Congenital Malformations Associated with a Ring 4 Chromosome

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Ring chromosomes in man have been described not only as interesting phenomena associated with irradiation and neoplasia (Levan, 1956; Tough *et al.*, 1960; Bender and Gooch, 1962; Jensen, 1966) but also as a probable cause of congenital malformations (Palmer, Fareed, and Merritt, 1967). In the cases of congenital malformations so far ascribed to ring chromosomes, the B group has been involved only once. However, the chromosome from which the ring was formed was thought to be a No. 5 (Rohde and Tompkins, 1965), and a ring 4 chromosome has not been reported.

The purpose of this paper is to describe a congenitally malformed infant with a ring chromosome of the B group which we consider to be a No. 4.

Case Report

The patient, a male weighing 1.88 kg. and measuring 44 cm. from crown to heel, was the first child of young Caucasian parents with an unremarkable family history. Pregnancy, lasting 40 weeks, was uneventful except for the first trimester when the mother was given γ -globulin intramuscularly after a rubella contact, and cyclizine hydrochloride for morning sickness. The congenital abnormalities were microcephaly (head circumference 30 cm.), brachycephaly, marked bilateral proptosis, coloboma of the left iris, harelip and complete cleft palate on the right side, flattened nose, bat-ear deformity on the left side, hypospadias, abnormally flexible carpo-metacarpal articulation of the thumbs bilaterally, a transverse palmar crease in the right hand, and bilateral overriding of the second toe on the third (Fig. 1). X-rays of both hands showed marked hypoplasia of the first metacarpals and of the phalanges of the thumbs, and wedging of the middle phalanges of the fifth digits with incurving as seen in Down's syndrome.

The child developed tachycardia and intermittent tachypnoea soon after birth. These persisted until the onset of respiratory distress and signs of congestive cardiac failure 3 days before death, which occurred at the age of 4 weeks.

Pathology. The brain was small (weight 296 g.), with poorly developed secondary fissuring, and microscopical examination showed primitive lamination and poor differentiation of neurones in the cerebral cortex. These findings suggested a general developmental retardation, or hypoplasia, of the brain in relation to other organs. In the heart the foramen ovale was found to be patent due to extensive fenestration of the septum primum. In both leaves of the diaphragm large areas of muscle were replaced by thin fibrous membranes, but

FIG. 1. Post-mortem photograph of the patient showing small head, proptosis, malformed ear, flattened nose, harelip, abnormal thumbs, and overriding toes.

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there was no significant herniation of abdominal viscera. The bowel was incompletely rotated and suspended by a single mesentery. The kidneys were very hypoplastic, each being about one-third normal size (weight 5 g.), and slightly dysplastic, microscopy showing a few small cysts and foci of haemopoiesis; in addition, most of the convoluted tubules were atrophic and dilated by granular proteinaceous material and cell debris. Extensive congestion and oedema and an early klebsiella bronchopneumonia were seen in the lungs. Death was attributed to renal failure and terminal bronchopneumonia.

Material and Methods

Buccal smears of the patient and his parents were examined for sex chromatin. Peripheral blood leucocytes were cultured by a modification of the micro-method of Evans (1965) and examined as follows: from each parent 50 metaphases were analysed microscopically and 5 karyotypes were prepared; from the patient 200 metaphases were analysed microscopically and 40 karyotypes were prepared—colcemid-free studies of the anaphase and telophase configurations of the ring, as well as autoradiography, were precluded by death.

Sternal bone-marrow taken from the patient at necropsy was examined by a 4-hour culture technique, 22 metaphases being examined microscopically.

Results

The parents show no sex-chromatin or chromosome abnormalities.

TABLE I

RESULTS OF CHROMOSOME ANALYSIS

Chromosome count	< 45	45	46	> 46	Poly-ploid
No. of cells	3	16	165	6	10
Monocentric ring	2	7	151	3	2
Dicentric ring	1		4	1	3
Two rings			2	2	1
Ring absent		9			4
Rod derived from ring			8		

Buccal smears from the patient are sex-chromatin negative. Table I summarizes the results of chromosome analysis. A modal number of 46 chromosomes is apparent. All cells containing this number are missing a member of the B (4–5) group, replaced in 91.5% by a monocentric ring chromosome (Fig. 2), in 3.6% by either two rings or a dicentric ring (Fig. 3), and in 4.9% by a rod chromosome which varies in length from cell to cell and is interpreted as a product of ring breakage with healing, rather than reunion, of the broken ends. Cells containing less than 46 chromosomes appear to be broken, and those with more than 46 chromosomes generally contain three chromosomes in the B group and two rings, or one ring plus an extra C group autosome.

FIG. 2. Karyotype of cell with 46 chromosomes showing the group 4–5 ring chromosome.

Fig. 3. Variant ring forms.

On account of their poor quality, bone-marrow preparations cannot be completely analysed; nevertheless, a single ring chromosome can be clearly identified in each metaphase.

Discussion

Ring chromosomes are known to behave irregularly at mitosis (Levan, 1956), so it is not surprising to find a few cells with multiple or variant ring forms in the present case. The majority of cells, however, contain one monocentric ring and are apparently lacking a B group chromosome. There can be little doubt that the ring is formed from this chromosome, since otherwise the cells would clearly be monosomic for a B group chromosome and non-viable. For the ring to occur so extensively in the two cell-lines examined it must have arisen either during parental germ cell meiosis or very early in embryogenesis, presumably from breakage and subsequent union of both arms of the chromosome. In the process fragments of genetic material would be lost so that the ring, behaving during subsequent embryogenesis as a partially deleted B group chromosome, might well be expected to cause the congenital malformations described.

Either chromosome 4 or chromosome 5 must be involved in the ring. Precise identification cannot be attempted in the absence of autoradiographic data, but a comparison of the abnormalities of the patient with those of reported cases with B group aberrations suggests that the chromosome is a No. 4. Absence of portion of the short arm of No. 5 is usually associated with the 'cri-du-chat' syndrome (Miller *et al.*, 1966b). The only previously reported case with a ring B group chromosome showed the features of the cat-cry syndrome and, accordingly, the chromosome was assumed to be a No. 5 (Rohde and Tompkins, 1965). Short arm deletion of a No. 4 chromosome has been suggested in 6 reported cases. In 1965, Wolf *et al.* described an infant with abnormalities different from those in the cat-cry syndrome in which autoradiography indicated deletion of a No. 4 rather than a No. 5 chromosome. Subsequently 5 other

cases, 2 lacking autoradiographic data but all with similar congenital malformations, have been reported (Hirschhorn, Cooper, and Firschein, 1965; P. L. Giorgi, M. Ceccarelli, and A. Paci, 1965, personal communication; Miller *et al.*, 1966a; Leão *et al.*, 1967). These 6 cases, which are summarized and compared with the present case in Table II, were considered by Leão *et al.* (1967) to constitute a separate clinical syndrome which they named the 'chromosome No. 4 partial deletion syndrome'. Though doubtful that the clinical features are constant enough to evoke a recognizable clinical syndrome, we are nevertheless sufficiently convinced by the similarity between the cases, by their dissimilarity to the cat-cry syndrome, and by the autoradiographic evidence, to conclude that the chromosome involved in all of them, and therefore in our own case, is the No. 4. We consider that the variation between the cases in no way invalidates this conclusion, the loss of genetic

TABLE II
ABNORMALITIES IN PRESENT CASE AND IN REPORTED CASES WITH DELETED SHORT ARM OF CHROMOSOME B 4

Abnormality	Present Case	Wolf <i>et al.</i> (1965)	Hirschhorn <i>et al.</i> (1965)	Giorgi <i>et al.</i> (1965, personal communication)	Miller <i>et al.</i> (1966a) Case 4	Miller <i>et al.</i> (1966a) Case 11	Leão <i>et al.</i> (1967)
Sex	M	F	M	F	M	M	M
Autoradiography		No. 4			No. 4	No. 4	No. 4
Cranial	+	+	+	+	+	+	+
Cerebral	+	+	+	+	+	+	+
Midline scalp defect	-	+	+		-	+	+
Coloboma	+	+	+		-	+	+
Proptosis	+	-	-				+
Cleft lip and palate	+	+	+	+	-	-	-
Malformed ears	+	+	+	+	+	+	+
Broad nose	+	-	-	+	-	+	+
Proven heart defect	+			+			
Uro-genital							
Renal hypoplasia	+			+			
Inguinal hernias	-	-	-		+	-	+
Hypospadias	+	Female	+	Female	-	+	+
Skeletal	+		+	+			+

+ = present; - = absent; blank = not described.

material in this type of chromosome aberration being inherently variable from case to case, and therefore unlikely to produce a constant pattern of congenital abnormalities.

Summary

An infant with microcephaly, proptosis, coloboma, harelip and cleft palate, hypospadias and renal hypoplasia, atrial septal defect, and skeletal abnormalities was found to have a karyotype monosomic for a B group chromosome and containing a ring chromosome. The ring chromosome was not identified by autoradiography but is considered to be a No. 4, since the associated congenital abnormalities are similar to those described in cases of deletion of the short arm of this chromosome.

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