A Patient with 45,XX,G-/46,XX,Gr Mosaicism

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This is a brief report on a patient with physical and mental maldevelopment who was shown to have a chromosome abnormality of an unusual type affecting the G (21-22) group.

Case History

She was an only child born when her mother was 26 and her father was 44 years of age. Her birthweight was 2850 g.

She was admitted at 23 weeks of age because of failure to thrive. Her weight increments had been slow throughout, and at 23 weeks of age she weighed only 4875 g., which was a long way below the 10th percentile. She was short of breath, and there was clinical and radiological evidence of cardiac enlargement, but she did not have a cardiac murmur. Cardiac catheterization showed the presence of a large persistent ductus arteriosus. This was ligated at 35 weeks of age and she made an uneventful recovery.

There was delay in mental development, which was not severe at first. At 23 weeks of age she was laughing loudly, vocalizing actively, able to go for objects and grasp them, though not able to transfer from hand to hand.

Her facial appearance suggested mongolism (Fig. 1) though this was by no means clear cut, and in a large gathering of paediatricians, opinion was about equally divided whether she was a mongol or not. Her head was short and broad, though not flattened posteriorly. Circumference 38 cm. was well below the 10th percentile and was small even in relation to her weight. She had a suggestion of mongoloid epicanthic folds and her palpebral fissures were slanting upwards and outwards. Shape of the mouth was, however, normal, the tongue was not scrotal, and Brushfield spots were absent. Ears and lower jaw were of normal size and shape. Though there was a single palmar crease on the left hand (Fig. 2), the right palm was normal. Little fingers were not incurved or short, and two interphalangeal creases were present. Finger-nails were normal. The gap between the first and second digits of the feet was not exaggerated. A radiograph of her pelvis did not show mongoloid changes. Dermatoglyphic patterns were not informative. Muscle tone appeared normal.

FIG. 1. Full face of 1-year-old patient.

FIG. 2. Left palm illustrating palmar crease.

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Physical and mental subnormality were more evident by 41 weeks of age, when she weighed 5.8 kg. and was 62.5 cm. She was not yet able to sit unaided, but tried. She grasped and transferred.

At 1 year of age she developed convulsions: sometimes these were major fits, but more often they were brief infantile spasms. A variety of anticonvulsant regimens failed to control the fits. At 16 months of age she was seen again, when the presence of infantile spasms was confirmed and her electroencephalogram showed a hypersarrhythmic pattern.

At 22 months of age she was grossly retarded and continued to have major convulsions. She was now unable to hold objects and did not respond to sound. She followed a light. She rarely smiled. She did not recognize her parents.

Dermatoglyphs. These were examined at 12 months. Dermal ridge patterns on the digits were poorly defined; epidermal scaling completely obscured possible patterns on the plantar surface of the feet and made inconclusive observation on the palms of the hands. The following points were, however, noted.

Digits on right hand: First an ulnar loop, second an ulnar loop, third an ulnar loop, fourth a whorl, and fifth a whorl.

Digits on left hand: First an ulnar loop, second no definite pattern, third an ulnar loop, fourth an ulnar loop or whorl, and fifth an ulnar loop.

Sex Chromatin and Chromosome Analysis.

The Patient. 120 suitable nuclei on buccal smear preparations derived from the patient were examined for sex chromatin; 37 nuclei had a single Barr body of normal size; no cell had a nucleus with more than one Barr body. A count of 31% is within the normal range for an individual with two X chromosomes.

Chromosome preparations were derived from venous blood and the chromosomes spread by drying in air. Chromosome counts are summarized in the Table. A total of 107 cells was examined from three different cultures. Cells with a count of 46 chromosomes had a normal female chromosome complement apart from the G (21-22) group. Only three normal chromosomes of the G group were apparent. The abnormal chromosome (Fig. 3 and 4) appeared to be a monocentric ring

chromosome, in diameter about the length of the long arm of the largest G chromosome in that metaphase plate. It, therefore, contains more genetic material than a normal G chromosome. Eight of the nine cells with 45 chromosomes had only three members in group G, and a ring chromosome was absent from these cells. No cell with two ring chromosomes was apparent. Dicentric ring chromosomes were not observed.

Though it is possible that repeated misdivision, with loss of the ring chromosome, may have occurred in culture, it seems more likely that these two types of cell—one with a ring chromosome and the other without the ring and with only 45 chromosomes—represent stemlines existing in the body of the patient.

The chromosome complements (blood culture) of the parents of the patient appeared normal.

Blood Groups. The blood groups of the patient and of her parents are as follows:

Patient: A₁, MNS, P₁+, R₁r, Lu (a-), Le (a+b-), Kell (a-b+), Fy (a-), Jk (a-b+), Wr (a-), C^w.

Father: O, NNss, P₁+, rr, Lu (a-), Le (a+b-), Kell (a+b+), Fy (a+), Jk (a+b+), Wr (a-), C^w.

Mother: A₁, MMS, P₁+, R₁r, Lu (a-), Le (a-b+), Kell (a-b+), Fy (a+), Jk (a+b+), Wr (a-), C^w.

Comment

A monocentric ring chromosome may be formed when terminal deletion of both arms of a chromosome is followed by a joining together of the exposed ends. A ring chromosome so formed is deficient in genetic material, but does not contain duplicated loci. Nevertheless, ring chromosomes genetically different from the original ring chromosome, and containing duplicated loci, may occasionally be expected to arise after bridge formation and unequal breakage at subsequent cell division. Again misdivision may lead to loss of a ring chromosome. Alternatively a monocentric ring chromosome with duplicated loci may be derived from a dicentric ring chromosome formed, by abnormal crossing-over, at meiosis. It may be presumed that, however produced, the large ring chromosome observed in our patient contains duplicated as well as deficient genetic material.

If indeed the abnormal chromosome in our patient is that usually involved in mongolism, then only part of a chromosome 21 is present in triplicate (partial trisomy-21), and it is reasonable to expect some of the clinical features of mongolism rather than the full clinical picture. All the abnormalities noted in our patient could be referred to partial trisomy-21. However, mental subnormality, poor physical development, and congenital heart disease

TABLE
CHROMOSOME COUNT IN PREPARATIONS DERIVED FROM PATIENT

Tissue	Chromosome Counts			
	45		46	
	Counted	Analysed	Counted	Analysed
Blood culture (1)	3	3*	37	10†
" " (2)	1	1*	18	5†
" " (3)	5	5*	43	5†

* Eight of the nine cells were 45,XX,G-.

† 46,XX,Gr.

FIG. 3. Cell line containing 46 chromosomes. Only three normal members in Group G. The abnormal ring chromosome is arrowed.

FIG. 4. Size of ring chromosome compared with that of normal member of G group in five cells.

are also features of 'antimongolism' (Lejeune *et al.*, 1964; Reisman *et al.*, 1966; Penrose, 1966; Engel *et al.*, 1966), associated with absence of a part of a G group chromosome (partial monosomy G). Our patient has one cell line with a part of a G group chromosome absent and a second cell line with complete monosomy for a G group chromosome. It is then possible to refer much of her mental and physical maldevelopment to this deficiency. Specific features of antimongolism were not, however, observed. Weleber, Hecht, and Giblett (1968) have suggested that a second G-deletion syndrome may be recognized. It is perhaps worthy of note that epicanthal folds is one of the several clinical features which Weleber and his colleagues regard as distinguishing this syndrome from that of antimongolism.

Summary

A female infant with poor physical and mental development and congenital heart disease was

investigated cytogenetically. Two cell lines with respect to chromosome complement were identified. One cell line contained 45 chromosomes and had a G group chromosome missing. The second cell line had, in addition, a small ring chromosome. The size of this ring chromosome was such that partial trisomy of a member of the group G was inferred.

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