ORIGINAL STUDIES

Scientific Article
UDC 616.721-002.77-089.168.1-06: 616.8-009.7-07: 616.153-074
DOI: 10.17816/pmj4115-12

THE CONCENTRATION OF SERUM NEOPTERIN IN PATIENTS WITH SURGICAL TREATMENT OF SPONDYLOARTHROSIS COMPLICATED BY FACET SYNDROME

A.Yu. Pronin[1,2], Yu.V. Karakulova[1], D.Yu. Sosnin[1]*

[1]E.A. Vagner Perm State Medical University,
[2]City Clinical Hospital № 4, Perm, Russian Federation

КОНЦЕНТРАЦИЯ НЕОПТЕРИНА СЫВОРОТКИ КРОВИ У ПАЦИЕНТОВ ПРИ ХИРУРГИЧЕСКОМ ЛЕЧЕНИИ СПОНДИЛОАРТРОЗА, ОСЛОЖНИВШЕГОСЯ РАЗВИТИЕМ ФАСЕТ-СИНДРОМА

А.Ю. Пронин[1,2], Ю.В. Каракулова[1], Д.Ю. Соснин[1]*

[1]Пермский государственный медицинский университет имени академика Е.А. Вагнера,
[2]Городская клиническая больница № 4, г. Пермь, Российская Федерация

Objective. To study the concentration of serum neopterin in patients before and after surgical treatment of pain syndrome caused by the formation of facet syndrome associated with spondyloarthrosis.
Materials and methods. The study involved 52 patients (32 men and 20 women) hospitalized to the neurosurgical department of the City Clinical Hospital No. 4. The main group consisted of 26 patients with

tel. +7 902 800 33 23
e-mail: sosnin_dm@mail.ru
[Pronin A.Yu. – Candidate for a Degree of the Department of Neurology and Medical Genetics, Neurosurgeon, ORCID: 0009-0003-9555-8014; Karakulova Yu.V. – MD, PhD, Professor, Head of the Department of Neurology and Medical Genetics, ORCID: 0000-0002-7536-2060; Sosnin D.Yu. (*contact person) – MD, PhD, Professor of the Department of Faculty Therapy №2, Occupational Pathology and Clinical Laboratory Diagnostics, ORCID: 0000-0002-1232-8826].

тел. +7 902 800 33 23
e-mail: sosnin_dm@mail.ru
[Пронин А.Ю. – соискатель кафедры неврологии и медицинской генетики, врач отделения нейрохирургии, ORCID: 0009-0003-9555-8014; Каракулова Ю.В. – доктор медицинских наук, профессор, заведующая кафедрой неврологии и медицинской генетики, ORCID: 0000-0002-7536-2060; Соснин Д.Ю. (*контактное лицо) – доктор медицинских наук, профессор кафедры факультетской терапии № 2, профпатологии и клинической лабораторной диагностики, ORCID: 0000-0002-1232-8826].

spondyloarthrosis complicated by chronic pain associated with facet syndrome. The comparison group (n=26) consisted of patients with pain syndrome in radiculopathy. The control group (comparable in gender and age) consisted of 10 people who underwent periodic examination. The concentration of neopterin in blood serum was determined by solid-phase enzyme immunoassay (ELISA) using the Neopterin ELISA kit (cat. No. 59321; lot ENO230) ("IBL", Germany).

Results. Statistically significant differences in the level of serum neopterin concentration (p = 0.0016) were revealed between the studied groups. The highest concentration of neopterin was noted in the comparison group, where it was 10.31 ± 2.02 nmol/l, exceeding the results of the control group (p=0.02256) and the main group (p=0.04996). Three months after surgical treatment of patients in the main group, the median content of serum neopterin decreased by 1.161 times (p = 0.049029).

Conclusion. Further studies to clarify the influence of pain on metabolic processes and neopterin in particular are required.

Keywords. Neopterin, spondyloarthrosis, radiculopathy, pain.

Цель. Изучить концентрацию неоптерина сыворотки крови у пациентов до и после хирургического лечения болевого синдрома обусловленного формированием фасеточного синдрома на фоне спондилоартроза.

Материалы и методы. В исследовании участвовали 52 человека (32 мужчины и 20 женщин), госпитализированных в нейрохирургическое отделение ГКБ № 4. Из них 26 пациентов со спондилоартрозом, осложнённым хронической болью, составили основную группу. Сравнительный анализ проводили с пациентами с болевым синдромом при радикулопатии (n = 26). Контрольную группу, сопоставимую по возрастному и половому составу, составили 10 человек, проходившие периодический осмотр. Для определения концентрации неоптерина в сыворотке крови использовали метод твердофазного иммуноферментного анализа (ИФА) (набор Neopterin ELISA, кат. No. 59321; лот ENO230, «IBL», Германия).

Результаты. Между исследованными группами выявлены статистически значимые различия в уровне сывороточной концентрации неоптерина (p = 0,0016). Наибольшая концентрация неоптерина отмечена в группе сравнения, где она составила 10,31 ± 2,02 нмоль/л, превысив результаты контрольной группы (p = 0,02256) и основной (p = 0,04996). Через три месяца после хирургического лечения пациентов основной группы медиана содержания неоптерина сыворотки крови снизилась в 1,161 раза (p = 0,049029).

Выводы. Необходимы дальнейшие исследования для уточнения влияния боли на процессы обмена веществ и, в частности, неоптерина.

Ключевые слова. Неоптерин, спондилоартроз, радикулопатия, боль.

INTRODUCTION

Spondyloarthrosis is manifested by degenerative damage to the intervertebral joints involving cartilage, bones, ligaments, and muscles. A specific symptom of spondyloarthrosis is chronic pain, which intensifies with movement, which is accompanied by limited mobility and unstable morning stiffness [1; 2]. In some cases, lumbar pain is caused by radiculopathy [3]. Pain syndrome associated with damage to the facet joints of the lumbar spine is less known. Its occurrence may be associated with trauma [4; 5] and effusion [6].

Spondyloarthrosis is associated with static–dynamic loads, age-related degenerative–dystrophic processes in osteochondral tissue, and metabolic disorders in the human body. A study described a change in the pool of amino acids in the blood plasma during severe chronic pain syndrome [7]. The study of the serum concentrations of not only nitrogenous compounds related to

amino acids, but also metabolites of nucleic acid metabolism, particularly derivatives of purines and pyrimidines, is of particular interest. Neopterin, a derivative of pterins, is one of the metabolites of purine metabolism, intensively studied in recent decades, and synthesized by cells of the monocyte–macrophage series under the influence of interferons [8; 9]. Changes in neopterin concentration are mainly caused by diseases that occur with the activation of cytotoxic immune response, particularly infectious diseases caused by viruses, autoimmune diseases, and tumor processes [10–13].

Previously, we performed a preliminary assessment of the concentrations of neopterin in the blood serum of patients with pain syndrome related to spondyloarthrosis of the lumbar spine before and after treatment [14]. However, the group of patients examined was quite heterogeneous and had various concomitant diseases. Thus, examining a more homogeneous sample with the inclusion of patients with pain syndrome that developed in patients with spondyloarthrosis or spinal cord root entrapment appears appropriate.

This study aimed to analyze the dynamics of changes in serum neopterin concentrations in patients before and after surgical treatment of chronic pain syndrome related with spondyloarthrosis-associated facet syndrome.

MATERIALS AND METHODS

This observational, cross-sectional case-control study was performed in compliance with the ethical principles of medical research involving human subjects as set out in the Declaration of Helsinki of the World Health Organization.

The study enrolled 52 patients (male, $n = 32$; female, $n = 20$) hospitalized in the neurosurgical department of City Clinical Hospital No. 4. The main group consisted of 26 patients hospitalized for spondyloarthrosis complicated by chronic pain due to facet syndrome. Considering that this group of patients received surgical treatment, the serum concentration of neopterin was determined twice, that is, before surgery during hospitalization and 6 months after surgical treatment. Treatment consisted of high-frequency denervation of the facet joints at the L4–S1 level on both sides.

The inclusion criteria were as follows: (1) pain syndrome, (2) facet syndrome (spondyloarthrosis) confirmed by MRI data, (3) radiculopathy ruled out, (4) ruled out concomitant diseases such as hypertension and diabetes mellitus, in the stage of decompensation, and (5) normal results of a general blood test and a general urinalysis, as well as biochemical blood tests.

The exclusion criteria were as follows: (1) oncological diseases, (2) viral and infectious diseases in the acute phase or <4 weeks after recovery; (3) autoimmune diseases; (4) stage of decompensation of diabetes mellitus, hypertension, and liver and kidney diseases; (5) age <18 years; (6) incapacity; (7) pregnancy; and (8) patient refusal to participate in the study.

The comparison group (n = 26) consisted of patients with pain syndrome caused by to radiculopathy. The control group consisted of 10 patients who underwent periodic examinations, did not present any complaints at the time of the examination, and had normal results of a general analysis of urine, blood, and biochemical blood parameters (glucose and total cholesterol). The groups were comparable in terms of sex ratio and age ($p > 0.05$). Their comparative characteristics are presented in Table 1.

Blood samples were collected by vein puncture into vacuum tubes with a coagulation activator. After clot formation, the samples were centrifuged for 15 min at 3000 rpm using an Elekon CLMN-R-10-02 centrifuge. After performing all necessary tests, the remaining serum samples were separated and aliquoted into microtubes (Eppendorf – 0.7 mL) and stored at Ÿ20 °C until further studies.

The concentration of neopterin was determined by enzyme-linked immunosorbent assay (ELISA) using the Neopterin ELISA test system (Cat. No. 59321; lot ENO230, IBL, Germany), with manufactured-reported sensitivity of at least 0.7 nmol/L. The optical density of the samples was measured on a StatFax 3200 vertical photometer (Awareness, USA). Data accuracy was monitored based on the measurement results of two control samples that were part of the test systems. The neopterin content in control sample 1 was 5.48 nmol/L, with an acceptable range of results of 3.5–8.1 nmol/l, and in sample 2, it was 23.34 nmol/L with an acceptable range of 13.6–28.2 nmol/L.

For statistical processing of the study results, Statistica version 7 (StatSoft Inc., USA) was used. For the results obtained in each group, arithmetic mean (*M*) and standard deviation (*SD)* were calculated for a normal distribution of the trait and *Me* (median) and interquartile range (25–75th percentile) for a nonnormal distribution. To assess the distribution of results within the sample, the Shapiro–Wilk test was used. Therefore, for further calculations,

Table 1

Characteristics of the study groups

Characteristics of patients	Main group	Comparison group	Control group
Number of patients examined	26	26	10
Sex ratio (men/women)	15/11	17/9	6/4
Age of subjects, years	39.35 ± 6.56 38 (35; 44) 27–53	39.69 ± 10.9 36.5 (31; 47) 20–68	35.1 ± 5.59 35 (33; 37) 25–46

N o t e: *– the numerator shows the mean value (*M*) ± standard deviation (*SD*), the denominator shows the median (*Me*) and interquartile range (25 % quartile; 75 % quartile); under the slant line, there are highest and lowest results.

Table 2

Concentration of neopetrin (nmol/L) in the study groups

Characteristics of patients	Main group		Comparison group	Control group
	before surgery	after surgery		
Number of patients examined, n	26	26	26	10
Neopterin concentration, nmol/L	9.03 ± 1.39 8.87 (7.93; 9.7) 8.87–13.7	7.93 ± 2.36 7.64 (6.47; 9.68) 3.19–11.91	10.31 ± 2.02 9.82 (8.71; 11.87) 8.15–14.89	8.21 ± 0.85 8.21 (7.36; 8.71) 7.07–9.72
Shapiro–Wilk *W* test	0.88573 ($p = 0.00762$)	0.96754 ($p = 0.56065$)	0.88409 ($p = 0.00703$)	0.94675 ($p = 0.63022$)
Kruskal–Wallis *H* test	*H* test = 12.86557; $p = 0.0016$ Median test: $(p_{1,3}) = 0.338734$; $(p_{1,2}) = 0.049955$; $(p_{2,3}) = 0.02256$			
Wilcoxon test	$p = 0.049029$		-	-

N o t e: * – the numerator shows the mean value (*M*) ± standard deviation (*SD*), and the denominator shows the median (*Me*) and interquartile range (25 % quartile; 75 % quartile); under the slant line, there are highest and lowest results.

nonparametric statistics methods were used (Table 2). To compare neopterin content, the Wilcoxon and Kruskal–Wallis tests were used in related and unrelated groups, respectively ($n > 3$). The median test was used to compare further results between individual unrelated groups. A statistical significance level value ≤0.05 was taken as the maximum permissible probability of a type 1 error (p).

RESULTS AND DISCUSSION

Descriptive statistics characterizing the concentrations of neopterin in the studied groups are presented in Table 2. Statistically significant differences in the serum levels of neopterin were revealed between the studied groups (Fig. 1).

Before treatment, when comparing neopterin levels between patients, a statistically significant increase ($p < 0.05$) was revealed in the comparison group in patients with radicular pain syndrome. The median serum level of neopterin in the comparison group was 1.088 times higher than that in the main group ($p = 0.049955$) and 1.197 times higher than the data in the control group ($p = 0.02256$) (Table 2). Thus, statistically significant between-group differences were detected.

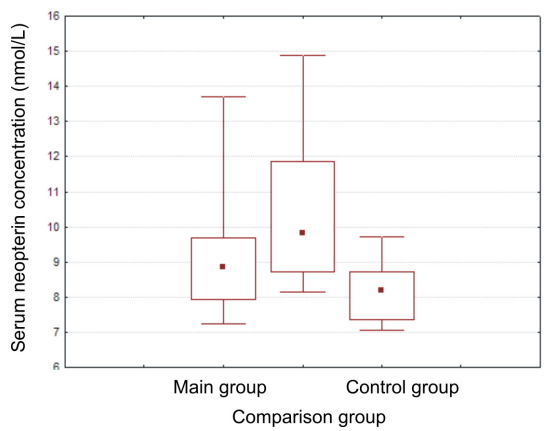

Fig. 1. Neopterin concentration (nmol/L) in the blood serum of the studied groups

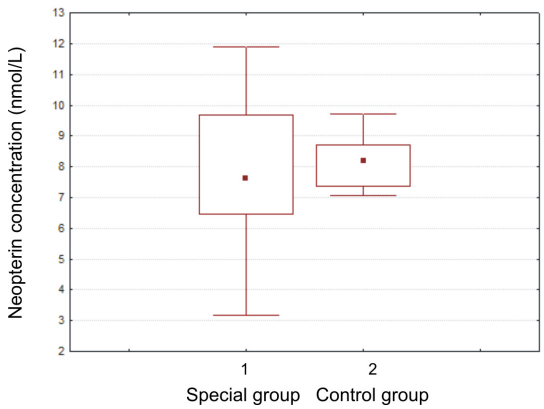

Fig. 2. Neopterin concentration (nmol/L) in the blood serum of patients of the main group after surgical treatment and control group

After surgical treatment, the serum concentration of neopterin in the main group with facet syndrome decreased statistically significantly (Wilcoxon test, $p = 0.049029$) and approached the indicators of the control group (Mann – Whitney *U* test, 114.5; $p = 0.589812$) (Fig. 2).

The higher concentration of neopterin in the blood serum of patients with pain syndrome caused by radiculopathy can be explained by the presence of neurogenic inflammation, which is accompanied by a greater release of proinflammatory factors that activate the antinociceptive purinergic system, in comparison with pain syndrome that develops in patients with spondyloarthrosis of the lumbar spine with facet syndrome development [15; 16]. In our opinion, this mechanism can lead to an increase in the serum concentration of neopterin [17; 18]. The prognostic value of studying the postoperative neopterin was identified in the authors' works when predicting postcholecystectomy syndrome[1] and other diseases [19].

Data are in poor correspondence with the preliminary results of the examination of patients who received high-frequency denervation of the facet joints [14]. However, with a more stringent selection of groups and an increase in the follow-up period to 3 months, this study revealed a statistically significant decrease in the concentration of neopterin in the blood serum.

An increase in the serum concentration of neopterin in the presence of diseases may be significant in the somatization of symptoms of diseases of internal organs [20]. In general, more studies are needed to clarify the role and pathogenesis of the effects of pain on the metabolism of tissues and organs.

CONCLUSIONS

1. The initial concentration of neopterin in spondyloarthrosis with the emergence of acute pain syndrome (facet syndrome) is not statistically significantly different from the examination results of the control group ($p = 0.338734$).

2. An effective treatment of pain syndrome caused by the compression of nerves in the area of the facet joints in spondyloarthrosis is accompanied by a statistically significant decrease not only in pain but also in the serum concentration of neopterin ($p = 0.049029$).

[1] O.V. Boyko, Yu.V. Kondrashova, A.V. Zhurikhin, and V.I. Boyko, RU patent No. 2498303.

3. Further research is necessary to clarify the effect of pain on metabolic processes.

References

1. *Kolotov E.B., Lutsik A.A.* Combination of discogenic pains and reflex syndromes of spondyloarthrosis (diagnosis and treatment). *Neurological Journal* 2009; 14: 3: 26–28 (in Russian).

2. *Reed M.L., Golish S.R., Schofferman J.* Interdisciplinary care for lumbar Spine disorders. Orthopaedic Knowledge Update: Spine 2018; 5: 127–150.

3. *Sadoha K.A., Golovko A.M.* Lumbar-sacral compression radiculopathy. *Medicinskie novosti* 2020; 1 (304): 9–15 (in Russian).

4. *Ra I.H., Min W.K.* Traumatic bilateral facet dislocation of lumbar spine: "double facet sign". Spine J. 2013; 13 (11): 1705–1707. DOI: 10.1016/j.spinee.2013.07.477

5. *Ridley W.E., Xiang H., Han J., Ridley L.J.* Shark's fin sign: Unilateral facet joint dislocation. J Med Imaging Radiat Oncol. 2018; 62: l: 1: 156. DOI: 10.1111/1754-9485.29_12786

6. *Laborie F., Béal C., Sigaux J.* Lumbar facet joint effusion. *Joint Bone Spine*. 2023; 90 (3): 105516. DOI: 10.1016/j.jbspin.2022.105516

7. *Alexander G.M., Reichenberger E., Peterlin B.L., Perreault M.J., Grothusen J.R., Schwartzman R.J.* Plasma amino acids changes in complex regional pain syndrome. Pain Res Treat. 2013; 2013: 742407. DOI: 10.1155/2013/742407

8. *Hamerlinck F.F.* Neopterin: a review. Exp Dermatol. 1999; 8 (3): 167–176. DOI: 10.1111/j.1600-0625.1999.tb00367.x

9. *Sviridov E.A., Telegina T.A.* Neopterin and its restored forms: biological role and participation in cellular immunity. *Advances in biological chemistry* 2005; 45: 355–390 (in Russian).

10. *Murr C., Widner B., Wirleitner B., Fuchs D.* Neopterin as a Marker for Immune System Activation. Current Drug Metabolism 2002; 3: 175–187. DOI: 10.2174/1389200024605082

11. *Karakulova Yu.V., Seksyaev N.E., Sosnin D.Yu.* The concentration of neopterin in the cerebrospinal fluid in HIV-infected patients with central nervous system damage. *Laboratory service* 2021; 10 (3): 21–27. DOI: 10.17116/labs20211003121 (in Russian)

12. *Berdowska A., Zwirska-Korczala K.* Neopterin measurement in clinical diagnosis. J Clin Pharm Ther. 2001; 26 (5): 319–329. DOI: 10.10 46/j.1365-2710.2001.00358.x

13. *Huang K., Du G., Wei C., Gu S., Tang J.* Elevated serum lactoferrin and neopterin are associated with postoperative infectious com-plications in patients with acute traumatic spinal cord injury. Arch Med Sci. 2013; 9 (5): 865–871. DOI: 10.5114/aoms.2013.38680

14. *Pronin A.Yu., Karakulova Yu.V.* Dynamics of indicators of neopterin and NSE in the blood serum of patients with pain syndrome with lumbar spine spondyloarthrosis before and after high-frequency denervation of facet joints. Neurological

readings in Perm: Materials of the interregional scientific and practical conference with international participation dedicated to the 100th anniversary of the Department of Neurology and Medical Genetics named after V.P. Pervushin, Perm, October 21–23, 2021. Perm: Perm National Research Polytechnic University 2021; 148–150 (in Russian).

15. *Mishra A., Agrawal D., Singh P.K.* Delayed presentation of post-traumatic bilateral cervical facet dislocation: a series of 4 cases. Neurol India. 2014; 62 (5): 540–2. DOI: 10.4103/0028-3886.144454

16. *Jain M., Khuntia S., Rao B.P.* Neglected Bilateral Facet Dislocation of the Cervical Spine with Intact Neurology: Reduction Technique. Asian J Neurosurg. 2020; 15 (3): 773–776. DOI: 10.4103/ajns.AJNS_27_20

17. *Pogorelova E.I., Budanova M.V., Panina O.A.* Neopterin as a prognostic factor of the course of acute respiratory infections. Modern achievements of chemical and biological sciences in preventive and clinical medicine: Collection of scientific papers of the All-Russian Scientific and Practical Conference with international participation, St. Petersburg, December 03, 2020. Edited by A.V. Silin, L.B. Gaikova. Part 1. St. Petersburg: I.I. Mechnikov Northwestern State Medical University 2020; 310–314 (in Russian).

18. *Gieseg S.P., Baxter-Parker G., Lindsay A.* Neopterin, Inflammation, and Oxidative Stress: What Could We Be Missing? Antioxidants (Basel) 2018; 7 (7): 80. DOI: 10.3390/antiox7070080

19. *Avanzas P., Arroyo-Espliguero R., Cosin-Sales J., Quiles J., Zouridakis E., Kaski J.C.* Prognostic value of neopterin levels in treated patients with hypertension and chest pain but without obstructive coronary artery disease. Am J Cardiol. 2004; 1; 93 (5): 627–9. DOI: 10.1016/j.amjcard.2003.11.035

20. *Euteneuer F., Schwarz M.J., Hennings A., Riemer S., Stapf T., Selberdinger V., Rief W.* Psychobiological aspects of somatization syndromes: contributions of inflammatory cytokines and neopterin. Psychiatry Res. 2012; 30 (195): 1–2: 60–65. DOI: 10.1016/j.psychres.2011.07.032

Funding. The study had no external funding.

Conflict of interest. The authors declare no conflict of interest.

Author contributions: A.Yu. Pronin collected the patient data, typed material, wrote the text, and performed statistical data processing (50 %). Yu.V. Karakulova created the idea of the article and the study plan, edited, and approval of the final text of the article (35 %). D.Yu. Sosnin performed laboratory tests (15 %).

Received: 07/30/2023
Revised version received: 12/20/2023
Accepted: 01/15/2024

Please cite this article in English as: Pronin A.Yu., Karakulova Yu.V., Sosnin D.Yu. The concentration of serum neopterin in patients with surgical treatment of spondyloarthrosis complicated byfacet syndrome. *Perm Medical Journal*, 2023, vol. 41, no. 1, pp. 5-12. DOI: 10.17816/pmj4115-12