Gender identity in congenital adrenal hyperplasia secondary to 11-hydroxylase deficiency

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The psychoendocrinology of the development of gender identity in patients with congenital adrenal hyperplasia (CAH) is poorly understood. Prenatal androgen exposure, postnatal hormonal influence, degree of external genitalia virilization, genital appearance, social rearing and other biological factors, are all thought to have an effect on gender identity development.[1-6] Late diagnosis and referral, which are common problems in our country, might have an adverse effect on normal gender identity development in female patients with CAH.[7] We describe two genetically female sisters with CAH secondary to 11-hydroxylase deficiency who were raised as boys and referred at the age of puberty to our clinic. We believe that the gender identity development in these two patients, who had the same medical and social background, was related to the extent of external genitalia virilization.

Cases

The older patient was 20 years old. She was a product of a full-term spontaneous vaginal delivery at home. She was found to have severe virilized external genitalia: a phallic-like structure with hypospadias and incompletely fused labioscrotal folds. She was raised and named as a boy and no medical advice was sought at that time. Her parents reported that she had behaved as a female since early childhood. She was interested in playing with girls and in girl's games, although she studied at male schools. She spent most of her time with her girlfriends and felt most comfortable when she dressed as a female. She was referred to our pediatric endocrinology clinic at the age of 16 years when she started to have irregular menstruation. Physical examination showed a short male-looking adolescent with acne and Tanner stage IV breast development. Her height was 133 centimeters. Her blood pressure was 140/88. Genital examination showed a phallus 7 centimeters in stretched length, a single perineal orifice and incompletely fused labioscrotal folds. No gonads were palpable. Laboratory evaluation revealed a normal female karyotype and normal electrolytes. An adrenocorticotropic hormone (ACTH) stimulation test showed a baseline cortisol (F) level of 28 nmol/L, ACTH of 201 ng/mL (normal, 0-46), 11-deoxycorticosterone (11-DOC) of 20 nmol/L (normal, 0.49-3.3), 17-hydroxyprogesterone (17-OHP) of 17 nmol/L and testosterone (T) of 7 nmol/L. Sixty minutes after the ACTH stimulation test, the F level was 30 nmol/L, the 11-DOC level was 141 nmol/L (normal, 2.2-6.8) and the 17-OHP level was 22 nmol/L. Radiological evaluation showed a normal uterus and fallopian tubes on ultrasound and a closed epiphyses on a bone age X-ray. Examination under anaesthesia combined with cystoscopy showed that her vaginal communication was just below the bladder neck and high in the urogenital sinus. Based on her biochemical and radiological evaluation, she was diagnosed as

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having 11-hydroxylase deficiency and was started on hydrocortisone 10 mg twice a day. She was evaluated by the pediatric psychiatrist who clearly confirmed her female gender identity and her strong wish to be converted to a female. Feminizing genitoplasty (clitoral reccesion) was performed at the age of 16 years and she was given a female name. She admitted her strong desire to get married and to be a mother.

The younger patient was 16 years old. He was born at home and raised and named as a boy based on the appearance of the external genitalia. His parents reported that he behaved as a male and was proud of that. He was interested in playing with boys and in boy's sports. He was dressed as a boy and had a short haircut. He was referred to our clinic at the age of 13 years. Physical examination showed a short stature, a masculine appearance, acne and Tanner stage IV pubic hair and stage II breast development. His height was in the fifth centile. His blood pressure was 130/80 mm Hg. Genital examination showed a phallus 7 centimeters in stretched length, a normal meatal opening at the tip of the glans penis with no hypospadias, and completely fused labioscrotal folds but the gonads were palpable. Laboratory evaluation revealed a normal female karyotype and normal electrolytes. An ACTH stimulation test showed a baseline F level of 42 nmol/L, an ACTH of 231 ng/mL, 11-DOC of 40 nmol/L, 17-OHP of 18 nmol/L and a T level of 7 nmol/L. Sixty minutes after ACTH stimulation, the F level was 45 nmol/L, 11-DOC was 114 nmol/L and 17-OHP was 20 nmol/L. Radiological evaluation showed a normal uterus and fallopian tubes on ultrasound, normal male urethra on the genitogram and a bone age of 16 years. He was diagnosed as having 11-hydroxylase deficiency and started on hydrocortisone 10 mg twice a day. His final height was 139 centimeters. He was interviewed by the pediatric psychiatrist who clearly confirmed his male gender identity and his strong wish to continue to be raised as a boy. We had several separate meetings with him and his parents and informed them that he would be an infertile man if he decided to continue to be raised as a man and there was a possibility that he would be a fertile women if he converted to his genetic sex. The patient, however, refused to change to his female genetic sex and admitted his strong wish to be a man forever. After more that one year of counseling and intensive psychiatric interview, he and his parents decided on a hysterectomy "to avoid menarche which might affect him psychologically" as his mother said. Hysterectomy, oophorectomy and a bilateral testicular prosthesis implantation were performed. Both patients were satisfied by the way they were managed and raised and there were no postoperative psychological complications.

Discussion

Berenbaum and Bailey studied the gender identity of 43 girls with CAH and found that 88% had a gender identity that overlapped with normal control girls. They suggested that prenatal androgen excess produces a small increase in the risk of atypical gender identify that does not correlate with the degree of genital virilization or the age at which genital reconstructive surgery was done.[8] In another study of gender identity in young females with CAH, none of 17 subjects had a conflict with her gender identity or was unhappy being a female.[9] Zucker et al reported that adult women with CAH were not gender dysphoric but differ from unaffected sisters in degree of gender identity.[10] Meyer-Bahlburg et al reported a gender female to male change in four 46, XX individuals with CAH who had a delay in medical and feminizing surgical therapy.[7] In this report, we described two genetically female sisters who had the same disease, 11-hydroxylase deficiency caused probably by the same mutation, who were exposed prenatally and postnatally to the same level and duration of androgens we believe and had the same social background. However, they had an opposite gender identity. The only difference in these two sisters was the degree of genital virilization. The older patient who decided to be converted to a female had hypospadias and incompletely fused labioscrotal folds. However, the younger patient with completely virilized external genitalia had a male gender identity. We suggest that prenatal androgens in affected females with CAH do not only play a role in the sex-types activities and interests as published,[11,12] but it may affect the gender identity completely towards the male side. We also conclude that the extent of external genitalia virilization, particularly the degree of hypospadias and not the duration or the level of prenatal or postnatal androgens exposure, is the main gender identity determinant in patients with congenital adrenal hyperplasia. This conclusion cannot be applied to genetically male patients with undervirilized external genitalia. Several case reports and small-scale studies[13-16] have shown that the majority of undervirilized genetically male patients such as those with cloacal extrophy, micropenis, absent penis, malformed penis and other intersex conditions who were reared as females will eventually declare themselves as males.

References

1. Money J. Amative orientation: the hormonal hypothesis examined. J Pediatr Endocrinol Metabol 2002; 15: 951-957
2. Ammini AC, Gupta R, Kapoor A, et al. Etiology, clinical profile, gender identity and long-term follow up of patients with ambiguous genitalia in India. J Pediatr Endocrinol Metabol 2002;15:423-430
3. Woelfle J, Hoepffner W, Sippell WG, et al. Complete virilization in congenital adrenal hyperplasia: clinical course, medical management and disease-related complications. Clin Endocrinol 2002; 56: 231-238
4. Kalu K, Slowikowska-Hilczer J. Sexual differentiation of the human brain. Przegl Lek 2000;57:41-44
5. Berenbaum SA. Effects of early androgens on sex-typed activities and interests in adolescents with congenital adrenal hyperplasia. Horm Behav 1999; 35:102-110
6. Slijper FM, Drop SL, Molenaar JC, et al. Long-term psychological evaluation of intersex children. Arch Sex Behav 1998; 27: 125-144
7. Meyer-Bahlburg HF, Gruen RS, New MI, et al. Gender change from female to male in classical congenital adrenal hyperplasia. Horm Behav 1996; 30: 319-332.
8. Berenbaum SA, Bailey JM. Effects of gender identity of prenetal androgens and genital appearance: evidence from girls with congenital adrenal hyperplasia. J Clin Endocrinol Metabol 2003; 88: 1102-1106
9. Ehrhardt AA, Baker SW. Fetal androgens, central nervous system differentiation and behavior sex differences. In: Friedman RC, Richart RM, Vande Wiele RL, eds Sex differences in behavior. New York: Wiley 1974; 33-51
10. Zucker KJ, Bradley SJ, Oliver G, et al. Psychosexual development of women with congenital adrenal hyperplasia. Horm Behav 1996; 30: 300-318
11. Berenbaum SA. Effects of early androgens on sex-typed activities and interests in adolescents with congenital adrenal hyperplasia. Horm Behav 1999; 35: 102-110
12. Hines M, Kaufman FR. Androgen and the development of human sex-typical behavior: rough-and-tumble play and sex of preferred playmates in children with congenital adrenal hyperplasia (CAH). Chid Dev 1994; 65: 1042-1053
13. Bin-Abbas B, Conte FA, Grumbach MM, et al. Congenital hypogonadotropic hypogonadism and micropenis: effect of testosterone treatment on adult penile size. Why sex reversal is not indicated. J Pediatr 1999; 134: 579-583
14. Diamond M, Sigmundson HK. Sex reassignment at birth. Long term review and clinical implication. Arch Pediatr Adolesc Med 1997; 151: 298-304
15. Diamond M, Sigmundson HK. Management of intersexuality Arch Pediatr Adolesc Med 1997; 151:1046-1050
16. Imperato-McGinley J, Peterson RE, Gautier T, et al. Androgens and the evolution of male-gender identity among male pseudohermaphrodites with 5Alpha-reductase deficiency. N Engl J Med 1979; 300: 1233-1237