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GENETIC ETIOLOGY OF PRIMARY PREMATURE OVARIAN INSUFFICIENCY

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SUMMARY – Primary premature ovarian insufficiency (PPOI) is characterized by hypergonadotropic amenorrhea and hypoestrogenism in women under 40 years of age. PPOI incidence is 1:10,000 in women aged 18-25, 1:1000 in women aged 25-30 and 1:100 in women aged 35-40. In 10%-28% of cases, PPOI causes primary and in 4%-18% secondary amenorrhea. The process is a consequence of accelerated oocyte atresia, diminished number of germinated cells, and central nervous system aging. Specific genes are responsible for the control of oocyte number undergoing the ovulation process and the time to cessation of the reproductive function. A positive family history of PPOI is found in 15% of women with PPOI, indicating the existing genetic etiology. Primary POI comprises genetic aberrations linked to chromosome X (monosomy, trisomy, translocation, deletion) or to autosomal chromosome. Secondary POI implies surgical removal of ovaries, chemotherapy and radiotherapy, and infections. Diagnostic criteria include follicle stimulating hormone level >40 IU/L and estradiol level <50 pmol/L.

Key words: *Primary ovarian insufficiency – etiology; Primary ovarian insufficiency – genetics*

Introduction

Premature ovarian insufficiency (POI) is characterized by hypergonadotropic amenorrhea and hypoestrogenism in women under 40 years of age. Diagnostic criteria are follicle stimulating hormone (FSH) level >40 IU/L and estradiol (E2) level <50 pmol/L[1]. The POI incidence is 1:10,000 in women aged 18-25, 1:1000 in women aged 25-30 and 1:100 in women aged 35-40[2]. POI causes 10%-28% of primary amenorrhea and 4%-18% of secondary amenorrhea[3]. The onset of the disease is a consequence of an accelerated process of oocyte atresia, i.e. a diminished number of germinated cells, and maturation of the central nervous system. Specific genes are responsible for the control of oocyte number undergoing ovulation process and cessation of the reproductive period[4]. A positive family history of POI was found in 15% of women with POI, confirming the existing genetic etiology[5,6].

Before the 20th week of gestation, the meiosis and mitosis processes go in parallel in the ovary and after that time, maturation and distribution of the future oocytes is completed. The number of oocytes is limited at birth; therefore, there will be no further production of this cell type. The maximum number of primordial follicles in the female fetus increases in 20-24 weeks of gestation, when the process of atresia starts. In the process of cessation, the number of primordial follicles decreases from 6-7 million to 1-2 million at birth, then to 300,000-400,000 on entering puberty. The ongoing process of steroidogenesis takes place up to the last follicle exists. It is well known that typical climacteric symptoms start when the number of primordial folli-

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cles decreases below 2500 in both ovaries. The increase in FSH starts shortly after age 30, while the number of the rest of the follicles correlates with further FSH increase after age 40.

Difference between the primordial and primary follicles is determined by layers of granulosa cells surrounding oocytes, with one layer in primordial follicles and multiple layers of cuboid granulosa cells in primary follicles. One of the possible etiologic factors for primary POI might be a disorder at the level of transmission from primordial to primary follicles.

Every woman younger than 40 with amenorrheic period is obliged to seek help at the gynecologist office. Symptoms of POI are psychological (nervousness, hot flushes, excitability, insomnia, depression, loss of libido, lack of concentration) and physical (parts of body feeling numb or tingling, muscle or joint pains, body weight increase). Hormone analysis (FSH, luteinizing hormone (LH), estradiol (E2), antimüllerian hormone (AMH), inhibin B, prolactin, progesterone, testosterone, free thyroxine (fT4) and thyroid-stimulating hormone (TSH)) is necessary. POI diagnosis is confirmed by FSH >40 IU/L and estradiol <50 pmol/L in women aged <40. When Addison's disease is suspected, adrenocorticotopic hormone (ACTH) stimulation test is performed. Karyotyping is necessary in women younger than 30. Ovarian biopsy is not a routine procedure. Dual energy x-ray absorptiometry is recommended in screening for osteoporosis.

Etiology

Premature ovarian insufficiency is divided into two main groups: primary POI (PPOI) and secondary POI (SPOI). The etiology of PPOI is shown in Table 1.

Table 1. Etiology of primary premature ovarian insufficiency

Genetic causes	• FSH receptor mutation, transcription factor mutation • Fragile X chromosome • Structural alteration and monosomy of the X chromosome • Chromosome X trisomy with or without mosaicism • Myotonic dystrophy
Enzyme deficiency	• 17α hydroxylase deficiency • Galactosemia
Gonadotropin structure/acting deficiency	• Biologically inactive gonadotropin • α and β subgroup deficiency • Receptor/post-receptor deficiency
Idiopathic	• Unknown cause

Genetic Causes

Follicle-stimulating hormone receptor gene mutation

In some families, familial PPOI occurrence is figured out (grandmother, mother and daughter) earlier in every consecutive generation. One of the possible causes is a mutation in the FSH receptor gene. Inactivated mutation of the FSH receptor (FSHR) gene damages adenylyl cyclase stimulation, while the receptor remains captured inside the cell. FSH is essential for normal follicle maturation. In the last 50 days of its development, maturation of the follicle is blocked. A large number of small follicles with no ability to progress further are present in women with PPOI. The most frequent mutation is present in exon 7 of the FSHR gene (FSHR, located on 2p chromosome), replacing Ala to Val at protein level. Mutations of the FSHR gene are related to FSH resistance, which leads to an increased FSH level and a decreased estrogen serum level. Women with total FSH resistance have hypoplastic ovaries and primary amenorrhea[7]. Some other forms of FSHR have been identified in women with PPOI and secondary amenorrhea, moderate ovary dysfunction and family history of PPOI[8]. These variances are rare and there is no direct influence in the etiology of PPOI[9,10].

Structural alterations of chromosome

X chromosome alterations are the most frequent genetic causes of PPOI, accounting for 12% of cases[6,11-13]. These alterations comprise complete monosomy or partial deletion, duplication or translocation of the X chromosome, as follows:

a) Turner syndrome (45X0) – the prevalence of X monosomy is 1:2500. Turner syndrome is characterized by lower height than normal, gonadal dysgenesis and primary amenorrhea[14]. Oocyte deprivation begins mainly in the early childhood as a consequence of accelerated follicle atresia[14].
b) Trisomy X (47 XXX) – usually does not cause particular problems, but in some cases PPOI

appears[15]. The genes located on the X chromosome are critical for the normal function of the ovary, thus any abnormality can induce PPOI[9,16]. Groswani *et al.*[17] found that 3.8% of women with PPOI had X chromosome trisomy.

c) Fragile X chromosome – expansion of trinucleotide tandem repeat CGG at the 5'UTR region of the FMR 1 gene (Xq27.3) was found in some PPOI cases. The CGG tandem repeat variation length is defined as normal (≤50), premutation (50-200) and full mutation (≥200 tandem repeats). Full mutation is associated with a fragile X syndrome, where mental retardation is the crucial sign[18]. Recently, some epidemiological studies have found connection of the premutation FMR1 gene with PPOI in 6% of sporadic cases and 13% of family PPOI[19]. FMR1 protein is expressed in fetal germ cells, as well as in granulosa cells of the mature follicle[20].

The carriers of the premutation alleles can exhibit 3 clinical forms, i.e. PPOI; lack of concentration/attention and other psychological changes; and neurologic disorders (tremor, ataxia, Parkinson's disease).

Hegerman *et al.*[21] indicated the association of PPOI with tremor, ataxia and Parkinson's disease, which could be one more proof of the important role of sex steroids in the brain.

In the most prominent number of cases, PPOI seems to be a multifactorial disorder. From this point of view, studies of the gene-DNA polymorphism are crucial in clarifying PPOI etiology. DNA or gene polymorphisms express the variants in hereditary basis, which could be found in the general population. From the phenotype point of view, they are in principle 'benign', but could also represent predisposition for certain, usually multifactorial disorders[22].

Polymorphisms in the genes encoding steroid hormone receptors, as well as their connection with different reproductive system disorders have been intensively studied in the last few years. It is well known that the forehand expression and proper coordination of the genes are fundamental for the normal growth and development of the ovary[23]. Polymorphisms important for PPOI are mostly unknown despite of the pathogenic defects identified in some candidate genes[24,25]. Therefore, in most PPOI cases, no clear etiologic factors were found, so they were classified as idiopathic PPOI.

Oocyte-specific transcription factors

In homozygous FOXL2 mutation, granulosa cells do not undergo transition from squamous to cuboid, and it is exactly the layer where the mistake comes from. This is the reason for the absence of secondary follicles, so oocyte atresia occurs[26]. The genes specifically expressed in oocyte are regulated through the specific transcription factors[12]. Mutations are identified in several genes encoding transcriptional factors important for folliculogenesis, i.e. NRA1, NOBOX, FIGLA and FOXL2[27-29].

Nuclear Receptor subfamily fifth group term 1 (NR5A1), known as steroidogenic factor 1, is a nuclear receptor which is implicated in early gonadal differentiation[29,30]. The NR5A1 gene is located at 9q33.3. Steroidogenesis is modulated through the regulation of the genes involved in the hypothalamic-pituitary--steroidogenetic axis, such as: STAR, CYP11A1, CYP17A1, CYP19A1, LH and INHA[30].

Homeobox protein (NOBOX) – the newborn ovary homeobox gene is an oocyte – is a specific expressed gene with an essential role in folliculogenesis and so one of the candidate genes for PPOI[28]. It is responsible for the specific transcriptional factor which regulates the genes important for early folliculogenesis[31]. Using the knockout mouse model, it has been proven that NOBOX regulates different gene expressions specific for the oocyte, including BMP-15 and GDF-9[31]. The lack of NOBOX expression is connected with accelerated oocyte loss after mouse parturition[30].

Folliculogenesis Specific Basic Helix-Loop-Helix (FIGLA), the embryo-specific transcription factor, regulates expression of the genes responsible for the initiation of folliculogenesis and coding the zona pellucida proteins (ZP1, ZP2 and ZP3) essential for fecundation and embryo survival. It is crucial for oocyte rebellion and formatting the primordial follicles[32]. Its lack leads to accelerated loss of postnatal primordial follicles in mice[33].

Forkhead Box L2 (FOXL2) gene is located on 3q23. Foxl2 protein exudes in the granulosa cells from the embryogenesis until the adult age[27]. The mutation of this gene leads to failure of granulosa cell differentiation, which induces early activation and exhaustion of primordial follicles[33]. The FOXL2 mutation is identified in 5% of non-syndromic PPOI patients, suggesting the possibility of idiopathic PPOI occurrence[27].

Helix-loop-helix (SOHLH) 1 and 2 are transcription factors important for PPOI. They are responsible for the follicle early growth and differentiation by control of a number of genes including NOBOX, FIGLA, BMP-15 and GDF-9[12]. The SOHLH2 gene is located on chromosome 13. This gene codes one of the factors which are crucial for spermatogenesis, oogenesis and folliculogenesis[12]. Zhao *et al.*[34] found three new SOHLH1 variations as the potential cause of PPOI in 364 Chinese women with PPOI.

Folliculogenesis growth factors

Bone morphogenetic protein 15 (BMI-15) is a member of the transforming growth factor ß (TGF-ß) superfamily. The gene is located at Xq11.2 and encodes an oocyte-specific growth and differentiation factor[35]. BMP-15 is involved in stimulating folliculogenesis and promoting follicle maturation by regulating granulosa cell differentiation and proliferation[36].

The growth differentiation factor 9 (GDF9) gene, a homologue of BMP-15, is also member of the TGF-ß superfamily and is located at 5q23.2. Like BMP-15, GDF-9 is oocyte specific and regulates primordial follicle development and stimulates granulosa cell proliferation and follicle maturation[30]. GDF-9 is also thought to play a role in steroidogenesis and modulation of FSH sensitivity in granulosa cell[37].

Inhibin alpha (INHA) gene encodes the alpha subunit of inhibin A and inhibin B, which together with their corresponding beta units (INHBA and INHBB), a class of dimeric glycoproteins, also belong to the TGF-ß superfamily[38]. Inhibins are produced primarily by granulosa cells and act on the pituitary by inhibiting FSH production[39]. Decreased inhibin production is associated with increased FSH production, leading to enhanced follicle recruitment and increased depletion of the follicular pool[11]. Indeed, women with idiopathic POI have lower serum levels of inhibins and higher serum FSH as compared with age-matched fertile controls, suggesting that inhibins play an important role in normal ovarian function[39].

Some of the gene candidates and their function in the pathogenesis of PPOI are shown in Table 2[40].

Table 2. Some of the gene candidates and their function in the pathogenesis of primary premature ovarian insufficiency

Gene	Gene locus	Function of a gene product
FMR1	Xq27.3	Oocyte development and maturation
NR5A	9q33.3	Steroidogenesis of the ovary
NOBOX	7q25	Early folliculogenesis
FIGLA	2q12	Zona pellucida gene regulation
FOXL2	3q23	Granulosa cell differentiation and follicle development
SOHL1/2	13q13.3	Early folliculogenesis
BMP-15	Zq11.2	Follicular maturation
GDF-9	5q23.2	Follicular maturation
INHA	2q33-36	Folliculogenesis regulation *via* FSH inhibition
FSHR	2p21	Growth and development of the follicle, steroidogenesis
LHR	2p21	Follicle maturation, steroidogenesis, ovulation
ESR1	6q25.1	Growth and development of the follicle

Receptors

Estrogen receptors

Estrogen receptors (ER) are transcriptional factors that occur in granulosa cells, as well as in many other tissues and are involved in the expression of different genes included in the cell growth and development[41]. There are two estrogen receptors known as ERa and ERb. Estrogen regulates gonadotropin release *via* ERa action, labeled with ESR1 on the hypothalamic-hypophyseal axis[42]. The ERa gene is located on 6q25-27 chromosome. Its promoter area comprises a polymorphic chain TA tandem repeat, associated with hereditary premature ovarian dysfunction, as well as with diminished bone mineral density and endometriosis.

The ERβ gene is located on the 14q23-24 chromosome. Estrogen improves folliculogenesis *via* ERβ[42]. On uncoding 3'-region of this gene, a polymorphic CA tandem repeat chain was recently identified, speculating about its connection with bone mineral density in women[43]. The functional role of these two polymorphisms has not yet been fully clarified; however, there is some evidence for their influence on the structure and function of the genes[44]. The connection between

these two microsatellite polymorphisms and PPOI has been demonstrated[45,46].

Progesterone receptor

The progesterone receptor (PGR) gene is situated on the 11q22 chromosome. A number of polymorphic regions have been discovered in this gene, and one of the functionally most important is the insertion/deletion of ALu sequence of 306 bp. It is believed that the insertion allele, labeled as PROGINS, has a protective function in the female reproductive system, either in the homozygous or heterozygous state[47].

Androgen receptor

Androgen receptor (AR) belongs to the nuclear transcriptional factors family. The only AR gene is located on chromosome X, Xq11-12. In this gene, polymorphism of a different number of CAG tandem repeats encoding the polyglutaminic chain of different lengths, has been identified. This chain influences the receptor function, so that longer tandem repeats are connected with a lower functional level of the receptor[48]. In fact, in the first exon of the AR gene, there are 2 microsatellite polymorphisms; the first one with CAG tandem repeats – (CAG)n and the second one with GGN tandem repeats – (GGN)n. A limited number of studies have found correlation of CAG repetitions in AR gene and PPOI[49,50], while others did not confirm this correlation[46,51]. For the GGN tandem repeat in Indian women, a significant correlation with PPOI has been reported[51].

Enzyme Deficiency

One of the etiologic factors for PPOI is deficiency of 17-a hydroxylase (17OH), as well as galactose-1-phosphate uridyltransferase (GALT). According the study by Waggoner *et al.*, shortly after puberty, 81% of affected women develop ovarian insufficiency together with primary or secondary amenorrhea[52].

Typical characteristics of women with the lack of 17OH are primary amenorrhea, high levels of FSH, LH, progesterone, deoxycorticosterone, hypertension and hyperpotassium alkalosis. Intracellular accumulation of galactose metabolite or lacking glycosylation decreases germ cell reserve[53].

Conclusion

Today, PPOI is considered as a multifactorial disease, where the phenotype is most probably the result of sequence variation in more than one gene. Ethnically distinct populations show differences in the gene-regulating pathways and genes causing PPOI.

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Sažetak

GENETSKA ETIOLOGIJA PRIJEVREMENE INSUFICIJENCIJE JAJNIKA

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Primarna prijevremena insuficijencija jajnika (PPIJ) je sindrom koji je obilježen hipergonadotropnom amenorejom i hipoestrogenizmom. Incidencija PPIJ je 1:10.000 kod žena starosti 18-25 godina, 1:1000 kod žena starosti 25-30 godina i 1:100 kod žena starosti 35-40 godina. U 10%-28% slučajeva PPIJ je uzrok primarnih, a u 4%-18% sekundarnih amenoreja. Bolest nastaje kao posljedica ubrzanog procesa atrezije oocita, smanjenja broja germinativnih stanica i starenja središnjeg živčanog sustava. Specifični geni su odgovorni za kontrolu broja oocita koji prolaze proces ovulacije i vrijeme prekida reproduktivne funkcije. Pozitivna obiteljska anamneza PPIJ nađena je u oko 15% žena s PPIJ, što ukazuje na postojanje određene genetske etiologije. Primarna insuficijencija jajnika (PIJ) dijeli se na primarnu i sekundarnu. U primarnu PIJ spadaju genetske aberacije vezane za kromosom X (monosomije, trisomije, translokacije, delecije) ili one vezane za autosomne kromosome. U sekundarnu PIJ spadaju kirurško odstranjenje jajnika, liječenje kemoterapijom i radioterapijom te infekcije. Simptomi su razdražljivost, nemir, gubitak libida, depresija, nesanica, dekoncentracija, napadaji vrućine, povišenje tjelesne težine, suhoća vagine i drugih sluznica. Kriteriji za dijagnozu su folikulostimulirajući hormon viši od 40 IJ/L i estradiol (E2) niži od 50 pmol/L kod žena mlađih od 40 godina.

Ključne riječi: *Primarna insuficijencija ovarija – etiologija; Primarna insuficijencija ovarija – genetika*