

Psoriatic arthritis: Current state of the problem

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The article presents data on the prevalence, pathogenesis, clinical picture, diagnosis, treatment of psoriatic arthritis (PsA). Despite significant scientific advances, this pathology remains a serious medical and social problem. The etiology and pathogenesis of PsA are not fully understood. It leads to imperfect treatment methods. Given the polymorphism of clinical picture, as well as the lack of specific laboratory parameters, the diagnosis of PsA, especially at early stage, presents considerable difficulties. It is necessary to remember about the possibility of developing such socially significant comorbid conditions as hypertension, ischemic heart disease, type 2 diabetes, obesity, metabolic syndrome, inflammatory bowel disease, eye damage in patients with PsA. The pathology of the nails in patients with psoriasis and its relationship with the development and course of PsA is particularly interesting. The progressive nature of the damage to the musculoskeletal system, leading to a decreased function of the joints, disability, and impaired social adaptation, therefore the early diagnosis of PsA and the choice of optimal therapy are current priorities. A multidisciplinary approach to the management of PsA patients will facilitate the timely detection of pathology, as well as improve the quality of life of patients and the outcome of the disease.

Keywords: psoriasis, psoriatic arthritis, enthesitis, comorbidity, nail damage.

Introduction

Psoriatic arthritis (PsA) is a chronic progressive immune-mediated inflammatory disease of the articular apparatus, which is associated with psoriasis [1; 2]. PsA is one of the most complex rheumatic diseases. Now PsA is of particular interest to doctors and researchers. In order to study psoriasis and psoriatic arthritis in detail, in 2003 a special organization GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) was created. GRAPPA unites the rheumatologists, dermatologists, specialists in radiology, epidemiologists, and geneticists from different countries, who would like to contribute to the management of PsA [3].

Initially, PsA was considered as a non-serious disease with a favorable course, however, at present, the attitude towards it has changed notably. It was found that 40–60 % of patients with PsA develop erosive lesions and deformities of the joints, which lead to their dysfunction, affecting the occupational activity and social adaptation. Regarding the impaired quality of life, severity, and outcomes, PsA is not inferior to rheumatoid arthritis and ankylosing spondylitis [4]. Absence of adequate treatment leads to progressive damage in joints and disability during first five years of the disease. Moreover, mortality in patients with PsA is increased compared with the population in men by 59 %, in women by 65 % [5–7].

Epidemiology

In recent years, significantly increased incidence of PsA and number of severe cases was detected [8]. Among early arthritis, PsA accounts for about 5–13% [9]. The prevalence of PsA depends on geographical location and prevalence of psoriasis in a certain area. In general, among population it constitutes 0.001–1.5% (0.05–1.2%) [2; 8]. In Europe and America, the prevalence varies from 0.02 to 0.42%, in Japan it is almost 0.001%, in China — 0.02%. The highest rates were determined in Sweden. Given the articular complaints in only 30% of patients with psoriasis, difficulties in diagnosing PsA, especially at the early stage, it can be assumed that the true prevalence of this pathology is much higher. As for the incidence, it ranges from 0.1 / 100,000 in Japan to 23.1 / 100,000 in Finland. According to the results of population-based studies, the incidence of PsA in different countries is 3–8 cases per 100,000 [8]. In the Russian Federation, according to the Federal statistical observation in 2014, the incidence rate is 2.3 cases per 100,000 populations [2].

Arthritis can develop at any age, but most often the onset of the disease occurs from 20 to 50 years. It is worth mentioning the juvenile form, which is observed at 9–12 years [10; 11]. There were no gender differences in patients with PsA [2; 10; 11]. The most common type of psoriasis in PsA patients is vulgar psoriasis. About 4–5% of cases of PsA are associated with guttate or pustular psoriasis.

Etiology and pathogenesis

Psoriasis refers to multifactorial diseases. It manifests in the complex interaction of various inherited and environmental factors. About 40% of patients with PsA have a family history of psoriasis [1; 10]. Risk of developing PsA in close relatives is increased by 27–50 times. Concordance among monozygotic twins is 35–70% compared with 12–20% for dizygotic twins [10]. In recent years, experts tried to isolate genetic markers of PsA [4]. It is known that HLA-B27 antigen is detected in every third of patients [1]. It should be noted that only 50% of patients with PsA and sacroiliitis or spondylitis are HLA-B27-positive [10]. It was established that onset of psoriasis is associated with the HLA-B13 antigens, B16, B17, B27, B38, DR4, DR7 and development of PsA — with HLA-B38 and HLA-B39. Presence of HLA-B27 is associated with axial skeleton damage, while DR4 is associated with erosive arthritis of peripheral joints [12]. Moreover, a link between peripheral PsA and the MICA gene has recently been revealed. Regarding radiographic progression, HLA-DR04 antigen is unfavorable [10].

The leading role in this disease pathogenesis is assigned to immune mechanisms. In psoriasis, the interaction between T-lymphocytes, keratinocytes, fibroblasts, and synoviocytes is disturbed. Genetically predisposed individuals after exposure to external factors form defective keratinocytes. These cells present a skin antigen that activate local immune responses. They involve phagocytes, CD4, CD8, B-lymphocytes, natural killers, which produce pro-inflammatory cytokines (interleukins IL-1, IL-8, tumor necrosis factor alpha — TNF α), interferons, colony-stimulating factors. Human body starts to synthesize antibodies in autoantigens, which damage its own tissues with formation in the blood circulating immune complexes (CIC). Normally, the CIC is eliminated by the phagocytic system, however, if it is inconsistent, an immunocomplex tissue damage develops [12–14].

One of the main inflammatory mediators in the pathogenesis of psoriasis is TNF α . It stimulates synthesis of other pro-inflammatory cytokines, as well as promotes accumulation of inflammatory cells in tissues through induction of intracellular adhesion molecules 1 (ICAM1), and increases vascular growth factor production (VEGF). Moreover, TNF α determines development of synovial inflammation and osteoclast-mediated bone destruction in arthritis. Patients with PsA possess pathological formation of IL-12 and IL-23. The link of genetic type of receptor for IL-23 with PsA development was established during these researches. IL-23 stimulates Th17 cells, producing pro-inflammatory factors, IL-17 among them. Genetic analysis showed that susceptibility to psoriasis development is associated with the changes in the IL-12B gene, which encodes IL-23 receptors.

Trauma, infectious agents (streptococcus, staphylococcus, fungal infection, HIV and other retroviruses), endocrine factors may play the role of provoking factor (puberty period, menopause and pregnancy), as well as gastrointestinal diseases (gastritis, cholecystitis, dysbacteriosis) and medication (lithium preparations, beta-blockers, aminoquinoline drugs, sometimes NSAIDs) [1; 12]. Stresses play an important role as triggering factor in both skin lesions and arthritis, but the immune-endocrine mechanisms of this phenomenon have not yet been studied. Obesity and smoking are also among the risk factors, especially in young people [8]. About 25% of patients have a history of previous joint injury — Koehner's phenomenon [10].

PsA is found in 4–42% of patients with psoriasis (according to some data, up to 47–48%) [2; 3; 6]. In most cases (67–70%) arthritis develops earlier than skin lesion. The period from the first cutaneous manifestations to development of arthritis, as well as from arthritis to dermatosis, can range from two weeks to 10 years and more [8]. On average, arthritis occurs earlier than psoriasis on 8–10 years. In 10–20% of patients, articular and skin syndromes appear simultaneously, in 15–20%, joint damage is ahead of the pathological changes in the skin. These forms are more common in children and people over 50 years [2; 5; 10].

There is no correlation between the severity of psoriasis and PsA. None of the forms or severity of psoriasis is believed to prejudice the development of arthritis [2; 11; 12]. However, in cohort observations, there was a high incidence of PsA in patients with advanced psoriasis [2]. It is believed that the prevalence and deformation of arthritis are more pronounced in patients with extensive skin lesions (PASI > 10) [10].

Clinical picture

Approximately 95% of patients with PsA have peripheral joints damage. In 5% of cases only spinal joints are involved in pathological process. Clinical options of arthritis may overlap, which creates heterogeneous combination of articular lesions. In men, spinal lesions are more common (at a ratio of approximately 3:1), as well as distal interphalangeal joints (DMFS), while in females, symmetric polyarthritis occurs more often [10].

Over the past few years, a number of PsA classifications have been proposed, but none of them has been accepted as the main one for patients with PsA. In 2006, classification scheme CASPAR (Classification criteria for Psoriatic Arthritis) was developed. According to this scheme, diagnosis of PsA requires signs of inflammation in joints (arthritis, spondylitis, enthesitis) and at least 3 points for the following: psoriasis at the moment — 2 points, psoriasis in history — 1 point, family history of psoriasis — 1 point,

dactylitis — 1 point, nail dystrophy — 1 point, negative rheumatoid factor (except latex test) — 1 point, X-ray signs of extra-articular bone tissue proliferation (on radiographs of the hands and feet) — 1 point [12; 15]. The specificity and sensitivity of CASPAR criteria equals 98.7% and 91.4%, respectively [16].

According to Moll and Wright, there are several clinical variants of PsA:

- 1) The predominant lesion of the distal interphalangeal joints (distal from). Arthritis DMFS is often associated with dactylitis and nail dystrophy.
- 2) Asymmetric mono-oligoarthritis (the number of inflamed joints does not exceed 4), which occurs most often — up to 70%. The pathological process may involve the knee, wrist, ankle, elbow, and interphalangeal joints of hands and feet.
- 3) Symmetric polyarthritis (rheumatoid-like form) — observed in 15–20% of cases.
- 4) Psoriatic spondylitis — rarely seen in isolation, in about 50% of patients it is combined with peripheral arthritis.
- 5) Mutilating arthritis (arthritis mutilans) is a rare clinical type of PsA, characterized by osteolysis of the articular surfaces, which leads to shortening of hand and/or feet fingers with the “telescopic deformation” and subluxation of them.

In addition to these classic subtypes of PsA, they are currently talking about enthesial and mixed subtypes.

The clinical picture of psoriatic arthritis is determined by peripheral arthritis, enthesitis, dactylitis, and spondylitis. Signs of peripheral arthritis include pain, swelling, and limited mobility of joints. In some cases, inflammation may cover three joints of one finger simultaneously with development of axial arthritis.

The pathological process can involve a single joint of hands and feet, DMPS arthritis, the first metatarsophalangeal joints, the first wrist-metacarpal joints, the first interphalangeal joints. Also, we can observe an isolated lesion of one or two knee joints.

A typical sign of PsA is dactylitis — acute or chronic inflammation of the finger tissue. The dactylitis is caused by an inflammation of flexor tendons and/or extensor tendons, which leads to pain, finger swelling, cyanotic-purple staining of the skin. As a result, the so-called “sausage” deformation of the finger is formed.

Enthesitis is inflammation in places of tendons to the bones attachment (entheses). Repeated episodes of enthesitis, spontaneous or provoked, are often observed in PsA. Clinical manifestations of enthesitis include pain, which intensity depends on location and severity of lesion, and their functions restriction. Enthesis of the lower extremities is involved in pathological process more often than the upper one. Often, enthesitis develops in heel, in place of attachment of Achilles tendon and plantar aponeurosis to calcaneus. Plantar fasciitis and Achilles tendon inflammation may be disabling. Typical localization of enthesitis can also include lateral epicondyle of humerus, medial condyle of femur, upper edge of patella, edges (wings) of iliac bones, the greater trochanters of femurs, spinous processes of vertebral bodies. Enthesitis can occur both in combination with articular lesion, and be isolated. Given large number and often deep localization of affected areas, clinical evaluation of enthesitis is difficult and requires ultrasound or MRI [17–19]. It was established that enthesitis detected during ultrasound may clinically be silent in patients. Recently, Michelsen et al. showed that using ultrasound of Achilles tendon in a group of patients with PsA, inflammation of the entheses or their structural changes were observed equally in patients with painful entheses and in those without clinical symptoms. Signifi-

cant proportion of patients with psoriasis who do not complain about the musculoskeletal problems, have ultrasound signs of synovitis. This fact confirms the relevance of modern research aimed at identification of subclinical articular inflammation and determining its significance in early diagnosis of PsA [19; 21].

Spondylitis is a predominant lesion of spine, which is often combined with peripheral arthritis. As an isolated form spondylitis can be observed in 4–5 % of cases. Psoriatic spondylitis manifests as inflammatory back pain (according to ASAS criteria), mainly in cervical and lumbar spine, chest pain during breathing, limited mobility, stiffness in human back. Often, spondylitis has no symptoms and does not lead to significant functional impairment. In most patients with involvement of axial skeleton, function of spine and the mobility of human chest remain more than 10 years.

The studies revealed several predictors of PsA severity: early debut of the disease, female gender, acute onset of arthritis, polyarthritis, high CRP and ESR, HLA-B27-positive psoriatic spondylitis, expression of the TNF-a-308 and TNF-b-genes 252 [10].

The features of laboratory diagnosis

PsA refers to the group of seronegative arthritis. It seems that the rheumatoid factor (RF) for it is usually negative. However, in 5–13 % of RF patients, it can be determined in low titer, which requires testing for the presence of antibodies to a cyclic citrullinated peptide (ACCP) [4; 6; 8]. Although ACCP is a highly specific marker of rheumatoid arthritis, these antibodies are also detected in 5 % of patients with PsA. Moreover, in 10–15 % of patients, antinuclear antibodies (ANA) can be detected [10]. In the study of Hagiwara S. Et al. it was shown that in patients with PsA, the presence of ACCP may be associated with lung pathology, more mature patients, the presence of rheumatoid factor and matrix metalloproteinases — 3, and also indicate possible resistance to TNF-alpha therapy [20]. Acute phase markers (ESR, CRP, fibrinogen) increase in about 50 % of cases, which usually correlates with a large number of affected joints and indicates an unfavorable prognosis. Anemia of inflammation, hypergammaglobulinemia with increased IgA and hypoalbuminemia are less common. Some studies have shown that an accelerated ESR is associated with an unfavorable prognosis of the disease and increased risk of death, and a high concentration of CRP indicates a risk of joint destruction [8]. About 20 % of patients have an increased level of uric acid in the blood. Primarily it is caused by a higher frequency of the metabolic syndrome in patients with psoriasis [7; 10]. Synovial fluid is regarded as inflammatory: it contains neutrophils, sometimes high cytosis is detected (more than 3000 / mm³); mucinous clot is disintegrating, with low viscosity; high concentration of protein is noted (more than 3g/dl) [21].

Extra-articular manifestations of PsA and comorbidity

The course of PsA may be complicated by extra-articular pathology. Eye diseases with PsA are an urgent and extremely difficult problem. Ophthalmopathy can occur in the form of uveitis, scleritis (episcleritis), keratitis, cataracts, glaucoma, and conjunctivitis. Iridocyclitis is one of the most frequent extraarticular lesions, occurs in 2–25 % of cases and is more characteristic of the axial form of PsA and HLA-B27 + patients. A relationship of ophthalmopathy in these patients with articular pathology, unfortunately, has not yet been determined [22].

In recent years, researchers have focused on high cardiovascular risk in patients with PsA, as well as on relationship between PsA and atherosclerosis [23; 24]. The occurrence of cardiovascular pathology in patients with psoriasis is associated with chronic systemic Th1-Th17-mediated inflammation. This process is accompanied by an increased level of proinflammatory cytokines (TNF α , IL-2, IL-6, IL-8, IL-17), which affect angiogenesis, adipogenesis, regulation of insulin production, activation of inflammatory cells and platelet.

Performed studies demonstrates that in comparison of general population with patients with PsA, the prevalence of atherosclerosis is 1.4 times higher, coronary heart disease — 1.3 times, diseases associated with impaired peripheral circulation — 1.6 times, sugar type 2 diabetes — 1.5 times, hyperlipidemia — 1.2 times, arterial hypertension — 1.3 times [24]. Cardiovascular disorders in patients with PsA in 36.2% of cases are the main causes of death. Moreover, a prospective study by W. Masson et al. showed that the risk of mortality in patients with psoriasis and cardiovascular diseases is 1.58 times higher than in general population. It is also necessary to note increased risk of such diseases as depression, alcoholism, lymphoma, inflammatory bowel disease, non-alcoholic liver damage in patients with PsA [2].

Patients with PsA often develop obesity and metabolic syndrome [25]. The relationship of these processes requires further study. It is known that white adipose tissue produces cytokines that are key in the pathogenesis of PsA, namely TNF α , IL-23, IL-17, IL-6, IL-1 β . An association was also found between elevated levels of leptin and resistin in the blood of PsA patients with a more severe inflammatory process in the joints and skin. Regarding the effect of diet and weight loss on the course of arthritis, it was shown that a low-calorie diet (640 kcal/day) for 6 months decreases disease activity, manifestations of enthesitis, and improved skin condition [26].

Onihopathy in patients with PsA

Nearly 50 % of patients with vulgar psoriasis and up to 80 % of patients with PsA have nail damage. Pathology of the nail plates is an important clinical marker of predisposition to PsA. Pitting and onycholysis are considered the most common nail changes [27–29]. There is evidence that dystrophy of the nails in patients with psoriasis can serve as an indicator of the ongoing inflammatory process of the distal phalanx, as well as of the extensor enthesitis of the fingers [30; 31]. Ultrasound signs of nail damage are often noted among patients with PsA, even when the nails are clinically healthy. Ultrasonography of the nail plates in patients with PsA shows the increased thickness of the nail bed and the nail matrix [32]. Doppler signal in the area of the nail bed is often more strengthened in patients with arthritis than without inflammation in the joints. Increasing thickness of the nail plate is associated with the duration of skin lesions, while the thickness of the nail bed is associated with the duration of arthritis. Moreover, the thickness of the nail bed correlates with the number of swollen joints. It was revealed that in patients with psoriatic onychopatia the cardiovascular risk increases. Changes in the nail plates even at the early stages of psoriasis indicate a significant change in cardiovascular activity [33].

Instrumental diagnostics

Instrumental diagnostics of PsA include a standard radiographic study of hands, feet, pelvis, and lower chest with lumbar grip. The characteristic X-ray changes in PsA include

joint space narrowing, bone remodeling (resorption terminal phalanges, large eccentric erosion osteolysis — deformation “pencil in glass”) and bone proliferation (marginal bone growths, periostitis, entezofity, bony ankylosis), asymmetric bilateral or unilateral sacroiliitis, paravertebral ossification, and regional syndesmophytes [34–36].

For the early diagnosis of synovitis, spondylitis, sacroiliitis, as well as inflammatory process in tendon-ligament apparatus, magnetic resonance imaging (MRI), high-resolution ultrasound (US) or skeleton scintigraphy are used [37–39]. Ultrasound allows to specify anatomical nature of lesion: tendopathy, myopathy, ligament injury, etc., and also to determine the para-articular fluid in the inflamed bags, which occurs often in arthritis [40]. According to the study, an interesting fact has been revealed: US-detected enthesitis injury is more often observed in patients with PsA than with SpA. Thus, with the low cost of ultrasound it can make a significant contribution to the diagnosis of joints pathology [41]. However, despite the existing instrumental capabilities, the problem of timely diagnosis of PsA continues to be relevant.

Treatment

At the moment, radical treatment of PsA does not exist. Drugs, which we use for PsA, help to prevent or to slow the X-ray progression, increase the duration and improve the quality of life, as well as reduce the risk of comorbid diseases. First of all, patients have to modify their lifestyle in general: stop smoking, restrict alcohol intake, observe work and rest, demonstrate sufficient physical activity, maintains optimal body weight [3].

Regarding pharmacological care, non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for PsA. These drugs help to reduce the severity of symptoms but do not affect skin symptoms, progression of joint destruction, and prognosis of the disease. Thus, according to ACR20, treatment of patients with celecoxib at a dose of 200 mg and 400 mg for 2 weeks improved the clinical response by 21 and 11 %, respectively. However, after 12 weeks of treatment, there were no clinical differences between patients receiving celecoxib and patients without therapy. At the moment there is no evidence of the benefits of any particular NSAIDs in PsA. Also, we don't know whether the manifestations of psoriasis become more pronounced during NSAID therapy [12].

In case of mono-/oligoarthritis, dactylitis, tenosynovitis, enthesitis of various localization, local administration of glucocorticosteroids (GCS) is carried out in the joints, in the area of the enthesitis, as well as along the tendons, avoiding direct administration of the drug to the tendon tissue. However, evidence of local GCS therapy for PsA is limited. Systemic treatment of corticosteroids is not carried out due to the high risk of worsening the course of psoriasis.

In case of NSAIDs ineffectiveness and severe peripheral arthritis it is necessary to prescribe basic anti-inflammatory drugs (DMARDs, disease-modifying antirheumatic drugs, DMARD). Methotrexate is the most common drug, which has a positive effect on skin and joint component of the disease. Leflunomide also showed its effectiveness in the treatment of arthritis and skin symptoms. Sulfasalazine has a positive effect on joint symptoms but is ineffective against skin damage. On the contrary, cyclosporin A contributes to the rapid improvement of the skin condition, but is less effective in musculoskeletal symptoms; as a result, this drug is preferred for moderately active PsA in combination with common forms of psoriasis, pustular psoriasis and erythroderma among

them. Evaluation of the effectiveness of DMARDs is carried out 3 and 6 months after the initiation of therapy. In randomized clinical trials, the ability of DMARDs to influence the manifestations of dactylitis, enthesitis, and spondylitis, as well as delay X-ray progression has not been proven [12; 15].

If the DMARDs are not effective in patients with PsA, the targeted synthetic drugs should be prescribed. This pharmacological group includes apremilast — a representative of a new class of small molecules (blockers of signaling pathways), an inhibitor of phosphodiesterase-4. Inhibiting PDE-4 inside the cell apremilast reduces the production of TNF α , IL-12, IL-23, IL-17, IL-22 and, thus, suppresses the inflammatory process.

Genetic biologicals engineering (GIBP) used in PsA include TNF α inhibitors (infliximab, adalimumab, etanercept, golimumab), monoclonal antibodies to IL-12/23 (ustekinumab), IL-17 blockers (secukinumab, ixkizumab). Biological agents have demonstrated high efficacy in the treatment of PsA. When we choose the GIBP, we have to envisage the availability of the drug to the patient, as well as the rate of onset of the expected clinical effect. Most patients with PsA have a good response to GIBP therapy 3–6 months after the start of treatment. In some of them, the effect may be absent or insufficient, so it requires a change from one drug to another. The use of GIBP can cause the development of a secondary treatment failure, which is primarily associated with the appearance of neutralizing antibodies to the drug. In this case, a change from one GIBP to another with less immunogenicity is also required. Concomitant use of methotrexate reduces the production of neutralizing antibodies to TNF α inhibitors and increases patient adherence to this therapy [12; 42].

In patient with a high degree of PsA activity, it is necessary to supplement therapy with extracorporeal blood purification methods. The most frequent method is plasmapheresis, that can be combined with ultraviolet and laser irradiation of blood.

The important components of treatment include physiotherapy and physical therapy. Photochemotherapy or systemic PUVA therapy is considered the most active physiotherapeutic method. Magnetic therapy, transcutaneous laser therapy, cryotherapy, acupuncture, electro- and phonophoresis with a solution of dimexidum, glucocorticoids are also used. In case of gross articular deformities, leading to pronounced impairment of articular functions, endoprosthesis replacement of the joints is should be considered. Moreover, when considering drug-free PsA therapy, it should be noted hydrotherapy in regions with hydrogen sulfide and radon springs.

Conclusion

Psoriatic arthritis remains an important problem of scientific and practical medicine and requires further study. A multidisciplinary approach to diagnosis and treatment of this disease, active cooperation of dermatologists with rheumatologists, and new therapeutic options contribute to the optimal management of patients with PsA, which can influence positively on the course of arthritis, skin process, concomitant pathology, improve the quality of life, and also will improve outcomes.

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