ANOTHER FACE OF PREMATURE OVARIAN INSUFFICIENCY: *BLEPHAROPHIMOSIS, PTOSIS, EPICANTHUS INVERSUS* SYNDROME (BPES)

Kolejne oblicze przedwczesnego wygasania czynności jajników: zespół *blepharophimosis*, *ptosis*, *epicanthus inversus* (BPES)

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Abstract

Premature ovarian insufficiency occurs in 1 in 250 women by the age of 35 years. Exposition to radiation, certain medications, and genetic predispositions are the most common causes. In addition to the relatively common Turner syndrome or Fragile X premutation carriage, it can also be caused by less well-known defects, such as the very rare *blepharophimosis*, *ptosis*, *epicanthus inversus* syndrome. Type 1 of this syndrome is characterized by specific phenotypic traits, perimenopausal symptoms and infertility due to premature ovarian insufficiency. A 23 year-old patient presented to the Department with *oligomenorrhoea* and primary infertility. Gynaecological examination did not reveal any abnormalities, but dysmorphic features, such as narrowing of horizontal aperture of the eyelids, ptosis, a skin fold arising from the lower eyelid and telecanthus, were noted. In family history, a similar phenotype was present in patients' grandfather, father and three of four brothers. Hormonal blood tests revealed very low levels of anti-mullerian hormone (0.65 ng/mL), indicating diminished ovarian reserve. Due to the risk of premature ovarian insufficiency, the patient underwent molecular testing, which revealed a pathogenic *FOXL2* allele, which confirmed the diagnosis of *blepharophimosis*, *ptosis*, *epicanthus inversus* syndrome. The woman was referred for a consultation at an infertility treatment centre, where she was qualified for an in vitro fertilization with a donor egg. Premature ovarian insufficiency becomes a serious problem, especially for women planning pregnancy. Detailed diagnosis and taking into account also less common causes of premature ovarian insufficiency remain important domains for practitioners of all specialties. Advances in assisted reproductive technology techniques enable maternity not only for women facing infertility, but also for those with a genetic burden.

Streszczenie

Przedwczesne wygasanie czynności jajników (przed ukończeniem 35. roku życia) występuje u 1 na 250 kobiet. Oprócz ekspozycji na promieniowanie lub leki może rozwijać się na podłożu genetycznym. Poza stosunkowo często stwierdzanym zespołem Turnera czy nosicielstwem premutacji w zespole łamliwego chromosomu X, jego przyczyną mogą być także mniej znane defekty. Przykład stanowi niezwykle rzadki zespół *blepharophimosis*, *ptosis*, *epicanthus inversus*, którego typ 1, oprócz charakterystycznych cech fenotypowych, manifestuje się objawami wypadowymi i niepłodnością – związanymi z przedwczesnym wygasaniem czynności jajników. 23-letnia pacjentka zgłosiła się Kliniki Endokrynologii Ginekologicznej z powodu *oligomenorrhoea* oraz problemu niepłodności pierwotnej. W badaniu ginekologicznym nie wykazano odchyleń, natomiast uwagę zwracały cechy dysmorfii na twarzy pacjentki – horyzontalne zwężenie szpary powiekowej, ptoza, fałd skórny na dolnym brzegu powiek i telekantus. W wywiadzie rodzinnym podobny fenotyp występował u dziadka, ojca i trzech z czterech braci pacjentki. Badania hormonalne wykazały niskie stężenie hormonu antymullerowskiego (0,65 ng/ml), wskazujące na zmniejszoną rezerwę jajnikową. Z powodu zagrożenia przedwczesnego wygasania czynności jajników w przebiegu zespołu genetycznego zalecono pacjentce badania molekularne. Wynik wskazywał na patogenny wariant allelu genu *FOXL2*, co potwierdziło rozpoznanie dziedziczonego w sposób autosomalny dominujący zespołu *blepharophimosis*, *ptosis*, *epicanthus inversus*. Pacjentkę skierowano na konsultację w ośrodku leczenia niepłodności, gdzie została zakwalifikowana do procedury *in vitro* z komórką jajową dawczyni. Przedwczesne wygasanie czynności jajników stanowi istotny problem u pacjentek planujących macierzyństwo. Szczegółowa diagnostyka, z uwzględnieniem także rzadkich przyczyn zespołu, pozostaje ważnym zadaniem lekarzy różnych specjalizacji. Postęp w zakresie technik wspomaganego rozrodu umożliwia realizację planów reprodukcyjnych zarówno pacjentkom zmagającym się z problemem niepłodności, jak i obciążonym genetycznie.

Keywords: POI; premature ovarian insufficiency; BPES; *blepharophimosis*, *ptosis*, *epicanthus inversus* syndrome

Słowa kluczowe: POI; przedwczesne wygasanie czynności jajników; BPES; zespół *blepharophimosis*, *ptosis*, *epicanthus inversus*

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Introduction

Premature ovarian insufficiency (POI; formerly premature ovarian failure, POF) is a clinical entity diagnosed in young women, where both symptoms and laboratory findings resemble those seen during physiological menopause. The incidence of POI is approximately 1 in 250 by age 35 years and 1 in 100 by age 40 years [1]. The clinical picture of POI consists of hypergonadotropic hypogonadism associated with high levels of tropic hormones produced by the pituitary gland, follicle stimulating hormone (FSH) and luteinizing hormone (LH), with low levels of sex hormones produced by the ovaries, mainly oestrogens. All this leads to menstrual disorders, perimenopausal symptoms such as hot flashes, vaginal dryness, palpitations, excessive sweating or mood swings, as well as infertility. The longer the duration of ovarian insufficiency in terms of hormone production, the higher the risk of reduced bone mineral density and osteoporosis, and the higher the cardiovascular risk due to oestrogen deficiency. According to the European Society of Human Reproduction and Embryology (ESHRE), the diagnosis of POI is based on FSH levels >25 mIU/mL measured on two occasions at least 4 weeks apart in a patient with infrequent menstrual cycles or amenorrhea for at least four months [2].

The processes underlying the development of POI include accelerated loss of ovarian follicles or reduced production of sex steroids. POI differs from the physiological menopause in women over 40 years of age by the presence of a causative factor other than age itself. Although the aetiology of POI varies widely, the definite cause remains unknown in up to 70% of cases [3]. The most common causes of POI include genetic factors, associated with both chromosomal aberrations and abnormalities in the expression of particular genes. Turner syndrome (monosomy X) is the most common aetiology in the former group. The second group includes carriership of *FMR1* premutation alleles (fragile X syndrome), as well as mutations of many other genes involved in folliculogenesis, steroid hormone production, and receptor signal transduction (among others, *BMP-15*, *XIST*, *FSHR*) [4]. The genetic background is important, so much so that it is estimated that whole-genome sequencing of the coding genome could identify the cause of POI in 30–35% of patients [3]. Other causes of POI include autoimmune disorders (adrenal insufficiency, polyglandular autoimmune syndrome, Hashimoto's disease) and the toxic effects of pharmacotherapy, chemotherapy and radiotherapy in particular. POI can also be a consequence of viral infections and metabolic abnormalities [5].

Blepharophimosis, *ptosis*, and *epicanthus inversus* syndrome (BPES), which has a prevalence of 1 in 50,000 births, may also be an extremely rare cause of POI [6]. This autosomal dominant genetic syndrome includes a characteristic set of phenotypic features: narrowing of horizontal aperture of the eyelids, drooping of the eyelids and a skin fold arising from the lower eyelid, as well as an increased distance between the inner corners of the eyes. The classification distinguishes between two types of BPES. In type 1 BPES, the phenotypic features described above are accompanied by POI symptoms, while type two can be diagnosed in individuals with isolated eyelid abnormalities (structure and position). Approximately 64% of BPES cases occur in women [7]. Due to the ophthalmic manifestation of the syndrome, patients are offered corrective surgical procedures to achieve a cosmetic effect but also to prevent short sightedness and strabismus [7].

FOXL2 mutation, located on the long arm of chromosome 3 (3q23), is responsible for BPES. Normal expression of the *FOXL2* gene product is responsible for eye and eyelid muscle development [8]. Additionally, it is involved in sex determination, regulates ovarian granulosa cell function and influences ovarian follicle development [9].

There are literature reports on the potential involvement of *FOXL2* overexpression in the pathogenesis of endometriosis and *FOXL2* mutation in the development of granulosa cell-derived ovarian cancer [10, 11]. In the case described below, the effect of the transcription factor SF-1, a product of *FOXL2* expression, on the production of antimullerian hormone (AMH) by ovarian granulosa cells appears to be most relevant [12].

Case report

A 23-year-old patient presented to the Department of Gynaecological Endocrinology due to infrequent menstrual cycles and primary infertility. She additionally reported noticeable vaginal dryness. Gynaecological examination revealed no abnormalities, but dysmorphic features, such as narrowing of horizontal aperture of the eyelids, ptosis, a skin fold arising from the lower eyelid and telecanthus, were noted. Family history showed a similar phenotype in the patient's grandfather, father and three of her four brothers. Hormonal findings ob-

tained during the first phase of the cycle were as follows: oestradiol 42 pg/mL, FSH 4 mIU/mL and LH 6.54 mIU/mL. Hormone tests performed during phase 2 of the cycle showed progesterone levels below 0.1 ng/mL.

Of particular note was the low AMH level (0.65 ng/mL), indicating diminished ovarian reserve. Other laboratory findings, apart from a slightly elevated androstenedione level (3.27 ng/mL) and an abnormal fasting glucose (5.7 mmol/L), remained within normal limits. Transvaginal ultrasound showed a normal anteverted uterus measuring 42 × 27 mm, with 6.6 mm thick endometrium, and both ovaries with normal echostructure, typically located, measuring 31 × 21 mm (right) and 25 × 15 mm (left). Due to the risk of a syndromic POI, the patient was referred for molecular testing. Genetic findings from Sanger sequencing indicated a mutant *FOXL2*, which confirmed the diagnosis of autosomal dominant BPES. After consultation at the infertility centre, the patient was qualified for an in vitro fertilisation (IVF) with a donor egg. Six months after initiating the diagnosis, the patient attended an appointment during which an ultrasound of the uterine cavity showed a foetus corresponding to a gestational age of 8 weeks. Apart from type 1 gestational diabetes mellitus, the pregnancy progressed normally. The patient gave birth by vaginal delivery at term to a healthy newborn weighing 2,980 g.

Discussion

Premature ovarian insufficiency should be seen as a spectrum including a range of clinical conditions. Biochemical POI with elevated FSH levels, reduced fertility and diminished ovarian reserve, but with regular menses, and overt POI with irregular or absent menstrual periods have been distinguished [13]. The described patient definitely did not present a typical picture of POI and did not meet the criteria for its diagnosis at the time of admission to the Department. However, due to the presence of a genetic syndrome in which POI can develop, in addition to the coexistence of diminished ovarian reserve and the lack of ovulatory cycles, a significant risk of POI in the near future was identified and measures were taken to enable the woman to achieve her desired pregnancy. Due to both infertility and a 50% risk of passing on the pathogenic gene variant to offspring, the woman was offered an IVF procedure with a donor egg.

Current guidelines emphasise the need to adequately address the patient's desire to preserve fertility. Although it is estimated that approximately 5–10% of women with POI have a chance of spontaneous pregnancy [14], assisted reproduction methods, IVF with a donor egg in particular, are considered the most appropriate option. Adoption of a child is the second option that the patient should be informed about. The indications for oocyte and ovarian tissue cryopreservation in women at risk of POI are increasingly reported in the literature [15]. This is particularly important given the alarming rise in the diagnosis of malignant tumours in increasingly younger women, resulting in an increasing incidence of POI as a result of ovarian tissue-destroying chemotherapy or radiotherapy. The extremely important role of oncofertility counselling in this group of patients is emphasised [16].

In the described case, the patient was also offered hormone replacement therapy to avoid the adverse effects of hormone imbalance. Underproduction of oestrogens increases the resorptive activity of osteoclasts and the loss of bone mineral density. This results in the development of osteopenia and osteoporosis, which can cause severe fractures [17]. The protective effect of female sex hormones on the cardiovascular system, proven in multiple studies, may also be lost in the course of POI. Patients will then be at an increased risk of endothelial dysfunction-related ischemic heart disease, as well as heart failure and myocardial infarction [18, 19]. According to current knowledge, hormone replacement therapy (HRT) is considered an appropriate approach to prevent both osteoporosis and cardiovascular incidents [20]. The supplementation also helps alleviate menopausal symptoms, while vaginal oestrogen is recommended in cases of increased urogenital atrophy.

It is also extremely important to consider POI in terms of its psychological impact, including psychosexual functioning of patients. Hormonal imbalance alone has an adverse effect on a woman's well-being (mood swings, depressive mood, reduced libido), and the diagnosis of POI in a very young patient with reproductive plans can significantly enhance this effect. In many cases, it will be reasonable to refer the patient for psychotherapeutic consultation [14].

Conclusions

POI affects approximately 1% of women before the age of 40 years, which makes it a significant problem in clinical practice, not only due to the aspect related to bothersome symptoms and the limited possibility of family planning, but also because of the long-term consequences of hypoestrogenism and the psychosocial aspect. Therefore, there is a need to increase the vigilance of endocrinologists and gynaecologists, but also general practitioners, ophthalmologists and other specialists to identify the symptoms reported by patients in order to react quickly and take appropriate diagnostic and therapeutic measures to protect the patient's fertility and general health. Owing to the dynamic development of molecular techniques, physicians have an expanding array of diagnostic tools at their disposal to make an appropriate diagnosis and quickly implement therapy. A detailed diagnosis, also taking into account the less common causes of POI, such as the described *blepharophimosis*, *ptosis* and *epicanthus inversus* syndrome, therefore remains an important task not only for gynaecologists. Current advances in assisted reproduction techniques make it possible to plan a family for both women struggling with infertility problems and genetically burdened patients.

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