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Clinical case report

Interstitial deletion of chromosome 15: two cases

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Summary. Two cases of interstitial deletion of chromosome 15 with similar clinical features are presented. In one case, assay of hexosaminidase A enabled us to confirm that the structural gene is located between 15q22 and 15q25 and that it is included in the deletion.

Introduction

Cases of monosomy 15 are rare, and the only syndrome of partial monosomy 15 defined to date is the Prader-Willi syndrome, with interstitial deletions of band 15q11 or 15q12 (Hasegawa et al. 1984). We observed two cases of partial monosomy of chromosome 15 with interstitial deletion between 15q21 and 15q25. As far as we know, no similar observation has been published before. Here we report on the two new clinical cases and compare their phenotypic features. In one case in which we succeeded in establishing a lymphoblastoid line, we studied hexosaminidase A (Hex A). Since the gene of the α subunit of hexosaminidase A has been mapped to chromosome 15 (q23q24) (Nakai et al. 1987), our results allowed us to conclude that the HEX α gene is included in the interstitial deletion described here.

Case reports

Case 1

LD was born as the second of two children to healthy unrelated parents in 1985. Her sister, born in 1982, is well, and the family pedigree is unremarkable. Growth retardation was noted at 16 weeks of gestation and amniocentesis revealed a 15q deletion. Delivery at week 36 was unremarkable. Her birth weight was 1800 g, length 43 cm, and head circumference 29.5 cm. The Apgar score was 6 at 1 min and 10 at 5 min.

Clinical examination shortly after birth showed proportional intrauterine growth retardation with a Dubowitz score of 36 weeks. Facial dysmorphism was noted with hypertelorism, epicanthic folds, narrow, slanting palpebral fissures, and a short nose. Abnormal insertion of the toes were also noted. Neurological examination was normal for gestational age. Because she had difficulty feeding, she was placed in a nursery for handicapped children when she was several months old.

Examination at 8 months showed growth failure (body length four standard deviations less than average) and severe psychomotor retardation with no acquired milestones. She was not able to follow movements with her eyes. She showed marked hypertonia, with arching of the body. She was still being bottle fed. Craniofacial dysmorphic features (Fig. 1) were now accompanied by a pale complexion; her face was expressionless. Her hair was sparse and fine. She showed narrowing of the palpebral fissures, slight microphthalmia, strabismus, hypopigmentation of the irides, microcephaly (−5 SDS), metopic bulging, microretrognathia with a constantly opened mouth, and an arched palate. Her ears were large with thick helixes and prominent tragi and antitragi. Her nose was short, and broad at the base with narrow nostrils. She had no abnormalities of the trunk. Her hands and feet were edematous and the insertion of her third toe was abnormal bilaterally. Dermatoglyphics were unremarkable except for shortness of the flexion folds and of the thumb fold. There was no heart murmur, but frequent cyanosis of the extremities. The urogenital system was normal. Clonic seizures of the extremities and epileptic apnea were the main neurological manifestations. The electroencephalogram showed many bilateral slow and paroxysmal bursts, and a brain scan at 5 months revealed moderate cortical atrophy. At age 18 months, clinical examination showed no further development. Her dysmorphic facial features were accentuated. She did not show any psychomotor development. Her weight was still four standard deviations below average (−4 SDS); her height and head circumference being between −4 SDS and −5 SDS. The child died at age 2 years of severe respiratory illness. An autopsy was not performed.

Cytogenetic study

The abnormality detected in the amniotic cells was confirmed in two cultures of blood lymphocytes, in which an interstitial deletion of the long arm of chromosome 15 was demonstrated with GTG-, QFQ-, and RBG-bandings. The patient's karyotype can be written 46,XX del (15)(q22→q25) (Fig. 3A). Her

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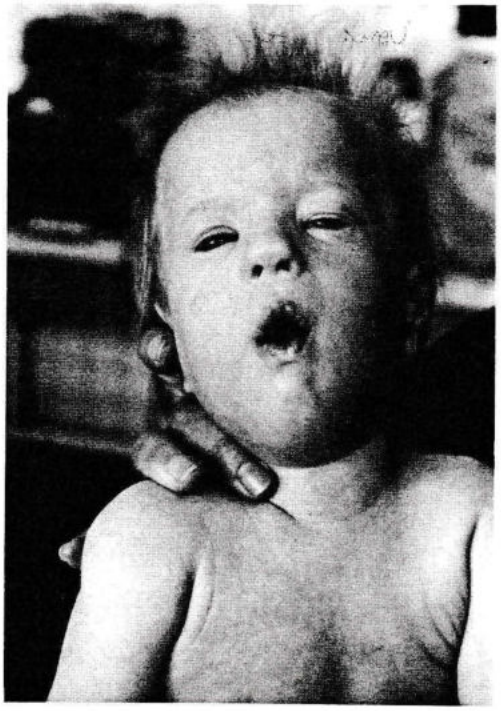

Fig. 1. Case 1, frontal view of the 8-month-old child with 15q−

parents and sister had normal karyotypes. We conclude that the patient had a de novo deletion.

Biochemical study

The specific Hex A assay with 4-methylumbelliceryl-β *N*-acetyl-glucosamine sulfate, electrophoresis, and chromatography on DEAE cellulose carried out on the serum, leukocytes, and lymphoblasts showed 40% Hex A in the patient (normal range, 70%–80%). This value corresponds to half of the normal level and is consistent with a hemizygous state due to the loss of one of the two strutural genes of Hex A. (Similar results were obtained in the laboratory of Dr. Kochl.)

Case 2

JB was born in 1983. She was the third child of a healthy unrelated couple, aged 31 (the mother) and 33 years (the father). Her two sisters, born in 1978 and 1980, were both in good health. The mother had had an early spontaneous abortion in 1985. The pedigree was otherwise unremarkable. The baby was delivered at term by Caesarian section because of fetal distress. She weighed 2950 g, with a head circumference of 34.5 and a length of 47 cm. The Apgar score was 2 at 1 min and 5 at 5 min. Respiratory distress required intensive care.

During the first few months of life, the baby fed poorly, requiring alimentation by nasogastric tube. At 7 months her length and weight were normal but she showed major psychomotor retardation and axial hypotonia. Facial dysmorphism (Fig. 2) included small, slanting palpebral fissures, moderate microphthalmia, and a coloboma of the left iris. The irides were hypopigmented. The bitemporal diameter was narrow. Her hair was fine and sparse, her hairline high on the forehead and clearing the temples. There was metopic bulging. Her mouth was open and triangular with microretrognathia; the palate was arched. Her ears were large with poorly defined

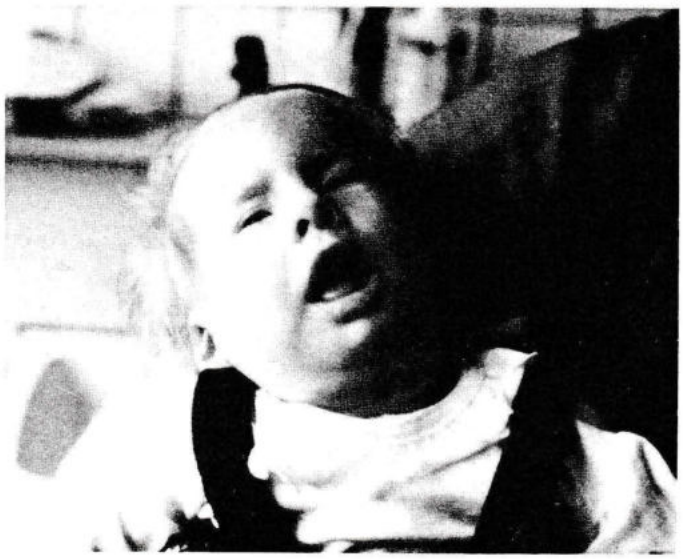

Fig. 2. Frontal view of case 2 showing facial features at age 8 months

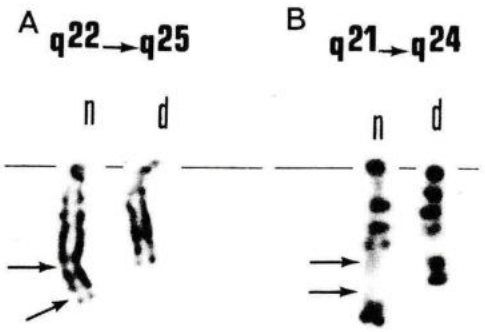

Fig. 3A, B. Cytogenetic analyses of the chromosomes 15. **A** Case 1 with breakpoints at q22–q25 (RBG-banding); **B** case 2 with breakpoints at q21→q24 (GTG-banding)

helixes. Hypotonia was marked by an expressionless face. The thorax and abdomen were normal; the extremities, edematous. Dermatoglyphics showed a single palmar crease bilaterally. There was clinodactyly and abnormal insertion of the toes. Study of the heart showed septal hypertrophy with dilatation of the aorta and the pulmonary artery. The EEG revealed a disorganized basal rhythm. Bilateral paresia of the diaphragm was noted. The child died rather suddenly at 8 months, probably because of respiratory distress. No autopsy was performed.

Cytogenetic study

Two lymphocyte cultures were performed. Cytogenetic study with GTG, QFQ, and RBG-bandings showed an interstitial deletion of 15q21–15q24 (Fig. 3B). The parents had normal karyotypes.

Discussion

Abnormalities involving chromosome 15 are very rare. They are usually partial trisomies (Lacro et al. 1984) and rings (Fryns et al. 1986). The published cases of interstitial deletions report various break points (Fryns et al. 1982; Oliver et

Table 1. Clinical features of two patients with partial deletion of chromosome 15

Patient	LD	JB
Age at last examination	16 months	8 months
Age of parents (father/mother)	28/26	33/31
De novo chromosomal abnormality	+	+
Delivery	Normal	Abnormal (placental hemorrhage)
Birth weight	1800 g (Intra-uterine growth retardation)	2950 g
Facial characteristics		
Pale complexion	+	+
Hypopigmentation of the iris	+	+ (bilateral)
Strabismus	+	−
Coloboma of the iris	−	+ (unilateral)
Microphthalmia	+	+
Hypertelorism	+	+
Epicanthus	+	+
Low, wide-set palpebral fissures	+	+
Narrow bitemporal diameter	−	+
Wide, short, small nose	+	+
Abnormalities of the ears	+	+
Metopic bulging	+	+
Microretrognathia	+	+
Arched palate	+	+
Fine, sparse hair	+	+
Abnormalities of the limbs		
Clinodactyly	−	+
Abnormal insertions of the toes	+	+
Edema	+	+
Neurological abnormalities		
Hypertonia	+	−
Axial hypotonia	+	+
EEG abnormalities	+	+
Abnormal brain scan	+	−
Convulsions	+	−
Cardiovascular abnormalities		
Cyanosis of the extremities	+	−
Cardiac malformation	−	+
Paresia of the diphragm	−	+
Developmental abnormalities		
Growth retardation	+	−
Psychomotor retardation	+	+
Feeding difficulties	+	+

al. 1978). We have found only one case of deletion of chromosome 15 with similar breakpoints (15q22–q24), in a child with Potter's syndrome who died 15 h after birth (Clark 1984). Besides Potter's syndrome (Type IIB), the baby showed growth retardation, cardiopathy, and joint abnormalities and therefore an apparently different phenotype from that of our patients.

Our two cases, in which the breakpoints were not exactly identical (case 1, q22–q25; case 2, q21–q24), presented rather similar facial dysmorphisms (Figs. 2, 3), the main signs of which were metopic bulging, narrow palpebral fissures with mongoloid slant, small nose with thick nostrils, and receding chin. In both cases the irides were pale, and the hair was very fine and sparse. Facial hypotonia, with open mouth, was similar in the two babies. Both had edema, slight malformations of the extremities, and respiratory problems. In Table 1 we summarize the different elements. In the gene map of chromosome 15, two genes have been localized to the region 15q21–15q25. The structural gene for hexosaminidase A was assigned to the long arm of 15 between q22 and qter by Chern et al. (1977). Then, on the basis of three patients with rearrangements of chromosome 15, Magenis et al. (1979) were able to exclude the regions pter–q14 and q25.1–q26.3. More recently, the HEX A gene was localized by in situ hybridization to 15q23–q24 (Nakai et al. 1987). In case 1, the assays revealed a decrease of HEX A compatible with the hemizygous state (this condition does not cause any symptoms in subjects heterozygous for Tay-Sachs disease). The PK_3 (PK_{M2}) structural gene was localized between 15q21 and 15qter by Kucherlapati and Ruddle (1975) and Van Heyningen et al. (1975) by somatic hybridization. This localization was confirmed by Hellkuhl et al. (1978) and Oliver et al. (1978). Our deleted cell line could help to pinpoint the PK3 gene locus on chromosome 15.

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