Sibs with tetrasomy 18p born to a mother with trisomy 18p

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SUMMARY We report a family with an 18p trisomic mother and two 18p tetrasomic daughters. The mother is phenotypically normal and healthy, but with an unusual type of trisomy 18p: 47,XX,del(18)(pter→p11.21),+i(18p) de novo. The older sister has microcephaly, mental retardation, an asymmetrical and peculiar face with low set ears, pinched up nose, high arched palate, small mouth, micrognathia, tapering fingers, asymmetrical length of legs, and an asthenic body. The younger sister was stillborn with extensive defects of the skull, congenital hydrocephalus, severe facial anomalies, and lumbosacral meningocele. Both daughters have inherited one normal chromosome 18 and an isochromosome 18p from their mother, and one normal chromosome 18 from their father. Although one quite similar family has been reported, to the best of our knowledge there have been no reports of families in which two daughters with tetrasomy 18p syndrome have been born to a mother with trisomy 18p with isochromosomes.

FIG 1 Case 1 showing the egg shaped face with pretty, delicate features at 27 months of age.

Based on a comparative analysis of 18 cases, Rivera *et al*¹ concluded that tetrasomy 18p constitutes a clinically and cytogenetically recognisable syndrome. Fryns *et al*² gave further support to the existence of such a clinical entity. We present a family in which two daughters with tetrasomy 18p were born to a mother with de novo trisomy 18p.

Case reports

Case 1, a 27 month old female, was born at 37 weeks' gestation, with a birth weight of 2045 g. She showed marked psychomotor retardation. Physical examination at this age showed height 81.5 cm (−1.76 SD), weight 9.0 kg (−2.33 SD), head circum-

ference 44.0 cm (−2.25 SD), and chest circumference 49.0 cm. She had microcephaly and her face was egg shaped with delicate, puppet-like features (fig 1). She had mild synophrys, long, curly eyelashes, anti-mongoloid slant, and bilateral internal strabismus. The ears were low set and the nose was pinched up. The mouth was rather small with a long philtrum, asymmetrical lips on crying, high arched palate, a shift of the uvula to the left, and relative micrognathia. She had clinodactyly of the fifth fingers bilaterally, tapering fingers, asymmetrical length of the legs, and muscular hypertonia.

Laboratory examinations showed a low level of serum IgA and low OKT4/OKT8 ratio. X ray examination indicated defects of the 12th ribs bilaterally and scoliosis, but intravenous pyelography did not disclose any abnormalities.

Case 2, her sister, was stillborn after emergency caesarian section because of massive bleeding at a gestational age of 29 weeks. Birth weight was 1010 g. At 20 weeks' gestation, chromosomal analysis of

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amniotic cells showed 47,XX,+i(18p). Immediately after birth, the following abnormalities were found: adhesion of the amnion to the fetal face with Simonart's bands, extensive defects of the skull, pronounced anomalies of the face, lumbosacral meningocele, and abnormal flexion of the lower extremities (fig 2).

FIG 2 Case 2. The stillborn neonate with Simonart's bands.

FAMILY HISTORY

The ages of the father and the mother at the birth of case 1 were 27 and 22 years, respectively. The father is normal and healthy with no family history of hereditary disease or mental retardation. Mental retardation was not evident in the mother. She is gravida 4 para 2, but the causes of her abortions are unclear. Her parents were also phenotypically normal.

CYTOGENETIC STUDIES

Cytogenetic analyses were performed using G, Q,

TABLE Clinical signs of tetrasomy 18p syndrome.

Clinical signs*	Rivera et al ¹	Fryns et al ²	Present case 1
Low birth weight	+	+	+
Failure to thrive	+	+	+
Early feeding difficulties	?	?	+
Delayed development	+	+	+
Mental retardation	+	+	+
Microcephaly	+	+	+
Facial asymmetry	?	+	+
Antimongoloid slant	?	-	+
Epicanthus	+	+	±
Small, pinched up nose	+	+	+
Small mouth	+	+	+
High arched palate	+	+	+
Micrognathia	+	+	+
Low set ears	+	+	+
Short neck	+	+	+
Slender, tapering fingers	?	?	+
Hypertonia	+	+	±
Hyperreflexia of deep tendons	+	+	±
Asthenic body habitus	+	+	+
Scoliosis	?	?	+
Others	Narrow shoulders and thorax	Asymmetrical lower limb length	

*Italics indicate features common to all cases.

FIG 3 C and G banded chromosomes of the mother and case 1. C banding showed one regular sized centromere in i(18p).

and C banding on peripheral blood lymphocytes and cultured skin fibroblasts. The karyotypes of both case 1 and case 2 were found to be 47,XX,+i(18p). The mother has one normal chromosome 18, one deleted chromosome 18, and an isochromosome 18p, so her karyotype is 47,XX,del(18)(pter→p11.21),+i(18p). The father and maternal grandparents had normal karyotypes. C banding showed normal sized centromeres on marker chromosomes of case 1 and the mother (fig 3).

Discussion

Lewis and John³ argued that a transverse break through the middle of such a centromere would produce telocentric chromosomes from each arm of a misdivided chromosome. Sometimes the centromere of such telocentrics are functionally complete, and so the resulting chromosome is stable. On the other hand, in such a telocentric chromosome the two chromatids may not separate after replication and so it becomes an isochromosome. Darlington⁴ also proposed that isochromosomes arise by misdivision of the centromere and this was supported in a review by de la Chapelle.⁵ Therefore, we believe that the most likely mechanism for the origin of trisomy 18p is a transverse break through the centromere of chromosome 18. Although isochromosomes have genetically identical arms, chromosomes morphologically similar to isochromosomes can arise through at least two other mechanisms. The first is a whole arm translocation and the second is unequal crossover within a pericentric inversion.⁶ Schmutz and Pino⁷ presented a case which could have arisen from either of these two mechanisms. Therefore, there is also a strong possibility that the deleted 18p and i(18p) in our cases may have originated from one of the above mentioned mechanisms.

Whatever mechanisms may be involved in the origin of the two abnormal chromosomes, case 1 and case 2 in our study are considered to have inherited one normal chromosome 18 and one i(18p) from their mother and one normal chromosome 18 from their father.

In 1984 Rivera *et al*¹ concluded that tetrasomy 18p actually constitutes a clinically and cytogenetically distinct syndrome based on the comparative analysis of 18 similar cases. The principal symptoms and signs are mental retardation, microcephaly, low set

ears, high arched palate, asthenic body habitus, and increased deep tendon reflexes. Such cases also present the following characteristic clinical picture: asymmetrical and delicate face with pinched up nose, small mouth, micrognathia, narrow shoulders and thorax, scoliosis, tapering fingers, frequent absence of distal flexion creases of the fingers, asymmetrical length of legs, and muscular hypertonia. A comparison of the clinical features of cases reported by Rivera *et al*,¹ Fryns *et al*,² and our case 1 is shown in the table. Features found in common in these cases, (low birth weight, feeding difficulties, delayed psychomotor development, mental retardation, microcephaly, small, pinched up nose, small mouth, high arched palate, micrognathia, low set ears, short neck, and asthenic body habitus) are italicised.

Only Taylor *et al*⁸ have reported a family resembling that described here, in which the mother was trisomic for 18p and one daughter was tetrasomic and the other monosomic for this chromosomal region. Therefore this family is probably the first in which two tetrasomic daughters were born to a mother with de novo trisomy 18p involving isochromosomes.

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