A first case of primary amenorrhea with i(X)(qter---q10::---qter), rob(13;14)(q10;q10), inv(9)(p13q33) karyotype

ABSTRACT

Primary amenorrhea (PA) refers to the absence of menarche by the age of 16–18 years although secondary sexual characters are developed. PA occurs in 1–3% of women in the reproductive age group. Various factors such as anatomical, genetic and hormonal factors reported to influence PA. We report triple chromosomal abnormalities of rob(13;14)(q10;q10), inv(9)(p13q33), i(Xq)(qter---q10::---qter) in a case of PA and short stature. Though proband has multiple chromosome aberrations, genotypic effect of only i(Xq) is evident as proband has PA and short stature. The rob(13;14) and inv(9), which are paternally derived may have role in later reproductive age. Therefore, chromosomal analysis is essential in such cases for the accurate diagnosis and management of the disease.

KEY WORDS: Primary amenorrhea, short stature, translocations, inversions, multiple chromosomal abnormalities

INTRODUCTION

Primary amenorrhea (PA) refers to the absence of menarche by the age of 16–18 years although secondary sexual characters are developed. PA occurs in 1–3% of women in the reproductive age group. Anatomical, genetic and hormonal factors play an important role in cases of PA. Chromosomal aberrations are the second most common cause of PA after Mullerian duct abnormalities. X chromosome abnormalities (deletions, iso X chromosomes), particularly monosomy X, are more common chromosomal abnormality seen in PA cases. Here we describe a rare karyotype with 45,X, rob(13;14)(q10;q10), inv(9)(p13q13), i(Xq)(qter---q10::--qter) in case of PA and short stature (SS).

CASE REPORT

A 14-year-old female was referred to cytogenetic laboratory for chromosomal analysis because of primary amenorrhea and short stature. The proband is the first born to the consanguineous parents. Her height was 122 cm (<third centile) and weight 23 kg (<third centile). She had absence of secondary sexual characters. Ultrasonography revealed hypoplastic uterus and ovaries. X-ray of right wrist and hand, right forearm revealed fused carpel bone centers, which is suggestive of bone age of 10 years. Hormonal evaluation showed elevated levels of FSH (65.91 mIU/ml) and reduced levels of LH (22.31 mIU/ml). Her prolactin and thyroid profile were within normal limits. The mother’s age at the time of birth was 20 years and father was 24 years. Parental reproductive history showed no family history of abortions, bad obstetrics history and children with mental retardation. The proband has three siblings including one younger sister and two younger brothers.

Cytogenetic study was carried out from proband, siblings and parents. Chromosomal preparation obtained from PHA-M stimulated peripheral blood cultures using standard procedure. Chromosomal preparations were subjected to GTG-banding and karyotyped according to ISCN 2005. At least 50 well spread and good-banded metaphases were scored in each case. Chromosomal analysis of the proband revealed 45,X, rob(13;14)(q10;q10), inv(9)(p13q33), i(Xq)(qter---q10::--qter) [Figure 1a and 1b]. Father’s karyotype was 45,XY,rob(13;14)
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(q10;q10),inv(9)(p13q33) [Figure 1c and d]. Both the male siblings karyotype was same as father’s karyotype i.e. 45,X,Y,rob(13;14)(q10;q10),inv(9)(p13q33). Proband’s younger sister’s chromosomal analysis was 46,XX,inv(9)(p13q33). Mother’s chromosomal analysis revealed normal karyotype. Fluorescence in situ hybridization (FISH) was performed using centromeric probe (14/22, X) and partial chromosome paint (PCP) (Xq, 9q) [Figure 2a–d]. The FISH results confirmed iso(Xq) with PCP Xq probe and inv(9) with PCP.

**DISCUSSION**

Chromosome aberrations such as 45,X, i(Xp) or i(Xq), and Xq deletions are frequently reported in patients with PA. The mosaicism of X chromosome including 45,X/46,XX or 45,X/46,X,iso(Xq) are also not uncommon in PA. FISH has advantage in detection of X chromosomal abnormalities in interphase cells of PA cases, which are not detected with routine GTG-banding. In our case, combination of GTG-banding and FISH investigation revealed 45,X,rob(13;14)(q10;q10),inv(9)(p13q33), i(Xq) (qter---q10::---qter) karyotype. This is the first case with multiple chromosomal abnormalities in a case of PA to our knowledge. Genotypic and phenotypic correlation of the present case showed short stature and primary amenorrhea and this may be due to absence of short arm of X chromosome (Xp). The direct phenotypic effect of t(13;14) and inv(9) not expressed as the translocation is balanced and inversion 9 is a common polymorphic variant.

The inheritance pattern of the chromosome abnormality in the family showed interesting transmission [Figure 3]. In case of proband, i(Xq) was originated de novo and other two chromosome abnormalities were transmitted from her father. The father’s chromosomal analysis showed t(13;14), inv(9) and found to be a carrier. The younger female sibling received only the inv(9) and other male siblings karyotype same as that of the father karyotype. The hormonal therapy may be helpful to achieve menstrual cycles as proband is a case of PA. Chromosome aberrations [t(13;14), inv(9)] were associated with infertility, repeated abortions, aneuploidy fetuses and bad obstetric history in general. The familial i(Xq) has not been reported in cases with PA or infertility. However, multiple genetic anomalies have a high risk for abnormal fetuses. The cytogenetically abnormal PA cases are difficult to treat, since the present case has common chromosomal abnormalities; some extent hormonal therapy such as, progesterone, estrogen can be given to improve reproductive life. However, proper genetic counselling and prenatal diagnosis for proband is essential for future pregnancies to rule out chromosomally abnormal fetuses.

**Figure 1:** (a) Proband metaphase showing rob(13;14),i(Xq),inv(9) (b) Karyotype showing i(X),(qter---q10::---qter),rob(13;14)(q10;q10),inv(9)(p13q33). (c) Father of proband metaphase showing rob(13;14), inv(9). (d) Karyotype showing rob(13;14)(q10;q10),inv(9)(p13q33)

**Figure 2:** (a) Proband FISH showing der(13)(Xq) with centromeric probes. (b) FISH with centromeric probe of X chromosome showing i(Xq). (c) FISH with partial chromosome paint (Xq) showing i(Xq). (d) FISH with partial chromosome paint (9q) showing inv(9)

**Figure 3:** Pedigree showing paternally derived rob(13;14) and inv(9) in proband and sibs
The cytogenetic investigations are essential in PA cases to detect sex chromosomal abnormalities, undetected mosaicism and multiple chromosome aberrations, which help in appropriate genetic counseling and management of the disease.

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