Incomplete trisomy 22 III. Mosaic-trisomy 22 and the problem of full trisomy 22

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Incomplete Trisomy 22

III. Mosaic-Trisomy 22 and the Problem of Full Trisomy 22

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Summary. A severely growth-retarded female newborn is described, who died a few hours after birth. About half of the clones and metaphases from an amniotic fluid cell culture (set up at the 35th week of gestation) and only 1/27 of the metaphases from a blood lymphocyte culture contained an additional No. 22 chromosome. Abnormal findings in the patient included a complex congenital heart defect, membranous anal atresia without fistula, distal limb hypoplasia, partial cutaneous syndactyly between second and third toes, and a left preauricular pit. On the basis of this case and other reports from the literature arguments for and against the existence of full human trisomy 22 are discussed. The conclusion seems likely, that full trisomy 22 usually presents a lethal condition in man, though at present an occasional survival cannot be excluded.

Introduction

In a series of papers on different types of incomplete trisomy 22, the question whether full trisomy 22 is compatible with life in man or not is discussed on the basis of cases from the literature and a new observation.

Case Report

Mother and father of the patient were 45 and 48 years old at her birth. The first pregnancy, nine years before the proposita's birth, terminated in birth of a stillborn at 38 weeks who weighed 2070 g and measured 47 cm in length; the second pregnancy, one year later, resulted in the delivery of a healthy male weighing 3110 g.

The gestation with the proband was complicated by thrombosis of the right leg during the first trimester. From the 32nd week, retarded fetal and uterine growth and repeated low estriol excretion (2.1–4.7 mg/24 h) and human placental lactogen (HPL) blood levels (1.5–2.6 mcg/ml) were found, and CTG at 34 weeks revealed late deceleration. At repeated ultrasound examinations the biparietal diameter was found to be subnormal (below 10th percentile). During the 36th week of gestation, cesarean section was performed because of persisting severe placental insufficiency. At that time, the uterine size corresponded to a gestional age of 30 weeks. Apgar was 4.5, and 5 after 1.5, and 10 min, respectively; the female newborn received immediate intensive care including artificial respiration. The placenta was "very small".

Clinical Examination at Birth (Fig. 1a, b). The patient was severely underweight for gestational age, hypotonic, and in respiratory distress, and revealed multiple anomalies. Measurements were: weight 1230 g, length 37.5 cm, and head circumference 27.3 cm (all far below the 3rd percentile). *Facies:* aspect of hypertelorism (canthal distances not measured), prominent nasal bridge, receding mandible, low-set and poorly formed auricles with a left preauricular pit. *Trunk:* signs of a congenital heart defect (3/6 systolic murmur, on chest films a dilated heart with diminished lung vascularity); hypoplastic labia majora, anal atresia without visible fistula. *Limbs:* tapering fingers (Fig. 2a, b) with severely hypoplastic nails, especially on the right side, clinodactyly of little fingers, hypoplasia of both thumbs; partial cutaneous syndactyly between second and third toes, severely hypoplastic toenails. She was hypotonic and jittering, but grasping, Moro and glabellar reflexes were normal positive.

Course. Following cardiac catheterization the child was extubated and suddenly died from cardiovascular failure at the age of 10 h.

Chest Radiographs. Bilaterally enlarged heart, normal osseous structures, 12 ribs.

Autopsy revealed a complex congenital heart defect (V.S.D., A.S.D., hypoplasia of the right ventricle, tricuspidal atresia, retro-esophageal position of the left subclavian artery) and membraneous anal atresia.

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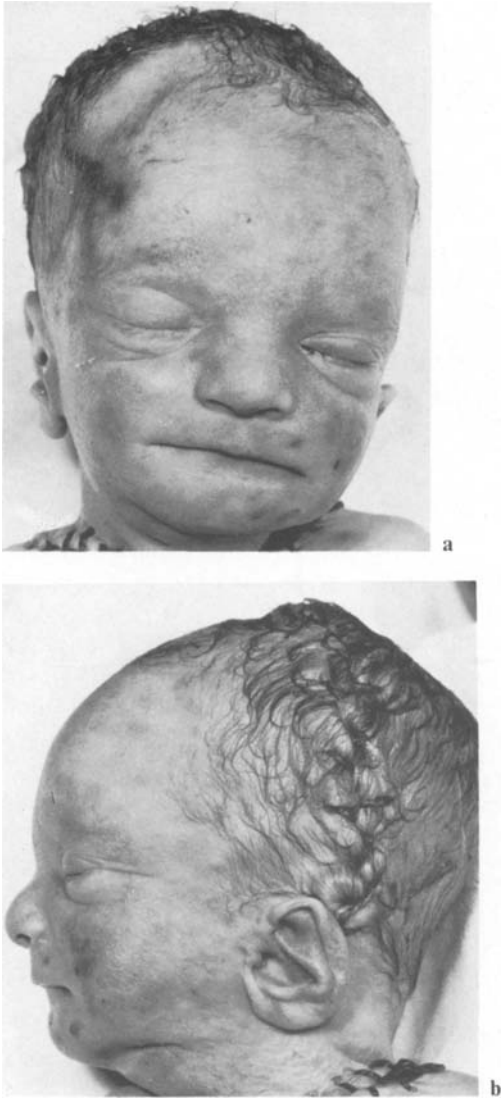

Fig. 1. Head of the patient, post mortem. Note high forehead, broad nasal bridge, small mandible, low-set and poorly shaped left ear with a preauricular pit

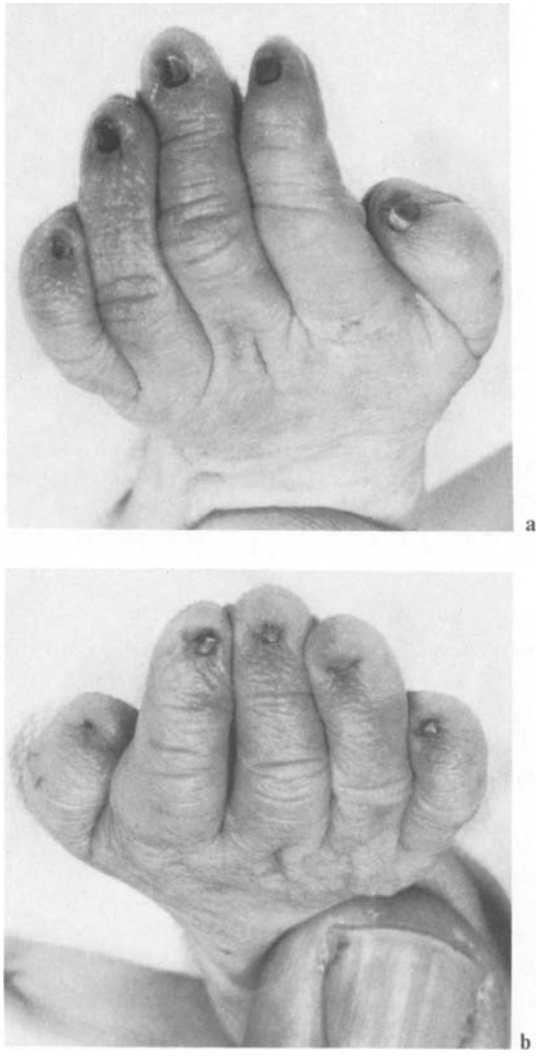

Fig. 2a, b. Both hands of the patient, post mortem. Note hypoplastic thumbs, clinodactyly of little fingers, and hypoplasia of nails, especially on the right side

Cytogenetic Investigations

Four days before the birth of the patient, an amniotic fluid sample, obtained at the occasion of puncture for lung maturation testing, was referred for cytogenetic analysis (indication: to avoid primary cesarean section in case of a non-viable chromosome aberration). However, section was performed before the result was obtained. After birth, a blood sample was also obtained for karyotype determination.

Amniotic cell culture and preparations were performed according to the method of Schmid (1975). Nine cell clones were analysed in situ. Eight metaphases from five clones had a normal 46,XX chromosome complement while seven metaphases from four clones had a 47,XX,+22 karyotype (G-banding). In addition, two metaphases lying with no obvious connection to a clone also had an additional No. 22 chromosome. A

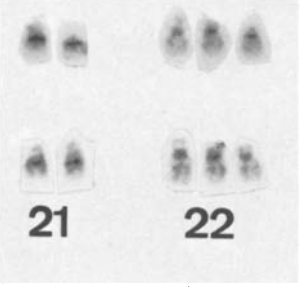

Fig. 3. Chromosomes 21 and 22 from two G-banded metaphases from an amniotic fluid cell culture of the patient. Note three Nos. 22

Table 1. Selected findings of the patient of the present report compared to another patient with mosaic-trisomy 22 (Pagon et al. 1979), three patients with possible full trisomy 22 (Pérez-Castillo et al. 1975; Cervenka et al. 1977; Iselius and Faxelius 1978), and the occurrence of these findings in patients trisomic for the proximal and distal segment of 22q

	Present patient	Pagon	Pérez-Castillo	Cervenka	Iselius	Common to partial trisomy of segments of 22q	
						prox-imal	distal
Maternal age at birth	45	37	38	26	30		
Paternal age at birth	48	48	38	30	31		
Trisomic cells in blood lymphocyte culture	1/27	0/100	all	all 77	all		
Trisomic cells in skin or amniotic fluid cells	9/17	33/33	?	?	?		
Severe prenatal growth retardation	+	+	+	(+)	+	−	+
Hydrocephalus	−	−	+	−	−	−	+
Downslanting palpabral fissures	−	+	+	+	−	+	−
Ocular coloboma	−	−	−	+	−	+	−
Preauricular malformation	+	+	+	+	−	+	−
Congenital heart defect	+	−	+	−	+	+	+
Mesenterium commune and/or malrotation	−	+	−	?	+	+	?
Renal malformation	−	+	+	?	+	+	+
Anal atresia	+	−	−	−	+	+	−
Genital hypoplasia or malformation	+	+	+	−	−	(+)	+
Distal limb hypoplasia	+	?+	+	−	?	−	+
Syndactyly 2/3 toes	+	+	−	−	−	(+)	+
Short postnatal survival	+	−	+	−	+	−	+

sample of the culture was trypsinized and subcultured, and seven further metaphases were analysed. Of the latter, three were 46,XX and four were 47,XX,+22 (Fig. 3). Twenty-seven metaphases from the blood culture were analyzed in conventional orcein-stained preparations. Only one mitosis had a 47,XX,+G chromosome complement, the other 26 were normal 46,XX.

In G-banded preparations, the three No. 22 chromosomes had long arms of similar size; one showed prominent satellites on the short arm, the other two had short arms of average size without any distinct difference. The diploid metaphases also contained the No. 22 with prominent satellites. The chromosomes of the parents could not be examined.

Discussion

The patient was mosaic-trisomic for an entire chromosome 22. A determination of the origin of the different No. 22 from the parents and thus of a first meiotic error or second meiotic or postzygotic misdivision was not possible, however, tha advanced ages of the parents indicate a prezygotic error and subsequent loss of one No. 22 at an early postzygotic division.

Trisomy of the proximal segment and the distal segment of chromosome 22 cause different clinical pictures (Schinzel et al. 1981; Schinzel 1981). The patient of the present report also had anal atresia and the preauricular pit observed in cases trisomic for 21pter→q11 (Table 1). The clinical picture of trisomy of the distal segment of 22q is not yet sufficiently known, however, the patient did not have the probably more consistent clinical features such as cleft palate and congenital hydrocephalus. Heart defects and renal malformations are common to both types of partial trisomy, and severe growth deficiency was consistently found in the few cases of familial trisomy of the distal segment of 22q, but it was also occasionally present in cases with family trisomy of the proximal segment.

In the literature we found only one case with cytogenetically convincingly documented mosaic-trisomy for the entire chromosome 22 (Pagon et al. 1979; see also Table 1). In one of the two other cases reported as mosaic-trisomy 22, one of the three Nos. 22 was probably smaller (Mollica et al. 1977), and in the other,

the cytogenetic documentation is of suboptimal quality (Osztovics and Ivády 1977).

Is full, non-mosaic trisomy 22 compatible with intrauterine survival up to term? It is not uncommon in spontaneous abortions (Boué et al. 1976; Creasy et al. 1976). Several patients with extra G-like chromosomes presenting banding patterns consistent with those of the No. 22 were reported as cases of "trisomy 22". A closer look at published karyotypes, however, shows that in many of them one No. 22 was smaller than the other two, and hence full trisomy 22 was most probably not present (Hirschhorn et al. 1973; Berger et al.1976; Mangold et al. 1976; Welter et al. 1978). Other cases were reviewed in a paper on unbalanced 11/22 translocations because, clinically and cytogenetically, at least some of them might represent undetected familial 11/22 translocations (Schinzel et al. 1981b). A few reported cases remain in whom an additional chromosome of the size and staining characteristics of the entire No. 22 was found in all analysed cells, and these cases are also included in Table 1 (Pérez-Castillo et al. 1975; Cervenka et al. 1977; Iselius and Faxelius 1978). The comparison shows that these cases have some features in common with partial trisomy of the proximal segment of 22; the similarity with cases trisomic for the distal segment is less striking, however, the latter syndrome is not yet clinically well known. Also, it must be considered that no every extra chromosome which looks like a full No. 22 will be an entire No. 22. Such an extra chromosome could, for example, be composed of the proximal segment of 22 and a segment of another chromosome whose banding pattern is similar to that of the distal segment of 22. Patients with partial trisomy of the proximal segment of chromosome 22 plus partial trisomy of another chromosome due to a familial reciprocal translocation are not uncommon: the unbalanced 11/22 translocation cases are possibly examples of this (Schinzel et al. 1980b), but there are also cases of partial trisomy of 22 (proximal segment) and 13 (distal segment) following familial 13/22 translocations (Kim et al. 1977; Mutchinick et al. 1978; Penchaszadeh 1979), and at least two cases of partial trisomy 22 (proximal segment) and 4p (distal segment) are known to the author (Aurias et al. 1978; personal observation).

An argument *against* the existence of full trisomy 22 is the lack of familial cases. Though Robertsonian translocations involving a No. 22 are not exceedingly rare, no case of unbalanced segregation of such a translocation has so far been reported. In contrast, several carriers of 22/22 Robertsonian translocations were detected because of repeated spontaneous abortions (Schwinger 1973; Farah et al. 1975; Maeda et al. 1976; Mameli et al. 1978). In large families with Robertsonian 14/22 translocation (Neu et al. 1975), 15/22 translocation (Fried et al. 1974; personal observation), and X/22 translocation in which the entire chromosome 22 was attached to Xq (Jenkins et al. 1974) there were high incidences of spontaneous abortions among the offspring of translocation carriers indicating that unbalanced products did not survive. In contrast to trisomies 18 and 21, there is also no example of tertiary full trisomy 22 resulting from a balanced non-Robertsonian translocation involving a No. 22. The only two reports of "trisomy 22q" due to de novo unbalanced 21/22 (Lalchev et al. 1978) and 22/22 (Fryns et al. 1979) Robertsonian translocations are not convincing in their cytogenetic documentation. No definite conclusion is presently possible regarding the existence or nonexistence of full trisomy 22 except that, if it exists in full-term human beings, it is probably very rare, with most cases not surviving very long.

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Note Added in Proof

Another case of mosaic-trisomy 22 was recently detected at examination of an amniotic fluid cell culture in our cytogenetic laboratory. At the time of amniocentesis the mother was 36 years old; she already had 2 healthy children. Amniocentesis was performed for advanced maternal age at $16^{1}/_{7}$ weeks of gestation. Ultrasound examination revealed that the fetal biparietal diameter was only 2.8 cm (mean for 14 weeks). Amniotic fluid cell growth was rather poor, and macrophages were observed in the cultures. *In situ* cytogenetic preparations were performed 10 days later. Six metaphases from 3 primary clones were 47,XX,+22, and 4 metaphases from 2 primary clones were 46,XX. Another 11 metaphases without evident connection to a distinct clone were analyzed: 6 were 46,XX and 5 were 47,XX,+22 (Q-banding).

Subsequently, a second ultrasound examination at $19^{3}/_{7}$ weeks of gestation revealed fetal death. Following prostaglandine application, a macerated female fetus was born one day later. Fetal weight was only 18 g (mean for gestational age: 190 g), placental weight was 73 g (mean: 150 g). The ears were clearly low-set, but further evaluation was impossible because of severe maceration. Autopsy disclosed autolysis of the inner organs, but no congenital malformation (courtesy of Dr. J. Briner, Institute of Pathology, University of Zurich).