African Journal of Urology
1110-5704

Vol. 14, No. 3, 2008
138-142

Original Article

Congenital Adrenal Hyperplasia: The Challenges of Management in a Developing Country

O. D. Osifo and N. J. Nwashilli

Paediatric Surgery Unit, Department of Surgery, University of Benin Teaching Hospital, Benin City, Nigeria

ABSTRACT

Objective: The management of congenital adrenal hyperplasia (CAH) is challenging, particularly in developing countries. The objective of this study is to report the challenges and outcome of management of this pathology at an institution in Nigeria.

Patients and Methods: All the children that were diagnosed with CAH at the University of Benin Teaching Hospital, Benin City, Nigeria, between January 2002 and December 2007 were included in this retrospective study. The parameters studied were: age, sex, mode of presentation, family history of similar lesions, findings on examinations and investigations, treatment given, challenges and outcome. The available parents/caregivers were interviewed in order to document their socioeconomic status, place of residence, level of education and level of awareness about CAH. The data obtained were analyzed using SPSS and presented as count, frequency and percentage, while continuous data were expressed as mean ± standard deviation.

Results: In total, 27 children aged between 2 and 15 (mean 8 ± 2.4) years were treated. Twenty-four of them were females and 3 males with a male-to-female ratio of 1:8. Delayed presentation, which was influenced by cultural beliefs and lack of awareness, was very common and none of the cases was diagnosed under 2 years of age. Genital manifestation was the reason for seeking medical consultation in 23 (85%) patients, while the 3 males (11%) and one female (4%) presented due to precocious puberty. All the females were mistakenly raised as males despite obvious deformity of the phallus. Establishing an accurate diagnosis was a major challenge due to the lack of facilities and manpower required, and a combination of clinical, radiological and biochemical laboratory investigations plus/minus mini-laparotomy was used. Although surgical and steroid replacement therapy was satisfactory, gender re-assignment was very challenging and required a multidisciplinary approach, counseling and relocation of the affected families.

Conclusion: Management was difficult mainly due to late presentation, and there is an obvious need for a public information campaign in our country in order to increase the awareness of CAH in order to avoid wrong gender assignment in neonates.

Keywords : Congenital adrenal hyperplasia, management, gender

Corresponding Author: Dr. O.D. Osifo, Paediatric Surgery Unit, Department of Surgery, University of Benin Teaching Hospital, Benin City, Nigeria, E-mail: Leadekso@yahoo.com

Article Info: Date received : 14/2/2008 Date accepted (after revision):10/7/2008

INTRODUCTION

Congenital adrenal hyperplasia (CAH), an inherited autosomal recessive gene defect, results in the lack of enzymes needed by the adrenal gland to make cortisol and aldosterone from cholesterol, with a resultant overproduction of androgens leading to female virilization and male precocious puberty[1-3]. Management of this pathology presents a great challenge, as the genital and metabolic manifestations require prompt fluid and electrolyte replacement, and early gender assignment should be done soon after birth[4-7]. In developed countries, the high level of awareness and advancement in technology assure

an early presentation, diagnosis and management. In sub-Saharan Africa, however, the management of CAH is associated with considerable difficulties due to the lack of awareness and basic facilities required to make an early diagnosis. Very often, patients present when they are already in shock from protracted fluid and electrolyte loss, and many babies with 21-hydroxylase deficiency die before presentation. Others present after they have been raised in the wrong gender for several years, and the problem of sex reassignment in a grown-up child remains a special challenge[8].

In many ethnic groups in Africa, despite the obvious abnormality of the phallus in patients with CAH, the majority of affected female children are raised as males. This is influenced by the cultural belief in the subregion that male children are to be preferred to female children. Those with a phallus resembling a penis are circumcised and raised as male children and normally never seek medical attention until puberty, when they develop secondary sexual characteristics, while those whose external genitalia appear female are subjected to female genital mutilation which involves complete excision of the hypertrophied clitoris, and these children will also not present unless there is associated hypertension[8,9]. This scenario makes the diagnosis and management of CAH very difficult in developing countries, particularly in sub-Saharan Africa. There is, therefore, a need to increase public awareness in order to encourage early presentation.

During the past six years, we managed 27 children with CAH. The aim of this study is to report the pattern of presentation, the level of awareness, the challenges of management of this condition and the outcome, so as to encourage early presentation.

PATIENTS AND METHODS

This prospective study was undertaken by three consultant pediatric surgeons and one consultant pediatric urologist at the University of Benin Teaching Hospital, Benin City, Nigeria. The patients were referred from hospitals in the state and neighboring states and admitted via the surgical outpatient clinic and emergency department of the hospital. All children diagnosed with CAH between January 2002 and December 2007 were included in the study. The parameters studied were: their age, sex, mode of presentation, family history of similar lesions, findings on examination and investigations, treatment given, challenges and outcome. Available parents/caregivers were interviewed to determine their socioeconomic status, place of residence, level of education and level of awareness about CAH. Thereafter, the parents and the patients were invited for counseling and the relocation process. Five children who were wrongly diagnosed and referred as CAH were excluded from the study.

The data obtained were analyzed using SPSS and presented as count, frequency and percentage, while continuous data were expressed as mean ± standard deviation.

RESULTS

During the study period, 27 children aged between 2 and 15 (mean 8 ± 2.4) years were seen at our institution. Twenty-four of them were females and 3 males with a male-to-female ratio of 1:8. All the children presented late; none of the cases was diagnosed at birth or at an age of less than two years. All the females were mistakenly raised as males despite obvious deformity of the phallus. Twelve of them grew up in families that already had many female children, while 8 were first-borns. None of the parents and caregivers interviewed had prior knowledge of CAH. The genital manifestation was the reason for seeking medical advice in 23 (85%) patients, while 4 (15%) presented due to precocious puberty (all the males and one female). Clitorimegaly was present in all the females and was the reason for seeking medical attention in 20 patients. The remaining three females mistakenly raised as males presented at 12, 14 and 15 years due to the absence of development

of male secondary characteristics; the patients were also worried about bleeding from the 'urethra' at menarche. Of the 24 females mistakenly raised as males, 22 had already been circumcised as males before presentation (Fig. 1), while the remaining two were referred after they had been sent for circumcision. There was no positive family history of CAH in any of the children. Nineteen (70%) were children of parents with a low socioeconomic background living in rural areas, while the remaining 8 (30%) were children from upper-class families. Thus, the socioeconomic status did not influence the mode of presentation and awareness of the pathology.

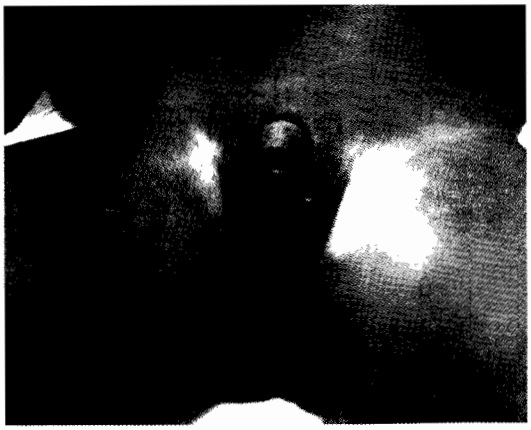

Fig. 1: A three-year-old female patient with congenital adrenal hyperplasia, assigned male gender and circumcised before presentation.

The diagnosis was based on a combination of clinical, biochemical and radiological investigations. Fifteen (56%) patients had 11-beta-hydroxylase deficiency, 11 (41%) 21-hydroxylase deficiency and 1 (4%) 17-hydroxylase deficiency. None of them presented with the clinical manifestations of salt loss, vomiting and shock. Eight children presented with associated headache and hypertension which was controlled with steroid replacement in 5, while 3 required additional antihypertensive medication. The electrolytes and urea of the patients were within the normal range. Giemsa banding karyotyping was not conclusive in 14 patients, and unfortunately there were no facilities for spectral karyotyping, chromatin mass and Y-fluorescence studies. Pelvic ultrasound and CT scan were useful in determining the internal organs in 18 children, while 9 children required mini-laparotomy to determine the internal organs. Their external genitalia were confusing due to the fact that they had been traditionally circumcised which had resulted in scarring. Of the 24 females, the vagina entered the urethra (urogenital sinus) below the external sphincter in 20 children (low type) and above the sphincter in 4 (high type).

Steroid replacement was the mainstay in management of the male patients. The females were more difficult to manage because they had been brought up in the wrong sex; treatment consisted of a combination of steroid replacement, clitoroplasty/ clitorectomy, vaginoplasty and counseling. Clitoroplasty and cut-back vaginoplasty were done in the 20 patients with low urogenital sinus, while clitorectomy and pull-through vaginoplasty were done in the 4 patients with high lesions, as they were already circumcised with resultant scarring. All the patients were successfully managed and no mortality was recorded. Reassigning the sex of the females mistakenly raised as males and counseling of these patients and their parents was particularly difficult. It was, therefore, supported by psychologists, psychiatrists, pastors and nursing counselors. All these patients had to be relocated to a different community because of the embarrassing new sex identity resulting in emotional and social disturbances.

Follow-up of some of these patients for four years revealed satisfactory treatment although no history of pregnancy has been reported after treatment. Adequate counseling and follow-up were helpful and no suicide attempt on account of this was recorded.

DISCUSSION

Androgens are involved in sexual differentiation and maturation and they

are reported to be in excessive amounts in patients with CAH. Various forms of genetic mutations resulting in the development of this pathology have been reported[1,8]. Although 21-hydroxylase deficiency has been reported to be commonest and to present with fluid and salt loss immediately after birth, 11-beta-hydroxylase deficiency was encountered more frequently in this series, and genital manifestation was the reason for presentation in most cases[9,10]. In fact, none of the children seen at our department was younger than 2 years, which may be due to the fact that many children with 21-hydroxylase deficiency die early.

An incidence of 1:10,000 live births for the severe forms of CAH and 10:10,000 live births for the mild forms has been reported[10]; 20 children seen in six years in this study had low urogenital sinuses.

The majority of our patients were females raised as males, with a male-to-female ratio of 1:8 as against a near equal sex distribution reported in the literature[1-10]. This may be due to the fact that many affected patients in developing countries would not seek medical attention, unless there is a disturbing reason. Therefore, female children raised as males who developed secondary female sexual characteristics at puberty were the commonest reason for seeking medical advice at our institution. On the other hand, in our environment, individuals with obviously female external genitalia are subjected to female circumcision involving total clitorectomy, and they will never seek medical attention thereafter; hence the higher female-to-male ratio recorded in this study.

Delayed presentation was quite common with a mean age at presentation of 8 ± 2.4 (range 2 to 15) years, which was due mainly to a lack of awareness. This is at variance with the age at presentation in developed countries[10,11] where neonatal and intrauterine diagnoses are feasible enabling the physicians to start early medical treatment and gender assignment[4-7]. Neither intrauterine nor neonatal diagnoses were possible in this series and the earliest diagnoses were made at the age of 2 years in female children who had already been assigned the wrong gender. They had been circumcised as males and presented due to an unusual shape of the phallus; similar cases have been reported by other authors from sub-Saharan Africa[8,9].

The management of such patients was particularly challenging and had to involve psychiatrists, psychologists and pastors because of the associated emotional disturbances. However, the lesions were sporadic in this series as no positive family history was elicited unlike the familial occurrence reported by other authors[9,11].

The impact of cultural beliefs in Africa that male children are preferable over female children was obvious in this study and contributed significantly to wrong gender assignment and the delay in presentation. Despite the obvious anomaly of the phallus, the majority of the affected girls were raised as males, especially in families with many female children, or following the parents' wish that the first-born should be male to be the head of the family later on. This finding is similar to that of other authors in this subregion[8,9].

The diagnosis in our cases was not easy, due to the delayed presentation and previous circumcision, the lack of facilities and personnel required and the low index of suspicion of the pathology in this subregion. Chromatin mass and Y-fluorescence studies were not feasible, while Giemsa banding karyotyping was not conclusive in many of the patients with many false negative results recorded[11-13]. Moreover, CT scan, pelvic ultrasound scan, laparoscopy and sinography were not always diagnostic, and mini-laparotomy had to be done in many patients to visualize the internal organs directly. Therefore, a combination of clinical, radiological and biochemical laboratory investigations was done in this study.

Surgical management was not as challenging, because the majority of the patients had low urogenital sinuses, and cut-back vaginoplasty was satisfactory in all. Those that had pull-through vaginoplasty required prolonged dilatation with a satisfactory outcome.

No technical difficulties were encountered despite the late presentation and the older age of the patients. Steroid replacement was satisfactory in controlling the symptoms in the majority of patients with only a few who required additional antihypertensive drugs to control the associated hypertension. The effects of steroid replacement on the external genitalia were not obvious in this series, because the patients were treated for a short period before genitoplasty.

Gender reassignment and retraining a grown-up child to accept a new sex identity is very difficult, as also reported by other authors[14-16]. However, counseling supported by psychiatrists, psychologists, pastors and nursing counselors was very helpful and no case of attempted suicide has been reported.

In conclusion, CAH was diagnosed late due to cultural beliefs, lack of awareness and facilities. This resulted in the problem that the majority of patients presented after the wrong gender had been assigned. Making the diagnosis was challenging and required a combination of clinical, radiological and biochemical laboratory investigations, at times combined with mini-laparotomy. Although surgical management was straightforward and steroid replacement therapy was satisfactory in controlling the symptoms, sex reassignment was difficult and required a multidisciplinary approach. The affected children and their families had to be relocated because of the emotional and social effects. A public enlightenment campaign is needed to increase awareness of CAH to ensure early presentation before a wrong gender is assigned.

REFERENCES

1. Kuribayashi I, Nomoto S, Massa G, Oostdijk W, Wit JM, Wolffenbuttel BH, et al. Steroid 11-beta-hydroxylase deficiency caused by compound heterozygosity for a novel mutation, p.G314R, in one CYP11B1 allele and a chimeric CYP11B2/CYP11B1 in the other allele. Horm. Res. 2005;63(6):284-93.

2. Peter M, Dubuis JM, Sippell WG. Disorders of the aldosterone synthase and steroid 11-beta-hydroxylase deficiencies. Horm.Res. 1999;51(5):211-22.

3. Peter M. Congenital adrenal hyperplasia: 11-beta-hydroxylase deficiency. Semin.Reprod.Med. 2002; Aug;20(3):249-54.

4. Thil'en A, Nordenstrom A, Hagenfeldt L, von Dobeln U, Guthenberg C, Larsson A. Benefits of neonatal screening for congenital adrenal hyperplasia (21 -hydroxylase deficiency) in Sweden. Pediatrics. 1998; Apr;101(4):E11.

5. Van der Kamp HJ, Noordam K, Elvers B, Van Baarle M, Otten BJ, Verkerk PH. Newborn screening for congenital adrenal hyperplasia in the Netherlands. Pediatrics. 2001; Dec;108(6):1320-4.

6. Berenbaum SA, Bailey JM. Effects on gender identity of prenatal androgens and genital appearance: Evidence from girls with congenital adrenal hyperplasia. J.Clin. Endocrinol.Metab. 2003; Mar;88(3):1102-6.

7. Forest MG. Recent advances in the diagnosis and management of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Hum.Reprod.Update. 2004; Nov-Dec;10(6):469-85.

8. Andrew M, Barr M, Davies E, Wallace AM, Connell JM, Ahmed SF. Congenital adrenal hyperplasia in a Nigerian child with a novel compound heterozygote mutation in CYP11B1. Clin.Endocrinol.(Oxf). 2007; Apr;66(4):602-3.

9. Agboola Abu CF, Aligwekwe PK, Olowu AO, Kuku SF. Congenital adrenal hyperplasia due to 11-hydroxylase enzyme deficiency in three siblings. A brief report. West Afr.J.Med. 1999; Apr-Jun;18(2):80-6.

10. Stanic M, Nesovic M. Kongenitalna adrenalna hiperplazija. [Congenital adrenal hyperplasia]. Med. Pregl. 1999; Nov-Dec;52(11-12):447-54.

11. Khan AH, Nasir MI, Moatter T. Characterization of pathogenic mutations in 21-hydroxylase gene of Pakistani patients with congenital adrenal hyperplasia and their family members --a preliminary report. J.Pak. Med.Assoc. 2002; Jul;52(7):287-91.

12. New MI. An update of congenital adrenal hyperplasia. Ann.N.Y.Acad.Sci. 2004; Dec;1038:14-43.

13. Shinohara O, Ishiguro H, Shinagawa T, Kubota C. False negatives at neonatal screening for congenital adrenal hyperplasia in two siblings with 21-hydroxylase deficiency. Endocr.J. 1998; Jun;45(3):427-30.

14. Ahmed SF, Morrison S, Hughes IA. Intersex and gender assignment; The third way? Arch.Dis.Child. 2004; Sep;89(9):847-50.

15. Bostwick JM, Martin KA. A man's brain in an ambiguous body: A case of mistaken gender identity. Am.J.Psychiatry. 2007; Oct;164(10):1499-505.

16. Berenbaum SA, Sandberg DE. Sex determination, differentiation and identity. N.Engl.J.Med. 2004; May 20;350(21):2204,6; author reply 2204-6.