Original Article

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Clinical Characteristics and Morbidity of Congenital Adrenal Hyperplasia at the Initial Presentation - Are we on Right Trend? A Descriptive Study at a Single Center

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Abstract

Background:

Congenital adrenal hyperplasia (CAH) is the commonest cause for adrenal insufficiency in children. Presentation can be varied from isolated genital virilization to significant circulatory compromise with life threatening salt wasting crisis. Newborn screening has been introduced in many European countries at present albeit lack of agreed consensus and heterogeneous evidence. The objectives were to describe the initial clinical presentation and diagnostic biochemistry of CAH and if the disease morbidity related to CAH has been improved with established paediatric endocrine services. Further, to assess the benefit from a possible future newborn screening program.

Methods:

A Case note review of patients with CAH diagnosed clinically and biochemically and followed up at large Paediatric endocrine service of Lady Ridgeway Hospital for children in Sri Lanka from 2015 to 2021 was undertaken. Data were collected both retrospectively and prospectively.

Results:

47 patients (Male 25 vs female 22). with CAH were included. The majority were 21-α hydroxylase deficiency (21 OHD) (74.4%) followed by 3 β hydroxysteroid dehydrogenase deficiency (3B-HSD) (21.2%) and 11β Hydroxylase deficiency (4.2%) respectively. Of the patients with salt loosing CAH due to 21 OHD, females presented significantly earlier compared to males (p=0.0117) with a mean presentation age of 12.06 days albeit a sex difference in incidence was not noted. Ambiguity of external genitalia was the commonest reason for referral in infancy (n=12, 40%) with a mean age of presentation 10 days. 58% (n=23) of salt-losing CAH was diagnosed within the first 2 weeks of life and treatment was started within 24 hours of diagnosis. No mortalities were reported during the study period.

Conclusion:

This cohort shows lesser morbidity and mortality in the absence of sex preference in incidence possibly due to increased awareness with improved paediatric endocrine service provision. Relatively delayed presentation of patients who had ambiguous Genitalia emphasizes a need of national consensus for a referral pathway for earlier diagnosis and commencing treatment. Introduction of a new born screening program may not be cost effective in the absence of severe morbidity and mortality.

Keywords: Congenital Adrenal Hyperplasia, Salt wasting, 17-hydroxyprogesterone (17 OHP), Neonatal screening

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Introduction

Congenital adrenal hyperplasia (CAH) is a recessively inherited endocrine disorder of cortisol biosynthesis with a reported incidence of 1:1000 - 20000 live births [1,2]. However, the prevalence varies depending on the geographical area [1,3]. CAH leads to increased secretion of adrenocorticotropic hormone (ACTH) resulting in adrenocortical hyperplasia with excess secretion of intermediate metabolites [1] and considered as the commonest cause of adrenal insufficiency in the neonatal period.

21- hydroxylase deficiency (21 OHD) due to mutations in CYP 21 A gene accounts for the majority over 90% [4]. 11 beta-hydroxylase deficiency (11 βHSD) and 3 beta-hydroxysteroid dehydrogenase deficiency (3 βHSD) are the next common subtypes of CAH [5].

Clinical features are determined by the defective steroidogenic enzyme and is related to the amount of loss of genetic material on the responsible gene [2]. There is a wide spectrum of clinical phenotypes varying from life-threatening adrenal crisis or salt wasting crisis to isolated simple virilization [6]. Children suffering from classic CAH usually present in the early neonatal period with circulatory collapse, hyponatremia, hyperkalemia, and pigmentation which accounts for nearly 75% of all, whereas the non-classic CAH presents at a later life with female virilization, precocious puberty or advanced bone maturation [7]. Girls with salt-wasting CAH are commonly diagnosed in the immediate post neonatal period due to virilization in contrast to males who will present to clinical care with a salt-wasting crisis or failure to thrive. The diagnosis can be delayed as CAH may mimic common neonatal diseases like sepsis. In girls, virilization causes initial difficulties in sex assignment and leads to multiple genital reconstructive surgeries creating greater parental stress [8].

Newborn screening is helpful to diagnose CAH, particularly in males before the salt-wasting crisis and is widely available in some countries including the United States, Australia, and Germany [9,10]. However, there is no established consensus on newborn screening and the current evidence is heterogeneous. Screening can be associated with a false positive rate leading to undue parental concerns, investigations, and stigma. The reported positive predictive value of new born screening is varied from 0.7% to 50% whilst the mean and median being 8.1% and 5.3% respectively[10]. It also possesses a false negative rate and provides a false reassurance, particularly on other less common subtypes of CAH like 3 βHSD which can present as a life-threatening adrenal crisis in an under-virilized boy [10–12].

Diagnosis of CAH can be confirmed genetically. Genotype may predict the severity and clinical outcome of the illness. The genotypic and phenotypic correlation may differ according to ethnicity. Milder mutations may demonstrate a significant variation in clinical presentation [13,14].

To understand the disease burden of CAH, this study was carried out retrospectively on 47 children diagnosed with CAH in a tertiary care referral center in Sri Lanka over 6 years. The aim is to assess the improvement of early referral and care, and potential benefit of introducing a new born screening program in Sri Lanka.

Methodology

This Retrospective case note review carried out on children diagnosed with CAH, aged up to 14 years at the Paediatric Endocrinology unit at the Lady Ridgeway Hospital for Children, the main endocrine referral center, from 2015 to 2021.

The diagnosis was made biochemically in children presented with suggestive clinical history in accordance with international Endocrine society clinical practice guideline on CAH(Table1) [2].

The data on, reason for referal, clinical features of initial presentation, biochemical data, and management at the presentation including acute care (fluid resuscitation, IV steroids, intensive care), and duration of hospital stay were collected. An early presentation was considered when the presentation was before the circulatory decompensation. The day of the initial clinical encounter was documented considering the birthday as zero. The Sex of raring in all ambiguous children who presented during early infancy was determined at a multi-disciplinary team meeting depending on degree of virilization, karyotype, imaging findings of internal genitalia and parental wish.

Statistical analysis of data was performed using SPSS 26. Categorical data were demonstrated as percentages and proportions whereas continuous data were median with interquartile range or as mean with SD. $P< 0.05$ was considered as statically significant. Ethical approval was obtained from the ethical committee of Lady Ridgeway Hospital for children, Colombo. Sri Lanka.

Results

47 children diagnosed with CAH were included. 25(53%) were males and 22(47%) were females. 85% of the cohort (40/47) had features of salt wasting.

Children with 21-hydroxylase deficiency with salt-wasting

Thirty infants had clinical and biochemical characteristics of salt wasting CAH due to21 OHD. A sex difference in the salt loosing group was not noted in this cohort (male = 15) table 2. The mean age of presentation was 18.6 days (range 3-60, SD - 13.54,95% CI +/- 4.069). Females presented slightly earlier compared to males and the mean age of presentation was 12.06 days (SD- 7.424, 95% CI- 3.889) while ambiguous genitalia being the commonest reason for referral, majority scaled on the Prader scale 2-3 (n=12, 80%) Figure 2 & 3. Females with ambiguous genitalis at birth were diagnosed with CAH at the mean age of 10 days (95% CI- 3.437). Two patients presented with failure to thrive whereas one presented with circulatory compromise requiring fluid resuscitation and neonatal intensive care. All the three of them noted to have ambiguous genitalia graded as 2-4 on the Prader scale subsequently.

Males presented significantly later compared to females at the mean age of 24 days (SD-15.457, p = 0.0117). Most male infants presented with failure to thrive/salt wasting (n=12.80%) and two required fluid resuscitation at presentation. Hyperpigmentation was noted in 17(57%) infants of both sexes (table 3).

Table 1: Clinical and biochemical categorization of CAH subtypes: DHEA- Dehydroepiandrosterone

21-hydroxylase deficiency	3β-hydroxysteroid dehydrogenase deficiency	11β-hydroxylase deficiency
Female with ambiguous genitalia Failure to thrive Salt loosing(hyponatremia) Increased pigmentation With increased 17OHP +/- inadequate response at ACTH stimulation +/- increased ACTH	Under-virilized boy With increased 17 OHP and Increased DHEA +/- inadequate response at ACTH stimulation +/- increased ACTH	Female virilization Advanced bone maturation With Hypertension at presentation and hypokalemia with increased 17OHP +/- inadequate response at ACTH stimulation +/- increased ACTH

Table 2: Clinical characteristics of children with salt-losing congenital adrenal hyperplasia due to 21OHD

		Reason for referral/Presentation		
	Total, n=30	Failure to thrive/ salt wasting, n=14	Adrenal crisis/ circulatory compromise, n=3	Female virilization, n=12
Sex (male: female)	1:1	6:1	2:1	
Age of presentation (median with IQR) in days	14(7-25.25)	24(11.5-40)	10	10(4-17)
Treatment commencement in days (median with IQR)	15(7-27.25)	25(12-40.25)	10	12(6-18)
Hospital stay (median with IQR) in days	5(4-7)	5.5(5-7)	5	4(3-5)

Table 3: Clinical features at presentation
(21 OHD- 21 hydroxylase deficiency,11 βHSD =11 beta-hydroxylase deficiency, 3 βHSD-3 beta-hydroxysteroid dehydrogenase deficiency)

Clinical features	Number of patients		
	21- OHD	3 βHSD	11β HSD
Ambiguous genitalia	20	10	02
Failure to thrive	21	09	00
Hyponatremia	21	09	00
Hyperkalemia	20	07	00
Hypokalemia	00	00	02
Hypertension	00	00	02
Hyperpigmentation	14	04	00
Advanced bone age	05	00	02
Seizures	01	00	00

Figure 1: Reason for initial presentation in infancy

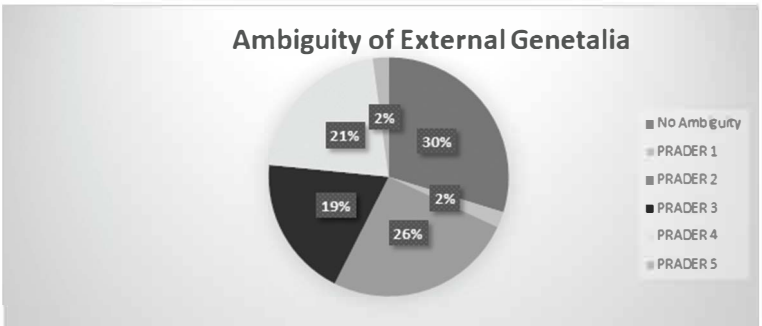

Figure 2: Ambiguity in the external genitalia

The median 17 hydroxyprogesterone(17OHP) value was 238.16 nmol/l (SD-531.66, 95%CI-193.628) and the highest mean serum cortisol value in the ACTH stimulation test was 119.3 nmol/l. only one child carried a family history of CAH. The mean duration of commencement of treatment was 18.6 days (SD-13.54)

Children with 21- hydroxylase deficiency without salt wasting

There were 5 female children (n=5) who presented with virilization and advanced bone age without evidence of salt wasting with reported onset of symptoms beyond infancy suggesting non classic subtype. The median age of presentation was 98 weeks (IQR 36.85-144.5). They had increased 17 OHP values (mean 114.4 nmol/l, SD- 69.5, 95%CI-60.923) and inadequate response in the ACTH stimulation test (mean 160nmol/l, SD -13.8) with advanced bone age (mean +2.6 years in TW20 method). The mean 17 OHP level was not significantly different from salt loosing CAH (p=0.6111).

Children with possible 3β hydroxysteroid dehydrogenase deficiency

Ten boys were managed as 3βHSD diagnosed clinically with genital ambiguity and biochemically with raised 17 OHP and Dehydroepiandrosterone (DHEAS) with inadequate cortisol response in the ACTH stimulation testing. Genital ambiguity was the commonest reason for presentation (n=8, 80%) while the failure to thrive was the second commonest (n=2, 20%). All the children had defects in virilization of external genitalia (EMS 4-7). The median presenting age was 12 days (IQR 6.25-14.75). All had salt-losing features and four (40%) had increased pigmentation at the first presentation. The median 17OHP was 60 nmol/l (IQR 58.64-65.75) and all had increased DHEAS by more than 40 nmol/l. The highest mean serum cortisol value in the ACTH stimulation test was 261nmol/l (SD 95.08).

Less common subtypes

Two girls presented during childhood with virilization and advanced bone age were found to have elevated blood pressure and comparatively low potassium level (mean 3.2mmol/l). Both of them had elevated 17 OHP (60 nmol/l). The mean presenting age was 5.5 years whereas the highest mean serum cortisol value in the ACTH stimulation was 190nmol/l. They were clinically classified as 11β HSD.

Discussion

This study describes the clinical characteristics and the disease burden due to CAH which is a treatable rare genetic disorder, in an unscreened population. There was no significant male or female predominance even though the number of boys was slightly higher which is consistent with the well-documented autosomal recessive inheritance [1,6], but in contrast to previous local literature which had prominent female presentation and raised the concern if males left undiagnosed [15] . This is possibly owing to increased awareness within primary care physicians and improved care provision in paediatric Endocrinology. However, the mean age of presentation and commencing treatment still remains same in consistent with previous local data and recent multicenter I-CAH registry data on unscreened populations[15,16] . However, the number of children who needed resuscitation and intensive care was much lesser [5,6] which is reassuring. The commonest reason for presentation for boys was the failure to thrive with associated adrenal insufficiency whereas it was virilization in girls. The majority of children showed significant virilization above Prader 2 drawing parental stress initially on sex assignment and later on sequential reconstructive surgeries. These data are consistent with previous literature [1] albeit there is ongoing debate regarding the age of feminizing surgeries in these children.

A significant difference between stimulated 17 OHP and cortisol values ware not demonstrated in salt-losing and non-salt losing phenotypes. However, mean 17OHP was lower in this cohort compared to the other studies [2,5,6]. Some Sri Lankan reference laboratories do not offer appropriate dilutions for very high 17- OHP values, which might have led to this observed difference.

The treatment has been started in the 1st 24 hours after the presentation in the majority of salt wasters. Females who had virilization at birth have been referred as outpatients after being discharged from the post-natal ward for endocrine evaluation with a slight delay despite, been identifying the ambiguity by the neonatologist on day one of life [5,16]. Half of them had salt wasting at the presentation to the endocrinology care. None of them had an adrenal crisis and required fluid resuscitation at the presentation. This emphasizes the necessity of national consensus on referral pathway for CAH for urgent assessment and commencing treatment.

The morbidity due to the hospital stay at the first presentation was less than one week which is comparatively lesser [5]. The reduced CAH-associated mortality and morbidity at the first presentation could be explained by the diagnosis and starting treatment before the occurrence of adrenal crisis.

The neonatal screening for CAH would provide the benefit of identifying salt-wasting CAH early, particularly in boys with 21 OHD [2,16]. Current methodology, assay 17-OHP in filter paper specimens carries low specificity resulting in a large number of false positives [10]. This may lead to a greater concern of undue parental stress, investigations, and also social stigma which carries a huge impact on a child's future, particularly in Asian culture. Further, these first-tier assays have a low sensitivity in diagnosing other CAH subtypes like 3βHSD. Hence, recent evidence suggests second-tier testing with an extended steroid profile which is costly and consumes more time [10,11]. Our data have demonstrated a significant disease burden of salt wasting 3βHSD which may not be diagnosed through the screening program. Additionally, a high 17-OHP value is a common finding in the immediate post neonatal period, prematurity and sepsis. In view of balancing the immediate diagnosis with accuracy, it is suggested to perform screening after completing 48 hours of

life[11]. Dutch neonatal screening program has demonstrated good sensitivity and higher positive predictive value. But some neonates had presented with crisis before the laboratory test report and this is a concern to consider when implementing a new born screening [17]. Further, screening may carry poor compliance with early discharge policies. To overcome this, some countries have implemented two screenings, one performed before discharge followed by the second on days 8-14 of life [11] which is costly. Considering all, the place for current first-tier neonatal screening methodologies for CAH in a resource-limiting Asian country like Sri Lanka is debatable.

Recent evidence suggests implementing molecular genetic analysis for screening programs given enhancing screening even though it is not used in current high-volume screening due to cost, time consumption, and complexity [10]. Genotyping would also help in diagnosis in challenging cases with equivocal biochemistry [14]. In a preliminary pilot study done in Sri Lanka on salt-wasting CAH children to describe the genotype using Multiplex ligation-probe amplification (MLPA), nearly a three-quarter failed to demonstrate copy number alterations [18]. Hence, further studies to identify local genotypic and phenotypic co-relation may require which would then help to diagnose pathogenic genetic variants, their characteristics, and prognosis of this chronic endocrine disorder.

Limitations

Due to lack of genetic facilities in this cohort, cases of 11β- hydroxylase could be under estimated while 3βHSD could be overestimated.

Conclusion

CAH is a treatable rare endocrine genetic disorder that may result in significant neonatal mortality and morbidity if left undiagnosed and untreated. This study population shows a comparatively less severe presentation with low mortality and morbidity, probably explains the enhanced knowledge of CAH of primary care physicians or due to a genotypic variation with lesser severity. Hence, the cost effectiveness of a neonatal screening program is to consider. However, commencing treatment relatively late on patients who had ambiguous genitalia at birth emphasize the need of national consensus on a referral pathway for endocrine services for urgent assessment.

Abbreviations:

ACTH	adrenocorticotropic hormone
3βHSD	3β-hydroxy steroid dehydrogenase deficiency
11 βHSD	11 beta-hydroxylase deficiency
CAH	congenital adrenal hyperplasia
DHEA	dehydroepiandrosterone
17OHP	17 hydroxyprogesterone
21OHD	21α-hydroxylase deficiency

Declaration:

This is an Audit carried out at the Endocrine Department, Lady Ridgeway Hospital for children, referring in to Clinical records, Ethical approval was obtained from the ethical review committee - Lady Ridgeway Hospital, Colombo, Written consent for participation and anonymous publication was obtained from all the participants.

This is a self-funded study. There are no conflicts of interests. The SPSS data sheet is available.

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