ORIGINAL ARTICLE

CLINICAL PROFILE OF PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA DUE TO 21 HYDROXYLASE DEFIICIENCY

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ABSTRACT

Introduction: 21 Hydroxylase deficiency is the most common enzymatic deficiency seen in XX-DSDs. 11-deoxycorticosterone and 11-deoxycortisol are deficient in the most-severe, "salt-wasting" form of this disease. This study aimed to see clinical profile of CAH patients in a tertiary care hospital.

Methodology: This study was carried over a period of 36 months. All patients who presented to hospital with features suggestive of congenital adrenal hyperplasia were examined thoroughly. These patients were evaluated for possibility of congenital adrenal hyperplasia after their initial resuscitation and stabilization.

Results: Over a period of 36 months, 40 patients with congenital adrenal hyperplasia were diagnosed. We diagnosed 32 cases as salt losing CAH. Median age of presentation was 36 days with range from 1- 90 days. 20 patients presented with recurrent vomiting, refusal of feeds, lethargy and dehydration. 23 of 32 patients presented in shock. 16 patients were products of consanguineous marriage. 26 cases had hyponatremia (<135mg/litre) at presentation. 17 patients had hyperkalemia (serum potassium>5.5mg/litre) at admission. 7 cases had hypoglycemia at presentation. 6 patients were diagnosed as having simple virilizing CAH. One patient presented at 5 years of age with precocious puberty and another presented during evaluation of undescended testis at age of four and a half years.

Conclusion: Congenital adrenal hyperplasia is a unique disorder due to very adverse outcomes and even death resulting from enzyme deficiency if left untreated; and associated social taboos There is a need to start neonatal screening for CAH in our country.

Keywords: Congenital adrenal hyperplasia, clinical profile, screening

INTRODUCTION

On a world-wide scale, XX-Disorders of Sexual Development is the commonest of type of Disorders of Sexual Development (DSD), forming 75% of DSDs, and is seen in all populations and race groups[1]. It is a result of an enzymatic deficiency in the cortisone / 11-deoxycorticosterone biosynthesis[2]. This deficiency gives rise to a build-up of precursors, which leads to a phenotypic androgenization. 21 Hydroxylase deficiency is the most common enzymatic deficiency seen in XX-DSDs[3]. This P450 enzyme (CYP21, P450c21) hydroxylates progesterone and 17-hydroxyprogesterone to yield 11-deoxycorticosterone and 11-deoxycortisol, respectively. These conversions are required for synthesis of aldosterone and cortisol, respectively. Both hormones are deficient in the most-severe, "salt-wasting" form of the disease. Slightly less-severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin; this is termed "simple virilizing disease". These 2 forms are collectively termed classic 21-hydroxylase deficiency. Patients with nonclassic disease have relatively mildly elevated levels of androgens and may be asymptomatic or have signs of androgen excess at any time after birth[3]. Clinical presentation is dependent, in part, on the genotype.

The objective of this study was to determine the clinical profile of patients with CAH (congenital adrenal hyperplasia) in a tertiary care hospital.

METHODOLOGY

This study was carried over a period of 36 months in the Pediatrics department of a tertiary care hospital

in North India. This study was approved by the institutional ethics committee. All patients who presented to hospital with features suggestive of congenital adrenal hyperplasia, viz dehydration, shock, electrolyte imbalances, failure to thrive, ambiguous genitalia, recurrent vomiting or genital hyperpigmentation were examined thoroughly. These patients were evaluated for possibility of congenital adrenal hyperplasia after their initial resuscitation and stabilization, as was demanded by their clinical condition. A written informed consent was sought from the parents of these children for inclusion in the study.

A family history of a sib death due to any similar illness as well occurrence of a similar clinical scenario in any other sib was enquired about. A history of consanguinity was also enquired about. Sex of the patients was determined on the basis of clinical examination and on basis of karyotyping when there was some genital ambiguity as per the Prader staging[4,5]. The diagnosis of Congenital adrenal hyperplasia was made as per the Endocrine Society guidelines.[6]

RESULTS

Over a period of 36 months, 40 patients with congenital adrenal hyperplasia were diagnosed in this study.

We diagnosed 32 cases as salt losing CAH. Median age of presentation was 36 days with range from 1-90 days (**Table 1**). 20 patients presented with recurrent vomiting, refusal of feeds, lethargy and dehydration. 6 presented with only complaints of lethargy and refusal of feeds. 4 patients presented during routine neonatal examination with ambiguous genitalia and two presented with a history unexplained sib deaths (**Table 2**).

6 of these patients had a family history of sib death. 23 of 32 patients presented in shock. 16 patients were products of consanguineous marriage. All patients were born at term with a mean birth weight of 3.04kg (range 2.3 - 4kg). Presentation weight of 13 patients was less than birth weight. 19 patients had suboptimal weight gain, below the expected norms. Mean phallus length in these patients was 1.86cm (range 1.5- 2.4cm) and mean phallus width was 0.9 cm (range 0.8-1.1cm). 24 of 32 cases had metabolic acidosis at presentation. 26 cases had hyponatremia (<135mg/litre) at presentation. 17 patients had hyperkalemia (serum potassium>5.5mg/litre) at admission. 7 cases had hypoglycemia at presentation, with a blood glucose level of less than 40mg/dl **(Table 3).**

Only one patient had adrenal hyperplasia on USG. Rest of the patients had a normal ultrasound scan.13 cases had ambiguous genitalia and karyotyping proved all of them to be females. 9 patients were phenotypically females and 10 were phenotypically males. All patients had 17-hydroxyprogesterone levels more than 20ng/ml. Out of 32 cases 28 had testosterone levels greater than pre-pubertal levels. 25 patients had serum cortisol levels<1 microgram/dl. Only one patient had low LH levels. Rest of the 31 patients had normal LH levels. Only one patient had a low FSH level. Rest of them had normal FSH levels.

Table 1: Baseline characters of Salt Losing CAH Patients

Characteristics	Measure (Range)
Median Age at presentation	36 days (1-90days)
Term vs Preterm Delivery	32:0
Consanguinity Vs Non-Consanguinity	16:16
Mean birth weight	3.04Kg (2.3-4Kg)
Mean Phallus Length	1.86cm (1.5-2.4cm)
Mean Phallus Width	0.9cm(0.8-1.1cm)

Table 2: Presenting Complaints of Salt Losing CAH Patients

Presenting Complaints	No. (%)
Shock	23(71.87)
Recurrent Vomiting, Refusal of feeds, lethargy & dehydration	20 (62.5)
Lethargy & refusal of feeds	6(18.75)
Ambiguous genitalia	4(12.5)
Unexplained sib deaths	2(6.25)

Table 3: Biochemical abnormalities in Salt Losing CAH Patients at presentation

Biochemical Abnormality	No. (%)
Metabolic acidosis	24(75.0)
Hyponatremia	26(81.25)
Hyperkalemia	17(53.12)
Hypoglycemia	7(21.87)

Table 4: Baseline characters of Simple Virilizing CAH Patients

Characteristics	Measure(Range)
Median Age at presentation	2 days (1day-5years)
Consanguinity Vs Non-Consanguinity	3:3
History of sib death Vs no history of sib death	1:5

6 patients were diagnosed as having simple virilizing CAH. The median age of presentation in these patients was 2 days (**Table 4**). These patients presented on routine neonatal examination- one on day 1st, 3 on 2nd day and 2 on 3rd day of life. One patient presented at 5 years of age with precocious puberty and another presented during evaluation of undescended testis at age of four and a half years. 3 of them were

products of consanguineous marriage and one had a history of sib death. None of them presented with shock. Anthropometry of 5 years old patient showed weight between 1 to 2SD above mean and height between 2 to 3SD above mean. Similarly anthropometry of four and a half years old patient was showing weight at 50th centile and height between 2 to 3SD above mean. All of them had normal electrolytes blood sugar and creatinine on presentation. All of them had raised 17 hydroxy progesterone levels. Three of them had testosterone levels above normal. All of them had normal cortisol, FSH and LH levels.

DISCUSSION

Congenital adrenal hyperplasia is a very unique distressing medical condition. Not only does this condition cause the medical problems due to enzyme deficiency, but it also causes enormous mental and emotional trauma to the family members of the affected virilized female patient. There is social stigma attached with this condition, with the result that the parents though distressed by the condition of an affected child, may feel shy of seeking medical attention. This is especially the scenario in the conservative societies of our part of the world where disorders of sexual development a considered a taboo.

In this study, we diagnosed 40 cases of congenital adrenal hyperplasia. 80% (32 patients) of these were salt losers. In this group of patients, 23 patients were received in shock. It is a known fact that CAH patients can present with adrenal crisis and shock, usually in the second week of life.[7] This is a life threatening condition unless identified quickly. It is the reason why universal screening for CAH has been advocated and started in developed countries.[6,8] It has been advocated that in absence of neonatal screening, the mortality in cases of CAH is 20-40%[9]. Our finding corroborates this fact that the adverse outcomes in these cases would have been prevented if neonatal screening for CAH would have been a norm in our country.

Recurrent vomitings, dehydration , refusal of feeds and lethargy were the presenting complaints in 20 patients (62.5% of salt losing group). This is the usual presentation in the patients with CAH[10]. In clinical practice, it will be prudent to examine the genitalia of an infant presenting with recurrent vomitings, so that any case of CAH with genital ambiguity and recurrent vomitings is not missed. 8 patients had a history of unexplained sib death, and this was the sole reason for seeking medical attention in two of them. These expired sibs may have been undiagnosed cases of CAH dying from adrenal crisis. This all the more emphasizes the need for neonatal screening for CAH. 19 patients (47.5%) were products of consannguineous marriage. As CAH is an autosomal recessive disorder, there are increased chances of this disorder occuring in babies born out of consanguineous marriages. Similar results were seen by Bhanji et al[11] in their study.

In our study, all the cases with salt losing type CAH had failure to thrive. It is a well known fact that CAH can present with failure to thrive.[12] Thus, CAH should be a differential diagnosis in every case of failure to thrive presenting in infancy. 26 patients in our study had hyponatremia at admission and 17 had hyperkalemia. This is a usual expected finding in cases of CAH due to deficiency of mineralocorticoids.[13] 6 patients were diagnosed to have simple virilizing CAH. Though these patients have less chances of mortality and are picked up earlier due to genital ambiguity, even these cases may suffer adrenal crisis in case of an intercurrent illness.[14] One patient was diagnosed to have CAH during evaluation of precocious puberty. Diagnosis of cases of non-classical CAH may be delayed due to their delayed presentation with precocious puberty.

CONCLUSION

Congenital adrenal hyperplasia is a unique disorder due to very adverse outcomes and even death resulting from enzyme deficiency if left untreated; and associated social taboos resulting in parents shying from seeking medical attention for a child with ambiguous genitalia.there is a need to start neonatal screening for CAH in our country so that deaths due to adrenal crisis in unrecognized patients are prevented.

REFERENCES

1. Sarah ML, Eric JNV, Thomas FK. A Practical Approach to Ambiguous Genitalia in the Newborn Period. Urol Clin N Am 37 (2010) 195–205
2. Tony H, Ivan McGown, David C, Ohn N, Gary M L, Mark H et al. The Clinical and Biochemical Spectrum of Congenital Adrenal Hyperplasia Secondary to 21-Hydroxylase Deficiency. Clin Biochem Rev. 2009;30:75-86.
3. Riepe FG, Sippell WG. Recent advances in diagnosis,treatment, and outcome of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Rev Endocr Metab Disord 2007;8:349-63.
4. Prader A. [Genital findings in the female pseudohermaphroditism of the congenital adrenogenital syndrome; morphology, frequency, development and heredity of the different genital forms.] [German]. Helv Paediatr Acta 1954;9:231-48.
5. Ogilvy-Stuart AL, Brain CE. Early assessment of ambiguous genitalia. Arch Dis Child 2004;89(5):401-7.
6. Phyllis WS, Ricardo A, Laurence SB, Lucia G, Terry WH, Deborah PM et al. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, September 2010, 95(9):4133–60.
7. Perrin C. White. Congenital Adrenal Hyperplasia and Related Disorders. In: Nelson Textbook of Pediatrics. Kliegman RM. 20th Edition. Elseviers Philadelphia ,2016. Section 576. PP 2717.

8. Honour JW, Torresani T. Evaluation of neonatal screening for congenital adrenal hyperplasia. Horm Res 2001;55:206-11

9. Pang SY, Wallace MA, Hofman L, Thuline HC, Dorche C, Lyon IC, et al. Worldwide experience in newborn screening for classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Pediatrics 1988;81:866-74.

10. Peter AL,Selma FW,Alan DR,Christopher PH. Disorders of Sex Development. In: Pediatric Practice Endocrinology. Michael SK. Mc Graw Hill.2010 Chapter 8. PP 304

11. Bhanji R, Khan AH, Balouch LL, Sabir Z, Nazir A, Billoo AG. Profile of children with congenital adrenal hyperplasia: A hospital study. J Med Pak Assoc.2004, 54:509-12

12. Sopfe J, Simmons JH**.** Failure to thrive, hyponatremia, and hyperkalemia in a neonate.Pediatr Ann. 2013 May;42(5):74-9.

13. Clayton PE, Miller WL, Oberfield SE, Ritzén EM, Sippell WG, Speiser PW. Consensus statement on 21-hydroxylase deficiency from the European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society. Horm Res 2002;58:188-95.

14. Gozzi TG, Harris NP, McGown IN, Cotterill AM, Campbell PE, Anderson PK, et al. Autopsy diagnosis of 21-hydroxylase deficiency CAH in a case of apparent SIDS. Pediatr Dev Pathol 2005;8:397-401.