Case Report

A Rare De Novo Balanced X; 1 Translocation in an Indian Female with Primary Amenorrhea

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Abstract

Background: Translocations involving X chromosome and an autosome are rather rare due to associated infertility in men and subfertility in women. X chromosome translocations are frequently associated with primary or secondary amenorrhea. In this report, a case of primary amenorrhea with a de novo balanced reciprocal translocation was presented between chromosomes X and 1.

Case Presentation: A 24 year-old proposita with the complaint of primary amenorrhea was found to have hypoplastic uterus and streak gonads with a normal hormonal profile. Chromosomal analysis of the proband revealed a de novo translocation of 46, X, t(X; 1) (q21; p32) chromosomal constitution. Parental karyotypes of the proband showed normal karyotype.

Conclusion: The observed translocation between chromosome X and 1 in the patient suggest either the disruption of a critical gene expression due to position effect or deletion of one or more essential genes in the disrupted long arm of the affected X chromosome. To the best of our knowledge, this is the first report from our ethnic group.

Key words: Abnormal karyotype, Balanced X autosome translocation, Gonadal dysgenesis, Primary amenorrhea.
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Introduction

Primary amenorrhea is the complete absence of menstruation. Amenorrhea is a normal clinical feature in pre-pubertal, pregnant, and postmenopausal women. It has a strong correlation with the expression of X chromosome. It has been reported that the percentage of chromosomal abnormalities varies from 15.9% to 63.3% in patients with primary amenorrhea (1, 2). It also accounts for 20% cases of patients with infertility. X; autosome translocations are uncommon and are associated with a variable phenotype with an incidence of approximately 1:30,000 live births. Due to non-random X-inactivation, the majority of X; autosome carriers that present with abnormal phenotypes include multiple congenital abnormalities, developmental delay, a recognizable X-linked syndrome or gonadal dysgenesis (3). In this report, the clinical, biochemical and cytogenetic aspects of a healthy, non dysmorphic 24 years old female with the complaint of primary amenorrhea was presented.

Case Presentation

The proposita, 24 year-old female with the complaint of primary amenorrhea, was referred to Institute of Genetics and Hospital for Genetic Diseases, Osmania University for cytogenetic evaluation in the year 2013. She was born to a non-consanguineous parent and her siblings were healthy. Her physical examination revealed normal height and weight of 168 *cm* and 73.5 *kg*, respectively. She showed fairly normal intelligence. Her biochemical laboratory investigations were found to be normal with a hormonal profile of 6.8 *ng/ml* of prolactin (normal range 3-25 *ng/ml*), 13.9 *mIU/ml* of follicle stimulating hormone (FSH ref

Table 1. Cases of balanced X; 1 translocations reported in literature

Sl. No	Reason for referral	Karyotype
1	Recurrent miscarriages	46,X,t(X;1)(p22.1;p31) de novo
2	Development delay	46,X,t(X;1)(p22.1:p32) de novo
3	Learning difficulties? Norrie fetus	46,X,t(X;1)(p11.4;p36.3) de novo
4	Multiple congenital anomalies/ Developmental delay	46,X,t(X;1)(q26;p22)mat
5	Mother: abnormal scan	46,X,t(X;1)(q26;p22) de novo

range. 10-15 *mIU/ml*) and 11.2 *mIU/ml* of luteinizing hormone (LH ref range. 10-15 *mIU/ml*). Thyroid profile was also found to be normal with TSH=0.66 *mIU/ml* (0.4-4.2 *mIU/ml*) T3=1.08 *ng/ml* (0.8-1.9 *ng/ml*) and T4=110 *ng/ml* (50-130 *ng/ml*). Ultrasound examination of the pelvis revealed bilateral streak gonads (right ovary: 2.1x 1.9 *cm* and left ovary: 2.7x2.1 *cm*) and a markedly hypoplastic uterus measuring 4.9x2.7 *cm*. Normal vagina and cervix were present and there was no abnormality of the external genitalia. The female had been on low level of contraceptive pills for several years for cyclic estrogen and progesterone replacement and to induce menses, but had never menstruated spontaneously.

Cytogenetic analysis of the peripheral blood lymphocytes of the proband was carried out according to the modified method of Moorhead et al. (4). Peripheral blood lymphocytes were stimulated with phytohemagglutinin and harvested at 68th *hr* with colchicine. Hypotonic treatment was given to the cells and then they were fixed with Carnoy's fixative. Standard GTG banding was done according to the method of Seabright (5). Karyotype analysis of 50 metaphases revealed a pattern of 46, X, t(X;1)(q21;p32), suggestive of a balanced sex autosome translocation involving the long arm of chromosome X and short arm of chromosome 1 (Figure 1). ISCN guidelines for the chromosomal nomenclature (2013) were followed for the karyotype analysis (6). The translocation was found to be de novo as the parental karyotypes were normal.

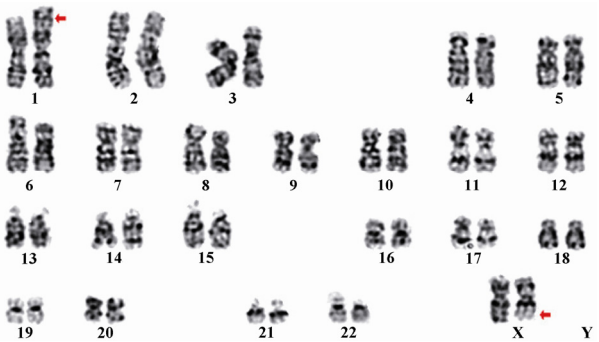

Figure 1. Karyotype showing 46, X, t(X;1)(q21,p32) chromosome constitution in a female with primary amenorrhea

Discussion

Genes essential for normal ovarian development are located on both arms of the X chromosome (7). An abnormality in the number or the structure of the X chromosome results in the disturbance in the normal process of translation of genetic sex and final determination of the phenotypic sex (8). Thus, the abnormal phenotypes are the consequences of the gene disruption, position effect or deletion at one of the break points resulting in haploinsufficiency of critical X linked genes.

The present study revealed a rare de novo sex autosome translocation in a female with primary amenorrhea. Cytogenetic analysis revealed 46,X,t (X;1)(q21;p32) karyotype indicating its possible association with amenorrhea. As there is no published data on X and 1 translocation with these break points, this case can be considered as a novel X, autosome translocation in primary amenorrhea. However, Waters et al. published a report on X autosome translocations from UK population with 104 cases from different laboratories in UK. Among them, 5 cases were found with X; 1 translocation with different clinical manifestations (Table 1) (9).

Vidhya et al. (2009) reported X; 7 translocation in a female with hypergonadotropic amenorrhea (10). Omrani et al. (2012) reported X; 9 translocation in a female with premature ovarian failure (11). Chen et al. (2014) reported an association of primary amenorrhea and mental retardation with concomitant unbalanced X; 6 translocation and X chromosome rearrangements (12). Additional studies showed that Xq13-q26 was particularly a crucial section of chromosome X, since loss or disruption of this region results in severe impairment in ovarian function (13). Our study is in agreement with the hypothesis supported by a review of balanced X autosome translocations

where 23 of 36 phenotypic females had POF (premature ovarian failure) with a break point between Xq13 and Xq26. The genes DIAPH2, XPNEP2, DACH2, POF1B, CHM and NXF5, are some of the candidates that are present on X chromosome which are interrupted by the Autosome and X translocations (14).

Our case report is believed to be the first description of a balanced X; 1 translocation with break points (Xq21 and 1p32) in a female with primary amenorrhea. As the proband manifested non dysmorphic features or developmental delay with normal hormonal profile, the impact of X; 1 translocation appears to be limited to ovarian structure and function. Since the break point was in the critical region of the X chromosome, therefore, it is probable that her chromosomal abnormality was responsible for her critical state. Thus, the reported de novo translocation in a phenotypically normal female with primary amennorhea could be due to the deleterious effects related to disruption of essential genes on X chromosome.

Conclusion

The X autosome translocations advance the understanding of clinical and cytogenetic basis for amenorrhea. Thus, the precise diagnosis and evaluation of patients with sex chromosome abnormality with conventional cytogenetic analysis is essential for the evaluation of phenotype and karyotype correlations, followed by genetic counseling.

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Conflict of Interest

The authors declare no conflict of interest.

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