Agenesis of the corpus callosum with mosaicism 46,XY/47,XY, extra ring chromosome

SUMMARY A case of agenesis of the corpus callosum with a chromosomal abnormality is reported. The patient was a male infant, born to phenotypically normal, non-consanguineous parents. He had an abnormal phenotype, mental retardation, and chromosome mosaicism 46,XY/47,XY,+r. Chromosomal analysis of both parents showed a normal karyotype. The origin of the small ring chromosome could not be determined and it is difficult to relate the phenotype of the infant to the cytogenetic findings.

This report concerns a male infant with agenesis of the corpus callosum, who had chromosome mosaicism with one cell line with a supernumerary small ring chromosome. This is the first instance in which an infant with agenesis of the corpus callosum has been found to have this abnormal karyotype.

Case report

The patient was referred to our clinic at the age of 15 months because of psychomotor retardation. He was the only child of healthy non-consanguineous parents and was born at term by caesarean section because of primitive metratonia after a normal pregnancy. The mother was 25 and the father 29 years old. Birthweight was 2880 g. The neonatal course was complicated by asphyxia, cyanosis, and difficulty in sucking. His growth and psychomotor development was poor during the first year of life; he first smiled at 7 months and gained control of the head at 13 months. The parents noted hypertonic episodes associated with cyanosis and apnoea lasting a few seconds when the child was 11, 13, and 14 months old. On admission his weight was 9450 g (10th centile), length 74 cm (3rd centile), and head circumference 44 cm (>97th centile). Physical examination (fig 1) showed a large head with frontal bossing, low set ears, hypertelorism and slight epicanthal folds, beak-like nose, chest with rickety alterations, undescended testicles palpable in the inguinal region, clinodactyly of the fifth finger, and very short second toes bilaterally.

FIG 1 General appearance of the patient.

The patient showed delayed psychomotor development, head control was poor, he was unable to sit or to make intelligible sounds, and the lower limbs were hypertonic. Evaluation of development was 0.62 with the Brunet-Lezine test.

Radiological examination showed normal bone maturation and a normal skull. No abnormalities were seen in the intravenous pyelogram. The electroencephalogram showed excess of irregular slow components. Ocular fundi were normal.

Computerised tomography (EMI brain scan) showed agenesis of the corpus callosum (fig 2) with dilated ventricles, a superiorly displaced third ventricle which separated the lateral ventricles, and increased interhemispheric scissure. This finding was consistent with that of pneumoencephalography.

CYTOGENETIC FINDINGS

Chromosome examination of the patient and his parents was performed on cultured lymphocytes by standard methods. Trypsin-Giemsa staining was used for banding. Careful analysis of 117 metaphases in the mother and 124 in the father showed a normal karyotype. In the patient's cells two cell lines were seen: one normal 46,XY, the other with 47 chromosomes. The supernumerary chromosome was a

FIG 2 EMI brain scan showing agenesis of the corpus callosum.

FIG 3 Metaphase plate showing a modal number of 47 chromosomes. The arrow indicates the small ring chromosome.

small ring; it was noted in 69 of 101 cells examined (fig 3), was the same size in all the cells, did not associate with acrocentric chromosomes, was negative for NOR staining, and the addition of methotrexate¹ to the cultures yielded no further information. C-banding showed the presence of centromeric heterochromatin in the ring chromosome (fig 4). The origin of the small ring chromosome could not be determined.

BIOCHEMICAL STUDIES

Red blood cells from 10 ml venous blood from the proband and his parents were separated by sedimentation from the leucocytes and plasma, washed twice with 0.9% NaCl, and lysed by addition of 1/1 (v/v) distilled water. The lysate was assayed for peptidase A activity. Peptidase A activity for the proband was 278.96 nmol/mg Hb/h; for the father it was 355.16 nmol/mg Hb/h; and for the mother

FIG 4 C-banding showing centromeric heterochromatin in the small ring chromosome.

it was 127.7 nmol/mg Hb/h (normal, 181.34 ± 25.28 , ranging from 37.81 to 331.52). The child/mid-parent ratio was 1.15 (normal, 0.94 ± 0.05 , ranging from 0.57 to 1.26). The absence of increased activity and abnormal child/mid-parent ratio seems to exclude the presence of band 18q23 of chromosome 18 in the ring.²

Laboratory investigations, including urinary amino-acid analysis, gave normal results.

Discussion

Agensis of the corpus callosum is a complex syndrome with a constellation of anomalies. The aetiology is unknown but in some families it may be genetically determined and conform to an X-linked recessive or an autosomal recessive type of inheritance. In some isolated observations cytogenetic defects have been identified: rare cases of trisomy 13, trisomy 18,³ trisomy 8,⁴ translocation,⁵ and triploidy⁶ are associated with agensis of the corpus callosum. In our case of agensis of the corpus callosum there was a chromosomal abnormality, but it is the first time that this syndrome has been associated with mosaicism for an extra small ring chromosome.

Cases of ring chromosomes of chromosome X and of autosomes are well known, but the ring is usually one of a modal number of 46 chromosomes. Very rarely, mostly in mosaicism, a small ring chromosome is present as a 47th chromosome producing partial trisomy. In the very few cases described^{7,8,9} the origin of the small ring was not identified and the phenotypes were not similar to our case; therefore, the origin of the ring was probably not the same. Furthermore, agensis of the corpus callosum was not reported to be present.

Therefore, even if it seems reasonable to attribute the phenotype of our patient to the chromosomal anomaly, it is more likely that the abnormal phenotype and the chromosomal abnormality are coincidental.

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