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Transmission of Cri-du-Chat Syndrome from a Normal Paternal Chromosome Translocation Carrier

Udayakumar Narasimhan[1*], Vidya Krishna[1#], Shruthi Mohan[2$], Solomon F.D. Paul[2+] and Teena Koshy[2]

[1]Department of Pediatrics, Sri Ramachandra University, Porur, Chennai 600 116, Tamil Nadu, India
[2]Department of Human Genetics, Sri Ramachandra University, Porur, Chennai 600 116, Tamil Nadu, India
E-mail: [*]<drnuday@gmail.com>, [#]<docvidya@yahoo.com>, [$]<mohan.shruthi@gmail.com>, [+]<wise_soly@yahoo.com.com>

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ABSTRACT A four-year-old girl with facial dysmorphism, microcephaly and global developmental delay was brought to the department of pediatrics for assessment. The genetic evaluation by conventional G banding analysis of somatic chromosomes identified an apparently balanced translocation, interpreted as t (5; 19) (p13.1; q14). The objective of this report was to assess the clinical manifestation of this chromosomal rearrangement and the possible familial implications. Chromosome analysis of the phenotypically normal patient's father showed an identical abnormal banding pattern for chromosomes 5 and 19. It was concluded that while the proband appeared to have inherited the chromosomal rearrangement from the father, the abnormal phenotype was possibly due to de novo imbalances at one of the breakpoints caused during genetic recombination events. This case report highlights the fact that for families with children with congenital abnormalities, an early diagnosis is important for providing personalized diagnostic and prognostic evaluation and also for genetic counseling on future reproductive risks.

INTRODUCTION

The frequency of chromosome reciprocal translocations is 1/673 to 1/1000 and is considered to be the most common structural rearrangements observed in humans (Keify 2012). The global incidence of chromosome aberration is reported as 5 percent in stillborns, 0.3 percent in newborns, 4.2 percent in 8th week of gestation, 2.4 percent in 12th week of gestation, 1.1 percent in 16th week of gestation, and 0.8 percent in 20th week of gestation (Schinzel 2005). Interestingly, these aberrations can occur de novo or through parental transmission.

While carriers of balanced translocations generally have a normal phenotype, during meiotic segregation, they may produce unbalanced gametes with segmental aneusomies of the chromosomes involved in the rearrangements, which in turn could lead to an increased risk of infertility, recurrent abortions or children with congenital malformations.

This report describes a family with a child with classic clinical features of Cri-du-Chat syndrome, except the cat like cry, in which an identical and apparently balanced abnormal chromosome rearrangement was identified in both the affected child and an unaffected parent. Despite the identical banding patterns, the parent was believed to be balanced because of his normal phenotype whereas the affected child was significantly unbalanced. The objective of this report was to assess the clinical manifestation of this chromosomal rearrangement and the possible familial implications.

Address for correspondence:
Dr. Teena Koshy, Ph.D.
Department of Human Genetics,
Sri Ramachandra University,
Porur, Chennai 600 116,
Tamil Nadu, India
E-mail: teenak@sriramachandra.edu.in

Clinical Report

A four-year-old girl was referred to our developmental clinic for assessment of global developmental delay. She was small for gestational age (SGA) baby of a non-consanguineous marriage. The antenatal and birth history was uneventful. On clinical examination it was observed that she had microcephaly, hypertelorism, broad nasal bridge, abnormal auricle, operated cleft lip, single palmar crease and flat feet.

Hypertonia of all limbs was noted but there was no abnormal cry. She also had a small ventricular septal defect (VSD) confirmed by echocardiography in the neonatal period.

On Gessell's childhood behavioral scale (GCBS), her developmental age was one year and two months. She had myopia which was corrected and mild sensorineural hearing loss in the right ear by brainstem evoked response audiometry (BERA). An MRI of the brain showed a reduction in volume of body and splenium of corpus callosum and brainstem.

METHODOLOGY

Cytogenetic Study

Cytogenetic analysis was carried out on phytohemagglutinin stimulated peripheral blood lymphocytes, cultured in Roswell Park Memorial Institute (RPMI) 1640 medium, using a standard protocol. Twenty-five G-banded metaphases were analyzed using Cytovision software and designated as per ISCN (2009) nomenclature at 550 bands per haploid genome.

The karyotype of G-banded metaphase of the proband revealed a derivative chromosome 5 arising from a translocation between short arm of chromosome 5 and long arm of chromosome 19. To ascertain the origin of the derivative chromosome 5 identified in the child, the parental samples were requested for cytogenetic studies. The mother had an apparently normal karyotype (46,XX) and the karyotype of father, who is phenotypically normal, revealed a similar rearrangement, with the karyotype representation in both the child and the father as 46, XY, t (5; 19) (p13.1; q14), depicted in Figure 1. FISH analysis using sub-telomeric probes (Vysis ToTelVysion) of the patient and paternal chromosome supported the karyotype findings (Fig. 2a and 2b).

OBSERVATIONS AND DISCUSSION

Lejeune and colleagues first reported Cri-du-Chat syndrome or deletion 5p syndrome in 1963. While the incidence of the disease is around 1 in 15,000 to 1 in 50,000 newborns, it may be an underestimation as there are cases with sub-microscopic deletions that are undetected by karyotyping. Approximately 85 percent of the cases result from de novo deletions and only 15 percent of cases are inherited. These arise from malsegregation of a balanced translocation in one of the parents where the parent is usually asymptomatic (Spinner et al. 2007). In the researchers' case report they describe a child with phe-

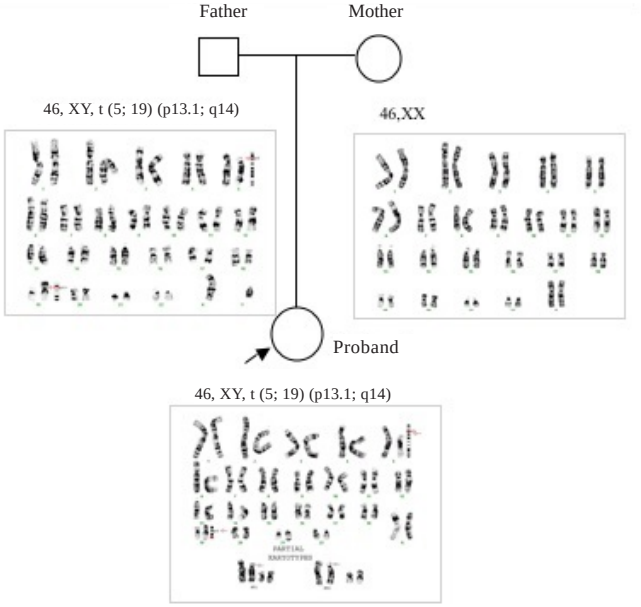

Fig. 1. G banded karyotype, the t(5;19) arrow in the father and our patient were seen. Her mother had a normal karyotype.

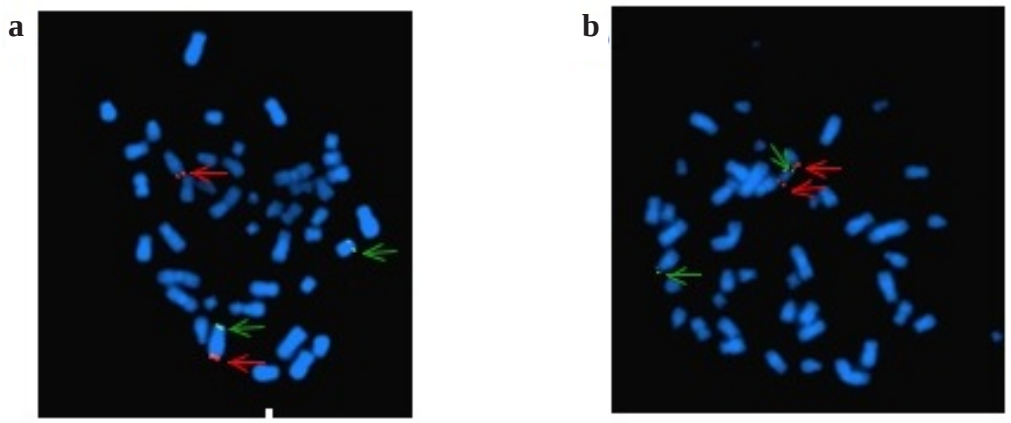

Fig. 2. FISH with specific probes for the subtelomeric regions of both the p arm and q arm of chromosome 5 and chromosome 19. Arrows indicae two 5q chromosome sub-telomeric signals two 5p sub-telomeric signal in Fig 2(a) and two 19p chromosome sub-telomeres and two 19q chromosome sub-telomeres in Fig 2(b) indicating a balanced translocation in the proband as observed in the karyotype

notype variations of the Cri-du-Chat syndrome resulting from the abnormal chromosome segregation of a paternal reciprocal translocation involving chromosomes 5 and 19.

5p deletions, whether terminal or interstitial, occur at different breakpoints. Hence, the variability seen among individuals may be attributed to the differences in their genotype (Nguyen et al. 2015). The critical regions for the typical cry and speech retardation have been mapped to 5p15.3 and dysmorphism, microcephaly and mental retardation to 5p15.2 (Overhauser et al. 1990). From the clinical manifestations, it can be assumed that the critical regions of 5p15.3 were involved in the chromosomal imbalance, as the proband did not manifest the typical cat like cry. However, it must be stressed that this needs to be confirmed by techniques such as array comparative genomic hybridization (array CGH) (Espirito et al. 2016), since there are limitations for detection in karyotyping and FISH, the techniques used in this report.

These deletions are mostly de novo, with the origin being paternal in 80–90 percent of cases. This is based on the hypothesis that there is possibly chromosome breakage during gamete formation in males (Overhauser et al. 1990; Mainardi et al. 2001). 10 to 15 percent are the result of an unbalanced parental translocation (Mainardi et al. 2006). In their review, Nguyen et al. have stated that there is "phenotypic heterogeneity among family members with the same deletion". In agreement with the researchers' report, there are parents of affected children with 5p– deletions who themselves have the same rearrangement or the deletion and yet do not appear to have any symptoms. Moreover, the siblings differ with respect to manifestation especially in growth and development in spite of having inherited the same deletion. Interestingly, families in which the deletion was maternally inherited were observed to have mild growth and developmental delays when compared with families in whom it was paternally inherited (Nguyen et al. 2015).

CONCLUSION

Thus it can be considered that the phenotypic complication in this case could be the crossing over and recombination at rearranged segments on both chromosome 5 and 19. A comprehensive follow-up of development could help to understand the expression of this unbalanced karyotype. For a parent with a balanced rearrangement with one affected child, the risk for subsequent sibling is around 5-30 percent. Thus, this report not only emphasizes the importance of public awareness regarding chromosomal rearrangements, especially in a country like India that has a high birth rate, it also highlights the significance of genetic counseling and prenatal diagnosis for prevention of recurrences and associated familial and societal stress

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