PREVENTION OF AMBIGUOUS GENITALIA IN CONGENITAL ADRENAL HYPERPLASIA

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Ambiguous genitalia is not an uncommon problem in Saudi Arabia.[1-3] Its most common cause is congenital adrenal hyperplasia (CAH) caused by any one of the three inborn errors of steroidogenesis; 21-hydroxylase (the most common), 11ß-hydroxylase, and 3ß-hydroxysteroid dehydrogenase deficiency in genetic female babies.[4] Advances in technology have made possible the prenatal diagnosis of CAH and subsequently, prenatal treatment with dexamethasone given to mothers throughout pregnancy and begun as early as possible has led to the prevention of virilization in at least three-fourths of affected infants.[5-23] In this article, prenatal dexamethasone therapy was given to a Saudi mother of children with CAH due to 21-hydroxylase deficiency. This has prevented ambiguity in the second daughter. This is believed to be the first published local experience of this mode of prevention therapy.

Case Report

A two-month-old male of a first-degree consanguineous couple presented with a history of recurrent vomiting and diarrhea and failure to thrive. He was found to have dehydration, hyponatremia, and hyperkalemia, and subsequently was diagnosed to have congenital adrenal hyperplasia due to 21-hydroxylase deficiency. He was therefore treated with hydrocortisone and 9-α-fluorocortisone. At the age of two years he was referred to the pediatric endocrine clinic at King Khalid University Hospital (KKUH), as per the wish of the family. Follow-up care was done and the parents were counseled.

The mother then gave birth to her second infant, who has ambiguous genitalia (Figure 1) and was immediately referred to KKUH for further management. She soon presented with hyponatremia and hyperkalemia. Appropriate replacement therapy was begun as explained above, with the addition of sodium chloride. Her chromosome analysis showed female karyotype (46,XX). Pelvic ultrasonography was not conclusive, but the genitogram showed female urethra. However, it had failed to visualize the uterus and the fallopian tubes. The 17-hydroxyprogesterone level was greater than 250 ng/mL (N = 0.21-1.4), androstendione level was 7.21 ng/mL (N=0.6-3.4), 11-deoxycorticosterone was 46.3 ng/mL (N=2.0-15), and renin >70 mg/mL/hr (N=0.68-1.38). Hormonal assay was performed in Bioscentia Laboratories (Germany). She then had clitoroplasty (clitoral recession) and vaginoplasty at one year of age, followed by vaginal dilatation at two and at three-and-one-half years of age.

Despite some hesitation, after genetic counseling, the parents decided to have a third child. They were also informed at this stage about the preventive value of dexamethasone given to the mother during pregnancy and the very possible side effects which have been reported. At five weeks of gestation, the mother was placed on dexamethasone tablets 0.5 mg twice a day. At 16 weeks of gestation, she was subjected to amniocentesis, where the amniotic fluid chromosomal analysis showed 46,XY male karyotype. Dexamethasone was therefore discontinued. She had already manifested a few side effects, e.g., excessive weight gain and acne. At term, she gave birth to a normal-appearing male with normal physical examination. At the age of 10 days, the baby unfortunately presented with fever and lethargy and was found to be

FIGURE 1. The genitalia of the second child (female) at birth.

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dehydrated, hyponatremic and hyperkalemic. He was therefore started on hydrocortisone, 9-α-fluorocortisone and salt and referred to KKUH. His hormonal values after holding his medications for one day showed cortisol 3.9 mg/dL (N=8-28), 17-hydroxyprogesterone 169 ng/mL, dehydroepiandrosterone (DHEA) 23.4 ng/mL (N=3-12), androstendione 1.1 ng/mL and renin 40 ng/mL/hr. The diagnosis of 21-hydroxylase deficiency was therefore confirmed and he was maintained on therapy.

Shortly afterwards, the mother became pregnant and oral dexamethasone 0.5 mg twice a day was commenced at seven weeks of gestation. Amniocentesis was performed at 16 weeks of gestation. Amniotic fluid was analyzed for chromosomes, HLA typing and 17-hydroxyprogesterone level. Chromosomes were 46,XX karyotype, HLA typing was A_2, AX, B_5 (51), BX, CWX, CWX. Family typing was also done (Figure 2). 17-hydroxyprogesterone was 0.2 ng/mL, which was normal. Dexamethasone, however, was not discontinued prior to amniocentesis. With the findings of 46,XX female karyotype, dexamethasone was continued. The patient again experienced inappropriate weight gain, acne and mild hypertension, but was able to continue therapy. The dose was reduced to 0.5 mg once a day during the last six weeks of pregnancy. At birth, the baby was noted to have mild posterior labial fusion but there was no clitoromegaly and the urethral opening and the vagina looked normal (Figure 3). At the age of eight days, she manifested clinical and biochemical features of salt-wasting and therefore was started on fluids, hydrocortisone, 9-α-fluorocortisone and sodium supplements. Her 17-hydroxyprogesterone was 300 ng/mL. The pediatric surgeon was happy with the appearance of the genitalia and saw no indication for any surgical intervention.

FIGURE 2. *HLA typing of the family presented.*

FATHER:

A2,A19(33)/B12(44),B5(51),BW4/CWX*,CWX/DR2(16), DRX,DR51/DQ6

MOTHER:

A2,AX/B5(51),B35,BW4,BW6/CW4,CWX/DR3(17),DR2(16), DR52/DQ6

SIBLINGS:

a) First child (boy)

A2,AX/B5(51),BX,BW4/CWX,CWX/DR2(16),DRX,DR51/DQ6

b) Second child (girl)

A2,AX/B5(51),BX,BW4/CWX,CWX/DR2(16),DRX,DR51/DQ6

c) Third child (boy)

A2,AX/B5(51),BX,BW4/CWX,CWX/DR2(16),DRX,DR51/DQ6

d) Fourth child (girl)

A2,AX/B5(51),BX/CWX,CWX

*X means that the patient is either homozygous or has an HLA type for which antiserum is not available.

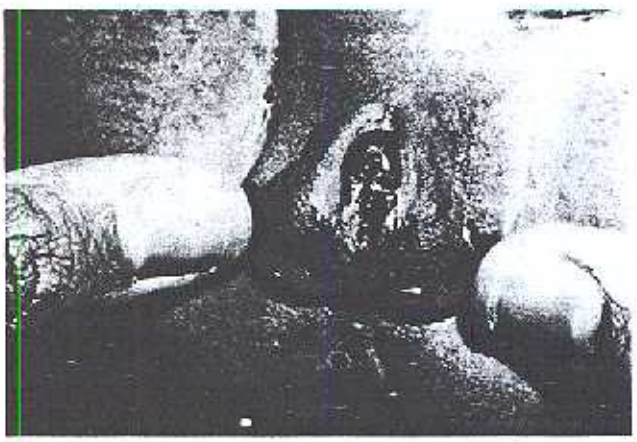

FIGURE 3. The genitalia of the fourth child. Result of antenatal dexamethasone therapy.

Discussion

Ambiguous genitalia is a medical, psychological, and social emergency.[1,3] Appropriate management with proper counseling may lead to a good outcome. On the contrary, ignorance or mismanagement can lead to devastating results, in particular, incorrect sex assignment.[25,26] It is therefore extremely important to find a preventive method to this problem, even if the cause of the disorder has no permanent cure. Upon exposure to androgens, virilization of the genitalia occurs very early during the intrauterine life, as the genitalia, the labioscrotal fold fusion in particular, is sensitive and responsive to androgen stimulation.[27] This happens in the first trimester. Beyond this period, any further ambiguity will be as clitoral enlargement only, as the clitoris, unlike the labioscrotal folds, is sensitive to androgens, both in the first trimester and afterwards.[27] Dexamethasone, given antenatally to mothers who have children with congenital adrenal hyperplasia to prevent ambiguity of the genitalia, has been in use for a few years.[5-23] The initial reports were rather discouraging, as the expected outcome of normal or near normal genitalia did not happen.[24] This was, however, most likely related to the fact that it was not used very early in pregnancy and the first trimester period was missed. Using dexamethasone as early as possible, however, resulted in reducing the degree of virilization in at least two-thirds of reported cases.[18,21,23,28] The combination of a dedicated family and medical team is always needed for such a program. The medical team should include an obstetrician, radiologist, geneticist, biochemist, immunologist, nurses, pediatric surgeon, and a pediatrician or pediatric endocrinologist. The latter usually coordinates the medical care and work. Fortunately, this was feasible in our setup. A few obstacles, such as not having all the related services under one roof, have luckily been

overcome. The remote residence of the family was also successfully overcome by the presence of the dedicated family, who has direct access to the medical team. This led to initiation of therapy very early during gestation, a problem which is very much anticipated in our community. It also made it possible to adjust the dose. We feel that such a program should be practiced more in this country, where congenital adrenal hyperplasia is common.[1,3] This will minimize the confusion which usually accompanies these cases when only faced at birth.[25,26] It will also ease the amount of surgical correction indicated in these cases.[29] Furthermore, the long-term function of the genitalia may be better. Side effects of dexamethasone to the mothers are almost unavoidable.[26] This was the case in the patient who presented. She manifested excessive weight gain, increased hair growth, hypertension and soft tissue edema. The dose was reduced slightly as per the recommendation of the literature.[28] Side effects are, however, the price paid for the good outcome of these babies.

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