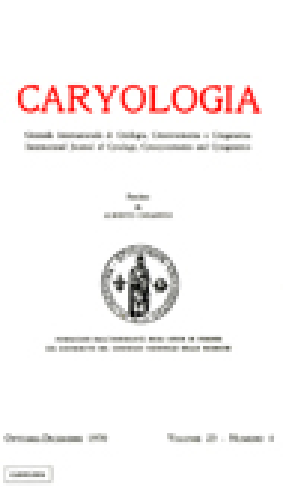

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A Case of Trisomy D_1 — Syndrome of Patau

G. Guanti[a], F. Del Sordo[b], P. Petrinelli[a] & E. Battaglia[a]

[a] Institute of Genetics, University of Bari, Bari, Italy

[b] Mesagne Hospital, Brindisi, Italy

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A CASE OF TRISOMY D_1 - SYNDROME OF PATAU *

G. GUANTI, F. DEL SORDO **, P. PETRINELLI and E. BATTAGLIA

Institute of Genetics, University of Bari, Bari, Italy
** Mesagne Hospital, Brindisi, Italy

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INTRODUCTION

The presence of an additional chromosome in D group was first described by PATAU *and coll.* (1960).

The syndrome, determined by this chromosomal aberration, characterized by congenital cardiopathy, ocular malformations, mental retardation, malformations of the central nervous system, cleft palate, often with harelip, and polydactyly, had been described in detail by BARTOLINI (1657) and amplified by KUNDRAT (1882). The syndrome, however, took the name of Patau, who was the first to study its chromosome set. YUNIS (1964) and GIANNELLI (1965) with autoradiographic techniques established that the supernumerary chromosome is a 13 (D_1). The incidence of D_1 trisomy in newborns is about 1 per 7602 live births, according to the data recently collected by TAYLOR (1968); it is probable, however, that it is much more frequent, considering that it has been found in a great number of miscarriages. Infant mortality is high in trisomy 13; the affected subjects rarely reach or exceed the age of 5 in consequence of severe malformations; rare cases, however, of trisomy carriers have survived up to the age of 10 (MARDEN *et al.* 1967; MAGENIS 1968).

In this paper are described clinical and cytogenetic findings in a patient with multiple malformations, typical of Patau's syndrome.

Case report

CML., a female infant, was the second child of healthy, unrelated parents (father 40 yrs, mother 42 yrs); her brother was perfectly normal. The

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patient was born, by eutocic delivery, two weeks over the fixed term. A great deal of amniotic liquid was noted; the placenta, of normal appearance, weighed about 400 g. She was hospitalized three hours after birth, with a diagnosis of blue asphyxia in female infant with multiple congenital malformations.

Physical examination

Birth weight: 3,350 g; height: 47 cm; head circumference: 35 cm; chest circumference: 31 cm; deep cyanosis; weak cry; feeble reflexes; generalized hypotonia; small palbebral fissures for blepharophimosis; bilateral microphthalmos; unilateral cleft lip and cleft palate (Fig. 1) dx; low-set malformed ears; bilateral polydactyly of the hands; flexion deformity of both thumbs; clinodactyly of the fifth finger; bilateral poly-syndactyly of the feet (Fig. 3); cutaneous and osseous aplasia of Vertex (ulceration of the scalp measuring about 1×2 cm with underlying parietal bone aplasia [Fig. 2]). Normal neck without pterigium; globous chest.

Respiratory apparatus: shallow and irregular respiration; crepitus indux at the bases pulmonis and along paravertebral grooves.

Heart: enlarged cardiac area; no thrills; apex beat palpable at 4th intercostal space; embryocardic sounds.

External genitalia: hypertrophy of the clitoris.

X ray examination of cranium: right eye socket smaller than left (Fig. 4).

X ray examination of chest: cardiac silhouette enlarged in toto, hilar shadows intensified; great vessels surmounted by an opaque cowl-shaped image.

Radiological data suggest the existence of a heart defect with thymomegaly.

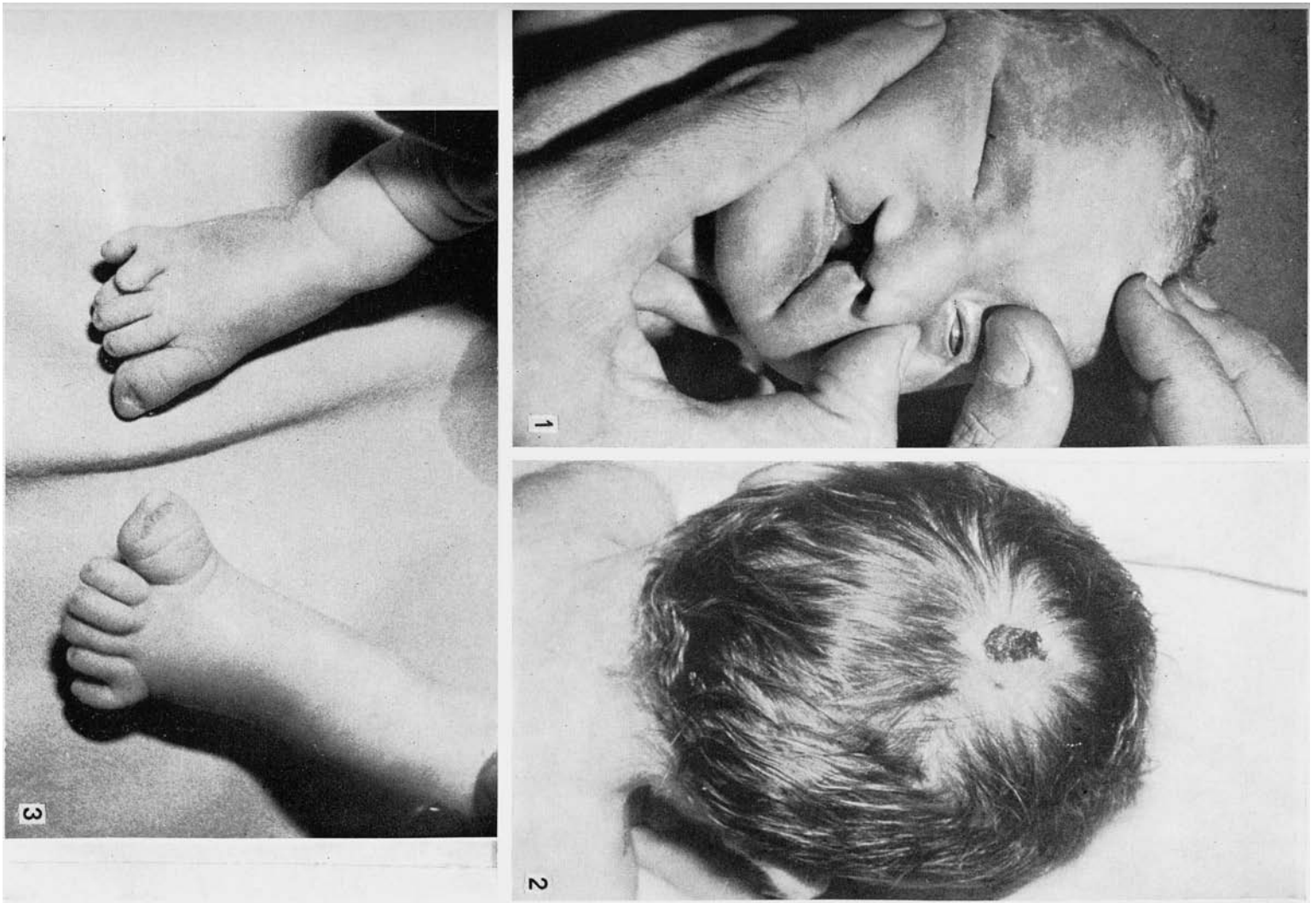
ECG: heart rate 152/m; atrioventricular block and troubles of intraventricular conduction of right branch; clinical, radiological and ECG data testified to the existence of septal defect typus Ostium Primum.

The patient died after 12 days with a clinical picture of acute pulmonary oedema.

Laboratory data

The peripheral blood smears showed, on 100 neutrophils, 40 with 1 or without nuclear projections and 60 with 2 or more. Many nuclei presented hook-like appendages as well as hypersegmentation.

Fig. 1. — See the text.
Fig. 2. — See the text.
Fig. 3. — See the text.



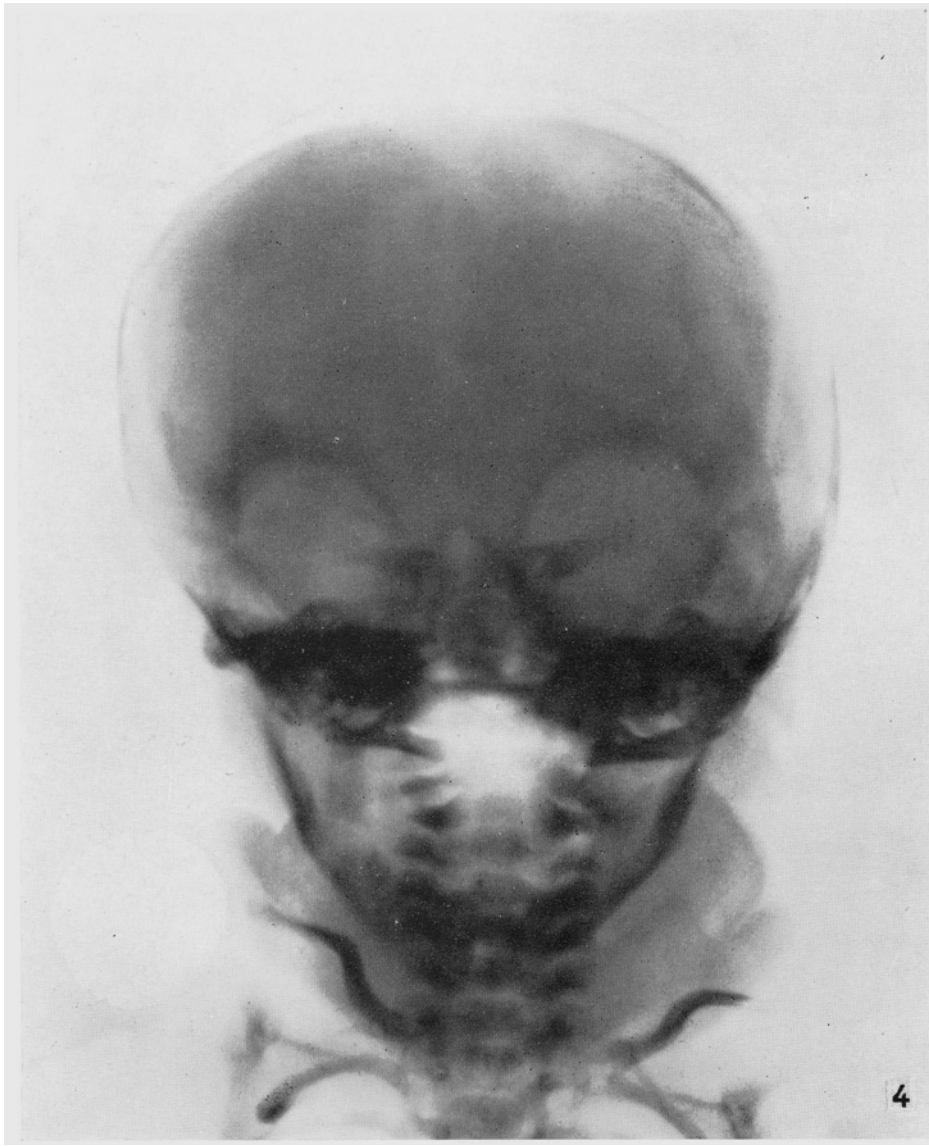


Fig. 4. — See the text.

No alteration in the transmission of blood groups was found.
Haemoglobin F: 62; Hb A_2 normal.
Dermal patterns: distal axial triradius, simian crease on both palms.
Cytogenetic investigations: the chromosomes examination was carried

out on peripheral blood, in accordance with the method adopted in this Institute.

The chromosomes of 90 mitoses were counted; of the 20 karyotypes photographed and reconstructed all showed 47 chromosomes with a supernumerary chromosome in group D (Fig. 5).

The origin of the trisomy may have been a meiotic non-disjunction verified during the gametogenesis of one parent, or a mitotic (post-zygotic) one; in the latter case it is more common to find a 46 normal/47 trisomic mosaicism, providing the error did not take place in the 1st division of the zygote, so giving rise to a 45, XX, D– non viable cell and to a 47, XX, D+ trisomic one.

The non-disjunction may take place both in the course of the maternal or paternal meiosis; however it appears more frequently during the oogenesis; the causes are not known but various hypothesis have been put forward.

According to POLANI (1960) the possible cause of the various numerical and structural alterations mostly involving the chromosomes D and G is their nucleolus-organizer function; according to BODMER (1961) the cause is due to a reduced efficiency in the chromosome pairing.

According to SLIZYNSKI (1960) the advanced maternal age plays a very important role in the determining of these alterations: in fact the prolonged permanence of the egg in dictyotene stage makes the progressive terminalization of the chiasmata possible so that chromosomes entirely separated move randomly to one of the poles.

The case we have described presents most of the typical features of Patau's syndrome: microphthalmos (particularly marked on the right, where the eye socket results smaller); cranio-facial malformations (with anomalies of the ears, cleft lip and cleft palate); alterations of the limbs (polysyndactyly, etc.); congenital cardiopathy; characteristics of the dermatoglyphics (distal axial triradius, simian crease, findings in agreement with those described by UCHIDA in 1962). The advanced maternal age is also in concordance with the data. Cutaneous and osseous aplasia of the Vertex, first described by KHAN (1965) in 13 of the 35 cases reported in his thesis, has been indicated by SABATINI (1966) as an useful diagnostic sign. Polyhydramnios, among the less frequent of the findings, has been described in a case of trisomy D_1 by DELLEPIANE *and coll.* (1965). In our patient also nuclear hook-like appendages and hypersegmentation of the polymorphonuclear neutrophils were present. HUEHNS and POWARS (1964) have attributed to such findings a diagnostic importance; it must be noticed however that these features have also been found in subjects with carcinomata or sarcomata (GRUNER 1915-1916) and in some normal adults (DAVIDSON and SMITH 1954); at the same time

FINE (1965), in a comparative paper, has noted appreciable differences between the neutrophils of normal newborns and those of trisomy 13-15 carriers. The persistence of abnormally high quantities of Hb F appears to be a constant characteristic of the trisomy D_1; however in the neonatal period it may be difficult to be certain of the elevation of its concentration in view of the inherent inaccuracy of the commonly used alkali denaturation method at high concentrations of Hb F.

According to HUEHNS (1964) the presence of haemoglobins containing γ and ε chains may represent an unbalance between genetic elements, structural and regulating, for the synthesis of these chains, consequent upon triplication of a chromosome of D-group.

According to WEINSTEIN (1965) the elevated levels of Hb F are a consequence of a non specific disturbance exercised by the supernumerary chromosome due to a generally retarded development of biochemical phenomena. The constant association between the high concentrations of Hb F and D_1 trisomy have suggested (HUEHNS 1964) that one of the chromosomes of D-group exerts a specific influence on the control of the transition from embryonic and fetal hemoglobin production to the normal adult form. The mechanism through which the chromosomal anomaly produces the malformations typical of Patau's syndrome is not yet known.

According to HALL (1964) the qualitative gene content of the extra chromosome may not be as important as the quantitative gene unbalance that it causes; the supernumerary chromosome would act mainly as a source of diffuse disturbance.

In other words, according to this hypothesis, only minor qualitative differences could be expected between the different trisomy syndromes; but instead there are found quantitative differences due to the amount of extra chromosome material present.

This disturbance, during embryogenesis, would show itself in a delay and a depression of the development processes and of the evolution of the various organs and tissues. The entity of the malformations may be variable, perhaps because of the interference of other genes; environmental factors are not to be excluded.

According to LEVKOFF (1964) the typical malformations of the trisomy may be consequent to the unbalance between the m-RNA precursors and the DNA. In other words the additional chromosome material in the nucleus would produce an unbalance between the RNA precursors and the DNA templates resulting in a competition among the templates, for the limited

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Fig. 5. — Karyotype of the proposita x 2400.

5

number of precursors. This competitive interference would result in a change in the apportionment of the messenger RNA molecules produced (the RNA templated by triplicate chromosome increases probably at the expense of that RNA templated by other chromosomes). Such abnormal distribution would, in turn, alter the pattern of cytoplasmic protein molecules produced.

MARIN-PADILLA (1964) believes that the chromosomal disorder can be expressed morphologically in 2 principle ways:

1) with the induction of an excess amount of tissue, both normal (1a) as well as abnormal (1b);

2) with a disturbance of induction in some organ systems.

1a) The excess formation of normal tissues may result in a local excess of tissues in various organs and lead, at times, to duplication of some of them (supernumerary lobulation of the liver, pancreas, kidney; polydactyly, etc.). In this case the anomalies might be the consequence of an unbalance between the excess tissue and the surrounding normal tissues.

1b) Excess formation of abnormal tissues. There are malformations in which an excessive amount of tissue, microscopically and often grossly abnormal, is present. This is particularly evident in the histologic study of pancreas, kidney, and less strikingly in the liver.

2) Some malformations might be consequence of defective formation of other structures that during the embryogenesis act as inductors. Probably some common anomalies (arrhinencephaly) are really secondary to defective formation of the skull blastema, particularly of the ethmoid bone.

YIELDING (1967), starting from examples taken from microrganisms, affirms that a cell with an extra structural gene and a corresponding extra regulator gene can effectively have a lower level of genetic expression than a cell with the normal complement of both genes if saturating levels of inducer are not present. This is presumably due to increased cellular concentrations of specific repressors. Redundancy of an entire chromosome could result in the suppression of many genetic loci corresponding to each regulated gene.

On this basis the extra chromosome would determine a reduced, unchanged or increased genetic expression in the case of « regulated » genes depending on the concentrations of the specific inducers present.

Non-regulated loci (constitutive) in contrast would be expected to show increased expression. RHODE *and coll.* (1963) have availed of the theory set out by JACOB and MONOD (1961) to explain the relation between chromosomal aberrations and malformations: the induction and the repression of the structural gene activity by the complex interaction of the Regulator and Operon serve to explain the regulatory mechanisms by which quantitative genic unbalance leads to biosynthetic disturbances. The immediate causes are

due to faulty induction and/or repression of the *Operator* loci because of monosomic and/or trisomic *Operons*; faulty repression of the *Operator* permits excess structural gene products to be produced. For normal repression to occur, competent « inhibitor » concentrations of end products (acting as co-repressor) must arise to 150% of normal. Teratogenesis may result from the following: a) excess gene products (protein or enzyme), b) excess or deficiency of the product or substrate, respectively, of the enzymatically governed reaction, or c) deprivation of essential metabolites due to accelerated syntheses which disturb concurrently active biosynthetic pathways of other loci. At the same time according to the authors the variations that the phenotype may present are the result of environmental influences during embryogenesis and therefore reflect the immediate availability of maternally derived metabolites, in particular small molecular substances including vitamins and probably hormones. In fact variations in the flux of these substances and the duration of their eventual deficiency will interact with quantitative genic unbalances directly responsible for the malformations, influencing their expression either positively or negatively.

In the trisomies of chromosomes carriers of a nucleolar organizer it is also possible, according to POLANI (1968), that the adding with the trisomic chromosome of an extra nucleolar organizer may alter the cell metabolism through an excessive production of nucleolar material and presumably of special types of RNA, that would result in alterations of the proteins and enzymes synthesis in the cell.

The mechanism by which the D_1 trisomy produces the malformations is unknown although a priori several possibilities exist. The chromosomal aberration is manifested particularly by alteration of structures, the development of which occurs in the 5th or 6th week of embryonic life. It is not to be excluded however that the cell functionality is altered before, and that the consequences make themselves felt on some of the most important morphogenetical events only towards the 5th or 6th week. Main consequences are a decreased proliferation and a defective differentiation of mesodermal structures. The anomalies of the brain and of the organs of special sense are possible exceptions, although these lesions may be explained as the results of changed inductive influences by cephalic mesodermal structure. The above explanation helps to clarify, for example, the origin of facial malformations typical of the trisomy 13-15. Embryologically the development of the face is in relation to the development of the frontonasal process superiorly, the maxillary processes laterally, and the mandibular processes inferiorly. The active proliferation of these mesodermal masses begins in 5 week-old embryos and the fusion is complete at the 8th week. A moderate degree of hypoplasia of the frontonasal process results in broad, flat nose, and sloping

forehead. A more serious hypoplasia causes cebocephaly; bilateral cleft-lip and cleft-palate take place when the median hypoplastic nasal part of the frontonasal process fails to fuse with the two hypoplastic maxillary processes. Mandibular clefts are rare as the fusion of the mandibular processes occurs very early in embryonic development towards the 2nd or 3rd week. The hypoplasia, however, of this structure, occurring at the 5th week of gestation, results in micrognathia. These data demonstrate how incomplete our actual knowledge of action mechanism of supernumerary chromosomes is and how interesting it is to study the problems connected with it.

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ABSTRACT

A case of D_1 trisomy is reported. The patient suffered of multiple congenital anomalies, which formed a characteristic pattern known as the « Patau's syndrome ».

Chromosome analysis from blood cultures showed a modal number of 47; the additional chromosome was a 13 (D_1).

The aneuploidy origin and the probable mechanism, through which the malformations typical of Patau's syndrome might be produced, are discussed.

RIASSUNTO

È descritto un nuovo caso di trisomia D_1. La paziente presentava anomalie congenite multiple tipiche della sindrome di Patau.

L'analisi del corredo cromosomico, effettuata su culture di sangue periferico, ha permesso di accertare la presenza di 47 cromosomi; il cromosoma soprannumerario è risultato essere membro della coppia 13 (D_1).

Viene discussa l'origine dell'aneuploidia e le probabili cause delle malformazioni tipiche della sindrome di Patau.