

THE DIAGNOSTIC VALUE OF NERVE GROWTH FACTOR AND C-REACTIVE PROTEIN IN PATIENTS WITH INTERSTITIAL CYSTITIS / PAINFUL BLADDER SYNDROME

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For citation: Sholan RF. The diagnostic value of nerve growth factor and C-reactive protein in patients with interstitial cystitis / painful bladder syndrome. *Urology reports (St. Petersburg)*. 2020;10(1):61-66. <https://doi.org/10.17816/uroved10161-66>

Received: 16.01.2020

Revised: 19.02.2020

Accepted: 19.03.2020

⊗ **Objective:** to determine the diagnostic value of nerve growth factor (NGF) and C-reactive protein (CRP) in patients with interstitial cystitis / painful bladder syndrome (IC/BPS). **Material and methods.** 44 patients with IC/BPS (main group) and 20 volunteers (control group) were examined. The average age of the patients of the main group was 46.4 ± 13.9 years, the control group – 35.3 ± 9.7 years. Cystoscopy and hydrodistension of the bladder were performed. The severity of pain was evaluated on a visual analogue scale (VAS). The concentration of NGF was determined in the blood by the method of ELISA, CRP by the immunoturbidimetric method. **Results.** The average total score on the VAS scale was 5.47 ± 0.91 , mild pain (2–4 points) was noted by 20.4%, moderate pain (5–6 points) – 54.5%, severe pain (7–8 points) – 25.0% of patients. Diffuse bleeding of the bladder mucosa in 45.4% of cases was observed. In IC/BPS patients the average NGF level was 11.23 ± 8.22 ng/ml, CRP – 3.56 ± 1.66 mg/l. The concentration of NGF exceeded the control level by 22.7% ($p < 0.05$), CRP – by 71.3% ($p = 0.015$). The correlation coefficient of NGF with CRP was $r = +0.179$ ($p = 0.42$), and the determination coefficient was $R^2 = 0.032$. **Conclusion.** Identified statistically significantly increased levels of NGF and CRP in the blood serum of IC/BPS patients confirm the presence of a systemic inflammatory reaction. A weak direct correlation is determined between NGF and CRP in patients with IC/BPS patients. The determination of serum NGF and CRP in combination with clinical data can be used to diagnose IC/ BPS.

⊗ **Keywords:** interstitial cystitis / painful bladder syndrome; nerve growth factor; C-reactive protein.

ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ ФАКТОРА РОСТА НЕРВОВ И С-РЕАКТИВНОГО БЕЛКА У ПАЦИЕНТОВ С ИНТЕРСТИЦИАЛЬНЫМ ЦИСТИТОМ / СИНДРОМОМ БОЛЕЗНЕННОГО МОЧЕВОГО ПУЗЫРЯ

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Для цитирования: Шолан Р.Ф. Диагностическое значение фактора роста нервов и С-реактивного белка у пациентов с интерстициальным циститом / синдромом болезненного мочевого пузыря // Урологические ведомости. – 2020. – Т. 10. – № 1. – С. 61–66. <https://doi.org/10.17816/uroved10161-66>

Поступила: 16.01.2020

Одобрена: 19.02.2020

Принята к печати: 19.03.2020

⊗ **Цель исследования** — оценить диагностическое значение фактора роста нервов (ФРН) и С-реактивного белка (СРБ) у пациентов с интерстициальным циститом / синдромом болезненного мочевого пузыря (ИЦ/СБМП). **Материалы и методы.** Обследовано 44 пациента с ИЦ/СБМП (основная группа) и 20 добровольцев (группа контроля). Средний возраст пациентов основной группы составил $46,4 \pm 13,9$ года, группы контроля — $35,3 \pm 9,7$ года. Всем пациентам проводили цистоскопию и гидродистензию мочевого пузыря. Выраженность боли оценивали по визуальной аналоговой шкале (ВАШ). Концентрацию ФРН в крови определяли методом ELISA, СРБ — иммунотурбидиметрическим методом. **Результаты.** Средняя сумма баллов по ВАШ боли составила $5,47 \pm 0,91$. Слабую боль (2–4 балла) отмечали 20,4 %, умеренную боль (5–6 баллов) — 54,5 %, сильную боль (7–8 баллов) — 25,0 % пациентов. В 45,4 % случаев встречалась диффузная кровотоочивость слизистой мочевого пузыря. Средний уровень ФРН у пациентов с ИЦ/СБМП составил $11,23 \pm 8,22$ нг/мл, СРБ — $3,56 \pm 1,66$ мг/л. Концентрация ФРН превышала контрольный уровень на 22,7 % ($p < 0,05$), СРБ — на 71,3 % ($p = 0,015$). Коэффициент корреляции ФРН с СРБ составил $r = +0,179$ ($p = 0,42$), коэффициент де-

терминации — $R^2 = 0,032$. **Заключение.** Выявленные статистически значимо повышенные уровни ФРН и СРБ в сыворотке крови пациентов с ИЦ/СБМП подтверждают наличие системной воспалительной реакции. Между содержанием ФРН и СРБ в сыворотке крови определяется слабая прямая корреляционная связь. Определение содержания ФРН и СРБ в сыворотке крови в сочетании с клиническими данными может быть использовано для диагностики ИЦ/СБМП.

🔑 **Ключевые слова:** интерстициальный цистит / синдром болезненного мочевого пузыря; фактор роста нервов; С-реактивный белок.

INTRODUCTION

The main symptom of interstitial cystitis/bladder pain syndrome (IC/BPS) is chronic pain (pressure or discomfort) associated with filling the bladder or defined in the bladder region. This pain is accompanied by at least one lower urinary tract symptom (frequent urination, urinary urgency, nocturia) in the absence of signs of infectious or other apparent lesions [1]. Depending on the definition of IC/BPS used, the prevalence of IC/BPS is estimated from 45 to 197 per 100,000 women, and from 8 to 41 per 100,000 men [2, 3]. The etiology and pathogenesis of IC/BPS currently remain unclear [4]. IC/BPS diagnosis is primarily based on assessing symptoms and ruling out diseases that can cause similar symptoms [5, 6]. IC/BPS significantly affects patients' psychoemotional state and causes a significant deterioration in their quality of life [7].

Inflammation that is accompanied by a change in the balance of cytokines and neurotransmitters, which leads to activation of the afferent sensory system and sensitization of the central nervous system, is considered a possible mechanism for the onset of pain in IC/BPS [8, 9]. Inflammation results in morphological changes in sensory and motor neurons that innervate the bladder [10]. This neuroplasticity can be explained by the association of bladder inflammation with long-term symptoms and pain after the inflammation resolves [11, 12].

In recent years, considerable attention has been paid to the study of IC/BPS biomarkers, namely, nerve growth factor (NGF). NGF is involved in the conduction and potentiation of nociceptive signals in peripheral tissues because of the binding of tropomyosin receptor kinase or tyrosine kinase receptors on afferent nerve endings [13, 14]. Clinical and experimental data indicate a direct relationship between increased NGF levels in bladder tissue and urine and the severity of clinical manifestations in IC/BPS [15]. NGF can potentially contribute to the generalization and maintenance of chronic in-

flammation in IC/BPS [16, 17]. This hypothesis is supported by our earlier data on the relationship between NGF levels and the counts of leukocytes and mast cells in the bladder wall in experimental IC/BPS [18].

Further study of urine or serum biomarkers in IC/BPS seems to be promising for increasing the efficiency of early diagnostics of the disease since establishing a diagnosis based only on clinical symptoms, and cystoscopic presentation seems insufficient.

The study aims to determine the diagnostic value of NGF and C-reactive protein (CRP) in IC/BPS patients.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of the Medical and Diagnostic Center of the Ministry of Health of the Republic of Azerbaijan. Informed consent was obtained from each patient and control group participant examined. The study was conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association "Recommendations for Physicians Involved in Biomedical Research with Human Participation" [19].

Forty-four IC/BPS patients (main group) and 20 volunteers (control group) were examined. IC/BPS was diagnosed based on characteristic cystoscopic findings after hydrodistention. The criterion for inclusion in the study was the presence of non-ulcer IC/BPS. The exclusion criteria were diabetes mellitus, arthritis, systemic lupus erythematosus, neurogenic dysfunction, and lower urinary tract infection. The subjects in the control group had no history of IC/BPS or lower urinary tract disease. The age of patients in the main group varied from 22 to 76 years and averaged 46.4 ± 13.9 years. The age of control group subjects was within the range of 17–53 years, with an average age of 35.3 ± 9.7 years. In the IC/BPS group, there were 41 women (93.2%) and 3 men (6.8%), and the control group included 19 women (95.0%) and 1 man (5.0%). Out of

41 IC/BPS patients, 12 women (29.3%) were of reproductive age, and 29 (70.7%) were premenopausal and menopausal. The men in the main group were 27–57 years old, with an average age of 43.3 ± 10.9 years. The average disease duration was 6.0 ± 2.8 years.

The patients underwent a comprehensive examination, which included general urological diagnostic methods, cystoscopy, and hydrodistention of the bladder. Diagnostic procedures were performed under general anesthesia using Olympus endoscopes (Japan) with 30- and 70-degree optics in the endoscopic operating room. The analysis of the cystoscopic presentation used an assessment system that included five classes (0 – no changes in the mucous membrane; I – rare glomerulation, in at least two quadrants; II – diffuse submucosal hemorrhage; III – diffuse mucosal bleeding; IV – Hunner's lesions). Patients' bladder pain severity was assessed using a visual analog pain scale (VAS).

The nerve growth factor concentration was determined in the blood by an enzyme-linked immunosorbent assay using the NGF Emax® kit on a Medispec 6000M apparatus (Israel). The blood serum CRP was measured using a Cobas c 311 autoanalyzer (ROCHE Diagnostics GmbH, Germany) by the immunoturbidimetric method.

Statistical data processing was performed using SPSS software for Windows (version 12.0, SPSS Inc., Chicago, IL, USA). Indicators were expressed as mean \pm standard deviation, and numbers and percentages. Correlation and regression analysis (Pearson coefficient) was performed. Statistical scores were considered significant at $p < 0.05$.

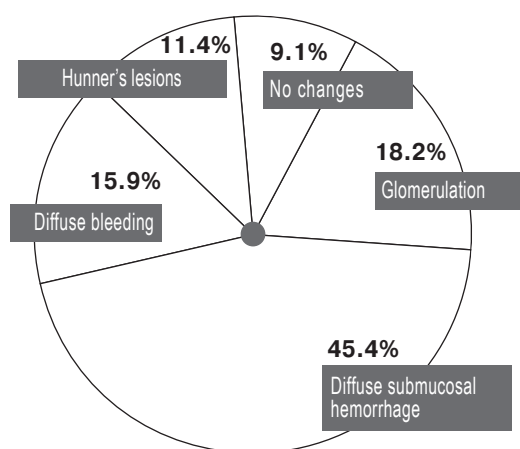


Fig. 1. Results of cystoscopy in patients with interstitial cystitis / painful bladder syndrome ($n = 44$)

Рис. 1. Результаты цистоскопии у пациентов с интерстициальным циститом / синдромом болезненного мочевого пузыря ($n = 44$)

RESULTS

The average VAS score was 5.47 ± 0.91 , whereas 9 (20.4%) patients indicated mild pain (2–4 points), 24 (54.5%) patients indicated moderate pain (5–6 points), and 11 (25.0%) patients indicated severe pain (7–8 points). Frequent urination (more than seven times a day) was noted in 27 (61.4%) patients, urinary urgency was detected in 11 (25.0%) patients, and urgent urinary incontinence was registered in 6 (13.6%) patients.

According to cystoscopy data, the anatomical capacity of the bladder ranged from 108 to 360 mL and averaged 276.0 ± 61.8 mL. The examination of the external urethral orifice revealed urethral polyps in 5 (11.4%) patients. In 4 (9.1%) patients, no changes in the mucosa were found (Fig. 1). Diffuse mucosal bleeding was the most common finding (45.4% of patients).

The results of determining the blood levels of NGF and CRP are presented in the Table.

The mean serum CRP level was significantly higher in IC/BPS patients ($p = 0.015$), and so was the mean serum NGF level ($p < 0.05$), compared with control values. IC/BPS patients' blood concentrations of NGF and CRP exceeded those of control levels by 22.7% ($p < 0.05$) and 71.3% ($p = 0.015$), respectively.

According to the data obtained, the proportion of patients with increased serum CRP (< 3.5 mg/L) in the main group was 63.6%, whereas, in the control group, it was 35.0%. Thus, an increased CRP level in IC/BPS patients was found 45.0% more often than in the control group ($p < 0.05$).

The results of the correlation analysis between NGF and CRP showed a weak, positive correlation

Levels of serum nerve growth factor and C-reactive protein in patients with interstitial cystitis/painful bladder syndrome and control group

Уровень фактора роста нервов и С-реактивного белка в сыворотке крови у пациентов с интерстициальным циститом / синдромом болезненного мочевого пузыря и группы контроля

Indicator	Main group ($n = 44$)	Control group ($n = 20$)	Statistical significance, p
NGF, ng/mL	11.23 ± 8.33 [1.70–113.70]	8.74 ± 4.93 [2.60–19.60]	< 0.05
CRP, mg/L	3.56 ± 1.66 [0.55–16.5]	1.02 ± 0.18 [0.30–1.80]	0.015

Note. NGF – nerve growth factor, CRP – C-reactive protein.

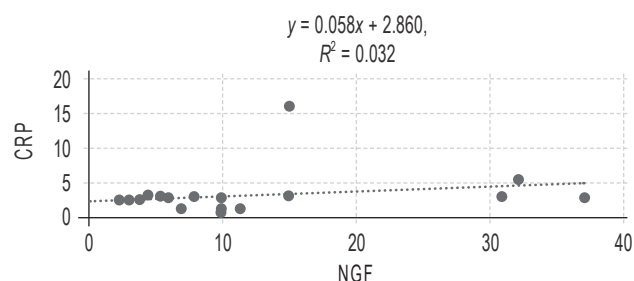


Fig. 2. Correlation of nerve growth factor and C-reactive protein serum levels in patients with interstitial cystitis / painful bladder syndrome ($n = 44$)
Рис. 2. Корреляция уровней фактора роста нервов (ФРН) и С-реактивного белка (СРБ) в сыворотке крови у пациентов с интерстициальным циститом / синдромом болезненного мочевого пузыря ($n = 44$)

in the main group ($r = +0.179$, $p = 0.42$), whereas the coefficient of determination was $R^2 = 0.032$. So, the factorial feature of NGF determined 3.7% of the CRP variance. The average approximation error characterizing the regression model's adequacy was 81.3% (Fig. 2).

In the control group, the correlation between NGF and CRP was also weak, but negative (Fig. 3).

In the control group, the Pearson correlation coefficient between NGF and CRP was $r = -0.187$ ($p = 0.43$), determination coefficient $R^2 = 0.035$, the factorial feature of NGF determined 3.5% of CRP variance. The average approximation error characterizing the regression model adequacy was 70.3%.

Thus, IC/BPS patients have increased NGF and CRP levels in their blood and a weak, direct correlation between them. The study did not reveal a correlation between NGF and CRP with VAS.

DISCUSSION

The main IC/BPS pathology is chronic inflammation. Inflammatory proteins in the blood serum are essential in the pathogenesis of this disease [4, 20]. The results of this study demonstrated an increase in serum levels of NGF and CRP in IC/BPS patients compared with the control group. The increased concentration of these indicators is associated with systemic chronic inflammatory conditions. Our results are comparable with those of other studies [8, 20]. It has also been reported that clinical characteristics and comorbidities did not reveal significant differences between IC/BPS patients with high and low serum NGF levels [20, 21]. These results suggest that, although chronic inflammation is involved in IC/BPS, the underlying phenotypic manifestations may differ depending on the disease subtype [8, 21]. Our data confirm the results of previous studies indicating that the determination of NGF levels in

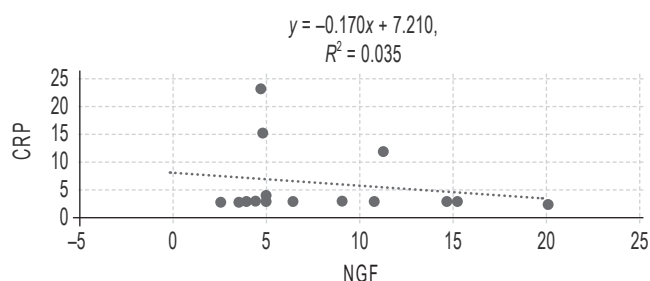


Fig. 3. Correlation of nerve growth factor and C-reactive protein serum levels in the control group ($n = 44$)

Рис. 3. Корреляция уровней фактора роста нервов (ФРН) и С-реактивного белка (СРБ) в сыворотке крови в группе контроля ($n = 44$)

the blood of IC/BPS patients is useful for both diagnosing conditions and studying disease etiology [8, 20, 21].

The revealed increase in serum CRP level also supports the concept of inflammation as a cause of IC/BPS. Our study showed that the proportion of IC/BPS patients with elevated CRP levels was significantly higher ($p < 0.05$) than in the control group. The results obtained were comparable with those of other studies [22]. Correlation analysis between NGF and CRP in IC/BPS patients revealed a weak, direct relationship. Also, a weak correlation between these indicators was noted in the study by Jiang et al. [8].

Since CRP is a nonspecific marker of inflammation, in cases when it is increased, it is necessary to examine the patient to detect inflammatory diseases. Although CRP cannot be considered a biomarker of local bladder inflammation, the determination of this indicator in blood serum can be useful in monitoring concomitant inflammatory diseases in IC/BPS patients.

CONCLUSION

1. The statistically significant increased levels of NGF and CRP in blood serum of IC/BPS patients confirm the presence of chronic systemic inflammation.
2. There is a weak, direct correlation between NGF and CRP in IC/BPS patients.
3. The determination of NGF and CRP levels in blood serum combined with clinical symptoms can be used to diagnose IC/BPS.

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