

RESEARCH ARTICLE

# Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: A five-year retrospective study in the Children's Hospital of Damascus, Syria

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## ABSTRACT

**Background:** Congenital adrenal hyperplasia (CAH) is one of the most common inherited metabolic disorders. 21-hydroxylase deficiency is responsible for the majority of cases (90-95%) and considered the most common cause of genital ambiguity. There are no statistics concerning the prevalence of this disorder in Syria, although the high rate of consanguineous marriages indicates a possible high prevalence. **Objectives:** This study aims to collect baseline information about CAH in Syria to evaluate the potential need of a screening program.

**Subjects and Methods:** All medical records of inpatients who had CAH as a final or presumptive diagnosis at the Children's Hospital of Damascus between 2008 – 2012, or were diagnosed elsewhere and then admitted at the hospital for the first time within the same period, were retrospectively reviewed and divided into two groups: confirmed and suspected cases.

**Results:** Eighty-nine cases were confirmed, 25 were still suspected. Of the 89 confirmed cases: 20 (22.5%) were males, 66 (74.1%) were females, and 3 were ambiguous. Sixty-one patients (68.5%) were of the salt wasting type and 28 (31.5%) were of the simple virilizing type. The mortality rate was 6.7%. Thirty-two females were assigned as males at birth. Seventeen cases (19.1%) underwent previous hospitalization. 69.7% of patients were not diagnosed during the first month of life. Of the 25 suspected cases: 12 were males, 8 were females and 5 were ambiguous. Confirmatory tests had not been performed because of death in 7 patients (28%) and early discharge upon parental request in another 7 patients (28%).

Conclusion: A mandatory screening program for CAH in Syria seems necessary due to the obvious lack of awareness, delayed diagnosis and high expected prevalence. However, further efforts are needed to confirm the effectiveness of such a program in the Syrian society.

Keywords: congenital adrenal hyperplasia, 21-hydroxylase deficiency, salt wasting type, simple virilizing type

## INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of disorders caused by a lack in one of the enzymes that mediate the adrenal corticoid hormone synthesis pathway which produces cortisol from cholesterol. It is inherited in an autosomal recessive pattern,<sup>(1,2)</sup> and known to be the most common cause of disorders of sexual differentiation,<sup>(3)</sup> especially in females.<sup>(4)</sup> This inherited disorder leads to a reduced production of glucocorticoids, over or under production of mineralocorticoids and androgens leading to a variety of clinical manifestations depending on the type of the defective enzyme and the severity of its deficiency. This may lead to a wrong gender assignment and death due to salt loss and dehydration.<sup>(2,5-7)</sup>

CAH represents a challenging disorder for physicians to diagnose due to its non-characteristic manifestations and the complexity of its biopathology especially in males because adrenal insufficiency signs are harder to notice, which contributes to higher mortality rates,<sup>(1)</sup> and higher morbidity including mental disability and neurological sequel than in females.<sup>(8)</sup> However, a recently published study performed in New Zealand stated that clinical diagnosis is unreliable in both genders as a fifth of females in the study would have not been diagnosed without screening.<sup>(9)</sup> This fact is supported by findings from a recent Swedish study which stated that neonatal screening improves survival in both genders, even in a country with a developed healthcare system like Sweden.<sup>(10)</sup>

There is significant variation in the prevalence and type of CAH between populations.<sup>(11)</sup> The nationwide prevalence of CAH in the literature ranges between a high of 1:282 in Southwestern Alaska and a low of 1:23344 in New Zealand.<sup>(12)</sup> It is reported that 90–95 percent of cases result from 21-hydroxylase deficiency,<sup>(1,13)</sup> followed by 11-beta-hydroxylase deficiency which is responsible for 5–8 percent of

cases.<sup>(14)</sup> The remainder of the enzymatic deficiencies account for less than 1 percent of reported cases.<sup>(7)</sup> The published data on the incidence of CAH in some Arab countries demonstrate relatively high rates such as 1:1209 in Alexandria, Egypt,<sup>(12)</sup> 1:5000 in Saudi Arabia<sup>(15)</sup> and 1:9030 in the United Arab Emirates.<sup>(16)</sup> The literature lacks epidemiologic reports regarding the prevalence, morbidity and mortality rates of CAH in Syria, with a population reaching 21.5 million in 2010 according to the United Nations Department of Economic and Social Affairs.<sup>(17)</sup> We hypothesize that Syria has a relatively high prevalence of CAH due to the high proportion of consanguineous marriages.

In this study, clinical and laboratory data of CAH cases in Syrian children admitted to the Children's Hospital of Damascus were collected to evaluate the potential need for a newborn screening program which is not currently established in the country for this disease or any other.

## SUBJECTS AND METHODS

According to the Children's Hospital of Damascus computer data, the codes of all medical records which included CAH due to 21-hydroxylase deficiency as a final or presumptive diagnosis between January 1<sup>st</sup> 2008 to December 31<sup>st</sup> 2012 were extracted, in addition to the codes of 21-hydroxylase deficiency patients who were diagnosed outside the hospital and admitted as inpatients for the first time during the same period. The presumptive diagnosis was based on non-specific clinical presentation such as, disorders of sex differentiation, vomiting, diarrhea, failure to thrive, precocious pseudopuberty and non-specific laboratory tests such as, electrolytes, blood gases and serum glucose. Cases of CAH are recorded on the hospital's electronic registration system following a confirmed or final diagnosis, when available, or under the possible diagnosis/group of suspected diagnoses when no specific diagnosis had been confirmed.

Confirmation was based on serum 17-hydroxyprogesterone (17-OHP) levels which were measured by DRG serum 17 $\alpha$ -OHP ELISA kit using the normal ranges adjusted for age mentioned in the kit. Normal ranges are shown in Table 1.

The adrenocorticotrophic hormone (ACTH) stimulation test was used to confirm one case with moderately elevated 17-OHP. CAH cases were classified as salt wasting (SW) if they had low serum sodium and high serum potassium and simple virilizing (SV) if they

**Table 1. Serum 17 $\alpha$ -OHP normal ranges**

Newborns	Girls	Boys	Boys and girls
1 month after birth	2.4 - 16.6 ng/ml	0.0 - 8.0 ng/ml	0 - 16.6 ng/ml
2 month after birth	1.6 - 9.7 ng/ml	3.6 - 13.7 ng/ml	1.9 - 9.8 ng/ml
3 month after birth	0.1 - 3.1 ng/ml	1.7 - 4.0 ng/ml	0.1 - 4.0 ng/ml
Children 3-14 years		0.07 - 1.7 ng/ml	

presented with prenatal virilization without salt loss. Patients were divided into males and females depending on karyotype except when it was unambiguous. In these cases the clinician reported sex was used.

A form was filled for each case containing the patient's clinical manifestations and laboratory investigations, in addition to age at diagnosis, phenotypic sex, genotypic sex, skeletal age, family history, death of siblings in early childhood, and the consanguinity of parents.

## RESULTS

During the study period, a total of 15,8149 children were admitted to the Children's Hospital of Damascus. The total number of reviewed records was 138. Based on serum 17-hydroxyprogesterone (17-OHP), 89 of the 138 cases were confirmed to have 21-hydroxylase deficiency CAH due to elevated levels (the confirmed group), and 24 were excluded due to normal levels. The remaining 25 cases did not undergo confirmatory tests so they were classified as suspected CAH cases (the suspected group).

### The confirmed group

The total number of confirmed CAH cases was 89 including 20 males (22.5%), 66 females (74.1%) and 3 cases of undetermined phenotypic gender which was not identified by karyotype. The Mode value for serum 17-OHP was > 20 ng/ml with a range of 7.4-390 ng/ml. Salt wasting accounted for

61 (68.5%) of cases while SV accounted for 28 (31.5%). Sex distribution and age at diagnosis for this group are shown in Table 2.

Karyotype was performed in 57 (64%) of the total 89 cases and it revealed that 32 patients were females considered to be males at birth and 3 were females with an undetermined phenotypic gender.

Parental consanguinity was present in 59 (66.3%) of the 89 cases. A family history of affected relatives was present in 13 cases (14.6%), 9 of which were in siblings, 3 in first-degree cousins and 1 in a sibling and a first-degree cousin. A family history of similar manifestations was present in 16 (18%) cases. In 9 of these 16 cases, the manifestations were present in one relative, 4 in two relatives, and 3 in several relatives. A family history of early childhood mortality (< 5 years) was present in 18 (20.2%) of the confirmed cases. Eight had manifestations similar to CAH and 6 had an unknown cause of death. Of these 18 mortality episodes, 15 occurred in siblings, 7 patients had one dead sibling and 8 suffered the loss of two dead siblings. A history of previous hospitalization with causes related to CAH, mostly repetitive vomiting with or without diarrhea was present in 17 (19.1%) of the 89 cases. They were discharged without diagnosis (7 one time, 6 two times, 4 several times). All of them were salt wasters. Mortality rate in this group was 6.7%. Diagnosis in the neonatal period (< 1 month) was established in 27 cases (30.3%).

**Table 2. Sex and age distribution of confirmed 21-hydroxylase deficiency patients**

	SW	SV
Total No.	61	28
M/F/ U D	19/39/3	1/27/0
Age at diagnosis: Median (range)	1.15 month (5days - 4.6 year)	5 months (10 days - 7 years)

SW: salt wasting; SV: simple virilizing; M: male gender; F: female gender; U D: undetermined gender which wasn't identified by karyotype. Sex was determined by karyotype except when it was an unambiguous. In these cases the clinician reported sex was used.

**Table 3. The presenting signs and symptoms in the confirmed and suspected group**

Signs and Symptoms	N (%)	
	The confirmed group (n = 89)	The suspected group (n = 25)
Virilization*	71 (79.8%)	5 (20%)
Vomiting	38 (42.7%)	9 (36%)
Failure to thrive	37 (41.6%)	12 (48%)
Hyperpigmentation	30 (33.7%)	12 (48%)
Asthenia	20 (22.5%)	6 (24%)
Diarrhea	19 (21.3%)	3 (12%)
Convulsions	9 (10.1%)	5 (20%)

\* The number of patients who presented with virilization was assessed with the exception of the 3 undetermined phenotypic gender cases.

Skeletal age was measured in 7 (7.9%) of the 89 cases and was advanced in 3 of them. Virilization was observed by parents since birth in 5 of the 28 SV cases, yet medical care was not sought until a later age of 7 years, 6 years, 1 year and 2 months, 5 months and 17 days and 5 months. Skeletal age was measured in two cases of these five cases and was advanced in both.

Virilization was the most common manifestation among this group followed by vomiting. The main manifestations at the time of presentation are summarized in Table 3.

### The suspected group

The total number of suspected CAH patients (patients who had CAH as a presumptive diagnosis but hadn't undergo confirmatory testing) was 25 (12 males, 8 females and 5 undetermined phenotypic gender which wasn't identified by karyotype). Of these suspected cases, 7 (28%) passed away before confirmation, while the remaining 18 (72%) were discharged before confirmation (7 of them upon their parents' request). The median age when admitted to the hospital was 2 months with a range of 1 day to 5.5 years. A history of previous hospitalization was present in 5 (20%) of the 25 suspected cases (2 one time and 3 several times). The main manifestations at the time of presentation are summarized in Table 3.

## DISCUSSION

Congenital adrenal hyperplasia is an autosomal recessive disorder considered one of the most common inherited metabolic disorders.<sup>(16)</sup> There is wide disagreement on the actual mortality rate from undiagnosed CAH.<sup>(18)</sup> On the other hand, there is clear consensus that screening for CAH decreases

mortality and morbidity (neurological damage or intellectual disability) rates due to prevention of salt wasting crises. It also shortens the time of incorrect sex assignment in virilized females and helps in avoiding precocious puberty and decreased final height.<sup>(19,20)</sup> High rates of consanguineous marriage are reflected by high prevalence of such disorders therefore, prevalence in Syria is expected to be high as the rate of consanguineous marriages accounts for 35.4% of all marriages in Syria<sup>(21)</sup> and was present in 65.2% of the confirmed cases in our study. The high prevalence of CAH reported in Egypt (1:1209),<sup>(10)</sup> Saudi Arabia (1:5000)<sup>(15)</sup> and United Arab Emirates (1:9030),<sup>(16)</sup> may be an indicator that this disorder may be more prevalent in Arab countries, including in Syria. This study demonstrated that 89 Syrian child were diagnosed with CAH between 2008 and 2012. Table 4 summarizes the results of similar retrospective studies conducted in different countries worldwide. Female patients outnumbered male patients (male to female ratio in the confirmed group was approximately 1:3) although the autosomal recessive inheritance of this disorder suggests that both sexes are at the same risk for CAH. This might be due to the fact that some males with the SV form may remain undiagnosed as it is easier to recognize the virilized genitalia in females. For the same reason, males with the salt wasting form are more likely to be missed than females, so they may be at higher risk of adrenal crises and may pass away without diagnosis. Wrong gender assignment was present in 32 of the 57 confirmed cases which had an identified genotypic sex, all of them were females thought to be males at birth. This reflects the inability of the healthcare staff to distinguish male genitalia from virilized female genitalia, which may be highly distressing to the patient's family if not discovered early.

**Table 4. Results of retrospective CAH studies conducted worldwide**

Authors of study	21-hydroxylase deficiency cases/ study duration	The medical centre where the study took place
Kandemir N. et al., 1997 <sup>(7)</sup>	234/25 years	Pediatric Endocrinology Unit, Hacettepe University, Turkey
Maiti A. et al., 2011 <sup>(23)</sup>	86/4.5 years	Tertiary care centre Eastern India
Al-Jurayyan N.A. et al., 1995 <sup>(11)</sup>	59/10 years	King Khalid University Hospital, Riyadh, Saudi Arabia
Azar M.R. et al., 2013 <sup>(24)</sup>	491/43 years	Tertiary care hospital, Iran
Lubani M.M. et al., 1990 <sup>(25)</sup>	54/10 years	Five medical paediatric centres in Kuwait, plus cases referred from other centres
Lim Y.J. et al., 1995 <sup>(22)</sup>	89/23 years	A children's hospital in Australia
Current study	89/5 years	Children's Hospital of Damascus

There is a considerable number of confirmed patients who had a history of CAH or similar manifestations in one or more relative (33.7%), which indicates the necessity of testing the relatives of an affected patient and educating them about this disease.

Some SW cases might be missed because they are at risk of encountering death before any medical care is requested or diagnosis is made.<sup>(22)</sup> This fact is supported by our study which showed that 19.1% of the confirmed patients underwent previous hospitalization and were discharged without obtaining a proper diagnosis one time or several times. All of them were salt wasters. This reflects the lack of the medical staff awareness toward such problems and increases the salt wasting patients' risk of having reoccurring adrenal crises which may be lethal. Mortality rate in this group was 6.7% compared with 1.7% of Syrian children under the age of five between 2005 and 2010 according to the United Nations Department of Economic And Social Affairs.<sup>(17)</sup>

Seven (28%) of the suspected cases passed away and another 7 (28%) were discharged early upon their parent's request. It is unclear whether these were

CAH cases that were missed for the different reasons previously mentioned however, their existence reflects the overall lack of awareness about this disease, particularly on the part of the parents. This is supported by delayed diagnosis of 5 SV cases whose genital ambiguity was observed by parents since birth and delayed the overall diagnosis age.

## CONCLUSION

The necessity of a mandatory screening program in Syria seems to be a rational need to avoid mortality caused by CAH and to reduce morbidity and the time needed for correct diagnosis, as more than half of the confirmed patients (69.7%) in our study were not diagnosed in the first month of life. However, further studies are needed to determine the cost-effectiveness and applicability of such a program in the Syrian society.

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