

DiGeorge Syndrome in a Child with Partial Monosomy of Chromosome 22

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ABSTRACT

A girl with severe neonatal hypocalcaemia, thymic hypoplasia, congenital heart disease and mental retardation in combination with a partial monosomy of chromosome 22, del(22)(pter-q11.3), is reported. Nine other patients with an association between partial monosomy 22 and a DiGeorge syndrome have been reported earlier, and this combination probably constitutes a deletion syndrome similar to the Prader-Willi and the aniridia-Wilms' tumour syndromes. However, the deletion of chromosome 22 is mostly due to a translocation, with trisomy for another chromosomal segment. Such a mechanism may explain the different clinical features seen in patients with partial monosomy 22. In the present case there was an unbalanced translocation with a probable trisomy of the short arm of chromosome 20 combined with the partial monosomy 22. Cytogenetic investigation with high resolution banding techniques is indicated in patients with thymic aplasia and suspected DiGeorge syndrome.

INTRODUCTION

DiGeorge syndrome is characterized by thymic hypoplasia, aplasia or hypoplasia of the parathyroids, congenital heart disease and dysplastic features. Most of these patients are severely ill during the neonatal period as a result of the hypocalcaemia. Later in life patients with DiGeorge syndrome have a proneness for infections (Lischner 1968, Conley et al. 1979).

The etiology of the DiGeorge syndrome is unknown, but it has been considered to be a developmental abnormality of the pharyngeal pouches (Robinson 1975). During the last years there have been reports of an association between partial monosomy of chromosome 22 and the DiGeorge syndrome (De la Chapelle et al. 1981, Kelley et al. 1982, Greenberg et al. 1984, Bowen et al. 1986, Augusseau et al. 1986). The present report describes a patient with DiGeorge syndrome and partial monosomy of the proximal long arm of chromosome 22.



Fig. 1. Frontal and lateral view of the present patient at the age of 4 months.

CASE REPORT

The patient, a girl now 3.5 years old, is the third child of a 35 years old woman. Two siblings, born by the mother in a previous marriage, were healthy, as also was the father of the patient. The mother had previously had one legal and one spontaneous abortion. In the mother's family there was a history of congenital heart malformations and cleft palate. Before the present pregnancy the mother had had transient hyperthyroidism, which was not treated. In early pregnancy the mother was treated with gestagen (Primolut-Nor^R, Shering AG) and bromocriptin (Pravidel^R, Sandoz) for a short period. At 28 weeks of gestation she had slight glucosuria, which was controlled by dietary restriction.

The girl was born in a normal delivery after 38 weeks of gestation. Her birth weight was 3.570 kg and length 0.5 m. At the age of 10 hours she exhibited tachypnoea and muscular hypertonus and was admitted to the local department of paediatrics. The following features were noted (Fig. 1): micrognathia, low- set dysplastic ears, hypertelorism and a mongoloid slant of the eyes, a long philtrum, an umbilical hernia, bilateral inguinal hernia and a sacral haemangioma. The child was given antibiotic treatment due to of suspected septicaemia and also phenobarbital for hypertonus and irritability. At 13 days of age her condition deteriorated with cyanotic spells and apnoea. Heart disease was suspected and she was referred to the Department of Paediatrics at the University Hospital of Uppsala. Physical examination revealed signs of pulmonary hypertension and at subsequent two-dimensional echocardiography persistent ductus arteriosus was diagnosed. This was later verified at heart catheterisation and ligated at the age of one year.

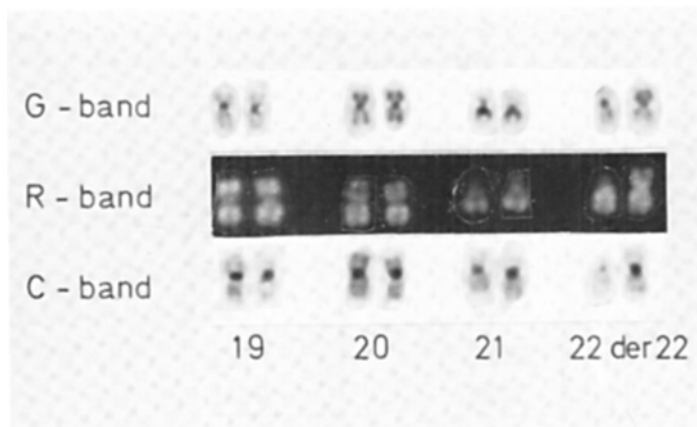


Fig. 2. G-, R- and C-banded chromosomes 19, 20, 21 and 22 of present patient with a partial DiGeorge syndrome.

In the neonatal period hyperphosphataemia and severe hypocalcaemia were observed. The serum calcium level was 0.99 mmol/l and serum albumin 30 g/l. The parathyroid hormone level in the serum was 0.27 arbitrary units (lower limit 0.4 arbitrary units). Since the hypocalcaemia did not respond to intravenous administration of calcium, treatment with 1,25-dihydroxycholecalciferol (Rocaltrol^R, Roche) was started. Initially, 0.25 ug was given daily, but this had no effect and the dose was increased to 0.75 ug daily. With this dose the serum calcium level was restored to normal. Since there were difficulties in administering capsules of 1,25-dihydroxycholecalciferol, a solution of the compound (1 ug/ml) was prepared. After treatment for one month the daily dose could be reduced to 0.50 ug. During the treatment no episode of hypercalcaemia was noted. The drug was temporarily discontinued at the age of one year, but was re-instituted because of recurrence of hypocalcaemia.

The mother showed no sign of hyperparathyroidism and was found to be normocalcaemic at repeated tests.

Lymphocyte function tests were performed in the child and a low response occurred to stimulation with *Branhamella catarrhalis*. Other stimulation tests were normal. In the peripheral blood some 12% of the white cells were atypical, with multilobulated nuclei.

The child's psychomotor development was retarded and she showed marked failure to thrive. At the age of four months she displayed little attempt at social contact and was hypertonic with reduced spontaneous movements. At the age of one year and two months she was still being partly fed through a gastric tube. She was not able to sit without support, grab objects, or turn from side to side and her speech development was extremely poor.

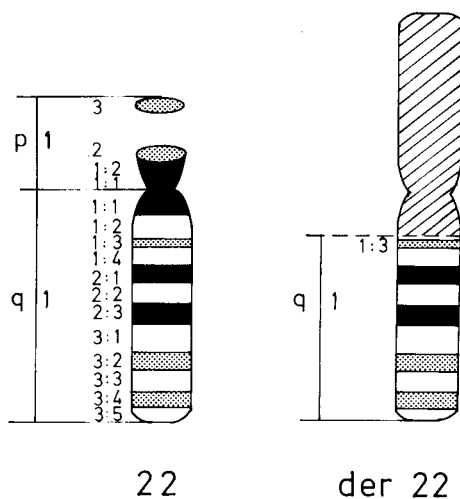


Fig. 3. Diagram of the patient's chromosomes 22, illustrating the breakpoints and the extra segment proximal to 22q11.3 of the derivative chromosome 22.

CYTOGENETIC INVESTIGATION

Chromosome preparations were made from peripheral blood cultures by standard methods. Q-banding (Caspersson et al. 1970), R-banding (Priour ey al. 1973), G-banding (Borsgård et al. 1974), High-resolution G-banding (Yunis & Lewandowski 1983) and C-banding (Chen & Ruddle 1971) revealed an abnormal chromosome 22 in cultured blood cells from the patient. Both parents had normal karyotypes. The derivative chromosome 22 of the patient (Figs. 2 and 3) had a normal q arm distal to band q11.3, but the p arm and proximal q arm (pter-q11.3) were deleted and an extra unidentifiable chromosome segment was translocated to 22q11.3. The C-banding showed an intensive staining constitutive heterochromatin of the centromeric region of the abnormal chromosome 22 (Fig. 2). From this finding one might draw the conclusion that the centromeric region does not come from an acrocentric chromosome, which usually has less intensive staining constitutive heterochromatin. The short arm of the abnormal chromosome 22 has a size similar to the short arms of the chromosome 19 and 20. After G- and R-banding the abnormal chromosome 22 showed a pattern similar to chromosome 20. Trisomy for the short arm of chromosome 20 gives rise to very variable phenotypical abnormalities and most patients appear to be normal at birth (Francke 1977). It could thus be reasonable to assume that the unidentifiable extra segment of the abnormal chromosome 22 constitutes the short arm and the centromeric region of chromosome 20. The patient thus could have a trisomy 20p apart from the partial monosomy 22 and have the karyotype 46,XX,-22,+der(22)t(20;22)(pter-q11;q11-qter).

Table 1. Clinical features of previous and present cases of the DiGeorge syndrome and with deletion of chromosome 22. + feature present, - feature not present.

	de la Chapelle et al. 1981				Kelley et al. 1982			Greenberg et al. 1984	Present case
	F	M	F	M	F	M	M	M	F
Sex									
Early death	3w	9h	7w	4w	6m	9m	10d	Alive 13m	Alive 14m
Hypo (+)/Aplasia Thymus	+	+	+	+	(+)	+	(+)	(+)	(+)
Congenital heart defect	+	+	+	+	+	+	+	+	+
Parathyroid hypoplasia	?	+	+	?		+	+	?	+
Hypocalcemia					+			+	+
Seizures						+			+
Cleft lip	+	-	+	+	-	+	-	-	-
Micrognathia					-	-	+	+	+
Small dysplastic ears	+	-	+	-	-	+	+	-	+
Hypertelorism						+		+	+
Antimongoloid slant								+	+
Broad philtrum								•	+
Failure to thrive									+
Mental retardation							+	-	+
Cysts of the kidneys	-	+	+	+		-	+	?	-

DISCUSSION

During recent years banding techniques have made it possible to delineate syndromes with deletions of small chromosomal segments. The most wellknown are the associations between the Prader-Willi syndrome and a deleted chromosome 15q (Ledbetter et al. 1981), retinoblastoma and a deleted chromosome 13q (Francke 1976), and the aniridia-Wilms' tumour syndrome and a deleted chromosome 11p (Riccardi et al. 1978).

The clinical and laboratory findings in our patient fit with the DiGeorge syndrome. Her disorders might be caused by a mixed chromosomal abnormality - monosomy of proximal 22q11 and trisomy of an extra, unidentifiable chromosomal segment. The girl shows a very similar clinical disorder compared to other patients with DiGeorge syndrome and a monosomy 22q, but without other chromosomal abnormalities involved (De la Chapelle et al. 1981, Kelley et al. 1982, Greenberg et al. 1984). The extra trisomic segment seems thus to contribute only marginally to the phenotypical features in the patient. This increases the probability that she has a trisomy 20p, since minor phenotypical abnormalities are reported in patients with trisomy 20p (Francke 1977). In other cases the deletion of chromosome 22 has been combined with a chromosomal aberration, which gives rise to most of the phenotypical abnormalities in

the patients. Bowen et al. (1986) reported an infant with thymic deficiency and deletion of chromosome 22, but otherwise a clinical picture typical of trisomy 18. This was due to an unbalanced $t(18;22)(q12.2;p11.2)$ pat rearrangement, resulting in a partial deletion of chromosome 22 and trisomy of chromosome 18.

Rosenthal et al. (1972) reported on a patient with monosomy 22 and thymic aplasia, but otherwise no clinical features typical of DiGeorge syndrome and Augusseau et al. (1986) reported a case with partial DiGeorge syndrome and a balanced translocation $t(2;22)(q14.1;q11.1)$. The association between partial monosomy 22 and DiGeorge syndrome was first pointed out in 1981 by de la Chapelle and co-workers. They postulated that the critical segment for DiGeorge syndrome is 22q11. So far nine patients with DiGeorge syndrome and deletion of chromosome 22 have been reported (Table 1) by de la Chapelle et al. (1981), Kelley et al. (1982), Greenberg et al. (1984) and present case. Seven patients had a complete form of the syndrome and died early (De la Chapelle et al. 1981, Kelley et al. 1982), and in four of these fatal cases cleft lip and cysts of the kidneys, malformations not typical for DiGeorge syndrome, were reported. Our patient and the patient of Greenberg et al. (1984) also had one feature (a broad philtrum) which is not typical of the DiGeorge syndrome, but otherwise showed a very similar clinical picture, exhibiting most of the features typical of the latter syndrome. It seems reasonable to assume that in the DiGeorge syndrome in many cases the basic defect is a small deletion of chromosome 22. Cytogenetic investigation with a high-resolution banding technique is therefore recommended in patients with congenital hypo/aplasia of the thymic gland. In the future, when there is more available DNA probes from this region, very small submicroscopical deletions will probably be detected in patients with normal karyotypes and DiGeorge syndrome.

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