X-Autosome Translocation with a Breakpoint in Xq22 in a Fertile Woman and her 47,XXX Infertile Daughter

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Summary. An unusual case is presented of a fertile woman heterozygous for a balanced X-autosome translocation t(X;12)(q22;p12) with a break-point (Xq22) in the critical region of the X chromosome. The karyotypes of her daughter, who is infertile, and one of her two sons are 47,XXX,t(X;12)(q22;p12) and 46,XY,t(X;12)(q22;p12) respectively. The literature on balanced X-autosome translocations in males and females involving both arms of the X chromosome is reviewed. All 23 of the 36 cases of females with balanced X-autosome translocation, that exhibited gonadal failure have a break-point between bands Xq13 and Xq26.

Introduction

Sarto et al. (1973) drew attention to a critical region of the human X chromosome, the structural integrity of which, they postulated, is necessary for normal ovarian function. Their evidence was that all females hitherto reported who were heterozygous for a reciprocal translocation with a break-point in this region had primary or secondary amenorrhoea. Summitt (1978) reviewed the literature and found that 13 of 18 females reported to be carriers of X-long arm autosomal translocations exhibited primary or secondary amenorrhoea. Seven of these cases were reported to have streak ovaries, one ovarian hypoplasia and one underdeveloped ovary. The X chromosome break-points of the 13 translocations were all located within the region Xq13–Xq26. The concept of a critical region in the X chromosome has also been supported by Phelan et al. (1977) and Dorus et al. (1979). The critical region therefore lies in the middle of the long arm and represents about two-thirds its length.

We present an exception to this rule: a woman heterozygous for a balanced X-autosome translocation with a breakpoint (Xq22) within the critical region who is nevertheless fertile. However the daughter, who is the proposita and who has apparently the same balanced translocation, but with an extra X-chromosome, shows gonadal failure and conforms to the rule.

Clinical Details

The proposita was born on the first of October 1959 and was first seen by one of us (P.H.) in November 1979 because of primary amenorrhoea. Thelarche and pubarche took place at about 16 years of age. The patient never used any oral contraceptives or other hormonal preparations. Except for the fact that she was subjected to surgery for a haemangioma in the right cheek there are no relevant particularities in her medical history. On physical examination at the age of 20 the patient's height was 187 cm, span 176.5 cm and weight 75.6 kg. In the right cheek the haemangioma was still visible. The fat distribution was infantile, there were a few axillary hairs. The pubic hair was scanty and the breast development was minimal (Fig. 1). There was no nipple development but glandular tissue was palpable on both sides, about 4 cm in diameter. The clitoris was conspicuously large with respect to the development of the secondary sexual characteristics. The labia majora did not completely cover the labia minora. There was a small introitus and the walls of the vagina were red. On vaginal inspection a small central unpigmented portio was seen. No cervical mucus was observed. On bimanual examination a small uterus was palpable but the adnexa were not palpable. Endocrine evaluation revealed a hypoestrogenic, hypergonadotrophic amenorrhoea. LH values were 33, 28, and 42 IU/L, respectively (MRC 68/40, normal 2–12 IU/L); FSH 43, 39, and 52 IU/L, respectively (MRC 68/39, normal 3–14 IU/L); and total urinary estrogen excretion 47 and 69 µmol/24 h, respectively (normal in proliferative phase 80–400 µmol/24 h). Thyroid, liver, pancreas and kidney functions, prolactin and testosterone levels, and 17-OHCS, etiocholanolone and androstene excretion were all normal.

The proposita is the eldest of three sibs; her two brothers were born on 16-5-1968 and 22-1-1970. The mother and the father of the patient measure 178 cm and 180 cm in height respectively. Relatives of the mother in particular are very tall.

The mother is phenotypically normal. Her age at menarche was 10 years. She had an irregular menstrual cycle ranging from 4 to 8 weeks and had her menopause at the age of 34 shortly after the birth of her third child.

There are many cases of cancer of the intestine in the mother's family. All seven of the mother's sibs are dead. Three of them died in childhood and the other four have three or four children each.

Physical examination of the youngest brother of the proposita revealed a normally developed prepubertal boy of 11 years.

Cytogenetic Findings

The karyotype of the proposita was determined from G-banded chromosomes in preparations from lymphocyte cul-
Fig. 1. The proposita

Fig. 2a-e. Chromosomes involved in the translocation from three cells of the proposita (top) and two cells from her mother. a and b Normal X, c derived X, d derived 12, and e normal 12

Discussion

A thorough search of the literature revealed 36 cases of women heterozygous for a balanced X-autosome translocation with a break-point in Xq. These are listed in Table 1 together with our case and her mother. Of the translocations with X-break-points located proximally in region q11-q13 and distally in region q26-q28, 13 carriers had a normal sex phenotype and 12 were of proven fertility. Excluding our case, there were 23 translocations with break-points in the region Xq13-q26; all of these had arisen de novo and all the carriers were infertile with various signs of ovarian insufficiency. Streak gonads or underdeveloped ovaries were found in all 13 cases subjected to exploratory laparotomy. These cases collectively confirm the rule first perceived by Sarto et al. (1973) and later supported by Phelan et al. (1977), Summitt et al. (1978) and Dorus et al. (1979) that the structural integrity of a region lying from Xq13 to Xq26 is necessary for normal ovarian development and function. We note that this definition of the ‘critical’ region leaves open the possibility that a proximal part of band q13 and a distal part of band q26 lie outside its limits, so that the case of Allderdice et al. (1978) and Yamamoto (1979) are not necessarily exceptions.

The mother of our proposita, however, bore three children and is a very clear exception. There are two possible explanations. The influence of the translocation on ovarian development, which is formally a position effect of a unique kind, could be a ‘recessive’ condition that can normally express itself because of functional hemizygosity due to inactivation of the normal X chromosome. Such inactivation is recognized to be a regular feature of all or nearly all cells in structural heterozygotes involving the X, as is the case in all the reports in Table 1. However, it is known from at least one report (Nichols et al.