A Deleted B Chromosome in a Mosaic Mother and her Cri du Chat Progeny

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Familial occurrence of chromosomal anomalies may be caused by: (1) numerical chromosomal abnormalities present in all or some of the cells of one of the parents (secondary non-disjunction), or (2) by a genetically determined tendency to meiotic or mitotic non-disjunction.

Structural chromosomal abnormalities such as translocations have also been described as frequent causes of familial chromosomal errors. It is the purpose of this paper to report the results of chromosome studies in a family in which two sibs carried a deletion of a short arm of a chromosome No. 5. One was a child with the typical cri du chat syndrome, the other was a fetus weighing 14 g. The mother was found to be a mosaic of normal cells and cells with a deleted B chromosome. A fertile mosaic of this type has not been reported before.

Material and Methods

Chromosomal analysis was carried out on cells from peripheral blood of a child with the cri du chat syndrome. Later the mother, her two living children, and a fetus, four of her five sibs, the maternal grandmother, and the father of the child with the cri du chat syndrome were also investigated (Fig. 1). The maternal grandfather and one of the mother's sibs were dead at the time of the investigations. A modification of the method of Moorhead et al. (1960) was used.

Other tissues were investigated by a modification of the method of Harnden (1960) (Philip, 1967). Autoradiographic studies were performed by the method of Freeland (1965).

Case Reports

The Mother. The mother was 33 years old and unmarried, and the father was 30, when the child with the cri du chat syndrome was born. General and gynaecological examination of the mother, who had always enjoyed good health, showed normal findings. With her first concubinary she had four pregnancies, one ending as a spontaneous abortion, one was legally interrupted, and two resulted in normal children. With her second concubinary she became pregnant twice; the first of these pregnancies resulted in the propositus with the cri du chat syndrome, the second was terminated by hysterotomy at four months' gestational age. At operation the internal genitalia were found to be normal, and biopsies from the following organs were removed from the mother for chromosomal analysis: skin, muscle, uterus, and right and left ovary. The fetus was dissected with the help of a dissecting microscope, removing tissues from skin, muscle, lung, and heart.

Child with cri du chat syndrome (propositus). This child, a boy, was born after an uneventful pregnancy, two weeks before term. Birthweight 2700 g. The child had severe asphyxia at birth with an Apgar score of 5 after 10 minutes, and made the first weak scream after 15 minutes. Assisted ventilation had to be given for 25 minutes. The physical examination showed the typical appearance of the cri du chat syndrome: microcephaly (head circumference 32.5 cm.), 'rounded face', hypertelorism, low-set, small ears with accessory fibromas, retronincognathia, short neck with loose skin, and simian creases of both palms. The fourth toes were displayed dorsally, and the fifth toes were both very small. The infant's cry was suggestive of the miaowing of a cat.

At follow-up examination at 1 year of age severe retardation was found together with generalized hypotonia. Height 70 cm., weight 7450 g., and head circumference 42 cm. The physical signs of the cri du chat syndrome, including the cat cry, were still typical.

Laboratory examinations. The only abnormal biochemical findings were: (1) slightly decreased serum albumin (3.92 g./100 ml.); (2) raised fetal haemoglobin level (59% at the age of 6 weeks); (3) very low activity of beta-D-glucosidases in the urine (0.06 units at 6 weeks of age) but increasing during the next three months to levels just below normal range of this age-group (0.295 units); and (4) moderately increased levels of amino acids in serum and urine (non-specific). The following parameters were all within normal range: urinary acid

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mucopolysaccharides, urinary arylsulphatase A and B, serum acetylcholinesterase, serum lactic acid dehydrogenase, and the following erythrocyte enzymes: pyruvate kinase, glutathione reductase, glucose-6-phosphate dehydrogenase and ATP-ase. The sweat electrolytes were also normal.

**Fetus with deleted B chromosome.**

*Patho-anatomical findings.* No gross abnormality of the placenta and the umbilical cord was found. Microscopical examination showed small collections of neutrophilic polymorphonuclears in the capsular decidua.

The fetus weighed 14 g, crown–rump length was 66 mm., and foot length 9 mm. The eyes were far set, but no other external abnormality was detected.

By dissection, no malformation of the organs or the skeleton was found. Microscopical examination of the organs revealed two anomalies: in the cortex of the kidneys a number of small cysts with flat epithelium among normally developing glomeruli and proximal and distal tubuli, and in the ovaries a reduced number of oocytes in relation to the age of gestation.

**Results**

The results of the chromosomal analyses are seen in the Table.

**The propositus.** The propositus (III.5) had a deletion of the short arm of a B chromosome in all investigated cells from blood.

Sixteen selected cells from a second culture, to which tritiated thymidine was added, were photographed. The results of the autoradiography of the B chromosome of nine of these cells are shown in Fig. 2. The deleted chromosome shows the labelling pattern generally assumed to be typical of chromosome No. 5.

**The mother (II.4).** In the first blood culture from the mother 7 cells in metaphase out of 100 analysed had the same structural abnormality in a B chromosome. In a second blood culture only 2 out of 50 cells had the Bp-chromosome; no autoradiographic examination was, therefore, attempted.

A complete analysis was carried out in all cells from the second culture with amodal numbers. In 9 of 10 cells with less than 46 chromosomes the missing chromosomes were apparently from different groups. One cell had a 45,XX,D – G –, t (DqGq), and another cell had a 47,XX,G + karyotype.

In the other investigated tissues from the mother the deletion was not found, except in one cell from the left ovary.

**The fetus (II.6).** The deleted chromosome was present in all investigated cells from skin, lung, and muscle from the fetus.

**The family.** Normal karyotypes were found in cells from blood from the maternal grandmother.
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(A.1), the 2 oldest children (III.1; III.2) of the mother, and in her 4 living sibs (II.1; II.2; II.3; II.5). The father (II.4B) of the child with cri du chat syndrome had a normal chromosome complement (Table).

Discussion

A deletion of the short arm of a chromosome No. 5 was found in 4–7% of cells from two blood cultures from the mother of a child who clinically and cytogenetically had the cri du chat syndrome. In only one cell from the left ovary of the mother the same structural abnormality was present. As she had two pregnancies where the zygote must have carried the deleted chromosome the number of ova with the deleted chromosome cannot have been negligible.

The propositus and the fetus both had a deletion of the short arm of a B chromosome in all the cells investigated. The propositus was a typical example of the cri du chat syndrome. The fetus only revealed minor abnormalities. In a recent review of 69 cases of cri du chat syndrome Mennicken et al. (1968) stressed that in more than 50% of the cases no malformation was found except the craniofacial dysmorphism; most of the malformations described were cardiovascular, two cases had renal abnormalities, and one case had hypospadia. The technical difficulties in the examination of a 66 mm. crown-rump fetus are obvious, and besides the abnormalities found, i.e. hypertelorism, slight cystic kidneys, and retarded development of the ovaries, other malformations may have been overlooked.

Mosaicism involving either sex chromosomes or autosomes is usually found in phenotypically

Fig. 1. The pedigree of the family.

abnormal patients, but ascertainment has most often been because of the abnormal phenotype. Mosaicism may, therefore, be present in the normal population in higher frequencies, than is now assumed (cf. Court Brown, Jacobs, and Brunton, 1965; Sergovich et al., 1969).

Fig. 2. The B group from nine different cells labelled with 3H thymidine.
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Apparantly normal people with mosaicism have thus been ascertained because of abnormal progeny. Trisomy C mosaicism has been published by Stolte, Evers, and Blankenborg (1964) and Bishun (1968) in normal mothers of abnormal children. Several reports have been published of women having children with Down's syndrome, who themselves were shown to be mosics of normal cells and cells trisomic for chromosome No. 21 (Blank et al., 1963; Smith et al., 1962; Schade and Schoeller, 1963; Weinstein and Warkany, 1963; Ferrier, 1964; Verresen, van den Berghe, and Creemers, 1964). In these cases the children were mongols with 100% trisomic cells.

Mosaics including cells with structural abnormalities, except for translocation chromosomes, are rare. Mosaicism with deletion of a chromosome No. 18 is reported by Lejeune et al. (1967). A deletion of one of the smallest elements (22?) together with a 46/47 mosaic was described by Pfeiffer, Schellong, and Kosenow (1962). Patients with mosaics including cells with a deleted chromosome No. 5 are reported by Zellweger (1966) and Roca et al. (1968) and a mosaic with a ring chromosome No. 5/normal cells by Steele et al. (1966). Warburton et al. (1969) in some cases of the cri du chat syndrome could only show very minute deletions of the short arm of the B chromosome. Therefore, the authors proposed that the phenotype of these patients was due to mosaicism, which they were unable to demonstrate.

Mosaics with mixtures of numerically normal and abnormal cells can reproduce. Their reproductive ability may, however, be hampered, and Kjessler (1965) found 5 cases of mosaicism among 130 men attending a sterility clinic.

Mosaicism may play a significant role among the causative factors of congenital malformations and abortions (cf. Bishun et al., 1964), and the findings in the reported family stress again the importance of investigation of the families in which congenital malformations are due to chromosome abnormalities.

Summary

The phenotypically normal mother of a child with clinically and cytogenetically verified cri du chat syndrome was found to be a mosaic of normal cells and cells with a deletion of the short arm of a B chromosome. The mother had another pregnancy terminated by legal abortion. The fetus had also the abnormal chromosome in all cells investigated. In cases of congenital malformations due to chromosome abnormalities, family studies are necessary for genetic counselling.

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