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Anxiety and depressive disorders in patients with primary painful bladder syndrome. Part 1: Symptoms and clinical progression

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ABSTRACT

The article is dedicated to affective disorders developing in patients with primary painful bladder syndrome. The causes of their development and influence on the quality of patients' life are considered. An overview of the etiopathogenic links between anxiety and depressive disorders and bladder pain is presented. it should be noted that common comorbidity with depressive and anxiety disorders is a risk factor for the unfavorable course and chronicity of pain conditions that requires to involve a psychotherapist or psychiatrist for examination and treatment of patients with primary painful bladder syndrome, and, if the somatoform nature of primary painful bladder syndrome is found, for prescribing relevant drug and non-drug treatment.

Keywords: primary painful bladder syndrome; depression; anxiety disorders; somatoform disorders; comorbidity.

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Тревожные и депрессивные расстройства у пациентов с первичным синдромом болезненного мочевого пузыря. Часть 1. Симптоматика и клиническое течение

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АННОТАЦИЯ

Статья посвящена аффективным расстройствам, развивающимся у пациентов с первичным синдромом болезненного мочевого пузыря. Рассмотрены причины их развития и влияние на качество жизни больных. Приводится обзор этиопатогенетических связей между тревожными и депрессивными расстройствами и болями в мочевом пузыре. Отмечено, что частая коморбидность с депрессивными и тревожными расстройствами выступает фактором риска неблагоприятного течения и хронизации болевых состояний, что определяет необходимость привлечения для обследования и лечения пациентов с первичным синдромом болезненного мочевого пузыря у врача-психотерапевта или психиатра, а при выявлении соматоформной природы данного заболевания назначения соответствующего медикаментозного и немедикаментозного лечения.

Ключевые слова: первичный синдром болезненного мочевого пузыря; депрессия; тревожные расстройства; соматоформные расстройства; коморбидность.

Как цитировать

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INTRODUCTION

Pain is one of the most common symptoms of both organic diseases and psychiatric conditions. Pain can be divided into nociceptive and neuropathic. Nociceptive pain develops in response to a direct stimulation of the peripheral pain receptors, while neuropathic pain results from abnormal changes in the nervous system. Nociceptive pain is usually acute, whereas neuropathic pain is always chronic. Acute pain occurs abruptly due to a direct action of a specific stimulus and resolves relatively quickly. Chronic or persistent pain is the pain that lasts at least 6 months. It is caused by functional changes in the nervous system and, therefore, it can occur without a direct damage to the tissues. This might be due to misperception of non-painful stimuli as painful (allodynia) or aggravated perception of painful stimuli (hyperalgesia). If acute pain serves adaptation, this ability is lost in chronic (persistent) pain leading to the disruption of nervous system functions, which decreases the quality of life, and has a negative effect on other types of perception, emotions, thinking and reactivity.

Chronic pelvic pain is a chronic or persistent pain in the pelvis [1]. It is divided into pain associated with a known pathologic condition, such as an infection or a tumor, and pain without an identifiable cause. The latter is also called chronic pelvic pain syndrome (CPPS), which is a part of the general term "chronic pelvic pain." According to the International Continence Society (ICS) CPPS is a chronic pelvic pain, most often associated with lower urinary symptoms and bowel, gynecologic and sexual dysfunction in the absence of an infection or any other underlying local pathologic process [2]. In 2021, the European Association of Urology recommended adding the term "primary" for such cases (chronic primary pelvic pain syndrome, CPPPS) [1]. The pain syndromes can be divided into urologic, gynecologic, gastrointestinal and musculoskeletal, depending on pain location. Urologic pain syndromes include bladder, urethral, prostatic, scrotal, testicular, epididymal, penile, and post-vasectomy pain syndromes [1].

One of the most common causes of chronic pelvic pain is primary bladder pain syndrome (BPS). This term indicates the presence of persistent or recurrent bladder pain accompanied by at least one of the following symptoms: increased pain intensity with a full bladder, urinary frequency, and nocturia, in the absence of signs of an infection or any other underlying condition [1]. The term was recommended by the European Society for the Study of IC/BPS (ESSIC) as a substitute for "interstitial cystitis" in 2006. The substitution was justified by the new term being more accurate and consistent with the understanding of the disease and the modern nomenclature of pain syndromes. The incidence of primary BPS varies greatly from 15 to 450 cases per 100,000 population due to symptom heterogeneity. In women, the incidence of BPS is 5–10 times higher than in men [2, 3]. In females, BPS is becoming one of the main causes of persistent dysuria [4].

It is well known that primary BPS is multifactorial in nature, and the pathogenesis of the disease is still not completely understood. Potential causes of primary BPS include bladder wall inflammation, urothelial dysfunction with or without disruption of the glycosaminoglycan layer, autoimmunity, ischemia, and others [5, 6]. The diagnosis of primary BPS is made after excluding the other obvious causes of bladder pain, which makes it the diagnosis of exclusion [7].

In many patients, treatment of primary BPS is minimally effective, which makes it a serious urological problem. Moreover, a lot of patients do not achieve any decrease in the symptom severity at all. It is mostly due to the presence of coexisting somatoform and affective disorders which influences the persistence of the clinical symptoms in BPS [8–11].

PAIN IN THE CONTEXT OF AFFECTIVE DISORDERS

Many studies and literature reviews confirmed the high incidence of coexisting chronic pain syndromes and affective disorders [12, 13]. The study by Thompson et al. [14] showed that the incidence of depressive and anxiety disorders is higher in patients with chronic pain compared to other chronic diseases ($p < 0.01$). Moreover, depressive and anxiety disorders are thought to be the most prevalent psychiatric conditions among patients with pain syndromes [12, 15, 16]. In average, about 30%–70% of patients with chronic pain report coexisting depression and/or anxiety disorder [17]. Various studies revealed the connection between pain and the symptoms of affective disorders, which is supported by various neurobiological and psychological mechanisms [18–20]. This fact is confirmed by experimental studies in animal models [21, 22]. Coexisting affective disorders influence the processing of information related to pain and the ability for emotional regulation [14, 23–25].

PERSISTENT SOMATOFORM PAIN DISORDERS AND COEXISTING AFFECTIVE DISORDERS

Pelvic pain, including that in BPS, can reflect the presence of a **somatoform pain disorder**. The latter is characterized by persistent, continuous, severe pain, which causes significant emotional distress and can neither be explained by physiologic processes nor organic diseases. In somatoform pain disorders, pain develops due to the presence of an emotional conflict or psychosocial problems severe enough to consider it being the cause of

the condition. Somatoform disorders often coexist with depressive and anxiety disorders and have the incidence of 20%–70% [26, 27]. Individuals with somatoform disorders have been established to be at a higher risk of depression and/or anxiety disorders compared with healthy individuals. The addition of a coexisting affective disorder increases the number of hospital visits, decreases the quality of life and increases the risk of chronization [28, 29]. In the cross-sectional study by Tu et. al [30] 224 patients diagnosed with depressive, anxiety and/or somatoform disorders evaluated the quality of life using the World Health Organization Quality of Life-BREF method (WHOQOL–BREF). The correlation between the quality of life and the presence of a psychiatric disorder was evaluated using multiple linear regression analysis. Depressive disorders were shown to negatively affect all the aspects of daily life (β = –0.278, –0.344, –0.275 and –0.268), while the presence of somatic symptoms and health anxiety primarily affected the physical state (β = –0.307). However, the presence of both depression and somatic symptoms correlated with a significant decrease in the overall quality of life (β = –0.287 and –0.318, respectively) [30].

It is known that in individuals who experienced physical and psychological abuse during childhood there is reactivity of the brain areas participating in the analysis of sensory information, including pain perception. Dalechek et al. [31] conducted a systematic review and meta-analysis of qualitative and quantitative evaluation of the correction between adverse childhood experiences (ACE) and anxiety and chronic pain conditions including 3,415 publications. There were 52 studies that met the inclusion criteria. The study revealed moderate correlation between anxiety and chronic pain (r = 0.30; 95% confidence interval (CI) 0.14–0.45, p < 0.01) and between anxiety and ACE (r = 0.26; 95% CI 0.15–0.36, p < 0.01). It was also noted that the study participants who had experienced ACE sought medical advice due to pain twice more often (odds ratio (OR) 1.99; 95% CI 1.53–2.60, p < 0.01] [31]. Moreover, the acquired negative experience has its own biological correlates characterized by changes in the nervous, immune and endocrine systems typical of affective disorders. If the stress factor persists to adulthood, the hypothalamic-pituitary-adrenal axis becomes activated through the corticotropin-releasing factor (CRF) signaling pathways [32, 33]. It leads to a persistent increase in the glucocorticoid levels and decreased serotoninergic and dopaminergic neuron activity, which, in turn, contributes to the amplification of the inflammatory processes. The recent study in animal models by Tian et al. [34] demonstrated the role of CRF signal transduction activation in the central nucleus of the amygdala in the chronization of stress-induced neuropathic pain exacerbation due to amplification of the synaptic plasticity. Nakamoto and Tokuyama [35] described the influence of early stress on the endogenous opioid system dysfunction, which serves as a predictor of pain chronization. There is a two-way net of interactions between central and peripheral nervous system (including pain perception), and endocrine and immune systems.

BPS AND COEXISTING AFFECTIVE DISORDERS

There is a high incidence of coexisting somatic and psychiatric disorders in patients with BPS. Depression, generalized anxiety disorder, social phobias are some common coexisting psychiatric conditions [8, 36, 37]. According to Brünahl et al. [36], 60% of patients with BPS are diagnosed with moderate to severe depression. Several studies showed a direct correlation between the pain intensity, affective symptom severity, and the level of distress [14, 38, 39]. In the systematic review by Riegel et al. [8], coexisting anxiety and depressive disorders were also reported to increase the risk of alcohol and drug abuse. Some patients with a long history of a pain syndrome experience high levels of hopelessness which, combined with coexisting depressive and anxiety disorders, is considered to be a factor of the high suicide risk [8].

Most patients with primary BPS are difficult to cure due to the comorbidity, which is most often represented by functional disorders of the genitourinary and gastrointestinal systems, fibromyalgia, tension and migraine headaches, and chronic fatigue syndrome [40–44]. It has been established that coexisting sexual disorders include both functional disorders and a specific group of sexual pain disorders, such as vulvodynia, dyspareunia, vaginism, and others [45–50].

The high incidence of comorbidity in patients with primary BPS, including coexisting affective disorders, is widely related to the psychologic mechanisms and individual psychological characteristics [8, 51]. Particularly, it is represented by the tendency to fixate on somatic-vegetative expression of emotions, appearing during frustration, which is called somatization. Some authors relate this mechanism to the development of masked depressions with “somatic symptom masks.” Another significant individual psychologic feature of such patients is somatosensory amplification, which means high susceptibility to physical sensations. At the same time, subjective perception of these sensations intensifies with the tendency toward catastrophization during cognitive processing [52–54].

The connection between primary BPS and affective disorders is confirmed by modern neuroimaging studies showing the role of the brain neuromotor connectivity disruption in the somatization process at rest [55–59]. Affective disorders can significantly influence the sensory-discriminative processing of somatic sensations,

including pain, which was demonstrated in studies of functional brain connectivity in patients with unexplained somatic symptoms [60].

Being persistent in nature, pelvic pain widely affects all aspects of life. Considering the great variety of patients' individual psychologic features, secondary gain might occur. In this case the pain and/or the disease in its general sense can be unconsciously considered as means to achieve the goals, alleviating conflicts and psychologic distress.

According to Kryuchkova and Soldatkin [11] with the reference to Smulevich, patients with primary BPS often have a pronounced alexithymia, which means a difficult in recognizing and expressing their feelings and emotions [11]. Lankes et al. [61] compared 3 groups of patients: 40 patients with somatoform disorders, 40 patients with depression and 40 healthy controls. The study participants filled in the questionnaire on alexithymia (Toronto Alexithymia Scale, TAS26) and depressive disorders (Beck's Depression Inventory, BDI–II). In addition, patients experiencing pain evaluated its intensity (Numeric rating scale for pain, NRS). A dispersion analysis revealed a statistically significant increase in the alexithymia parameters in both groups of patients compared with the control group ($p < 0.001$), which was the highest in patients with pain disorders (52.0 ± 9.5). Regression analysis confirmed the results to be partly due to the presence of coexisting depressive disorders in the group of patients with somatoform disorders [61]. Alexithymia is accompanied by specific cognitive impairment, including rigid thinking and decreased critical perception of the disease. Patients might insist on additional examination by urologists, gynecologists and other specialists to reveal unidentified organic causes of pain. Concrete thinking and difficult in switching attention contribute to the continuous control of pain intensity and its influence on genitourinary system function. Individuals with primary BPS were shown to catastrophize the pain and fixate on the worst negative outcomes possible [62–64]. For example, in severe cases, pain might be felt as extremely severe, agonizing, and exhausting, thus interfering with normal life activities, although there is not enough medical evidence to make that conclusion. It is often accompanied by the fear of provoking or increasing pain, which might lead to behavioral restrictions, later causing other symptoms associated with inactivity (muscle weakness and stiffness, muscle aches with minimal exercise). The patient has a hypertrophied perception of the disease, feeling hopeless and anxious, with the anxiety often being generalized. The patient's focus on pain and physical symptoms leads to the formation of a hypochondriac perception and behavior, and increased sensitivity to organic stimuli. Patients often interpret normal signs of organ functioning as abnormal and pay attention to them, noting the smallest changes.

Several studies in patients with chronic pelvic pain revealed a correlation between low pain threshold due to increased sensitivity to painful stimuli and high levels of introversion and neuroticism [65–68]. Riegel et al. [8] conducted a systematic review analyzing 69 original studies of a psychiatric disorder associated with chronic prostatitis / chronic pelvic pain syndrome in males. The authors selected articles describing various psychosocial factors (pain catastrophization, stress, personal issues, social aspects), coexisting psychiatric disorders (depression, anxiety disorders, drug and alcohol abuse) and the quality of life. According to the authors' conclusions, the persistent character of pain and severe distress is associated with worsening asthenic disorders, emotional lability, insomnia, and decreased functionality of mental processes, including memory and attention, and risk of the development of a coexisting affective disorder.

In patients with the signs of hysterical personality disorder, conversion mechanisms such as transformation of negative emotions and their substitution with organic symptoms might play a major role in the development of primary BPS [69–75]. Fishbain [76] noted these patients to have secondary gain, such as avoidance of difficult life situations due to the thought that sick people are always forgiven, or gaining help, support and attention, which the patient cannot get otherwise.

The type of pain perception and individual experience of unpleasant bodily sensations is a separate topic for discussion. In psychology literature, the idea of subjective disease perception is a crucial intrapsychic construct, defining a person's emotional state, behavior, and quality of life when facing a disease [77–80]. It significantly affects treatment compliance, doctor-patient relationships, and the risk of developing secondary somatogenic complications, such as secondary depression, anxiety disorders, nosophobia, post-traumatic stress disorder and others [11].

CONCLUSION

The diagnosis of primary BPS, as well as CPPPS in general, is the diagnosis of exclusion. It is made if the diagnostic methods do not reveal infectious, oncologic or traumatic causes, which might explain the symptoms. In the absence of a confirmed underlying cause, patients with CPPPS are likely to have a somatoform disorder. In patients with primary BPS, coexisting depressive and anxiety disorders appear to be a risk factor for an unfavorable disease course, development of chronic pain conditions, and decreased quality of life. Thus, the diagnosis and treatment of these patients should include a therapist or a psychiatrist with prescription of an appropriate drug and non-drug therapy, provided the somatoform nature of BPS is confirmed.

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