Severe mental retardation in a boy with partial trisomy 10q and partial monosomy 2q

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Summary. A severely mentally subnormal child with many physical stigmata was shown to have the karyotype 46,XY,-2,+der(2),t(2;10)(q31;q24)pat. Full evaluation of this patient's karyotype depended on the family studies. It was shown that a balanced translocation t(2;10) was present in 4 normal males in 3 generations.

New cytogenetic methods have greatly extended the scope for recognition of chromosome anomalies. In the event of a patient with an unbalanced chromosome rearrangement being born to a balanced translocation carrier parent, it is now possible to identify the duplication and deficiency segments of the chromosome involved. The clinical features of such a patient can then be compared with those of patients who have similar duplications and deficiencies to identify the common phenotypic abnormalities.

In our patient the long arms of both a chromosome No. 2 and No. 10 are involved in the translocation. Patients with unbalanced translocations involving the long arm of a No. 2 chromosome (Ricci *et al*, 1968; Lozzio and Karrison, 1969; Bijlsma *et al*, 1971; Francke, 1972; Forabosco *et al*, 1973) have been described. Unbalanced translocations involving a No. 10 chromosome appear to be more frequent (Francke, 1972; De Grouchy *et al*, 1972; Laurent *et al*, 1973; Talvik *et al*, 1973; Mulcahy *et al*, 1974; Roux *et al*, 1974; Yunis and Sanchez, 1974; Kroyer and Niebuhr, 1975), which is surprising since until recently the No. 10 chromosome could not be distinguished from other C group chromosomes with conventional staining methods.

Patients with unbalanced translocations and their relatives can also be informative for gene mapping.

Case history

The proband (III.1) was the first born of unrelated parents, after an uneventful pregnancy and spontaneous vertex delivery. The birthweight was 2.85 kg. Development was slow in all fields. From the age of 6 months he had epileptic seizures which were both *grand mal* and Jacksonian in type; his electroencephalogram showed generalized epileptic discharges but no localizing abnormalities. The seizures were partially controlled with phenytoin 50 mg b.d. At age 10, he could only walk with considerable support. He had no speech development and responded to loud sounds only, with no attempt at localization. His level of comprehension was assessed at around 4 months and his postural and manipulative development at 10 months. He was totally dependent on others for all basic needs. He was microcephalic (head circumference 48.5 cm) and he had an odd face (Fig. 1). The eyes were microphthalmic and deeply set with an antimongoloid slant to the palpebral fissures. There was an intermittent squint and bilateral ptosis. The optic fundi appeared normal. There was no nystagmus. There was a long philtrum to the upper lip, the nares were somewhat anteverted, the ears low set, and the palate was highly arched. The chest had a gross degree of pectus excavatum and bilateral cervical ribs were present. The penis was small, the scrotum normal, and there was no evidence of secondary sex characteristics. The upper limbs showed a cubitus valgus deformity and some wasting of muscles distal to the elbow. The hands showed ulnar deviation of the fingers, which were spindle shaped, with a degree of hypoplasia of the pulp of the distal phalanges. The thumbs were small and proximally placed. There were no fixed contractures of the fingers, but they adopted a flexed position (Fig. 2). The little fingers had two flexor creases. There was a radio-ulnar synostosis. In the legs there

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were no contractures of hips or knees, and both hips were in joint. The feet showed a valgus deformity, there were bilateral longitudinal plantar creases, and a wide gap between the hallux and second toes together with syndac-

FIG. 1. Facial view of the proband at age 11. Note the ptosis and microphthalmia.

tyly of the proximal two phalanges of the fourth and fifth toes bilaterally.

At the age of 11 years 5 months he died suddenly during an epileptic fit. At necropsy the following additional findings were noted. The cardiovascular system

FIG. 2. Hands of the proband showing radial deviation of the little fingers and ulnar deviation of the index and middle fingers.

was normal and the lungs showed only acute congestive changes. The liver, spleen, and kidneys were also normal as were the ureters and the bladder. The left testis was absent. On the right side there was a small cystic structure containing seminiferous tubules lined by mainly immature Sertoli cells, but a few spermatogonia were detected.

The brain was swollen and the cerebral hemispheres were small. There was conspicuous dilatation of the lateral ventricles and a reduction of central white matter consistent with the degree of hydrocephalus. The aqueduct was narrowed in the middle third but there was no occlusion. There were a number of other abnormalities (further details can be supplied on request) but histologically there was no evidence of a storage disorder. The pituitary was very small (0.2 g) and congested, but was histologically normal.

The dermatoglyphs of the proband and his family will be published separately.

Cytogenetic studies

Chromosome analysis was made on cells from a peripheral blood sample grown for 3 days by a modification of the method of Hungerford (1965). Initially the cells from the proband were examined after having been stained with aceto-orcin and one No. 2 chromosome appeared shorter than the other. G-banding by the ASG technique (Sumner *et al.*, 1971), confirmed that one No. 2 chromosome did not have the correct banding pattern on the long arm (Fig. 3a), but the exact origin of

FIG. 3. G-banded partial karyotypes from (a) the proband (III.1) and (b) the proband's father (II.2).

this anomaly was not immediately obvious. Chromosome analysis of the proband's parents revealed that his father had a balanced translocation, his karyotype was 46,XY,t(2;10)(q31;q24) (Fig. 3b) (Paris Conference, 1971). The mother's karyotype was normal 46,XX. Therefore, it was now possible to say that the proband's karyotype was 46,XY,-2,+der(2),t(2;10)(q31;q24)pat; he was trisomic for 10q24→10qter and was monosomic for 2q31→2qter.

Family studies

The pedigree is shown in Fig. 4. The proband's parents and all other members of the family were fully examined and were found to be entirely healthy. All the normal males in this family were found to carry the (2;10) translocation, whereas the females were normal 46,XX. No cytogenetic or necropsy studies could be performed on the abortuses.

Genetic marker studies

The genetic markers were studied by the M.R.C. Human Biochemical Genetics Unit. As the assignment

FIG. 4. Pedigree of family K316, MRC 3312, showing the cytogenetic findings in 8 family members and their MNS and ACP₁ status.

of ACP₁ and MNSs to chromosome 2 has been suggested (Mace *et al*, 1975) particular attention was paid to these markers, which are shown in Fig. 4.

Discussion

None of the patients with unbalanced translocations previously described is monosomic for a similar length of 2q, (2q31→2qter), and it is a little surprising that the patient survived the neonatal period since he was monosomic for a large segment of chromosome material. However, several patients with unbalanced translocations involving 10q are trisomic for a similar length (10q24→10qter), and a comparison of the phenotypic features has been made by Kroyer and Niebuhr (1975). The patient described by de Grouchy *et al* (1972), who was trisomic for 10q, was stillborn at term and no necropsy was permitted, so data are scanty. Her external appearance, however, was somewhat similar to the other cases listed. In most patients with this syndrome mental retardation is accompanied by a characteristic facies (particularly ptosis and microphthalmia), microcephaly, and widespread skeletal abnormalities (Table). The other chromosome involved in the translocation has varied widely (either 1, 3, 4, 13, 15, 18, or 22) and it is of interest that partial monosomy of these has not greatly influenced the gross clinical abnormalities. There is a need for more experience of such anomalies, identified either clinically or on the basis of a demonstrable trisomy of 10q. Partial trisomy 10 is clearly compatible with life and in the association of

TABLE

PHENOTYPIC FEATURES OF THOSE PATIENTS WITH PARTIAL 10q TRISOMY WHO SURVIVED EARLY INFANCY

Clinical Features*	Schutt (1966) (updated) 46XX,der(4),t(4;10)	Reference and other Cytogenetic Features						
		Francke (1972) 46XX,der(15),t(10;15)	Laurent <i>et al</i> (1973) 46XX,der(1),t(1;10)	Talvik <i>et al</i> (1973) 46XY,der(14),t(10;14)	Roux <i>et al</i> (1974) 46XY,der(22),t(10;22)	Yunis and Sanchez (1974) 46XY,der(15),t(10;15)	Kroyer and Niebuhr (1975) 46XX,der(18),t(10;18)	Present Case 46XY, der (2), t(2;10)
Age (alive/dead)	18 years (alive)	4 years (dead)	9 months (dead)	11 months (dead)	4 years (alive)	6 years (alive)	18 years (alive)	11 years (dead)
Microphthalmia	+	+	+	+	Not stated	+	+	+
Prosis	+	+	+	+	+	+	+	+
Micrognathia	+	+	+	+	+	+	+	+
Palatal abnormality	Cleft palate	Agnesis of palate	Cleft palate	High-arched palate	-	-	-	High-arched palate
Scoliosis	+	-	-	+	-	+	+	+
Other skeletal abnormality	+	-	Osteoporosis	+	-	+	+	+
Miscellaneous	Muscle hypotonia	-	Systolic murmur (no necropsy)	Patent foramen ovale	-	Renal and cardiac lesions, muscle hypotonia	-	Epilepsy

+ = Abnormality present. - = No abnormality present.
* All patients had severe mental and growth retardation, low set ears, a depressed nasal bridge and, with the exception of Francke's patient, microcephaly.

mental retardation, facial, and skeletal abnormalities, it has similarities to trisomy or partial trisomy 8 (Lejeune and Rethoré, 1973).

Our family provides further information on the mapping of chromosome 2. Since the patient, monosomic for part of 2q, is a heterozygote at the red cell acid phosphatase (ACP₁) and MNS loci, these loci cannot be in the chromosome region 2q31→2qter, substantiating previous reports (Mace *et al.*, 1975). The data, combined with linkage information from other families, have been presented elsewhere (Higgins *et al.*, 1975).

It is noteworthy that 4 normal males in this family carry the translocation and that the proband is also male; other families with partial trisomy 10q have had no preponderance of males. The future management of this family depends very much on the provision of facilities for antenatal diagnosis and if necessary on selective termination of pregnancy. Such measures are of special importance in families where partial trisomy 10q may arise, since patients with this chromosome abnormality have severe mental retardation plus physical deformities and may well survive into late childhood.

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