POLYMORPHISM OF CHRONIC PELVIC PAIN IN PATIENTS WITH ENDOMETRIOSIS

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ABSTRACT

The purpose of the study is to establish casual relationships of chronic pelvic pain in women with genital endometriosis. There were examined 120 women with genital endometriosis and chronic pelvic pain: main group 1 (n=44) and 2 (n=41) and comparison group 3 (n=35), without pelvic pain, average age of patients was 35.28±0.59 years. Assessment of pelvic pain was carried out using the 10-point visual analog scale (VAS), the McGill pain questionnaire. The level of personal anxiety was determined according to J. Taylor's method. Hamilton's scale (HAM-D) was used to assess symptoms of depression. The levels of interleukins (IL)-10, IL-6, and tumor necrosis factor-α (TNF-α) were determined using a solid-phase enzyme-linked immunosorbent assay. Diseases of the gastrointestinal tract in group 1 - 75.0% versus 37.14% in group 3, and diseases of the genitourinary system had a statistically significant ($p<0.05$) advantage in the progression of pelvic pain in. According to the McGill questionnaire, the highest level of pain intensity was determined in the group 1 - 2.45±0.17 (0.76), the lowest in the group 3 - 1.65±0.17 (0.75), which is statistically reliable between groups ($p=0.001$). Correlation analysis in women of the main clinical groups determined that the level of depressive disorder ($r=0.35$; $p=0.001$) and the level of personal anxiety ($r=0.28$; $p=0.003$) were directly related to the duration of chronic pelvic pain by a direct relationship of medium strength. A direct moderate correlation was established between the intensity of pelvic pain according to VAS and the duration of pain ($r=0.3;1$ $p<0.001$). A decrease in the anti-inflammatory IL-10 and an increase in the pro-inflammatory IL-6, TNF-α was determined during the progression of pain compared to patients without pelvic pain ($p < 0.05$), TNF-α was correlated with the duration of the pain history, which was accompanied by frequent relapses of the disease and increased levels of anxiety and depression. Risk factors for pelvic pain were identified in patients with endometriosis, an objective assessment of pain, psycho-emotional status, and cytokine imbalance was given. An effective relationship between the chronicity of pelvic pain, cytokine profile, disorders of psycho-emotional status, and accompanying extragenital pathology was established.

Keywords: endometriosis, pelvic pain, psychological status, interleukins, extragenital pathology.

Introduction

Endometriosis is a disease which is characterized by systemic inflammatory disorders and thus is of interest to a wide variety of obstetrician-gynecologists, surgeons, gastroenterologists, urologists, and neurologists because it is often associated with chronic pelvic pain. Endometriosis is estimated to affect 10% of women of reproductive age [1], extrapolating to approximately 190 million women worldwide based on World Bank population estimates for 2017 [2]. However, the true prevalence of endometriosis is uncertain, as a definitive diagnosis requires surgical imaging. Treatment consists of surgical removal of lesions and the use of hormonal drugs, often with side effects and variable effectiveness. In 2008, US health care costs for endometriosis were approximately $4,000 per patient, similar to costs for other chronic diseases such as type 2 diabetes, Crohn's disease, and rheumatoid arthritis. Treatment costs, including chronic pelvic pain, dysmenorrhea, deep dyspareunia, dysuria, dyschezia and infertility, are much higher because these symptoms affect a woman's physical, mental, sexual, and social well-being [3]. Pelvic pain can be both inflammatory and neuropathic in nature, characterized by potential sensitization of the central nervous system, which can lead to constant pain even after removal of endometrial lesions [4]. Chronic pelvic pain (CPP) that does not respond to conventional treatment develops in approximately 30% of patients with endometriosis [5]. The reasons why some patients do not respond to traditional methods of treatment is the multifactorial nature of chronic pelvic pain in endometriosis, which may include concomitant conditions (interstitial cystitis, bladder syndrome, irritable bowel syndrome) and central sensitization, which is the basis of the disorder and pain recurrence [6]. The etiology of CPP is associated with endometriosis and may include direct endometriosis-specific factors (stage of spread, invasiveness of the disease) [7] and/or indirect factors, such as dysfunction of the urinary bladder, pelvic floor (related to myofascial mechanisms) or sensitization of the nervous system [8,9].

Considering the diversity of the etiology of pelvic pain, one should always carry out a comprehensive assessment not only of gynecological causes, but also of other systems and organs, including the gastrointestinal, genitourinary, psychological state, immunological disorders and imbalance of the cytokine system, in which the role in the occurrence of pain is insufficiently studied. Cytokines are responsible for the inflammatory reaction and its regulation. The activation of immune cells triggers signaling pathways that cause the release of inflammatory cytokines, which then contribute to the accumulation of many types of cells at the site of inflammation [10,11], and the dysfunction of the immune system itself affects the expression of pro- and anti-inflammatory cytokines [12]. Identifying the factors associated with the chronicity of pelvic pain is a difficult task due to its multifactorial nature and certain potential influencing

factors, [13] but they can be identified using a thorough history and complex research methods.

The purpose of the study is to establish the causal relationships of the chronicity of pelvic pain in women with genital endometriosis.

Research materials and methods. The research was carried out as part of the research work of the Department of Obstetrics, Gynecology and Perinatology, Faculty of Postgraduate Education of the Dnipro Medical University "Diagnosis and preventive treatment of obstetric and gynecological diseases in extragenital pathology", state registration No 0120U101467, completion period - 2020-2023 The research was carried out in accordance with the main provisions of GCPICH and the Declaration of Helsinki, methodologically it was based on the use of a system approach to the set of studies conducted in women with gynecological pathology and was determined by a defined goal and specific tasks. Examination of women was completely voluntary, subject to obtaining informed consent of women for examination and treatment, the possibility of conducting it was carried out in accordance with the requirements of the bioethical committee of the Dnipro State Medical University in compliance with the main provisions of the protocols of the Orders of the Ministry of Health of Ukraine No 319 dated 06.04.2016., "About approval and implementation of medical and technological documents on the standardization of medical care in genital endometriosis".

There were examined 120 women with genital endometriosis treated in the gynecological department of the MNCI "Clinical Hospital of Emergency Medical Care" of the Dnipropetrovsk City Council, which is the clinical base of the Department of Obstetrics, Gynecology and Perinatology of the FPE of the Dnipro State Medical University. General clinical examinations were carried out, the assessment of this pain was determined by a 10-point visual analog scale (VAS). The degree of expression of the pain syndrome was determined using the McGill Pain Questionnaire (MPQ). The main indicators were calculated: sensory; affective; index of the number of selected words (descriptors) (INSW), assessment of pain, ranking index of pain (RIP). The level of personal anxiety was determined according to the method of J. Taylor "Anxiety Scale" (J. Taylor "Anxiety Scale"), the Hamilton scale (HAM-D) was used to assess depression symptoms. The levels of interleukins (IL)-10, IL-6, tumor necrosis factor-α (TNF-α) were determined in blood plasma using a solid-phase enzyme-linked immunosorbent assay.

The reliability assessment of mean differences for quantitative traits with a normal distribution was carried out for unrelated samples taking into account homo- or heteroscedasticity of variances according to the Student's test (t) for unrelated samples, the Student's T-test for related samples, Fisher's test (F) according to one-factor analysis of variance ANOVA; Multiple comparisons were performed with Scheffe's correction. Statistical processing was performed using STATISTICA 6.1 software (StatSoft Inc., serial number AGAR909E415822FA) and MedCalcStatisticalSoftwaretrialversion 17.4 software package.

Results and their discussion. Under our observation there were 120 women with genital endometriosis (GE), the control group consisted of 85 women with GE and chronic pelvic pain (CPP) (groups 1 and 2), the comparison group consisted of 35 women with GE without pelvic pain (VAS 0-3 points), without statistically significant differences in age between the main groups - 35.37±0.68 years (M±m) and the comparison group - 35.28±0.59 years. Taking into account the course of endometriosis with CPP in patients of groups 1 and 2, statistically significant differences ($p<0.05$) were established regarding the duration of CPP and severity of pain according to VAS, which required defining subgroups according to VAS (7-10 points) of subgroup 1-a (course of CPP up to 3 years), and 1-b (course of CPP 4-6 years) and subgroups according to VAS (4-6 points) 2-a (course of CPP up to 3 years) and 2-b (course of CPP 4-6 years). The average value of pelvic pain according to VAS in group 1 was 8.10±0.14 points (in subgroups: 1-a - 7.96±0.15 and 1-b - 8.28±0.23); in group 2-a - 5.44±0.12 points (in subgroups: 2-a - 5.58±0.17 and 2-b - 5.44±0.12).

In most cases, patients complained of dysmenorrhea (80%), dyspareunia (75%); dysuria (46%), dyschezia (36%), psychoemotional disorders. Almost all women in the control group experienced provoking factors for chronic pelvic pain. The assessment of the odds ratio (OR) as an estimate of the probability of the appearance of moderate or severe pain under the influence of the studied factors showed that dysmenorrhea and dyspareunia increased the chances of a severe pain syndrome (OR more than 1, which indicates an increased risk) (Table 1).

Table 1

Assessment of provoking factors for chronic pelvic pain in study population [11]

Factors	Moderate pelvic pain			Severe pelvic pain		
	OR	95 % CI	*p*	OR	95% CI	*p*
Dysmenorrhea	571,74	32,37 - 10099,74	*<0,001*	16,01	4,56 - 56,22	*<0,001*
Dyspareunia	66,21	3,93 - 1114,39	*0,004*	12,67	5,15 - 31,16	*<0,001*
Dyschezia	7,79	0,44 - 138,69	*0,162*	3,12	0,71 - 13,75	*0,133*
Dysuria	16,86	0,98 - 289,21	*0,051*	3,43	1,15 - 10,23	*0,027*

In our study, the comorbidity of dysmenorrhea with extragenital diseases was determined, that is, pathological changes in one organ can affect the dysfunction of another organ. Therefore, we analyzed the frequency of extragenital pathology in the studied patients as certain potential factors influencing the course of CPP. Thus, a statistically significant ($p<0.05$) advantage was given to diseases of the gastrointestinal tract and genitourinary system in the main group 1 - 75.0% versus 37, 4% in the comparison group. Exacerbation of gastrointestinal tract diseases was also due to uncontrolled intake of painkillers and hormonal drugs. The structure of diseases of the cardiovascular system was dominated by a high frequency of vegetative-vascular dystonia, which is a consequence of an impaired psycho-emotional background in women (Table 2).

Cross-sensitization of the pelvic organs is considered one of the factors contributing to the increase of pelvic pain, and involves the transfer of harmful stimuli from the affected pelvic organ to the adjacent normal structure, which leads to functional changes of the latter [14], and is considered by researchers as a manifestation of the "visceral syndrome" caused by the commonality of pathogenetic pain mechanisms, as well as general afferent and efferent innervation, blood circulation, and the musculoskeletal system [11].

Table 2

Incidence of somatic pathology in control groups and comparison group

Pathology	1-a group (n=24)		1-b group (n=20)		2-a group (n=20)		2-b group (n=21)		group 3 (n=35)		*p***
	n	% (95 % CI)	n	% (95 % CI)	n	% (95 % CI)	n	% (95 % CI)	n	% (95 % CI)	
Existing	24	100,0 (86,2 – 100,0)*	20	100,0 (83,89 – 100,0)*	13	65 (43,29 – 81,88)	18	85,71 (65,36 – 95,02)*	16	45,71 (30,47 – 61,81)	***<0,001***
Gastrointestinal diseases	14	58,33 (38,83 – 75,53)	15	75 (53,13 – 88,81)*	7	35 (18,12 – 56,71)	12	57,14 (36,55 – 75,53)	13	37,14 (23,17 – 53,66)	***0,038***
Chronic tonsilitis	4	16,67 (6,68 – 35,85)*	6	30 (14,55 – 51,9)*	3	15 (5,24 – 36,04)	0	0 (0 – 15,46)	0	0 (0 – 9,89)	***0,004***
Genitourinary diseases	9	37,5 (21,16 – 57,29)*	7	35 (18,12 – 56,71)*	2	10 (2,79 – 30,1)	4	19,05 (7,67 – 40)*	0	0 (0 – 9,89)	***0,001***
Iron-deficiency states	2	8,33 (2,32 – 25,85)	3	15 (5,24 – 36,04)	0	0 (0 – 16,11)	0	0 (0 – 15,46)	0	0 (0 – 9,89)	***0,037***
Vascular diseases	4	16,67 (6,68 – 35,85)	10	50 (29,93 – 70,07)*	3	15 (5,24 – 36,04)	13	61,9 (40,88 – 79,25)*	4	11,43 (4,54 – 25,95)	***<0,001***
Endocrine diseases	0	0 (0 – 13,8)	1	5 (0,89 – 23,61)	0	0 (0 – 16,11)	0	0 (0 – 15,46)	0	0 (0 – 9,89)	*0,283*

Notes. *p* – differences between groups according to Pearson's $\chi 2$ test, including Yates correction:* – *p<0.05* compared to group 3; ** – between groups 1 and 2 and group 3 [11].

McGill Questionnaire (MPQ) data made it possible to obtain not only a quantitative, but also a qualitative description of the pain syndrome. Pelvic pain associated with GE can be a multidimensional phenomenon consisting of physiological, sensory, affective, cognitive and behavioral components. Therefore, the highest indicators of the level of pain intensity (2.45±0.17), ranking index of pain (19.35±1.75), the number of selected descriptors (9.65±0.62) were determined in subgroup 1-b compared to patients of group 2 (2-a, 2-b), respectively (1.65±0.10.75); (11.29±0.88); (6.33±0.35) differences between these subgroups were statistically significant ($p=0.001$).

A direct, moderate correlation between pain according to the VAS and MPQ was determined: the Pearson correlation coefficient between the indicator according to the VAS and pain intensity of - $r=0.33$ ($p=0.002$); INSW - $r=0.54$ ($p<0.001$); sensor INSW - $r=0.48$ ($p<0.001$); affective INSW - $r=0.41$ ($p<0.001$). The difference in pain intensity between the main groups depended on the long course of endometriosis with chronic pelvic pain, and differences in the patients' perception of pain (sensory and psychoemotional). In 22% of patients of the main group 1, more pronounced emotional disorders were noted, which was characterized by a 2-fold increase in affective (emotional) INSW over sensory INSW. In connection with this, it was necessary to make a connection between pain and the psycho-emotional state of the patients, with the determination of the assessment of the level of reactive and personal anxiety and depressive disorders.

Personal anxiety was measured according to J. Taylor's method (J. Taylor "AnxietyScale"), 40% of patients from subgroup 1-b and 8.33% from subgroup 1-a had a high level of personal anxiety (Table 3).

Table 3

Assessment of personal anxiety scores in patients with CPP of the main clinical groups and comparison group

Scores	Main groups (1 and 2)				Group 3 (n=35)	*p*
	1-a (n=24)	1-b (n=20)	2-a (n=20)	2-b (n=21)		
Level of anxiety, n (%)						
Low level (0-6 points)	0 (0)	0 (0)	2 (10,0)*	2 (9,52)*	16 (45,71)	*<0,001**
Moderate level (from 6 to 20 points)	22 (91,67)*	12 (60,0)	18 (90,0)*	19 (90,48)*	19 (54,29)	*<0,001**
High level (more than 20 points)	2 (8,33)	8 (40,0)*	0 (0)	0 (0)	0 (0)	*<0,001**

Notes. $p^{\#}$ – differences between groups 1 and 2 and group 3 according to one-way analysis of variance ANOVA: # – *p<0.001* compared to group 3; p * - differences between subgroups 1 and 2 group and group 3 according to Pearson's $\chi 2$ criterion: * - *p<0.05* comparable to group 3 [11].

At the psychological level, the patients felt anxiety, tension, worry and nervousness. At the physiological level, the anxiety reaction manifested itself in women in increased heartbeat and breathing, elevated blood pressure, increased sweating, increased general excitability, which acquired a negative emotional color.

The Hamilton Depression Rating Scale (HAM-D) was used to assess depressive symptoms. Depressive symptoms were observed in 72.8% of patients in the main group (mild - in 42.3%, moderate - in 21.1%, and severe - in 9.4%). There was a positive correlation between the severity of depressive disorders and the intensity of pelvic pain, which was determined in 70.0% of patients of group 1-b ($p<0.001$) (Table 4).

Table 4

Assessment of depression according to Hamilton Depression Rating Scale (HAM-D) in patients with CPP of the main clinical groups and comparison group

Scores of depression degree	Main groups (1 and 2)				Group 3 (n=35)	*p*
	1a (n=24)	1b (n=20)	2a (n=20)	2b (n=21)		
Depressive disorder, n (%)						
Norm (0-7)	0 (0)	2(10,0)*	12(60,0)	9(42,86)*	27 (77,14)	*<0,001**
Mild degree (8- 13)	16(66,66)	4(20,00)	6(30,0)	10(47,6)*	7(20,0)	*0,002**
Moderate (14-18)	8(33,33)*	6(30,0)*	2(10,0)	2(9,52)	1(2,86)	*0,007**
Severe (19- 22)	0 (0)	8(40,0)*	0 (0)	0 (0)	0 (0)	*<0,001**

Notes. $p^{\#}$ – differences between groups 1 and 2 and group 3 by one-factor analysis of variance ANOVA: # – *p <0.001* comparable to group 3; p * - differences between groups 1 and 2 and 3 according to the Pearson $\chi 2$ criterion:* - *p<0.05* comparable to group 3

When conducting a correlation analysis between the psycho-emotional state of the patients (depressive disorders and anxiety level) and the duration of pelvic pain and recurrences of the disease, a direct relationship of medium strength was determined, respectively (r=0.35; p=0.001 and r=0.28; p= 0.003 respectively).

The influence of cytokines on the central nervous system has been proven in many studies. Thus, in our study, peripheral levels of IL-6, IL-10, and TNF-α were increased in the plasma of patients with depression compared to those of the control group [8].

Correlation dependence between imbalance of interleukins and duration of pelvic pain was determined. Direct correlation: r=0.28; p=0.002 was determined with an increase in the level of pro-inflammatory TNF-α, and an inverse correlation: r=-0.30 with a decrease in anti-inflammatory IL-10. To assess cytokine imbalance as a physiological phenomenon from the point of view of the compensatory-adaptive process in the immune chain regulation, the correlation coefficient between TNF-α/IL-10 was used (Table 5).

Table 5

Levels of interleukins profile in patient population with genital endometriosis and CPP and comparison group

Indicators M±m (SD)	group 1 (n=44)	group 2 (n=41)	group 3 (n=35)	*p*
IL-10 (pg/ml)	8,15±0,8* (3,57)*	4,90±0,38* (2,43)	7,7±0,73 (3,87)	***<0,001***
IL-6 (pg/ml)	9,13±2,48 * (11,09)	3,62±0,28* (1,79)	3,69±0,38 (2,02)	***<0,001***
TNF-α (pg/ml)	11,67±2,15* (9,62)	4,27±0,46 * (2,97)	1,88±0,34 (1,79)	***<0,001***
TNF-α/ IL-10 (pg/ml)	1,6±0,26* (1,15)	1,07±0,16* (1,00)	0,28±0,04 (0,22)	***<0,001***

Notes. *p* – differences between subgroups and groups by one-factor analysis of variance ANOVA

In the formation of the level of pain, pro-inflammatory IL-10 and TNF-α play a more significant role, affecting the level of pain directly, compared to anti-inflammatory IL-6, which, compared to them, affect the level of pain indirectly. This indicates that these indices of the clinical activity of inflammation are quite objective criteria reflecting the severity of the pain syndrome and impairment of the psychosomatic status [11].

Conclusions. Based on the conducted studies, risk factors for CPP in patients with endometriosis were identified, an objective assessment of pelvic pain was given, and it was determined that cytokine imbalance depends on the intensity and duration of pelvic pain, as well as on the psycho-emotional state of the woman.

CPP is a dynamic process that is affected by a complex interaction of provoking factors: extragenital pathology (diseases of the gastrointestinal tract and urinary system), psycho-emotional state, as well as pro-inflammatory mechanisms in the immune system. Cross-organ sensitization of the pelvic organs implies a pathological interaction of peripheral nerve pathways, which contributes to the exacerbation of chronic pelvic pain in patients with genital endometriosis. Thus, women with chronic pelvic pain should receive care from a multidisciplinary team of specialists consisting of an obstetrician-gynecologist, a gastroenterologist, a urologist, a neurologist, and a psychotherapist/psychiatrist.

Further investigation and understanding of immunological changes in endometriosis and pelvic pain will help to use T-cell-directed immunotherapy in the future. Identification and understanding of interorgan and central sensitization in endometriosis, as well as clinical differentiation of pain characteristics, will shift treatment away from a predominantly lesion-based approach and provide a broader range of therapeutic targets aimed at inhibiting pain receptors [9,10].

The author declares that there are no conflicts of interest.

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