Case Report

The Dilemma of Sex of Rearing: A Case of a 45,X/46,XY Neonate with Hydrocolpos

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A B S T R A C T

Background: A rare disorder of sex development is 45,X/46,XY mosaicism, which is phenotypically very heterogenous, ranging from normal male (or female) to that of genital ambiguity of varying degrees.
Case: We report a case of a neonate with 45,X/46,XY mosaicism and hydrocolpos, and we point out the dilemma and the difficulty in gender assignment.
Summary and Conclusion: Gender assignment of cases with frank genital ambiguity is often difficult to be determined, because several factors have to be taken into consideration, such as genital appearance, anticipated urological and sexual function, capacity for future fertility, gonadal malignancy risk, and psychosocial factors. A multidisciplinary approach is definitely needed in the management of such cases.
Key Words: Hydrocolpos, Ambiguous genitalia, 45,X/46,XY mosaicism

Introduction

Disorders of sex development (DSD) are congenital conditions in which the development of the chromosomal, gonadal, or anatomical sex is atypical. The estimated incidence rate of newborns who present with ambiguous genitalia at birth is 1 in 4500-5500 births.[1] Among the broad variety of DSDs, 45, X/46, XY mosaicism is rare, with an estimated incidence of 1.5 per 10,000 newborns. It is considered to be a very heterogeneous condition and the management of these cases is difficult and challenging, because the gender assignment is often difficult to be determined. We report a case of a newborn with ambiguous genitalia at birth and 45, X/46, XY mosaicism.

Case

A 3-day-old newborn was referred to the Neonatology Unit of our Department of Pediatrics for further investigations because of ambiguous genitalia. The baby was born at term by uncomplicated vaginal delivery weighting 3070 g. Prenatal ultrasound, at 22 weeks of gestation, showed a hypertrophic clitoris. There was no history of prenatal androgen exposure and there were no other family members with atypical genital development.

On examination, the infant had a 2.5-cm long clitophallus, labioscrotal fusion without hyperpigmentation, a perineal orifice with spontaneous urination, and unpalpable gonads (Fig. 1). There were no other dysmorphic features. Blood glucose and serum electrolyte levels were repeatedly normal. On postnatal day 4, basal serum 17-hydroxyprogesterone levels were 3.82 ng/mL (normal values, 0.82-4.2 ng/mL), dehydroepiandrosterone sulfate 56.5 μg/dL (normal, 73-367 μg/dL), androstendione 5.18 ng/mL (normal, 0.05-0.35 ng/mL), total testosterone 135 ng/dL (male normal, 75-400 ng/dL), anti-Müllerian hormone (AMH) 138 pmol/L (normal male value, 100-3330 pmol/L), luteinizing hormone less than 0.1 mUI/mL, follicle-stimulating hormone 0.135 mUI/mL, adrenocorticotropic hormone 20.13 pg/ml (normal, 7-63 pg/mL), cortisol 4.63 μg/dL (normal, 2.24-18 μg/dL), and dihydrotestosterone 0.51 ng/dL (male normal, 2-10 ng/dL). Pelvic ultrasonography revealed intra-abdominal left and right gonads with the echostructure of testicles and the presence of a vagina and uterus (Fig. 2). To clarify the relation of the lower urinary system to the Müllerian structures, a voiding cystourethrography was performed. After catheterization of the perineal meatus, voiding cystourethrography failed to image the bladder but depicted a cavity (Fig. 3A), which was confirmed by a repeat ultrasound examination to be a hydrocolpos (Fig. 3B). Cytogenetic analysis of peripheral blood lymphocytes showed a 45,X(47)/46,XY(16) mosaicism with a percentage of 46,XY chromosomal cell line of 25.3% (on the basis of 16/63 metaphases studied). Sex-determining region Y gene was present. Because 45,X/46,XY mosaicism is associated with Turner syndrome due to the 45,X cell line,[2] cardiac and renal evaluation was performed. No cardiac or renal anomaly was identified.

The newborn was managed by a multidisciplinary team comprising neonatologists, pediatric endocrinologists, radiologists, urologists, gynecologists, psychologists, and

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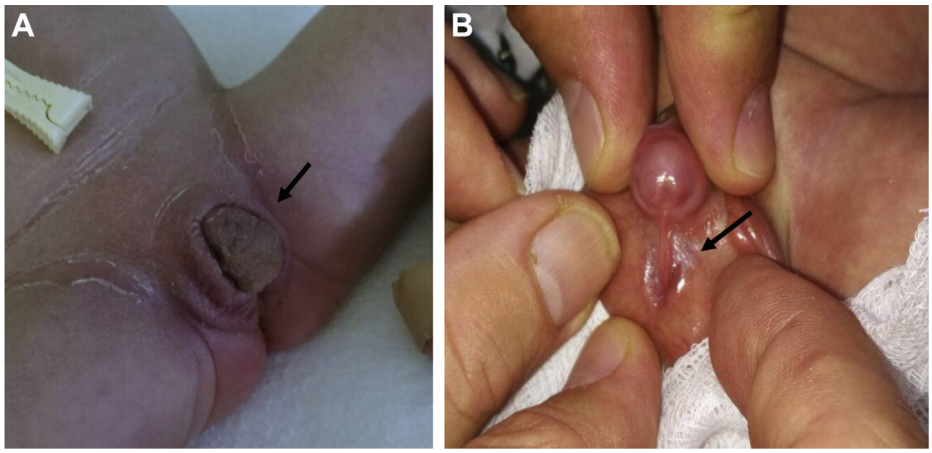

Fig. 1. Patient's ambiguous genitalia: (A) labioscrotal fusion and clitophallus; and (B) perineal orifice.

geneticists, and each of the specialties contributed in the decision-making. The pediatric endocrinologists played a major role in the orchestration of the discussions and raised the 2 main issues, namely future sexual function and future fertility but also the question of the masculinization of the brain due to the antenatal effect of the circulating testosterone. It was clarified to parents that the decision about the sex of rearing should take into consideration the pros and cons of each sex in this individual case. It was therefore explained that in the case of male sex assignment, the antenatal and perinatal action of testosterone might contribute to the male sex identity and orientation and the presence of the testicles might have a role in the secretion of testosterone during puberty and early adolescence contributing to normal sexual function. The testicles could be retained for a certain period of time, however, dysgenetic testicles bear a high risk of gonadoblastoma and therefore they should sooner or later be removed. In this scenario, future fertility could be ascertained through sperm donation and initiation and maintenance of puberty and future sexual function would necessitate the long-term administration of testosterone. In case of female sex assignment, because of the presence of a uterus, cervix, and vagina there is the possibility of fertility through egg donation. However, in this case, estrogens and later progesterone should be administered for the initiation of puberty and development of female secondary sexual characteristics and should be continued until the age of normal menopause. The geneticists explained the role of the 2 cell lines, namely 45,X, and 46,XY in the karyotype. The pediatric radiologists confirmed that the pelvic ultrasonography revealed a uterus and a vagina of normal size for the age of the patient. The pediatric urologist was involved in the discussion for the surgical approach of the reconstruction of the perineal hypospadias, whereas the pediatric gynecologist expressed the opinion that this patient could function as a female in adulthood. The psychologists/psychiatrists accompanied the parents through all of these discussions and helped them to get answers to their fears and ambivalent feelings. They emphasized to the parents that their child has the potential to become a well adjusted, functional member of the society regardless of the final decision for gender selection. The parents were repeatedly involved in the discussion concerning sex of rearing and they finally chose the male sex assignment.

Our baby was managed conservatively and the uterus was left in place. Upon follow-up, 1 of the 2 gonads spontaneously moved to the inguinal canal at the end of the first month of life and toward the scrotum later on, and the hydrocolpos was also spontaneously resolved. Gonadal biopsy along with orchidopexy has been scheduled, and the urologists aimed to repair the perineal hypospadias. The infant's growth will also be carefully followed because 45,X/46,XY mosaicism has been associated with short stature that appears to respond well to growth hormone treatment.[3]

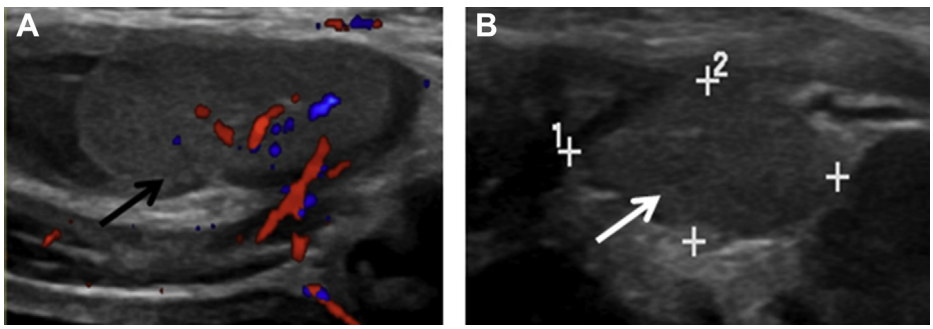

Fig. 2. Ultrasound images of the right inguinal canal shows (A) an incompletely descended testis with normal shape, echotexture, and blood flow (black arrow), whereas the left testis (B) is shown intra-abdominally (white arrow).

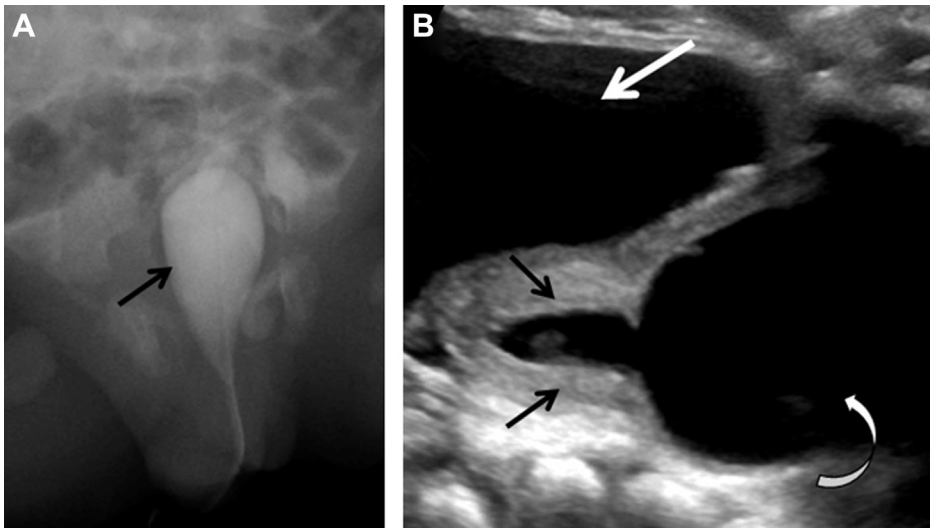

Fig. 3. (A) A voiding cystourethrography failed to depict the bladder, because of the difficulty to find the external urethral orifice. A distended vagina (hydrocolpos) is shown (arrow). (B) Ultrasonography of the pelvis showing hydrocolpos (curved arrow) behind the full bladder (white arrow). The body of the uterus is shown with a small amount of fluid inside (black arrows).

Summary and Conclusion

The first-line testing in a neonate with ambiguous genitalia includes measurement of serum electrolytes, 17-hydroxyprogesterone, androgens, AMH (to assess the existence of testicular tissue), and gonadotropin levels, as well as karyotype analysis (or fluorescence in situ hybridization analysis) to identify sex chromosomes. Among the broad variety of DSD, 45,X/46,XY mosaicism is rare, with an estimated incidence of 1 per 10,000 newborns.[1,4] It is mainly associated with mixed gonadal dysgenesis, but also with bilateral streak gonads or, very rarely, with ovotesticular DSD. The phenotype of the newborns bearing this mosaicism is very heterogeneous ranging from phenotypically normal male (or female) to that of genital ambiguity of varying degrees.[5] Among all cases of 45,X/46,XY mosaicism, those with frank genital ambiguity are the most challenging ones to manage because gender assignment is often difficult to be determined. Several factors have to be taken into consideration regarding sex of rearing including genital appearance, anticipated urological and sexual function, probable adult gender identity/gender dysphoria, capacity for future fertility, gonadal malignancy risk (estimated at 15%-30%)[6,7] and psychosocial factors (familial, social, or cultural).[1,3] The degree of virilization of the external genitalia and the presence of gonads with testicular features in the labioscrotal folds along with a male hormonal profile favors the decision toward male sex assignment. However, in this particular case, the presence of the hydrocolpos, points also to the lack of either production or function of the AMH during sexual differentiation. An external masculinization score (EMS) has been suggested by Ahmed et al[8] with 12 as the maximum score for normal male infants; calculation is on the basis of scrotal fusion, penile length, position of urethral meatus, and location of gonads. Our patient's EMS was 4.5. According to Cools et al,[6] infants with an EMS higher than 7 are those who have the best conditions for choosing male sex of rearing. However, in published series of 45,X/46,XY mosaicism with ambiguous genitalia, an overlapping in EMS between those who have been raised as male and female exists.[3,8] It has been shown that EMS does not always reflect the true masculinization of the gonad; for example, testicular tissue was found in patients raised as girls because of a low EMS.[3] It was also suggested that different distributions of 45,X and 46,XY chromosomal cell lines among tissues reflect the wide variety of the phenotype. As expected, the proportions of 45,X and 46,XY cell lines in the gonads rather than those in blood lymphocytes best correlate with the degree of virilization.[5] Moreover, androgen levels have been implicated in gender-related behavior through organizational effects on the developing brain.[1]

In our case, on the basis of the karyotype, the presence of testicles, which seem to have potential for testosterone secretion, and the willing of the parents, the male sex of rearing was chosen. Nevertheless, the future fertility still remains an open question. Martinerie et al[9] conducted a long-term observational study of 45,X/46,XY patients born with ambiguous genitalia and raised as boys, and according to them most of these patients are infertile. Moreover, the risk of neoplasia of a dysgenetic testicle should also be taken into consideration, because gonadoblastoma is found in high prevalence in patients with 45,X/46,XY mosaicism and dysgenetic gonads; the risk being highest for intra-abdominal gonads.[7,10] A regular follow-up with the future necessity of removal of the intra-abdominal testicle if this is dysgenetic has been discussed. Meanwhile, bringing the testis down into the scrotum might potentially improve fertility and allow for better tumor surveillance using ultrasound.

Management of infants with DSDs should be individualized and focused on the best possible quality of life.[1] A multidisciplinary approach is definitely needed.[11] The trend in recent years is to avoid, if possible, irreversible surgical

procedures during infancy, thus leaving options open for the future until the child is able to consent.[1]

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