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Mosaic Aneuploidy in a Diabetic Child and his Mother

By

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The case of a diabetic child and his mother is reported. Karyotype examination revealed a considerable increase in the number of the hypo- and hyperdiploid cells as compared to the controls. The mosaic aneuploidy was detectable in both lymphocyte and fibroblast cultures. The chromosomal deficiency appeared mostly in group F and the surplus chromosome belonged morphologically to the group C. Besides the mosaic aneuploidy a 46,XY,C+F− and 46,XX,C+F− aberration was also observed where the possibility of a translocation of one of the F chromosomes has been considered.

Some decades ago, attention has been drawn by Wagner et al. [14] to the frequent simultaneous occurrence of diabetes and developmental anomalies in childhood. Some authors then found an association of diabetes with Turner's syndrome [6, 8], others of diabetes and Klinefelter's syndrome [11] or Down's disease [9]. Data obtained in our patient material revealed that multiple developmental malformations, partly due to chromosomal anomalies, occur in diabetics considerably more frequently than expected on the basis of data for the general population [1].

The data suggest the possibility that [1] a slight causal relationship may exist between the chromosomal anomaly and diabetes; or [2] the mother's prediabetic or diabetic state may predispose to the development of chromosomal aberrations. This latter supposition has been supported by the animal experiments of Yamamoto et al. [13].

In the following, we shall report the case of a child with diabetes, in whom the karyotype examination revealed a greater number of hypo- and hyperdiploidy than usual. An abnormally high frequency of hypo-hyperdiploidy was found in the mother, too.

Report of a Case

The patient was a boy 16 years of age. His paternal grandmother was diabetic, but no diabetes was known in the mother's family. In the boy, diabetes had manifested itself at the age of 13 years while growth retardation had become obvious even before the disease was diagnosed. At admission his height was 154 cm, and he had been sexually mature for a year. Besides the tempestuous course of the

diabetes, the boy's mental state was somewhat abnormal; he did not follow the doctor's instructions, he showed a tendency to deliquency and is therefore kept in a semiclosed institution.

Both in the child and his mother, we have performed chromosomal examinations first in lymphocyte then in fibroblast cultures. Results are shown in Table I, while in Table II the dif-

TABLE I

Aneuploidy in a diabetic child and his mother

		No. of cells examined	45 >	45								46 C+F—	46	47
				A	B	C—X	D	E	F	G	Y			
Diabetic child	Lymphocyte cultures	60	7 11.7%				1	1	7	1		3 5%	38 63.3%	2 3.3%
							10; 16.7%							
	Fibroblast cultures	62	8 12.9%						5	1		6 9.7%	39 63.6%	3 4.8%
									6; 9.7%					
	Total	122	15 12.2				1	1	12	2		9 7.3%	77 63.4%	5 4.0%
							16; 13.1%							
Mother	Lymphocyte cultures	100	13 13%				1	1	2	4	1	5 5%	71 71%	2 2%
							9; 9%							
	Fibroblast cultures	32	4 12.5%				1	1	4	4	1		16 50%	1 3.1%
							11; 34.4%							
	Total	132	17 12.9%				2	2	6	8	2	5 3.7%	87 65.9%	3 2.4%
							20; 15.1%							

TABLE II

Aneuploidy in control cases

	No. of cells examined	45 >	45								46 C+F—	46	47
			A	B	C—X	D	E	F	G	Y			
Lymphocyte cultures from 25 normal individuals	500	51 10.2%				5	4	3		1		436 87.2%	
						13 2.6%							
Fibroblast cultures from 12 normal individuals	501	59 11.3%			2	3		3		1		433 86.6%	
						9							
								1.7%					
Total	1001	110 10.9%			2	8		7	3		2	869 86.9%	
						22							
									2.2%				

ferences found at the control examinations are indicated. (The lymphocyte and fibroblast cultures of 25 respectively 12 chromosomally normal individuals served as controls.) In our diabetic patient, cells with 45 chromosomes have been found in a relatively high percentage. In the control examination, cells with 45 chromosomes were found with a frequency of 1.7% and 2.6% in the fibroblast and in the lymphocyte cultures, respectively. On the other hand, the chromosome number of 45 occurred with a frequency of 9.7% in fibroblast cultures and of 16.7% in the lymphocyte cultures. The missing chromosome in the cells from the proband was most frequently identified as an F group chromosome: 12.0% and 8.5% of the cells from the lymphocyte and the fibroblast cultures, respectively, showed a chromosome missing from this group. On the contrary, no chromosomes were found missing from the F group in the control cultures. The significance of the differences was evidenced by means of the four field contingence test. The results showed that in the lymphocyte culture an increased frequency of the chromosome number of 45 ($\chi^2 = 24.51$; $p < 0.001$) as well as that of chromosomes missing from the F group ($\chi^2 = 12.78$; $p < 0.001$) were highly significant. In the fibroblast cultures, the differences both in the chromosome number of 45 ($\chi^2 = 13.27$; $p < 0.001$) and in the deficiency in the F group ($\chi^2 = 11.07$; $p < 0.001$) were equally significant (Fig. 1). Cells with 47 chromosomes were also found with a frequency of 3.3% in the lymphocyte cultures and 4.8% in the fibroblasts. The surplus chromosome belonged to group C. A further type of cells was found in 5.0% of the lymphocytes, and in 9.7% of the fibroblasts. These cells showed a normal chromosome number of 46, but they had a plus chromosome in group C and one chromosome missing from the F group. The frequency of the chromosome number under 45 was the same as in the controls.

The resemblance of the mother's phenotype to that of the child has prompted us to perform a chromosome examination in the mother. A chromosome number of 45 was found in 34.4% of the fibroblasts and in 9.0% of the lymphocytes. The difference between these values and those found in the controls was significant ($\chi^2 = 83.50$; $p < 0.001$ for fibroblasts; $\chi^2 = 9.70$; $p < 0.01$ for lymphocytes). The preferential loss of a chromosome from the F group was found also in the mother, but the difference in the lymphocyte culture was not significant ($\chi^2 = 1.10$; $p > 0.05$). A chromosome number of 47 was found in the lymphocyte cultures in 2.0%, and in the fibroblasts in 3.1%, the plus chromosome belonged morphologically to group C (Fig. 2). The karyotype 46, XX, C + F − occurred in 5% of the lymphocytes, but none was found in the fibroblasts (Fig. 3). The ratio of cells with a chromosome number under 45 corresponded to that of the control cultures. The ratios of hypo- and hyperdiploidy found in the control and in the index cultures are shown in Fig. 4.

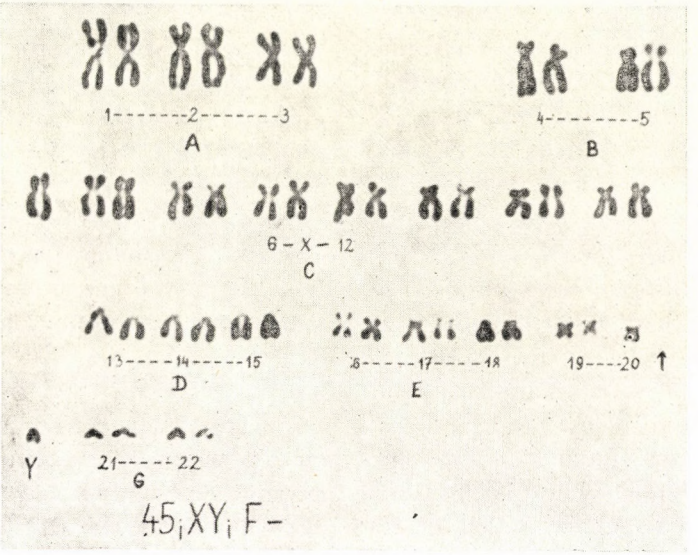

FIG. 1. Karyotype of a cell with 45 chromosomes from lymphocyte cultureof diabetic child

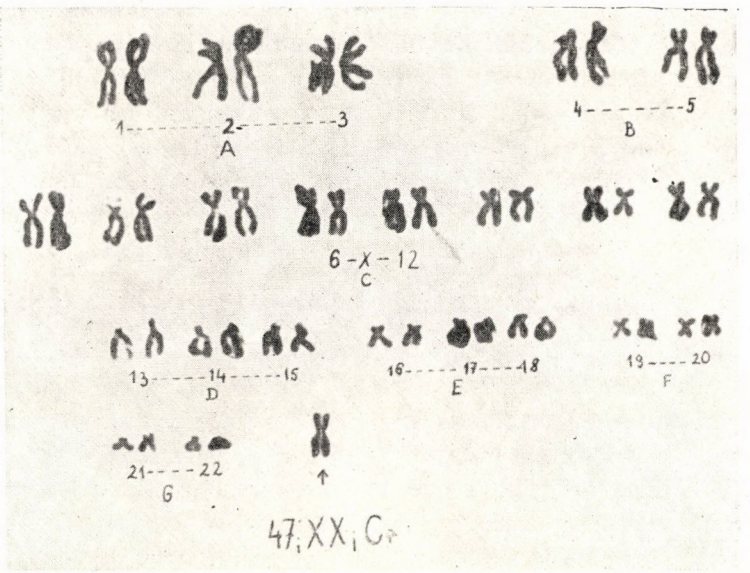

FIG. 2. Karyotype of a cell with 47 chromosomes from fibroblast culture of the mother

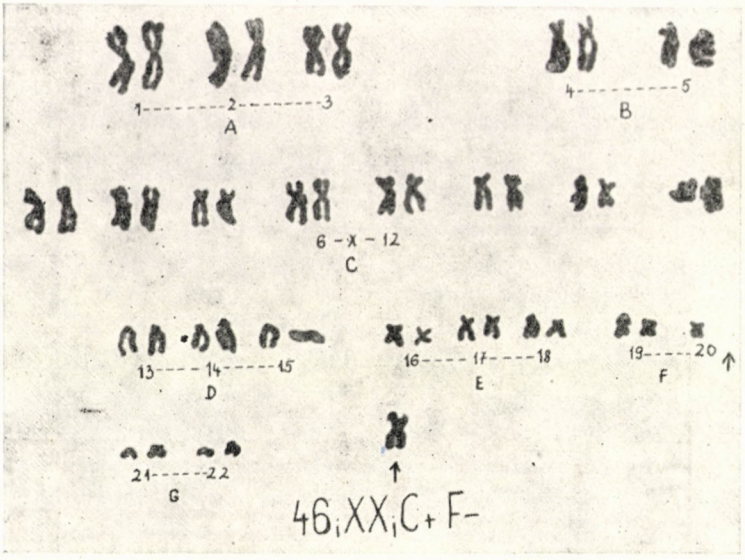

FIG. 3. Karyotype of a cell with 46 (C+F−) chromosomes from lymphocyte culture of the mother

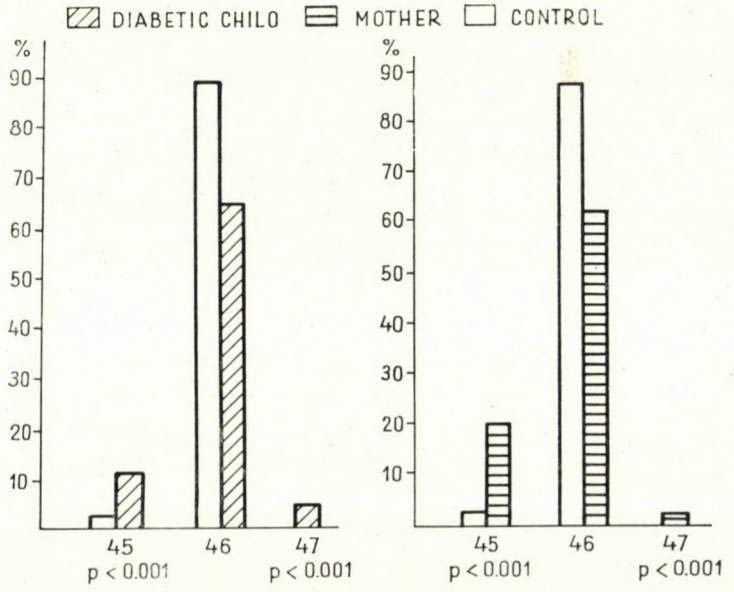

FIG. 4. Comparison of chromosome numbers from fibroblast and lymphocyte cultures

Discussion

In both the diabetic boy and his mother besides the double aneuploidy —45,XY,F—/46,XY/47,XY,C+ and 45,XX,F—/46,XX/47,XX,C+, respectively, another chromosome anomaly occurred: 46,XY,C+F— and 46,XX,C+F—, respectively. Though the missing chromosome in cells with 45 chromosomes belonged to different chromosome groups, a preferential loss of an F group chromosome seemed to be well established by the statistical tests. The extra chromosome in the cells with 47 chromosomes and in part of those with 46 chromosomes looked morphologically like belonging to the C group, but the possibility of being a translocation chromosome, especially in the cells with 46 chromosomes, could not be excluded either.

In the literature, familial accumulation of numerical chromosomal anomalies has been reported and also double aneuploidy occurring in the same person has been observed in patients with Turner's and Down's syndrome. Yamamoto et al. [13] observed mosaic aneuploidy in animal experiments. They found that in the offspring of rats with alloxan diabetes, the number of hypo- and hyperdiploid cells increased. Other authors described an accumulation of congenital malformations in the offspring of rats treated with alloxan [7]. In these animals, both the chromosomal anomalies and the congenital malformations could be prevented by insulin treatment [5].

The cytological picture seen in our case was similar to that observed by Yamamoto et al. [13]. There were no data which would have indicated a prediabetic state of the mother, although this possibility cannot be excluded. It is, however, certain that considerably more intricate correlations exist in human than in animal diabetes.

The genetics of diabetes is far from being clear. Besides recessive inheritance, the possibility of dominant inheritance also exists. Certain observations indicate that diabetes in old age shows rather a dominant inheritance while juvenile diabetes seems to be transmitted like a recessive trait [10]. More recent data, however, yield convincing evidence that in the case of diabetes, a polygenic inheritance may be supposed [3]. On the basis of experiments performed in Chinese hamsters it has been stated that in the transmission of the disease at least 4 or 5 genes are involved [4].

It is well-known that several diseases predispose to diabetes. Besides those mentioned in the introduction some authors have observed that diabetes may develop also in association with Prader–Willi's syndrome in childhood [12]. Recent examinations have revealed a relationship between diabetes and 16 genetic diseases. Diabetes may thus be considered a multifactorial disease [2]. The relationship between the chromosomal anomalies found and the occurrence of diabetes in our case is not clear. As mentioned above, an interrelationship seems to exist between diabetes and chromo-

somal anomalies and, according to present knowledge, a relationship may exist between chromosomal anomalies and autoimmune processes. Chromosomal anomalies may influence cell growth, enzyme production, permeability of the cell membrane and the sensibility of tissues to hormones. In consequence, in the case of chromosomal anomalies the influences predisposing to diabetes may become effective [2]. In multifactorial inheritance it may be supposed that the aneuploidy may have a role in the manifestation of diabetes.

There is no characteristic chromosomal alteration known which would be in direct causal relationship with diabetes. On the other hand, several observations point to the simultaneous occurrence of diabetes and chromosomal anomalies, thus a slight indirect connection may exist between them. Therefore, the collection of data referring to this problem is incontestably of great importance and clinical observations may contribute to the elucidation of the problem.

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