Complex chromosome rearrangement with ankyloblepharon filiforme adnatum

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Abstract
A Caucasian boy with a de novo complex chromosome rearrangement owing to six chromosome breaks was small for gestation with microcephaly, complex heart defect, hypotonia, left auricular pit, simian creases, and ankyloblepharon filiforme adnatum. The rearrangement included two translocations, t(15;21) (q22;q22) and t(3;11)(q21;q11), with the derivative 3 showing in addition pericentric inversion (p11q11) and interstitial deletion (q11q21). Based on parental satellite polymorphisms of chromosomes 15 and 21, the paternal gamete appeared to be the source of the chromosome rearrangement. There was no evidence of mitotic chromosome instability. A review of 36 reported patients with complex chromosome rearrangements secondary to more than four breaks indicates that complex chromosome rearrangements are compatible with gamete survival, zygote formation, and postnatal life. The latter is usually compromised by structural defects, growth retardation, and often mental retardation.

In humans, congenital complex chromosome rearrangements (CCR) are rare yet have been reported on numerous occasions. By definition, they involve more than two chromosome breaks with exchange of segments among at least two chromosomes. CCRs have been divided into two categories: familial, with a chromosome aberration present in one or both parents, and de novo. In both categories the CCR can be unbalanced or balanced, that is, without detectable loss or gain of a chromosomal segment, detected by current cytogenetic techniques. Patients with CCR have been further categorised according to the number of detected chromosome breaks: those with four or fewer breaks (group I) and those with more than four breaks (group II). Group I contains numerous reports of double translocations. In group II there are at least 36 reported patients.

Ankyloblepharon filiforme adnatum (AFA) is the mildest form of congenital fusion of eyelid margins that persists postnatally, and by definition it consists of a partial thickness fusion of the central portion of the margins with sparing of the canthi. The ocular globe is anatomically intact. AFA is usually a sporadic solitary developmental anomaly of unknown cause or a part of malformation syndromes caused by mutant genes or chromosome abnormalities. We report a Caucasian male toddler with six breaks, four derivative chromosomes, and AFA.

Case report
At birth fused eyelids, hypotonia, left auricular pit, simian creases, and small for gestational size (birth weight 2407 g, length 46 cm, and head circumference 30 cm at 39 weeks' gestation) were noted. He was the product of the first pregnancy of a healthy, non-consanguineous, 20 year old mother and 22 year old father. The pregnancy was uneventful. However, the mother had a history of chronic cystitis with antibiotic treatment and dilatation.
of the urethra; this was months before the conception. She smoked 10 cigarettes per day. Street drugs, ethanol, and x ray exposure were denied. The mother worked in an insurance office with computers and the father worked in a restaurant. The delivery was spontaneous vertex and Apgar scores were 7 and 8 at one and five minutes, respectively. Persistent cyanosis and a systolic murmur led to an echocardiogram and cardiac catheterisation. A complex heart defect consisted of a double outlet right ventricle, an endocardial cushion defect, a hypoplastic left ventricle, a common AV valve, a large VSD, and hypoplastic pulmonary arteries. A Blalock-Hanlon septotomy and banding of the pulmonary artery were performed. The fusion of the eyelids was partial and involved the mid portion of the palpebral fissures. It consisted of two strands of extensible tissue, 2 mm wide. The strands connected the approximated eyelid margins. Anterior and posterior ocular segments were normal. On the second day of life surgical lysis of the lids was performed.

At the age of 2 years 10 months his weight was 11 kg, height 84 cm, and head circumference 45 cm. All measurements were 3.5 SD below the mean for age and race. Round flattened facies with a pointed chin and a flat occiput were present (fig 1). Epicanthic folds, upturned nose, and retrognathia were noted. Outer canthal distance was 8.3 cm (85th centile) and inner canthal distance was 3 cm (80th centile). There was no evidence of neurological deficit yet history a mild developmental delay was documented. There was a history of additional cardiac surgery, Fontan procedure, inguinal herniorrhaphies, and bilateral vesicoureteral reflux.

**CYTOGENETIC STUDIES**

Trypsin Giemsa banding (GTG) of peripheral lymphocytes and skin fibroblasts showed 46 chromosomes in all 36 metaphases analysed. There was no increased number of gaps or breaks. Only one normal homologue of pairs 3, 11, 15, and 21 was noted. The other homologue appeared abnormal (fig 2). A translocation 3;11 was apparent with breakpoints at 3q21 and 11q11. In addition, the derivative chromosome 3 showed a pericentric inversion p11q11 and a small interstitial deletion q11q21. Another apparently balanced translocation involved chromosomes 15 and 21 with breakpoints at 15q22 and 21q22 (fig 3) (table). The parental karyotypes were normal.

**Discussion**

Our patient showed a unique phenotype most probably secondary to a de novo CCR with six chromosome breaks and four derivative chromosomes. The fact that only one homologue of each chromosome pair was aberrant and the absence of a normal cell line suggested a prezygotic occurrence of the breaks in one of the parental gametes. Satellite polymorphisms on chromosomes 15 and 21 in the parents were informative, showing a paternal origin of both derivatives. The lack of informative polymorphisms on chromosomes 3 and 11 left a theoretical possibility that the t(3;11) might have originated in the maternal gamete. However, de novo occurrences in both parental gametes are unlikely. Thus, the sperm was implicated as the source of the CCR. As in all reported group II CCR patients, the cause of the breaks in this patient remains unknown. A major 'catastrophe' within the gamete appears

Figure 2  Karyotype of the proband. Arrows indicate the breakpoints.
A vague yet plausible pathogenetic mechanism for the CCR. As to phenotype-karyotype correlations, it is still impossible to link clinical manifestations to the breakpoints. The interstitial deletion 3q can be expected to be of more importance for the aberrant phenotype than the balanced rearrangements. On the other hand, the phenotype did not match the reported phenotype of monosomy 3q11q21. Thus, a probable modifying effect of disrupted genes at the other breakpoints makes comparisons difficult. Four of the six breakpoints, 3p11, 11q11, 15q22, and 21q22, have been reported in other CCR patients, yet in these reports the overall CCR involved different combinations of derivative chromosomes and, as expected, the phenotypes were dissimilar. A caveat regarding numerous breakpoints in reported CCRs is that with cytogenetic techniques alone, the exact site of the breakpoints frequently remains debatable and subject to interpretation. Our patient is not an exception in this regard; the apparently balanced t(15;21) interpreted as q22;q22 could be q15;q11.2. In addition, the 15q12 band of the derivative homologue was rather prominent, although conclusions concerning this notoriously variable region are cytogenetically difficult. Thus, on a molecular level there might be additional aberrations rendering the t(15;21) unbalanced. A further study of one of the reported patients with CCR showed seven instead of the initially reported five breakpoints. It is expected that respective DNA probes will improve the accuracy of breakpoint determination. At present, investigators are only trying for exact determination of the breakpoints and correlation with fragile sites. Attempts at phenotype-karyotype correlations without molecular confirmation are speculative.

As a clinical manifestation AFA has not been reported in group II CCR patients. However, it is a part of the normal fetal development with separation of eyelids before 32 weeks' gestation. As in the reported patient, a failure of eyelid separation is unlikely to indicate a specificity for a particular breakpoint. In addition, the developmental timetable for the fusion/separation of the eyelids is quite lengthy, extending between the 8th and 32nd weeks of gestation.
weeks. Thus, to elaborate on the disruption of eyelid fusion/separation as a sign of dysmorphogenesis would be highly speculative. On the other hand, just as for the other major and minor phenotypic aberrations, the numerous breakpoints must have played a role, either dissecting functional genes or displacing modifier genes leading to the disruption of the chronogenetic table and lack of eyelid separation at 39 weeks’ gestation.

In regard to CCRs and their pathogenesis, knowledge is still in the descriptive, morphological stage and currently only a few subspecialists know that congenital CCR is a biological phenomenon in humans which, on occasion, is compatible with zygote survival and postnatal life despite phenotypic aberrations. Increased awareness of CCR is necessary and will contribute to the understanding of these patients.

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