Chromosome Mosaicism in a Mentally Retarded Mother and Her Daughter

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Mosaicism for a chromosome of group G (21-22) has been described in many patients with typical Down's syndrome (Clarke, Edwards, and Smallpeice, 1961; Blank, Gemmell, Casey, and Lord, 1962; Smith, Therman, Patau, and Inhorn, 1962; Nichols, Coriell, Fabrizio, Bishop, and Bogg, 1962; Weinstein and Warkany, 1963; Lindsten, Alvin, Gustavson, and Fraccaro, 1962; Hayashi, Hsu, and Chao, 1962) and in some non-mongoloid people with varied clinical conditions (Bieseke, Schmid, and Lawlis, 1962; Turner and Jennings, 1961; Fitzgerald, 1962; Dunn, Ford, Auersperg, and Miller, 1961; Zellweger, Mikamo, and Abbo, 1962; Sparkes, Veomett, and Wright, 1966).

Familial transmission of an extra chromosome from one generation to the next is relatively rare, but has been detected in some cases in which a mosaic trisomy G-normal was found in the apparently normal parent of a mongol child (Smith *et al.*, 1962; Blank *et al.*, 1962; Weinstein and Warkany, 1963; Verresen, van den Berghe, and Creemers, 1964; Ferrier, 1964). However, repeated mosaicism in two generations is, to our knowledge, very infrequent. It is the purpose of this paper to report the occurrence of mosaicism in a mother and her 17-year-old daughter. Both were mentally retarded but did not exhibit physical signs of mongolism.

Case Reports

The mother was a 38-year-old, obese, mentally retarded, white woman, whose weight was 60 kg. (132 lb.) and height 150 cm. (5 ft.). On psychological testing, a high degree of oligophrenia was found. Biological maturation corresponded to 6 years of age (Bender's Classification), and a mental age of 8½ was found (Terman-Merrill test). The urinary excretion of 5-OH

indolacetic acid while on a normal diet was determined in two different samples and gave the following results: 2 mg. for a urine volume of 1000 ml. and 1 mg. for 1200 ml. (Udenfriend, Titus, and Weissbach, 1955, which gives a normal value of 6-8 mg.).

The father was a normal white man, 41 years old.

There were four sibs: an apparently normal 6-year-old boy, two mentally retarded boys of 13 and 14, and a mentally retarded girl of 17. The 13-year-old boy was subject to epileptic attacks which consisted of clonic convulsions of the left arm and left side of the face, followed by loss of consciousness for 2 or 3 minutes. The electroencephalogram was normal. The diagnosis made by the neurologist was of a syndrome of retarded maturation of the central nervous system. The 14-year-old boy had never been examined by a physician, but the father said he had convulsive attacks and a mental development similar to his 13-year-old brother.

The 17-year-old girl was mentally retarded, obese, hypertensive, and hypothyroid. Her weight was 52.2 kg. (114.8 lb.) and height 150 cm. (5 ft.). Blood pressure was 160/100 mm. Hg. The facies was not mongoloid and the skin was dry and coarse. Her breasts, axillary, and pubic hair were normally developed and she has had regular menstrual periods since the menarche at 12 years of age (Fig. 1). On psychological testing at age 15, an IQ of 22 was found. Goodenough's test showed a mental age of 7 years 5 months, while Terman-Merrill's test showed a mental age of 7 years 2 months. Biological maturation corresponded to 5 years of age (Bender's test).

Hypothyroidism was confirmed by chemical studies. Serum protein-bound iodine was 3.7 µg./100 ml., ¹³¹I uptake was 10% at 3 hours, 24% at 24 hours, and 20% at 48 hours, and a basal metabolic rate of -25% was found. The electrocardiogram was normal. The value of urinary 17-ketosteroids was 7.36 mg. in 24 hours, the urinary excretion of hydroxycorticoids was 1.72 mg. in 24 hours, and the urocytogram was trophic. No phenylpyruvic acid was found. The blood serotonin levels were 1280 mµg. and 1980 mµg./1000 ml. (Udenfriend, Weissbach, and Clark, 1955) with normal values of 100 µg. to 300 µg./1000 ml.). The urinary excretion of 5-OH indolacetic acid was studied while on a normal diet, and 3 mg. were detected in 900 ml. urine.

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FIG. 1. Photograph of the daughter at the age of 15 years.

After a diet with high tryptophan content (4 bananas plus normal diet) the 5-OH indolacetic acid values were still low: 2 mg. in a sample of 650 ml. and 5 mg. in another of 800 ml. After loading with 3 g. tryptophan the excretion of 5-OH indolacetic acid increased only to 7 mg. for 600 ml.

Cytogenetic Findings

The chromosomes of the mother were studied in one short-term culture of peripheral blood (Moorhead, Nowell, Mellman, Battips, and Hungerford, 1960). The daughter's chromosomes were analysed in two blood cultures and one bone-marrow sample prepared according to the following method: 12×10^6 cells were cultured in 10 ml. of TC 199 plus 30% human AB serum for 24 hours; colchicine to a final concentration of 5×10^{-6} M was added for 5 hours, followed by treatment with hypotonic Hank's solution for 30 min., fixation in 3:1 absolute alcohol-acetic acid, and staining with Giemsa or Unna's blue.

TABLE
SUMMARY OF CHROMOSOME ANALYSIS OF
THE MOTHER AND DAUGHTER

Case	Culture	No. of Cells Counted	Chromosome Counts				Percentage of Trisomic Cells	No. of Cells Karyo-typed		
			44	45	46	47		45	46	47
Mother	Blood	117	1	4	89	19	16.2	4	9	6
Daughter	Blood	48	0	0	38	10	19.8	—	3	3
	Blood	58	0	1	47	10		—	3	6
	Bone-marrow	15	0	0	11	4		—	2	2
	Total	121	0	1	96	24		—	8	11

Chromosome counts are summarized in the Table. In the blood culture obtained from the mother 117 cells were examined. A count of 46 chromosomes was found in 89 cells, and 47 chromosomes were present in 19 cells. Four cells with 45 chromosomes and one with 44 chromosomes presented a random loss of a chromosome of group C (6-12). In nine cells with 46 chromosomes, a normal female chromosome complement was found, and in six cells with 47 chromosomes, an extra small acrocentric chromosome was observed.

In the three cultures obtained from the daughter, 121 cells were studied: 96 cells with 46 chromosomes, 24 cells with 47 chromosomes, and one with 45 chromosomes were found. The analysis of the karyotype of eight cells with 46 chromosomes showed a normal female chromosome complement, and 11 cells with 47 chromosomes exhibited an extra small acrocentric chromosome similar to the one present in the cells with 47 chromosomes of the mother.

The extra small acrocentric chromosome was approximately of the same size as the chromosomes of group G(21-22-Y), but it could not always be matched with either pair 21 or 22 (see Fig. 2, 3, 4, and 5). The long arms were similar to those observed in the chromosomes of group G, but the short arms appeared to be like those of pair 18 rather than satellites. This chromosome was never found to enter into association with other acrocentrics, and morphologically it is very difficult to decide if it is an extra chromosome 21, 22, a Y, or a fragment of another chromosome.

Positive sex chromatin was found in the buccal smears, and only single Barr bodies of normal size were found in all the positive cells.

Discussion

Several examples of trisomy G (21-22) without clinical mongolism have been described but they do not represent a characteristic syndrome which might be ascribed to trisomy 22. The first case was an example of the Sturge-Weber syndrome (Hayward and Bower, 1960). However, in other patients with this syndrome studied by the same authors (1961), as well as in two analysed by Lehmann and Forssman (1960), a normal karyotype was found. On the other hand, Patau, Therman, Smith, Inhorn, and Picken (1961) found a translocation in one of three patients with Sturge-Weber syndrome. A segment morphologically similar to a 21 or 22 chromosome was found translocated to a chromosome 13-15, and these authors postulated that the syndrome could be caused by a partial trisomy of an autosome which was probably not a number 22. The extra fragment could not be detected when it was translocated into a big submetacentric chromosome but was observed when it was translocated into an acrocentric chromosome (case of Patau *et al.*, 1961) or when it was present as an extra centric fragment, morphologically similar to a chromosome G, as in Hayward and

FIG. 2. Groups E and G from six cells showing the additional G-like chromosome. The three upper lines are from karyotypes of the mother and the other three are from karyotypes of the daughter.

Bower's case. Other published cases reported as possible trisomies 22 or trisomy G without mongolism may be explained in the same form.

The low frequency of non-mongoloid G trisomics, as compared with mongolism, and the fact that trisomy G has been found in spontaneously aborted fetuses (Carr, 1965), might be accounted for if most of the cases with trisomy 22 died during embryogenesis. On the other hand, the many different syndromes observed in non-mongol G trisomics indicate that only a few cases are probably true trisomy 22 or mosaics for such trisomy, while many others may be partial trisomies for a fragment of another

autosome. Examples of morphological G trisomics, in which a chromosome other than 22 was considered to be involved, have been described by several authors. Gustavson, Hagberg, Finley, and Finley (1962) found an extra acrocentric fragment in two sibs with mental deficiency, micrognathia, microcephaly, cleft palate, and low-set malformed ears. Due to the clinical findings, the authors considered that the small acrocentric was a fragment of a chromosome of group D (13-15) or E (17-18). In another case in which a mosaic for an acrocentric larger than a 21 but smaller than a 13-15 (Crawford, 1961) was observed in a mentally retarded child with

FIG. 3. Metaphase and karyotype from cultured lymphocyte of the mother showing the extra G-like chromosome.

low-set ears, micrognathia, interventricular septal defect, hydronephrosis, and hydroureter, the author suggested that the extra chromosome could be a deleted 17-18. The possibility that an extra acro-

centric chromosome might be part of a translocation morphologically similar to a 21-22 chromosome was postulated by Vislie, Wehn, Brøgger, and Mohr (1962), in two mentally retarded sibs with malformed

FIG. 4.—Metaphase and karyotype of a cell from the daughter's blood culture.

cranium, epicanthi, low-set ears, and generalized hypotonia, because the karyotype of the mother showed a reciprocal translocation between two chromosomes of the group D (13–15) and E (17–18).

The new chromosome, T_1 , was morphologically similar to one of group C (6–12), while the T_2 was like a G (21–22).

In our cases, it is difficult to determine if the extra

FIG. 5. Metaphase and karyotype of a cell from the daughter's bone-marrow.

acrocentric is a number 21, a 22, or a fragment of another chromosome. The possibility of mosaicism for trisomy 21 seems to be very unlikely. Not only were physical signs of mongolism absent, but high blood serotonin levels were found. The presence of low 5-OH indolacetic acid excretion in both mother and daughter agrees with the alteration of tryptophan metabolism described by Jerome, Lejeune, and Turpin (1960) in mongolism. However, the high blood serotonin levels, in contrast to the low values observed in mongols (Tu and Zellweger, 1965), suggested that the alteration in our patients was related to an abnormal excretion of serotonin or a reduced conversion into 5-OH indolacetic acid, while in mongolism it has been shown that the conversion of 5-OH tryptophan into 5-OH typtamine (serotonin) is blocked. Mosaicism for trisomy 22 cannot be excluded, because the true phenotype of trisomy 22 is not known. The clinical features of our cases, however, differ from all others described as possible trisomies 22. The idea that the extra chromosome might represent a Y cannot be accepted because both cases are phenotypic females with no sign of sterility or intersexuality. On the other hand, the female phenotype and mental retardation might support the hypothesis that the extra chromosome is a deleted X and the two cases represent mosaics XX/XXx. Unfortunately, autoradiography was not performed to find out if the small acrocentric was a late replicating chromosome, but the fact that only one Barr body was found in all the positive sex chromatin cells of the buccal smear is an argument against such a possibility. Moreover, the size of the extra chromosome, which is smaller than the short arms of the X, makes it necessary to postulate that two breaks have occurred to give rise to such a fragment. On the contrary, a fragment representing the short arm of another chromosome such as one of the group B (4-5) of some chromosomes of group C (6-12) as well as one of the arms of chromosome 16 could be morphologically similar to one chromosome of group G (21-22-Y). A single break near the centromere and the loss of the acentric fragment might originate a G-like chromosome fragment. Its presence in addition to a normal chromosome complement would represent a partial trisomy for a region of a chromosome whose phenotypic expression might be different if compared with the syndromes produced by trisomy G (21-22), E (17-18), or D (13-15). This seems to be the most likely explanation for our cases. Not only does the phenotype differ from the known trisomy syndromes, but the morphology of the extra chromosome can be explained if we consider it as a centric fragment originated by deletion of one arm

of an autosome or one of the two new chromosomes resulting from a reciprocal translocation.

Familial transmission of a centric fragment has been reported by Smith, Steinberger, Steinberger, and Perloff (1965) and other examples are known of extra fragments present in addition to normal karyotypes (Ishmael and Laurence, 1965; Frøland, Holst, and Terslev, 1963). The occurrence of familial mosaicism, however, is rare and has been described previously only in a few instances. Tzoneva-Maneva, Bosajieva, and Petrov (1966) observed mosaicism XY/XYX in a father and his son affected by an idiopathic hypertrophic osteoarthropathy. Zellweger and Abbo (1965) reported a family with one mosaic XO/XY and three mosaics for a balanced translocation D/D in three different generations. The last authors postulated that an autosomal dominant gene could be responsible for the abnormal mitosis leading to repeated mosaicism. The hypothesis of R. Grell (1962), based on experimental studies in *Drosophila*, is another explanation suggested for the unusual families with association of non-disjunction and translocation as well as for the occurrence of non-disjunction during meiosis when a small duplicated chromosome is present in the gonads (R. Grell and Valencia, 1964). Small duplicated chromosomes are also known to be lost during division of somatic cells in *Drosophila* (E. Grell, 1966, personal communication) and our cases might represent one example, in man, of the same mechanisms that are known to occur in *Drosophila*.

In sum, we think that the extra chromosome observed in the two members of the family reported here is a fragment of an autosome. It might have been originated during gametogenesis of one of the parents of the mother, and by non-disjunction passed to the zygote of the mother together with a normal chromosome complement. During embryogenesis it was probably lost in many of her somatic cells giving rise to the normal cell line observed in the blood cultures. Nevertheless, the fragment present in the gonadal cells of the mother might have been transmitted to her three abnormal descendants. Unfortunately we could only study one of the three retarded sibs, due to lack of cooperation of the family, but we know that the three presented the same degree of mental retardation, and at least the mother and daughter showed a clone of cells with the same extra chromosome that we consider as a fragment of a longer autosome. The frequency of such fragments in humans is still unknown, but they might represent the only viable forms of trisomy for regions of chromosomes whose complete trisomy is lethal.

Summary

Mosaicism 46/47 was observed in a mentally retarded girl 17 years old, and in her mother, who was also mentally deficient. The girl presented with obesity, hypertension, and hypothyroidism. Increased serotonin levels were found in the blood, but decreased excretion of 5-OH indolacetic acid was demonstrated in the urine. The mother was also obese and exhibited low 5-OH indolacetic acid excretion. Two other sibs were mentally retarded but were not studied cytogenetically. The karyotypes of the mother, studied in blood culture, and the chromosomes of the daughter, obtained from one bone-marrow and two blood cultures, showed a normal cell line and one trisomic for a small acrocentric chromosome. The extra chromosome appeared to be, morphologically, one of group G (21-22). However, it seems very unlikely that it is a number 21, due to the absence of signs of mongolism and the presence of high blood serotonin levels, in contrast to the low serotonin values found in mongolism. The possibility that it represents a chromosome 22 cannot be completely excluded, but the clinical findings are different from all the others reported in cases interpreted as 22 trisomics. The idea that it might be a Y is not supported by the phenotype, while the size of the extra chromosome and the fact that only one Barr body was found in the cells with positive sex chromatin seems to rule out the hypothesis of a deleted X. Therefore, it is considered that the most likely possibility is that it represents a centric fragment of an autosome.

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