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CASE REPORT

Turner's syndrome mosaicism 45X/47XXX: An interesting natural history

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ABSTRACT. Mosaicism 45X/47XXX is a sporadic form of ovarian dysgenesis. Many of the cases previously described were characterized by a variable phenotype expression. We here report the case of a 33-yr-old woman with recent secondary amenorrhea, weight loss and breast regression. Her menarche had occurred at the age of 11 yr and 6 months and her menstrual cycles had been regular until the age of 28; then, oligomenorrhea and hypertricosis developed. A pelvic ultrasound showed enlarged polycystic-like ovaries and normal uterus. She was treated with ethynil-estradiol and cyproterone acetate for one year. At the age of 31 yr, she underwent a pelvic ultrasound - which revealed normal volume of the ovaries - and hormonal assays including FSH (69 UI/l), LH (113 UI/l), 17β-estradiol (88 pg/ml), plasma androgens and cortisol levels within normal ranges. No organ-specific autoantibodies toward ovaries, steroid-producing cells or adrenals were found. At the age of 33 yr, there was ultrasound evidence of streak-like ovaries. The patient's height was 145 cm and her weight 45 kg. She had normal female external genitalia, abnormal upper-to-lower body segment ratio, webbed neck, low posterior hair line, *cubitus valgus*, short and asymmetrical 4th metacarpi, hallux with lateral deviation and moderate scoliosis. No increase in ovarian steroids were found after GnRH-analogue triptorelin (0,1 mg sc) administration. The karyotype analysis on peripheral blood lymphocytes showed a mosaic 45X (90% cells) and 47XXX (10% cells). Diagnostic pelviscopy confirmed streak gonads. Chronic lymphocytic thyroiditis was diagnosed but no cardiovascular or kidney abnormalities were found. A neuro-psychological evaluation revealed emotional and social immaturity, disorders in motorial coordination, visual-spatial organization, as well as reading difficulties and impaired complex phrase construction. The presence of several somatic features of Turner's syndrome, neuro-psychological disorders and an interesting natural history probably depended on the quantitative proportion of 45X to 47XXX cell-lines in different tissues and organs. Estrogen and progestin replacement therapy led to weight gain, re-appearance of secondary sexual characteristics and a mild improvement in mental equilibrium.

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INTRODUCTION

Turner's syndrome is a sporadic disorder, believed to occur in 1/1500-2500 live-born girls (1-3) and has serious lifetime consequences such as cardiovascular system abnormalities, hypertension, estrogen deficiency, infertility and impaired skeleton integrity (2). Molecular studies comparing proband and parental X polymorphisms have shown that the maternal X chromosome is retained in about two thirds of subjects with Turner's syndrome and the paternal X in the remaining one third (4, 5). A mosaic chromosomal complement has been recently reported in more than half of Turner subjects (2, 3). Moreover, the presence of cell-lines different from 45X in the fetal membranes has been hypothesized as necessary for fetal survival (2, 3). As a matter of fact, an accurate karyotype examination has evidenced the association with one or

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more of the following cell- lines in a part of women with Turner's syndrome: 46XX, 46XY, 47XXX, 47XXY, 47XYY, fragments of the X and/or Y chromosomes (6, 7). Possibility of a cryptic mosaicism has been supposed in other cases (2). While the phenotype characteristics of the 45X karyotype have been widely described (3, 6, 8, 9), reports on the specific features of the mosaicism are less frequent (6, 7, 10). The natural history of a few cases of mosaic chromosomal pattern 45X/ 47XXX has been described and different expressions of somatic stigmata of Turner's syndrome - mostly milder than that associated with 45X karyotype - have been reported (7, 10). The typical phenotypic and gonadal expression of Turner's syndrome can be modified by the presence of an individual mosaic constitution.

We describe the case of a young woman with secondary amenorrhea in whom a karyotype examination was requested on the basis of her short stature and findings of several skeletal features of Turner's syndrome.

CASE REPORT

A 33-yr-old white woman was referred to us because of recent amenorrhea, breast regression and weight loss. Her previous physical and mental development was reported within normal limits; menarche had occurred at the age of 11.5 yr. Her menstrual cycles had been regular until the age of 28 yr, after which oligomenorrhea and hypertricosis developed. Transparietal pelvic ultrasound showed enlarged polycystic-like ovaries (left 39.7x22 mm; right 38.7x23.7 mm) and normal uterus (Fig. 1) (11). Both ovaries were characterized by a peripheral array of multiple small follicles (3-10 mm) and increased amount of stroma relative to the number of follicles. An incomplete endocrine evaluation, summarized in Table 1, suggested a mild-degree hyperandrogenism. She was prescribed ethynil-estradiol (0.035 mg/day) and cyproterone acetate (2 mg/day) treatment for one year, during which her hypertricosis improved and her menstrual bleeding normalized.

At the age of 31 yr, 2 yr after the withdrawal of any treatment, oligomenorrhea persisted, the patient therefore underwent pelvic ultrasound – which showed normal ovarian volume (left 27x17 mm; right 25x13 mm) and a hormonal evaluation – which indicated hypergonadotropic oligomenorrhea (Table 1).

At the age of 33 yr, when she was admitted to our department, she weighed 45 kg and was 145 cm tall (BMI: 21.4 kg/m^2). At the physical examination, she presented with normal external genitalia; abnormal upper-to-lower body segment ratio (U>l); webbed neck; low posterior hair line; short and asymmetrical

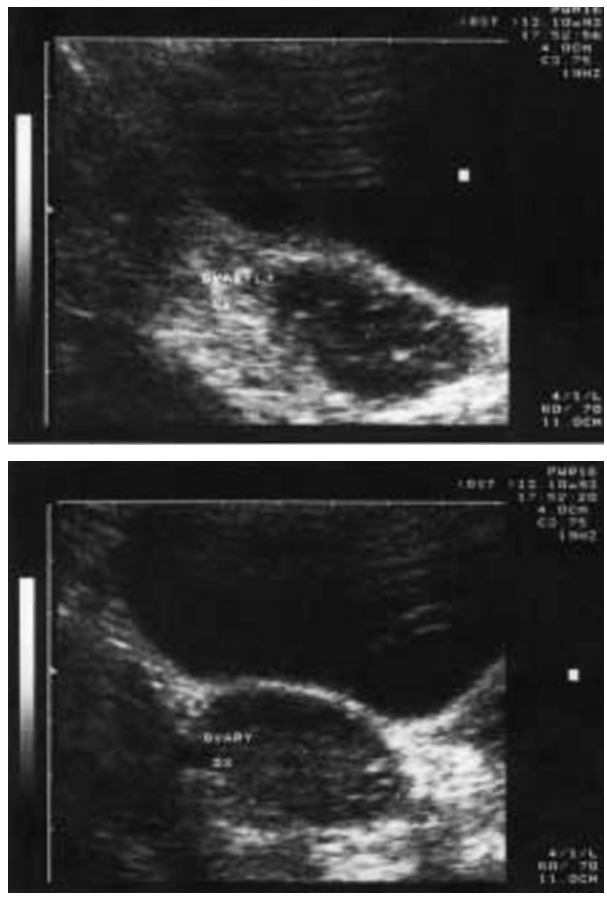

Fig. 1 - *Pelvic ultrasound carried out at the age of 28 yr showing enlarged polycystic-like ovaries.*

4th and 5th metacarpals, shorter on the left hand; *genu valgum*; arcuate *thybiae*; hallux with lateral deviation; moderate dorsal scoliosis previously treated with an orthopedical corset. Routine laboratory results were within normal ranges, including the response to standard glucose tolerance test (70 gr of glucose *per os*). Cortisol concentrations were within normal ranges and organ-specific autoantibodies toward ovaries, steroid-producing cells and adrenals – detected by indirect immunofluorescence technique (12, 13) – were negative. Only anti-thyreoglobulin autoantibodies were increased (450 U/l; normal: <50 U/l), whereas thyroid function was normal, with a TSH value of 1.4 μU/ml. These findings, together with thyroid ultrasound features of diffusely dyshomogeneous hypoechoic pattern, suggested a chronic autoimmune thyroiditis. Other organ-unspecific autoantibodies (anti-mitochondria, anti-smooth muscle, antinuclear, anti-double strand DNA) were absent and immunoglobulines were within the normal range.

Table 1 - *Hormone levels at different ages.*

	At baseline			After GnRHa administration*	Normal range (at baseline)
Age	28 yr	31 yr	33 yr	33 yr	
FSH	ND	69	78	198	5.0-30 U/l
LH	ND	113	49	96	5.0-60 U/l
17β-estradiol	44	88	<20	<20	50-220 pg/ml
Progesterone	0.6	0.4	0.1	0.5	0.3-25 ng/ml
17-hydroxyprogesterone	1.02	0.29	0.1	0.1	0.1-2.9 µg/l
Androstenedione	2.95	2.09	1.9	1.1	1.0-2.0 ng/ml
Testosterone	0.5	0.9	<0.2	<0.2	0.2-0.9 ng/ml
Prolactin	ND	13.7	9.0	ND	5.0-25 µg/l

*GnRH-analogue, triptorelin 0,1mg in acute sc administration; the responses are expressed as maximum peaks at times 30, 60, 120, 180 and 240 min for LH and FSH; and after 16, 20 and 24 h for steroids. Factors for converting steroid conventional units to SI units: 17-hydroxyprogesterone: µg/l=3.026 nmol/l; androstenedione: ng/ml=3.492 nmol/l; testosterone: nmol/l=3.467 ng/ml; progesterone: nmol/l=3.180 ng/ml; 17β-estradiol: pmol/l=3.671 pg/ml. ND: not determined.

Pelvic ultrasound revealed streak-like gonads and decreased uterus size (Fig. 2). An acute GnRH-analogue stimulation test (triptorelin, 0,1 mg sc) (14) revealed FSH and LH hyperresponsiveness at times 30, 60, 120 and 240 min, while no ovarian steroid response was present after 16, 20 and 24 h (Table 1). The karyotype analysis performed by banding technique on 100 peripheral lymphocyte nuclei showed a mosaic pattern of 90% of 45X cells and 10% of 47XXX cells. The diagnostic pelviscopy confirmed bilateral streak gonads; no biopsy was performed. 2D and M-mode echocardiogram recordings, pulsed-wave Doppler of the heart, ECG, abdominal ultrasound and urography did not reveal any structural alterations of the cardiovascular and urinary systems.

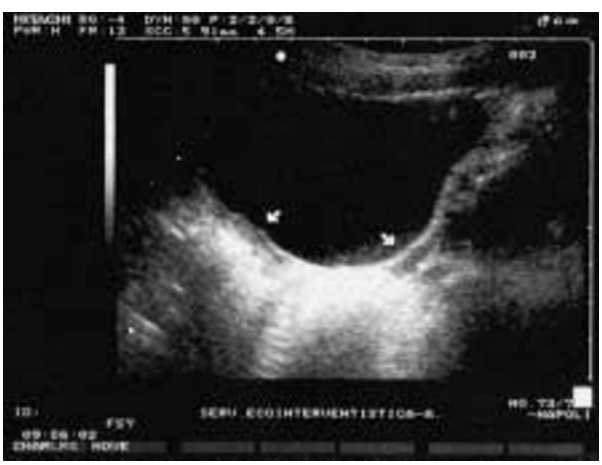

Fig. 2 - *Pelvic ultrasound carried out at the age of 33 yr showing small streak-like gonads.*

At the neuro-psychological evaluation, which included a semi-structured psychological colloquium, there was evidence of impaired visual-spatial organization (continuous difficulty in finding the nurses station or doctors office inside the hospital building) and motorial coordination (rough movements and difficulty in coordinating the movement of her hands and legs), difficulties in the construction of more complex phrases, reading difficulties, emotional and social immaturity, strong dependence on the parental figures, particularly the mother. Moreover, exaggerated reactions to external stimuli, behavioral impulsiveness, inability to plan future actions, and unstable moods were also apparent.
Replacement therapy with estrogen (ethinyl-estradiol 0.3 mg/day) and progestin (gestodene 0.075 mg/day) was prescribed, which led to weight gain and re-appearance of secondary sexual characteristics, as documented during the 12-month follow-up. The patient reached 51 kg (BMI: 24.3 kg/m^2) and reported an improved mental equilibrium. The latter was not objectively documented and the patient did not return for further follow-up.

DISCUSSION

While variable phenotype characteristics of the 45X karyotype have been widely described, with short stature and ovarian dysgenesis as the only clinical findings invariably present (3), cases of women with the 47XXX karyotype – characterized by less severe abnormalities – have been less frequently reported (7). Most of the latter were evaluated in adult age and presented with normal height (mean±SD, 167.9±7.7 cm), secondary amenorrhea in about

37% cases and skeletal abnormalities ranging between 0-5%. Cardiovascular and/or renal abnormalities have been reported in less than 4% of them and immune-related disorders in about 3% (7). However, no linear correlation has been found between karyotype and phenotype expression in subjects with chromosomal aberrations (4). Turner's syndrome seems to be characterized by a more variable phenotype expression than the 47XXX phenotypes. This can reflect the simultaneous presence of different genetic material under the form of cryptical mosaicism or sex chromosome fragments in Turner subjects. However, the identification of a mosaicism is strongly dependent on the evaluation method and varies from 34% with conventional cytogenetic techniques to 74% using reverse polymerase-chain-reaction assays (2, 15, 16).
The patient described above presented with short stature and multiple skeletal abnormalities, typical of Turner's syndrome. Nevertheless, her menstrual cycles had been regular for 17 yr. The ovarian failure appeared after a 2-yr period of hyperandrogenism and polycystic-like ovarian abnormalities that probably reflected progressive follicular athresia with persisting androgen production from stromal ovarian tissue. As a matter of fact, the greater decline in ovarian androgen production than in estrogen production has been described in post-menopausal women after the physiological menopause (17). Consequently, the ovaries become primarily androgen-producing glands able to maintain gonadotropin responsiveness for many years (17). Similarly, the high androgen production rate in this patient could be due to the increase in gonadotropin secretion, which stimulates steroidogenesis in ovarian hilar or stromal cells (18). The period of hyperandrogenism was likely stopped by the development of streak-like gonads and was accompanied by a BMI decrease (24.8 kg/m^2 in the period of polycystic-like ovary diagnosis and 21.4 kg/m^2 at the moment of the diagnosis of mosaicism).
Fortunately, only chronic lymphocytic thyroiditis was identified but no cardiovascular or urinary tract disorders were found. An increased evidence of autoimmune disorders in patients with gonadal dysgenesis has been observed. In particular, Turner's syndrome seems to be frequently associated with increased thyroid antibodies and hypothyroidism (3). The patient described above presented increased anti-thyreoglobulin antibodies but normal thyroid function; however, she would need further follow-up of the thyroid function.
The multiple psychological problems affecting our patient, including verbal difficulties and social immaturity, allow to hypothesize a loss of the paternal X chromosome in the 45X cells, an event more frequently described. Significantly better social adjustment mediated by higher verbal and executive function tasks has been found in Turner women who retain the paternal X chromosome, compared with those who retain the maternal one (19). The existence of genetic *locus* for social cognition has been suggested, that should be imprinted on the paternally derived X chromosome, but silenced on the maternally derived one (19). In fact, pilot interviews and observations showed that 45X females with maternal X chromosome lacked flexibility and responsiveness in social interactions (19). In addition, also the X polysomy could contribute to the problems in speech and language development in our patient (20).
Mosaic chromosomal pattern 45X/47XXX is a quite rare type of ovarian dysgenesis. The presence of several stigmata of Turner's syndrome in our patient and of the period of normal ovarian function probably depended on the quantitative proportion of 45X to 47XXX cells during the differentiation of somatic and germinal cells. The ratio of 45X to 47XXX primordial germ cells or blastemal components seems to be the major determinant of the definitive gonadal structure and function in patients with such mosaicism (6). Similarly, the quantitative ratio of the cell lines in peripheral tissues could affect the phenotypic stigmata. However, a variable sex chromosome constitution has been reported in different tissues and different areas of the same tissue (21). The ovarian function in 45X/47XXX women has been described as ranging from normal - associated with spontaneous pregnancies (21) - to completely absent with mono- or bilateral streaked gonad findings (6). Moreover, the premature ovarian failure can be explained in part by a further loss of the X chromosome with age (22).
Nevertheless, the lack of direct karyotype-phenotype correlation in patients with sex chromosome alterations indicates that several factors are involved in the development of the phenotypes and these relationships have not yet been completely clarified (6, 23). Moreover, the mechanisms by which the mosaicism occurs in different tissues are still unknown, as are the factors influencing survival of an aneuploid cell line.
The 45X/47XXX mosaicism was diagnosed quite late in our patient despite the several evident clinical features of Turner's syndrome, probably due to the quite normal sexual development and the long period of regular menstrual cycles. However, sex-chromosomal alteration should be always suspected when at least two clinical features of the disorder exist (2). It is very important to perform an accurate diagnosis of the karyotype and to search for all the possible impairments described in Turner's syndrome and related mosaicisms, because the consequences of a late diagnosis of this illness are severe and life-long.

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