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NAT2 and *CYP1B1* genetic polymorphisms in patients with genital endometriosis depending on tolerability of melatonin

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BACKGROUND: Genital endometriosis is one of the most pressing problems of modern gynecology. Melatonin is a promising drug with a potentially curative effect on endometriosis.

AIM: The aim of this study was to conduct a comparative analysis of the genetic polymorphism of some genes encoding enzymes involved in melatonin metabolism.

MATERIALS AND METHODS: The genetic polymorphism in the *NAT2* and *CYP1B1* genes encoding enzymes involved in melatonin metabolism in patients with different tolerance to this drug was analyzed by PCR-RFLP analysis.

RESULTS: In patients with genital endometriosis, the presence of a wild-type allele (N) of the *NAT2* gene was associated with poor tolerance of melatonin. The *NAT2* (N / N) rapid acetylator phenotype combined with the low catalytic activity of *CYP1B1* (C / C) occurred more frequently in endometriosis patients having poor melatonin tolerability compared to the group of patients who tolerated the therapy well.

CONCLUSIONS: For patients with genital endometriosis with the wild-type (N) allele of the *NAT2* gene, melatonin administration is inappropriate due to numerous side effects during the drug use.

Keywords: genital endometriosis; melatonin; side effects; gene polymorphism; *NAT2*; *CYP1B1*.

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Особенности полиморфизма генов *NAT2* и *CYP1B1* у пациентов с наружным генитальным эндометриозом в зависимости от переносимости мелатонина

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Обоснование. Наружный генитальный эндометриоз представляет собой одну из наиболее актуальных проблем современной гинекологии. Перспективным препаратом с потенциально лечебным эффектом в отношении наружного генитального эндометриоза является мелатонин.

Цель — провести сравнительный анализ полиморфизма отдельных генов, кодирующих ферменты, вовлеченные в метаболизм мелатонина.

Материалы и методы. Методом полимеразной цепной реакции и полиморфизма длин рестрикционных фрагментов проанализированы полиморфизмы генов *NAT2* и *CYP1B1*, кодирующих ферменты, вовлеченные в метаболизм мелатонина, у пациентов с различной переносимостью данного препарата.

Результаты. У больных наружным генитальным эндометриозом аллель дикого типа (N) гена *NAT2* ассоциирован с плохой переносимостью мелатонина. Фенотип «быстрого» ацетилирования по *NAT2*(N/N) в сочетании с низкой каталитической активностью *CYP1B1*(C/C) встречался чаще у пациенток с наружным генитальным эндометриозом и плохой переносимостью мелатонина по сравнению с пациентками, хорошо переносившими терапию.

Заключение. Больным наружным генитальным эндометриозом с аллелем дикого типа (N) гена *NAT2* назначение мелатонина нецелесообразно в связи с развитием многочисленных побочных эффектов на фоне его применения.

Ключевые слова: генитальный эндометриоз; мелатонин; побочные эффекты; полиморфизм генов; *NAT2*; *CYP1B1*.

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BACKGROUND

External genital endometriosis (EGE) is one of the most pressing problems of modern gynecology, owing to both the high incidence of the disease and the variety of its clinical manifestations such as pain syndrome, infertility, and miscarriage and its recurrent nature. Endometriosis is detected in 70% of female patients visiting a doctor with complaints of pain syndrome and in 35%–50% of infertile patients [1, 2]. To date, there is no universal method that would guarantee complete cure of EGE and full remission. Despite existing methods of combined treatment, endometriosis is characterized by high recurrence rate, which leads to repeated surgical interventions. Along with the surgical removal of foci, pathogenetically grounded hormonal therapy is at the forefront in treatment of the disease [3]. However, the disadvantages of hormone-modulating regimens should also be noted, namely, the impossibility of pregnancy during the treatment with most drugs that have an antigonadotropic effect, the occurrence of serious side effects, and the ineffectiveness of standard treatment regimens in some patients. In this regard, further study of the pathogenesis of endometriosis, search for new drugs with a therapeutic effect on the disease, and description of such effects are important and urgent tasks in modern gynecology.

Melatonin is one of the most promising therapeutic drugs for genital endometriosis. It is an indoleamine-type hormone synthesized from serotonin by secretory cells of the pineal gland through the action of N-acetyltransferase (NAT) and oxindole-O-methyltransferase [4]. Melatonin receptors are present in many organs of the reproductive system, including the mammary glands, myometrium, granulosa cells, etc. [5]. Melatonin is a powerful antioxidant [6,7] and has antitumor and oncostatic effects. Exogenous administration of this drug leads to a decrease in the incidence of tumors, while pinealectomy stimulates tumor growth [2,8].

The development of endometriosis is known to be associated with ineffective inflammatory response, oxidative stress, excessive proliferation, neoangiogenesis, and altered production and reception of steroid hormones. Melatonin exerts its therapeutic effect in endometriosis by neutralizing free radicals that are cytotoxic [6] as well as by suppressing the synthesis of proinflammatory cytokines, changing the production of matrix metalloproteinases, and modeling the processes of angiogenesis [9,10]. Melatonin is known to reduce the activity of aromatase, increasing the expression of estrogen sulfotransferase, which suggests the antiestrogenic effect of this pineal gland hormone [2]. The therapeutic effect of melatonin was described by T.J. Ness using 10 mg of melatonin administered daily to patients for 8 weeks for the treatment of endometriosis-associated pain [11].

The high efficacy of melatonin, as well as its positive dose-dependent effect on resorption and reduction of endometrioid heterotopias was demonstrated in a study of a model of surgically induced endometriosis in Wistar rats [12]. In clinical practice, melatonin showed a more pronounced positive effect on EGE patients in terms of reducing pain and improving psychoemotional state as part of combination therapy compared with standard hormone-modulating therapy [13].

The data obtained supports the use of melatonin as a promising and effective drug for the treatment of endometriosis. The antigonadotropic effect of melatonin is dose dependent. However, in some patients, this drug causes a number of side effects, such as headache, sleep disturbances in the form of frequent nocturnal awakenings, insomnia, nausea, and pronounced morning sleepiness, which prompt patients to discontinue the course of therapy.

It can be assumed that poor patient tolerance to the drug is associated with a polymorphism in genes encoding enzymes involved in melatonin metabolism.

This work aims to perform a comparative analysis of the polymorphism of some genes encoding enzymes involved in melatonin metabolism.

MATERIALS AND METHODS

DNA samples were obtained from 59 female patients of reproductive age with EGE, established by operative laparoscopy and confirmed through histological examination. The disease was staged according to the revised classification of the American Fertility Society (R-AFS). All patients received melaxen at a dose of 6 mg daily for 2–6 months.

Genomic DNA was extracted from peripheral blood lymphocytes in accordance with the method described in the manual by J. Sambrook et al. with some modifications [14].

Polymorphic variants of genes *NAT2* and *CYP1B1* were determined by polymerase chain reaction (PCR) with specific oligo primers followed by restriction analysis. For amplification, a programmable thermal cycler from "DNA-Technology" (Moscow) was used. A mixture for amplification with a volume of 25 μL included 15 nM of each primer, 67 mM of Tris-HCl (pH 8.8), 16.6 mM of ammonium sulfate, 6.7 mM of $MgCl_2$, 6.7 μM of EDTA, 10 mM of mercaptoethanol, 170 μg of BSA, 1.0 mM of each dNTP, and 1 U of DNA polymerase (Bion, Moscow). The primers CYP1B1 F CGTGGGGAGGGACCGTCTGC and CYP1B1 R TCTCCGGGTTAGGCCACTGC were used to amplify the *CYP1A1* gene fragment. Primers *NAT2* F 5'<GCT GGG TCT GGA AGC TCC TC>3' and *NAT2* R 5'<TTG GGT GAT ACA TAC ACA AGG G>3' were used to amplify the *NAT2* gene fragment.

Table 1 presents the PCR conditions.

Restriction of the amplified DNA fragments was performed in accordance with the manufacturer's recommendations (Sibenzim).

Table 1. Conditions for the polymerase chain reaction

Gene	Denaturation	Denaturation	Renaturation	Synthesis	Synthesis
	32 cycles				
NAT2	94°C — 7 min	94°C — 1 min 10 s	52°C — 1 min 15 s	68°C — 1 min 30 s	72°C — 7 min
CYP1B1	95°C — 4 min	95°C — 40 s	60°C — 40 s	72°C — 40 s	72°C — 5 min

Table 2. Restriction endonucleases and analysis of polymorphic variants of metabolism genes

Gene	Polymorphism	PCR product size	Endonuclease	Allele and size of restriction fragments
CYP1B1	L432V	227 bp	Pst I	I; 208 + 19 bp V; 227 bp
NAT2	C481T	547 bp	Kpn1	S1; 547 bp
	G590A	547 bp	Taq1	S2; 392 + 15 bp
	G857A	547 bp	BamH1	S3; 547 bp

Note: bp — base pairs; PCR — polymerase chain reaction.

PCR products were hydrolyzed with a restriction endonuclease (Table 1) at 37°C for 16 h in 10 μl of a reaction mixture containing 5 μl of amplification agent, 3 μl of water, 1 μl × 10 of the buffer recommended by the manufacturer for each restriction endonuclease, and 10 U (0.5 μl) of restriction endonuclease.

Restriction endonucleases and analysis of polymorphic variants of metabolism genes are presented in Table 2.

Completeness of hydrolysis was assessed by the results of electrophoresis in 7.5% polyacrylamide gel (PAAG).

PAAG was stained with an aqueous solution of ethidium bromide (0.5 μg/ml), viewed in ultraviolet light on a Macrovue 50 trans illuminator (Pharmacia LKB, UK), and the image was recorded using a video gel documentation system (Vilber Lourmat).

Table 3. Frequency distribution of genotypes and alleles of the *NAT2* gene in patients with external genital endometriosis

Genotypes/alleles	External genital endometriosis	
	n	%
N/N	4	6.78
S1/N	17	28.8
S2/N	3	5.1
S3/N	1	1.7
S1/S1	12	20.3
S1/S2	11	18.64
S1/S3	–	–
S2/S2	7	11.86
S2/S3	4	6.77
Всего	59	100
Аллели		
N	29	24.58
S1	52	44.1
S2	32	27.1
S3	5	4.2

Results were processed statistically using Microsoft Excel 2002. Significance of the frequency differences was determined using the exact two-tailed Fisher test using the standard formula, taking into account the Yates' correction for paired comparisons with the control group and using the chi-square test (χ^2) with the standard formula as well as the Yates' correction for paired comparisons and Bonferroni correction for multiple comparisons with the control group.

RESULTS

Polymorphisms of the genes arylamine-NAT 2 (*NAT2*) and cytochrome P450 1B1 (*CYP1B1*) were studied. DNA samples were obtained from the peripheral blood lymphocytes of 59 patients with stages I–IV EGE according to the R-AFS classification, confirmed laparoscopically and histologically, who received melatonin therapy at a dose of 6 mg daily for 2–6 months. Melatonin was well tolerated by 64% (n = 38) of patients; 36% (n = 21) had poor tolerance to the drug and its side effects (drowsiness, frequent nocturnal awakenings, headaches, and insomnia), due to which they opted to discontinue the drug.

The product of the gene *NAT2* is known to play an important role in acetylation of aromatic and heterocyclic amines and drugs containing aromatic amine groups and to participate in melatonin metabolism.

The homozygous state for the *N* allele of the *NAT2* gene in the group of EGE patients was registered in 6.78% of cases (Table 3).

The proportion of EGE patients, homo- and heterozygous (genotypes *S1*/*N*, *S2*/*N*, and *S3*/*N*) for the *N* allele, belonging to the category of "fast" acetylators, was 42.37%. The frequency of the wild-type (*N*) allele in the group of EGE patients was 24.58%.

In patients with poor tolerance to melatonin, the frequency of the wild-type (*N*) allele was significantly higher

Table 4. Frequency distribution of genotypes and alleles of the *NAT2* gene depending on melatonin tolerance

Genotypes/alleles	Good tolerance		Poor tolerance		*p*
	n	%	*n*	%	
N/N	1	2.6	3	14.3	>0.05
S1/N	9	23.7	8	38.1	>0.05
S2/N	1	2.6	2	9.5	>0.05
S3/N	1	2.6	–	–	>0.05
S1/S1	9	23.7	3	14.3	>0.05
S1/S2	10	26.3	1	4.76	>0.05
S1/S3	–	–	–	–	–
S2/S2	5	13.2	2	9.5	>0.05
S2/S3	2	5.3	2	9.5	>0.05
Total	38	100	21	100	
Alleles					
N	13	17.1	16	38.1	0.02
S1	37	48.7	15	35.7	>0.05
S2	23	30.3	9	21.8	>0.05
S3	3	3.9	2	4.76	>0.05

(38.1%) than in patients with good tolerance to the drug (17.1%) (Table 4). Homo- and heterozygotes for the *N* allele (fast acetylation phenotype; genotypes *N/N*, *S1/N*, *S2/N*, and *S3/N*) were registered significantly more frequently in the group of patients with poor drug tolerance compared to the group who had no side effects and whose tolerance to melaxen was good (61.9% and 31.6%, respectively; $p = 0.024$) (Fig. 1). According to odds ratio (OR), the carriage of the wild-type allele (*N*) increases the risk of poor melatonin tolerance 3.5-fold (OR = 3.521; confidence interval (CI) = 1.154–10.742).

Cytochrome P450 1B1 (*CYP1B1*) is a member of the cytochrome P450 gene family and encodes one of the main enzymes involved in estrogen hydroxylation and antioxidant protection (detoxification phase 1 enzyme). This enzyme is involved in the degradation of melatonin. There are several polymorphic variants of the *CYP1B1* gene, one of which is the 4326 C/G polymorphism (*L432V, rs1056836*), associated with a higher catalytic activity compared to the wild-type allele.

When analyzing the frequency distribution of genotypes and alleles of the *CYP1B1* gene, no significant differences were revealed in the subgroups with different degrees of tolerance to melatonin. The polymorphic allele *G*, associated with increased catalytic activity, with poor drug tolerance was found somewhat more often than that with good tolerance (47.6% and 38.2%, respectively) (Table 5).

The frequencies of some combined *NAT2* and *CYP1B1* genotypes, characteristic of different levels of melatonin accumulation in the body, have been analyzed. For the maximum accumulation of melatonin, the genotype corresponding to the phenotype of "fast" acetylation by *NAT2* (accumulation of endogenous melatonin) and low catalytic activity of *CYP1B1* (slowing down the degradation of both endogenous and exogenous melatonin) are most typical, and for the minimum accumulation, the genotype corresponding to the phenotype of "slow" acetylation by *NAT2* (accumulation of endogenous melatonin) and high catalytic activity of *CYP1B1* (slowing down the degradation of both endogenous and exogenous melatonin) are most characteristic. A significant increase in the incidence of the N/N(*NAT2*)+C/C(*CYP1B1*) genotype corresponding to the phenotype of rapid melatonin accumulation in patients with poor drug tolerance (14% and 0%, respectively; $p = 0.04$) was revealed (Fig. 2).

According to the OR coefficient, carriage of the combined genotype N/N(*NAT2*)+C/C(*CYP1B1*) increases the risk of

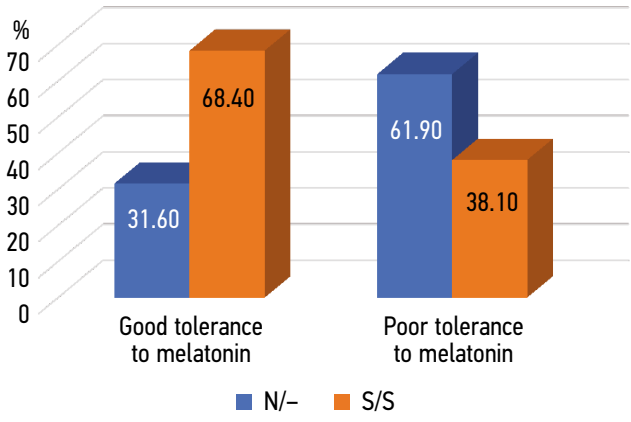

Fig. 1. Frequency distribution of *NAT2* genotypes depending on melatonin tolerance

Table 5. Frequency distribution of genotypes and alleles of the *CYP1B1* gene in patients with external genital endometriosis, depending on tolerance to melatonin

Genotypes/alleles	Good tolerance		Poor tolerance	
	%	*n*	%	*n*
C/C	42.1	16	28.6	6
C/G	39.4	15	47.6	10
G/G	18.4	7	23.8	5
Total	100	38	100	21
Alleles				
G	38.2	29	47.6	20
C	61.8	47	52.4	22
Total	100	76	100	42

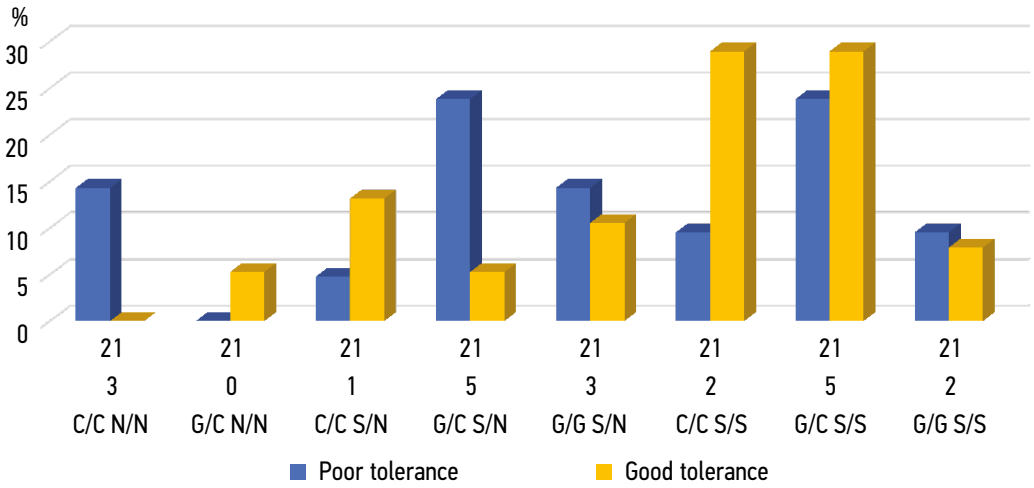

Fig. 2. Frequencies of combined genotypes for the *NAT2* and *CYP1B1* genes in patients with different degrees of melatonin tolerance

poor melatonin tolerance 14-fold (OR = 14.568; CI = 1.002–100.742).

Thus, the study of the *NAT2* gene polymorphism revealed that the wild-type (*N*) allele of the *NAT2* gene in EGE patients is associated with poor melatonin tolerability. When analyzing the frequencies of the combined genotypes *NAT2* and *CYP1B1*, it was also found that the phenotype of "fast" acetylation by *NAT2* (*N*/*N*) in combination with a low catalytic activity of *CYP1B1*(*C*/*C*) was more common in patients with poor melatonin tolerance than in patients who tolerated the therapy well. It can be assumed that the poor tolerance to the drug in individuals with the combined genotype N/N (*NAT2*) +C/C (*CYP1B1*) is due to a sufficient level of endogenous melatonin synthesis and insufficiently rapid inactivation of both endogenous and exogenous melatonin.

CONCLUSION

Melatonin can be considered effective both as a component in combination therapy and as monotherapy for EGE patients with pain and infertility. However, the use of melatonin in clinical practice in a number of women as part of combination therapy for EGE is not always possible due to a number of reasons, the main ones being poor drug tolerability and existence of side effects.

Based on the study results, it was established that in EGE patients, the wild-type (*N*) allele of the *NAT2* gene is associated with poor melatonin tolerance. It was also noted that the phenotype of "fast" acetylation by *NAT2*(N/N) in combination with a low catalytic activity of *CYP1B1*(C/C) was more common in patients with endometriosis who did not tolerate melatonin well than in those who tolerated the therapy well.

The results obtained substantiate the need to continue research in this field for a deeper understanding of the disease pathogenesis as well as the use of melatonin as targeted therapy. However, in EGE patients with the wild-type (*N*) allele of the *NAT2* gene, administration of melatonin was considered inappropriate due to the occurrence of numerous side effects.

ADDITIONAL INFORMATION

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