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SHORT COMMUNICATION

MATERNAL UNIPARENTAL DISOMY FOR CHROMOSOME 22 IN A CHILD WITH GENERALIZED MOSAICISM FOR TRISOMY 22

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SUMMARY

We report on a case of generalized mosaicism for trisomy 22. At chorionic villus sampling (CVS) in the 37th week of pregnancy, a 47,XX,+22 karyotype was detected in all cells. The indication for CVS was severe unexplained symmetrical intrauterine growth retardation (IUGR) and a ventricular septal defect (VSD) was noted. In cultured cells from amniotic fluid taken simultaneously, only two out of ten clones were trisomic. At term, a growth-retarded girl with mild dysmorphic features was born. Lymphocytes showed a normal 46,XX[50] karyotype; both chromosomes 22 were maternal in origin (maternal uniparental disomy). Investigation of the placenta post-delivery using fluorescence *in situ* hybridization showed a low presence of trisomy 22 cells in only one out of 14 biopsies. In cultured fibroblasts of skin tissue, a mosaic 47,XX,+22[7]/46,XX[25] was observed. Clinical follow-up is given up to 19 months.

KEY WORDS: trisomy 22; uniparental disomy; chromosomal mosaicism

INTRODUCTION

The detection of a (mosaic) trisomy in routine cytogenetic analysis of chorionic villus sampling (CVS) can be a diagnostic problem. In 1–2 per cent of the analysed cases, disparity occurs between the prenatally investigated cytotrophoblast cells and the chromosomal constitution of the fetus (Leschot *et al.*, 1989), which makes counselling difficult. In a case of trisomy, mosaicism might be explained by post-zygotic non-disjunction limited to the cytotrophoblast (Crane and Cheung, 1988), but most cases probably originate as trisomic conceptuses, followed by the loss of the extra chromosome (Stengel-Rutkowsky *et al.*, 1990). In this respect, the term 'trisomic zygote rescue' is used, for some initially aneuploid pregnancies may survive due to the presence of a normally diploid cell line. When the loss of the extra chromosome affects the embryonic progenitor cells and a diploid fetus occurs, there is a theoretical 1 in 3 chance that this may result in uniparental disomy (UPD) (Hall, 1990). In cases of UPD, an abnormal phenotype may occur if the chromosomes involved carry imprinted genes. Another as yet unresolved matter is whether confined placental mosaicism (CPM) interferes with normal fetal growth.

Here we describe a case of trisomy 22 detected after CVS at 37 weeks of pregnancy, performed because of IUGR, followed by further prenatal

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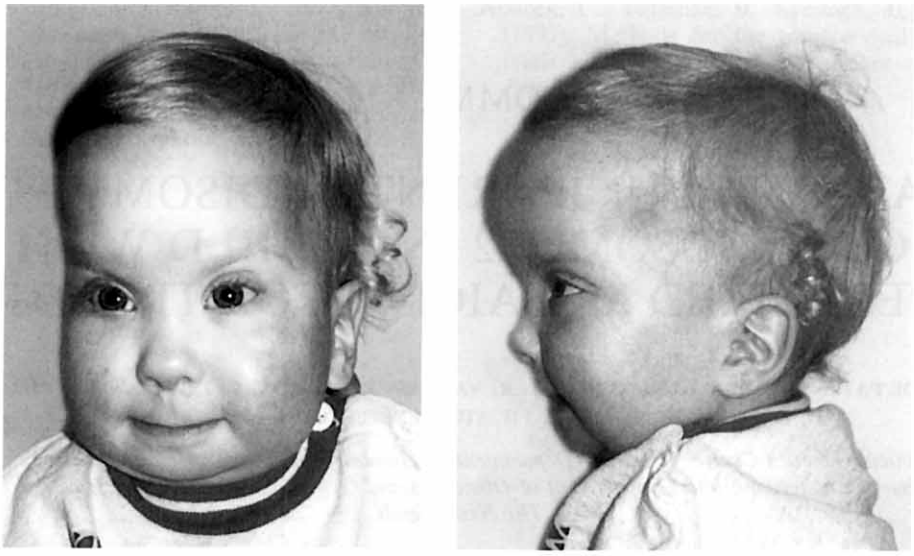

Fig. 1—Patient at the age of 19 months, frontal and side view. Note the frontal bossing, upslanted palpebral fissures, micrognathia, and low-set ears

and postnatal investigations. This case has been mentioned briefly in an earlier report (Schuring-Blom *et al.*, 1994, case 8).

CASE REPORT

Transabdominal CVS and simultaneous amniocentesis were performed in a 34-year-old woman (gravida 3, para 1) at 37 weeks of pregnancy, because of unexplained IUGR noted at 34 weeks of pregnancy. With ultrasound investigation, severe symmetrical growth retardation ($\ll$p2.3) was observed with normal Doppler flow measurements in the umbilical artery and a normal amount of amniotic fluid, in combination with a ventricular septal defect (VSD). There was no family history of mental retardation, congenital malformation, or hereditary disease. The parents were not consanguineous.

Spontaneous labour began at 39·6 weeks of gestation and a girl weighing 1625 g (<p2.3 according to Kloosterman, 1970) was delivered without complications. Apgar scores were 7 and 9 at 1 and 5 min, respectively. Clinical examination directly after birth revealed various dysmorphic features, such as epicanthal folds, upslanted palpebral fissures, proptosis, a broad nasal bridge, a short nose, a long and smooth philtrum, a small mouth, low-set ears with a preauricular pit at both sides, micrognathia, a simian crease, clinodactyly of the fifth fingers and hypoplastic nails, a cardiac souffle, and a sacral dimple. Additional investigations revealed a perimembranous VSD, which was successfully operated on at the age of 5 months, and she was finally discharged from hospital. Clinical follow-up studies at the age of 6, 12, and 19 months (Fig. 1) revealed growth retardation (all measures at 19 months still below p3), delayed motor development, and hypotonia. The dysmorphic features are summarized in Table I.

MATERIALS AND METHODS

Cytogenetic analysis was performed on cytotrophoblast cells of the chorionic villi and on cultured amniocytes using standard techniques. Cord blood was sampled for cytogenetic analysis of lymphocytes after birth. Conventional cytogenetic analysis and fluorescence *in situ* hybridization (FISH) using a paint for chromosome 22 (Cambio) were performed. From the placenta (355 g), 14 random biopsies were taken of *ca.* 30 mg each. From each biopsy, slides were made from a cell suspension consisting mainly of cells from the cytotrophoblast (Schuring-Blom *et al.*, 1993) and FISH was carried out on interphase nuclei. For the detection of chromosome 22, a centromere-specific probe, p14.1 (Archidiacono

Table I—Clinical findings in the present case compared with full trisomy 22 and with cases of mosaic trisomy 22

	Full trisomy 22* (n=28, perc.)	Mosaic trisomy 22† (pos./total number)	Present case
Severe IUGR	100	3/3	+
Growth retardation	100	1/1	+
Mental retardation	100	1/1	+
Hypotonia	50	2/2	+
Microcephaly	61		+
Frontal bossing	29	1/1	+
Hypertelorism	57	1/1	+
Epicanthus	39		+
Broad nasal bridge	50		+
Long philtrum	25		+
Ear anomalies	100	3/3	+
Micrognathia	86	1/1	+
Cleft lip/palate	68		−
Short webbed neck	43		−
Congenital heart disease	79	1/2	+
Renal malformations	54	1/2	−
Genital hypoplasia	57	3/3	−
Hypoplastic nails	43	1/1	+
Transverse palmar crease	18		+

*Based on Fahmi *et al.* (1994).
†Based on Pagon *et al.* (1979) and Schinzel (1981).

et al., 1995), was used. For each biopsy, 100–200 nuclei were counted.

Fibroblasts of the skin biopsy, taken at cardiac surgery, were cultured and used for standard cytogenetic analysis. Molecular investigations were performed on umbilical cord blood of the proband and peripheral blood from both parents using standard methods. The primers for microsatellite loci used for haplotyping the proband and her parents are listed in Table II. To confirm paternity, microsatellite markers from chromosome 15 were used, also listed in the table.

RESULTS

Table III shows the results of the prenatal and postnatal cytogenetic investigations. A 47,XX,+22[12] karyotype was found at CVS. In amniocytes, the trisomy 22 cell line was also detected in addition to a normal cell line (8/10 clones normally diploid). Only normal 46,XX[50] metaphases could be detected in lymphocytes. FISH on interphase nuclei (n=50) with a paint for chromosome 22 gave a similar result.

In the 14 random placental biopsies investigated with interphase FISH, trisomy 22 cells were present in only one of the biopsies in a low percentage of about 20 per cent, thus showing a considerable difference with the results of the CVS at 37 weeks of pregnancy.

Fibroblasts from the skin tissue analysed cytogenetically showed a 47,XX,+22[7]/46,XX[25] karyotype.

With molecular investigations, two of the five chromosome 22 markers were informative and no inheritance of paternal alleles could be found (Table II). The CYP2D and IL2RB loci displayed a uniparental maternal heterodisomy. The chromosome 15 markers showed a normal segregation of paternal alleles.

DISCUSSION

The patient in this study was shown to have generalized mosaicism for trisomy 22, detected only after the analysis of skin tissue. Recently Henderson *et al.* (1996) also stressed the importance of analysing various tissues in such cases.

Table II—Results of the PCR analysis of microsatellite loci in the proband and her parents. A box indicates an informative allele constellation for chromosome 22

Locus	Probe	Location	Allele		
			Proband	Father	Mother
D22S257	MFD51	22q11	12	22	12
D22S156	MFD33	22q11.2	23	12	23
D22S258	MFD162	22q11.2	12	13	12
IL-2RB	PCR	22q11.2–q12	24	13	24
CYP2D	PCR	22q13	13	24	13
GABRB3	PCR	15q12	23	12	33
ACTC	PCR	15q13–q21	12	11	22
D15S108	MFD102	15q13–q22.2	12	11	22

Table III—Cytogenetic and FISH results of the present case

	GTG (no. of cells)		FISH (percentage)	
	Disomy	Trisomy	Disomy	Trisomy
Chorionic villi (cytotrophoblast)	0	12	nd	nd
Amniotic fluid	8	2	nd	nd
Lymphocytes	50	0	100*	0
Fibroblasts	25	7	nd	nd
Placenta:				
Biopsy 1–13	nd	nd	85·4–93†	0–7·6
Biopsy 14	nd	nd	75	19·7

*Paint 22 (Cambio).
†Probe p14.1 (Archidiacono *et al.*, 1995).
nd=not done.

The clinical features are in accordance with other reported cases of (mosaic) trisomy 22 (Table I). The extra chromosome 22 is apparently of maternal origin. In order to illustrate how careful one should be in drawing conclusions from cytogenetic and/or molecular cytogenetic investigations, the results of the various tests and the consequent conclusions are discussed in their successive order.

The prenatal results and the normal outcome in lymphocytes, combined with the results of the DNA investigations (maternal UPD), seemed to suggest that for this particular patient the growth retardation and clinical features might have been caused by the presence of trisomy 22 in the placenta, or by UPD for chromosome 22, or by a combination of both. Kalousek and Dill (1983) reported on an infant with IUGR and mosaic trisomy 22 confined to the placenta, suggesting a correlation between CPM and IUGR. Supporting this view, Stioui *et al.* (1989) described in more detail a similar case, with full trisomy 22 present in the placenta after birth at four sampled sites. In our case, although a 47,XX,+22 karyotype was found prenatally at CVS, only one out of 14 placental biopsies showed a trisomy 22 to be present in 20 per cent of the cells. Clinical examinations of our patient were highly suggestive of a (mosaic) trisomy 22, so we felt it necessary to investigate additional tissue(s). Moreover, Palmer *et al.* (1980), Kirkels *et al.* (1980), and more recently Schinzel *et al.* (1994) concluded that transmission of a t(22q;22q) resulting in UPD of

maternal origin seemed to have no adverse impact on the phenotype. Fibroblasts of the patient's skin tissue gave proof of the presence of a trisomy 22 cell line in addition to a normal cell line.

We compared the clinical data with the abnormalities as described for (mosaic) trisomy 22 (Table I): cases of mosaic trisomy 22 as described by Pagon *et al.* (1979) and Schinzel (1981), and cases of possibly full trisomy 22 as reviewed by Fahmi *et al.* (1994). In their report, Fahmi *et al.* gave the frequency of various features in 27 patients with trisomy 22. To the figures we added the case mentioned in their report, resulting in a slight change of some frequencies. It seems justified to conclude that the clinical findings in the case presented here are caused by the presence of the trisomic cells, rather than by UPD of maternal origin.

The aberrant cell line found at CVS proved to be present as a mosaic in the placenta, as well as in amniocytes and fibroblasts. In lymphocytes only a diploid cell line could be detected, showing heterodisomy of maternal origin for at least two markers. Three other markers were not informative but do not contradict the concept of maternal heterodisomy either. Therefore we think that the most obvious scenario in this case is to assume a trisomic conceptus, followed by the loss of one of the three chromosomes 22. We think that this case might be an example of 'trisomic rescue', which might also be a possible explanation for the three cases described by Palmer *et al.* (1980), Kirkels *et al.* (1980), and Schinzel *et al.* (1994) in which only lymphocytes were investigated. In the patient presented here, loss of one of the chromosomes 22 must have occurred post-zygotically, but at such an early stage that mosaicism could be found in the embryo as well as in extraembryonic tissues, resulting in generalized mosaicism.

It is worth noting that we were directed by the results of the prenatal investigations towards a search for the possible presence of UPD or trisomy 22. Otherwise a correct diagnosis for this patient would have been unlikely.

In cases of unexplained IUGR or an extremely low birth weight, particularly in combination with dysmorphic features, it is advisable to (also) investigate extraembryonic tissue, for this may show the way in making a definitive diagnosis.

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