Trisomy-18 Syndrome Caused by Translocation or Isochromosome Formation*

A Case Report with Bibliography

Hj. MÜLLER, E. M. BÜHLER, E. SIGNER, F. EGLI,
and G. R. STALDER

University Children's Hospital, Basel, Switzerland

A girl with the clinical and pathological characteristics of Edwards' syndrome (Edwards *et al*, 1960) and with a karyotype showing only one morphologically recognizable chromosome 18 is reported. The 2nd and the additional 3rd chromosome 18 were replaced by 2 metacentric chromosomes of different size. Possible mechanisms of origin of the abnormal chromosomes are discussed.

Case Report

Clinical Findings. The proposita (Fig. 1) was the 3rd child of healthy Italian parents having no common ancestors and without any family history of malformations. The mother indicated no previous abortions. The first 2 children are living and clinically well. The karyotypes of the parents were found to be normal. Birth of the proposita occurred spontaneously 2½ weeks before term following an uneventful pregnancy. The father was 31 years of age at that time, the mother 25 years. The placenta was said to be normal by the obstetrician, however amniotic fluid contained meconium. The baby became blue asphyxotic and was referred to our hospital.

Birth weight was 2380 g, body length 45 cm, and head circumference 31.5 cm.

The head had a prominent occiput with widely spaced sutures. There was a flat bridge of the nose. The proposita showed micrognathia, high arched palate, low set malformed ears, small eyes with a slight mongoloid slant of the palpebral fissures, and peripheral paresis of the left facial nerve.

The thorax was barrel shaped with widely spaced

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FIG. 1. The proposita at the age of 1½ months.

darkly pigmented nipples and dextrocardia with ventricular septal defect.

Hypertrophy of the clitoris was noted.

There were closed fists on both hands, showing the characteristic feature of 2nd finger overriding the 3rd and the 5th finger overriding the 4th. She had hypoplasia of the middle phalanx of both little fingers and bilateral club feet. There was general hypertonicity and pronounced lanugo hair on the skin.

Dermatoglyphics. Palmar creases and finger prints are shown in Fig. 2. Symmetrical arches were present

FIG. 2. Dermatoglyphics of the propoita.

on all finger tips. The distal flexion creases were absent on the left 3rd, 4th, and 5th fingers and on the right 4th and 5th fingers. The axial triradius was found to be distally displaced on the left hand.

Necropsy Findings. Increasing respiratory acidosis developing in the 3rd week of life necessitated artificial respiration. The infant died of resistant pneumonia at the age of 4 months.

The post-mortem findings of the heart and great vessels, the gut, and the genitourinary system are compared with those of 99 cases of trisomy 18 in Appendix I.

In addition our case showed abnormal lobulation of the lung, ie, 3 lobes of the left lung and one large middle lobe on the right side. The brain was not studied extensively. Commonly occurring malformations of the brain in trisomy 18 are extensively summarized in the papers of Passarge *et al* (1966), Sumi (1970), and Terplan, Lopez, and Robinson (1970).

Chromosome Findings (Fig. 3). The chromosome number was 47 in 63 lymphocyte metaphases examined. There were 21 normal pairs of autosomes and 2 X-gonosomes, but only one chromosome No. 18. The 2nd and additional 3rd chromosome 18 were replaced by 2 metacentric chromosomes, one was the size of a C

FIG. 3. Karyotype of the propoita.

chromosome, the other one the size of a G chromosome. In Fig. 3 these 2 abnormal chromosomes have been arranged in the E-group. In 10 suitable karyotypes arm and centromeric indices were measured, both abnormal chromosomes had an arm index of 1 and a corresponding centromeric index of 50.

Autoradiography with tritiated thymidine showed that in 24 out of 32 metaphases examined at the time when there was only little labelling over chromosome 17, DNA replication was at its peak in the long arms of chromosome 18, whereas the centromeric region and the short arms had almost completed DNA synthesis. At this stage the large metacentric chromosome shows symmetrical intense labelling of both arms, whereas the small metacentric is practically unlabelled.

We interpret the large metacentric chromosome to consist mainly of 18 long arm material, the small metacentric to be mainly derived from 18 short arm material.

Discussion

Although phenotypic expression of the various chromosome aberrations is well known to vary considerably, there are presently some rather well defined chromosomal disorders which can be clinically diagnosed in most instances.

Our case was clinically diagnosed as trisomy 18, since it showed most of the typical signs of the disorder. Dermatoglyphic features (Uchida, Patau, and Smith, 1962) as well as post-mortem findings were consistent with this diagnosis.

The karyotype along with the autoradiographic findings can be interpreted in 2 ways.

1. Either a translocation trisomy resulted from non-disjunction after break events in both chromosomes 18 under consideration. In one chromosome 18 the break occurred in the proximal portion of its long arm; in the other, the break occurred in its short arm. The large metacentric chromosome resulted when the broken long arm of one chromosome 18 joined to the other chromosome 18, which lacked only a short arm piece. The small metacentric arose from the joining of the tiny short arm piece of one chromosome 18 to the rest of the broken long arm of the other chromosome 18. Thus, the 2 metacentric chromosomes represent the entire chromosome material of 2 normal No. 18 chromosomes.

The E group chromosomes, especially chromosome 18, are often involved in reciprocal translocations (see review by Hamerton, 1969). In the cytogenetic literature, several cases have been described with most of the signs of clinical trisomy 18—in which translocation of the long arm of a chromosome 18 on to a chromosome of groups B, C, and D occurs (see Appendix II). Two apparently normal chromosomes 18 were always present.

Rohde, Lee, and Sapin (1963) reported a girl with the signs of Edwards' syndrome. In this case the long arm of one chromosome 18 was translocated onto the long arm of another chromosome 18, the small deleted chromosome 18 had been lost. From these reported cases, it appears that the trisomy of the long arm of chromosome 18 is the important factor in the development of the phenotype of Edwards' syndrome.

2. The second possible interpretation is that the isochromosome formation of both products of a transverse centromeric break occurred in a chromosome 18 in meiosis I. Two unstable telocentric chromosomes result from misdivision of the centromere. In meiosis II the chromatids of both telocentric chromosomes were not separated and migrated to the same pole. During the next replication period, the so-called isochromosomes (Darlington, 1938 and 1939) were formed with genetically identical arms and median centromeres, changing the genetic balance of the karyotype.

Little is known about the ultrastructural morphology of the centromere region (Luykx, 1970). Thus, a satisfactory model for the events taking place in the centromere along with its junctional errors, which brings into account the current knowledge of centromere ultrastructure, would be difficult to formulate. McClintock (1932) was able to show that, in plants, ionizing radiation caused horizontal breaks and both fragments of centromere continued to function. The mechanism of origin of the so-called isochromosomes was only introduced into the textbooks by Darlington in 1938 and 1939.

Most instances of isochromosome formation in man involve the X chromosome. Presumptive isochromosomes of C, D, and G group chromosomes and of the long arm of the Y chromosome have been described (see Appendix III). Isochromosomes of the long arm (Miller, Rostafinski, and Hyde, 1965; Neu and Kaji, 1969) and of the short arm (Ishmael and Laurence, 1968) of chromosome 18 have also been suspected. Contrary to these reported cases, we found that in all examined karyotypes, the presumptive isochromosomes of both arms of the same original chromosome were present together.

Which of the 2 possible mechanisms of origin is responsible for the chromosomal constellation of our case cannot be determined. Only by their pairing behaviour in meiosis or by proof of their similar genetic make-up on both arms, could the 2 metacentric chromosomes be identified as isochromosomes. Possibly, the fluorescence—or one of the new annealing techniques—would have been

of help in establishing the exact nature of these chromosomes. Unfortunately, the child died (in 1969) before these techniques were available.

Summary

A female infant with the characteristic phenotype of Edwards' syndrome is reported. Her karyotype can be interpreted either as 47,XX,18+,t(18p+;18q-) or 47,XX,18-,18pi+,18qi+. A bibliography of other cases in the literature is given in the appendices.

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Appendix I

Necropsy Findings in 99 Cases of Trisomy 18 Compared with the Present Case

Findings	No. of Cases		Present Case
	Reported	Total	
Congenital heart disease	93	99	+
Ventricular septal defect	66	89	+
Atrial septal defect	36	86	+
Persistent ductus arteriosus	51	81	
Coarctation of aorta	14	85	
Pulmonary valve anomaly	23	69	
Aortic valve anomaly	13	69	
Anomaly of peripheral vessels	9	69	
Miscellaneous	5	84	
Gastrointestinal anomalies	45	69	+
Malrotation of intestine	15	70	+
Meckel's diverticulum	33	80	+
Omphalocele	7	69	
Thin diaphragm eventration	17	79	
Miscellaneous	5	69	
Genital anomalies	20	69	+
Cryptorchidism	11	16	
Hermaphroditism	5	69	
Penile hypoplasia	1	16	
Vulval aplasia	2	51	
Vulval hypoplasia	4	51	
Uterus bicornis	2	51	
Vaginal atresia	1	51	
Renal anomalies	59	85	
Polycystic renal cortex	14	82	
Duplication	17	69	
Horseshoe kidney	20	82	
Hyperplasia unilateral (contralateral kidney normal)	1	69	
Hypoplasia (unilateral)	1	69	
Hamartoma	1	69	
Ectopic kidney	7	69	
Rotation anomaly	1	69	
Hydronephrosis/ureter (Fetal lobulation)	12	82	
	1	69	

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Appendix II

Bibliography of Translocation Trisomics Resulting in Duplication of the Long Arm of a Chromosome 18

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Appendix III

Bibliography of Presumptive Isochromosomes in Man

Isochromosome C

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Isochromosome D

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