De novo simultaneous reciprocal translocation and deletion

SUMMARY A female infant with severe mental retardation, general hypotonicity, and a history of generalised oedema, cyanosis, heart murmur, and nystagmus in the first days of life was found to have both a translocation and a deletion. Her karyotype was 46,XX,del(21)t(18;21)(18p ter→18q11::21q21→21q ter;21p ter→21q11::18q11→18q ter). The karyotype of both parents was normal. The proposita is the result of a three break point exchange and is monosomic for part of the dark band q11 q21 of chromosome 21. It is suggested that in cases with mental retardation and apparent balanced de novo reciprocal translocation a small undetected deletion in one of the chromosomes involved in the translocation could explain the mental retardation.

De novo simultaneous occurrence of reciprocal translocation and deletion (as a result of three break points) has apparently not been previously described. Three break points occur occasionally in man. Two children with insertion translocation (and, thus, three break points) were described among the 45 children with autosomal reciprocal translocations found among the 54 749 children examined in six studies of unselected children (Nielsen and Rasmussen, 1976). The present report describes the phenotype of a child who is monosomic for part of the dark band q11 q21 of chromosome 21 as a result of de novo simultaneous occurrence of reciprocal translocation and deletion 46,XX,del(21)t(18;21) (q11;q11 q21).

Case report

The proposita was born on 2 March 1975 in Rumania. The father and mother were 45 and 41 years of age, respectively, at the time of her birth. They were both Ashkenazi Jews and were not related. They had one normal son and four previous pregnancies terminated by induced abortion, without medical indication, because the pregnancies were not wanted. The pregnancy with the proposita was normal and there were no bleeding episodes. The only drugs taken during the pregnancy was reserpine to reduce high blood pressure in the sixth month of pregnancy. Delivery was spontaneous and normal. Birthweight was 3100 g. The child was born with generalised oedema of the face and limbs and a systolic heart murmur; cyanosis and nystagmus were recorded. The child's condition improved and she left hospital at the age of 12 days. Hypotonia was diagnosed at the age of 6 weeks. Her development was slow and she was not able to sit up or stand. The child was admitted at the age of 16 months to this hospital and the diagnosis of severe mental retardation was established and chromosomal investigation was initiated.

Cytogenetic studies

Chromosome investigations were performed on phytohaemagglutinin stimulated peripheral lymphocytes. Chromosome banding was obtained by the trypsin method (Seabright, 1971).

The karyotype (Fig. 1 and 2) of the proposita had both a translocation and a deletion and was found, with banding techniques, to be 46,XX,del(21)t(18;21) (18p ter→18q11::21q21→21q ter;21p ter→21q11::18q11→18q ter). Part of the dark band q11 q21 of chromosome 21 was deleted (the breaks probably occurred near the distal edge of both 21q11 and 21q21) and therefore the child was monosomic for part of that band. The karyotype had two abnormal elements (Fig. 2 and 3). A small submetacentric marker that was the smallest chromosome in the karyotype, as well as a large acrocentric of almost the size of No. 15. The small marker did not have any dark band. This karyotype was found in all the one hundred cells that were counted from two cultures taken on two separate occasions. Buccal smear was, as expected, X chromatin positive.

The karyotype of both parents was normal. We were unable to investigate the family further since the parents declined to co-operate.

Discussion

Wahrman et al. (1976) reviewed the literature and showed on the basis of a family previously reported by Schmidt et al. (1972) that monosomy for most of all the dark band of chromosome 21 has no obvious physical effects but is accompanied by mental retardation. The present case gives further support to the above finding.
Jacobs (1974) discussed the correlation between euploid structural chromosome rearrangements and mental subnormality. Laurence and Gregory (1976) mentioned the possibility that in de novo balanced translocation, some deletion may have occurred which is not detectable even by the banding techniques. De novo simultaneous occurrence of reciprocal translocation and deletion should be less common than simple deletion as simple deletion requires only two break points, while reciprocal translocation and deletion is based on three break points. Three break points on two chromosomes are also required for production of insertion translocation but those cases have a balanced karyotype and, therefore, have usually a normal phenotype, and are not likely to be selected against in early embryonic stages, as is the case in deletions. Still the extreme rarity of simultaneous occurrence of reciprocal translocation and deletion may perhaps be explained by undetected small deletions in cases of apparently balanced reciprocal translocations. A small deletion that would be detected because of assymetry in length within a pair of homologous chromosomes when arranging the cut-out photographed chromosomes may be less likely to be detected when the chromosome is involved in a reciprocal translocation and has no homologue with which to be compared.

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In the ‘cri du chat’ syndrome, the deletion of chromosome 5 short arms may sometimes go unnoticed when a more complex chromosome rearrangement is associated. We present one such case wherein the deletion is only identifiable using chromosome banding techniques.

Case report

This male infant is the first child born to a healthy 25-year-old mother and 27-year-old father. A 2-year-old brother is normal. The family history is negative with the exception of a first pregnancy terminating in spontaneous abortion at 2 months. After an uneventful full-term pregnancy, birthweight was 2250 g. On the third postnatal day, considerable hypotrophy necessitated his admission to hospital.

Physical examination yielded the characteristic anomalies of hypertelorism, epicantic folds, downward-slanting palpebral fissures, moon-shaped facies, and an underscended left testis. In addition, a peculiar high-pitched cry was noted, evoking the diagnosis of a ‘cri du chat’ syndrome. Using conventional staining techniques, the karyotype in 1968 showed that the two no. 5 chromosomes were morphologically normal but there was a translocation between a no. 2 and a group D chromosome. Parental karyotypes were normal.

Complete re-examination was performed at age 7 years and showed hypotrophy (weight, 17 kg; height, 115 cm; span, 119 cm; lower segment, 54 cm) with considerable microcephaly (head circumference, 48 cm; thoracic circumference, 55 cm). The cranial and facial malformations (Fig. 1a and 1b) consisted of the previously noted signs in addition to a poorly outlined philtrum, absence of the lateral inferior incisors with poor dental articulation, and large external ears with highly pronounced auricular helices. Thoracic asymmetry was evident with flattening of the left hemithorax; hypotonic abdominal musculature and umbilical hernia were present. Anomalous dermatoglyphic patterns were found with bilateral simian creases and diminished total ridge count (Table).

Psychomotor retardation was severe, with an intelli-

Fig. 1a and 1b  The propositus at age 7 years.