

CONGENITAL ADRENAL HYPERPLASIA: EXPERIENCE AT CALCUTTA

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ABSTRACT

Eight patients (7 females, 1 male) with congenital adrenal hyperplasia (CAH), were seen over a 24-month period beginning from March 1988. Seven patients had 21 hydroxylase (21-OH) deficiency while one had 11 beta hydroxylase deficiency. Of the 7 patients with 21-OH deficiency, 3 were of the salt losing (SL-CAH), and 4 were of the non-salt losing (NSL-CAH) type. The patients with NSL-CAH were diagnosed by their elevated 17-hydroxyprogesterone (17-OHP) levels. The 3 cases with SL-CAH were diagnosed on the basis of ambiguous external genitalia, typical electrolyte picture, normal female internal genitalia, sex chromatin and response to steroids. In one patient post-ACTH 17 OHP was alter measured. All 3 patients with SL-CAH were assigned the male sex. Sex reassignment was advised for two children; one accepted the advice and the child is doing well; one family did not accept sex reassignment and the child died. One patient died due to non-availability of fludrocortisone. Six patients are under follow-up. All are doing well except one patient with NSL-CAH who started treatment late. We conclude that a high index of suspicion, early diagnosis and meticulous patient education are the key features of successful management of CAH in India.

Key words: Congenital adrenal hyperplasia.

Congenital adrenal hyperplasia (CAH) has a variable incidence ranging from 1 in 490 among Yupik eskimoes to 1 in 43,674 in Japan(1,2). The commonest form of CAH is due to 21 hydroxylase (21-OH) deficiency. This enzyme deficiency causes inadequate production of cortisol leading to increasing ACTH stimulation with accumulation of cortisol precursors. As these precursors are androgenic, they cause virilization in females and precocious puberty in males. In the salt losing type (SL-CAH), the enzyme deficiency extends to the zonal glomerulosa, causing mineralocorticoid deficiency. SL-CAH can present as a neonatal emergency. In the non-salt losing type (NSL-CAH) virilization is the main feature; some cases may present in adult life(3).

The diagnosis of 21-OH deficiency is established by measuring 17-hydroxyprogesterone (17-OHP) levels preferably after ACTH stimulation(4). It is of paramount importance to diagnose the condition as early as possible. With proper treatment, girls can have normal growth and pubertal development and preserve their child bearing capacity. Neonatal screening programmes are in operation in some areas(5).

The gene for 21-OH deficiency is located on chromosome 6. It is in linkage disequilibrium with HLA genes(6) and a specific probe is available for diagnosis(7). It is, therefore, possible to offer antenatal

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Received for publication: April 5, 1991;

Accepted: January 25, 1992

diagnosis and genetic counselling. Treatment of the condition *in utero* has been tried by giving the mother dexamethasone, but the results are not completely satisfactory(8).

This article is based on the local experience on managing 8 patients with CAH over a 24 month period starting from March 1988.

Case Reports

Case 1 presented at 8 weeks of age, with vomiting. Ambiguous genitalia were noted at birth but the child was assigned male sex. At the time of examination, the child was dehydrated with marked clitoromegaly and enlarged, unfused labial folds. Serum Na^+ was 121 mmol/L, K^+ 5.4 mmol/L, and urea 49 mg/dl. The buccal smear was sex chromatin positive and an abdominal ultrasonogram was normal for a girl. She was stabilized on fludrocortisone 100 $\mu\text{g}/\text{day}$ and betamethasone oral drops 125 $\mu\text{g}/\text{day}$. Gender reassignment was advised and accepted by the parents. Follow-up after 7 months showed a 75% regression of the clitoris. Length and weight were satisfactory at the 10th percentile and the sex reassignment was well accepted by the family. She is under regular follow-up. Post ACTH 17-OHP measured at another institution was 120 ng/ml, which confirmed the diagnosis.

Case 2 presented at 5 weeks of age with severe dehydration and prerenal failure. The serum Na^+ was 124 mmol/L, K^+ 5.6 mmol/L and urea 54 mg/dl. The parents had assigned male sex to the child and did not feel that ambiguous genitalia was a problem. The child had clitoromegaly, labial fusion, and a positive sex chromatin. The child was stabilized on intravenous fluids and hydrocortisone (HC) 15 mg/kg/

24 h. The patient's electrolyte abnormalities could not be controlled on oral betamethasone and the parents could not afford fludrocortisone. It was, therefore, decided to stabilize her on oral HC from a reconstituted vial of injection HC. The parents were taught to administer HC orally using an insulin syringe. It was found that using one vial every 2 weeks. HC 3 mg per day orally could normalize the patient's electrolytes. An ultrasonogram of the abdomen and pelvis showed normal female internal genitalia. The patient was discharged on this minimum treatment. The parents were resistant to the idea of sex reassignment and they later reported that the child had died. Subsequently, another child was born to these parents clinically identical to *Case 2*, who died at 2 months age.

• *Case 3* presented at the age of 1 month with severe vomiting, marasmus, clitoromegaly and labial fusion. Serum Na^+ was 116 mmol/L and K^+ 5.8 mmol/L. The electrolytes normalized on IV fluids and HC 15 mg/kg/24 h. The sex chromatin was positive and an ultrasonogram demonstrated the presence of normal kidneys and normal female internal genitalia. SL-CAH was diagnosed and the patient needed fludrocortisone in addition to HC for stabilization. After 3 months of treatment, the clitoris regressed by 50% and electrolytes were normal. Unfortunately, a regular supply of fludrocortisone could not be ensured and the patient died 4 months later.

Case 4 presented at age 9 months with a history of slow recovery from minor chest infections. On examination she had mild clitoromegaly and was otherwise normal. The electrolytes were normal. The addition of betamethasone 50 $\mu\text{g}/\text{kg}/\text{day}$ resulted in rapid recovery. Later 17-OHP levels were

measured 12 hours after stimulation with 40 units of ACTH gel. A value of 370 ng/ml was recorded. This was abnormally high and was felt to be due to 21-OH deficiency. The simultaneous cortisol value was 14 µg/dl, indicating inadequate cortisol production (lower limit of normal of post ACTH cortisol = 20 µg/dl). The patient was not put on regular medication but advised to take steroids during stressful events. During the last 8 months, the patient's growth has been 'along the curve' and her bone age is normal.

Case 5 presented with hirsutism at 17 years. She had developed irregular menstrual cycles over the last 2 years with occasional periods of secondary amenorrhea. On examination, she had a BP of 140/95 mm Hg and mild clitoromegaly. The patient was investigated and the possibility of Cushing's syndrome and polycystic ovaries (PCOs) were eliminated. 17-OHP levels were normal. She had elevated levels of urinary 17-OH steroids (17-OHS) 45 mg/24 h (normal range 6-18 mg/24 h), and her 17 ketosteroids (17-KS) were 17.5 mg/24 h (normal range 4-15 mg/24 h). On dexamethasone, the levels could be suppressed to 3.9 mg/24 h for 17-KS and to 5 mg/24 h for 17-OHS. A specific diagnosis of 11-hydroxylase deficiency was made and the patient was started on dexamethasone 0.5 mg daily at bed time. After 5 months, the patient reported decrease of hirsutism and restoration of normal periods.

Case 6 presented at an age of 3 months with clitoromegaly and labial fusion. Her electrolytes were normal. She underwent clitoroplasty and vaginoplasty and was put on prednisolone. She was re-evaluated 11.5 years after the diagnosis. She had menarche 4 months previously and her bone age was at par with her chronological

age. Her height was at the 25th percentile (Harvard) and weight at 50th percentile. Her basal 17-OHP level was 2.0 ng/ml (range in adult females -0.1 to 3.9 ng/ml). Her ACTH stimulated 17-OHP level was 124 ng/ml. She was advised to continue on prednisolone and is being monitored clinically and by regular free testosterone levels.

Case 7 was a first cousin of *Case 6*. She presented at 3 years of age with clitoroplasty and vaginoplasty. She was put on prednisolone but her endogenous adrenocortical secretion could never be satisfactorily suppressed. When doses sufficient to cause suppression were used, Cushing syndrome was caused, while doses just short of producing Cushing syndrome, caused inadequate suppression. When reviewed at age 13 years, she was mildly virilized. Her weight was at the 90th percentile, height under the 3rd percentile and bone age advanced to 18 years. Her basal 17-OHP level on a prednisolone dose of 6.25 mg/day, was 12.6 ng/ml (range 0.1 to 3.0 ng/ml). Her testosterone was 0.42 ng/ml (normal range 0.1 to 0.2 ng/ml). She had primary amenorrhea, for which she was started on cyclical estrogen/progesterone tablets. Recently, the patient developed hirsutism and was put on cyproterone acetate and estrogen with good results. However, whenever her dose of prednisolone had been increased to 7.5 mg/day, she developed cushingoid features.

Case 8 was a boy aged 6½ months who presented with virilization. He was in Tanner stage 2 but his testes were not enlarged and his bone age was 1 year. His testosterone level was in the pubertal range 3.4 ng/ml (post-pubertal range 3-12 ng/ml) and his basal 17-OHP level was 1.9 ng/ml (pre-pubertal range 0-0.6 ng/ml). His electrolytes were normal and beta HCG was un-

detectable. A diagnosis of NSL-CAH due to 21-OH deficiency was made and the child was put on betamethasone drops, 20 $\mu\text{g/kg}$. Follow-up after 1 month showed regression of virilizing features. After 3 months, testosterone was in prepubertal range (1.0 ng/ml) and growth was normal.

The presenting features of these subjects are summarized in the *Table*.

Discussion

Babies with ambiguous genitalia are invariably assigned male sex in India. Great resistance is usually encountered when sex reassignment is suggested. Patience and tact are needed in abundance on the medical side to successfully educate the family. The family, including grandparents, must have a certain level of general education to understand the implications of the diagno-

sis. Primary care personnel need to realize that ambiguous genitalia in a newborn constitute a medical emergency until SL-CAH is ruled out. The initial assignment of sex in these cases needs to be carefully considered so that a psychologically traumatic sex reassignment does not become necessary in future.

There are several constraints to the proper management of CAH in our setting. 17-OHP assays are not always available or affordable. Indeed in a case of SL-CAH presenting as an emergency, we feel that the constellation of clinical and biochemical features is sufficiently compelling to begin treatment with hydrocortisone. Prior to the availability to 17-OHP assays, the clinical picture (ambiguous external genitalia, dehydration and abnormal electrolytes) and good response to steroids were suffi-

TABLE—Summary of the Eight Subjects

Case No.	Presenting age	Type	Diagnosis	Treatment	Result
1	8 weeks	SL-CAH	Clinical, electrolytes, therapeutic response + 17-OHP	Betamethasone + Fludrocortisone + sex reassignment	Excellent
2	6 weeks	SL-CAH	-do- 17-OHP not done	Oral HC	Patient died, sex reassignment not accepted.
3	1 month	SL-CAH	-do-	Betamethasone + Fludrocortisone	Fludrocortisone could not be procured, patient died.
4	9 months	NSL-CAH	ACTH stimulated 17-OHP levels.	HC during stress	Excellent
5.	17 years	NSL-CAH	11 β hydroxylase deficiency.	Dexamethasone	Excellent
6.	3 months	NSL-CAH	17-OHP	Prednisolone	Good
7.	3 years	NSL-CAH	17-OHP	Prednisolone + Cyproterone + Ethinyl estradiol	Poor, as adrenals are autonomous.
8.	6½ months	NSL-CAH	17-OHP	Betamethasone	Good

cient to diagnose SL-CAH in a girl with normal internal genitalia and positive sex chromatin. We feel that the risks of 24 hour urine collection by catheter outweigh the potential increase in diagnostic accuracy.

Later, an ACTH stimulated 17-OHP level can be obtained for confirmation. The peak value should exceed 100 ng/ml, regardless of therapy (Dr Ricardo Aziz, University of Alabama, Birmingham, personal communication). In our series 17-OHP levels were measured in all the patients except Nos. 2 and 3. Unfortunately, water soluble ACTH for diagnostic use is not easily available in India. However, various ACTH gel preparations are available, with poorly characterized pharmacodynamic profiles. We have used these preparations in a dose of 30 units of ACTH given intramuscularly with blood sampling being performed 12 hours later.

Case 1 with salt losing CAH (SL-CAH) was successfully managed. The critical factor for management was the acceptance of sex reassignment by parents and family. Once this was achieved, the medical team and the family could work together towards a common goal.

In *Case 2* with SL-CAH, sex reassignment was unacceptable to the family. The therapeutic regime available to us was unsatisfactory. Fludrocortisone was indicated but the parents could not procure it. We, therefore, treated her with reconstituted HC injection administered orally. In spite of the manufacturer's injunction to use a reconstituted vial within 24 hours, we found that the patient could be maintained in a stable state even if each vial was used for 2 weeks. Hence, this was the treatment advised. The child was however, lost to follow-up and later died.

Case 3 who came from an adoption agency, died due to lack of a regular supply of fludrocortisone.

Case 4 had a rather unusual variant of NSL-CAH. It presented as mild cortisol deficiency in the first year of life. In general these patients do not need supplementary steroids once they are older(9).

Case 5 had a rare form of CAH, estimated to be 1 in 100,000 population. She presented as a case of hirsutism and was thoroughly worked up only because PCOS was excluded. The specific diagnostic assay was not available in India (11 deoxycortisol) but the urinary steroid excretion pattern in presence of hypertension was sufficiently specific to make a diagnosis.

Case 6 with NSL-CAH had a satisfactory response as treatment was started at 3 months age. However, in *Case 7* with a similar condition, treatment was started at 3 years, by which time, the adrenals had become particularly autonomous. *Case 8*, the only male patient, is progressing satisfactorily.

Oral hydrocortisone, the drug of choice, is not freely marketed in India. Fludrocortisone has to be imported. We have used betamethasone drops in infants when glucocorticoid suppression alone was desired and administered injection HC only when a mineral corticoid effect was required. No pharmaceutical company in India makes low strength glucocorticoid tablets. Therefore, dose titration is not sufficiently accurate and patients often fluctuate between undersuppression and Cushing syndrome.

Monitoring of patients should ideally be clinical and biochemical. Clinical parameters include hirsutism, clitoromegaly, menstruation, weight and height. A pre-

cisely maintained height record is a sensitive index of adequacy of treatment, as both over-treatment and understatement will cause the height curve to level off. The most sensitive biochemical index is now thought to be plasma rennin activity (PRA) for both SL and NSL-CAH. Testosterone or 17-OHP assays can be used but DHEA assays are not recommended. PRA assays are not generally available and technically difficult (blood must be kept at 0°C from time of collection). Thus, clinical assessment remains the most useful method of follow-up.

Genetic counselling and antenatal diagnosis of CAH are now practicable. Affected female fetuses may be treated *in utero*(8).

CAH although rare, needs a multi disciplinary management approach from the time of birth. An accurate diagnosis can be made within the limits imposed by our lack of diagnostic sophistication, provided the diagnosis is kept in mind. Non-availability of drugs and inability to diagnose the rare forms of CAH are serious limitations. However, if adequate treatment is begun early, highly satisfactory results may still be obtained.

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