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Congenital Adrenal Hyperplasia: Diagnostic Features in a Limited Resource Country, Senegal

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Abstract

Introduction: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive diseases characterized by enzymatic deficiencies in the biosynthesis of adrenal steroids. The most common 21-hydroxylase deficiency is characterized by a cortisol deficiency and an excess of androgens, with or without aldosterone deficiency. In our countries, in the absence of neonatal screening, the diagnosis is most often late leading to life-threatening complications. The aim of this study was to describe the diagnostic features of CAH at the Albert Royer National Children's Hospital (ARNCH) in Dakar. **Patients and method:** We conducted a retrospective, descriptive study carried out at the pediatric endocrinology department of ARNCH from 2015 to 2019. All children aged under 15 with a form of CAH were included. Socio-demographic data, family history, clinical and biochemical data at presentation were collected. Patients were noted as presenting with Disorder of Sexual Development (DSD) with dehydration, DSD without dehydration, dehydration without DSD, precocious puberty. The Prader's scale was used to determine the degree of external virilization. These data were entered and analyzed with Epi Info version 7.2. **Results:** A total of 32 patients were included, representing 74.41% of the causes of disorder of sexual development (DSD) and 84.21% of the causes of adrenal insufficiency. These were 27 girls (84.37%) and 5 boys (15.63%). The mean age was 19 ± 34.6 months. DSD was the main finding (87.5%). It was associated with dehydration in 22 cases (68.75%). 21-hydroxylase deficiency represented 93.75% of the cases with salt wasting in 73.33% of the cases. **Conclusion:** The diagnosis of CAH was delayed lead-

ing to life-threatening adrenal crises. In the absence of neonatal screening for CAH in Senegal, there is a need to train healthcare workers to recognize neonates with DSD early and refer them timeously for specialist care.

Keywords

Congenital Adrenal Hyperplasia, Disorder of Sexual Development, Adrenal Insufficiency, Senegal

1. Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive diseases characterized by enzymatic defects in the biosynthesis of adrenal steroids. The common point of all these conditions is the decrease in cortisol production, which leads to an increase in the secretion of pituitary ACTH and an adrenal hyperplasia [1]. The most common and prototypical example of CAH (95%) is caused by 21-hydroxylase deficiency. It is characterized by a cortisol deficiency and an excess of androgens, with or without aldosterone deficiency. Less frequent types of CAH are 11α-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase deficiency, 17β-hydroxylase deficiency, or exceptionally StAR and P450 oxidoreductase deficiencies [2].

It is a relatively rare condition, affecting 1 in 15,000 births [3]. The severity of CAH depends on the degree of the deficiency in 21-hydroxylase. From a clinical point of view, three subtypes of 21-OH deficiency (21-OHD) have been identified: The salt wasting (SW) form of CAH is characterized by a life-threatening metabolic crisis, typically presenting in the first weeks after birth, with salt-loss, hyponatremia, hyperkalemia, dehydration, shock, and signs of ambiguous genitalia in females but not in males. The simple virilizing (SV) form is usually recognized by a variable degree of clitoris hypertrophy, posterior labial fusion in females and pseudo precocious puberty in males. The nonclassical form is rarely diagnosed before the onset of puberty and usually is suspected in females because of hirsutism and menstrual cycle irregularities [4]. It is most often revealed in newborns with an abnormality of the external genitalia without palpated gonad; or around 8 - 15 days of signs of adrenal insufficiency (vomiting, hypoglycemia, lack of weight gain, dehydration) with hyponatremia, hyperkalemia and acidosis. Life-saving neonatal screening test of 17 hydroxyprogesterone on blotting paper for classic congenitaladrenal hyperplasia due to 21OH deficiency made exceptional this situation in western countries.

There is a lack of reporting on the prevalence of CAH in resource-poor countries such as Senegal, affecting diagnosis, treatment and management outcomes. Lack of screening facilities results in delayed and missed diagnosis and a high mortality in salt-wasting forms. In this context we conducted this study with the aim of describing the diagnostic features of CAH at the Albert Royer National Children's Hospital (ARNCH) in Dakar.

2. Patients and Method

It was a retrospective, descriptive study conducted at the pediatric endocrinology service of the ARNCH from 2015 to 2019. ARNCH is the main referral center for pediatric patients with endocrine problems in Senegal. All children aged under 15 with DSD and/or adrenal insufficiency with biochemical investigations were initially included. Patients with causes other than CAH were secondarily excluded. Data was collected from follow-up or hospitalization records. The following information was recorded: age at the time of diagnosis, sex, age of the mother, gravidity and parity, parental consanguinity, family history of DSD, unexplained death in the neonatal period, salt loss syndrome in siblings. Clinical symptoms were also recorded (DSD with dehydration, DSD without dehydration, dehydration without DSD, precocious puberty). The Prader scoring system was used to determine the degree of external virilization. The patients' biochemical values (serum electrolytes and blood glucose) and levels of sex steroids at presentation, before the initiation of hormone replacement (17-hydroxyprogesterone (17-OHP), progesterone, pregnenelone, 17 hydroxypregnelone, dehydroepiandrostenedione (DHEA-S), androstenedione, cortisol and ACTH) were recorded. The treatment received (hydrocortisone, fludrocortisone) and the outcome (survival, lost to follow-up, death) in short term (during hospitalization) and medium term (during 6 months after the diagnosis) were also noted.

The data was entered via Excel (Microsoft office 2016) and analyzed with Epi Info software version 7.2.

The description was made by means of position parameters, dispersion and illustrations in the form of tables and graphs appropriate according to the type of variables.

The absolute and relative frequencies have been presented in frequency tables, or summarized on suitable graphs. The quantitative variables were summarized according to the mean with its standard deviation, but also the median and the extremes.

3. Results

A total of 80 patients were seen at the pediatric endocrinology clinic during the study period for suspected CAH: 43 cases of DSD and 38 cases of adrenal insufficiency.

Among these cases, 32 patients had a diagnosis of CAH, representing 74.41% of the causes of DSD and 84.21% of the causes of adrenal insufficiency.

3.1. Age at Presentation

The mean age was 19 ± 34.6 months ranging from 2 days to 144 months. The median was 4.5 months and mode 1 month.

Only 6 of our patients (18.75%) have been diagnosed during the first month of life (**Figure 1**).

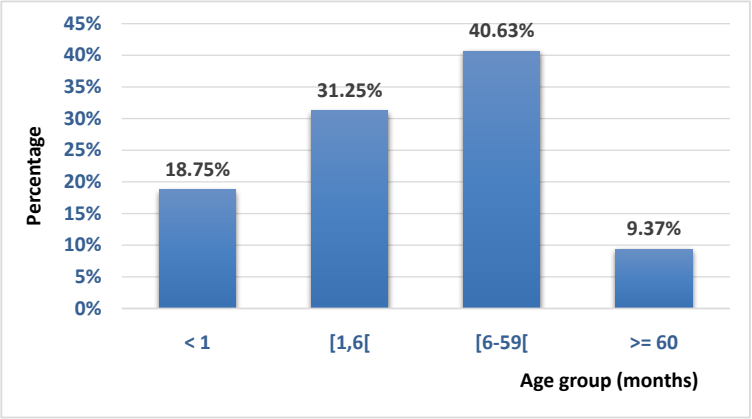

Figure 1. Age of the patients at the presentation.

3.2. Sexe Distribution

The population consisted of 27 girls (84.37%) and 5 boys (15.63%) with a sex ratio of 5.4.

3.3. Age of Mothers at the Beginning of Pregnancy

The mean age of mothers was 30.25 ± 5.9 years ranging from 23 and 45 years. The median was 33 years and the mode 25 years.

3.4. Data from Family History

Parental consanguinity and neonatal death were found in 78.12% and 43.75% respectively (Table 1).

3.5. Clinical Presentation at the Diagnosis

DSD was the main finding (87.5%). It was associated with dehydration in 22 cases (68.75%) (Table 2).

3.6. Distribution According to Physical Examination of the External Genitalia

External genitalia examination was normal in 3 out of 5 boys.

In girls, clitoris hypertrophy was constant (100% of cases). Prader stage 4 was the most prevalent (55.56%). Table 3 summarizes the distribution according to the results of the clinical examination.

3.7. Baseline Biochemical Findings

The serum electrolyte and 17OH progesterone tests were performed in all cases. In 24 cases (75%), serum electrolytes showed hyponatremia and hyperkaliemia. Table 4 summarizes the distribution according to the biochemical assessment.

3.8. Distribution According to Enzyme Deficiencies

21-hydroxylase deficiency was the most prevalent (93.75%). The majority

Table 1. Distribution by family history.

	Number	Percentage (%)
Gravidity		
Primigravida	8	25
Paucigravida	13	40.62
Multigravida	11	34.38
Term		
Prematurity	3	9.7
Term	29	90.3
History of neonatal death		
Yes	14	43.75
History of salt loss		
Yes	5	15.62
Parental consanguinity		
Yes	25	78.12
Family history of DSD		
Yes	3	9.37

Table 2. Clinical presentation of patients.

	Girls n (%)	Boys n (%)	Total n (%)
DSD with dehydration	**20 (74.07)**	**2 (40)**	**22 (68.75)**
DSD without dehydration	**6 (22.22)**	**0**	**6 (18.75)**
Dehydration without DSD	**0**	**1 (20)**	**1 (3.12)**
Pseudo precocious puberty	**1 (3.70)**	**1 (20)**	**2 (6.25)**
Weight loss	-	**1 (20)**	**1 (3.12)**
Total	**27 (84.38)**	**5 (15.62)**	**32 (100)**

DSD = Disorder of sexual development.

(73.33%) had classic salt-wasting form and 20% had simple virilizing form and 6.67% a non-classical form (Table 5).

3.9. Treatment and Outcome

All children received Hydrocortisone. Mean initial dose was 26 ± 3.56 mg/m^2 and maintenance dose 12 ± 2.42 mg/m^2 of the body surface. Of the 24 children with mineralocorticoid deficiency, only 4 (16.67%) had a substitution with fludrocortisone.

Short- and medium-term outcome was favorable in all cases. No death has been reported. However, 9 children (28.12%) were lost to follow-up.

Table 3. Distribution by physical examination of the external genitalia in girls (n = 27).

	Number	Percentage (%)
Clitoris Hypertrophy		
Yes	**27**	**100**
Labioscrotal folds		
Striated and pigmented	**3**	**3.12**
Smooth	**24**	**88.88**
Number of urogenital orifices		
Unique	**19**	**70.37**
Double	**8**	**29.63**
Gonads palpated		
No	**25**	**92.59**
Posterior labial fusion		
Yes	**19**	**70.37**
Prader stage		
1	**7**	**25.93**
2	**1**	**3.70**
3	**4**	**14.81**
4	**15**	**55.56**

Table 4. Biochemical values of patients.

	SW CAH (mean ± SD)	SV CAH (mean ± SD)
Natremia (mmol/l)(n = 32)	121 ± 11	139 ± 7
Kaliemia (mmol/l) (n = 32)	6.4 ± 0.7	4.3 ± 0.4
Glycemia (mg/dl) (n = 32)	78.4 ± 34	82 ± 10
17 OHP (ng/ml (n = 32)	28.83 ± 19.5	38.66 ± 56
17 OH Pre (ng/ml) (n = 6)	256.80 ± 12.5	-
DHEA-s µmol/l (n = 15)	2.2 ± 2.10	7.3 ± 5.22
ACTH (pmol/l) (n = 8)	80.9 ± 43.5	39.3 ± 45.95
Cortisol (nmol/l) (n = 15)	135 ± 62	146 ± 45

SW = Salt-wasting; SV = simple virilization; 17OHP = 17 hydroxyprogesterone, 17OHPre = 17 hydroxypregnenolone, DHEA-s = Dihydroepiandrostenedione; ACTH = Adrenocorticotrophic Hormone

4. Discussion

CAH is the main cause of DSD (74.41%) and the main cause of adrenal insufficiency (84.21%) in children. The diagnosis is late in our context (19 months). This is due to the absence of systematic newborn screening and the ignorance of this pathology by health care professionals. A South African study had found

Table 5. Distribution according to enzyme deficiencies.

	Girls		Boys	TOTAL n (%)	
	Number	%	Number	%	
21 Hydroxylase	27	100	3	60	30 (93.75)
CSW	20	74.08	2	66.67	22 (73.33)
SV	6	22.22	0	00	6 (20)
Non classical	1	3.70	1	33.33	2 (6.67)
3β-Hydroxysteroid dehydrogenase	0	0	2	40	2 (6.25)
11β-hydroxylase	0	0	0		0
17α-hydroxylase	0	0	0		0
StAR	0	0	0		0
Total	**27**	84.37	5	15.63	32 (100)

CSW = classical salt wasting; SV = simple virilization; StAR = Steroidogenic Acute Regulator.

that this delay was greater in the forms with simple virilization [5]. In Europe, this same delay was noted before systematization of neonatal screening [6]. The female predominance in our study is probably due to the normality of external genitalia in boys. This situation exposes them to the risks of severe dehydration with a shock which can be life-threatening, as shown by the high rate of neonatal deaths in the siblings of affected families (43.75%). Indeed, DSD constitutes the clinical feature in girls, which allows the diagnosis to be made earlier before the onset of salt loss syndrome. However, there is no significant gender difference in the large western cohorts [7]. DSD at birth, present in 87.5% should make it possible to evoke the diagnosis earlier before the onset of the salt loss which was present in 74.07% of girls at the time of diagnosis. It is important to emphasize on systematic examination of newborns in the delivery room, especially external genitalia examination.

21-hydroxylase deficiency represented 93.75% of the causes of CAH, with salt wasting in 73.33%. This is close to the figures found in the literature where 21-hydroxylase deficiency accounts for 95% of CAH, classic salt wasting forms represent 2/3 of case against 1/3 for simple virilizing forms [2] [4]. It is due to a mutation in the CYP21A2 gene located in a complex genetic region at chromosome 6p21.3 where it lies in close proximity to a highly homologous pseudogene, CYP21A1P. CYP21A2 and CYP21A1P are arranged in tandem repeats with the C4A and C4B genes, which encode complement 4 [8]. To date, over 200 CYP21A2 mutations have been reported [9]. 3β-hydroxysteroid dehydrogenase deficiency was found in 2 boys (6.25% of cases). It was revealed by DSD and salt wasting. It is the third most common deficiency after 11β-hydroxylase deficiency [10] [11]. 3β-hydroxysteroid dehydrogenase type 2 deficiency is caused by HSD3B2 gene mutations and characterized by impairment of steroid synthesis in the gonads and the adrenal glands. This leads to decreased cortisol, aldosterone, and androstenedione concentrations [12]. The clinical presentation varies ac-

cording to the type (severity) of the genetic mutation and may include salt-wasting in both sexes, incomplete masculinization in males, and virilization in females. [13] [14].

However, none of our patients had a molecular biology exam in our study. This is due to the unavailability of certain examinations in public structures and poor health coverage. Indeed, these exams are only available in the private sector in a poor population and more often without access to health coverage. It is important to vulgarize universal health coverage and make accessible molecular diagnostic methods.

Other types of HCS that are 11β-hydroxylase deficiency, 17α-hydroxylase deficiency, P450 oxidoreductase deficiency and StAR (congenital lipoid hyperplasia) deficiency were not found in our study. They are causes rarely described in the literature [15] [16] [17] [18].

Non-classical forms represented 6.67% (2 cases). It was a boy and a girl, all revealed by a pseudo precocious puberty. These forms, more common in girls with hyperandrogenism, vary from 0.6% to 9% of CAH [19].

Study Limitations

This was a retrospective descriptive study, which is accompanied by the usual issues of data integrity such as missing data. However, to our knowledge, this review is the first and largest study evaluating clinical presentation and biochemical profiles in children with CAH in Senegal. The information generated has important implications, as it can be used to prevent deaths from an adrenal crisis in unrecognized patients.

5. Conclusion

The diagnosis of CAH was delayed in males and females. Three-quarters of females with genital abnormality were missed at birth and presented with life-threatening adrenal crises. This missed and delayed diagnosis probably results in a high mortality rate and under-reporting of cases especially in boys. In the absence of neonatal screening for CAH in Senegal, there is an urgent need to educate and train healthcare workers to recognize neonates with DSD early and refer them timeously for specialist care.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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