Original Contribution

Congenital Adrenal Hyperplasia: Experience from Dhaka Shishu (Children) Hospital, Bangladesh

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There is a scarcity of data on congenital adrenal hyperplasia (CAH) in Bangladesh. This study aimed to collect baseline information and identify relevant issues specific to the disease. We analyzed the retrospective analysis of medical records of pediatric patients attending Dhaka Shishu (Children) Hospital, Dhaka, for serum 17-Hydroxyprogesterone (17-OHP) measurement and documented to have CAH from December 2008 to December 2020. The diagnosis was supported by biochemical findings and confirmed by serum 17-OHP assay and karyotyping. The relevant clinical data were descriptively analyzed. A total of sixty (60) patients with the diagnosis of CAH were enrolled. Among them, 40(66.7%), 15(25.0%) and 5(8.3%) patients had salt-wasting (SW), simple virilizing (SV) and non-classical (NC) CAH, respectively. Karyotypically, 45(75.0%) were girls and 15(25.0%) were boys. At presentation, 30(50.0%) were initially assigned as female and 24(40.0%) were male and in 6(10.0%) cases, the sex was not assigned. All six cases of unassigned sex were proven to be female by karyotype, while ninecases assigned as males were proven to be females; overall, 15(25.0%) patients were incorrectly assigned sex at the initial presentation. Patients with SW form of disease presented at an earlier age (median age 1.0 months) than those with SV form (median age 12.0 months). Boys were diagnosed later than girls. CAH should be diagnosed earlier, irrespective of the sex of the child, to prevent death from the salt-losing crisis and proper gender assignment. In a resource-poor country like Bangladesh, we should emphasize building awareness among the general population and caregivers for early clinical identification of the cases and proper referral.

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Key words: Congenital adrenal hyperplasia, Salt-wasting CAH, Simple virilizing CAH, Non-classical CAH, 17-OHP

Introduction

Congenital adrenal hyperplasia (CAH) includes a group of autosomal recessivedisorders that result from the deficiency of an enzyme involved in the steroidogenic pathway for cortisol biosynthesis. Deficiency of 21-Hydroxylase, resulting from mutations or deletions in the CYP21A gene, is the commonest cause of CAH, accounting for almost 90.0% of cases[1]. Other enzyme deficiencies causing CAH are 11β-Hydroxylase, 3β-Hydroxysteroid dehydrogenase, 17α-Hydroxylase, steroidogenic acute regulatory protein P450-oxidoreductase[2]. Clinical presentations of CAH vary widely depending upon the type and severity of enzyme defects. The most severe form, salt-wasting CAH, constitutes 75.0% of classical CAH presents with hyponatremia, hyperkalemia, anda raised 17-Hydroxyprogesterone (17-OHP) level is found in both male and female newborns;genetic females have features of virilization in addition. The remaining 25.0% is the milder form, simple virilizing, present as ambiguous genitalia and marked virilization of the female neonate, often causing uncertainty in the sex assignment[3]. The non-classical form (late-onset) presents as precocious puberty in later childhood due to persistent elevation of ACTH. This form may also present at puberty or adulthood with signs of androgen excess, including affectedstature, advanced skeletal age, hirsutism, acne, amenorrhea or infertility[3,4].

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Delayed diagnosis of classic salt-wasting CAH may result in a life-threatening adrenal crisis and improper sex assignment in other forms. On the other hand, timely diagnosis and treatment in the form of replacement hormone therapy correct hormone deficiencies and save lives[5]. Specific enzyme studies are hardly availablein Bangladesh, and the diagnosis of CAH is primarilymade on clinical judgment and elevated 17-OHP levels. Data on CAH is also scarce here. This study describes the baseline information in this field and identifies relevant issues specific to this disease in Bangladesh.

Methods

A retrospective analysis of available medical records of pediatric patients attending Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh, for serum 17-Hydroxyprogesterone (17-OHP) measurement and documented CAH from December 2008 to December 2020 was performed. Dhaka Shishu (Children) Hospital is a 665 bedded largest pediatric hospital in the country. The hospital provides primary, secondary, and tertiary health care services for Dhaka city and receives patients referred from all over the country. The age criteria wereone day to 12 years. The hospital's clinical laboratory database was used to find all children registered for 17-OHP testing for any reason. Clinical findingswere reviewed for documentation of CAH as the diagnosis made by the physician.The institutional review board approved the study protocol. A total of 70 patients diagnosed with CAH were initially enrolled; ten were omitted due to the incompleteness of data. Finally, 60 patients with a diagnosis of CAH were analyzed. Most patients with acute symptoms presented directly at the emergency department and were admitted to the hospital. Some of these patients got admitted via the outpatient departments of pediatric endocrinology or pediatric surgery. Data were collected on age, the child's assigned sex at presentation, diagnosis on admission, relevant family history and clinical manifestations. Data regarding physical findings, including vital signs and complete genital examination, were collected from the admission files. Genetic sex in this study was determined based on karyotyping reports available at the hospital records. Investigations' records that were done for patient care and diagnosis of disease according to the need of the individual patient included random plasma glucose, serum electrolytes, arterial bloodgas analysis (ABG), pelvic ultrasonography (USG), serum 17-OHP, serum dehydroepiandrosterone sulfate (DHEAS) and plasma renin assay. A semi-structured predesigned questionnaire was used to extract clinical and biochemical information. Patients were classified as having salt-wasting (SW) CAH if they had signs-symptoms of mineralocorticoid deficiency with either hyponatremia (serum sodium <134 mmol/L) and hyperkalemia (serum potassium >5mmol/L). Female children were classified as having the simple virilizing (SV) form of CAH if they had prenatal virilization of the externalgenitalia 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. Levels of 17-OHP were correlated with the clinical classification of CAH[6]. We analyzed data using the Statistical Product and Service Solutions version 26.0 software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The categorical variables were represented as percentages and measurable variables as the mean±standard deviation (SD) or median (interquartile range, IQR). Oneway ANOVA, Chi-square test, and nonparametric tests were performed to compare the variables among patients with salt-wasting, simple virilizing and non-classical CAH. P value ≤0.05 was considered statistically significant.

Results

Among 60 patients, 40(66.7%) patients had salt-wasting (SW), 15(25.0%) had simple virilizing (SV) and the rest 5(8.3%) had non-classical (NC) CAH. At presentation, 30(50.0%) were initially assigned as female, 24(40.0%) as male and sex was not assigned in six (10.0%) cases. According to karyotype, 45(75.0%) were girls and 15(25.0%) were boys. All 6(10.0%) cases of ambiguous sex were genetically female, while in 9 males, the karyotype was female. Overall, 15(25.0%) patients were incorrectly assigned sex initially, either as male or ambiguous sex (Table I). Parental consanguinity was found in 16(26.7%) cases, family history of a similar disease was seen in 15(25.0%) cases and history of sibling death was explored in 9(15.0%) cases (Table I).

Table I: Demographic data of the CAH patients (n=60)

Variables	All (n=60)	Salt wasting (n=40, 66.7%)	Simple virilizing (n=15, 25.0%)	Non-classical (n=5, 8.3%)	p value
Assigned sex					
Male [n (%)]	24 (40.0)	15 (37.5)	06 (40.0)	03 (60.0)	
Female [n (%)]	30 (50.0)	21 (52.5)	07 (46.7)	02 (40.0)	0.842
Not assigned [n (%)]	06 (10.0)	04 (10.0)	02 (13.3)	00 (00.0)	
Genetic sex					
Male [n (%)]	15 (25.0)	12 (30.0)	00 (00.0)	03 (60.0)	0.012
Female [n (%)]	45 (75.0)	28 (70.0)	15 (100.0)	02 (40.0)	
Age at presentation (months) [Median (range)]	2.0 (1-72) IQR (1-9.75)	(1-4) IQR (1-2)	12.0 (1-30) IQR (8-20)	42 (30-72) IQR (33-69)	<0.001
Consanguinity present [n (%)]	16 (26.7)	12 (30.0)	03 (20.0)	01 (20.0)	0.711
Had family history of CAH [n (%)]	15 (25.0)	15 (37.5)	00 (00.0)	00 (00.0)	0.007
H/O sibling death	09 (15.0)	09 (22.5)	00 (00.0)	00 (00.0)	0.071
Socioeconomic status					
Poor [n (%)]	39 (65.0)	26 (65)	11 (73.3)	02 (40.0)	0.306
Lower middle [n (%)]	14 (23.3)	09 (22.5)	02 (13.3)	03 (60.0)	
Middle [n (%)]	07 (11.7)	05 (12.5)	02 (13.3)	00 (00.0)	

IQR= interquartile range

Patients with SW form of CAHpresented at an earlier age [1(1-2) months, median (IQR)] than those with SV form [12(8-20) months, median (IQR)] and NC from [42(33-69) months, median (IQR)]. Boys were diagnosed later [3(1-4) months, median (range)] than girls [1(1-3) months, median (range)] in both the forms (Figure 1).

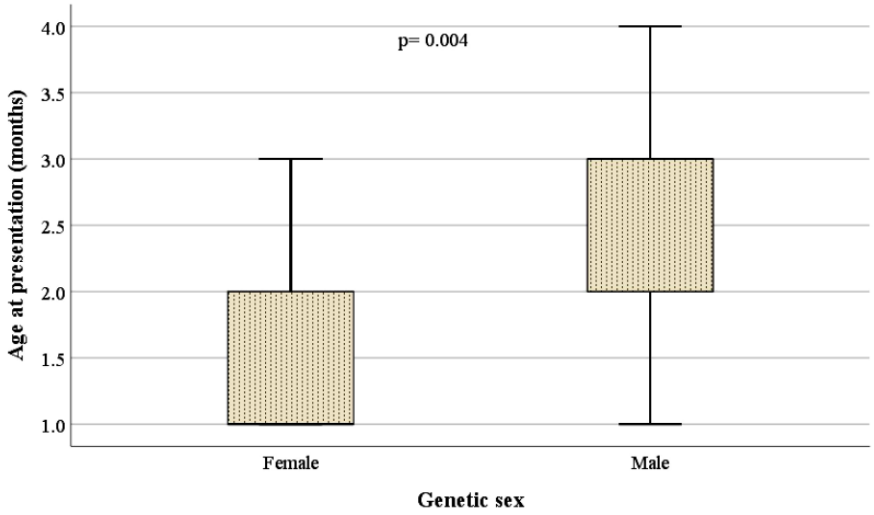

Figure 1: Age at presentation of children with salt-wasting type CAH (n=40) [Median age: female 1 (range: 1-3), male 3 (range: 1-4) months]

Patients of SW form (40 cases) presented with acute symptoms including dehydration±shock in all 40 cases, vomiting in 27 cases, and diarrhea in 19 cases, failure to thrive was documented in 25 cases. Twenty-one cases of SW CAH had clitoromegaly, 19 had the persistence of urogenital sinus, 3 had labioscrotal fusion, 18 had scrotalization of skin and 10 cases had pigmentation [Table II].

Table II: Clinical and biochemical findings of the CAH patients (n=60)

Variables	All (n=60)	Salt wasting (n=40, 66.7%)	Simple virilizing (n=15, 25.0%)	Non-classical (n=5, 8.3%)	p value
Diarrhea [n (%)]	19 (31.7)	19 (47.5)	00 (00.0)	00 (00.0)	0.001
Vomiting [n (%)]	27 (45.0)	27 (67.5)	00 (00.0)	00 (00.0)	<0.001
Failure to thrive [n (%)]	25 (41.7)	25 (62.5)	00 (00.0)	00 (00.0)	<0.001
Penile enlargement [n (%)]	05 (08.3)	00 (00.0)	02 (13.3)	03 (60.0)	<0.001
Pubarche [n (%)]	09 (15.0)	00 (00.0)	07 (46.7)	02 (40.0)	<0.001
Dehydration±shock [n (%)]	40 (66.7)	40 (100)	00 (00.0)	00 (00.0)	<0.001
Clitoromegaly [n (%)]	30 (50.0)	21 (52.5)	09 (60.0)	00 (00.0)	0.058
Urogenital sinus [n (%)]	25 (41.7)	19 (47.5)	06 (40.0)	00 (00.0)	0.126
Labioscrotal fusion [n (%)]	08 (13.3)	03 (07.5)	05 (33.3)	00 (00.0)	0.028
Scrotalization of skin [n (%)]	18 (30.0)	18 (45.0)	00 (00.0)	00 (00.0)	0.002
Pigmentation	16 (26.7)	10 (25.0)	06 (40.0)	00 (00.0)	0.198
Serum Na^+ (mmol/L) (Mean±SD)	124.95±11.28	117.98±6.36	138.60±2.10	139.8±2.39	<0.001
Serum K^+ (mmol/L) (Mean±SD)	5.6±0.9	6.21±0.38	4.44±0.32	4.26±0.49	<0.001
Hypoglycemia [n (%)]	28 (46.7%)	28 (70%)	00 (00.0)	00 (00.0)	<0.001
Acidosis in ABG [n (%)]	35 (58.3)	35 (87.5)	00 (00.0)	00 (00.0)	<0.001
Serum 17-OHP (nmol/L) [Median (range)]	16.15 (3.9-19.7) IQR (10.35-18.2)	17.6 (10.2-19.7) IQR (16.125-18.375)	9.6 (7.7-12.2) IQR (8.7-11.4)	4.4 (3.9-4.8) IQR (4.0-4.65)	<0.001

Patients of SV form (15 cases) had no acute symptoms, presented with different grades of virilization. Seven were phenotypically female, six were male, and two were ambiguous. All phenotypic males and ambiguous cases were genetically female as determined by karyotyping. Among the SV cases, 9 had clitoromegaly, 6 had the persistence of urogenital sinus, 5 had labioscrotal fusion, and 6 cased had pigmentation (Table II). Five (8.3%) patients presented with NC CAH, three were male, and two were female. Their prominent symptoms were precocious puberty manifested by penile enlargement in 3 cases and pubarche in 2 cases (Table II). The features of mineralocorticoid deficiency (hyponatremia, hyperkalemia and acidosis) and glucocorticoid deficiency (hypoglycemia) were evident only in SW cases. SW cases had higher levels of 17-OHP than SV and NC cases (Table II).

Discussion

Classical CAH was 92% of our cases in this study. Among them, SW cases were more than twice that of SV cases (2.7:1). Results also found similar with findings from developed countries,where SW was twice common as SV form[6,7,8]. On the contrary, studies in Indiaand Turkey revealed a higher prevalenceof SV cases than SW form[9,10,11]. The findings of this study may be that our hospital is the largest referral centerin the country, and most of this study patients were admitted through the emergency department. In this study, girls

were more common than boys, and among SW cases,the ratio was 2.3:1.Similar results were found in Pakistan and India[12,13]. In addition, girls with salt-wasting features presented earlier than boys with similar manifestations due to genital ambiguity in female children, which helps diagnose CAH. On the other hand, diagnosis of salt-wasting form is frequently missed among boys due to normal genitalia. Bajpei et al. observed thatthe diagnosis of SW form was not considered as many as 72.0% of boys at the time of admission[9]. This finding emphasizes thatscreening for CAH may be beneficial in our population and the need to increase awareness among primary health care providers about the careful consideration of the diagnosis of CAH in children with the salt-loosing crisis. Total 15(25.0%) of our cases had either incorrectly assigned or not assigned their gender during the initial assessment. All of them were found genetic females diagnosed after karyotyping. Bhanji et al. observed a similar[12]. Among our patients, six genotypic females, who were considered male at birth, male sex were preserved as already established male gender identity since birth.Future social, emotional, and physical complications could be avoided if they were correctly diagnosed earlier by neonatal screening. No precise prediction regarding the prevalence of CAH in Bangladesh is possible from this study. Only admitted cases were enrolled, and all the patients were below sixyears of age. Patients here are primarily from poor socioeconomic status and critically ill patients referred from remote areas.CAH cases,particularly SV and NC variety, are likely to be seen at other centers and private clinics. Furthermore, many cases do not even visit physicians due to poverty or social stigmata; some have no acute illness. Positive family history of similar cases among SW forms (37.5%) in this study was in agreement with a study from Egypt[14]. History of consanguinity (26.7%) was low among our patients thanin most Arab countries (76.5%)[15]. However, these groups should be considered high risk and arranged prenatal or neonatal screening to rule out the diagnosis of CAH. More than two-thirds of this SW cases presented with at least one feature of salt-wasting crisis, consistent with other studies[14,16,17]. Such presentation helped us initiate treatment with hydrocortisone replacement without delayand therefore had remarkable success in outcome. Biochemical findings, particularly hyponatremia with hyperkalemia, were present in almost all of this SW cases, irrespective of the sexual identity of the patients. We suggest testing serum electrolytesasan early identification pointer of adrenal crisis in clinically suspected cases. Analysis of serum 17-OHP and karyotyping were done in all of our cases. As there is no scope of genetic analysis or enzyme assay in our country, raised serum 17-OHP is considered an important diagnostic tool for CAH in this study. The investigation facilities for CAH are far from satisfactory in most institutions in Bangladesh. There is a need to develop such facilities in at least some selected regional centers and include chromosomal analysis and serum 17-OHP assays. The present situation of management is also needed to be improved much. Hydrocortisone in oral form, which is the mainstay of prolonged treatment of CAH, is available from only one pharmaceutical company as 10 mg tablet. However, most young infants require a meager amount (1-1.5mg/dose) in divided doses which is not convenient with the existing preparation. Fludrocortisone is another essential medicine for salt-wasting cases that remains unavailable most of the time.

Conclusion

CAH is not a very rare disease in this setting. The majority (n=60, 66.7%) of our cases presented with acute illness, salt-losing type, and female outnumbered male children. Another group (25%, n=15) of patients presentedfor severe virilization. Probably many CAH patients without acute symptoms, especially non-classical type, remain undiagnosed in their early life. Delayed diagnosis remains a critical issue to properly managing acutely ill patients, and others suffer from multiple social and physical complications in later life. Twenty-five percent (n=15) of our cases were incorrectly gender assigned initially, which could be a reason for their future social harassment without proper treatment.

Limitations

We recruited only the hospital-admitted admitted patients in the study,not representing the total number of cases visiting the hospital with DSD. There was no scope for genetic analysis or enzyme assay for DSD diagnosis. Long-term follow-up data were not available for analysis.

Recommendations

Any pediatric case with hyponatremia and hyperkalemia should be considered as CAH until proved otherwise. Building awareness among the general population and caregivers for early clinical identification of the cases and proper referral should be emphasized. Genetic analysis in cases of CAH is required for better counseling to parents. A multicenter study covering all CAH patients over a prolonged period, including follow-up, will help better understand the actual situation.

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