

Congenital adrenal hyperplasia Due to 21-hydroxylase deficiency: consequences of delayed diagnosis - can it be prevented?

Abdullah S. Al-Herbish, FAAP, FRCPC, Nasir A. Al-Jurayyan, FAAP, FRCPC
Abdullah M. Abu Bakr, MsEd, FRCPC, Muhammad A. Abdullah, FRCPC (Ed.)

Abstract Objective: To determine consequences of delayed diagnosis in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency.

Design: Patients are drawn from a retrospective cohort study conducted on all patients with congenital adrenal hyperplasia.

Setting: Pediatric Endocrine Unit, King Khalid University Hospital, Riyadh, Saudi Arabia.

Results: Sixty-two children with 21-hydroxylase deficiency were involved. Twenty-one (33.9%) were males and 41 (66.1%) females. Consanguinity was documented in 30 (62.5%), similar disorders in the same family in 18 (37.5%), more than one affected child in 12 (25%) and neonatal and infant deaths in 22 (45.8%) families. The mean age at diagnosis was 0.6 year (range; 0-8.5) for males and 0.4 year (range; 0-6) for females. Of the total, 57 (92%) were salt losers. All males except one presented initially with salt-losing crises. Ambiguity of the genitalia of variable degrees was present in all females. This led to wrong sex assignment in 20 (48.8%). Sex reassignment was rejected for socio-cultural reasons in 7 (35%) precocious puberty and ultimate short stature were present in 5 patients (8.1%).

Conclusion: These results indicate that in the absence of clinical awareness and newborn screening, diagnosis is often delayed. Physicians' awareness and active measures towards establishing neonatal screening programs are urgently required. Prenatal diagnosis and dexamethasone therapy are also highly recommended for families at risk to prevent severe virilization in females with this disorder.

Saudi Medical Journal 1996; Vol. 17 (1)

Keywords: Congenital adrenal hyperplasia, 21-hydroxylase deficiency

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is a well-defined autosomal recessive disorder in which affected individuals present with progressive prenatal and postnatal virilization, with or without evidence of mineralocorticoid insufficiency.¹ In Saudi Arabia, this is not an uncommon disorder.^{2,3} Failure of early recognition and, hence, prompt treatment may lead to grave consequences.^{4,9}

In an attempt to examine the effects of the delayed diagnosis in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, we retrospectively reviewed the medical records of 62 patients with this disorder who were followed-up at King Khalid University Hospital (KKUH), Riyadh. We also highlight the importance

of early detection and discuss various aspects of prevention.

Material and methods The patients are drawn from a retrospective cohort study conducted on all patients with congenital adrenal hyperplasia who were seen between January 1984 and July 1994 at the endocrine unit of the (KKUH), Riyadh. The diagnosis of 21-hydroxylase deficiency was suspected on clinical grounds and confirmed by high plasma concentrations of 17-hydroxyprogesterone. The salt-losing state was confirmed by the presence of hyponatraemia, hyperkalaemia, natriuria and raised plasma renin activity with low or normal serum aldosterone concentrations.¹ All hormones were measured commercially by Bio-Scientia Laboratory,

From the Endocrine Division, Department of Pediatrics, King Saud University, Riyadh (AL-HERBISH, AL-JURAYYAN, ABU BAKR), and from the Department of Pediatrics, Security Forces Hospital, Riyadh (ABDULLAH).

Received September 1994. Accepted for publication in final form April 1995.

Address correspondence and reprint request to: Dr. Abdullah S. Al-Herbish, PO Box 90533, Riyadh 11652, Saudi Arabia.

Germany.

Data collected for each patient included, age at diagnosis, actual and given sex at presentation, place of birth, clinical presentation including reason for diagnosis; relevant family history, and results of all laboratory and ancillary investigations performed. Chromosomal analysis, abdominal ultrasonography and genitography were done when appropriate. The degree of severity in virilization of the female external genitalia was determined by applying Prader Classification.¹⁰ Bone age, and predicted adult height were done using Greulich and Pyle Atlases.¹¹ Pubic hair and breast development stages were rated according to the Tanner Staging System.¹²

Results During the period under review; 62 patients from 48 families were diagnosed as having congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Nine of them were born at King Khalid University Hospital whilst the rest were referred from other hospitals. Out of the total, 52 (83.9%) were born in-hospital and 10 (16.1%) at home. Consanguinity was documented in 30 (62.5%) of the families, and family history of a similar disorder was found in 18 (37.5%) families. Twelve families had more than one affected child. Thirty-six (26 males and 10 with ambiguous genitalia) neonatal and infant deaths occurred within 22 (45.8%) families.

There were 21 (33.9%) males and 41 (66.1%)

Table 1 - Degree of virilization of the external genitalia (Prader Classification in 41 females with CAH due to 21-hydroxylase deficiency).

Classification	No. of cases (%)
Type 1, Clitoral hypertrophy	1 (2.5%)
Type 2, Clitoral hypertrophy, urethral and vaginal orifices present but very near	5 (12.2%)
Type 3, Clitoral hypertrophy, single urethral orifice, posterior fusion of the labia majora	13 (31.7%)
Type 4, Penile clitoris, perineo-scrotal hypospadias, complete fusion of the labia majora	18 (43.9%)
Type 5, Complete masculinization (normal looking male genitalia) but no palpable testes	4 (9.7%)

females, giving male to female ratio of 1:2. The mean age at diagnosis was 0.6 year (mean; 0-8.5) for males and 0.4 year (mean; 0-6) for females. Of the total, 57 (92%), 20 males and 37 females, were salt-losers. All males except one presented initially with salt-losing crises, manifesting as vomiting, diarrhea, dehydration, feeding difficulties, failure to thrive and sepsis-like illness. Fifteen male patients were readmitted at a mean age of 2 months (range 0.5-7), while another five were diagnosed at an earlier age, mean 8 days (range; 2-12) having had the history of other affected siblings. One male child was diagnosed at a later age (8.5 years), having had a younger sibling presented with ambiguous genitalia. He was found to have precocious puberty. Ambiguity of the genitalia of variable degrees was present in all females, Table 1. This led initially to wrong male sex assignment in 20 (48.8%). Their mean age at presentation was 7 months (range; 1 week-6 years). Six of them were home deliveries. Seven rejected sex reassignment for socio-cultural reasons. Precocious puberty and ultimate short stature were already present in 5 patients (4 females and 1 male).

Discussion CAH is the most common adrenal disorder in infancy and childhood. It results from deficiency in the activity of one of the five enzymes required for cortisol biosynthesis. More than 90% of cases are due to 21-hydroxylase enzyme deficiency.¹ Failure of early recognition of affected newborns may lead to life-threatening adrenal crises in the neonatal period.^{3,4} The presence of ambiguous genitalia may also lead to incorrect male sex assignment in the genetic female and its attendant medical and psychosocial consequences.^{3,5,7,9} Furthermore, delayed diagnosis may also result in several other complications, including acceleration of skeletal maturation with ultimate short stature, premature development of secondary sex characteristics in male children, and further virilization in females.^{3,5,7,9}

This study indicates that the diagnosis was often delayed and thus optimal medical treatment precluded. Equally important observations are the increased number of neonatal and infant deaths, associated with high rate of consanguinity in the population studied. Saedi-Wong et al¹³ showed that the rate of consanguineous mating in the Saudi population is as high as 54.3%. Furthermore, the high frequency of salt-loss (92%) in contrast to what has been reported in the literature,^{1,4,9} with the

abnormal male-to-female sex ratio (1:2) of an autosomal condition may indicate that more cases, particularly the non-salt-losers, have been missed. It is worrying that the diagnosis in most males occurred only after they experienced a salt-losing crisis, and more than that number died in infancy. Surprisingly, while ambiguity of the external genitalia was present in all female patients, which could help in early diagnosis, yet 50% of those were inappropriately sex-assigned, and only correctly diagnosed after experiencing salt-losing crises. Unfortunately, in 7 patients, sex reassignment was rejected for socio-cultural reasons. Similar findings have been reported before.^{2,3,7,9} This emphasizes the importance of immediate and correct sex-assignment in the newborn period to achieve a stable medical and psychosocial outcome. On the other hand, while female patients with non-salt-losing form may have ambiguity of the genitalia and wrongly assigned as males, they are also as males subjected to the development of precocious puberty and ultimate short stature which was observed in 5 of our patients.

More awareness among physicians of the prevalence of the disease coupled with careful evaluation of the external genitalia and early referral, if necessary, would help to reduce the incorrect assignment of sex, and the mortalities associated with adrenal crises. 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. This certainly should be feasible as it requires clinical judgement and awareness only. Currently, neonatal screening for congenital adrenal hyperplasia due to 21-hydroxylase deficiency utilizing¹⁷ hydroxyprogesterone level has added another quick and convenient method for diagnosis.^{3,14-16} This can be organized as mass screening for boys as has been established elsewhere.^{13,14-16} The feasibility within the local health services is not very difficult in view of the successful programmes for neonatal screening for another important disorder, namely congenital hypothyroidism.¹⁷ Furthermore, prenatal diagnosis and maternal dexamethasone therapy in families at risk have proven to be safe and effective in preventing or at least minimizing the virilization of

the external female genitalia.^{1,18}

Acknowledgment We would like to thank Miss Alicia C. Evarola for her secretarial assistance.

References

1. Miller WL, Levine LS. Molecular and clinical advances in congenital adrenal hyperplasia. *J Pediatr*, 1987; 111: 1-17.
2. Abdullah MA, Katugampola M, Al-Habib S, et al. Ambiguous genitalia: Medical, socio-cultural and religious factors affecting management in Saudi Arabia. *Ann Trop Paediatr*, 1991; 11: 343-348.
3. Saiman H, Abanamy A, Ghassan B, Khalil M. Congenital adrenal hyperplasia. *Ann Saudi Med*, 1991; 11: 9-14.
4. Qazi QH, Thompson MW. Incidence of salt-losing form of congenital virilizing adrenal hyperplasia. *Arch Dis Child*, 1972; 47: 302-304.
5. Pang S, Murphy W, Levine LS et al. A pilot newborn screening for congenital adrenal hyperplasia in Alaska. *J Clin Endocrinol Metab*, 1982; 55: 413-420.
6. Fife D, Rappaport EB. Prevalence of salt-losing among congenital adrenal hyperplasia patients. *Clin Endocrinol*, 1983; 18: 259-264.
7. Lebovitz RM, Pauli RM, Laxova R. Delayed diagnosis in congenital adrenal hyperplasia: need for newborn screening. *Am J Dis Child*, 1984; 138: 571-573.
8. Viridi NK, Rayner PHW, Rudd BT, Green A. Should we screen for congenital adrenal hyperplasia? A review of 117 cases. *Arch Dis Child*, 1987; 62: 659-662.
9. Lubani MM, Issa ARA, Bushnaq R et al. Prevalence of congenital adrenal hyperplasia in Kuwait. *Eur J Pediatr*, 1990; 149: 391-392.
10. Prader A. Der Genitalbefund beim Pseudohermaphroditismus femininus des kongenitalen adrenogenitalen syndromes. *Helvet Paediat Acta*, 1954; 9: 231-248.
11. Greulich WW, Pyle SI. *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Second Edition. Stanford University Press, 1959; Stanford.
12. Tanner JM. *Growth at adolescence*, 2nd Edition, Blackwell Scientific Publications, Oxford 1962.
13. Suedi-Wong S, Al-Frayh AR, Wong HYH. Socio-economic epidemiology of consanguineous matings in the Saudi Arabian population. *J Asian Afr Studies*, 1989; 24: 247-252.
14. Pang S, Wallace MA, Hofman L, et al. Worldwide experience in newborn screening for congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Pediatr*, 1988; 81: 866-874.
15. Solym J, Hughes IA. Value of selective screening of congenital adrenal hyperplasia in Hungary. *Arch Dis Child*, 1989; 64: 388-342.
16. Thompson R, Sergeant L, Winter JSD. Screening for congenital adrenal hyperplasia: Distribution of 17- α -hydroxyprogesterone concentrations in neonatal blood spot specimens. *J Pediatr* 1989; 114: 400-404.
17. Al-Nuaim A, El-Desouki M, Al-Jurayyan N et al. Neonatal screening for congenital hypothyroidism: incidence, imaging, feasibility, and difficulties of a nationwide program. *Ann Saudi Med* 1992; 12: 129-134.
18. Pang S, Clark AI, Freeman LC, et al. Maternal side effects of Prenatal Dexamethasone Therapy for Fetal Congenital Hyperplasia 1992; 75: 249-253.

ملخص:

الهدف: دراسة عواقب تأخير تشخيص الأطفال الذين يعانون من تضخم الغدة الكظرية الوراثي المتسبب في نقص أنزيم ٢١ هيدروكسيليز.

الطريقة: لقد استخلص هؤلاء الأطفال من دراسة لكل الأطفال الذين يعانون من هذا المرض.

المكان: وحدة الغدة الصماء لدى الأطفال - مستشفى الملك خالد الجامعي - الرياض - المملكة العربية السعودية.

النتائج: لقد شخصت ٦٢ حالة (٢١ «٣٣,٩٪» ذكور و٤١ «٦٦,١٪» إناث) من ٤٨ عائلة بمرض تضخم الغدة الكظرية الوراثي المتسبب عن نقص أنزيم ٢١ هيدروكسيليز، ولقد كانت هناك قرابة ما بين ٣٠ (٦٢,٥٪) عائلة منهم ووجد نفس المرض من نفس العائلة في ١٨ (٣٧,٥٪) عائلة حيث كان هناك أكثر من طفل مصاب في العائلة ناتجا في ١٢ (٢٥٪) عائلة وحالة وفاة وليد أو رضيع في ٢٣ (٤٥,٨٪) عائلة. إن معدل العمر عند التشخيص كان ٠,٦ سنة (٠-٨,٥) للذكور و٠,٤ سنة (٠-٦) للإناث هذا وكان ٥٧ (٩٢٪) من العدد الكلي من نوع فاقد الأملاح، وكان تشوه الأعضاء التناسلية على درجات متفرقة موجودا عند كل الإناث، وقد أدى هذا إلى إطلاق جنس الذكورة على ٢٠ (٤٨,٨٪) أنثى. هذا وقد رفض التعديل إلى الجنس الصحيح لأسباب اجتماعية في سبع حالات (٣٥٪). لقد أصيب خمسة (٨,١٪) بالبلوغ المبكر مع قصر القامة المتوقع.

الاستنتاج والتوصيات: إنه في غياب الحس والوعي السريري والكشف المبكر عن الحالات، فغالبا ما يتأخر التشخيص، وتؤكد على أهمية وعي الأطباء والخطوات الجادة حول البدء في برنامج الكشف المبكر لتشخيص هذه الحالات في عمر مبكر، هذا وتجدر الإشارة إلى أن علاج الأمهات وقت الحمل بالديكساميثاسون يوصي به وذلك لمنع تشوه الأعضاء التناسلية المصاحبة لهذا المرض عند إصابة الإناث به.

مفتاح الكلمات: تضخم الغدة الكظرية الخلقي، نقص أنزيم ٢١ هيدروكسيليز.