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# Phocomelia and Trisomy E[1]

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Aneuploidies and structural anomalies of chromosomes are gaining significance as teratogens. Various combinations of minor and major malformations have been associated with different chromosomal aberrations. Although their clinical manifestations overlap to some extent, a fair correlation exists between certain chromosomal aberrations and the respective clinical syndrome. This is certainly true for mongolism and trisomy 21 or partial trisomy 21. In the few exceptional cases of mongolism with a seemingly " normal " karyotype, the assumption of a microscopically unrecognizable partial trisomy 21 (translocation of the mongolism chromosome to one of the larger chromosomes) was made to bridge the apparent discrepancy between chromosomal and clinical findings (18, 19). The clinical signs and symptoms of trisomy D and trisomy E are rather characteristic, although none of them is pathognomonic for either one of the two trisomies, and many of them are common to both. They do not occur with the same frequency in the two conditions. Malformations of the brain, eyes, and ears as well as cleft palate and cleft lip are more frequent in trisomy D, while renal anomalies occur more often in trisomy E.

The clinical picture of 70 cases of trisomy E (including 11 cases of partial trisomy E) has been analyzed elsewhere (59) and can be summarized as follows. Severe failure of growth and retardation of psychomotor development are constant findings. Micrognathia, high arched palate, low set ears, prominent occiput, flexion deformity of fingers, short sternum, muscular hypertonia, limitation of hip abduction, congenital heart disease (notably ventricular septal defect, patent ductus arteriosus, and valvular malformations) as well as specific dermatoglyphic patterns (arches on all fingers) are present in the great majority of cases. Single umbilical artery, anomalies of the urogenital tract, intestinal malrotation, heterotopias of pancreatic tissue, diaphragmatic hernia or eventration, rockerbottom feet, and other malformations of the extremities are findings of somewhat lesser frequency.

We were able to study an infant with trisomy E who, in addition to some of the malformations mentioned above, showed phocomelia of one arm with absence of radius, first metacarpus, and phalanges of the thumb and shortening of the ulna and

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humerus. The purpose of this paper is to present this case with particular reference to the problem of phocomelia and its different causes.

The proband (61-11374), a white female, was the product of her mother's ninth and last pregnancy. The father was 42 and the mother 37 years old at the time of her birth. The pregnancy was uneventful. The infant was born at term, but her birthweight was only 2,000 grams. She was cyanotic and had to be kept in an incubator for several days. She was admitted to the University Hospital because of cardiorespiratory difficulties and failure to gain weight. Throughout her stay in the hospital she had a grunting and rapid respiration with substernal retraction. Her color was dusky. Perioral cyanosis was present. Body weight, height, and head circumference at 2 months were 2,310 grams, 44 and 32 centimeters, respectively. The anterior fontanel was widely open and measured 30 by 30 millimeters. The occiput was prominent, and a persistent metopic suture was present. Her eyes had a mongoloid slant. Media and eye grounds were normal. She had large, somewhat deep set ears, a very high arched palate, and a severe micrognathia. The chest was bulging. The sternum was very short. A Grade II systolic murmur was heard all over the precordium but was loudest along the left sternal border. Moist rales were present over both lungs. A sacral dimple was surrounded by a tuft of hair. The right arm, particularly the right forearm, was longer than the left. The fingers of the right hand were in flexion position. The right thumb was relatively small. There was a fourfingerline, and the right fifth finger had only one interdigital line. The left arm was considerably malformed and showed a slightly shortened upper arm and a very short forearm. The left hand was kept in adduction. The thumb consisted of a small soft tissue appendix attached to the hand by a thin bridge of cutaneous tissue. The four other fingers were kept in flexion position. A fourfingerline was present. The hips were fixed in adduction. There was considerable generalized muscular hypertonia. The tendon reflexes were hyperactive. Feet and toes were small. The great toes of both feet were considerably shorter than the second toes.

An intravenous pyelogram revealed a normal appearing right kidney, while the left kidney was not fully visualized. Urinalysis was normal. X-rays of the thorax and chest revealed cardiomegaly and patchy pneumonitis. The ribs appeared very thin. The skull revealed a slightly prominent occiput. No radiological abnormalities were observed in the spine, pelvis, femora, or right arm. The left humerus was a few millimeters shorter than the right. The left ulna was 2 centimeters shorter than the right. The left radius, metacarpus I, and phalanges of the thumb were absent. Four ulnar rays of phalanges were present.

An electrocardiogram revealed atrial tachycardia, a two to one block, and right ventricular hypertrophy.

Chromosomal analysis using a modification of the method of Moorhead et al. (39) revealed 47 chromosomes in 29 cells. Photographs were taken and the karyotype showed the supernumerary chromosome to be a small submetacentric chromosome belonging to the 16-18 group.

The child remained in respiratory distress and did not gain weight in spite of

adequate gavage feeding. She died 2½ weeks after admission. An autopsy was performed. In addition to the external anomalies, several internal anomalies were found.

The heart weighed 48 grams, and the right side was tremendously dilated. The ductus arteriosus was patent and 1.0 centimeter in external diameter. There was a valvular-competent, patent foramen ovale. There was a 1.2 centimeter interventricular septal defect located at the junction of the membranous and muscular portions of the septum and postero-inferior to the papillary muscle of the conus. The right and left ventricles were 5 and 6 millimeters thick, respectively. The external diameters of the pulmonary artery and the aorta were 1.7 and 0.9 centimeters, respectively. The origins of the medium-sized, muscular pulmonary arteries showed adventitial and medial hypertrophy. Eighty per cent of the pulmonary parenchyma demonstrated acute and chronic aspiration pneumonitis, congestion, and patchy hemorrhage. *Escherichia coli* was cultured from the lung.

The umbilical ring was 0.8 centimeter in diameter. A pouch arose from the right hemidiaphragm immediately lateral to the junction of its muscular and tendinous portions. It protruded 1.0 centimeter into the thorax and was 1.0 centimeter in diameter. Its wall was composed of pleura, muscle, and peritoneum. It contained a 1.0 by 1.0 centimeter nodule of liver which arose from the superior surface of the right lobe. The cecum and ascending colon were attached to the posterior abdominal wall by a mesentery. Microscopic renal cortical cysts lined by flattened epithelium were seen occasionally. The right ureteral orifice was patulous. Each ovary appeared to be replaced by a single transparent cyst (2.5 by 1.5 centimeter in diameter). The cyst walls contained a thin rim of compressed ovarian cortex and were lined by flattened thecal cells. Ten to 15 primordial follicles were seen in two microscopic sections (one section of each ovary). Several minute cysts, similar to the larger ones, were present in the compressed stroma. A uterus bicornis duplex and a double vagina were present. Subependymal cortical heterotopia were present in the brain.

In summary, the proband, product of the ninth pregnancy of a 37-year-old mother, presented a syndrome suggestive of trisomy E. The clinical diagnosis was confirmed by the chromosomal analysis. The left arm showed an impressive deformity consisting of the absence of radius, metacarpus I, phalanges of the thumb, and adduction of the hand. The latter malformation was consistent with moderate phocomelia. Its significance as a sign of trisomy E and its relationship to phocomelias of other origin will be considered in the following discussion.

Phocomelia of the upper extremities in its most pronounced form consists of complete aplasia of the long bones, radius, ulna, humerus, and sometimes even scapula. The hands arise directly from the shoulders like the flippers of a seal. Less complete forms of phocomelia are encountered more often. They show all transitional stages from the above-mentioned severe malformation to its mildest form consisting of hypoplasia of the thumb only. Shortened forearms with absence of radius and hypoplasia or absence of thumb are among the most frequent forms of phocomelia. Phocomelia occurs in one or both arms and can affect the legs as well.

The latter are usually less severely involved. In some instances hypoplasia of the great toe may represent the only manifestation of lower extremity involvement.

Phocomelia gained widespread notoriety after its sudden increase when thalidomide was used widely. The incidence of phocomelia before this drug became available (thalidomide was first synthesized in 1954) was estimated to be between one in 22,000 (1) and one in 70,000 (51) live births. It rose to one to three in 1,000 live births in areas where thalidomide and related drugs were used (50). After withdrawal of the drug, the incidence of phocomelia fell again, yet the malformation did not fully disappear (31, 37). Thus thalidomide cannot be the only cause of phocomelia. A number of other etiological factors were listed which can be grouped in three main categories: hereditary, cytogenetic, and environmental causes.

Several forms of heritable phocomelia have been described (8, 35, 43, 52). In most families the disorder is transmitted as an autosomal dominant trait. In rarer instances autosomal recessive inheritance was found (14). Hereditary phocomelia combines with other malformations such as congenital heart defects, genitourinary anomalies, etc. (28). Moreover, phocomelia is not infrequently found in Fanconi anemia (also called familial pancytopenia with congenital defects). McDonald and Goldschmidt (36) collected 43 cases of Fanconi anemia from the literature of which 23 had thumb anomalies, and some had uni- or bilateral aplasia of the radius (6, 41). While the malformations associated with Fanconi anemia are obviously present at birth, its hematological findings become apparent only after a number of years. In other words, there is a delay of that part of the gene effect which is responsible for the depression of hematopoiesis in Fanconi anemia. However, in recent years cases have been reported in which the pancytopenia was present already at birth or shortly thereafter (60). In some instances of the latter condition, a leukemoid blood picture was found instead of the usual granulocytopenia (7, 11, 47). Whether or not these different manifestations are variations of the same genetic defect is not known. The classical form of Fanconi anemia is supposedly transmitted by a single autosomal recessive gene with pleiotropic gene effect. Very recently, however, Fanconi (12) conjectured that Fanconi anemia could be due to a chromosomal aberration. Indeed, chromosomal fragmentation, ring formation, and other structural anomalies have been found in some cases. However, the cause and effect relationship of this finding has not been elucidated (13, 23). Similar chromosomal anomalies are produced by various environmental factors such as X-rays and different chemicals. One wonders, therefore, whether or not the chromosomal anomalies found in Fanconi anemia could represent a secondary manifestation due to some primary biochemical or other alteration present in this disease.

The case presented in this paper raises the question whether or not phocomelia could be caused by trisomy E. In reviewing the literature, we found that phocomelia occurs in about 10% of all cases of trisomy E (tab. 1). Besides the well documented cases listed in tab. 1, manifestations suggestive of minor forms of phocomelia were observed in a number of cases. Townes et al. (53) described the thumbs in one of their cases as " disjointed and functionless, seemingly attached only by the overlap-

**Tab. 1. Reported cases of trisomy E with phocomelia**

| | Voorhess | Trowell | Kajii | Gagnon | Oikawa I | Oikawa II | Pers. ob. |
|---|---|---|---|---|---|---|---|
| Maternal age in years | | | 24 | 20 | (advanced) | | 37 |
| Number of previous pregnancies | 6 | | 0 | 1 | | | 8 |
| Number of abortions | 1 | | 0 | 0 | | | 0 |
| Durations of gestation in weeks | | | 34 | 41 | | | 40 |
| Birth weight in grams | 1,470 | | | 3,600 | | | 2,000 |
| Growth failure | + | + | | | + | + | + |
| Microcephaly | | + | | | + | + | + |
| Prominent occiput | + | | + | + | + | + | — |
| Mongoloid slant | | | | | | | + |
| Microphthalmia | | + | | | | | |
| Epicanthus | + | | + | | + | | |
| Small fissure, ptosis | | | | | + | | |
| Hypertelorism | | | + | | | | |
| Bifid nose | | + | | + | | | |
| Low set ears | + | + | | + | + | + | + |
| Small ear canal | | | | | | | + |
| Microglossia | | + | | | | | |
| Micrognathia | + | | + | + | + | + | + |
| Triangular mouth | | | + | + | | | |
| High arched palate | + | | + | + | + | | + |
| Short sternum | | | + | + | | | + |
| Congenital heart lesion | + | | + | + | + | | + |
| Ventricular septum defect | | | + | + | | | + |
| Fallot's tetralogy | + | | | | | | |
| Pulmonary stenosis | | | | + | | | |
| Valvular abnormality | | | + | | | | + |
| Diaphragm defect, eventration | | | + | | | | + |
| Lung anomaly | | | + | | | | |
| Hypertrophic pylorus | + | | | | | | + |
| Intertinal malrotation | | | + | | | | + |
| Meckel's diverticulum | | + | | | | | |
| Small stomach | | | | | + | | |
| Aberrant pancreas | | | + | | | | |
| Kidney anomaly | | + (horseshoe) | | | | + (agenesis-left) | |
| Exomphalus | | | + | | | | |
| Cryptorchism | | | + | | | | |
| Flexion deformity of fingers | | + | | + | + | + | + |
| Absence of radius | Left | Left | | | Left | Left | Left |
| Absence of ulna | | | | | | Left | |
| Short forearm | Left | | Right | | | | |
| Phocomelia | | | Left | | | | Left |
| Oligodactyly | Left | Left | Both | Both | Left | Left | Left |
| Hypoplasia of thumb | | | | | | | Right |
| Short hallux | | + | + | | | | + |
| Muscular hypertonia | | | | + | + | | + |
| Dislocation of hip | | + | | + | | | |
| Adducted hip | | | | | + | | + |
| Uterus bicornis | | | | | | | + |
| Age at death (weeks) | 4 | 6 | Birth | 32 | | | 10 |

ping skin ". El-Alfi et al. (10) mentioned a very short right forearm in their case. Smith et al. (49) observed in one case (Case 8) that " the thumbs appeared small and were relatively small on the base ". Absence of the thenar muscles was found in cases reported by Hecht et al. (20). Smith et al. (48) reported smallness of the first metacarpal bone in one case, while Holman et al. (24) mentioned some anomalies of the thumb in one of their cases without giving a detailed description. Shortness of the great toes, on the other hand, is mentioned in many cases of trisomy E. (5, 9, 17, 20, 48). Figure 3 in the publication of Holman et al. (24) presents a striking example of hypoplasia of the great toe. All these findings suggest that moderate or mild forms of phocomelia are not uncommon in trisomy E. The clinical findings of trisomy E with phocomelia do not differ from those of trisomy E without phocomelia. These considerations indicate that phocomelia is a manifestation of trisomy E (number 18 chromosome) and conversely that trisomy E represents one of the causes of phocomelia.

In contrast to the hereditary forms of phocomelia, which are due to a single mutant gene, E trisomic phocomelia is caused by an abnormal number of presumably wild type genes. As in other aneuploidies, the mere presence of an abnormal number of wild type genes suffices to produce a teratogenic effect.

Among the environmental factors causing phocomelia, thalidomide is certainly the best known. Thalidomide embryopathy has been extensively discussed in the literature of the last few years and does not warrant more than renewed emphasis of its past clinical importance. However, one interesting feature should be mentioned here. Several authors investigated the karyotypes of patients afflicted with thalidomide embryopathy. Pfeiffer and Kosenow (45) found a normal karyotype in 12 cases. Hirsch (21) studied 5 cases of thalidomide embryopathy and found a non-modal number of chromosomes in 30% of 275 examined plates, while only 10% aneuploid cells were usually found in her laboratory. Most of the abnormal cells studied by Hirsch, however, were hypodiploid, and only 7% of the cells were hyperdiploid. We are inclined to consider hypodiploid cells, particularly if the hypodiploidy is due to loss of autosomes, as artifacts since cells with autosomal monosomy are usually nonviable. Other drugs than thalidomide have been accused of causing phocomelia, for instance stelazine or trifluoperazine (18, 25), in human beings. More studies are necessary to determine whether this drug is a teratogen. Lack of riboflavin, thallium, insulin, sulfonamides, and other compounds produce phocomelia-like malformations in experimental animals (22, 29). However, it is well known that the result of animal experiments does not necessarily apply for human pathology. Maternal infection has been incriminated as teratogenic in humans (26), although the evidence is not well established.

It is surprising to notice that the multiple malformations associated with phocomelias of different pathogenetic origin are somewhat similar and that the clinical picture of the different phocomelias overlaps to some extent. One wonders whether or not a common factor could be involved in the pathogenesis of phocomelias of different etiology. With respect to thalidomide embryopathy, Lenz (34) emphasizes that:

" The pattern of thalidomide malformations follows the pattern of glycogen accumulation preceding the morphologically discernable organ anlagen. The anlagen with the most conspicuous accumulation of glycogen, i. e., bones, muscles, intestines, kidneys and auditory meatus, are preferentially affected by thalidomide, whereas the anlagen which are not marked by glycogen deposition, i. e., the central nervous system, the gonads, the liver and the spleen, are spared. Possibly, thalidomide blocks an enzyme which helps to make embryonic glycogen available as a source of energy for the budding organ anlagen ".

It may be conjectured that a similar mechanism plays a role in the production of hereditary and E-trisomic phocomelias. There are, however, obvious differences between these conditions. Thalidomide, if given between the 34th and 50th days of gestation, always causes phocomelic alterations. No thalidomide embryopathy has been described without involvement of the extremities. Phocomelia, however, is not consistently present in Fanconi anemia or trisomy E. These conditions, on the other hand, although they differ somewhat from each other, show in general a wider spectrum of clinical manifestations than thalidomide embryopathy.[1] Further investigations are needed to understand the intricacies of resemblances and differences of phocomelia of different cause.

In conclusion it can be said that the altered genome for Fanconi anemia (point mutation) and that of trisomy E (chromosomal mutation) has a less specific, less constant effect on the anlagen of the limbs than thalidomide, although the former have a somewhat more general teratogenic effect than the latter.

## Summary

A case of trisomy E with phocomelia of one arm is presented and the hitherto reported cases of trisomy E with phocomelia are listed. The different causes of phocomelia are discussed. Similarities and dissimilarities of the clinical picture of conditions associated with phocomelia are presented.

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RIASSUNTO

Viene presentato un caso di trisomia E con focomelia di un braccio, ed aggiunto un elenco dei casi finora riportati di tale associazione. Vengono discusse le varie cause della focomelia e vengono indicate somiglianze e differenze del quadro clinico in condizioni ad essa associate.

RÉSUMÉ

Les AA. présentent un cas de trisomie E avec phocomélie d'un bras, ajoutant une liste des cas rapportés jusqu'à présent de cette association. Les différentes causes de la phocomélie sont discutées; en outre, sont indiquées les ressemblances et différences du tableau clinique en des conditions associées.

ZUSAMMENFASSUNG

Verf. beschreiben einen Fall von E Trisomie mit Phokomelie eines Armes und fügen sodann eine Liste an von den bisher beschriebenen Fällen gleicher Art. Es folgt eine Erörterung der verschiedenen Ursachen der Phokomelie und eine Beschreibung der Ähnlichkeiten und Unterschiede im klinischen Bild bei Assoziationen mit Phokomelie.