eISSN 2181-1326
9 772181 132009

CAJM

Central Asian Journal of Medicine

Tashkent Medical Academy Press

eISSN: 2181-1326

Scientific Journal

This journal had been publishing since 2018

4
2022

MINISTRY OF HIGHER AND SECONDARY SPECIALIZED EDUCATION OF THE REPUBLIC OF UZBEKISTAN

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Central Asian Journal of Medicine

№ 4 / 2022

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Central Asian Journal of Medicine

№4/2022

Central Asian Journal of Medicine

THE ROLE OF INFLAMMATORY MARKERS AS IL-6, TNF-a, INF-y WITH PSORIATIC ARTHRITIS AND RATES OF COMORBIDITY

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ABSTRACT

Psoriatic arthritis (PsA) is simultaneously affected by the peripheral joints and skin in rheumatology. Several proinflammatory cytokines are produced in PsA and they induce inflammation of joints, nails, skin, and also internal organs. Serum cytokines levels play an important role in the pathogenesis of PsA by stimulating autoimmune reactions and influencing them continuously.

Purpose. This study aimed to identify how to influence the serum level of inflammatory markers as IL-6, TNF-a, and INF-y to disease course and duration. As well as, determine triggers and comorbid conditions of the disease.

Material and Methods. The study included a number of 170 participants. The participants were divided into 2 groups as 150 patients with PsA who fulfilled the CASPAR criteria and 20 healthy controls. Patients underwent history, clinical examination, x-ray, assessment of Psoriasis Area and Severity Index (PASI) score, and were determined HLA-27 gene, the serum level of inflammatory markers as IL-6, IFN-y, and TNF-a. Blood samples were collected from all participants. The serum levels of inflammatory markers were measured by solid-phase sandwich enzyme-linked immunosorbent assay technique.

Result. In the early and late stages of the disease, the serum level of inflammatory markers as IL-6, TNF-a, and INF-y in patients with PsA was significantly higher (130,2pg/ml, 292,1 pg/ml, and 80,2 pg/ml in early-stage and 140,0 pg/ml, 362,2 pg/ml, and 82,4 pg/ml respectively $p<0,05$) than the healthy group. Significantly elevated serum TNF-a was higher than INF-y and IL-6 in the early and late stages of PsA patients. In patients with PASI<30 all cytokines levels were reliably lower than in patients with PASI>30. Erosion arthritis was found in x-ray, who were increased levels of cytokines than non-erosion arthritis were common almost in lower levels of cytokines. Moreover, cytokines HLA-B27 gene who was positive, are a considerably rise than negative patients.

Conclusion. In our study triggers of disease were found as psoriasis, trauma, stress, and hypothermia. Elevated serum levels of cytokines had occurred in the early and late stages of the disease. Notably, the early phase of disease was initially increased TNF-a levels. Elevated serum levels of cytokines were correlated with activity, the severity of PsA and PASI scores.

Key words: psoriatic arthritis, IL-6, IFN-y, TNF-a, HLA-B27, psoriasis.

INTRODUCTION

Psoriatic arthritis is a chronic autoimmune disease of joints, and also affects nails, skin, as well as internal organs. Although the main risk factor for PsA is considered Psoriasis, it is not predictable for the occurrence of joint damage. Approximately, 10-30% of psoriasis can develop to PsA. PsA has a clinical heterogeneity as arthritis, enthesitis, dactylitis, anterior uveitis, and spine manifestations also occur. During PsA has some comorbidity conditions such as obesity and metabolic syndrome.

The etiology of PsA is unknown, although genetic and epigenetic triggers influence the manifestation of the disease [1]. In addition, in patients with PsA occurs an imbalance between the pro-inflammatory and anti-inflammatory responses of the immune system. As a result of anti-inflammatory cytokines level is decreased, while pro-inflammatory cytokines level is increased significantly.

The under pathogenesis of psoriasis plays a pivotal role in T-helper 1 (Th-1) and in the early stage can influence the duration of the disease. In PsA, in the skin and joints occurs pathogenetic reactions by neutrophil infiltration. Originally, INF-y is a protein and this protein is able to protect organisms from viral infection. However, this protein is divided into three classes by structural and functional as well as their ability to bind receptor complexes on the cell surface. Furthermore, type I INFs are principally produced to respond to viral infection of cells, and they are also divided into subgroups (IFN-α/β/ω) by their cellular origin. stimulated Type II INFS, known as INF-y, is produced essentially by T lymphocytes, natural killers following activation by immune and inflammatory stimuli rather than viral infection. INFs play an initial trigger for developing further inflammation. TNF-α has a positive correlation with PASI [5].

Currently, many people suffer from obesity, and obese people have an association with the extra-production of proinflammatory cytokines. Moreover, PsA is a very common comorbid state with obesity, and also metabolic syndrome, type 2 diabetes mellitus, and cardiovascular diseases [3]. Obese patients are produced high levels of leptin and become resistant to it. Leptin increases the expression of adhesion molecules and cytokines in the vascular endothelium, such as TNF-α and IL-6, which also act on the endothelium [7]. The increased leptin simultaneously influences and stimulates the inflammatory reactions and the appearance of metabolic syndrome [12]. Metabolic syndrome is associated with greater expression of adhesion molecules and platelet factors in patients with PsA. Subsequently, this process can contribute to the process of atherosclerosis and the increased cardiovascular risk [2]. Obesity is a protected function of organisms that are mediated by TNF-a and IL-6 to chronic inflammation. Another point is that

these two cytokines are responsible for inhibiting the production of adiponectin and, thereby, altering their metabolic and immunological functions [8]. The adiponectin is inhibited by proinflammatory cytokines. The relationship between adiponectin and TNF-a can be a predictor of PsA development. Thus, this will be useful for differentiating psoriasis from PsA.

Materials and Methods.

The study participants consisted of 150 patients with PsA from Tashkent medical academy, the department of rheumatology. All participants (68 males and 82 females, mean age 42,5±11,2) with fulfilling the diagnosis of PsA according to the criteria of Moll and Wright [6]. And also, age and sex-matched 20 healthy controls were enrolled in the study. Control groups were healthy, without any PsA symptoms, inflammation, or psoriasis. Healthy donor blood was collected. Patients were medication-free for at least 3 months prior to this study. To evaluate the disease activity, clinical observation of 52 joints (the EULAR 44 joint count added to DIP joints of hands) was performed. Skin affection was determined using the PASI score. Before inclusion in this study, all participants were informed and signed by each patient.

Exclusion criteria were included patients with severe liver and chronic kidney disease, infertility, anemia, and alcohol intake. Pregnancy and breastfeeding women, children (<18 age) were also excluded. All observational data and history taking were noted.

In the laboratory, parameters were included erythrocyte sedimentation rate, C-reactive protein, levels of IL-6, TNF-a, and INF-y. Gene expression was assessed HLA-B27. Measurement of cytokines levels in serum was done by ELISA. Blood was collected in peripheral veins from all patients. The seru levels of inflammatory markers were measured by solid-phase sandwich enzyme-linked immunosorbent assay technique according to the instructions (Cytokines, CPB, Russia). Instrumental methods of observation were used x-ray method.

All collected data were compared by Microsoft Office Excel-2016 and statistical analysis was done with t-student. $P<0,05$ was considered to be significant.

Results.

Clinic assessment. Clinical features of PsA are diverse manifestations. It depends on disease duration and activity also. In our study, from initial psoriasis rash signs to PsA has been averagely passed for 12,4 ± 0,3 years. As a result of history taking as triggers of the disease, we were found that in PsA 40 percent of patients were severe psoriasis rash, 24 percent of patients with trauma, and approximately equal patients with hypothermia (18,6%), stress (16,7%), and acute

infections (13,4%). The given Table 1 shows the duration of disease in the number of patients. Moreover, in our study patients were divided into 2 groups as early stage and late stage of the disease. In addition, we were considered early stage until 2 years and late-stage after 2 years of PsA.

Table 1

Duration of PsA	Number of all patients n=150	In percent % 100%
Until 2 years	65	43,3
2-5 years	42	28
6-10 years	32	21,4
More than 10 years	11	7,3

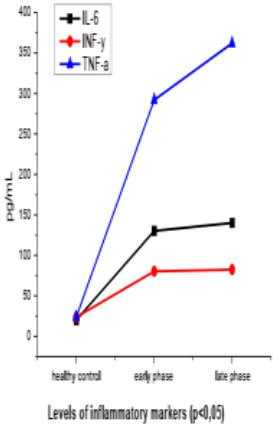
Our results indicate that 34,6% of patients relatives had a family history of psoriasis. This shows that psoriasis and psoriatic arthritis have a genetic susceptibility. The average time between the onset of psoriasis and the debut of PsA was 12,4 years. Interestingly, 30%, 12%, and 57% of patients were found hypertension, type 2 diabetes, and various stages of obesity.

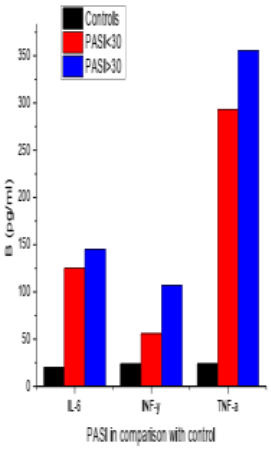
Although asymmetric oligoarthritis was included in almost 95,3% of patients in the early stage of disease, symmetric polyarthritis was also found 24,7% (p-value<0.001) in the late stage of the disease.

In the early stage, levels of TNF-alpha were significantly higher than other determined cytokines levels (Fig. 1). While levels of other cytokines were also increased and remained constant in the late-stage of disease. In the late stage, the TNF-a level again rose gradually.

IL-6 was elevated in both groups, it is able to enhance keratinocyte proliferation. However, who was PASI>30 with the severe course and larger skin lesion, IL-6 levels were 3,5 times higher (p-value<0,05) than the control group (Fig. 2). A correlation was revealed between the level of proinflammatory cytokines IL-6 and TNF-α in comparison with patients with moderate disease activity. The obtained results indicate that the increased level of TNF-α reflects the activity of the inflammatory process.

In our research was determined that 88% of patients were found skin lesions until arthritis manifestation as well as 10,6 % of arthritis before psoriasis rash. Interestingly, 1,3 % of patients were determined only arthritis without any skin lesion. However, in this group of patients, close relatives were psoriatic rash. Apart from this, all pro-inflammatory cytokines levels were increased in patients with erosion arthritis in comparison to non-erosion arthritis (Fig. 3). The among of patients 91% and 19% were found polyarthritis and oligoarthritis respectively.





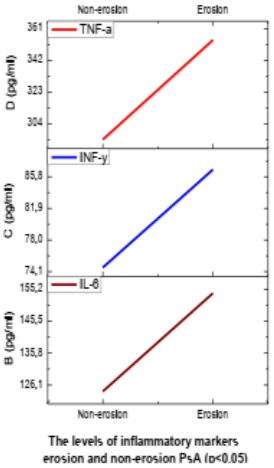


Figure 1 Figure 2 Figure 3

PSA has a tendency with HLA-B27. Our study levels of cytokines were significantly increased in HLA-B27 positive groups inverse correlation was found between HLA-B27 values and Schöber's test (p=0,02). There was no significant correlation between HLA-B27 and age at psoriasis diagnosis, arthritis diagnosis or PASI score.

Table 2

Parameters	Control, n=20	HLA-B27 negative, n=22	HLA-B27 positive, n=38
IL-6	20,0±2.0	122,2±17,61	147,9±10,23
INF-y	23,8±1,75	77,8±5,02	83,2±4,14
TNF-a	23,9±1,67	298,4±20,63	330,2±23,22
P<0,05			

Negative HLA-B27 had a tendency to correlate with hands and wrists arthritis (p=0,07) but There was no significant association between HLA-B27 and psoriasis' physical symptoms, extra articular manifestations and none specific skin or joint involvement (except hands and wrists arthritis).

Discussion

Cytokines are small, biologically hyperactive molecules. Multiple epidemiological studies have suggested the association between psoriasis and psoriatic arthritis. Our evidence that pro-inflammatory cytokines, IL-6, INF-y, and TNF-a as key factors stimulate severe inflammation and occurs chronic inflammation. In addition, INF-y induces macrophages to release high levels of other cytokines including TNF-a and IL-6. Produced TNF-a is present at higher levels in synovial fluid and in psoriatic plaques of patients with PsA [9,10].

Our results consistent with hypothesis that increased levels of cytokines in PsA is associated with a systemic pro-inflammatory gradient from inflamed joints and skin. We found that compared with controls, the serum levels of IL-6, INF-y, and TNF-a were significantly higer in patients with PsA. This cytokines may play crucial role of pathogenesis of PsA. Tamilselvi Elango, Haripriya Dayalan et al. research also showed increased levels of IL-6 in patients with PsA than the control group. PsA has a vary phenotypes and this phenotypes are strongly assosiated with different HLA-B27 alleles. In many cases have an association with HLA-B27 [11]. The interaction of HLA-B27 with PsA phenotypes in our study was severity of disease and erosive arthritis. Our study has reflected phenotypes merely with HLA-B27 and our study has some limitations. PsA patients occur 2 types of bone changes as bone destructive (erosions) or resorbing features (osteolysis). Moreover it can be seen with periostitis, ankylosis and in some patients both destructive and bone formation processes may occur. Even though in some picture it can be found. Our research work shows that all cytokines levels were raised in patients with erosive arthritis.

Some researchers said that the different phenotypes may be reflected by different genotypes. The interval between the onset of psoriasis and the development of PsA was influenced by the patient's HLA type. After the debut of psoriasis to the onset of PsA can extend the time interval. Commonly, it extends from 10 to 15 years [4]. Our result showed an average of 12,4 years between psoriasis and manifestation of PsA.

Khan et al, and Marsal et al observed the change in the manifestation of arthritis patterns over time in patients with PSA. They revealed that patients were often examined with oligoarthritis and later progressed to polyarthritis. After successful treatment occurred opposite direction as reducing the number of damaged joints. Our study also indicated that in the early stages of disease oligoarthritic manisestation was the most higher than polyarticular damage of joints.

The transition from psoriasis to PsA has several risk factors. The severity of psoriasis is the most important risk factor for manifesting and progressing PsA. Apart from risk factors, PsA has an association with co-morbid conditions. The most associated co-morbid condition with PsA is obesity. However, obesity is a dose-dependent condition and it depends on an increased body mass index. Increased BMI is associated with the risk of PsA. Above all, we also found the association between obesity and PsA in our research. Consequently, a well-recognised risk factor for transition psoriasis to PsA is hereditary. Being a close relative is increased developing PsA formation.

In conclusion, elevated serum levels of cytokines had occurred in the early and late stages of the disease and they are correlated with activity, the severity of PsA, and PASI score. Triggers of disease may be psoriasis, trauma, stress, and hypothermia. However, all determined cytokines are increased in PsA, inhibition of the significantly raised levels of TNF-a may be effective than other cytokines inhibitors as inhibitor IL-6 and INF-y.

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