Biochemical characteristics of distal vessels endothelium in patients with syndroms of lumbosacral radiculopathies and others neurological syndromes lumbar osteochondrosis in recrudescence phase

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Abstract: The content of C-reactive protein (CRP), interleukin-1 β (IL-1 β), endothelin -1 (E-1), soluble adhesion molecules of vascular endothelium-1 (sVCAM-1) and soluble molecules of intercellular adhesion -1 (sICAM-1) in peripheral blood of patients suffering from neurologic syndromes of dorsolumbar osteochondrosis (lumbalgia, lumboishialgia, lumbosacral radiculopathy) in recrudescence phase was investigated. CRP concentration in blood serum was determined by highly sensitive quantitative method (hs-CRP), based on the reaction of immunoprecipitation with reagent sets “Thermoscientific” firm, USA. Endothelin-1, sVCAM-1, sICAM-1 content in blood serum was determined by means of immunoenzymometric analysis method. The research was carried out with standard diagnostic reagent set of the “BioMedica”, “Bender MedSystem»” (BMS201, BMS 232) firm, (Austria), and the apparatus “Multiscan” of the Labsystem firm (Finland). Statistically significant ($p < 0,05$) concentration increase of C-reactive protein, interleukin-1 β (IL-1 β), endothelin -1, sVCAM-1 and sICAM-1 in peripheral blood serum in patients having lumbosacral radiculopathy in comparison with the test-group and with groups of patients suffering from syndromes of lumbalgia and lumboishialgia was found out.

Keywords: C-Reactive Protein (hs-CRP), Interleukin-1 β (IL-1 β), Endothelin – 1 (E-1), Lumbosacral Radiculopathies, Soluble Adhesion Molecules of Vascular Endothelium - 1 (sVCAM-1), Lumbalgia (Lumbodynia), Soluble Molecules of Intercellular Adhesion - 1 (sICAM-1), Lumboishialgia

1. Introduction

According to WHO the most common causes of life quality worsening limitation of physical activity resulting in temporary incapacity for work and even to invalidity, are

dorsalgias [1, 2]. As a rule they require a long-term treatment and complex rehabilitation. The main and chief reason of “Low Back and Neck Pain” is, to present day knowledge, vertebral osteochondrosis [3, 4, 5,].

In the 60-70s of the XX century the founders of vertebroneurology: Ya.Yu. Popelyansky, V.P. Veselovsky,

O.J.Kogan, I.R. Shmidt determined vertebral osteochondrosis as a multifactor disease with genetic predilection, characterized by degenerative-dystrophic changes in intervertebral disks and contiguous tissues with the secondary involvement of peripheral and central nervous system [6].

Pathogenetic mechanisms of the dorsalgias formation are related to vertebrogenic disorders of peripheral nervous system at the lumbar sacral osteochondrosis (LSO) - one of degenerative-dystrophic spine diseases (DDSD), - caused by irritation of synuvertebral nerve endings or compression of spinal cord nerve root due to structural dystrophic changes of spinal motion segment (SMS) [6,7- 10].

LSO neurological syndromes are divided into vertebral and extravertebral. Vertebral syndromes only the damaged SMS and are expressed affect as musculotonic reactions in the damaged segment region in response to synuvertebral nerve irritation. On lumbar level they are lumbago and lumbodinia. Extravertebral syndromes – lumbar ischialgia, lumbar-sacral radiculopathy (LSR) are formed on the background of vertebral syndrome, but show themselves out of the spine [9, 11, 12]. LSO neurological syndromes, in present day classification, are usually divided into reflexory-pain (lumbago, lumbodinia, lumbar ischialgia) and root syndromes [8, 10, 11]. Syndromes with more than 2 weeks duration: lumbodinia, lumbar ischialgia and radiculopathy – are the most wide-spread among spondylogenic neurological disorders [9, 13].

Choosing the tactics of LSO neurological syndromes treatment it is necessary to take into account either clinical or pathogenetic differences of LSO syndromes [14, 15]. But in many cases exact differential diagnostics of LSO neurological syndromes is rather complicated, as far as every of them represents an intricate complex of symptoms and at the same time all LSO neurological syndromes have a great number of mutual symptoms. The diagnostics is more difficult because of polyethiology and plurality of pathogenesis mechanisms: various types of LSO degenerative-dystrophic damages, various basic mechanisms of peripheral nerve disorders: compressive, vascular, autoimmune – inflammable and so on [13, 16, 17].

Differential diagnostics of reflexory pain syndromes (lumbodinia and lumbar ischialgia) and of lumbar-sacral radiculopathy (LSR) is of special importance.

LSR accounts for 70% [13, 15] of disorders of peripheral nervous system and for 37,4% of spine degenerative-dystrophic diseases [13], and exactly these disorders causes a long term incapacity for work and inability.

All the above – mentioned problems need additional diagnostic criteria to be found out for differential diagnostics of LSO neurological syndromes in recrudescence stage.

At present the notion of pathogenesis of LSO extravertebral syndromes is gradually changing. For a long time LSO has been considered a local process, limited to one or several spinal motion segments (SMS); now the opinion is changing and LSO is believed to be a system pathology

process, comprising skeleton-muscle-arthritis system, vascular and immune systems and involving central regulation mechanisms [7, 15].

Peripheral vascular disorders like ischemia hemodynamic disturbances and microcirculation help to show vegetative-vascular, reactive-inflammable, stagnant and other reactions in clinic picture of radiculopathy [11, 12, 9, 13, 17].

Neurovascular disorders are important and obligatory clinic demonstration of lumbar sacral radiculopathy (LSR) development. According to the classification of V.P. Veselovsky (1991), depending on dominating vascular disorders they are divided into arterial venous and mixed [7, 12].

In all cases the ischemic component was one of the main mechanisms of vascular disfunction, leading to the formation of compression-ischemic radiculopathy in lumbar section. According to Khabirov F.A. (2001), V.V. Belyakov, A.B. Sittel et al. (2002), one of the reasons of radiculopathy of lumbar-sacral section may be spondylogenic compression of epidural venous plexuses with the development of venous stasis (especially in the space of dural venouses and in place of root penetration through scleromeninx), which brings to its ischemia due to the spasm of feeling vessels [10, 16]. Other possible mechanisms of compression neuropathy formation is the compression and ischemia of the nerve that comes across the muscle affected by spasm [7, 10, 18, 19]. These disorders are developing on the background of reactive inflammable processes, reaction of cellular and humoral immunity appearing in the range of dystrophically changed intervertebral disk [10, 13, 20, 21].

So, the obtained data speak for the fact, that only LSR are accompanied by local inflammatory, vascular-reactive, immune processes, that is not observed with other LSO syndromes [15, 17].

Nevertheless, taking into account serious condition of a patient under LSR recrudescence it can be hardly supposed that the processes are of strict local character and do not affect general hemodynamics (vascular system on the whole), and are not the signs of a system inflammatory process. But the notions of mechanisms of pathology process formation under LSR with peripheral vascular disorders involved are not supported by the data on the intima of peripheral vessels.

The confirmation of peripheral vascular disorders as the most important ethiological and pathogenic component under LSR may become detection of markers of inflammation and disfunction of vascular endothelin in peripheral blood stream under this pathology.

The aim of the given investigation was to detect interrelation of a system inflammatory process and vascular disfunction in formation of LSP and others neurological syndromes of lumbar osteochondrosis in recrudescence stage.

2. Material and Methods

The investigation was carried out on the basic of neurology department of Clinical Hospital of Barnaul Railway Station, Barnaul of Altai District, Russia. The conditions agreed to the

demands of “WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subject” with amendments of 2000. All patients have signed written informed consents.

352 patients took part the investigation, they were divided into four main groups. Among the examined patients there were 300 cases with deferent neurological syndromes of lumbar osteochondrosis in recrudescence period.

There were 65 % (195) men and 35 % (105) women. The age ranged from 20 to 55. The mean age was $41,1 \pm 9,7$. The examinees were divided into three groups: 75 with lumbodinia syndrome – group 1; 75 patients with lumbar ischialgia syndrome – group 2; in group 3 there were patients with lumbar sacral radiculopathy – 150 subjects – with various localization of root damage of spinal cord nerves. Among them the compression of the nerve root L4 was identified in 6 patients (4%), L5 – in 26 (17%), S1 – in 52 patients (35%), biradicular syndrome (L5, S1) was detected in 66 patients (44%).

All the patients underwent routine neurological and vertebroneurological examination according to the techniques by Y.Yu. Popelyansky and F.A. Khabirov [6, 8, 10]. Additional techniques included: classical x-ray study of lumbar-sacral region of spine, CI/MRI of lumbar spine region.

The results of 52 healthy subjects without neurological signs of lumbar-sacral osteochondrosis served as the control; the patients were comparable in age and sex with main groups.

Criteria for being excluded from the control and investigation groups were the following diseases: IHD, hypertensive disease, hyperlipidemia of various genesis, accelerated ESR syndrome, diseases of lower limbs vessels, chronic infectious and viral and autoimmune diseases, inflammatory arthrosis diseases of a different etiology, diseases of YII- and ENT-organic in recrudescence phase. Therefore all the patients underwent clinical biochemical examination: clinical blood and urine analysis, blood chemistry with fibrinogen and prothrombin index determination, lipidic blood spectrum, ECV, duplex of lower limbs vessels; the examinees were consulted by a therapist.

Concentration of CRP (hs-CRP) in blood serum was determined by extremely sensitive quantitative method (in the interval from 0.1g/l), based on the reaction of immunoprecipitation with latex strengthening, using reagent sets (“Thermoscientific” firm, USA). Concentration of IL-1 β was determined by enzyme-linked immunosorbent method, using standard reagent sets (“Bender Med System 224/2” firm, Austria), in accordance with the instructions. Gauging curve, plotted on IL-1 β standards, in all the interval of investigated values, had a linear character.

Endothelin-1 concentration in blood serum was determined with enzyme-linked immunosorbent assay method. A standard set of reagents of “BioMedica” firm (Austria) was used.

sICAM-1 and sVCAM-1 concentration in blood serum was determined with enzyme-linked immunosorbent method with the help of commercial sets (“Bender MedSystem”, Austria (BMS201, BMS232)), used for purposes of research only.

For all biomarkers investigated the concentration of samples being determined were in the range of sensitivity,

recommended for identifying in standard sets.

Statistical analysis of the data obtained was performed using nonparametric methods (after checking up the normality of distribution of the found values). Mean values differences of quantitative intergroup parameters were determined with the Mann-Whitney U test for values, disconnected by pairs. Correlation analysis was made with Spearman’s rank correlation method. The results are shown graphically as histograms or in the table in the form of corresponding median (M) value for each investigated groups, standard deviation (SD) for each event is pointed out. The criterion of statistical accuracy of the obtained results was considered the value $p < 0.05$, commonly used in medicine. Statistical analysis was performed on SPSS.

3. Results and Discussion

We determined the content of hs-CRP, IL-1 β , endothelin-1, soluble molecules of adhesion: of vascular endothelium-1 (sVCAM-1) and molecules of intercellular adhesion (sICAM-1) in peripheral blood of patients with neurological syndromes of lumbar sacral osteochondrosis (lumbodinia, lumbar ischialgia, lumbar sacral radiculopathy) on the background of tough criteria of excluding accompanying vascular malformation.

hs-CRP concentrations in blood serum of the examined patients are shown in Figure 1.

Figure 1. Concentration hs-C-reactive Protein (mg/l) in Blood serum.

C – control (IV group), (n=52);

L – patients with lumbodinia syndrome (I group), (n=75);

LI – patients with lumbar ischialgia syndromes (II group), (n=75);

LSR-patients with lumbar-sacral radiculopathy syndromes (III group), (n=150);

Difference are significant between the group of patients with LSR syndromes and the control, (***) - $p < 0,001$.

Difference are significant the group of patients with LSR syndromes and other groups, (### - $p < 0,001$).

So, we can conclude that mean concentration values of CRP in all groups of the examined did not exceed normal ones (10-11mg/l). But taking into consideration the purpose, we used highly sensitive quantitative method of CRP concentration determination, that enabled to detect differences in hs-CRP content in blood serum in the range of low CRP concentrations (less than 10-11 mg/l) on subclinical

level. According to current knowledge, under the absence of system pathological processes, connected with tissue damage, infectious and autoimmune disorder, causing considerable grown of CRP in blood serum, slight evaluation of CRP in the range of 3-10 mg/l is connected with inflammatory or non-inflammatory affection of vascular walls [22].

Figure 1 shows, that different in hs-CRP concentration in blood serum in patients with syndrome of lumbodynia, lumbar ischialgia and control group were not revealed ($p > 0,05$).

At the same time in patients with lumbar sacral radiculopathy a vivid increase hs-CRP concentration in blood serum in comparison with the control group, as well with groups of patients with lumbodynia and lumbar ischialgia syndromes ($p < 0,03471$, $p < 0,03024$, $p < 0,03512$,

respectively for each case). The mean increase was 164% in comparison with control group of healthy people. hs-CRP concentration in blood serum in patients with lumbar sacral radiculopathy in recrudescence stage was equal to $8,85 \pm 1,66$ mg/l, that was maximum in our investigation. The increase at hs-CRP content in blood serum before revealing the concentrations is characteristic exactly for peripheral vessel disorders. [22, 23, 24].

With careful exclusion of other possible peripheral vascular pathology, the increase of hs-CRP content in patients with LSR significantly exceeded hs-CRP values in group of patients with lumbodynia ($3,50 \pm 1,05$ mg/l, $p < 0,00085$) and lumbar ischialgia syndromes ($3,80 \pm 1,01$ mg/l, $p < 0,00732$) (Figure 1).

Table 1. Interleukin-1 β Content in Blood Serum of Patients with Different Neurological Syndromes of Lumbar-Sacral Osteochondrosis

Investigation groups	Group I (lumbodynia syndromes) M $\pm$ SD (n = 75)	Group II (lumboischialgia syndromes) M $\pm$ SD (n = 75)	Group III (LSR syndromes) M $\pm$ SD (n = 150)	Group IV (Control) M $\pm$ SD (n = 52)
IL-1 β , pg/ml	0,66 $\pm$ 0,08	1,21 $\pm$ 0,48	5,47 $\pm$ 0,37**	0,58 $\pm$ 0,07

Note - ** differences are significant between the group of LSR patients and all the rest of groups, ($p < 0,01$).

Table 1 shows that IL-1 β content in the control group corresponds to reference values of the norm for healthy examined subjects, given in the test-system “Bender MedSystem” and agrees with the data of other authors who used either analogous ordinary reagent sets, or sets of other firms [25, 26].

This study detected clear expression of IL-1 β only in group of patients with LSR syndromes in recrudescence stage, Table 1 demonstrates IL-1 β concentration equal to $5,47 \pm 0,37$ pg/ml; it was 9 times higher than in the control ($0,58 \pm 0,07$), ($p < 0,00912$). In patients with lumbodynia syndromes IL-1 β concentration correspondent to $0,66 \pm 0,08$ pg/ml, that certainly did not differ from values of the control, and was more than 8 times less, than in LSR patients ($p < 0,01$).

In patients with lumbar ischialgia syndrome IL-1 β concentration in blood serum was $1,21 \pm 0,48$ pg/ml, that was surely not different from the control and 3,9 times less than in the group of patients with LSR ($p < 0,00653$).

The determined IL-1 β level in patients with LSR correlated with values, characteristic for non-infections inflammatory processes [27, 28, 29].

Endothelin-1 content in blood serum of patients with different neurological syndromes of LSO in recrudescence stage in given in Figure 2.

Figure 2 shows significant increase (more than 3 times) of E-1 content in LSR patients in comparison with the control ($p < 0,00075$) and groups of patients with other syndromes of LSO – lumbodynia and lumbar ischialgia ($p < 0,00086$, $p < 0,00073$, respectively for each case). E-1 concentration in blood serum of examined patients (control group) and groups with lumbodynia and lumbar ischialgia syndromes did not differ statistically ($p > 0,05$). There also was no difference in E-1 content in groups with lumbodynia and lumbar ischialgia ($p > 0,05$).

Figure 2. Endotheline-1 concentration (fmol/ml) in blood serum.

C – control (IV group), (n=52);

L – patients with lumbodynia syndrome (I group), (n=75);

LI – patients with lumbar ischialgia syndromes (II group), (n=75);

LSR-patients with lumbar-sacral radiculopathy syndromes (III group), (n=150);

Difference are significant between the group of patients with LSR syndromes and the control, (***) - $p < 0,001$).

Difference are significant between the group of patients with LSR syndromes and other groups, (### - $p < 0,001$).

It is known that the most part (up to 70-75%) of E-1 in secreted by endothelial cells in the directions of smooth muscle cells of a vascular wall and the rest – by smooth muscle cells themselves [30]. Coupling of E-1 with specific receptors on smooth muscle cells membranes results in their contraction, and, therefore, in vasoconstriction – one of the most important mechanisms of peripheral vessel disorders under LSR. The detected increase of E-1 concentration in blood serum in the group of patients with LSR in recrudescence stage confirms that E-1 takes part in the processes of formation of ischemia disorders of peripheral

blood from under this pathology.

In connections with the fact that CRP and E-1 are factors, causing inductions of adhesion molecules expression either in vitro or in vivo systems [31, 32], for further study of endothelin state of peripheral blood stream in patients with neurological syndromes of LSO, we investigated expression of soluble adhesion molecules of vascular endothelium 1 (sVCAM-1) and intercellular adhesion molecules 1 (sICAM-1) with endothelial cells.

These proteins of globulins superfamily are found out in blood serum under different pathology states, accompanied by

endothelial dysfunction [33, 34]. Results are given in Table 2.

Table 2 demonstrates that recrudescence stage of only one of investigation neurological syndromes of lumbar sacral osteochondrosis – lumbar sacral radiculopathy (LSR) syndromes – is accompanied by increase content of sVCAM-1 and sICAM-1 in peripheral blood serum. Concentration of sICAM-1 really increased by 102% in comparison with healthy subjects of the control ($p < 0,00645$), and by 107% and 53% in comparison with groups of patients with lumbodinia and lumbar ischialgia syndromes ($p < 0,00472$ and $p < 0,03615$ respectively for each case).

Table 2. Adhesion Soluble Molecules Content in Blood Serum in Patients with Different Neurological Syndromes of Lumbar -Sacral Osteochondrosis

Examined groups/ Markers of endothelial dysfunction	Group I (lumbodinia syndromes) M ± SD (n = 75)	Group II (lumboischialgia syndromes) M ± SD (n = 75)	Group III (LSR syndromes) M ± SD (n = 150)	Group IV (Control) M ± SD (n = 52)
sVCAMng/ml	939,71±123,22	962,13±135,21	1864,82±138,91**	930,64±123,21
sICAM ng/ml	503,13±146,92	680,81±131,54	1043,91±111,72**	517,34±94,22

Note: **: Differences are significant between the group of LSR patients and all other groups, ($p < 0,01$).

Concentration sVCAM-1 really increased by 101% with regard to healthy subjects of the control ($p < 0,00726$) and by 98% and 94% compared to groups with lumbodinia and lumbar ischialgia syndromes ($p < 0,00748$ and $p < 0,00962$ for each case respectively).

Similar variants of adhesion molecules expression were recorded before in case of CNS damage of vascular etiology, peripheral diabetic neuropathies, diseases of vascular etiology in ophthalmology [33, 34, 35, 36].

Adhesion molecules concentration sVCAM-1 and sICAM-1 in patients with LSR syndromes in recrudescence stage had a clearly seen correlation relationship with factors of proinflammatory process and endothelial dysfunction.

So, we detected real correlation relationships of medium force between sICAM-1 concentration and the concentration of hs-CRP ($r = 0,44679$, $p < 0,001$, $n = 150$) (Figure 3).

Figure 3. Correlation link between sICAM-1 and hs-CRP

sICAM-1 concentration and the concentration of IL-1 β ($r = 0,25411$, $p < 0,001$, $n = 150$) (Figure 4)

Figure 4. Correlation link between sICAM-1 and IL-1 β

There is identified real weak correlation relationship between sVCAM-1 concentration and the concentration hs-CRP ($r = 0,17878$, $p < 0,028$, $n = 150$) (Figure 5).

Figure 5. Correlation link between sVCAM-1 and hs-CRP

A strong real one-between sVCAM-1 concentration and the concentration of IL-1 β , ($r = 0,75955$ $p < 0,001$, $n = 150$) (Figure 6).

Figure 6. Correlation link between sVCAM-1 and IL-1 β

In LSR patients in recrudescence stage we determined mean real correlation relationship between the concentration of sICAM-1 and sVCAM-1 and between each other ($r = 0,33015$, $p < 0,001$, $n = 150$) in peripheral blood serum (Figure 7).

Figure 7. Correlation link between sVCAM-1 and sICAM-1

We also revealed real correlation relationship of mean force between the concentration of sICAM-1 in peripheral blood serum and endothelin-1 concentration, ($r = 0,42845$, $p < 0,001$, $n = 150$) (Figure 8).

Figure 8. Correlation link between sICAM-1 and endothelin-1

Real weak correlation relationship between sVCAM-1 concentration and that of endothelin-1, ($r = 0,24709$, $p < 0,0023$, $n = 150$) (Figure 9).

Figure 9. Correlation link between sVCAM-1 and endothelin-1

4. Conclusion

Therefore, increased concentration of endothelin-1, soluble adhesion molecules: of vascular endothelium-1 (sVCAM-1) and molecules of intercellular adhesion-1 (sICAM-1), in peripheral blood serum in LSR patients in recrudescence stage, on the background of high concentrations of biochemical factors – markers of proinflammatory processes: hs-CRP and IL-1 β , speak for the signs of a inflammatory process in peripheral blood stream, accompanied by endothelial cells disfunction. At the same time the absence marked changes of the investigation parameters in blood serum under recrudescence of other neurological LSO syndromes (lumbodinia and lumbar ischialgia) indicate that the pathological process in peripheral vascular wall is a link of pathogenesis and might be one of the main mechanisms of LSR syndromes development in recrudescence phase.

The obtained results confirm the notion about peripheral vascular disorders under LSR as the most important etiological and pathogenetical factors of spondylogenic compression ischemic radiculopathies formation [7, 15, 16, 17]. So it can be concluded, that the pathological process in a peripheral vascular wall is a link of pathogenesis and one of the mechanisms of lumbar-sacral radiculopathy formation.

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