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Edwards' Syndrome with Double Trisomy (Possible Tetrasomy) of the E Group Chromosomes (17—18)

By

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The case of a 141-day-old infant with Edwards' syndrome is reported. Chromosome analysis revealed 46/XY, 47/XY (trisomy 17—18) and double trisomy of chromosomes 17 and 18 in 60% of the cells examined. Pathogenesis, pathology and clinical signs of the disease are discussed.

Trisomy, the genetic disorder characterized by the presence of three instead of two homologous chromosomes, has two forms, one affecting only the sex chromosomes, e.g. triple X in females and another with three instead of the usual two autosomal chromosomes. Autosomal trisomy (trisomy of chromosome 21) was first reported in 1959, in a child with Down's syndrome [16]. Later EDWARDS et al. [14] observed trisomy of chromosome 17 in a case of multiple congenital anomalies. A similar case was reported in the same year by PATAU et al. [21], they considered, however, the extra chromosome to belong to chromosome pair 18.

The chromosome pairs 17 and 18 are poorly distinguishable in routine specimens, therefore the term trisomy 17—18 (E—1 trisomy) is used. By acetoorcein treatment, phase-contrast microscopy and autoradiography YUNIS [31] has recently shown that chromosome 18 was the trisomic one. PATAU et al. [21] found trisomy of chromosome pairs 13—15 in a patient with extensive congenital malformations, and LEWIS [17] described trisomy of chromosome 16 in an adult female. Several instances of 6—12 trisomy were found in patients with congenital malformations of the genital organs and fingers, and mental retardation [14, 22, 25].

Several cases of trisomy 17—18 have been reported during the recent years; HECHT et al. [12], LA GRUTTA et al. [9], WEBER and WENDEL [29] collected 32, 85 and 192 cases, respectively.

REPORT OF A CASE

Ny. I. a male infant, was born at term with a weight of 2400 g on August 15, 1966, from the second pregnancy of the 36 years old mother. The first child is healthy, in the family history no relevant facts were found. During her pregnancy the

mother was healthy, except for some minor bleeding during the 3rd month.

Exhibiting symptoms of emphysema and cardiac incompensation the baby was transported to a children's hospital in the country where he was given antibiotic and digitalis treatment. His condition improved. Congenital anomalies of extremities, heart and other organs were registered. He was discharged after two months, but readmitted a week later with severe bronchitis and bronchopneumonia. Two weeks later the patient was referred to us.

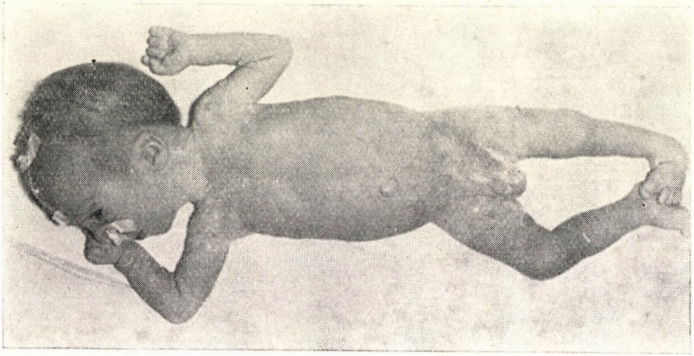

FIG. 1. Edwards' syndrome. Characteristic position of hands and feet

At admission the infant weighed 3100 g and measured 53 cm in length. He appeared wasted, his skin was loose, wrinkled, exhibiting bright red, inflamed spots. His expression was abnormal (Fig. 1). The occipito-bregmatic axis was considerably increased, the occipital region was protruding. The skull appeared as if it were deformed by some intracranial process. The head circumference was 38 cm, the palpebral fissures were antimongolic; convergent strabism and hypertelorism were present. The mouth was extremely small (micrognathia). Both ears were set low, the left lower than the right. The longitudinal diameter of the left ear was 5 mm less than that of the right.

The large fontanel measured 30 × 30 mm. The palate had a gothic arch. The hair was reddish, scanty at the temples, thin and poor. The eyebrows were similarly thin and poor, medially they were even missing. The thorax was shield-shaped, having a circumference of 32 cm. The sternum was short, the right clavicle curved; it exhibited the callus of a healed fracture. The heart extended to the medioclavicular line, cranially to the 2nd intercostal space, and reached 0.5 cm beyond the right edge of the sternum. A systolic murmur was heard, with the maximum at the left side of the sternum in the 4th—5th intercostal space. Sternal and intercostal retraction of the chest was observed on both sides, accompanied with tachypnoea, catarrhal moist rales, harsh breathing.

The patient had an umbilical hernia of hazelnut size and a right inguinal hernia, the left testicle was palpable in the inguinal canal. The liver and the spleen reached below the costal margin by 3.5 and 2.5 cm, respectively. The right leg was 2 cm longer than the left. The left foot was fixed in the ankle, rotated inward and turned upward. The left hip joint could not be abducted. Syndactyly was present between the 2nd and 3rd toes of both feet. The infant was listless and showed no physiological motility.

On the X rays the base of the skull was short, flat, steep. The cranial bones were normal. The glenoid cavity was malformed, steep (dysplasia). In spite of the deformities, ossification on the lower extremities

was normal. On the electrocardiogram the electric axis was in mid position, deep S_{I-II} waves, deviation to the right of the R axis in the chest leads, sinus rhythm were seen. Blood type, 0, Rh positive. Urine, normal. ESR, 36 mm/h. RBC, 2.840,000; Hgb, 10.2 g per 100 ml; WBC, 14 000.

Ophthalmology showed normal conditions.

Audiologic examination was carried out with some difficulty owing to the anomalous posture of the head. After several attempts it was established that from 10—15 cm distance a 110 decibel sound of 1000 Herz elicited a reaction which consisted of sudden movements of the head and extremities. The auropupillar reflex was lacking, the presence of cochlear activity was presumed.

After admission Sigmamycin therapy was started to control bilateral bronchopneumonia; no improvement ensued. Blood transfusions were given to correct the increasing anaemia. Then cefaloridine therapy was started. The infant kept losing appetite and weight, remission and recidives of pneumonia alternated. Aureomycin and neomycin were without any effect.

The excessive bronchial discharge was relieved by repeated suction. In spite of intensive treatment the patient died of cardiorespiratory failure at the age of 4 and a half months.

The clinical picture suggested a chromosome anomaly. After two unsuccessful attempts to cultivate blood cells, bone marrow was obtained twice from the tibia for chromosome analysis. Direct chromosome preparations of bone marrow cells were prepared with the technique of TJIO and WHANG [26]. The sex chromatin test was negative (3—5%) in both the blood and the buccal mucosa smears. The result of chromosome analysis performed on a total of 50 cells was as seen in Fig. 2.

Autopsy revealed hypertrophic and dilated heart ventricles, dilatation of the initial part of the pulmonary artery containing one normal and one oversize valve. The centre of the latter was connected with the artery's wall by a thin endocardial cord. The initial part of the aorta was also dilated and only two semilunar valves were present. The oval foramen and the ductus arteriosus were present, the great vessels were normal. The adrenals were smaller than normal, their cortex and medulla being equally reduced. There was in addition parenchymal degeneration of the liver, heart and kidneys, disseminated bronchopneumonia, septic spleen.

Discussion

The chromosome pattern and the clinical picture unequivocally pointed to Edwards' syndrome (trisomy 17—18, group E). In addition to the XY and XY + 17 trisomy mosaicism, trisomy was present in both the 17 and 18 chromosome pairs in the majority of cells, which could be evaluated as either 17 or 18 tetrasomy. To our knowledge only 4 cases of double trisomy have been reported in Edwards' syndrome. Although the absence of sex chromatin supported the diagnosis of autosomal trisomy, on rearrangement of the karyotype a simple autosomal trisomy 17 or 18 with chromosome constitution XXY mosaicism could have been suggested. In the latter case, however, one would have expected a sex chromatin number higher than the 3—5% actually found.

According to SMITH [24] and EDWARDS et al. [4] the incidence of trisomy 17—18 is 0.1—0.2% in liveborns. This figure will certainly increase in the future as at present

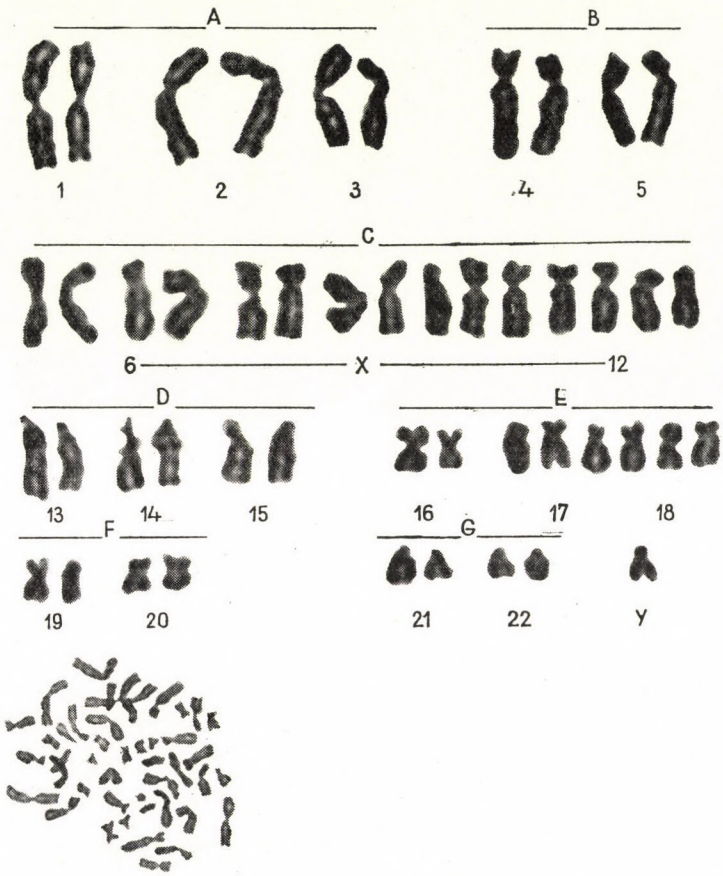

FIG. 2. Double 17—18 trisomy

Karyotype	XY	XY + trisomy 17 tetrasomy of one of them	XY + trisomy 17 + 18	XY + fragment or
No. of cells	5	10	30	5

newborns with trisomy 17—18 usually die before chromosome analysis would have revealed the diagnosis. CARR [2] found two cases of trisomy 17—18 in a total of 54 spontaneous abortions, thus he considered the disorder to occur more frequently in embryos and foetuses than in newborns. According to some literary data liveborns with trisomy are mostly females.

The characteristic signs of Edwards' syndrome are the short head circumference with a short biparietal diameter and a thin face with micrognathia. Narrow, high (gothic) palate, small mouth, narrow palpebral fissures, protruding nuchal bone and a saddle-nose complete the picture. The ears are set low and are asymmetrical owing to incomplete cartilage devel-

opment. Sometimes two thick, shapeless skin folds substitute the ears. The meatus is irregular, frequently even lacking. In 3 out of the 13 cases of BUTLER et al. [1] facial palsy contributed to the grotesque expression of the face. In half of the cases a pterygium was also present; microphthalmia, iris coloboma and glaucoma may also occur. The present case displayed most of the above symptoms, with the exception of the relatively rare ophthalmological signs.

The thoracic and abdominal organs exhibit relatively few though characteristic lesions. Hypermotility of the shoulder is frequent. The clavicle is thin, sometimes aplastic. The sternum is short, making the thorax flat and shield-shaped. The nipples are hypoplastic and often localized laterally from the medioclavicular line. Inguinal hernia was observed in 11 out of the 16 cases described by SMITH [24] while BUTLER et al. [1] registered two cases of umbilical hernia with significant diastasis of the abdominal rectus muscle. The present case showed most of the characteristic thoracic changes, together with an inguinal and an umbilical hernia.

Systolic murmur, with or without cyanosis, due to a congenital heart defect and a patent ductus arteriosus, is frequent, but a diastolic murmur is seldom heard. The patients being usually in poor condition, cardiac catheterisation was mostly omitted and this is the main reason for the scarcity of relevant data in the literature. In our patient autopsy revealed a patent oval foramen and a patent ductus arteriosus together with malformations of the pulmonary and aortic valves.

In the trisomy 17—18 syndromes, malformations of the extremities are almost as frequent as those of the face. The fingers assume a characteristic spastic position, all of them being in full flexion, with the thumb pressed against the palm. The index is above the others, while the little one is bent above the fourth one. On extending the fingers by force they will assume a strong ulnar inclination. Syndactyly of the 2nd and 3rd toes is frequent. Aplasia of the tarsal or metatarsal bones may also occur.

In our case the fingers were fixed in flexion and resisted stretching. Syndactyly was also present. In addition, the left lower extremity was shorter than the right one and the left foot was in a 70% varus position. The left coxal joint was also dysplasic. As to this latter sign we found no reference in the literature, although BUTLER et al. [2] reported two cases in which abduction of the thigh was inhibited. Fingernail hypoplasia has been present in about half of the cases.

According to UCHIDA et al. [28] in trisomy E 17—18 the finger and palmprints exhibit specific, characteristic patterns. Unfortunately, these symptoms have not been examined in our patient.

The symptoms observed in the present cases and the symptoms mentioned in the literature are shown in Tables I and II.

TABLE I

Gross changes observed at autopsy by BUTLER et al. [1] and GANASSI et al. [6a] in 12 and 56 cases, respectively

	Total No of cases/ lesion present	Cases observed by the authors
Cardiovascular system	68/65	+
Ventricular septal defect	68/64	+
Patent ductus arteriosus	68/48	+
Patent foramen ovale	56/22	+
Bicuspid, aortic and pulmonary valves	68/26	+
Gastrointestinal system		
Ectopia or other anomaly of the pancreas	56/6	
Malrotation of the intestines	56/9	
Meckel's diverticle	68/17	
Anomalies of anus and rectum	56/5	
Atresia of bile duct	56/2	
Urogenital system		
Horseshoe kidney	68/16	
Anomalies of the renal pelvis and/or the ureter	68/14	
Hypoplasia of the ovary	7/2	
Other anomalies		
Diaphragmatic hernia or eventeration	68/17	

As mentioned above, the specific chromosomal alteration in Edwards' syndrome is the trisomy of chromosome 17 or 18. In the case observed by us, the majority of the cells examined exhibited trisomy of both the 17 and the 18 chromosomes, which could also be considered to represent a tetrasomy of one of the chromosomes or, else, it was an exceptional case of double trisomy or 17—18 tetrasomy. From the 50 cells examined only 5 contained the 46/XY karyotype. Double trisomy or tetrasomy was found in 30 cells, and simple trisomy in 10. The other 5 cells were of the XY karyotype and contained chromosome fragments. These chromosome fragments in the cells with 46 chromosomes probably originated from the labile excess autosomes.

Double trisomy, even in its mosaic form must be considered a rarity. In the cases of UCHIDA et al. [28], ENGEL et al. [3], RICCI and BORGATTI [23], HAAS and LEWIS [10] the trisomy 17—18 was associated with Edwards' syndrome; HAYLOCK [11], ZELLWEGER et al. [31] and PFEIFFER et al. [22] found trisomy associated with that characteristic of Klinefelter's syndrome; GAGNON et al. [6], HSU et al. [13] and MARKS et al. [18] described autosomal trisomy associated with mosaicism 48/XX (trisomy 18 + 21) and 46/XX. Deletion and break of long chromosome arms in Edwards' syndrome was described by DE GROUCHY [8]

TABLE II

Symptoms of the common trisomies

	Trisomy D 13—15 Patau's syndrome	Trisomy E 17—18 Edwards' syndrome	Trisomy G 21/22 Down's syndrome
Skull	Dyscephaly Microcephaly Cleft palate Cleft lip Hyperplasia of nasal bone	Dyscephaly, Micrognathia	Brachycephaly (saddle-nose, gothic palate, tooth anomalies)
Eye	Microphthalmy Hypertelorism Epicanthus Cataract	Hypertelorism Epicanthus	Mongolian eye Epicanthus Spots on iris Cataract
Ear	Low set dysplasic ears	Low set dysplasic ears	Small ears (low set)
Nervous system	Arhinencephaly Psychomotor retardation Central respiratory disturbance	Poor psychomotor reactivity	Disturbance of psychomotor development Idiocy
Heart	Ventricular septal defect Anomalies of the large vessels	Ventricular septal defect Anomalies of the initial part of the aorta	Arterial septal defect (Persistent atrioventricular ostium)
Extremities	Polydactyly Clenched fist Syndactyly	Characteristic flexion Contracture of the hands	Short extremities Hyperflexible joints Muscular hypertension Clinodactyly
Skeletal system	—	Shield-shaped thorax Short neck	Short neck
Skin	Haemangiomas	Cutis laxa Low forehead	Cutis laxa (on the neck) Low forehead
Urogenital system	Anomalies of the external genital organs	Malformation of the kidney Hypospadias	Cryptorchidism Epihypospadias
Gastrointestinal system	Malrotation	Meckel's diverticle	Stenoses Atresia
Sex distribution	equal	gynaecotropy 13:29	equal
Life expectation	6 months	3 months	50% lethality within the first 5 years
Mother's age	32.7	35.5	above 30 in 2/3 of the cases
Father's age	34.2	37.7	—

while GENEST et al. [7] found a case displaying a ring chromosome.

Primary nondisjunction during meiosis is thought to be the cause of trisomy 17—18. Some authors consider the advanced age of parents, especially of the mother, a predisposing factor. Others [27] emphasize the significance of exposure to radiation. According to their opinion, chromosomal damage resulting in trisomy may occur after exposure not only of the mother during pregnancy but also of any parent prior to conception. The same authors have drawn attention to the paradoxical relation between postmature birth and the low birth weight of newborns with trisomy 17—18 (Table III). ENGEL et al. [3] suggested the possible role of certain metabolic disorders, e.g. diabetes mellitus and autoimmune diseases (thyroid autoimmunity). According to FORBES and ENGEL [5] and MELLON et al. [19] chromosomal nondisjunction is more frequent in families genetically disposed to autoimmune diseases. ZELLWEGER et al. [31] supposed that double trisomy may result if both gametes contain an extra chromosome; at fertilization two aneuploid gametes are incited.

TABLE III

Trisomy 17—18

	Cases reported in the literature	Case observed by the authors
Average age of mother	23 years	36 years
Average age of father	35 years	36 years
Average birth weight	2315 g	2400 g
Proportion of girls	80%	—
Age at death	90 days	141 days

In the present case the characteristic clinical and pathological picture of Edwards' syndrome was associated with a 46/XY, 47/XY (trisomy 17), 48/XY (trisomy 17 + 18) mosaic chromosome pattern. This is considered a rarity because 60% of the examined cells displayed trisomy in both the 17 and 18 chromosome without any exposure to radiation in the history. The parents, especially the mother, were relatively aged and the full-term newborn was born with a low weight. The presence of chromosome fragments was suggestive of disturbed mitosis. Chromosome anomalies have been supposed to be the cause not only of the congenital malformations, but also of the infant's poor resistance.

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