



A case of premature ovarian failure (POF) in a 31-year-old woman with a 47,XXX karyotype

Przypadek przedwczesnego wygasania czynności jajników u 31-letniej kobiety z kariotypem 47,XXX

Piotr Skalba, Anna Cygal, Zuzanna Gierzyńska

Department of Gynaecological Endocrinology, Medical University of Silesia, Katowice

Abstract

A case of POF in a 31-year-old woman with karyotype 47,XXX. The aim of the study was to discuss a case of POF in a 31-year-old patient with polysomy 47,XXX. The described karyotype is not usually associated with this characteristic physical phenotype. In some rare cases, menstrual disorders, sterility, secondary amenorrhoea, premature menopause, and low intelligence are found.

Our observations revealed the necessity for cytogenetic examination in all women at reproductive age with symptoms of premature ovarian failure. According to the data found in literature, patients with POF and karyotype disorders belong to the risk group of premature death, mostly for cardiologic reasons. Raising patient awareness about the risk may have a positive effect on quality of life and regularity of check-ups.

(Pol J Endocrinol 2010; 61 (2): 217–219)

Key word: premature ovarian failure, polysomy 47,XXX, secondary amenorrhoea

Streszczenie

Przypadek POF u 31-letniej kobiety z kariotypem 47,XXX (zespół przedwczesnego wygasania czynności jajników [POF, *premature ovarian failure*]). Celem pracy była analiza przypadku 31-letniej kobiety diagnozowanej z powodu POF, u której stwierdzono polisomię 47,XXX. Opisywany kariotyp zwykle nie jest związany z charakterystycznymi cechami fenotypowymi. Tylko w niektórych przypadkach stwierdza się: zaburzenia miesiączkowania, niepłodność, wtórny brak miesiączki, zespół przedwczesnego wygasania czynności jajników i deficyty intelektualne.

Obserwacja autorów pracy wykazała konieczność badania cytogenetycznego u wszystkich kobiet w wieku rozrodczym z objawami POF. Dostępne dane z piśmiennictwa identyfikują pacjentki z POF i nieprawidłowościami kariotypu jako grupę zagrożoną przedwczesnymi zgonami — głównie z przyczyn kardiologicznych. Uświadomienie ryzyka tym pacjentkom może wpłynąć na korzystne zmiany stylu życia i regularność badań. (Endokrynol Pol 2010; 61 (2): 217–219)

Słowa kluczowe: przedwczesne wygasanie czynności jajników, polisomia 47,XXX, wtórny brak miesiączki

One of the causes of premature ovarian failure (POF) is related to chromosomal abnormalities. Portnoi et al. [1] performed cytogenetic examinations in 90 patients with diagnosed POF and found an abnormal karyotype in 8.8% of cases. The group also included one case of 47,XXX. Other literature data confirm that the 47,XXX karyotype may be associated with POF revealing itself in during puberty as well as the reproductive period. According to Goswami [2], 3.8% of women with POF have the 47,XXX karyotype. In women with POF and the 47,XXX karyotype, autoimmune disorders of thyroid and/or adrenal glands may occur.

It is estimated that 1 woman in 1000 has an additional X chromosome, and that those women do not display characteristic symptoms, suggesting the described disorder. [3] Therefore, they do not demonstrate the typical phenotype of the 47,XXX women. Women with X polysomy may display: underdevelopment of secondary sex characters, retarded sexual maturation, and primary or secondary amenorrhoea caused by premature ovarian failure. Congenital defects may also occur, including: obliteration of the duodenum, congenital hyperplasia of adrenal glands (11 β -hydroxylase deficit), cheilognathopalatoschisis, a contracture of the



distal phalanx of the fifth finger, epicanthal fold, and transverse flexion creases of the palm. In some cases, mental impairment is found. It must be emphasized that a large group of the patients do not display any phenotypical abnormalities or traits of mental impairment. [4]

Case report

The patient, AH, aged 31, was admitted to the clinic due to a secondary amenorrhoea, hot flushes, and secondary infertility. The patient had secondary education and was employed as a clerical worker. AH spontaneously miscarried a 10-week pregnancy two years previously. The miscarriage was an arrested abortion. In 2007 the patient had a uterine myoma enucleated surgically in the course of a laparotomy. The patient had two elder, healthy sisters. Her parents were under 30 years old at the time of her birth. She menstruated for the first time at the age of 12. Then she menstruated irregularly at intervals of 60–180 days. The menstruations were abundant, with clots and accompanying pain complaints.

As a girl, she developed normally. At the moment of admission to the clinic, at the age of 31, she was 167 cm tall, weighed 52 kg, and her BMI was 18.65. She had an asthenic female body build. A gynaecological examination revealed normal vulva and perineum, and female pubic and axillary hair. Ectopy was found on the vaginal part of the uterine cervix. The body of the uterus was slightly enlarged, in retroflexion, with poor mobility. The adnexa on both sides were impalpable and painless in examination.

The results of hormone level determination were as follows: FSH: 127.90 mIU/ml, LH: 11.87 UI/L, E_2 : 67.77 pmol/L, free testosterone: 0.99 pg/ml, total testosterone: 0.28 nmol/L, 17-OH: 0.50 ng/ml, androstendione: 2.08 ng/ml, TSH: 1.032 uIU/ml, fT_3 : 2.92 pg/ml, fT_4 : 1.09 ng/dL. Daily profiles of prolactin and cortisol were normal. No antithyroid or antiadrenal antibodies were found in the blood. The COMBI test (AMA, APCA, ASMA, LKM) and the anticardiolipin tests were negative.

An ultrasonographic examination of the pelvis minor, performed with an intravaginal probe, showed: the body of the uterus in retroflexion, with size 41 × 52 mm, of a slightly non-homogeneous echo pattern; endometrium — 6 mm thick, homogeneous; right ovary of size 29 × 21 mm, 6 ml volume, with two echo-negative areas of 10 and 8 mm in diameter; and left ovary of size 18 × 15 mm, 2 ml volume. A cytogenetic examination, performed by GTG technique with the degree of band resolution according to ISCN: 400–500, after an analysis of 58 metaphase plates, an X chromosome trisomy was diagnosed: 47,XXX. The examination was performed at the Cytogenetic Laboratory of the Depart-

ment of Medical Diagnostics at the Silesian Centre of Child's and Mother's Health of the Medical University in Katowice. A psychologist's consultation revealed the patient's normal psychological condition.

Discussion

X chromosome trisomy is a result of sex chromosomes not being disjuncted in the first meiotic division. The defect is closely related to the mother's age: the older the mother, the higher the risk of XXX trisomy occurring in the daughter. According to Deng et al. [5], in cases of X polysomy, the additional X chromosome comes from the mother.

The first case of a woman with X trisomy was described by Jacobs in 1959 [6]. Apart from a secondary amenorrhoea, she did not display any other psychic, physical, or sexual disorders.

The standard diagnostic procedure in the case of young women with primary or secondary amenorrhoea should include a cytogenetic examination. The principle is understood and accepted by most gynaecologists in the case of women under the age of 25; in older patients the examination is usually not performed, as the described case demonstrates.

As has been emphasized in the introduction, there is no typical phenotype for women with 47,XXX. In women with 47,XXX polysomy and POF, immunological disorders may occur. In 2003 Masanori et al. [7] described a patient with 47,XXX polysomy and a coexisting pure red cell aplasia (PRCA), manifesting itself with anaemia and panmyelophthisis. Michalak et al. [8] described a 47,XXX patient with premature ovarian failure and autoimmune disorders. Goswami [2] examined 52 patients with POF and found that in 2 of them, besides X trisomy, an autoimmune thyroid disease occurred. Lanoble et al. [9] presented a 47,XXX patient with systemic visceral lupus. Even though our patient did not display immunological disorders or disorders of the thyroid and adrenal glands, the additional X chromosome may still play an important role in the functioning of the immunological system, and special medical care should be given the patient.

Harmon et al. [10] suggest that the additional X chromosome in a woman may determine her tall stature. This is not confirmed by our case, in which the patient had a normal stature of 167 cm, or by another case described previously in our centre, in which the patient was of short stature.

Some women with X polysomy become pregnant. There have been descriptions of children with Down syndrome being born from mothers with the 48,XXXX karyotype [5]. Kesaree and Wolley [11] described the

case of a woman with the 49,XXXXX karyotype with retarded physical and mental development. Goswami [2] described a woman with POF and 47,XXX karyotype, who became pregnant twice. The first pregnancy ended in a premature birth and idiopathic thrombocytopenia being diagnosed in the child. From the second pregnancy a child with cerebral hernia was born and died soon thereafter.

According to Barr et al. [12], who presented 12 of their own cases of X triploidy as well as an extensive review of literature, the 47,XXX trisomy does not cause structural and functional changes of the reproductive system. Among the 101 women described, 73 menstruated regularly or irregularly, had normally developed breasts, and did not display any significant disorders of the reproductive system. Twenty-eight women bore children, among whom boys prevailed. In 29 children, cytogenetic examination was conducted, with normal results in 24 cases. The review of literature quoted by the author may, however, include cases of women with 46,XX/47,XXX mosaicism as well.

In our centre, 2 cases of pure 47,XXX trisomy were observed in the period from 1999 to 2009. The first woman was infertile, while the patient described in the present work had one arrested miscarriage.

The study conducted by Swerdlow et al. [3] on a group of 542 X polysomy patients demonstrated that the risk of incidence and mortality due to a neoplastic disease was not higher than in the general population, while the mortality rate due to a non-Hodgkin lymphoma was significantly higher. A higher number of cardio-vascular deaths was also found.

It should be assumed that 47,XXX trisomy increases the risk of ovarian dysfunction or pathology.

As was stressed in the introduction, some patients with 47,XXX polysomy do not display mental retardation or phenotypical disorders, have normal reproduc-

tive functions, and their offspring are characterized by normal chromosome complement. Patients with X trisomy live shorter lives; therefore a correct diagnosis may facilitate taking decisions regarding the prevention and treatment of diseases accompanying this disorder.

The standard diagnostic procedure should include a cytogenetic examination. The principle is understood and accepted by most gynaecologists and endocrinologists in the case of women under the age of 25; in older patients the examination is frequently neglected. The described case of a 31-year-old patient with POF and the 47,XXX karyotype confirms the above observation. We recommend, therefore, that a cytogenetic examination should be performed in patients with primary ovarian failure.

References

1. Portnoi MF, Aboura A, Tachdjian G et al. Molecular cytogenetic studies of Xq critical regions in premature ovarian failure patients. *Hum Reprod* 2006; 21: 2329–2334.
2. Kesaree N, Wolley PV. A phenotypic female with 49 chromosomes, presumably XXXXX. *J Pediatr* 1963; 63: 1099.
3. Goswami R. Prevalence of triple X syndrome in phenotypically normal women with premature ovarian failure and its association with autoimmune thyroid disorders. *Fertility and Sterility*, Volume 80, Issue 4: 1052–1054.
4. Swerdlow AJ, Schoemaker MJ, Higgins CD et al. Mortality and cancer incidence with women with extra X chromosomes: a cohort study in Britain. *Hum. Genet.* 2005; 118: 255–260
5. Barr ML, Sergovich FR, Carr DH, Saver EL. The triplo X female. *Can Med Assoc J* 1969; 101: 247–258.
6. Deng HX, Abe K, Kondo I et al. Parental origin and mechanism of formation of polysomy X: an XXXXX case and four XXXXY cases determined with RFLPs. *Hum. Genet.* 1991; 86: 541–544.
7. Jacobs P, Baixe AG, Brown C et al. Evidence for the existence of the human, „Superfemale“. *Lancet* 1959; 423.
8. Masanori D, Hisanori M, Yuiko N et al. *International. J of Hematology* 2003; 77: 354–358.
9. Michalak D, Zacur HA, Rock JA, Woodruff JD. Autoimmunity in patient with 47,XXX karyotype. *Obst Gynecol* 1983; 62: 667–669.
10. Lanoble L, Kaplan G. Systemic lupus erythematosus in women with primary 47,XXX hypogonadism. *Rev. Med. Interne* 1987; 8: 430–432.
11. Harmon RJ, Bender BG, Linden MG et al. Transition from adolescence to early adulthood: adaptation and psychiatric status of women with 47,XXX. *J Am Acad Child Adolesc Psychiatry* 1998; 37: 286–291.
12. Witek A, Skalba P, Zięba M. Pituitary tumor in woman with 47,XXX karyotype — case report. *Med. Sci. Monit.* 2001 7: 304–307.