Congenital adrenal hyperplasia: hospital based study

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Summary:

Background: Congenital adrenal hyperplasia is a family of autosomal recessive disorders of cortisol biosynthesis. Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of mineralocorticoid deficiency or excess; incomplete virilization or premature puberty in affected males; and virilization or sexual infantilism in affected females. The most frequent is 21-hydroxylase enzyme deficiency, accounting for more than 90% of cases.

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Objectives: to review cases of congenital adrenal hyperplasia registered in children welfare teaching hospital- medical city- Baghdad.

Patients and method: This study included all patients who were presented and registered in the endocrine clinic of the children welfare teaching hospital- medical city complex as a case of congenital adrenal hyperplasia from the 1st of January 1990 till the 1st of Jun 2009. Demographic informations together with epidemiological, clinical, diagnostic and therapeutic data of the patients were collected.

Results: The total number of patients was 60 patients with mean age (6.321) +/- (3.996) SD and male to female ratio of 2:3. Seventy percent of patients presented within the 1st 6 months of life, 61.9% of them were females. Thirty-one (51.7%) patients were delivered in the hospital including 72% of those who were presented within the 1st month. Forty six (76.7%) patients were presented with ambiguous genitalia with or without other presentations, 8 (13.3%) patients presented with salt losing only and 6(10%) patients presented with pseudo precocious puberty with or without other presentations. Consanguinity between the parents was present in 86.7% of patients, 33.3% of patients had positive family history of similar condition, 36.7% of patients had positive family history of neonatal death due to dehydration or abortion and only 3.3% of patients had history of hormonal therapy during pregnancy. Twenty two (36.7%) patients were reared with false sex, 95.5% of them were females reared as males, 33.3% of them accept to change their names & sex of rearing to definitive sex as females and one male (4.5%) patient reared as female had change his name and sex to male. Seventy percent of patients were diagnosed as 21 hydroxylase deficiency, both salt loser (71.4%) and non salt loser (28.6%), (10%) as 11 hydroxylase deficiency, (18.3%) as 3β hydroxysteroid dehydrogenase deficiency both salt loser (54.5%) and non salt loser (45.5%) and (1.7%) as17 hydroxylase deficiency.

Conclusions: The commonest form of congenital adrenal hyperplasia in Iraq is 21 hydroxylase deficiencies**.** There was delay in the diagnosis in spite of hospital delivery, and this may lead to psycho-social problems for the patients and their families regarding changing the sex of rearing. Many patients having genital anomalies did not operate upon yet.

Key words: congenital adrenal hyperplasia, ambiguous genitalia, 21-hydroxylase deficiency, children welfare teaching hospital.

Introduction:

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of cortisol biosynthesis (1), which represents a complex and heterogeneous group of conditions, characterized by defects in one of the five enzymes involved in adrenal steroidogenesis (2). Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of mineralocorticoid deficiency or excess; incomplete virilization or premature puberty in affected males; and virilization or sexual infantilism in affected females (1). The most frequent is 21-hydroxylase enzyme deficiency, accounting for more than 90% of cases (1, 3, 4, 5). The disease is classified into the following forms: The classical form with the most prominent feature being the virilisation of external genitalia and/or the body (simple virilising form) or the virilisation of external genitalia and/or the body with renal salt wasting as defined by hyponatremia, hyperkalemia, inappropriate natriuresis and low serum and urinary aldosterone levels (salt-wasting form of CAH) (1, 6, 7, 8). So female infant with classical CAH typically have ambiguous genitalia at birth because of exposure to high concentrations of androgen in utero and it is the most common cause of ambiguous genitalia in 46XX infants. While boys with classical CAH, have no signs at birth except subtle hyperpigmentation and possible penile enlargement (9). Thus, the diagnosis may not be made in boys until signs of adrenal insufficiency develop. Because patients with this condition can deteriorate quickly, infant boys are much more likely to die than girls. For this reason, many states and countries have instituted newborn screening for this condition (1). 11 beta-hydroxylase deficiency is the second most frequent cause of CAH (5). Approximately two thirds of patients become hypertensive, although this can take several years without treatment to develop and all signs and

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symptoms of androgen excess that are found in 21-hydroxylase deficiency may also occur in 11-hydroxylase deficiency (1).

3ß-hydroxysteroid dehydrogenase (3ß-HSD) deficiency occurs in fewer than 2% of patients with adrenal hyperplasia. In classical form, the infants are prone to salt wasting crises, the boys are incompletely virilized and the girls are mildly virilized with slight to moderate clitoral enlargement (1). 17-hydroxylase deficiency occurs in less than 1% of patients with adrenal hyperplasia in which affected males are incompletely virilized and present as phenotypic females (but gonads are usually palpable in the inguinal region or the labia) or with sexual ambiguity (male pseudohermaphroditism) (1). Females present with normal external genitalia but failure to develop secondary sex characteristics and primary amenorrhea. Both sexes have hypertension, hypokalemic alkalosis, and failure to progress into puberty (5).Lipoid adrenal hyperplasia is a rare disorder; the patients are usually unable to synthesize any adrenal steroids. Salt-losing manifestations are usual, and many infants die in early infancy (1).

The therapeutic goal is to use the lowest dose of glucocorticoid that adequately suppresses adrenal androgens and maintains normal growth and weight gain (3, 10). Patients should be monitored carefully for signs of iatrogenic Cushing's syndrome (3). The preferred drug is hydrocortisone (i.e., cortisol) in maintenance doses of 10 to 20 mg per square meter of body-surface area per day in three divided doses (3, 11). Doses of up to 100 mg per square meter per day are given during adrenal crises and life-threatening situations. Infants with the salt-wasting form require supplemental mineralocorticoid (usually 0.1 to 0.2 mg of fludrocortisone daily) and sodium chloride (1 to 2 g daily in addition to glucocorticoid treatment)(3).Regarding sex assignment; the presence of ambiguous genitalia may lead to incorrect male sex assignment in the genetic female and its attendant medical and psychosocial consequences (12, 13). Female patients with classical CAH have been found to have more male-typical childhood play than unaffected girls (14, 15).

Nevertheless with CAH have been found to identify as female and do not have gender –identity confusion (16,17), the effect of postnatal androgen exposure might differ from that of prenatal androgen exposure (9). Improvements in the surgical correction of genital anomalies over the past two decades have led to earlier use of single-stage surgery between two and six months of life in girls with 21-hydroxylase deficiency, a time when the tissues are maximally pliable and psychological trauma to the child is minimized, revision in adolescence is often necessary (18).

The aim of this study was to review all cases which were diagnosed as congenital adrenal hyperplasia and registered in the endocrine clinic of children welfare teaching hospital (CWTH) in the Medical City Complex - Baghdad.

Patients and method:

This retrospective study included all patients who were presented and registered in the endocrine clinic of the children welfare teaching hospital- medical city complex as a case congenital adrenal hyperplasia from the 1st of January 1990 till 1st of June 2009.

Data were collected from their case sheets and from the patients and their parents during their visits to the clinic for follow up:

1. Name, date of birth, place of delivery (hospital or home) and rearing sex
2. Date and mode of presentation which includes ambiguous genitalia, salt loser (vomiting and diarrhea with dehydration or failure to thrive), pseudoprecocious puberty and others as hypertension or as combination of more than one mode of presentation.
3. Family history which includes history of consanguinity between the parents, history of same condition in the same family or their relatives and history of abortion or neonatal death because of dehydration with or without ambiguous genitalia in the same family.
4. History of hormonal therapy during pregnancy.
5. Findings on examination at the time of presentation including:

a) Signs of dehydration, or failure to thrive and blood pressure measurement using appropriate cuff for age. b) Examination of genitalia and the findings were classified as either normal, ambiguous (male with hypospadius, undescended testes or female with enlarged clitoris, partially fused and rugase labia majora, and a common urogenital sinus in place of a separate urethra and vagina (9) or pseudo precocious puberty (male with pubic hair with enlarged penis and pre pubertal size of the testes or female with pubic hair and ambiguous genitalia).

6. The investigations which were done at the time of presentation or later and included in the study are serum glucose, potassium, sodium , chloride , blood urea and those with high potassium (more than 4.4 meq/L) and low sodium (less than 130 meq/L) regarded as salt loser (1)

X ray of the wrist to estimate bone age done by the radiologist in children welfare teaching hospital at time of presentation and later especially in patients with signs of precocious puberty.

Ultrasound of the abdomen, pelvis, inguinal region and scrotum to detect the genital organs were done for all patients at time of presentation.

Chromosomal analysis to confirm the definitive sex of the patients was done at the time of the presentation or later when it became available (Male XY, Female XX).

Hormonal assessment was done for some of the patients in private labs as they were not available in medical city labs and they were not accurate.

7. The medical treatment for all patients were cortisone acetate tablets (15-20 mg /m^2/day) and fludrocortisone tablets (0.05- 0.3 mg/day) if the patient is salt loser (1). History of surgical

operations as recession of the clitoris and/or vaginoplasty was reported.
Reassignment to true sex for those with false rearing sex reported. The data collected were arranged and tabled in number, percent (%), and mean +/- SD.
The association between variables measured by using Chi-square test, with P value <0.05 considered significant.

Results:
The total number of patients was 60 with mean age (6.321) +/- (3.996) SD, with male to female ratio of 2:3. Forty-two (70%) patients presented within the 1st 6 months of life with 26 (61.9%) of them were females and 25 (41.7%) presented within the 1st month (table 1).

Table 1: Distribution of patients according to age at presentation and definitive sex

Age at presentation (months)	Male NO. (%)	Female NO (%)	Total NO (%)
< 1	8 (32)	17 (68)	25 (41.7)
>1-6	8 (47.1)	9 (52.9)	17 (28.3)
>6-12	3 (50)	3 (50)	6 (10)
>12	5 (41.7)	7 (58.3)	12 (20)
Total	24 (40)	36 (60)	60 (100)

Thirty-one (51.7%) patients were delivered in the hospital and 29 (48.3%) patients delivered at home. Eighteen (72%) of those who were present within the 1st month delivered in the hospital and 7 (28%) patients delivered at home, while 4 (33.3%) of those who were present after 12 months delivered in the hospital and 8(66.7%) patients delivered at home (P value 0.0594) (table 2).

Table 2: Distribution of patients according to age at presentation and place of delivery

Age at presentation (months)	Hospital NO (%)	Home NO (%)	Total NO (%)
< 1	18 (72)	7 (28)	25 (41.7)
>1-6	6 (35.3)	11 (64.7)	17 (28.3)
>6-12	3 (50)	3 (50)	6 (10)
>12	4* (33.3)	8 (66.7)	12 (20)
Total	31 (51.7)	29 (48.3)	60 (100)

*All 4 patients had same rearing and definitive sex (male).

Forty six (76.7%) patients were presented with ambiguous genitalia with or without other presentations, 8 (13.3%) patients presented with salt losing only and 6(10%) patients presented with pseudo precocious puberty with or without other presentations (apart from ambiguous genitalia).
Forty two (70%) patients presented within the 1st six months of age had ambiguous genitalia with or without other presentations versus 12 (20%) patients who were presented after 6 months of age (P value is 0.005) (Table 3).

Table 3: Distribution of patients according to age at presentation and mode of presentation.

Age at presentation (months)	Ambiguous genitalia only No. (%)	Ambiguous genitalia And salt losing No. (%)	Ambiguous genitalia+ Hypertension No. (%)	Salt losing only No (%)	Pseudo precocious puberty (Spp)				
					Spp only No(%)	Spp+ salt losing No(%)	Spp+ hypertension No(%)	Spp+ Ambiguous genitalia+ Hypertension No. (%)	Total No. (%)
< 1	9 (36)	12 (48)	0 (0.0)	4 (16)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	25 (41.7)
> 1-6	2 (11.8)	10 (58.8)	1 (5.9)	4 (23.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17 (28.3)
> 6-12	1 (16.7)	3 (50)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (10)
> 12	4 (33.3)	1 (8.3)	0 (0.0)	0 (0.0)	3 (25)	1 (8.3)	2(16.7	1 (8.3)	12 (20)
Total	16 (26.7)	26 (43.3)	3 (5)	8 (13.3)	3 (5)	1 (1.7)	2 (3.3)	1 (1.7)	60 (100)

Regarding family history, consanguinity between the parents was present in 52 (86.7%) patients, 20 (33.3%) patients had positive family history of similar condition, 22 (36.7%) patients had positive family history of neonatal death due to dehydration or abortion and only 2 (3.3%) patients had history of hormonal therapy during pregnancy.

Seven (11.7%) patients had hypertension and 23(38.3%) patients had advanced bone age at presentation or later during follow up.

Detection of the genital organs by ultrasound examination was accurate in 57 (95%) patients although it was repeated more than once in some patients to reach correct findings.

All the patients (100%) were receiving cortisone replacement and 36 (60%) were receiving floudrocortisone tablets (table 4).

Table 4: Demographic characters, examination, investigations and treatment of the patients with congenital adrenal hyperplasia.

Character	Male No. (%)	Female No. (%)	Total No. (%)
Sex	24 (40)	36 (60)	60 (100)
History of consanguinity	20 (38.5)	32 (61.5)	52 (86.7)
Positive family history of similar condition	8 (40)	12 (60)	20 (33.3)
Positive family history of neonatal death due to dehydration or abortion	10 (45.5)	12 (54.5)	22 (36.7)
History of hormonal therapy during pregnancy	2 (100)	0 (0.0)	2 (3.3)
Hypertension	5 (71.4)	2 (28.6)	7 (11.7)
Advanced bone age	10 (43.5)	13 (56.5)	23 (38.3)
Ultrasound detecting reproductive organs	23 (40.4)	34 (59.6)	57 (95)
Chromosomal study	24 (40)	36 (60)	60 (100)
Medical treatment	Cortisone Acetate tab.	24 (37.9) / 36 (62.1)	60 (100)
	Fludrocortisone Tab.	13 (36.1) / 23 (63.9)	36 (60)
Surgical operation	0 (0.0)	2 (100)	2 (3.3)

Twenty one (35%) patients reared as males were proved to be females , while only one (1.7%) patient reared as female was proved to be male (table5).

Table 5: distribution of patients according to sex identity.

Sex	Rearing sex No. %	True sex No. %
Male	44 (73.3)	24 (40)
Female	16 (26.7)	36 (60)
Total	60 (100)	60 (100)

P value was 0.0005

Regarding sex reassignment , 22 (36.7%) patients were reared with false sex , 21 (95.5%) females were reared as males ,7 (33.3%) of them accept to change their names & sex of rearing to definitive sex as females and one male (4.5%) patient reared as female had change his name and sex to male.

Forty- two (70%), patients were diagnosed as 21 hydroxylase deficiency, both salt loser (71.4%) and non salt loser (28.6%), 6 (10%) patients were diagnosed as 11 hydroxylase deficiency, 11(18.3) patients were diagnosed as 3 beta hydroxysteroid dehydrogenase deficiency both salt loser (54.5%) and non salt loser (45.5%) and one patient (1.7%) was diagnosed as 17 hydroxylase deficiency (table 6).

Table 6: distribution of patients according to the possible types of congenital adrenal hyperplasia

Type of congenital adrenal hyperplasia	Male NO (%)	Female NO (%)	Total NO (%)
21 hydroxylase deficiency (salt loser)	8 (26.7)	22 (73.3)	30 (50)
21 hydroxylase deficiency (non salt loser)	1 (8.3)	11 (91.7)	12 (20)
11 hydroxylase deficiency	4 (66.7)	2 (33.3)	6 (10)
3beta-hydroxysteroid Dehydrogenase deficiency (salt loser)	5 (83.3)	1 (16.7)	6 (10)
3beta-hydroxysteroid dehydrogenase deficiency (non salt loser)	5 (100)	0 (0.0)	5 (8.3)
17 hydroxylase deficiency	1 (100)	0 (0.0)	1 (1.7)
Total	24 (40)	36 (60)	60 (100)

Discussion:

In this study, the mean age of patients was (6.321) +/- (3.996) SD with 40% males and 60% females which is nearly similar to Karamizadeh Z et al (44.3% males and 55.7% females) (8), Ali H (35% males and 65% females) (19) and Austerian study (43% males and 57% females) findings (6).

Although the disease is autosomal recessive (1), we notice the predominance of female patients which may be due to the fact that some of the affected males died during the neonatal period or passed undiagnosed because more than 90% of the cases due to 21- hydroxylase deficiency in which the male had normal genitalia at birth (1). Seventy percent of patients diagnosed before 6 months of age especially the females (61.9%), because they were born with ambiguous genitalia, so the family seeks medical advice early while the males were born with normal external genitalia which may delay the diagnosis. This finding is similar to Abdullah S et al findings (0.6 year for males and 0.4 years for females) (20).Thirty-one (51.7%) patients were delivered in the hospital and 29 (48.3%) at home, compared with Abdullah S et al findings (83.9% in hospital and 16.1% at home) (20), this may be due to the fact that home delivery is still usual in Iraq. Sixteen (26.7%) patients were presented with ambiguous genitalia alone which is similar to Karamizadeh Z et al findings (26.9%) (8), but higher than Ali H findings (22.5%) (19), while 43.3% were presented with ambiguous genitalia and salt losing which is higher than Karamizadeh Z et al findings (22.6%) (8), and lower than Ali H findings (60%) (19). Seven patients (11.7%) studied were presented with precocious puberty which is higher than Abdullah S et al findings (8.1%) (20), and lower than Karamizadeh Z et al findings 18.2% (8).This may be due to the delayed diagnosis of those cases. Consanguity was present in (86.7%) of patients which is nearly similar to Ali H findings (85%) (19), and higher than Abdullah S et al findings (62.5%) (20).This may be due to the fact that it is autosomal recessive disease and consaningious marriage is still common in Iraq. Family history of similar condition was present in (33.3%) of patients which is lower than Migeon CL et al findings (37.5%) (10) and higher than Salman H et al findings (22.5%) (13).

Family history of neonatal death and abortion was present in (36.7%) of patients which is lower than Abdullah S et al findings (45.8%) (20) and higher than Ali H findings (17.5%) (19), this can be explained as it is autosomal recessive and possibility of neonatal death especially in males with wrong diagnosis as sepsis and dehydration. Two (3.3%) patients had history of hormonal therapy during pregnancy which is lower than Ali H findings (7.5%) (19).Hypertension was founded in (11.7%) of patients which is nearly similar to Karamizadeh Z et al (13%) (8) but it was not reported in Ali H (19). Advanced bone age was founded in (38.3%) of patients at presentation and follow up which is higher than Ali H findings (30%) (19) which is may be due to late presentation and/ or irregular treatment.The accuracy of ultra sound examination in detecting genital organs was (95%) while it was only (77.5%) in Ali H (19) which means that there is improvement in the skill of our staff in the hospital. All patients (100%) used cortisol as replacement while only (60%) of patients were receiving floudrocortisone although irregular as it was not available always and we still use floudrocortisone for salt loser patients only although it is now recommended for non salt loser patients and allows mananegment with lower dosees of glucocorticoid (11).Surgical operation for external genitalia was done for 2 (3.3%) patients as some of them did not need such operations and we don't have trained surgeon to do such operations. Twenty two (36.7%) patients had wrong sex assignment at birth compared with (48.8%) of Abdullah S et al (20). sex reassignment were rejected by (66.7%) of them compared with (35%) of Abdullah S et al (20). This may be due to delayed diagnosis and consequently the psycho-social problems which will be raised for the family after changing the sex (12). Forty two (70%) patients had 21- hydroxylase deficiency which is lower than Perrin C. findings (90%)(1), and Karamizadeh Z et al findings (85.2%) (8), but higher than Ali H findings (65%) (19), 71.4% of them were salt loser and 28.6% were simple virilizing which are nearly similar to Perrin C. findings (70% versus 30%) (1), and different from Austerian study findings (64.7% versus 35.3%) (6), from Merke DP findings (67% versus 33%) (9) and from Ali H findings (60% versus 40%) (19), but still it is the most common form of congenital adrenal hyperplasia.Ten percent had 11- hydroxylase deficiency which is lower than Karamizadeh Z et al findings (13.04%) (8) and higher than Perrin C. findings(2%) (1). Eleven (18.3%) patients had 3β hydroxysteroid dehydrogenase deficiency which is higher than Ali H (15%) (19), Karamizadeh Z et al (0.87%) (8) and Perrin C. (<2%) (1) Findings. One (1.7%) patient had 17- hydroxylase deficiency which is higher than Perrin C findings (<1%) (1).

Conclusion:

The commonest form of congenital adrenal hyperplasia in Iraq is 21 hydroxylase deficiency and in spite of hospital delivery, there was delay in the diagnosis beyond one month of age, and this may lead to death and if not, it may lead to psycho-social problems for the patients and their families regarding changing the sex of rearing. Congenital adrenal hyperplasia should be suspected in every newborn with ambiguous genitalia and /or severe dehydration especially if there is positive family history. So proper clinical examination of all infants in the neonatal period to include genital examination is always mandatory, this will positively influence the appropriate diagnosis at the proper time so that specific work –up is carried out and consequences of delayed diagnosis are avoided, and we need to apply a neonatal screening test for every newborn. As many patients having genital anomalies did not operate upon yet, Surgeon should be trained to do the surgical correction of these genital anomalies.

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