

The change in the level of cytokines in blood and synovial fluid in the posttraumatic period of patients with deforming osteoarthritis as continuous chronic disease.

Величкина Антонина Борисовна

Кандидат наук

Российский государственный медицинский университет, Москва, Россия

E-mail: ant-velichkina@yandex.ru

Pain in the different departments of the bottom extremities of such damage is the most frequent reason for seeking medical attention [1]. Acute pain syndrome causes not only a sharp deterioration in the quality of life of patients due to movement restrictions, but the reaction of all physiological systems. Expressed activation of sympathoadrenal system in acute pain leads to impaired function of the respiratory, cardiovascular, gastrointestinal, urinary systems [2-4]. Constant sharp pain leads to increased levels of adrenocorticotrophic hormone (ACTH) and cortisol, catecholamines, interleukin-1, low levels of insulin, water-electrolyte disorders (delay Na⁺, liquid) [3]. Moreover, a sharp pain leads to violation of regeneration processes, changes in the activity of the immune system and hypercoagulable, raising the risk of thrombus formation. [3]. Patients may develop psychoemotional disorders - anxiety and/or depression. And these disorder, in turn, can aggravate the pain syndrome.

It is well known, that anxiety-depression conditions lead to lower pain thresholds (the change in the perception of pain) that is associated with overexpression of substance P to change the currency of serotonin, etc. to increase muscle tension, which also increases the severity of pain.

Domestic and foreign researchers proved that at the different stages of traumatic disease, as in deforming arthrosis, expressed by painful reaction forces to suffer all the organs and systems, the most significant changes relate to the immune system is affected all links from stem cell to cell-effectors, and the fact of development of immunodeficiency is of no doubt.

The imbalance of cytokine regulation launches a consecutive chain of reactions leading to the violation of circulation, the occurrence of hypoxia, alveolar and interstitial edema of the lungs, damage to the metabolic functions of the lungs.

The actual problem of the modern approach to the management of patients with traumatic injuries with the purpose of forecasting, prevention and treatment of post-traumatic conditions, is to evaluate in this period, the dynamics of cytokine profile circulating in synovial fluid, and the patterns of their production by mononuclear cells of the victims of this profile.

Research objective

To determine the effectiveness of diagnosis and treatment of post-traumatic arthrosis of the knee-joints with the definition of proinflammatory cytokines in deforming osteoarthritis in blood serum, and also directly in synovial fluid, assess their importance to the objective of making the diagnosis, stages of deforming osteoarthritis and to assessing the quality of treatment.

Material and methods of research

In a clinical study involved patients, with their informed consent, patients treated in the Department of General surgical intensive care and trauma Department of the Moscow urban clinical hospital № 14 named after V.G. Korolenko, and № 54 in the period from 2010 to 2013 (table 1).

In accordance with the purpose and objectives of this study were examined 144 patients with post-traumatic arthrosis (with a history of traumas of a various nature) in age from 23

to 64 years (average age $43,2 \pm 5,7$). Out of all examined patients men was 63 (43.7 per cent), women - 81 (56,3%).

As the control group, 18 relatively healthy people aged from 30 to 57 years (average age $45,5 \pm 4,3$) were examined. Table №1.

All of the examined person, depending on the stage of post-traumatic arthrosis, (acute and chronic classification) were divided into 4 groups.

The 1st group consisted of 48 patients with 1st stage of deforming osteoarthritis, 2nd - 38 patients with stage 2nd stage of deforming osteoarthritis, 3-th - 35 patients with 3rd stage of deforming osteoarthritis, 4th - 23 patients with 4th stage of deforming osteoarthritis.

Table № 2. Stage of deforming arthrosis was determined in accordance with classification [7].

Table №1

Distribution of patients according to sex and age.

Table №2

The distribution of patients depending on the stage of post-traumatic arthrosis.

Investigations were carried out at the time of hospitalization prior medical interventions. During the research the following methods were used: clinical, physical, instrumental, follow-up, radiation (MRI, CT, R-graphy), endoscopic, laboratory.

The synovial fluid from the affected knee was received during medical diagnostic puncture. The definition of Pro-inflammatory cytokines: IL-1, IL-6 and TNF-a in the blood serum and synovial fluid of the knee joint performed by ELISA on the immunofermental analyzer Abbott AXSYM" using standard kits ProCon ("Protein contour", St. Petersburg, Russia). Data were processed statistically using Student's t-test.

Results

The tables present the results of the IL-1, TNF-a (table 3) and IL-6 (table 4) in the serum of patients with deforming osteoarthritis at different stages of the pathological process. As can be seen from table 1, the content of IL-1 and TNF-a in the blood serum of the control group averaged $58,4 \pm 9,41$ PCG/ml and $46.5 \pm 11,4$ PCG/ml, respectively. Analysis of the results of determination of IL-1R in the serum of patients DK showed that in all stages of the disease, in addition to IV, the contents of this cytokine exceeded the control values in varying degrees of severity.

The highest levels of IL-1R in blood serum was revealed in patients with 1st stage of deforming osteoarthritis. Then downwards in the following order : in patients with 2nd , 3rd and finally, 4th stage of disease on average, respectively, he was $234,4 \pm 12,4$; $198,7 \pm 16,6$; $88,2 \pm 6,15$ (in all cases $p < 0.05$) and $47.4 \pm 4,45$ PCG/ml.

While the levels of IL-1R in the serum of patients with the 1st stage of the disease was 4.0 times; stage 2 - 3.4 times; the third stage is 1.5 times higher than in control. And only in patients with stage 4 of deforming osteoarthritis contents IL-1R did not differ from the control. A similar pattern was observed when determining the contents of TNF-a in the serum of patients with deforming osteoarthritis, and only in contrast to the level of IL-1R in patients with 4th stage of deforming osteoarthritis contents of TNF-and remained significantly higher than in control. So, the content of TNF-a in patients with of deforming osteoarthritis of the I, II, III and IV stage of disease on average, respectively, amounted to $330,7 \pm 24,5$; $210,5 \pm 17,3$;

123,4±15,3 and 98,5±12,7 PCG/ml (in all cases $p<0.05$) (table no. 3).

Table №3

The results of determination of IL-1, TNF-a in the serum of patients with DEFORMING OSTEOARTHRISIS at different stages of the pathological process

Subgroup(n=144)
IL-1 (pcg/ml)
TNF(pcg/ml)
Veracity
Test group(n=21)
58,4±9,41
46,5±11,4
$p<0,05$
Patients with DOA I-st (n=48)
234,4±12,4
330,7±24,5
$p<0,05$
Patients with DOA II-st (n=32)
198,7±16,6
210,5±17,3
$p<0,05$
Patients with DOA III-st (n=27)
88,2±6,15
123,4±15,3
$p<0,05$
Patients with DOA IV-st (n=16)
47,4±4,45
98,5±12,7
$p<0,05$

The table № 4 presents the results of determination of IL-6 in blood serum of patients with deforming osteoarthritis at different stages of the pathological process. As can be seen from pic., the content of IL-6 in blood serum in the control group averaged 4,2±0,77 PCG/ml the Results of determination of IL-6 in blood serum in patients with deforming osteoarthritis have shown that at the early stages of the disease (stage I and II), this figure was significantly exceeded the control values, while in the later stages of deforming osteoarthritis excess of contents IL-6 revealed no significant differences. The highest levels of IL-6 in blood serum was revealed in patients with 2nd stage of deforming osteoarthritis (12,4 within (2.5 PCG/ml; $p<0.05$). In patients with 1st , 3rd and 4th stage of disease it on average, respectively, amounted to 9.2±1,74 ($p<0.05$); 5,7±1,12 and 5.1±0,63 PCG/ml (table 2).

Table №4

The results of determination of IL-6 in blood serum of patients with deforming osteoarthritis at different stages of the pathological process

Subgroup (n=144)

IL-6(pcg/ml)

Veracity

Test group(n=21)

4,2±0,77

p<0,05

Patients with DOA 1st stage (n=48)

9,2±1,74

p<0,05

Patients with DOA 2nd stage (n=32)

12,4±2,5

p<0,05

Patients with DOA 3rd stage (n=27)

5,7±1,12

p>0,05

Patients with DOA 4th stage (n=16)

5,1±0,63

p>0,05

Table №5

The content of proinflammatory cytokines in the synovial fluid of the patients with different stages of deforming osteoarthritis (M±m)

Groups

n

IL-1, pcg/ml

IL-6, pcg/ml

TNF-a, pcg/ml

1st

2

634,3±34,7

7,7±1,76

998,9±41,1

2nd

5

722,1±123,4

9,3±1,54

546,3±21,5

3rd

10

117,8±39,2

4,04±1,21

168,2±9,72

4th

17

91,2±7,4

4,47±0,97

136,9±7,36

Test group

18

16,1±6,3

6,2±0,9

35,2±4,6

Note. n - is the number of the examined persons.

The table. № 5 shows the results of determination of IL-1, IL-6 and TNF-a in the synovial fluid of patients with different stages of deforming osteoarthritis. As seen from table, the highest values of cytokines in synovial fluid was noted in patients with 1st and 2nd stages of deforming osteoarthritis, and in advanced cases, this figure is decreasing. Comparative analysis of results of definition of cytokines in synovial fluid and serum showed that in the knee joint of patients with deforming osteoarthritis levels of IL-1 and TNF-were higher and IL-6 levels were even lower than in serum. So, in patients with 1st stage of deforming osteoarthritis the content of IL-1 in synovial fluid was 2.7 times higher, and in patients with 2nd , 3rd and 4th stage DKK 3.6; 1,3 and of 1.92 times respectively higher than in the serum (in all cases $p<0.05$). The content of IL-6 in synovial fluid, unlike IL-1, was below the corresponding values in the serum. So, in patients with 1st stage of deforming osteoarthritis 1.2 times (no clear results), and in patients with 2nd , 3rd and 4th stage of deforming osteoarthritis 2.7 times; 2,98 and 5.2 times respectively (in all cases $p<0.05$). Similar results were observed when determining the contents of TNF-a in the synovial fluid and serum.

Analysis of the obtained results showed that the content of Pro-inflammatory cytokines in blood serum varies depending on the stage of deforming osteoarthritis. So, the content of IL-1R in the serum of patients with deforming osteoarthritis, except persons with 4th stage of disease was significantly higher than the corresponding control. The level of IL-6 in blood serum of patients with deforming osteoarthritis significantly exceeded the targets only in the early stages of the pathological process (I and II stage), while the contents of TNF-a in all

stages of the disease was significantly exceeded the control value. Comparative analysis of the contents of proinflammatory cytokines in blood serum and synovial fluid showed that in the hearth of the pathological process (in the knee-joints in patients with deforming osteoarthritis) levels of IL-1 and TNF-a were much higher than the corresponding values in circulating blood, but the number of IL-6 on the contrary was lower.

Based on the data, it is clear that in the initial stages of development of DEFORMING OSTEOARTHRITIS proinflammatory cytokines play a key role in determination of the destructive potential of effector cells of the inflammatory process of the affected joint, probably through their autostimulator, and first of all of neutrophilic granulocytes [2] and may possibly be a key marker for early detection of damage. By reducing inflammatory potential in the later stages of the pathological process, in the lesion of the knee joint, in fact, the processes of fibrogenesis become stronger. A very important point, that supports this thesis is that there is a reduction of the contents of the system of Pro-inflammatory cytokine IL-6 *in situ*, that is, in the synovial fluid of the affected joint in the later stages of DEFORMING OSTEOARTHRITIS.

Thus, on the basis of the results of our research and literary data, we can say that the presence of Pro-inflammatory cytokines in the affected joint indicates pathological restructuring of the extracellular matrix and its loss [13].

Conclusion

The results obtained in a comparative study of contents of proinflammatory cytokines (IL-1, IL-6 and TNF-a) in the blood serum and synovial fluid at various stages of deforming osteoarthritis showed that the determination of the spectrum of cytokines in the hearth of the pathological process, in our opinion, is the most perspective and can be a key marker for early detection of damage and organizations of the active preventive measures of deformation processes in the joints in the early post traumatic period of the accident victims, mainly affecting the lower limbs.

LITERATURE

1. Biochemical analysis of synovial fluid of patients with diseases and damages of large joints: Manual for physicians. 1999. P. 24 .
2. Davydov S.O., Tsyrendorzhiev D.D., Voitovich A.V. Functional state of blood neutrophils in patients with deforming osteoarthritis of the hip // materials of the VII Congress of traumatologists and orthopaedists of Russia. Novosibirsk, 2002. Vol. 2. P. 208.
3. Kolobov S.V., Yarema I.V., Zairatyants O.V. 2001 Chronic inflammation. M., 1991. P. 272.
4. Ketlinsky S.A., A.S. Simbirtsev, Cytokines. SPb., 2008 P.550
5. Korotaeva T.V. Methods of evaluating the activity, and criteria for assessing response to therapy. - M., 2007 - P. 51-54.
6. Korotaeva T.V. International indices of evaluating the activity of functional status and quality of life of patients with rheumatic diseases. - M., 2007 -P. 88
7. Mironov S. P., Omelianenko N.P., Orlicky A.K. and others. Osteoarthritis: modern state of problem (analytical review), " Vestn. traumatol. and orthopedist. 2001. No. 2. P.96-99.
8. Nasonova V.A. Rheumatology. - M.: Medicine, 2008 - P. 457
9. Nasonov E.L. The use of Infliximab (monoclonal antibodies to TNF) in rheumatology: new facts and ideas // Rus.medical magazine - 2004 - № 12. - P. 64-73.
10. Appleyard R., Ghosh P., Swain M. The relationship of the structure of articular cartilage

to its resistance to compressive loading // J. Bone Jt. Surgery. 1996. Vol. 78-B, Suppl. II & III. P. 126-127.

11. Hung H.H., Mangham D.C., Treadwell B.W., Towle C.A. Expression of chondrocyte interleukin-1 in human osteoarthritis (OA) // J. Bone Jt. Surgery. 1996. Vol. 78-B, Suppl. II & III. P. 185-186.

12. Little C. The effect of growth factors on articular cartilage repair // J. Bone Jt. Surgery. 1996. Vol. 78-B, Suppl. II & III. P. 125.

13. Lotz M. Cytokines in cartilage injury and repair // Clin. Orthop. 2001. № 391, Suppl. P. S108-S115.

14. Pelletier J.P., DiBattista J.A., Roughley P. et al. Cytokines and inflammation in cartilage degradation // Rheum. Dis. Clin. N. Am. 1993. Vol. 19. P. 545-568.

15. Scully S.P., Lee J.W., Ghert M.A., Qi W. The role of extracellular matrix in articular chondrocyte regulation // Clin. Orthop. 2001. № 39, Suppl. P. S72-S89.

Annotation

Key words: cytokine interleukin (s), tumor necrosis factor, synovial fluid, deforming osteoarthritis

The work presents the results of a comparative study of contents of proinflammatory cytokines (IL-1, IL-6 and TNF-a) in the blood serum and synovial fluid of patients with different stages of deforming osteoarthritis accident victims, mainly affecting the lower limbs.

It is shown that the content of Pro-inflammatory cytokines in blood serum and synovial fluid varies depending on the stage of deforming osteoarthritis. So, the content of IL-1 in serum of patients with deforming osteoarthritis, except persons with senior 4th stage was significantly higher than in the control. The level of IL-6 in blood serum of patients with deforming osteoarthritis significantly exceeded the targets only in the early stages of the pathological process (I and II stages), while the contents of TNF-a in all stages of the disease was significantly exceeded the control value. Comparative analysis of the contents of proinflammatory cytokines in blood serum and synovial fluid showed that in the heart of the pathological process (in the joints of patients with deforming osteoarthritis) levels of IL-1 R and TNF-a was much higher than the corresponding values in circulating blood and the content of IL-6, on the contrary, below.

Thus, the survey results show that in the initial stages of development of deforming osteoarthritis proinflammatory cytokines play a central role in determination of the destructive potential of effector cells of the inflammatory process in the affected joint.

Key words: cytokine, interleukin(s), tumor necrosis factor, synovial fluid, deforming osteoarthritis

Information about the authors

Antonina Velichkina

Candidate of Medical Science

The Department of disaster medicine and life support

State educational institution of higher professional education Moscow State University of Medicine and Dentistry named after A.I. Evdokimov

Delegatskaya 20/1, Moscow, Russia

For information about the availability of printed works in national and international databases:

Contact tel.: (919) 778-83-43

E-mail: ant-velichkina@yandex.ru

Victor Nahaev

Professor

The Department of disaster medicine and life support

State educational institution of higher professional education Moscow State University of Medicine and Dentistry named after A.I. Evdokimov

Delegatskaya 20/1, Moscow, Russia

For information about the availability of printed works in national and international databases:
100

Contact tel.: (985) 998-86-13

E-mail: vinakhaev@yandex.ru

Nikolay Yarigin

Professor

The Department of disaster medicine and life support

State educational institution of higher professional education Moscow State University of Medicine and Dentistry named after A.I. Evdokimov

Delegatskaya 20/1, Moscow, Russia

For information about the availability of printed works in national and international databases:
150

Contact tel.: (916) 197-12-85

E-mail: yarmk@mail.ru

Julia Duzhinskaya

Candidate of Medical Science

The Department of disaster medicine and life support

State educational institution of higher professional education Moscow State University of Medicine and Dentistry named after A.I. Evdokimov

Delegatskaya 20/1, Moscow, Russia

For information about the availability of printed works in national and international databases:
20

Contact tel.: (916) 593-70-89

E-mail: selms@yandex.ru