advanced in 13 patients.

Twenty five patients were on hydrocortisone, 20 on thrice and 5 on twice daily doses. Of the 5 patients who were on prednisolone, 3 were above 16 years, one was 9 years and one 7 years old. All children on prednisolone had height below 5th centile. Twelve of the 25 children on hydrocortisone had a bone age done. It was advanced in 11 and normal in one. Eighteen of 22 patients with salt wasting were on fluorocortisone in a dose of 25-200 ug/day.

Of 24 girls, 20 had undergone one or more genital surgeries at an average age of 31 months. The average age of surgery was 4 months in children who had presented to our hospital in the immediate neonatal period.

Five girls had attained menarche at a mean age of 14.6 years. Four had regular menstrual cycles and one was oligomenorrhic. One boy was above 9 years. He is now 12 years old and has precocious puberty with height above the 95th centile, bone age of 16 years and Tanner 4 pubertal stage.

Discussion

As in other series(9) the majority were girls. More than half the children were short. This could be due to overtreatment with glucocorticoids. Prospective studies have shown significant negative correlations between growth velocity and glucocorticoid doses(10). But inadequate treatment can lead to elevated adrenal androgens and premature epiphyseal fusion(11).

Less than half our patients had a 17OHP level done 3 or more times a year. The mean 17OHP on follow up was not adequately suppressed and might have contributed to the growth retardation. Initially we had aimed for a normal 17OHP, but currently we aim at a value between 1-10 ng/mL as recommended(2). There were wide intra-individual variations in the 17OHP values which could have been due to sampling at different times of the day. We now check 17OHP, 2 hours after the morning dose of Hydrocortisone.

Bone age was assessed at least once in half

TABLE II–*Age-wise Distribution of Height*

Height centile	Number of patients as per age		
	< 3years	3-10 years	>10 years
< 5th	4	8	6
5-95th	4	2	1
>95th	1	4	0

Key Messages

- Patients with CAH should be followed up every 3-4 months.
- 17OHP should be kept between 1-10 ng/mL and not suppressed to normal levels.
- Hydrocortisone is the preferred glucocorticoid in children.

the patients only. Annual assessment would have helped to consider insufficient androgen suppression or excess glucocorticoids as the cause for growth retardation and make necessary dosage adjustments. This was exemplified in one of the 17 children whose height was below 5th centile. Her average dose of Prednisolone was 5.59 mg/m^2 and bone age was delayed. Her mean 17OHP was 6.0 ng/dL. She has been switched over to Hydrocortisone and on follow up at 6 months, her growth velocity has improved. Her bone age will be repeated at the end of one year. Majority of our patients were on hydrocortisone and the mean dose of 18.09 mg/m^2/day was acceptable. The mean dose of Prednisolone of 4.34 mg/m^2 was in the upper range of the recommended dosage. Mineralocorticoid replacement in our patients seemed to be adequate.

The average age of first surgery was 31 months. The delay was because these patients presented to us late in life.

Pubertal status was appropriate in most. Only one of the girls who had attained menarche had oligomenorrhoea. One boy had precocious puberty.

Conclusion

We identified several areas where patient care could be improved. These are (*i*) frequent follow up and periodic biochemical testing 3-4 times yearly; (*ii*) Bone age should be performed annually; (*iii*) the timing of 17OHP testing should be standardized–either at 8 am or two hours after the morning dose of hydrocortisone. Time of sampling should be maintained the same for each patient during follow up visits; and (*iv*) 17 OHP should be maintained between 1-10 ng/mL, and not suppressed to normal levels.

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Bone Mineral Density in Response to Two Different Regimes in Rickets

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The aim of this study was to compare the bone mineral density (BMD) of two different treatment regimens in infants with nutritional vitamin D deficient rickets (VDR). Ten patients (Group 1) were treated with a single dose of 600,000 IU of oral vitamin D_3 and another ten patients (Group 2) were treated with 20,000 IU/day of oral vitamin D_3 for 30 days. BMD was measured in the lumbar spine twice in all infants before the treatment and on the 31st day after initiating the treatment. The increases of BMD after treatment compared to pretreatment levels were statistically significant in both groups (P=0.005 in Group 1 and P=0.047 in Group 2). The increments of BMD were statistically similar between Group 1 and 2 (P=0.096). The present study suggests that these two different treatment regimens bring about similar healing in BMD.

Key words: *Bone mineral density, Nutritional rickets, Vitamin D.*

RICKETS signifies a failure in mineralization of growing bone or osteoid tissue. The predominant cause is nutritional vitamin D deficiency rickets (VDR) due either to inadequate direct exposure to ultraviolet rays in sunlight or inadequate intake of vitamin D, or both(1,2). There are various regimens of vitamin D replacement treatment(1-6). Two preferable regimens are daily administration of 20,000 IU/day of vitamin D for 2-4 wk or