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Case Series

46, XX Male, 46, XY Female and 46, XX- 46XY Female Variants: Rare Stories we Must Consider in the Assessment of the Disorder of Sex Development

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Abstract

Disorders of sex development (DSD) are congenital conditions, which carried a typical or abnormal development of chromosomal, gonadal or the anatomical sex. The definitive diagnosis of DSD relies on clinical examinations, hormonal studies, gonadal histology, chromosome (karyotype) analysis and genetic testing. 46, XX testicular disorder of sex development is a rare clinical condition with a reported incidence of 1:20.000 in newborn males. People with this disorder have male external genitalia. Gonadal dysgenesis may occur in individuals with an apparently normal male who carried 46, XY chromosomal complements, and the phenotype may be indistinguishable from 46, XX gonadal dysgenesis. These individuals have a vagina, uterus, and fallopian tubes. Germ cells in the gonads are lost before birth. The phenotypic spectrum is so variable that some children are raised unequivocally as females, while others, even with mutations in the same gene, may be assigned to the male sex. Sex chromosome mosaicisms like 45, X/46, XY or 45, X/47, XYY have been documented as major causes of ambiguous genitalia. As individuals with this genetic image possess both ovarian tissue and testicular tissue, depending on the individual, gonads (ovaries or testes) may function fully, partly, or not at all. We highlighted the clinical, chromosomal, and hormonal features of three cases with such rare stories of DSD who were admitted and managed in our clinic. The important for submitting such findings will assist our team: pediatric surgeons, gynecologists, pediatricians and, endocrinologist to develop future management strategies when they are enrolled or confronted with such cases.

Keywords: 46, XX Male; 46, XY Female; 46, XX- 46XY Female

Introduction

Disorders of sex development (DSD) are congenital conditions, which carried a typical or abnormal development of chromosomal, gonadal, or the anatomical sex. They occur in approximately 1 in 4 - 5 thousand live birth [1]. The definitive diagnosis of DSD relies on clinical examinations, hormonal studies, gonadal histology, chro-

mosome (karyotype) analysis, and genetic testing [2]. Currently, a specific molecular diagnosis is only made in approximately 50% of patients with DSD, however, reducing costs of next-generation sequencing; exome and complete genome sequencing offer much richer possibilities for understanding the complexity of this disorder in the future [3]. 46, XX testicular disorder of sex development is a rare clinical condition with a reported incidence of 1:20.000 in newborn males [2]. De la Chapelle., *et al*. first described it in 1964 [4]. It is a condition in which individuals with two X chromosomes in each cell, the pattern normally found in females, have a male appearance. People with this disorder have male external genitalia. It is a rare genetic syndrome, characterized by a complete or partial mismatch between genetic sex and phenotypic sex, which results in infertility because of the absence of the azoospermia factor region in the long arm of the Y chromosome [5]. Gonadal dysgenesis may occur in individuals with an apparently normal male who carried 46, XY chromosomal complements, and the phenotype may be indistinguishable from 46, XX gonadal dysgenesis with normal stature. Actually, this is entirely predictable because the loss of testicular tissue before 7 - 8 weeks of embryogenesis was studied half a century ago by Jost to produce such a phenotype in rabbits. Sex chromosome mosaicisms like 45, X/46, XY or 45, X/47, XYY have been documented as major causes of ambiguous genitalia [6]. For example, the clinical phenotype of the patients with 45, X/46, XY mosaicism is broad, ranging from women, with or without Turner syndrome, to apparently normal males, with intervening variable abnormal phenotypes [7]. Several other rare mosaic karyotypes have also been reported in a different set of phenotypic features of DSD. In our study, we reported the clinical, chromosomal, and hormonal features of three cases with rare stories of DSD who were admitted and managed in our pediatric surgery clinic.

Ethics statement

Written informed consents were obtained from the patients' parents who participated and managed in this report for publication and any accompanying images. The study conformed to the guidelines of the institutional review board of our Institution, which approved its ethical aspects.

Case Report

Case 1

A 13-month-old infant has visited our clinic when the parents were worried about genital ambiguity. The mother reported that antenatal fetal sonograms between the 14 - 24 weeks of gestational age were compatible with a female fetus, while at the 28 weeks the diagnosis was compatible with a male fetus with hypospadias. No hints about any evidence of endocrinopathies or hormonal exposure during pregnancy, no history of genetic syndromes, ambiguous genitalia, or previous precocious neonatal death in the family. Parents are consanguineous and their previous two children are healthy. On initial physical examination: The penile length was 2.1 cm with proximal hypospadias, both testes were in superficial inguinal sites, both were hypoplastic and well developed vaginal orifice (Figure 1A and 1B). Pelvic ultrasound: no evidence of Mullerian duct structures, no obvious female pelvic organ, with bilateral small size undescended testis, both in mid inguinal regions (Figure 2). Karyotype with standard Giemsa-trypsin GTG banding analysis of the proband's prepared lymphocytes culture technique, number of cultures were 2 and the metaphases counted, analyzed and karyotyped were 50. With the application of Fluorescence *in situ* Hybridization (FISH) based karyotyping, the studies revealed 46, XX with chromosome deletion in the long arm (the proximal breakpoint appeared to be in band X q 13.2 and the distal one in band X q 26.1) (Figure 3A and 3B). The hormonal screening revealed, 17-Hydroxyprogesterone 1.10 ng/ml, Dehydroepiandrosterone sulfate (DHEA-S) conventional unit and SI unit 17 micro g/dl, 0.54 micro mol/l respectively. Luteinizing hormone (LH) conventional unit and SI unit 0.21 mIU/ml, 0.21 IU/ml respectively. Follicular stimulating hormone (FSH) 0.76 IU/L, serum estradiol (SE) conventional unit and SI unit 3.50 pg/ml, 12.83 pmol/L respectively. Serum progesterone 0.20 ng/ml. Serum calcium 6.8 mg/dL, other biochemistry (electrolytes) profiles were normal. After the family consent regarding the sex rearing, we arrange the patients for gonadal biopsies, which revealed in both scrotal sides, just immature seminiferous tubules lined by small cuboidal cells, with no evidence of Leydig cells, with ovarian stroma and corpus albicans (Figure 4A and 4B). Diagnostic laparoscopy approach was planned to pick up a more precise image about the pelvic genital organ. Given the controversy and complexity of decision making surrounding gonadectomy for this patient and the policy applied after the family counseling and agreement, serial follow up of the patient was mapped with a multidisciplinary team.

Case 2

A 1-year-old child, born of consanguineous marriage, presented to our clinic when the parents were worried about the sex despite

Figure 1A and 1B: A: Genital ambiguity. B: The penile length was 2.1 cm with proximal hypospadias, both testes were in superficial inguinal sites, both were hypoplastic and well developed vaginal orifice (arrows).

Figure 3A and 3B: A: Fluorescence in situ Hybridization (FISH) based karyotyping, the studies revealed 46, XX with chromosome deletion in the long arm. B: The proximal breakpoint appeared to be in band X q 13.2 and the distal one in band X q 26.1.

Figure 2: Pelvic ultrasound: no evidence of Mullerian duct structures, no obvious female pelvic organ, with bilateral small size undescended testis, both in mid inguinal regions.

Figure 4A and 4B: Gonadal biopsies histopathology results, A: In both scrotal sides, just immature seminiferous tubules lined by small cuboidal cells. B: No evidence of Leydig cells, with ovarian stroma and corpus albicans.

their thought the patient is phenotypically female. The mother had previously undergone two induced abortions during her first trimester for unknown personal issues and had not conceived again in the subsequent 4 years. Other past medical, family, and developmental histories were not contributory. The mother reported that

antenatal fetal sonograms between the 18 - 28 weeks of gestational age were compatible with a female fetus, while after the 28 weeks the diagnosis was compatible with a male fetus with bilateral undescended testis and hypospadias may be associated. The mother presented a history of thyroid surgery and hormonal exposure during her pregnancy, no history of genetic syndromes, ambiguous genitalia, or previous precocious neonatal death in the family. General and systemic examinations regarding the milestones were weight: 9.3 kg, length: 63.5 cm, head circumference 43 cm, and the family pointed, the child is mentally and physically slow. The penile (proximal hypospadias) length vs clitoris(clitoromegaly) was 1.8 cm, underdeveloped labial folds, with no evidence for scrotum or any testis in the superficial inguinal sites, and well developed proximal urethra and small tiny vaginal orifice (Figure 5A and 5B). Pelvic ultrasound revealed evidence of Mullerian duct structures, a small uterus, cervix, with bilateral small size streak like gonads (unremarkable ovaries), and right ectopic kidney situated in the right lower quadrats. Laboratory profiles revealed 17 OH progesterone 1.1 ng/ml, progesterone 0.30 ng/ml, serum-free testosterone 0.01 ng/ml, prolactin 13.47 ng/ml, LH 0.17 mIU/ml, FSH 3.85 IU/L, estradiol(E2) < 10 pg/ml, anti-Mullerian hormone > 9 ng/ Serum calcium 7.6 mg/dL ml, serum sodium and potassium were in normal range. Thyroid function tests were applied: free T3 2.82 nmol/ml, free T4 231.59 nmol/ml, and the thyroid-stimulating hormone was in the normal range. Karyotype with standard Giemsa-trypsin GTG banding analysis of the proband's prepared lymphocytes culture technique revealed 46, XY in a phenotypic female (Figure 6). Diagnosis of DSD was submitted and the parents were thoroughly educated and counseled about in accordance with clinical guidelines for the management of this disorder in childhood. Parents were instructed about the risk of gonadal tumor and were advised gonadectomy but they refused that at the time of counseling. They were counseled in detail about future rearing including fertility. Our decision to follow and re-evaluate the child every 6 months with a multidisciplinary team.

Figure 5A and 5B: A: The penile (proximal hypospadias) length vs clitoris(clitoromegaly) was 1.8 cm, underdeveloped labial folds, with no evidence for scrotum or any testis in the superficial inguinal sites(arrowed). B: Well developed proximal urethra and small tiny vaginal orifice.

Figure 6: Karyotype with standard Giemsa-trypsin GTG banding analysis of the proband's prepared lymphocytes culture technique revealed 46, XY in a phenotypic female.

Case 3

An 11-month-old apparently male infant, born of non-consanguineous marriage was referred to our pediatric surgery clinic with a complaint of undifferentiated external genitalia. No antenatal events or studies have been presented apart from a single antenatal US study (28 weeks) that suggested that it was consistent with male genitalia. The parents expressed an image of delayed milestones. Surgeons and clinicians team initiated the clinical and physical assessment of the patient: length 54 cm, weight 6.5 kg, and head circumference 40 cm. A small phallus (penile length 1.3

cm) normally located external meatus, with a short ventral length and a penoscrotal web, underdeveloped scrotum versus labioscrotal folds fusion, and no palpable external gonads (Figure 7A and 7B). Accordingly, the ultra-sonographic examination of the lower abdominal and groin region failed to locate any external gonad or bilateral ovaries, a small infantile size uterus will be located. A left dilated hydroureter and hydronephrosis were detected, left vesicoureteral reflux on the left was suggested. Magnetic resonance imaging (MRI) of the pelvis with ultrasound correlation (native study), revealed a small size uterus, cervix with no evidence of gonads bilaterally. An echocardiographic screen revealed an atrial septal defect with right atrial enlargement and tricuspid regurgitation. To identify the cause of the phenotype observed in the patient, cytogenetic analyses were submitted. Karyotype with standard Giemsa-trypsin GTG banding analysis of the proband's prepared lymphocytes culture technique, number of cultures were 2 and the metaphases counted, analyzed and karyotyped were 50. With the application of FISH based karyotyping, the studies revealed 46, XX, 46, XY female karyotype (97% female, 3% XY) and 46, XX deletion, X deletion was found in the long arm (the proximal breakpoint appeared to be in band X q 22 and the distal one in band X q 24) (Figure 8). Thus, made our team believed that the observed novel mosaic karyotype in our patient is the cause of ambiguous genitalia. Hormonal screening revealed, 17-Hydroxyprogesterone 0.90 ng/ml, LH conventional unit and SI unit 7.22 mIU/ml, 7.2 IU/ml respectively, FSH 39.67 IU/L, serum estradiol (SE) conventional unit and SI unit < 9 pg/ml, < 32.99 pmol/L respectively. Serum progesterone 0.10 ng/ml, serum testosterone 0.01 ng/ml. Thyroid function and serum electrolytes tests were normal. Genetic counseling recommended and the pathological condition was explained to the family. Careful follow-up was imitated so that the future family planning and patient's gender identity can be determined accordingly.

Figure 7A and 7B: A: Small phallus (penile length 1.3 cm), normally located external meatus, with a short ventral length and a penoscrotal web. B: Underdeveloped scrotum versus labioscrotal folds fusion, and no palpable external gonads (arrowed).

Figure 8: FISH based karyotyping revealed 46, XX, 46, XY female karyotype (97% female, 3% XY) and 46, XX deletion; (X) deletion in the long arm, the proximal breakpoint appeared to be in band X q 22 and the distal one in band X q 24 (arrowed).

Discussion

By review of the literature, about 150 patients with classical XX male syndrome had been reported. Clinical phenotypes about 46, XX DSD have been pointed to three groups, including males with normal phenotype, males with genital ambiguities and males with true hermaphrodites [8]. 46, XX testicular disorders of sex development may also be named 46, XX sex reversal, non-syndromic 46, XX testicular DSD, XX male syndrome, and XX sex reversal. Ovotesticular DSD, which is characterized by the presence of both testicular and ovarian tissue in the gonads of the same individual and testicular DSD characterized by full development of both gonads as testes without any evidence of ovarian tissue [9]. In some affected people, the underlying cause is unknown. In most cases, the condition occurs sporadically in people with no family history of the condition. Gender role and gender identity are normally reported as male, this condition may occur if the SRY gene (is usually found on

the Y chromosome) is misplaced onto the X chromosome [10]. Despite the diagnosis of SRY positive patients (mark about 80 - 90%) is usually achieved in adulthood during infertility investigation, the limitation in our first case (the resources did not allow this assessment at the time of the workup). This generally occurs to do an abnormal exchange of genetic material between chromosomes (a translocation). If a fetus is conceived from a sperm cell with an X chromosome bearing the SRY gene, it will develop as a male despite not having a Y chromosome. This form of the condition is called SRY-positive 46, XX testicular disorder of sex development [11]. About 10 - 20% percent of those with 46, XX testicular disorder of sex development do not have the SRY gene; including patients with ovotesticular-DSD, which is characterized by the presence of both testicular and ovarian tissue in the gonads of the same individual [12]. Here we think that our first case was under this presentation, which is an unusual form of the XX male syndrome.

The early stages of testicular formation require the action of several genes, of which one of the earliest and most important is the sex-determining region of the Y chromosome (SRY). The 46, XY disorders is an uncommon entity occurring in a ratio of 1: 80,000 in the general population. They presented a spectrum of different conditions including 46, XY complete gonadal dysgenesis (Swyer syndrome), 46 XY, partial gonadal dysgenesis (Denys-Drash syndrome, Frasier syndrome), ovotesticular DSD, testicular regression syndrome (vanishing testes syndrome), Leydig cell aplasia/hypoplasia, testosterone biosynthesis defects, POR gene abnormality, persistent Mullerian duct syndrome, 5 alpha-reductase type 2 deficiency and complete and partial androgen insensitivity syndromes [13]. Very early in embryogenesis, the fetus has a 46, XY karyotype but with mutations of the SRY gene such that the testes never form and anti-müllerian hormone is not produced, thereby resulting in a female phenotype [14]. These individuals have a vagina, uterus, and fallopian tubes. Germ cells in the gonads are lost before birth. However, within the spectrum of patients with partial gonadal dysgenesis, some patients have Mullerian structures, which are not apparent macroscopically but can be seen on histological evaluation. Although some cases occur sporadically, genetic counseling may be offered to affected families and should be adapted depending on the mode of inheritance associated with the genetic anomaly identified. Important expectations depending on the FISH mapping dealing with many studies that hypothesized the chromosomal rearrangements in Xq including (region I include choroideremia gene (CHM), premature ovarian failure 1B (POF1B), diaphanous homolog 2 (DIAPH2), and dachshund homolog 2 (DACH2) are frequently associated with premature ovarian failure and have defined a POF critical region. The phenotypic spectrum is so variable that some children are raised unequivocally as females, while others, even with mutations in the same gene, may be assigned to the male sex, others may be frankly ambiguous [15-17]. The genetic causes are as widespread as in complete gonadal dysgenesis. Family counseling offered to our second patient because of the suspected future especially at adolescence time when a lack of pubertal development and hypogonadotropic hypogonadism may be clearly will present. They instructed about the possibility of tumor development from the gonadal remnants (the risk of gonadoblastoma and dysgerminoma in women especially with Swyer syndrome has been estimated to be between 15 to 35%) and current practice is to perform bilateral gonadectomy as soon as the diagnosis is made [10,11].

46, XX/46, XY is a chimeric genetic condition caused by having two distinct cell populations within the body. This map arises in utero from the combination of an XX zygote and an XY zygote (which otherwise would have developed into twins) into a single embryo [18]. 46, XX/46, XY is sometimes associated with Intersex conditions such as ambiguous genitalia and hermaphroditism, but in many cases phenotypically normal male or female development occurs. Due to the physical variation, genetic mapping is the only way to reliably submit a diagnosis. 46, XX/46, XY is possible if there is direct observation of one or more of the following: small phallus midway in size between a clitoris and a penis and incompletely closed urogenital opening (shallow vagina) and abnormal urethra opening on the perineum [19,20]. As individuals with this genetic image possess both ovarian tissue and testicular tissue, depending on the individual, gonads (ovaries or testes) may function fully, partly, or not at all [21]. The life expectations of our (case 3) were counseled with parents about these relevant details include the issues of sexual ambiguity, genital surgery, possible infertility (rare cases with normal male and normal female phenotype have also been ascertained as an incidental finding), and gonadal tumors. The expectation issue of cardiac condition and normal intelligence were an important component of our counseling.

Conclusion

We highlighted DSD cases were extremely rare, with complex mechanisms leading to a large spectrum of clinical manifestations ranging from ambiguous genitalia to normal male phenotype. The important for submitting such findings will assist our team: pediatric surgeons, gynecologists, pediatricians and, endocrinologist to develop future management strategies when they are enrolled or confronted with such cases, by improving the outcome through a precise workup design to provide the optimal evaluation, diagnosis, and management roadmaps of potential cases of DSD.

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Conflict of Interest

The authors declare that they have no competing interests.

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