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# MODE OF PRESENTATION AND SHORT TERM RESPONSE TO TREATMENT IN CASES OF CONGENITAL ADRENAL HYPERPLASIA (CAH) DETECTED OVER A PERIOD OF ONE YEAR AT MILITARY HOSPITAL RAWALPINDI

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## ABSTRACT

***Background:*** Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition which not infrequently presents with life threatening emergencies. Awareness of physicians regarding these presentations is a prerequisite for a prompt diagnosis and life saving treatment. In view of the prevalence of the condition as reported from tertiary care centres within the country and other parts of the globe, we carried out a study in the department of paediatric medicine at the Military Hospital Rawalpindi to determine the modes of presentation of congenital adrenal hyperplasia (CAH) and to observe the short term response to treatment.

***Material and Methods:*** The study extended over a period of one year from Aug 2003 to July 2004. All children presenting with vomiting, dehydration, shock, failure to thrive and ambiguous genitalia were examined and investigated thoroughly. The mainstay of the diagnosis was a raised level of serum 170HP in a child with suggestive clinical features.

***Results:*** A total of 30 children were fournd to have CAH during the study period. The major clinical features a presentation were vomiting 8(26.7%), ambiguous genitalia 7(23.3%), vomiting and ambiguous genitalia 10(33.3%), shock 4(13.3%) and failure to thrive 1(3.3%). All the patients were followed up after initiation of treatment and response was observed.

***Conclusion:*** The study highlights the importance of common clinical symptoms life vomiting being the presenting features of CAH and the effectiveness of replacement therapy in ameliorating life threatening emergencies due to this condition.

**Keywords:** Congenital adrenal hyperplasia (CAH), 17 hydroxy progesterone (17OHP), Cytochrome p450 protein (CYP)

## INTRODUCTION

CAH is a genetic disorder characterized by a deficiency in the hormones cortisol and aldosterone and an over-production of the hormone androgen, which is present at birth and affects sexual development. The disorder is inherited as an autosomal recessive defect in inborn enzyme synthesis. As such there is history of early neonatal death in the family. The clinical manifestations of the disease relate to the degree of cortisol deficiency, aldosterone deficiency, or deficiency of both and, in some cases, to the accumulation of precursor adrenocortical hormones. These precursors cause abnormalities such as virilization or hypertension when present in supraphysiologic concentration many of the

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enzymes involved in cortisol and aldosterone syntheses are cytochrome p450 proteins designated CYP. CYP21 refers to 21-hydroxylase, CYP11B1 refers to 11-beta-hydroxylase, and CYP17 refers to 17-alpha-hydroxylase. Excess adrenal androgen production begins in early fetal life in classic CAH-21 affected infants, and causes abnormal growth of girls' clitoris and masculinization of the genital-urinary structures. Severely affected girls may be mistaken for boys at birth. Affected boys have no genital malformations at birth, but continued androgen excess causes unusually fast body growth. Inappropriately early puberty leads to premature completion of growth and short final adult height [1- 3].

Severe forms of congenital adrenal hyperplasia are potentially fatal if unrecognized and untreated because of the severe cortisol and aldosterone deficiencies that result in salt wasting, hyponatremia, hyperkalemia, dehydration, and hypotension[1,6,7]. Females with some forms of adrenal hyperplasia (i.e., CYP21 deficiency, CYP11B1, partial 3-beta-hydroxysteroid dehydrogenase deficiency) have ambiguous genitalia at birth (classic virilizing adrenal hyperplasia) or subsequently become virilized in childhood (simple virilizing adrenal hyperplasia) or in adolescence and adulthood (nonclassic virilizing adrenal hyperplasia). Males with CYP21 deficiency are not generally identified in the neonatal period because their genitalia are normal. If the defect is severe, resulting in salt wasting, these male infants are seen at 1-4 weeks of age because of failure to thrive, recurrent vomiting, dehydration, and shock. Some infants are initially misdiagnosed with gastroenteritis or pyloric stenosis [1,2,6].

Hyponatremia and hyperkalemia should raise the possibility of adrenal insufficiency. Two forms of adrenal hyperplasia (i.e., CYP11B1 deficiency, CYP17 deficiency) result in hypertension [1,2,6,7] Congenital adrenal hyperplasia occur among people of all races. Congenital adrenal hyperplasia because all forms of congenital adrenal hyperplasia are autosomal recessive disorders, both sexes are affected with equal frequency [1]. All children including newborn who have vomiting and/or dehydrating are diagnosed as acute gastroenteritis. This results in certain inborn errors of metabolism especially CAH being overlooked, inappropriately treated and results in increasing preventable mortality earlier in life. The purpose of study is to describe our experience of identifying CAH in terms of their presentation and short term treatment.

## PATIENTS AND METHODS

This descriptive study was carried out in pediatric department of military hospital Rawalpindi from July 2003 to Aug 2004. The main aim of the study was to find out the main modes of presentation of CAH and to see the response of treatment on short term basis. A successful response to replacement therapy observed within a period of two to four was cessation of vomiting, need for intravenous fluid therapy and failure to thrive. All patients suspected to have CAH i.e. with clinical features and raised serum levels of 170HP were included in the study.

A detailed history (vomiting, failure to thrive, sibling death) followed by thorough physical examination (blood pressure, hydration, girls for ambiguous genitalia and boys for precocious puberty) was carried out. Investigations done included complete blood count, blood sugar, serum urea and electrolytes (sodium 130 – 150 mmol/l; potassium 3.5 – 4.0 mmol/l), karyotyping and serum17OHP levels (Normal < 100 ng/dl). Classical salt wasting variety have 17 OHP levels > 2000 mg/dl; Classical virilizing > 1000 ng/dl and nonclassical = 100 - 200 ng/dl. Karyotyping was done in patients with ambiguous genitalia to establish the diagnosis of CAH in our study. Classically they had to be female karyotype who was virilized [4]. Patients that had other reasons for ambiguous genitalia and failure to thrive like renal

tubular defects etc were excluded from the study. All investigations were carried out in Armed Forces Institute of Pathology Rawalpindi and the pathology department of army medical college.

All patients were treated with replacement therapy including hydrocortisone 50 mg/M2 stat followed by 1000 mg / M2/ day 6 hourly, tapered to 20 mg / M2 /day. In salt losing variety initially normal saline 20 ml / kg was repeated if necessary followed by florinated steroid ( fludrocortisone – 0.15 mg / M2 ) was given. The response to the standard paediatric practice was studied.

## RESULTS

Total of 30 patients were diagnosed to have CAH. The age range of children was from 4 to 180 days with a mean age at the time of presentation was 39.67 days. (table-1) the sex distribution was almost equal (table-2). The main clinical features included vomiting, ambiguous genitalia, dehydration and failure to thrive (table-3). Investigations of all the patients showed raised levels of 17OHP. Karyotyping was done in patients with ambiguous genitalia.

All cases diagnosed to have CAH were put on replacement therapy. Short term response was observed after a period of 4 weeks. All cases showed positive response shortly after the initiation of therapy.

The patients who presented with failure to thrive started gaining weight. As vomiting was the major symptom at presentation, it responded well to treatment. Children presenting with ambiguous genitalia were put on replacement therapy and later referred for surgical treatment i.e. clitoroplasty.

## DISCUSSION

CAH is mainly disease of early infancy as the mean age of presentation in our study is

**Table-1: Salient features of the 30 cases studied.**

| | |
|---|---|
| Mean age of presentation (days) | 39.67 |
| Male: female ratio | 1.5:1 |
| Major symptom/sign (vomiting n ambiguous genitalia | 10(33.3%) |
| Positive Family history/Neonatal death | 10(33%) |

**Table-2: Gender distribution.**

| | No of Patients | Percentages |
|---|---|---|
| Female | 13 | 43.3% |
| Male | 17 | 56.7% |

**Table-3: Presenting features of the cases.**

| | No of Patients | Percentages |
|---|---|---|
| Vomiting | 8 | 26.7% |
| Ambiguous genitalia | 7 | 2.3% |
| Vomiting and ambiguous genitalia | 10 | 33.3% |
| Failure to thrive | 1 | 3.3% |
| Shock | 4 | 13.3% |

**Table-4: Treatment.**

| | No of Patients | Percentages |
|---|---|---|
| Hydrocortisone | 7 | 23.3% |
| Hydrocortisone and fluodrocortisone | 23 | 76.7% |

39 days. It is widely present all over the world with equal male to female ratio [1,2]. The present study also shows the same result with mean age of presentation being 39.67 days. However there is slight male preponderance in our study (56.7%). Clinical features observed in this study are in conformity with other studies .The frequent modes of presentation include vomiting, ambiguous genitalia, shock and failure to thrive [1,2]. Some patients presented just one symptom and other with two or three signs and symptoms together.

Most of the children in our study presented with persistent vomiting since birth. This was initially thought of, because of intestinal obstruction like pyloric stenosis or

simple regurgitation of milk, which is much more common in young infants. Vomiting, as the only presenting feature makes the diagnosis little difficult but it is often associated with ambiguous genitalia especially in females i.e. clitoromegaly. Females are recognized because of ambiguous genitalia, but males have normal genitalia and are not diagnosed until later, often with a salt losing crisis [8]. Another important clinical sign was failure to thrive. It was present along with vomiting and also as the lone presenting feature. Salt losers also presented in a state of shock. The standard for diagnosis was raised levels of 17OHP [4,5]. As the diagnostic facilities are easily available, diagnosis at an early age with initiation of treatment is possible. 21 hydroxylase deficiencies (CYP 21) is the most common form. Approximately 50 % of patients with classic congenital adrenal hyperplasia from CYP 21 deficiency have salt wasting due to inadequate aldosterone synthesis. One third of patients in our study presented with evidence of salt wasting [8]. Being an autosomal recessive disorder, there is 25 % chance that the condition will be found in the siblings of the patient. In our study there was an increased incidence (33% of the patients) of disorder in siblings of patients in our study. Incidence in all the patients could not be found as some of the patients were the first issues of the parents. Even in those, in whom the disorder was suspected, only clinical diagnosis was thought of on the basis of early neonatal death. However efforts should be made in establishing prenatal diagnosis possible as intrauterine dexamethasone during the first trimester helps in reducing chances of ambiguous genitalia. This is done via chorionic villus sampling in first trimester at 8 weeks gestation [1-3]. Amniocentesis at 12 weeks can also be done. As a prenatal management measure, Dexamethasone (10 – 20 ug /kg / day) at diagnosis of pregnancy is started. Stop the treatment in boys and unaffected girls. Affected girls in whom dexamethasone should be continued, maternal urinary estriol (target < 375 ng/ dl) are followed up [8,9].

## CONCLUSION

Following points are drawn from our study:

- CAH is basically a disease of early infancy
- The usual presenting complaints are very common like vomiting, dehydration and failure to thrive.
- Prompt treatment with replacement therapy can effectively abort a life threatening state.

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