□ CASE REPORT □

Pentasomy X Mosaic in Two Adult Sisters with Diabetes Mellitus

Shigeru NAKANO, Atsuko SASAME, Sadahide AZUKIZAWA, Toshikazu KIGOSHI, Kenzo UCHIDA, Hiroaki TAKAHASHI* and Shinpei MORIMOTO

Pentasomy X mosaic in two adult sisters with non-insulin dependent diabetes mellitus is described. The younger sister had schizophrenia, and both were mentally retarded, but no apparent somatic abnormalities were found. Chromosome analyses revealed karyotype 45,X/46,XX/47,XXX/48,XXXX/49,XXXXX mosaic with a low frequency of aneuploidy on cultured peripheral lymphocytes and 46,XX on cultured skin fibroblasts in both sisters. The low frequency of X chromosome aberration may be responsible for the lack of somatic abnormalities and the long life in both sisters. The association of pentasomy X mosaicism and diabetes mellitus however appears to be coincidental.
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Key words: X chromosome aneuploidy, aged siblings, glucose intolerance

Introduction

Pentasomy X and its mosaicism, rare X chromosomal constitutions, are generally found in young (neonate to childhood) females because of concomitant mental and somatic abnormalities; mental retardation and mongoloid face, congenital heart disease and various skeletal anomalies are associated (1–10). However, to our knowledge there are no reports of adult women with these X chromosome abnormalities. We recently examined two adult sisters with pentasomy X mosaic. They were diabetic and mentally retarded but they had no somatic abnormalities.

Case Reports

Patient 1

A 56-year-old unmarried woman was admitted to our clinic on October 13, 1991, because of polydipsia, polyuria and fatigue with a six-month history of untreated diabetes mellitus. Her mother's younger brother had diabetes mellitus. The parents, who did not have a consanguineous marriage, were apparently healthy. They had three children. The present patient was the first child of a 20-year-old mother and a 26-year-old father. The second child was patient 2 and the third child died of pneumonia at age 3. She had menarche at age 17 and menopause at 50. On physical examination, her behavior was quiet, shy and timid. Intelligence quotient (IQ) obtained from the results of WAIS-R tests was 55, verbal IQ 62 and performance IQ 50. Her height was 143 cm, weight 38 kg and head circumference 53 cm. Her blood pressure was 98/58 mmHg; the pulse rate was 74 beats/min and regular. She had no apparent somatic abnormalities (Fig. 1). Her fundus oculi showed preproliferative diabetic retinopathy. The remainder of the physical examination was unremarkable except for diminished tendon reflexes and decreased vibratory sensation in both lower extremities and slight pedal edema. Roentgenograms of the chest, abdomen and skeletal survey were unremarkable. Electrocardiograms were also normal and no abnormal findings were obtained on an echocardiogram. The fasting plasma glucose (FPG) and plasma immunoreactive insulin (IRI) levels were 12.7 mmol/l (normal range 3.4–6.2 mmol/l) and 40.2 pmol/l (normal range 35.9–179.3 pmol/l), respectively, with glycosuria but without ketonuria or proteinuria. Plasma IRI levels revealed a delayed hyperresponse to a 75 g oral glucose load with excessive hyperglycemia (Table 1). Insulin sensitivity was good (Table 1). The HbA_{1c} was 10.7% (normal range 5.0–6.4%), and the 24-hour urinary excretion of C-peptide immunoreactivity (CPR) was 9.7 pmol (normal range 6.2–40.5 pmol/day). The other data of laboratory examination such as blood cell count, serum electrolytes, lipids and transaminases were all normal. Renal function was also within normal

From the Division of Endocrinology, the Department of Internal Medicine and *the Division of Human Genetics, Medical Research Institute, Kanazawa Medical University, Kanazawa
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Reprint requests should be addressed to Dr. Shigeru Nakano, the Division of Endocrinology, Department of Internal Medicine, Kanazawa Medical University. Uchinada, Ishikawa 920-02, Japan

a 24-hour urinary CPR excretion of 11.9 pmol. Plasma IRI levels showed a delayed hyperresponse to a 75 g oral glucose load with excessive hyperglycemia, and insulin sensitivity was good (Table 1). The other laboratory data including complete cell count, serum electrolytes, lipids and transaminases were within normal limits. Endocrinological data were all within normal limits except for high plasma LH and FSH levels with normal responses to LH-RH (Table 2). Anti-thyroid antibodies were absent.

Cytogenetic findings

Cytogenetic examinations were done in the two sisters because of their mental retardation of unknown origin. Chromosomal analyses were performed on cultured peripheral blood lymphocytes on two occasions and cultured skin fibroblasts on an occasion using a Trypsin-Giemsa (GTG) banding procedure (11, 12) originally described by Seabright (11). Karyotype 49,XXXXX found in the patients 1 and 2 on peripheral lymphocyte culture is shown in Fig. 2. Table 3 shows the results of the distribution of X chromosome counts. In both patients, metaphases of the lymphocytes showed karyotype

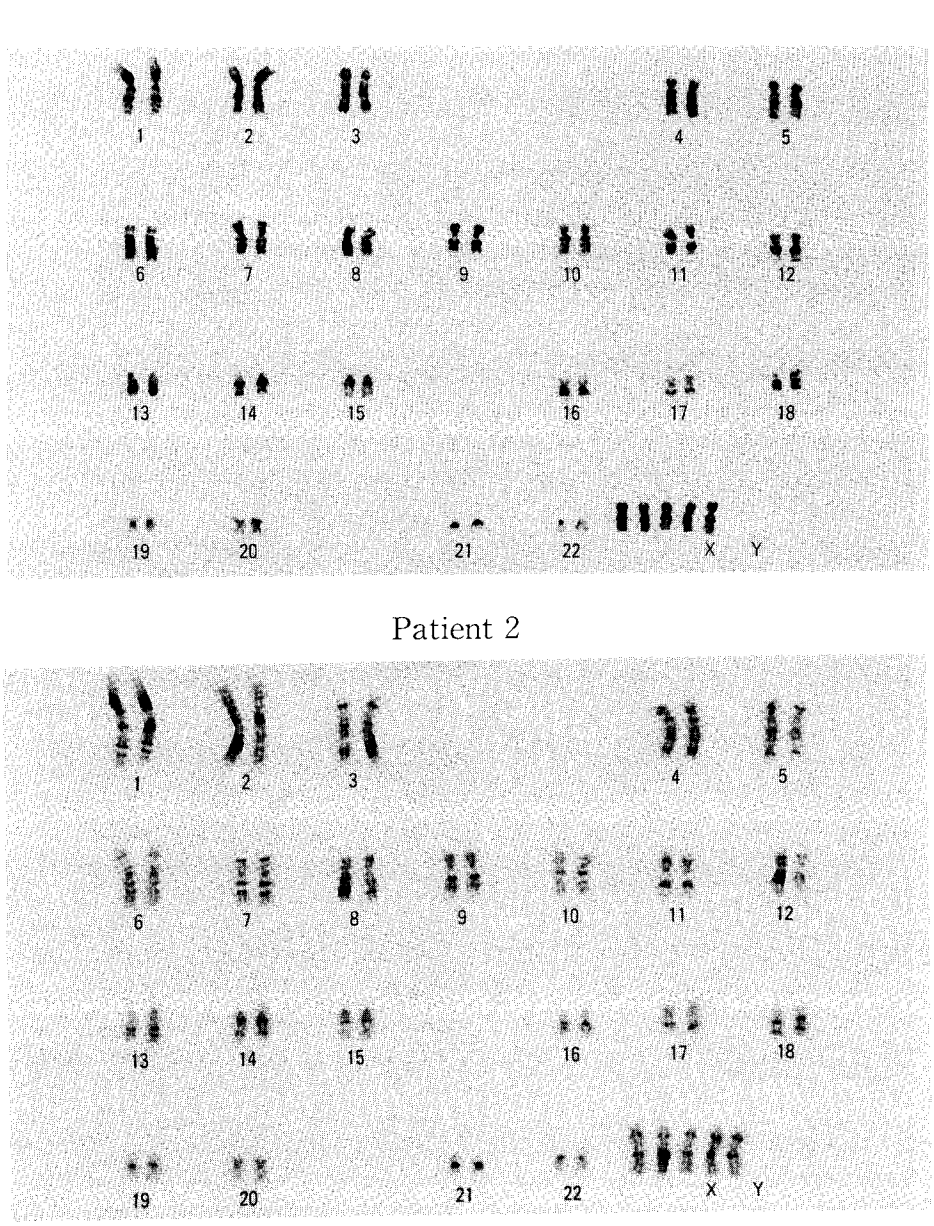

Fig. 2. Karyotypes of patients 1 and 2.

Table 3. Chromosome Count in Patients 1 and 2

	Culture	Number of chromosomes 45	46	47	48	49	Total No. of cells
Patient 1	Blood 1	1	23	3	2	1	30
	2	8	112	6	0	1	127
	Fibroblast	0	100	0	0	0	100
Patient 2	Blood 1	0	27	1	1	1	30
	2	8	83	4	0	1	96
	Fibroblast	0	90	0	0	0	90

45,X/46,XX/47,XXX/48,XXXX/49,XXXXX mosaic, whereas those of the fibroblasts were normal, showing a 46,XX karyotype.

Discussion

We describe two adult siblings with a karyotype 45,X/46,XX/47,XXX/48,XXXX/49,XXXXX mosaic. Girls with a pentasomy X generally have characteristic mental and somatic abnormalities (5), which include mental retardation, mongoloid face, short neck, simian crease, clinodactyly of the finger V and congenital heart disease. These girls have a poor prognosis due to severe cardiac failure and infectious diseases (1–10). Although girls with a pentasomy X mosaic also had clinical abnormalities basically similar to those in girls with a classic pentasomy X (6–10), many of those with a pentasomy X mosaic were not associated with severe cardiac anomalies. The girl reported by Gordon and Paulsen (8) was found at the age of 19 with premature menopause for two years. She had no mental or somatic abnormalities.

Appearance of abnormal manifestations in the patients with a pentasomy X and its mosaic presumably is related to the frequency of five X chromosomes on chromosomal analyses. The frequency of a 49,XXXXX karyotype on the cultured peripheral lymphocytes was more than 90% in girls with classic pentasomy X (1–5) and less than 50% in girls with a pentasomy X mosaic (6–10). This frequency in the girl reported by Gordon and Paulsen (8) was 1%. In the present two patients the frequencies of five X chromosomes on the cultured peripheral lymphocytes were 1.9% and 2.0%, respectively. Furthermore, the X chromosome constitution in patients with X chromosome mosaicism is known to vary in different tissues and even in different areas of the same tissue (13). The X chromosomes in cultured skin fibroblasts in the two sisters were normal, showing 46,XX. Thus, these two sisters had a low frequency of X chromosome abnormality. Such a low frequency of X chromosome aberration may be the reason for the lack of apparent somatic abnormalities, leading to a long life in the two sisters.

Familial occurrence of pentasomy X mosaicism in the present sisters is of genetic interest. It has previously been reported only in two female neonates from one family by Genoud et al. (4). Genetically, aneuploidy of five X chromosomes is considered to result from nondisjunction during meiotic phases of ovular maturation, and subsequent fertilization by an X-bearing sperm (1, 5). Although chromosomal analysis was not available in the parents of the present patients, formation of pentasomy X mosaic in these two sisters also may be ascribed to the two separate phases of nondisjunction at maternal meiosis (8).

The present two sisters had NIDDM with retinopathy and neuropathy. The association of diabetes mellitus in patients with pentasomy X and its mosaicism has not been reported, however the previously reported patients were all very young (1–10). Moreover, none of the recorded parents of these patients had diabetes mellitus (1–10). The present patients had a family history of diabetes mellitus on the mother's side, and their plasma IRI responses to a 75 g oral glucose load were compatible with those observed in patients with NIDDM. The association of NIDDM in the two sisters therefore appears to be irrelevant to X chromosome aberration. In addition, although the elder sister had positive anti-thyroid antibodies and the younger sister had schizophrenia, the relation of positive anti-thyroid antibodies or schizophrenia with pentasomy X mosaic is not clear.

Based on the findings of these two patients it is recommended that pentasomy X mosaic should be considered as a cause of mental retardation of unknown origin, especially in adults and adolescents.

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