

THE INCREASED PREVALENCE OF CONGENITAL ADRENAL HYPERPLASIA IN SAUDI ARABIA: THE ROLE OF CONSANGUINITY AND MULTIPLE SIBLINGS INVOLVEMENT

Nasir A. M. Al-Jurayyan, MD

Professor and Head of Endocrine Division
&

Huda, A. Osman, MRCPCH (UK), DCH (Ireland)

Senior Registrar in Pediatric Endocrinology
Department of Pediatrics

College of Medicine and King Khalid University Hospital
King Saud University, Riyadh, SAUDI ARABIA

ABSTRACT

Background. Congenital adrenal hyperplasia is a group of autosomal recessive disorder resulting in the deficiency of one of the enzyme required to synthesize cortisol.

Design and setting: A retrospective – hospital based study, conducted at King Khalid University Hospital, Riyadh, during the period 1989 – 2014.

Materials and Methods: Medical records of patients diagnosed with congenital adrenal hyperplasia were reviewed retrospectively.

Results during the period under review (1989 – 2014), 95 Saudi patients were diagnosed with CAH; 76 (80%) patient (21- α -hydroxylase deficiency), 15 (15.8%) patients (11- β -hydroxylase deficiency), and 4 (4.2%) patients (3- β -HSD). Consanguinity was found in 56 (58.9%) patients. Thirty-one (55.4%) families had more than one affected child.

Conclusion: High rate of consanguineous mating and multiple siblings involvement in the Saudi population were important factors contributing to the increased prevalence of the disorders.

Keywords: Congenital adrenal hyperplasia, Consanguinity, prevalence, Saudi Arabia

INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting in the deficiency of one of the enzymes required to synthesize cortisol.¹ Ninety to ninety-five percent of cases of CAH are due to a deficiency in the 21-hydroxylase enzyme. A result of this deficiency is increased production of corticotrophin – releasing hormone (ACTH), which leads to adrenal hyperplasia and the production of excess adrenal androgens. Aldosterone deficiency may or may not be involved in CAH, depending on the severity of the 21-hydroxylase deficiency. A significant difference in the pattern have been reported in the different regions of the world.²⁻³

In Saudi Arabia, there are few limited reports indicating the prevalency of the of the disease.⁴⁻⁵

The aim of this study was an attempt to explore the different factors leading to the high prevalence in Saudi Arabia.

MATERIALS AND METHODS

Medical records of all infants and children under the age of 18 years who were born and/or referred to the pediatric Endocrinology service at KKUH, Riyadh during the period from January 1989 to December 2014 with the diagnosis of CAH were reviewed. Data included age, sex, place of origin, family history, and results of all the relevant laboratory investigations were reviewed.

Diagnosis of CAH was suspected on clinical grounds and confirmed in all patients by detailed endocrine investigations. Diagnosis of classical 21 – hydroxylase deficiency was confirmed by high plasma concentration of 17-hydroxyprogesterone, elevated plasma concentrations of 11-deoxycortisol with suppressed plasma renin activity are confirming the diagnosis 11- β -hydroxylase deficiency CAH, while the presence of normal 17-hydroxyprogesterone with increased dehydroepiandrosterone (DHEA) level associated with low concentration of androstenedione and testosterone on clinically suspected subjects are confirming the diagnosis of 3- β -hydroxyprogesterone dehydrogenase deficiency (CAH).

A salt-depleting state was confirmed by the presence of hyponatremia, hyperkalemia, natriuresis and raised serum renin activity with low or normal serum aldosterone concentration.⁵ All the hormones were measured commercially by Bioscientia laboratory, Germany. Chromosomal analysis, abdominal ultrasound, genito-graphy or magnetic resonance imaging (MRI) were done when appropriate.⁶

RESULTS

One hundred and three patients from 62 families were diagnosed to have CAH in the period under review (1989-2014). Eight patients from six families were excluded from the study as they were from different nationalities. Seventy-six (80%) of Saudi patients were due to 21-hydroxylase deficiency, 15 (15.8%) patients have 11- β -hydroxylase deficiency, enzyme, while four 4.2% patients with 3- β -hydroxysteroid dehydrogenase deficiency, Table 1. Consanguinity and multiple siblings involvement is quite common, table 2, which shows the relationship between the enzyme deficiency and family history in 95 patients with CAH. Consanguinity was found in 56 (58.9%). Thirty-nine neonatal and infant deaths occurred within 25 (44.6%) families. Thirty-one (55.4%) families had more than one affected child.

DISCUSSION

Congenital Adrenal hyperplasia (CAH), is the most common inherited adrenal disorder caused by a steroidogenic enzyme deficiency that is characterized by adrenal insufficiency and variable degrees of hyper or hypo androgeny manifestations, depending on the type and severity of the disease. The estimated prevalence worldwide is variable (1 in 10,000) and the annual incidence shows a marked geographical variation from 1 in 409 (Yupik Eskimos) to 1 in 67,000 live births in North America.¹⁻³ No real data reported from Saudi Arabia, however Al Jurayyan et al⁽⁵⁾ estimated the incidence to be 1 in 5,000 live births from cases delivered at King Khalid University Hospital. The most frequent form of CAH is classical CAH due to 21-*alpha*-hydroxylase deficiency which accounts from 90-95% of cases. CAH is caused by a mutation in the CYP21A2 gene located in chromosome 6p21.3 which encodes form an enzyme that controls cortisol and aldosterone production.⁷

Lubni et al⁸ has reported an incidence of 1 in 9,000 live births from neighboring Kuwait. Although we are referring to a highly selective group, the pattern of enzyme deficiency in our series is somewhat different, in that 21-hydroxylase deficiency remains the most common but it accounts for 80%. Ninety percent of these were salt-looser. The pattern of referral might be a contributory factor.

In Saudi Arabia, Al Meshari et al⁹, El Mouzan¹⁰, Al Hazmi et al and Saedi-Wong et al¹² showed a high consanguinity rate in our population. The high parity rate with involvement of multiple siblings within the family with the high rate of consanguinity could be a major contributing factor.

In conclusion, though further studies are needed to see the prevalence, incidence and pattern of the disease. Our data support the contention that a high rate of consanguinity and multiple sibling involvement were important contributing factors.

Table 1 Distribution of 95 Saudi patients with CAH according to enzyme deficiency

Enzyme Deficient	No. of Patients	%
21-hydroxylase	76	80%
11-hydroxylase	15	15.8%
3-β HSD	4	4.2%
Total No. of Patients	95	100%

3-β HSD – 3-β-hydroxysteroid dehydrogenase
CAH – Congenital adrenal hyperplasia

Table 2 The relationship between enzyme deficiency and consanguinity in 95 Saudi patients with CAH

Enzyme Deficient	No. of Patients	No. of Families	Consanguinity	
			1 st degree	2 nd degree
21-hydroxylase	76	47	44	3
11-hydroxylase	15	7	5	2
3-β HSD	4	2	2	-
Total No. of Patients	95	56	51	5

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REFERENCES

1. Speiser PW, White PC Congenital adrenal hyperplasia. N Engl J Med 2003; 349 (8); 776-788.
2. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet 20015; 365:(21) 25-36.
3. Khan AH, Aban M, Razaj Ulhaq N, Jabbar A, Moatter T. Ethnic disparity in 21-hydroxylase gene mutations identified in Pakistani congenital adrenal hyperplasia patients. BMC Endocrine Disorders 2011; 11:5 doi: 10.1186/1472-6823-11-5.

4. Salman H, Abanamy A, Ghassan B, Khalil M. Congenital adrenal hyperplasia. *Ann Saudi Med* 1991; 11: 9-11.
5. Al Jurayyan NAM, Al Herbish AS, Abo-Bakr AM et al. Congenital adrenal hyperplasia in a referral hospital in Saudi Arabia: Epidemiology, pattern and clinical presentation. *Ann Saudi med* 1995; 15 (5): 447-50.
6. Al Jurayyan NAM. Imaging of disorder of sex development. *Ann Saudi Med* 2013; 33(4): 363-7.
7. Mohamed S, El Kholy S, Al Jurayyan N, Al Nemri AM, Abu-Amero KK. A CYP21A2 gene mutation in patients with congenital adrenal hyperplasia. Molecular genetics report from Saudi Arabia. *Saudi Med J* 2015; 36(1): 113-6.
8. Lubani MM, Issa, ARA, Bushnaq R, Al Saleh QA, Dudin KI, Reavy PC, El Khalifa MY. Prevalence of congenital adrenal hyperplasia in Kuwait. *Eur J Pediatr* 1190; 149: 391-392.
9. Al Meshari AA, Hassounah M, Al Gewaiser AA. Maternal mortality in the kingdom of Saudi Arabia. 1410-1412 H. Riyadh, King Saud Press 1992;25;32.
10. El Mouzan MI, Al Salloum AA, Al Herbish AS, Qurachi MM, Al Omar AA. Consanguinity and major genetic disorders in Saudi children: a community-based cross-sectional study. *Ann Saudi Med* 2008;28 (3) 169-173.
11. El Hazmi MA, Al swailem AR, Warsy AS, Al Swailem AM, Sulaimani R, Al Meshari AM. Consanguinity among the Saudi Arabian population. *J Med Genetics* 1995;32(8) 623-626.
12. Saedi-wong S, Al Frayh AR, Wong HYH. Socio-economic epidemiology of consanguineous matings of the Saudi Arabian population. *Journal of Asian and African Studies* 1989; 24: 247-52.