Cri-du-Chat Syndrome Combined with Partial C-Group Trisomy*

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Case Report

K.C., a Caucasian female (Fig. 1), weighing 2250 g was delivered following an uneventful pregnancy. She was noted to have very low-set ears, apparent hypertelorism, micrognathia, webbed neck, low posterior hair line, a prominent occiput with a midline occipital strawberry nevus with hairy tuft, hyperlaxity of joints, hyperelasticity of the skin and bilateral hip dysplasia. A weak cat-like cry was noted and direct laryngoscopy revealed poor approximation of the posterior portions of the vocal cords. Congenital heart defect was felt to be compatible with an endocardial cushion defect. Intravenous pyelogram was normal.

At one year of age she was 1.1, 3.0, and 3.8 standard deviations below the mean for height, weight, and head circumference. She shows marked developmental retardation manifested by lack of vocalization, sitting, or transferring.

The family history (see pedigree in Fig. 2) reveals that a sib (III.2) of the probanda died at 1 month of age after a very stormy course consisting of respiratory infections, congestive heart failure, and failure to thrive, along with a cat-like cry and facial features similar to those of our patient. Chromosome studies were not available.

Another sib (III.1) aged 6, appears to be a normal male with normal intelligence. Both parents are physically and mentally normal. The rest of the family history is negative.

Results

Karyotype analysis of 113 cells in the probanda revealed the modal number to be 46 chromosomes. A consistent finding in these cells is the absence of one of the group B chromosomes and the presence of an extra chromosome (T_1) (Fig. 3). Study of 118 cells from the probanda's mother and 35 cells from the normal sib consistently revealed the same absence of a group B chromosome with the presence of the extra T_1 chromosome and, in addition, a missing C-group chromosome and the presence of another

extra chromosome the size of a No. 16 (T_2) (Fig. 3). Karyotype analysis of the probanda's father, maternal grandmother, and grandfather was found to be normal.

Sex chromatin studies of the buccal smears of the probanda, her mother, and a sib were consistent with phenotypic sex.

Tritiated thymidine studies consistently revealed that 2 of the 3 morphologically normal B-group chromosomes can be paired as late replicators and the 3rd has an early replicating pattern like that of the T_1 chromosome. The T_2 chromosome was not late replicating.

Fluorescent microscopy after Atebrin staining consistently revealed that the T_1 chromosome was that chromosome of group B that manifests maximum fluorescence in the long arms between 30% and 60% of the distance from the centromere. It was also consistently found that the unpaired C-group chromosome was the one characterized by lack of fluorescence on the long arm just distal to the centromere, and maximum fluorescence on the long arm between 30% and 70% of the distance from the centromere. It is this chromosome that is the most metacentric of the shorter of the chromosomes of group C.

Measurements of the short arms of the 3 morphologically normal group B chromosomes and of the short arms of T_1 were made in 25 cells. The length of the short arm of T_1 was found to be, on the average, 57.0% longer than the average of the short arms of the 3 B-group chromosomes. This excess in short arm length of T_1 over the group B chromosomes was added to total length measurements of T_2 and these sums were compared to measurements of the rest of the C-group.

It was found that: (1) the sum was shorter than the 2 longest pairs of the C-group in all cells measured and shorter than the 3 longest pairs in 92% of cells measured. (2) This sum was longer than the shortest chromosome of the C-group in 96% of cells measured. (3) The centromere index

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in all cells measured when the sum was added to the long arm of T_2 was 0.326 ± 0.029 with a range of 0.280–0.385. (4) The centromere index in all cells

FIG. 1. The probanda.

measured when the sum was added to the short arm of T_2 was 0.422 ± 0.018 with a range of 0.394–0.462.

Anthropometric measurements revealed a small head, narrow face, and small stature with relatively normal ear size and eye measurements (Table I).

No unusual or abnormal dermatoglyphic patterns were noted in the probanda or other family members.

Discussion

Since Lejeune *et al* (1963 and 1964) first described the clinical and cytogenetic findings in the 'maladie

FIG. 2. Pedigree of the family with presumed genotypes for those systems which provided information on linkage.

TABLE I
ANTHROPOMETRIC MEASUREMENTS

	Mean with Standard Deviations (Pryor, 1966)	Probanda	Standard Deviation from Mean
Head			
Circumference	46.2 ± 1.50	40.5	-3.8
Length	15.9 ± 0.76	14.8	-1.4
Breadth	12.3 ± 0.47	10.5	-3.8
Face			
Height	7.1 ± 0.59	9.3	+3.7
Bizygomatic	10.3 ± 0.42	8.4	-4.5
Ears			
Breadth	2.7 ± 0.29	Left 2.7 Right 2.85	Left -1.7 Right +0.52
Length	4.7 ± 0.42	4.0 4.45	-1.7 +0.60
Eye			
Inter-pupillary (Pryor, 1969)	4.5 ± 0.53	4.6	+0.1
Inner canthus	2.5 ± 0.31	2.5	—
Outer canthus	6.5 ± 0.60	6.6	+0.1
Trunk			
A-P thoracic	12.2 ± 0.99	9.5	-2.8
Lateral thoracic	14.6 ± 1.15	13.8	-0.8
Bi-iliac	13.3 ± 1.02	10.4	-2.8
Height	30.0 ± 1.50	28.3	-1.1
Weight	21.5 ± 2.00	15.5	-3.0
Sitting height	47.5 ± 1.00	45.0	-2.5

FIG. 3. Partial karyotypes of mother, sib, and proposita with fluorescence of T_2 .

du cri du chat', the medical literature has supported a syndrome constancy.

Cytogenetically, the vast majority of cases have been shown to be caused by a deletion of the short arm of one of the early replicating pair of chromosomes in group B. Exceptions to this have included a number of cases with ring chromosomes and translocations.

The present case manifests clinical features of the cri-du-chat syndrome and also additional ones. The chromosomal findings are interpreted as 2 chromosomal breaks occurring in one of the grandparental gametes producing a balanced translocation in the proposita's mother. The proposita received the abnormal maternal 'B' group chromosome and the

normal one of the maternal 'C' group pair with a resulting monosomic state for a small portion of the 'B' short arm explaining the cri-du-chat syndrome and a trisomic state for a portion of the 'C' long arm. The proposita's sib (III.1) received both abnormal maternal chromosomes and therefore has a balanced chromosomal complement and is a translocation carrier.

Lejeune and Berger (1965) reported a family which had cytogenetic abnormalities almost exactly the same as our carrier case, and he believed the involved chromosomes to be No. 5 and No. 9. On the basis of the great variability in clinical complexes reported in C-group trisomy mosaics and partial C-group trisomies, a specific syndrome definition is

premature at the present time. However, as more sophisticated methods of chromosome identification are developed and more thorough family studies are undertaken to identify cases, partial trisomy syndromes should become better delineated.

Despite the fact that there still exists controversy regarding the differentiation between chromosomes No. 4 and No. 5 by autoradiography, our findings suggest that the translocation (T_1) chromosome is the one which has been defined to be No. 5.

In considering the results of the fluorescent studies, it was concluded that the T_2 chromosome is No. 11. The measurement data combining length and centromere index findings confirm the conclusion that the T_2 chromosome is No. 11.

The linkage data do not exclude linkage between either the ABO or Rh locus and the T_2 chromosome, or between the MNS and haptoglobins loci and the T_1 chromosome.

Descriptions of patients with the cri-du-chat syndrome consistently discuss hypertelorism and rounded facies. Pryor (1966 and 1969) has given us objective measurements for inter-pupillary distance and also for facial height-breadth measurements. We find that, although the proposita looks as if she has hypertelorism, the interpupillary distance is normal. An additional finding is that the facial breadth is 4.5 standard deviations below the mean. This combination of normal interpupillary distance with decreased facial breadth gives rise to the appearance of hypertelorism. In a similar manner, the approximation of facial width and height is presumed to explain the clinical observation of rounded facies.

We strongly feel that in the description of clinical

syndromes, especially those with chromosomal abnormalities, the importance of relative facial and other anthropometric measurements instead of subjective statements, cannot be overstressed. Birth defect literature of all types is sadly in need of objective criteria for the diagnosis of many features such as wide nasal bridge, low-set ears, retrognathia, high-arched palate, and others. Very few objective criteria are available to us. The use of the ones that are available is imperative.

Summary

A family with chromosomal translocation between a B-group and a C-group chromosome was studied. It is theorized from measurement, thymidine, and fluorescent data that the involved chromosomes are No. 5 and No. 11.

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