

Profile of Children with Congenital Adrenal Hyperplasia - a Hospital Study

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Abstract

Objective: To collect baseline information on congenital adrenal hyperplasia (CAH) and to identify relevant issues specific to this disease in Pakistan.

Methods: A retrospective analysis of medical records of pediatric patients registered for serum 17 hydroxyprogesterone (17-OHP) measurement and documented to have CAH in the period 1987 to 1998 was carried out at The Aga Khan University, Karachi (AKU). The clinical notes were reviewed for documentation of CAH as the diagnosis.

Results: Of the 152 children registered for 17-OHP testing, sixty-three were diagnosed with CAH. Salt wasting, simple virilization and non-classical CAH was found in 40 (63%), 18(29.0%) and 5 (8.0%) patients respectively. Twenty-one (33.9%) patients were incorrectly assigned sex and of these, 20 (32.2%) patients were females who were either considered males or just not assigned gender. Parental consanguinity was found in 33 (52.3%) cases. No case had a history of similar features in either parent but in 19 (30.6%) cases similar features were present in siblings. Sixteen cases (25.4%) had a history of sibling death in the neonatal period and 7 had a history of sibling death in infancy. Maternal obstetric histories identified 3 (4.8%) cases with a history of still birth(s) and 4 (6.4%) with a history of abortion(s).

Conclusion: Children with CAH should be diagnosed early as a rational and judicious choice of sex assignment is a critical aspect of treatment. The high rate of consanguinity emphasized the need to establish the true incidence of the defect in Pakistani population (JPMA 54:509;2004).

Introduction

Among various disorders of indeterminate sexuality, congenital adrenal hyperplasia (CAH) is the most common cause of ambiguous genitalia in the newborn.¹ Being an autosomal recessive enzymatic disorder, CAH is caused by a defect in any of the five-enzymatic steps required to synthesize cortisol from cholesterol in the adrenal cortex.² In 95% cases of CAH there is a deficiency of 21-hydroxylase (21-OH) enzyme. In 5-8% of cases the deficiency is of 11- β -hydroxylase while other defects constitute less than 1% of all reported cases.²

Clinical presentations of CAH vary depending upon the enzyme defect. The severest form (salt wasting) presents in the neonatal period with hyponatremia, hyperkalemia and a raised 17-hydroxyprogesterone (17-OHP) level in both male and female newborns and features of virilization in a genetic female. A milder form (simple virilizing) may present as

ambiguous genitalia and marked virilization of the newborn female often causing uncertainty in sex assignment.³ A non-classical form (late-onset) has also been described that presents as precocious puberty in later childhood. This form may also become evident at puberty or adulthood with signs of androgen excess including tall stature, advanced bone age, acne, hirsutism, amenorrhea or infertility.^{2,3} Studies have indicated variable incidence of non-classic 21-OH deficiency in children presenting with an early onset of pubarche or adrenarche as well as in adolescent and adult females with hirsutism.⁴ It has been suggested that non-classical 21-hydroxylase deficiency is the most frequent autosomal recessive genetic disorder in humans with a prevalence in Ashkenazi Jews of 3.7% (1/27) and in a diverse population of 0.1% (1/1,000).⁵

There is a significant lack of data on CAH in

Pakistan. Since enzyme studies are not routinely available in Pakistan to document a specific enzyme deficiency, the diagnosis of CAH depends on clinical judgment in addition to elevated serum 17-OHP levels. In this study we performed a survey of pediatric patients with CAH to collect baseline information on the subject and to identify relevant issues specific to this disease in Pakistan.

Methods

A retrospective analysis of medical records of pediatric patients registered for serum 17-OHP measurement and documented to have CAH in the period 1987 to 1998 was carried out at The Aga Khan University, Karachi. The age criteria was 1 day to 12 years. The database in the clinical laboratory was used to find all children who were registered for 17-OHP testing for any reason. Clinical notes were reviewed for documentation of CAH as the diagnosis made by the physician. Cases excluded were patients registered for 17-OHP testing but had no clinical notes or summaries available for review.

A questionnaire was used to extract clinical and biochemical information. Patients were classified as having salt wasting (SW) if they had symptoms and signs of mineralocorticoid deficiency with either serum sodium levels of <134 mmol/l and serum potassium levels >5 mmol/l. Female patients were classified as having the simple virilizing (SV) form of CAH if they had prenatal virilization of external genitalia, but no signs of severe mineralocorticoid deficiency. Patients were classified as non-classical (NC) if they developed signs of virilization at any time in childhood. Sex, both at presentation and after chromosomal analysis, chronological age, bone age, family history of any similarly affected member or child death, and parental consanguinity were also recorded from the file.

Statistical Analysis

Descriptive statistics were used to analyze the data with SPSS version 10.6

Results

One hundred and fifty two children were registered for 17-OHP testing and seen by physicians at The Aga Khan University Hospital between 1987 and 1998. Sixty three of these patients satisfied our inclusion criteria, 44 patients were excluded since they did not have CAH as their diagnosis. The remaining 45 cases were excluded, as their medical records were inaccessible at the time of data collection due to technical reasons.

Forty patients (63.4%) presented with Salt-wasting CAH (SW); among them 17 were males, 11 females and 12 cases were of ambiguous sex. All

12 cases of ambiguous sex were shown by karyotype to be female, while in two males the karyotype was female. The median age at presentation was 1 month. Vomiting (25 cases), failure to thrive (24 cases), and diarrhea (12 cases) were predominant SW features. Features of virilization like clitoromegaly (23 cases), persistence of urogenital sinus (17 cases), ventral binding, fusion of labioscrotal fold, and scrotalization of skin (12 cases), were seen.

Eighteen (28.6%) patients presented with simple virilization CAH; 6 were phenotypic females, 2 were phenotypic males and 10 were ambiguous. Karyotype was performed in 3 of the 6 phenotypic females and confirmed their female gender. Karyotype in 1 of the 2 phenotypic males showed it to be a female. Results of karyotype in 9 ambiguous patients showed female sex. The median age at presentation was 2 months.

Five (7.9%) patients presented with non-classical CAH, prominent symptom of precocious puberty; 4 were male and 1 female. Results of karyotyping in 2 were in conformity to the assigned sex. The median age at presentation was 5.5 years.

CAH was diagnosed during the neonatal period in only 29 (50%) cases presenting with SW and / or SV. Table 1 shows the median age distribution in different clinical types of CAH. The minimum age at presentation was 1 day in 9 cases and the maximum was 12 years in 1 case.

Among the 63 cases, 23 were phenotypic males, 18 were phenotypic females and 22 were ambiguous. Genotype was assessed in 34 cases and it revealed that 6 (20.7%) of the 29 phenotypic males were actually females (46 XX) while 14 (87.5%) of the 16 ambiguous cases were female (46 XX) and 1 (6.2%) was male (46 XY). Overall, 21(33.3%) patients

were incorrectly assigned sex and of

Table. Clinical and biochemical profile of children with CAH.

Clinical types of CAH	Clinical features	No. of cases	Median age at presentation (range)	Median 17-OHP (ng/ml)	Mean Na (mmol/l)	Mean K (mmol/l)
Salt Wasting N = 40	Diarrhea	12				
	Vomiting	25				
	Convulsions	4				
	Failure to thrive	24	1 month	92.0		
	Clitoromegaly	23	(1 d - 5.5 months)	4.1 - 400	124	6.55
	Urogenital Sinus	17				
	Scrotalization of skin	12				
	Pigmentation	9				
	Pubarche	3				
	Clitoromegaly	12				
Simple Virilizing N = 18	Urogenital sinus	6				
	Fusion of labioscrotal folds	6	2 months	90.6	137.2	4.38
	Scrotalization of skin	7	(1 day - 12 years)	(4.3 - 333.2)		
	Pigmentation of skin	5				
	Pubarche	5				
Non-Classical N = 5	Early pubarche	5				
	Penile enlargement	4	5.5 years (1.7 - 6 years)	47.6 (14.1 - 195.5)	137	3.98

these, 20 (31.7%) patients were females who were either considered males or just not assigned gender. Parental consanguinity was found in 33 (52.3%) cases. No case had a history of similar features in either parent but in 19 (30.6%) cases similar features were present in siblings. Among those with similar features in siblings, 11 cases had 1 sibling

affected, 4 cases had 2 siblings affected, 3 cases had 3 siblings affected and in 1 case 4 siblings were affected. Sixteen cases (25.4%) had history of sibling death in the neonatal period and 7 had a history of sibling death in infancy. Maternal obstetric histories identified 3 (4.8%) cases with a history of still birth(s) and 4 (6.3%) cases with a history of abortion(s).

Of the 63 cases, bone age was determined in 22 (34.9%) cases and found to be compatible with chronological age in only 1 (1.6%) case. Bone age was advanced in 21 (33.3%) cases.

Discussion

It is evident that the majority of male children presented with SW early on and precocious puberty at later ages. Females mostly presented early with either or both of SW and SV. The results of this study emphasize that screening for CAH may be beneficial in our population because late presentation may be detrimental to a child's well-being especially when gender is incorrectly assigned.

No clear prediction regarding the prevalence of CAH in Pakistan is possible from this study. Patients with CAH are likely to be seen at other centers also. Although the incidence of CAH is not known, it is expected to be high due to the high prevalence of parental consanguinity among our population. The fact that 47.7% of patients are from non-consanguineous marriages implies that the gene(s) frequency for CAH is probably common in our population. Studies have shown that a worldwide incidence of this disorder was estimated to be 1:14, 199 live births for homozygous patients, 1 : 60 for heterozygous subjects and a gene frequency of 0.0083. The incidence in an Asian population (Japan) (1:15,800) did not differ significantly from that of the Caucasian population.⁴ It has been shown that in some populations, the overall incidence detected by screening was higher than the result of case surveys.^{4,7-9} The direct benefit of CAH screening was the prevention of adrenal crises and its sequelae, the reversal of incorrect sex assignment, and early diagnosis of females with CAH. Newborn screening for this disorder was shown to be cost effective when its cost is compared to the lifetime contribution of a productive citizen. Neonatal screening or prenatal diagnosis and treatment are advisable to the high-risk group with a sibling who has CAH. Such neonates should, at least, be investigated by serum 17-OHP analysis some days after birth to rule out the 25% risk for CAH. Even in our group there is a significant number of children who had affected

siblings and/or a history of multiple fetal demise.

Genetic studies indicate that boys and girls are at equal risk for CAH. However, the prevalence of CAH is higher among girls than boys with this disease. Males with the non-classical form remain undiagnosed. In addition, some males with severe 21-hydroxylase deficiency probably succumb to SW crisis in infancy. It is possible that some of the boys in these studies have died without a correct diagnosis.⁸ The other alternatives are that boys with SV CAH are diagnosed considerably later than girls or they remain undiagnosed. This accentuates the need to study the entire family where intersexuality is present. There was a significant diagnostic delay demonstrated in both young and old children. Two of the girls in our study with classical CAH were brought to medical attention at 8 and 9 years of age. The delay in health-seeking could be attributed to poverty and ignorance in a few, and lack of awareness of the primary care physician in the rest. The referral of such patients should be accelerated by education of the personnel involved and more importantly, by screening. The positive effect of neonatal screening has been shown. Neonatal screening would also decrease the age at diagnosis.⁴ An elevated level of 17-OHP is considered diagnostic for CAH due to 21-OH enzyme deficiency and can be used for screening. The fact that over 30% of females were inappropriately assigned gender at birth indicates the inability of the person who assigns gender in differentiating true male genitalia from virilized female genitalia. Majority of ambiguous cases turned out to be genotypic females. In the 6 genotypic females who were considered as male at birth, male sex was preserved due to already established male gender identity at the time of diagnosis.

These patients will remain infertile and are prone to development of emotional and social complications. In addition to this, late diagnosis also results in advancement of bone age, which ultimately causes short stature in these patients.

References

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