Clinical Brief

Unbalanced X; Autosome Translocation

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ABSTRACT

Unbalanced X; autosome translocation can result in multiple congenital abnormalities/mental retardation syndrome due to chromosomal imbalance. Here is described a patient with developmental delay, microcephaly, agenesis of corpus callosum , spasticity, seizures and dysmorphism as a result of meiotic malsegregation of balanced X; autosome translocation in mother. Present case signifies the importance of chromosomal analysis in a patient with developmental delay/ mental retardation and discuss lyonization in cases with X; autosome translocation. **[Indian J Pediatr 2006; 73(9): 840-842]**
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X-autosome translocations are rare, being estimated to occur in about 1/30,000 live births. In case of X; autosome translocation if the translocated chromosome is lyonised, the genes on the translocated autosome also get inactivated; though the spreading of gene silencing occurs in continuous or discontinuous fashion.[1] The mechanism of inactivation of genes on the translocated segment of an autosome is not clear. Association of XIST RNA to sequence content of a chromosome is fundamental to the lyonization; but is not seen in translocated autosome segment which otherwise carries all hallmarks of inactivation.[2] In balanced X; autosome translocation the normal X chromosome is inactivated preferentially to prevent deleterious monosomy of the translocated autosomal segment. Thus female carriers of balanced X; autosome translocations are generally phenotypically normal. However, in unbalanced X; autosome translocation heterozygote, the effects of chromosome imbalance may be mitigated by selective inactivation of the abnormal X. Inactivation is bidirectional and is initiated at X inactivation centre at Xq13 by a cis acting gene called XIST gene (X inactive specific transcripts).[3] Inactive X replicates its DNA later in the S phase of the cell cycle than does the active X; this replication asynchrony can be diagnosed by replication banding.

Inactivation of normal X in unbalanced translocation is a rare but possible event, to confer a survival advantage to the conceptus. Here is described a female child with an unbalanced Xq14q translocation resulting in monosomy of 14pter→q11.2 and Xq28→qter as result of meiotic malsegregation of maternal balanced translocation.

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CASE REPORT

Proposita at first examination was a 5-month-old female child born of nonconsanguineous marriage to a phenotypically normal couple. She was born as full term by normal delivery with Apgar score of four at 1 minute and seven at 5 minutes. Her birth weight was 2.75 Kg. Other anthropometric parameters at birth are not available. Child had uncomplicated neonatal course. There was no history of convulsions. She had poor growth and development. There was no social smile, mother recognition at the age of 5 months. She had not achieved head control. At the age of 5 months her weight was 4.4 Kg (3rd centile), head circumference was 37.1 cm (3rd centile) and crown heel length was 55 cm (3rd centile). Examination showed microcephaly, small anterior fontanelle, tongue-tie, high arched palate, anteverted nostrils, low set ears, absent ear lobules, thick eyebrows (Fig 1). There was generalized hypertonia, scissoring, fisting, poor head control, and brisk tendon reflexes in lower limbs. Babinski sign was negative. At the age of 13 months she developed generalized tonic spasms. Fundus was normal. Rest of the examination was normal. Diagnostic procedures for developmental delay included a brain MRI scan which showed hypoplasia of corpus callosum with micrencephaly and cerebral atrophy. Thyroid function evaluation, screening for inborn error of metabolism by plasma thin layer chromatography, urine gas chromatography and mass spectrometry was normal.

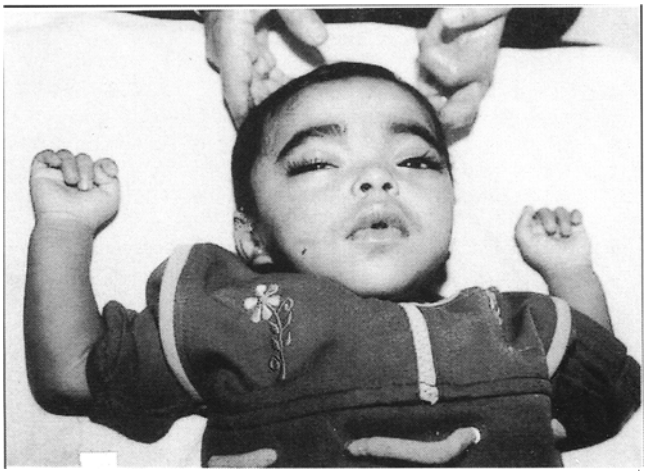


Fig. 1. Facial dysmorphism, Note microcephaly, anteverted nostrils, low set ears, thick eyebrows.

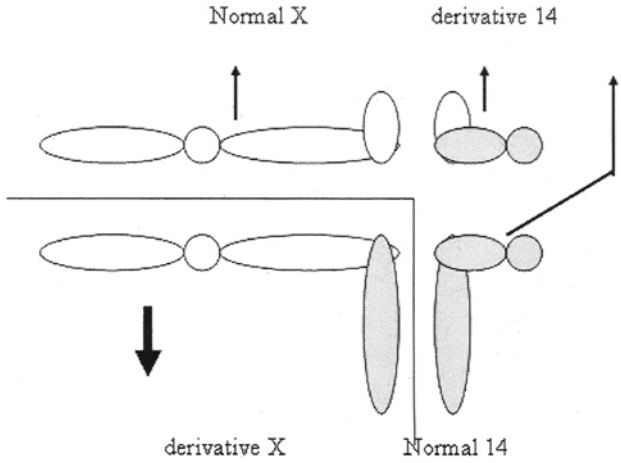
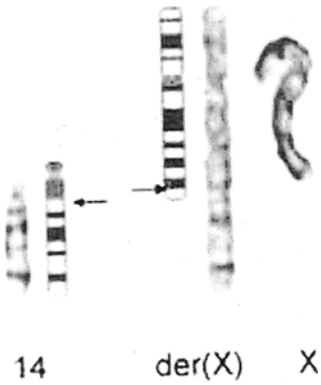


Fig. 3. Tertiary monosomy. The presumed pachytene configuration during gametogenesis in the heterozygote of unbalanced reciprocal translocation between chromosome X and 14. Arrows indicate movements of chromosome to the daughter cells in a 3:1 tertiary segregation; heavy arrow shows the monosomic complement



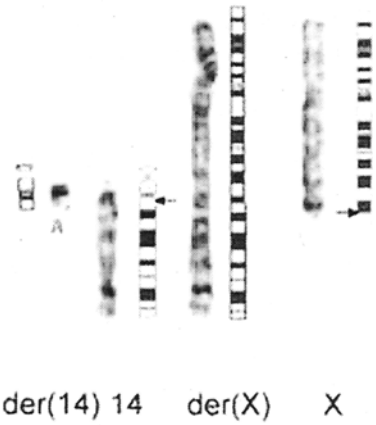


Fig. 2(a). Partial karyotype of patient showing der X, normal X and 14.
Fig. 2(b). Partial karyotype of mother showing der(X), der (14), normal X and 14 Breakpoints are shown at ideogram of normal 14 and normal X at 11.2 and 28 regions respectively

No abnormalities were detected on hematological and biochemical tests for renal and liver function. Chromosomal analysis showed proband's karyotype as 45, X, der(X) t(X;14) (Xpter→Xq28::14q11.2→14qter)mat,-14. Her mother was a balanced translocation carrier for the same translocation and her karyotype was 46, X, t(X; 14) (q28; q11.2) [Figs. 2(a) and 2(b)]

DISCUSSION

The patient has partial monosomy of 14pter→q11.2 and Xq28→qter as result of 3:1 malsegregation with tertiary monosomy of a maternal balanced Xq; 14q translocation as depicted in Fig 3. She has undergone skewed X inactivation pattern because cells in which the derivative X is inactivated would be functionally monosomic for 14q11.2→qter, which may not be compatible with survival. Therefore, being a live born with unbalanced X-autosome translocation, the normal X in most of the patient's cell is likely to be inactivated resulting in monosomy for Xq28→qter and 14pter→q11.2.

Several genes responsible for nonsyndromic X linked mental retardation are mapped to Xq28. Some of these are FMR2/ FRAXE, FRAXF, GDP dissociation inhibitor 1, MECP2 (methyl CpG binding protein), and SLC6A8 (Solute carrier family 6, member 8).[4]

Partial monosomy of 14q is also associated with mental retardation. Several authors have shown that the deletion of 14q11.2-14q13 to be associated with microcephaly, psychomotor retardation, and hypotonia, with gastro esophageal reflux disease, seizures, and agenesis/ hypoplasia of corpus callosum.[5,6,7] Levin *et al* and Bruyere *et al.* described Holoprosencephaly in cases with del(14)

(q11.1q13) or (q11.2q21) respectively and proposed 14q13 as a locus for Holoprosencephaly.[8,9]

The present case had microcephaly, mild dysmorphism, developmental delay, seizures, and hypoplasia of corpus callosum. The hypoplasia of corpus callosum is described in some cases of 14q11.2. But the described phenotype in the present case can be attributed to the partial monosomy of Xq28 as well as 14q11.2 regions. The patient's mother with this single segment X; 14 translocation, is at higher risk for partial trisomy or monosomy for regions of 14q and parts of X chromosome proximal or distal to Xq28 due to meiotic 2:2 or 3:1 malsegregation and can result in either unbalanced gametes or undergo recurrent miscarriages.

The present case signifies the importance of chromosomal analysis in a patient with developmental delay/ mental retardation and the need for parental karyotyping in the presence of structural rearrangement. De novo rearrangements carry a negligible risk whereas there is a substantial risk for recurrent miscarriages or having a child with unbalanced karyotype in inherited translocations requiring prenatal diagnosis. Molecular analysis with microsatellite markers can precisely delineate the exact break points and can help in future gene mapping studies for mental retardation.

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