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Case Report Open Access

A New Female Case with 47,XXY Karyotype and SRY

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Abstract

Objective: Numerical abnormalities of sex chromosome, 47,XXY karyotype, have the clinical phenotype of Klinefelter syndrome. Very few 47,XXY cases with a female phenotype have been reported. The testicular feminization syndrome is a female phenotype with a male karyotype (46,XY). Most of these cases have SRY (testis-determining factor). The genetic explanation of this phenomenon is not very clear.

Methods: Clinical examination, conventional cytogenetic analysis, fluorescence insitu hybridization and molecular genetic analysis, polymerase chain reaction (PCR), were done on a 17-year-old female patient.

Results: Clinical examination revealed that the case had a female external genitalia, breast development and pubic hair. Some clinical findings of the patients are unique and not similar to the other cases reported in the literature. The present case has different clinical features including normal phenotype, breast development and normal gentelia, tubes, ovaries, but hypoplastic uterus. Cytogenetic analysis and fluorescence in situ hybridization revealed that the Y chromosome was normal; both fluorescence in situ hybridization (FISH) and the polymerase chain reaction (PCR) shown the presence of SRY gene. However, PCR analysis revealed the deleted sequences of AZF region.

Conclusion: This is a new distinct female case with 47,XXY in spite of the presence of a Y chromosome and the normal SRY. Undertake published cases in the literature and present case, each case should be considered as a different identity in female phenotype with 47,XXY karyotype and SRY, but the deletion of AZF region on the long arm of chromosome Y.

Keywords: Primary amenorrhea; Infertility; 47,XXY karyotype; SRY gene; Sex reverse

Introduction

The testicular feminization syndrome is described as having a female phenotype with a male karyotype (46,XY) by Morris [1]. The features of this syndrome have normal external female genitalia with a blind ending vagina, inguinal or intra-abdominal testis and absence wolfian and mullerian derivates. Most of patient may come to clinics due to inguinal hernia or primary amenorhea. However, this syndrome shows some varieties such incomplete testicular feminization. Griffin and Wilson described that patients with incomplete testicular feminization may have clitoromegaly and selected wolfian duct derivative [2]. For example, it has hypoplastic seminal vesicles and ejaculatory ducts. For the both syndromes, the main reason is absence or malformation of androgen receptor [2]. The frequency of testicular feminization has been reported in 1/20000 to 1/64000 newborns [3].

Most of individuals with 47,XXY karyotype are exclusively males phenotypes who are presenting with the clinical phenotype of Klinefelter syndrome (KS) because of the Y chromosome. KS represents the most commonly found human sex chromosomal abnormality with an incidence of one in 500 newborn males. However, individuals with 47,XXY presenting female phenotypes with this condition are extremely rare. In the literature, different cases with 47,XXY karyotype and clinical features have been reported. Most of these cases were diagnosed androgen insensitivity syndrome while the others were reported in ranged from the infertility to the completely fertile female case. Here, we present a distinct phenotypic new female case with 47,XXY karyotype.

Materials and Methods

Case

The written informed consent for the genetic analysis was obtained from the patient and her family members. A 17-year-old phenotypic female case applied to the Obstetrics and Gynecology clinics due to the primary amenorrhea. She was 73.0 kg, height 172 cm and arm span 160 cm. Her parents could not conceive baby for seven years. During this period both parents took medications under the control of doctors, but they could not remember what they used. At seven years of their marriage, she had a mischarge in the second month of her pregnancy. Four years later, they had a healthy boy, and followed this case. Her pregnancy was uncomplicated. At the diagnosis, the father

was 54 years and normal phenotype. The other family members were also normal. The family history revealed no consanguinity, ambiguous genitalia, inguinal hernias in any reproductive problems. The physical examination of the case showed a mature female with a normal facial appearance. The clitoris was enlarged 2 cm. The labia major and minor are normal. Breast and pubic hair development were also normal. Hormonal assay was also done.

Radiologic assay

The magnetic resonance (MR), pelvic sonography and laparoscopic examinations were done.

Cytogenetic and FISH studies

Karyotype analysis was done by using peripheral blood cell culture according to conventional lymphocyte culture from the patient and her parents. Karyotyping by using GTG banding was performed. Fluorescence *in situ* hybridization (FISH) was performed by using SRY and chromosome X specific probes (Vysis, USA) on metaphase spreads of patients.

Molecular analyses

DNA was extracted from patient's blood leucocytes by using the DNA kit (Vivantis, Malesia) according to manufacturer's protocols. The presence of Y chromosome was examined by using commercial kit (Diagen AŞ, Ankara, Turkey) according to manufacturer's protocols for co-amplification of Y-specific (SRY), chromosome Y centromeres region. Detection of microdeletions of chromosome -Y AZF region was done by using human chromosome-Y deletion detection kit (Promega, UK) according to manufacturer protocol. All polymerase chain reactions (PCR) were performed in an Aplied Biosystem 2720 Thermocycler. PCR products were separated on a 1.5% agarose gel electrophoresis in Tris-Acetic acid-EDTA (TAE) buffer and stained with ethidium bromide.

Results

The clinical female phenotype patient was evaluated. Hormonal assay showed 17-hydroxy progesteron: 0.57 (normal 0.11-4.0 ng/ml); cortisol: 12.6 a.m (normal 2.5-12.5 pg/dl); PRL: 6.1 (normal 2.5-46.0 ng/ml); FSH: 0.93 mU/ml (normal 2.8-11.3 mIU/ml); LH: 0.14 mU/ml (1.1-11.6 mIU/ml); E2: 78.6 pg/ml (normal 0-160 pg/ml); P4: 0.82 ng/ml (normal 0.33-1.2 ng/ml); DHEAS: 30 pg/dl (normal 35-430 pg/dl); free testosterone: 0.65 pg/ml (8.8-27.0 pg/ml); total testesteron: 20 ng/dl (normal 63-120 ng/dl). The MR examination revealed not bilateral inguinal hernias and testes. Pelvic sonography revealed a normal vagina, uterus and ovaries. Laparoscopic examination showed normal tubes, ovaries and hypoplastic uterus. Ovarian biopsy revealed a normal ovary tissue. The patient was treated with cyclic estrogen and progesterone (premarin-farlual) for six months. At the initial of this treatment, the patient responded to medication. She has been having a regular menstruation since the treatment. Cytogenetic analysis revealed a 47,XXY karyotype (Figure 1). All metaphase showed the same pattern, indicating no evidence of mosaicism. Both parents have normal karyotypes. FISH results showed the presence of one copy SRY and two copies of chromosome X (Figure 2). PCR analyses revealed the presence of SRY region on chromosome Y (Figure 3). However, PCR analysis revealed the deleted sequences of AZF region spanding to sYPR3, sY127, sY128, sY130 (AZFb); sY133, sY145, s153, sY152 (AZFd); sY242, sY254, sY157 (AZFc).

Figure 1: GTG-banded partial karyotypes of the patient showing XXY chromosomes.

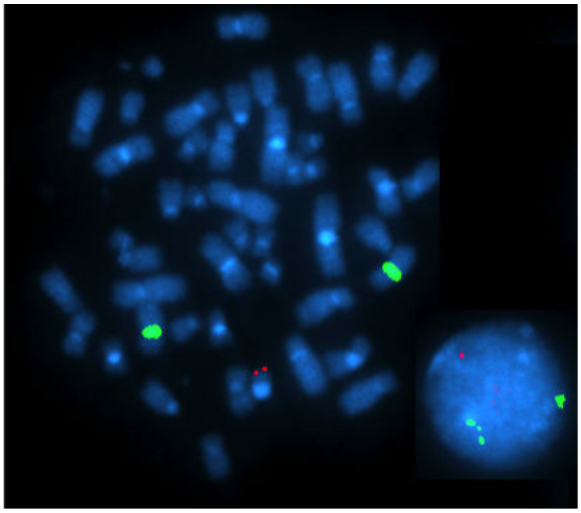

Figure 2: FISH analysis with SRY (red) and chromosome X-specific alpha satellite (green) DNA probes.

Discussion

Phenotype and genotype correlation is very important for individual identity. The presence of Y chromosome bearing SRY lead to the development of sex in a male phenotype during the embryogenesis. However, abnormal Y or X chromosomes may result in female or intersex phenotype. In addition, numerical abnormalities of sex chromosomes may reveal abnormal phenotype. A 47,XXY karyotype is mostly male phenotype. This present report presents a female phenotype with 47,XXY karyotype, SRY positive, but there was the deletion of AZF regions of chromosome Y. So far, small number of cases with the same karyotype was reported in the literature. However, their clinical findings were different in case-to-case, who were in different ages. The clinical findings and SRY status of those cases were variable. So far, approximately 15 female cases with 47,XXY karyotype have been reported in the literature. Most of reported female cases

were diagnosed with androgen insensitivity syndrome [3-11]. The remaining cases had different clinical features [12-15].

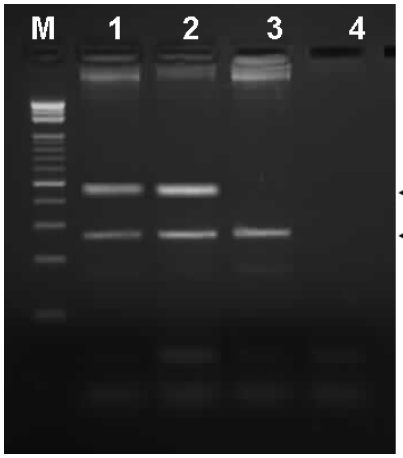

Figure 3: Molecular analysis of SRY. Lane M is the size marker (100 bp); lanes 1, patient; line 2, positive control (normal male); line 3, normal female; line 4, negative control (dH_2O).

In present study, our case is another instance of complete sex reversal in a case with 47,XXY karyotype, presence SRY and the deletions of some AZF loci. The breast development was well. There are female type pubic hair, vulva, vagina, uterus, tuba and ovary in normal development. PCR and FISH studies revealed that SRY and AZF region were presence. In contrast, Lin et al. reported 47,XXY female case has SRY deletion and her ovaries had completely failed. Similar, case in the previously reported 47,XXY female cases, structure variations on the Y chromosome were also reported in a fertile female. This fertile female had given birth to a normal son, and daughter who had same Y chromosome abnormality as in her mother [14]. Uehara et al. reported that the patient was absence of breast development, pubic hair cervix, uterus and narrow vagina, immature vulva [8]. On the other side, Thangaraj et al. reported a case having well-developed breast, presence female type pubic hair, absence of cervix, vagina in 5 cm, prepubertal uterus and labioscrotal folds vulva [12]. A 23 years old female case reported by Scully et al. had no well-developed of breast, absence of pubic hair, cervix, vagina, uterus, and hypertrophic labial folds [16]. However, this case has bilateral inguinal testes in 2 cm [16]. Gerli et al. reported a 25 years old female patient who had a prepubertal breast development, well developed pubic hair, absence of cervix, blind vagina in 3 cm, absence of testes and uterus and normal clitoris and normal female type vulva [5]. Very recently, Lin et al. reported a 47,XXY female with ovarian failure [5]. In addition, two other cases were described by German J. and Vessel M., and Müller et al. but there was some different clinical findings of the cases were different [3,6].

Clinical findings of the present case were similar to the case described by Thangaraj et al. [12]. However, the present case had a hypoplasic cervix although they reported that the case did not have a cervix. The other cases were completely different from our case, for the other clinical findings. Our case showed a normal hormonal level and other biochemical parameter for female. Thangaraj et al. reported that the case had a higher level of prolactin than that in normal female while the other hormones were in normal level for female [12]. However, Uehera et al. and Scully et al. reported that their cases had a high level of FSH and LH, but the level of prolactin was normal [8,16]. The remaining cases reported by others authors were not described in the detail of their hormonal profiles. Therefore, the present case was not compared with those in hormonal assay and biochemical results.

Conclusions

In conclusion, we report on an unusual 47,XXY female case, presenting the different clinical features and SRY status. Present case and the previous reported other cases with 47,XXY show different clinical findings, ranging androgen insensitivity to fertility. Thus, each case could be unique and therefore they need specific attention to diagnosis and treatment.

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Declaration of Interests

Authors declare that there is no conflict of interest.

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