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Chromosome Studies in 2 Patients with Suspected "Cri du Chat" Syndrome[1),2)]

By

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(With 2 Text-figures and 2 Tables)

Rapid advances in cytological techniques of late years have surprisingly promoted the development of human cytogenetics, and established a series of significant associations between chromosomal changes and congenital or hereditary disorders. Current literature refers to a variety of autosomal as well as sex-chromosomal abnormalities in association with disease conditions.

Lejeune and his coworkers (1963) have reported a new syndrome associated with partial deletion of the short arm of one of B chromosomes. Clinical features of this syndrome are characterized by growth failure, mental retardation, microcephaly, epicanthal folds, antimongolian slants, hypertelorism, and a cat-like cry, the most outstanding character, based on which the term "cri du chat" syndrome was applied. Since then on, a variety of this syndrome, different in degree of clinical character, has been subjected to chromosome studies (Böök *et al.*, 1963; Dumars *et al.*, 1964; Lejeune *et al.*, 1964a, b; Macintyre *et al.*, 1964; Punnet *et al.*, 1964; Bergman *et al.*, 1965; Dyggve and Mikkelsen, 1965; Genest *et al.*, 1965; Grouchy and Gabilan, 1965; Hijmans and Shearin, 1965; Kajii *et al.*, 1965; Lejeune *et al.*, 1965; McCracken and Gordon, 1965; Urano *et al.*, 1965).

In the course of a chromosomal survey conducted by Professor Makino the authors have had an opportunity to study the chromosomes of two patients with the suspected "cri du chat" syndrome. This paper deals with some karyological features of these patients.

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2) This paper is dedicated to Professor Sajiro Makino, Zoological Institute, Hokkaido University, Sapporo, in honor of his sixtieth birthday, June 21, 1966.

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Clinical records: Case 1 is a baby boy, aged 12 months, born to his parents who are physically and mentally normal. The delivery was 4 weeks ealier than expected, and at birth he weighed 2.7 kg. The mother has had no other conceptions. The mother's and father's ages at the birth of the patient were 26 and 29 years, respectively. No familial or congenital diseases were known to occur in the relatives other than the propositus. The patient exhibited the characteristic mewing cry. Other abnormal clinical findings were severe mental retardation, hypotonia, microcephaly, low-set ears, growth failure and ventricular septal defect. Antimongolian slant, epicanthus and strabismus were not detected. Moonface was inconspicuous. The dermal patterns of hands and soles were within normal limits, unlike the most "cri du chat" cases so far recorded (Table 1). On the basis of the above clinical findings, this patient was diagnosed as "cri du chat"-like syndrome.

Case 2 is a 28-year-old man. He is the fourth child of the parents who are normal in phenotype. The second elder brother of the propositus has hoarseness as well as failure to thrive. The third elder brother has a skin cancer, and younger sister is congenitally infirm. Two other brothers are healthy. At the time of birth of the propositus the ages of his mother and his father were 27 and 35, respectively. Birth weight was 3.95 kg. He is now complaint of hoarseness, blurred vision with cataract and growth failure, being 149 cm in height and 42 kg in weight. Clinical examinations revealed dermatrophy, moonface, hypertelorism, microcephaly, slightly malformed low-set ears, epicanthus and slight mental retardation. Based on these clinical features the patient was initially diagnosed as either Werner's syndrome or "cridu chat" syndrome. Further examinations failed to detect any positive evidence for the presence of hypotonia, congenital heart defects, micrognathia, strabismus, antimongolian slant, and short neck. Dermatoglyphic analysis furnished no significantly abnormal findings (Table 1).

Table 1. Dermatoglyphics of two cases under study

Case no.		Digital patterns					Axial triradiu in t' position	Simian line	Hullucal area
		1	2	3	4	5			
1	Right	UL	UL	UL	UL	UL	0	0	L^t
	Left	UL	UL	UL	UL	UL	0	0	L^t
2	Right	W	W	UL	W	W	0	0	W
	Left	W	UL	UL	W	W	0	0	W

UL: ulnar loop. W: whorl. O: none.
L^t: loop tibial.

Cytological findings

Short-term cultures of leucocytes derived from peripheral blood provided specimens for chromosome preparations. Slides were made according to the modified method of Moorehead *et al.* (1960). Leucocytes of 3 or 4 days in culture were treated with colchicine (10^{-7}M) for about 90 minutes. The specimens were then treated with a 0.5 per cent sodium citrate solution for 20 minutes, fixed with

Carnoy's fixative, air-dried on slides and stained with Giemsa.

The results of chromosome counts in the two cases here considered indicated that they had a normal diploid number, 46 (Table 2). Two representative karyotype analyses from 10 well-spread metaphase plates in each case, are as shown in Figures 1 and 2. In both cases there were no identifiable chromosomal abnormalities: all cells analyzed had 22 normal autosomal sets with an XY sex-chromosome constitution. There was no sign of the deletion in the short arm of any one of four B chromosomes.

Table 2. Chromosomeal findings in two patients studied

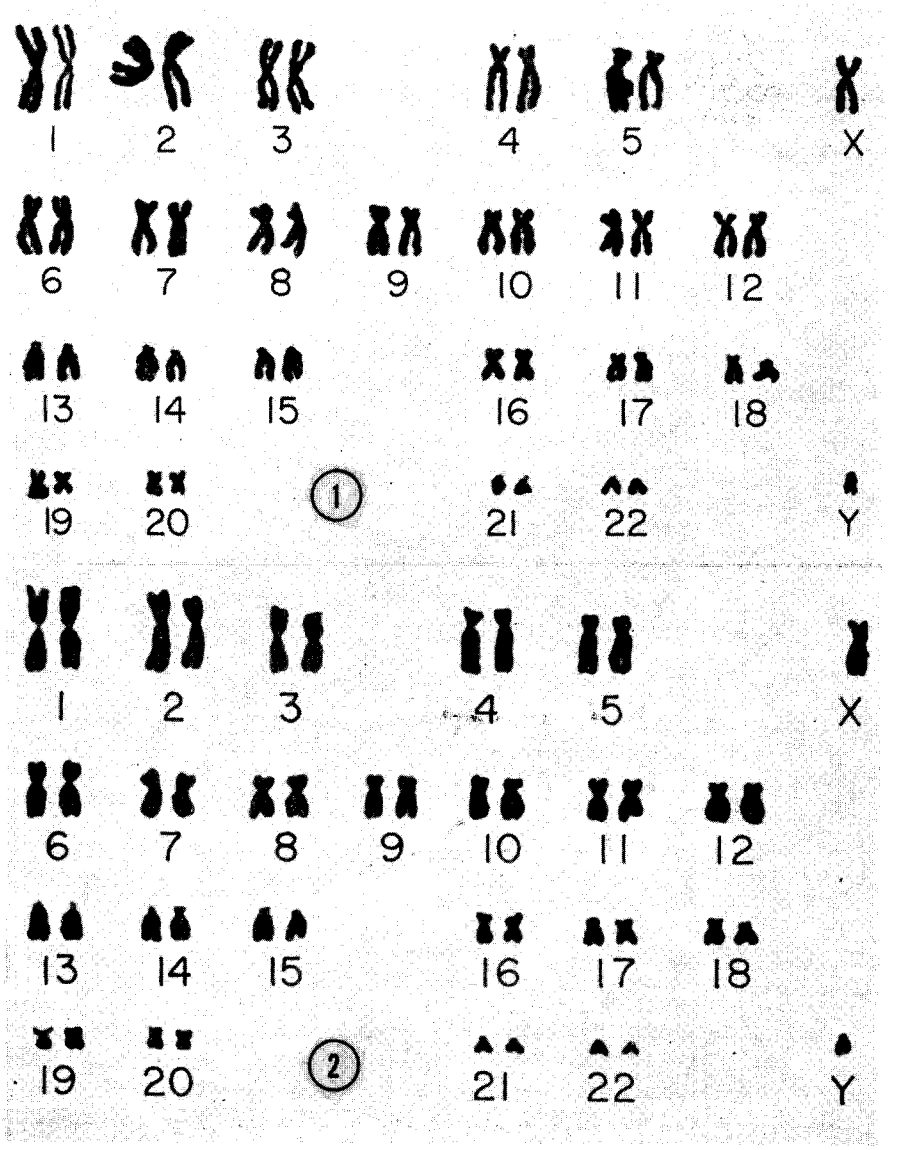
Case no.	Chromosome counts				No. of cells observed	No. of cells analyzed	Chromosome constitution
	44	45	46	47			
1	0	1	25	0	26	10	46, XY
2	0	1	22	0	23	10	46, XY

Remarks

Following the first description in three cases with "cri du chat" syndrome by Lejeune *et al.* (1963), some twenty cases with the same syndrome have been reported to date. It was reported that these cases showed a consistent karyotype anomaly characterized by the deletion of the short arm of one of group B chromosomes. Referring to the literature it is apparant that the magnitude of the deletion vary in more or less degree from case to case (German *et al.*, 1964). No clinically typical case of "cri du chat" syndrome with a normal chromosomal complement has yet been reported so far. Particularly case 1 of the present study showed many clinical symptoms characteristic to this syndrome, while he possessed a normal karyotype. The situation is quite similar to some cases of Down's syndrome: they showed characteristic symptoms of the syndrome, but their karyotypes were apparently normal. (Schmid *et al.*, 1961; Hall 1962; Makino *et al.*, 1962; Muramoto and Takagi, 1964; Makino, 1965). Hall (1962), working on a typical case of Down's syndrome with a normal karyotype, stated that, although trisomy 21 is a reliable sign of Down's syndrome, the correlation may not be an absolute one. A similar explanation may also be applicable to the present cases. Since the deletion is variable in degree from case to case in reported cases, a variety of symptoms may occur in the "cri du chat" syndrome. Further, a possibility can not be neglected that a minute deletion, indetectable by current techniques, have occurred on the short arm of one of B chromosomes. Furthermore, mosaicism would not be overlooked in the "cri du chat" syndrome.

The abberent chromosome of the "cri du chat" syndrome has generally been described as of a No. 5 by many authors since Lejeune *et al.* (1963). German *et al.* (1964), by the application of autoradiographic techniques, showed that the

abnormal chromosome is one of the pair in B group characterized by relatively early completion of DNA synthesis in the long arms. On the other hand, a de-



Figs. 1-2. Karyotypes of the patients showing a normal chromosome complement in each. 1: case 1. 2: case 2.

letion of short arm of No. 4 chromosome identified by autoradiographic studies was reported by Wolf *et al.* (1965). It is thus apparent that further chromosome survey with a variety of materials is requested in this syndrome.

Summary

Two patients, 12 months and 28 years of age, and clinically suspected as "cri du chat" syndrome, were screened for chromosomal abnormality. It was shown that both cases had an apparently normal karyotype, without evidence for the deletion in the short arm of four chromosomes in group B.

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