Female Pseudohermaphroditism In A 68 Year Old Patient: A Case Report

Selda SIMSEK¹, Aysegul TURKYILMAZ¹, Hilmi ISI¹, Diclehan ORAL¹,
Selahaddin TEKES¹, Ahmet YALINKAYA²

¹Department of Medical Biology and Genetics of Medicine, University of Dicle, 21280, Diyarbakir, Turkey
²Department of Obstetrics and Gynecology of Medicine, University of Dicle, 21280, Diyarbakir, Turkey

Abstract

Background: The aim of this study is to evaluate a man-like patient of 68-year-old who was referred to our department with history of hermaphroditism.

Case: A 65 years old patient was referred to Dicle University Medical Faculty Department of Medical Biology for karyotype analysis. On systemic, gynecologic and ultrasound examination of the patient was detected 150 cm height, 55 kg weight, female phenotype, female type breasts and hair, approximately 3,5 cm clitoris, normal labium major, fused labium minor, 0.5x1.0 cm opening and 9 cm depth of vagina, 60x37x30 cm size of uterus and 20x15 mm each ovaries. The patient had menstruated regularly during reproductive period from menarche to menopause. The karyotype of patient was performed in peripheric blood sample. The chromosomal constitution of the patient whose Barr Body was positive, was found to be 46,XX. Molecular PCR (polymerase chain reaction) technique for detection of SRY (specific region of Y chromosome) sequences is used to determine whether the SRY gene is present in the patient. The SRY gene in this case was negative.

Conclusion: In spite offemale karyotype and phenotype the patient lived as a male until 65 years. This case has ignored due to social and economic conditions, therefore we think that the patient can be considered for publication.

Keywords: Female Pseudohermaphroditism, Karyotype, Delayed Diagnosis.
**Introduction**

XX maleness is a rare syndrome\(^1\) with a frequency of 1 in 20 000-25 000 males.\(^2\) XX males exist in different clinical categories with ambiguous genitalia or partially to fully mature male genitalia, in combination with complete or incomplete masculinization.\(^3\) Genetic analysis of sex reversed subjects with a phenotypic sex different from that in the karyotype has been important in the identification and characterization of the sex determining region on the Y chromosome (SRY). SRY is the candidate gene for the testis determination. It resides within 35 Kilobase region of the Y chromosome immediately proximal to the Pseudoautosomal region I (PAR I). When the SRY gene is present, testes are formed and in its absence gonads develop into ovaries. 46, XX males are distinct from XX truehermaphrodite and have a male habitus, small testes, azoospermia with no evidence of uterus or ovaries. Different pathogenic mechanism have been suggested which can lead to 46,XX sex reversal. These may be recombination between X and Y chromosomes, mosaicism with a prevalent XX lineageand a hiddencryptic lineage containing a Y chromosome, and mutation in genes other than TDF can trigger testis determination in XX (SRY negative) males.\(^4\)

XX male syndrome is a condition where the sex chromosomes of an individual do not agree with the physical sex of the affected person. Normally, there are 46 chromosomes, or 23 pairs of chromosomes, in each cell. The first 22 pairs are the same in men and women. The last pair, the sex chromosomes, is two X chromosomes in females (XX) and an X and a Y chromosome in males (XY). With XX male syndrome, the person has female chromosomes but male physical features. The majority of persons with XX male syndrome have the Y chromosome gene SRY attached to one of their X chromosomes. SRY is the main genetics witch for determining that a developing embryo will become male. The rest of the individuals with XX male syndrome do not have SRY detectable in their cells. Hence, others genes on other chromosomes in the pathway for determining sex must be responsible for their male physical features.\(^3,4\)

Here we report a man-like patient of 68-year-old who was referred to our department with history of hermaphroditism.

**Case Report**

The 66 female of relatives of DMD/BMD males were screened for RFLP using four intragenic probes. The four RFLP sites examined in this study were all within Xp21 and the DMD/BMD locus. The 66 females of relatives of DMD/BMD boys were screened for pERT 87-15/XMnI, pERT 87-15/BamHI, pERT 87-8/TaqI, and 38/TaqI polymorphisms within the dystrophin gene by PCR-RFLP analysis.

After PCR-RFLP of 66 of females of DMD/BMD patients relative analyzed for these polymorphisms and the frequencies of observed heterozygosity were found to be in correlation with the expected heterozygote frequencies for these polymorphisms. Our investigation indicated that 70 % of all relatives at risk were heterozygous for at least one of these intragenic RFLP, detected by PCR-RFLP. The heterozygote frequencies of four different polymorphic markers (pERT 87-15/XMnI, pERT 87-15/BamHI, pERT 87-8/TaqI, and 38/TaqI ) were detected using PCR based RLFP analysis. The expected heterozygote frequency for these polymorphic markers were found to be 0,50 for pERT 87-15/ XMn I, 0,33 for 87-8/Taq I, 0,50 for pERT87-15/Bam HI and 0,49 for 138/Taq I respectively (Table I). After screening females for the same polymorphic markers the observed heterozygote frequencies were found to be 0,77 for pERT 87-15/ XMn I, 0,36 for 87-8/Taq I, 0,77 for pERT87-15/Bam HI and 0,57 for 138/Taq I, respectively (Table II).
Materials and Methods

We obtained chromosome preparations from routine peripheral blood lymphocyte cultures. At least five GTG banded metaphases (minimal 500 bandlevel) were evaluated for couple. Karyotypes were recorded according to the commendations of the international standing committee on human cytogenetic nomenclature 1995. Peripheral blood cultures were set up in F-10 nutrient media and with 20% fetal bovine serum. The cultures were stimulated with phytohaemagglutinin (PHA-M) and incubated for 72h at 37°C. The cultures were arrested with colchicine (10 mg/ml) at 70,5th h and treated with 0.075 M KCl. The cultures were fixed with cornoyfixative (methanol: Aceticacid, 3:1). The chromosomes were prepared on prechilled slides and stored for three days at room temperature for ageing of the slides. The chromosome preparations were subjected to GTG-banding using standard procedure. Briefly, the slides treated with trypsin-EDTA in Sorensen's buffer for 30 second and stained with giesma stain. At least 30 well spread and banded metaphases were analyzed under microscope and karyotyped according to ISCN 2000.

Discussion

The XX male syndrome, first described by de la Chapelle et al. (1) in 1964, occurs in about one in 20,000 newborn males.² Then Rajender et al. reported a case of SRY-negative XX male having fullymature normal male genitalia with infertility as the main anomaly in 2006.³ In 2009, Vilain⁵ and his colleagues proposed that this condition results from translocation of Y material including sex determining region (SRY) on Y chromosome to the X chromosome.⁵ Berkovitz ⁶ and Vilain et al. reported 46, XX males which were negative for SRY using PCR analysis.⁵,⁶ Vorona et al. explained aspects of endocrinologic and epigenetic features of the 46, XX male syndrome compared to 47,XXY Klinefelter patients.⁷ Thus, for the complete workup of XX males, it is important that conventional cytogenetic analysis be followed by FISH technique or PCR analysis to determine the presence of SRY gene. These investigations indicate that the amount of Y specific material contributes to the phenotype heterogeneity. Inspite of the fact that SRY is the testis determining factor (TDF), it is likely that other genes are also involved in pathway of sex determination and differentiation process as both upstream and downstream regulator genes.³-⁷ Lang et al. reported a case in the German-speaking region of female pseudo hermaphroditism diagnosed in an elderly person with uncomplicated virilizing congenital adenogrenitial syndrome due to 21-hydroxylase deficiency (deletion of CYP21 gene). This case demonstrated the necessity of thorough examination which could have given an early indication of the underlying condition in their report.⁸ Our study emphasized the importance of early diagnosis for the patients with XX male syndrome and the other sex chromosome disorders.
References
5. Vilain E. J. 46,XX Testicular Disorder of Sex Development, Gene Reviews, Bookshelf ID: NBK1416, Last Update 2009
Figure 1 and 2: Metaphase spread and karyotype showing 46,XX chromosomal complement.