



Acta Genet Med Gemellol 44: 1-7 (1995)

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Received 17 January 1995

Final 20 February 1995

Amenorrhea in Gonadal Dysgenesis, Caused by Chromosomal Translocation

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Abstract. A healthy 23-year-old woman with amenorrhea was examined at the Mendel Institute. She had been amenorrheic for 4 years, and had not responded to hormone treatment. We therefore decided to study her family tree and karyotype. We describe the results of our study here: the patient was found to have gonadal dysgenesis, caused by translocation of a fragment of the X to a 12 chromosome, resulting from a break at q21, at the end of the q-arm.

INTRODUCTION

The first case-report of woman affected by primary amenorrhea presenting a balanced X; autosome translocation was made in the early 1970s [3]. It described a woman with the karyotype 46,XX,t(12q;Xq) (Xq;12q). Using 6 other cases of X; autosome translocations which were known of at the time, the author speculated that a particular region of the X, located between Xq13-q25, must be intact in both chromosomes for normal ovarian development to take place. This hypothesis was subsequently confirmed by a study which located the critical zone in two chromosome segments, Xq13-q22 and Xq22-26, separated by a narrow band of Xq22. Breaks occurring in this narrow band of Xq22 did not appear to cause abnormal ovarian development [2].

More recently, a larger study of 118 adult females with translocations of the X was reported [4]. In these 118 women, X;autosome translocation involved all the autosomes. In 45 of the 118 women studied, the break occurred in the critical area of the X linked to gonadal dysgenesis, and was manifested in either primary or secondary amenorrhea. In only 6 of the remaining 73 women did the break occur outside the critical zones, despite these women's presentation of ovarian dysgenesis. 33 women presenting characteristics either similar or dissimilar to Turner's Syndrome did not present gonadal dysgenesis. Six women from this last group had breaks occurring outside the critical zone,

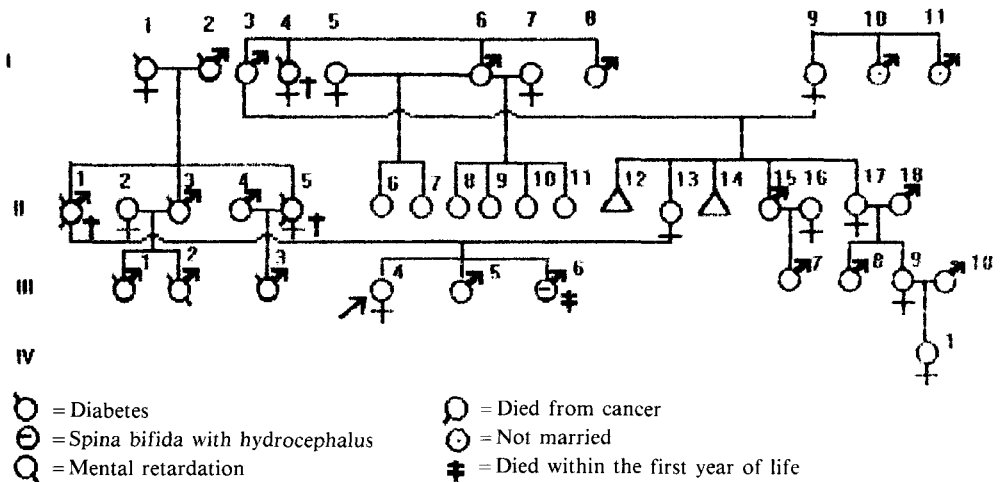
and presented three or more symptoms of Turner's Syndrome, as well as various forms of mental retardation.

Six carriers of chromosomal translocations and one inversion carrier, in whom breaks occurred at the centre of the critical area of the Xq22 band, had normal gonadal development. A pair of female dizygotic twins who were carriers of a chromosomal inversion was the subject of an earlier study [1]. One twin presented normal gonadal development, while her cotwin presented secondary amenhorrea and mild mental retardation. Thirty-one women affected by chromosomal inversion, who had breakpoints within the critical region of the X, and who presented either primary or secondary amenhorrea, have been reported from the literature [4].

CASE-STUDY

Pedigree of the patient's family

In the first generation, diabetes was found in the patient's paternal grandparents, and a case of diabetes in the siblings of the patient's maternal grandmother. There were 3 cases of diabetes in the second-generation male members of the family, and two of these diabetic males died of cancer: one of the patient's uncles, from cancer of the kidney, and the patient's father, from lung-cancer. Two second-generation female members of the family had aborted spontaneously. The patient had a brother who died of spina bifida and hydrocephalus, at the age of 10 days.



Anamnesis

The patient was born on 14.11.1971 and was healthy. The menarche occurred at the age of 11 years. From the menarche onwards, the patient had alternating poly-hypermenorrhea and oligospaniomenorrhea, with progressive amenorrhea over the past 4 years.

At the age of 19, following a gynaecological examination, the patient was unsuccessfully treated orally with a course of progestagen (medroxyprogesterone). A menstrual cycle was induced by treating the patient with an intramuscular course of natural progestagen. A blood sample to detect ovarian and hypophysis hormone levels, suggested ovarian dysfunction (high levels of gonadotrophin FSH and LH, and below-average levels of estradiol were measured). The patient was treated with a course of estrogen-progestogen, which induced a regular menstrual cycle. (In this hormone therapy, the patient was treated orally with a 21-day course of estradiolvalerate, and during the last six days was simultaneously treated with an intramuscular course of natural progesterone. After completion of the 21-day course, hormone treatment was then withdrawn for 7 days, for an undetermined number of cycles). The withdrawal of therapy resulted in amenorrhea and a mild hypertrichosis of the face and limbs.

Objective examination

This resulted negative, except for soreness of the epigastrium when touched. Ferriman-Gallwey score (simplified to evaluate the level of hypertrichosis) equal to 6 (r.v. ≤ 4 with max. = 16). Height 160 cm; weight 68.5 kg; index of body mass equal to 26.8 kg/sqm. (r.v. 19-24) as for simple ponderal excess.

Structural and hematological parameters

ECG within normal range. RBC 4,400,000/mmc. WBC. 5,500/mmc (N39, E3, B1, L49, -M8). Blood platelets 217,000/mmc. Routine parameters normal, in particular: cholesterol 208 mg/dl (140-250); triglycerides 73 mg/dl (37-145); uric acid 5.4 mg/dl (3-8).

Basal hormonal parameters

T3, 1.17 ng/ml (0.7-2.1); T4 98 ng/ml (50-110); TSH 0.58 μ U/ml (0.3-3.5); FT3 2.8 pg/ml (1.7-4.3); FT4 17.8 ng/ml (7-23); anti-thyroglobulin and anti-microsomal autoantibodies negative. FSH 62 mU/ml (0.5-12); LH 21 mU/ml (0.5-12); prolactin 510 μ U/ml (80-650); estradiol 35 pmol/l (50-400); progesterone 0.48 nmol/l (0.5-4.0), total testosterone 0.9 nmol/l (0.3-3.0) and free 3.1 pmol/l (1.5-12); DHEAS 2.3 μ g/ml (0.3-3.5); 17-0H-progesterone 0.45 nmol/l (0.5-4.0); androstenedione 0.87 ng/ml (0.2-3.0). Repetition of the test a short time afterwards gives similar results.

Dynamic hormonal parameters

Table 1 - Oral glucose tolerance test (OGTT)*

Time (mins)	0	30	60	90	120	180	240	300
Glycemia (mg/dl)	87	135	107	97	102	105	90	86
							<i>peak r.v. < 180</i>	
Insulinemia (μ U/ml)	10	95	91	58	78	62	15	6.7
							<i>peak r.v. < 100</i>	

*glucose dose 100g

Table 2 - TRH test (200 μ g intravenous) within normal range

Time (mins)	-15	0	30	60	120	180
TSH (μ U/ml)	1.2	0.75	9.5	6.1	2.6	1.7
						<i>peak r.v. < 17</i>

Table 3 - Metoclopramide hydrochloride test (10 mg per os) as for central dopaminergic hyperactivity

Time (mins)	-15	0	30	60	120	180
TSH (μ U/ml)	2.4	2.0	1.7	1.5	2.2	2.2
PRL (μ U/ml)	868	537	336	206	4412	3332
GH (ng/ml)	0.32	0.29	0.36	0.30	0.34	5.6

Table 4 - Intramuscular HCG test (10000 U.I.)

Time (days)	0	1	2	3
Estradiol (pmol/l)	10	10	29	73
				<i>(r.v. > 180)</i>

Table 5 - Intramuscular FSH test (375 U.I.)

Time (days)	0	1	2	3
Estradiol (pmol/l)	10	10	46	10
				<i>(r.v. > 150)</i>

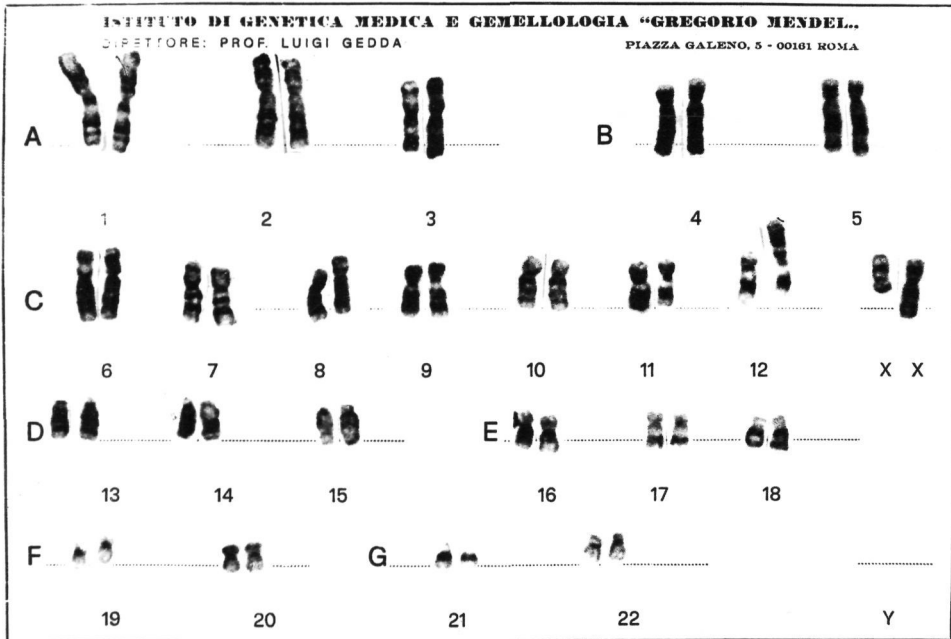


Fig. 1. Patient's karyotype

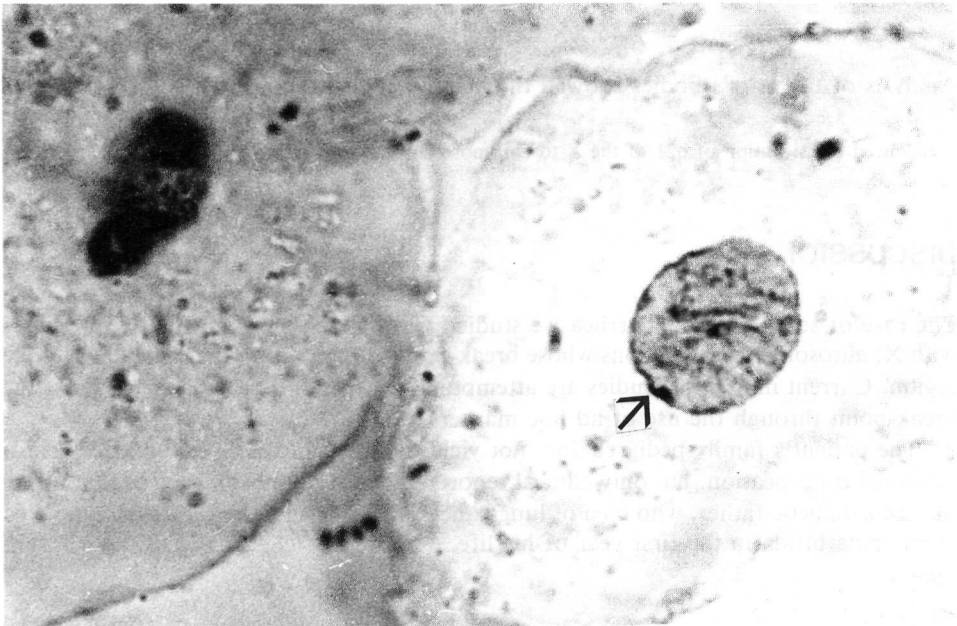


Fig. 2. Barr's bodies in cell nuclei from an oral smear ($\times 2500$). Aceto-orcein staining

Pelvic ultrasound scanning

Uterus in median position, retroflexed, and morphovolumetrically normal (diam. 67mm; anteropost. 28mm; transverse 32mm) with normal aspect. Endometrial echopattern barely visible. L. ovary in situ and of normal size (26 × 15 × 18 mm); position and size (24 × 14 × 16 mm) of r. ovary also normal. Echostructures of both ovaries homogeneous, with no adnexal changes echographically discernible in either. No effusion was present in the Douglas.

Karyotype analysis

The analysis was carried out on T-cell lymphocytes, taken from a peripheral blood sample using the Ficoll density gradient. The cells were then cultivated for 72 hours in a medium with PHA added, without bovine fetal serum. After 71 hours, the cells were stopped in metaphase by the addition of colchicine (final concentration 0.01 µg/ml). The cell cultures were treated with a hypotonic solution (KCl 0.075 M) and fixed by methanol-absolute and acetic acid-glacial (ratio 3:1).

After slide preparation, the chromosomes were analysed by C and G banding. G-bands were obtained by digestion with a trypsin solution (0.05% - trypsin 1:250 in Dulbecco's PBS). Digestion was followed by staining in a Giemsa solution (5% - pH 6.8). C-bands were obtained by predigestion in HCl 0.2 N and digestion in Ba(OH)₂ (5%. 46 C), followed by staining in a Giemsa solution (pH7).

The following karyotype was obtained:

46,XX, trcp(X;12) (q21;pter)*

Analysis of the Barr's bodies showed the inactivation of the entire X.

* Balanced translocation of q21 of the X to chromosome 12

DISCUSSION

The case of secondary amenorrhea we studied was of the type presented by probands with X; autosome translocations whose break-points occur within the critical Xq13-q22 region. Current molecular studies are attempting to better localise and characterise the break-point through the use of ad hoc markers.

The patient's family pedigree does not yield data which can be explained by chromosomal translocation, but only clinical reports (mentioned above), such as that of the patient's diabetic father, who died of lung-cancer, and of one of her brothers, who died from spina bifida in the first year of his life.

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