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Predisposing Factors of the Psoriatic Disease

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ABSTRACT

The psoriasis is a chronic inflammatory immune-mediated, proliferative skin disease, that can involve the skin, nails and joints, affecting 1 to 3% of the population. The triggering factors (local trauma, drugs, infectious, psycho emotional stress, smoking), that may provoke psoriatic disease are an object of systemic and thorough studies and also include the family predisposition and immune mechanisms of the inflammatory process, leading to development of psoriatic plaques. The essential role is possessed by the genetic predisposition, followed by the immune disturbances, that can trigger a chronic inflammation, damaging the skin and joints. The final steps leading to psoriatic disease are the disturbed proliferation and differentiation of the keratinocytes. The antimicrobial peptides are acting like mediators of inflammation process. Their role is also to attract immune cells, in order to produce active cytokines. The antimicrobial peptide cathelicidin LL-37 is capable to connect the derived DNAs and RNAs in the cytosol from the damaged epithelial cells and to present them to the dendritic cells, triggering the inflammatory chain, therefore cathelicidin is a subject of further studies, aimed to found a factor, that consolidate all other triggers of the disease.

Keywords: psoriasis, cathelicidin, triggering factors

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INTRODUCTION

Psoriasis vulgaris is a genetically determinate, chronic, immune mediated, inflammatory disease affecting 1 to 3% of the population. It was established recently, that despite known joint manifestations, psoriasis is also associated with several disorders of glucose and lipid metabolism, higher cardio-vascular risk, increased risk of neoplasms and impaired life quality. According to that concept, psoriasis is accepted as a systemic disease, involving primarily skin and joints. The social effects and complications of psoriatic disease are determined by its frequency and comorbidities, as: cardio-vascular diseases; autoimmune disorders; metabolic syndrome; skin neoplasms, psychological disturbances. (1,2) More than 125 million of people of the world suffer from psoriasis and are imposed to risk of associated diseases and comorbidities. In 2008 the treatment of psoriatic patients in USA costs 11,25 billion US dollars. (3)

Manifestations of psoriasis in adults

Nowadays, the pathogenesis of psoriasis is considered as a complex multifactorial process. The essential role is possessed by the genetic predisposition, followed by the immune disturbances, that can trigger a chronic inflammation, damaging the skin and joints. Detailed genetic studies revealed the role of HLA-Cw6, known also as a PSORS1 to be a risk factor for the disease. (4–6) Despite the PSORS1, more than 41 genetic alleles could be related to the psoriasis development. The genetic diversity of the disease is still a subject of investigations. (5,7,8)

Overall, 1 to 3% of the population are affected by psoriasis, and the rule for geographic distribution is to follow the tendency of increase to the poles. In the tropical and subtropical regions of the world the burden of disease should not be underestimate and is influenced by genetic, ecologic and endemic factors typical for the area. Some authors stated, that the male gender is more affected by psoriasis, with a pick incidence between 3 and 4 decades, but others in contrast agreed to the fact of equal distribution between males and females. (5,9,10)

Griffiths C et al. divides the clinical types of psoriasis to localized and widespread. Among the localized types are: flexural psoriasis (psoriasis intertriginous), facial psoriasis (seborrheic type), scalp psoriasis, palm and soles (nonpustular) psoriasis and limbs and truncal psoriasis. (11) Among the widespread types of psoriasis are: psoriasis guttatae; generalized pustular psoriasis and psoriatic erythroderma (with or without systemic manifestations) with involvement of more than 90% of the body surface. Localized and widespread forms of psoriasis may have progressive course or stable clinical course. Depending of the thickness and size of the plaques the psoriasis may be divided to: thin plaque (≤0.75 mm) and thick (> 0.75 mm) plaque psoriasis; small (≤ 3 cm) and large plaque (>3 cm) plaque psoriasis.

According to Hensler and Christophers, there are two types of psoriasis, according to the age of onset: type 1 psoriasis, developing before 40-year age, mainly with genetic predisposition and type 2 psoriasis, with age of onset >40 years. (10,11)

Manifestations of psoriasis in children

The psoriasis is a chronic inflammatory immune-mediated, proliferative skin disease, that can involve the skin, nails and joints and affects both adults as well as children. It is accepted that in 1/3 of the patients the disease started at child age. Early onset of psoriasis is a risk factor for the development of comorbidities, as obesity, diabetes and arterial hypertension. The children suffering from psoriasis have defined predisposing factors in 6.6%; the phenomenon of Koebner is positive in 27.9% of cases. Interestingly, a lot of young patients (87.1%) report for itching at the places of plaques and this sign corresponds to the current view, that the psoriasis can be consider as a pruritic dermatosis, not only the pustular, erithrodermic and guttate forms of disease, but also the "conventional" type with plaques. (12,13) An open question is the reason for this difference in symptoms of disease, that in classic textbooks is a part of non-pruritic dermatoses. Data from recent studies also reveal other distinctions, not in agreement with the former postulates. For instance, the state that the patients with psoriatic onychopathy are generally not prone to mycotic nail infections is not already been accepted.

The presence of psoriatic arthritis in children varies, according to published studies from 1.1% to 10%. The diagnostic criteria for psoriatic arthritis, like CASPAR criteria for adults, are still disputable. (9,14) The large difference of the frequency of psoriatic arthritis can be due partly to the lack of accepted and validated classification and criteria to review the data from children. There is also clear geographic distribution of psoriasis in children, as in North India the prevalence of the disease in 6-14 year dermatological patients is 0.02%. In contrast, data from similar investigation in our Balkan region, in the North Greece assess the frequency of psoriasis of 2.6% among 940 children, aged 0-18 years, with various dermatoses. (15)

The clinical manifestations of psoriatic disease in children include: typical plaque psoriasis in 60.6% and psoriasis of the soles in 12.8% of series. Nails are affected in 31% of the children and the findings have a whole spectrum, characteristic for adult psoriatic disease. (12)

Factors, inducing psoriasis

The suggested factors, that may provoke psoriatic disease are an object of systemic and thorough studies and include the family predisposition and immune mechanisms of the inflammatory process, leading to development of psoriatic plaques. The scientific methods consist of observational studies, various experimental models, noninvasive and invasive tests

in order to evaluate and describe the complex and complicated characteristics of disease in the cellular and subcellular level.

Trauma and psoriasis

The trauma, as a factor, inducing the development of psoriatic plaques is well established and clarified in the classic textbooks as Koebner phenomenon. Heinrich Koebner (1838-1904) reported in scientific meeting in 1872 and described in 1877 the appearance of psoriatic lesions after traumatic influence in the non-affected skin in patients with psoriasis. (16) Later, Wolf Renbök established the pseudo-phenomenon or reverse Koebner phenomenon, consisting of reversible evolution of plaques after a mechanical effect. The frequency of positivity of Koebner phenomenon varies between the patients with psoriasis ranged 11 to 75%, according to the reference publication, observed population and experimental conditions. (17)Also defined as Koebner phenomenon are other recently added effects of provocation of psoriatic lesions after stimulations like burns, surgical incisions, insect's bytes, frictions, allergic and irritative reactions, X-ray exposure, local application of medications, suction pumps, acupuncture, etc.). The Koebner phenomenon (known also as isomorphic sign) had been a subject of experimental studies, because it is supposed to be a model for understanding the pathogenesis of all phases of psoriatic disease. (18)

Drug-induced psoriasis

Numerous medications, that may provoke psoriasis were described in the most of textbooks during last three decades. Among them are: beta-blockers; drug used to treat malaria; nonsteroidal anti-inflammatory drugs; lithium agents. (5) According to the relationship with induced psoriasis, therapeutic agents can be divided to: drugs with proven association with the development of the disease and drugs with significant, but not supported by large studies and finally drugs with described in sporadic manuscript, that may induce or aggravate psoriasis. (19)

Infectious factors and psoriatic disease

The viral and bacterial infections are objects of investigations both as a principal factor, directly inducing the psoriatic disease, or as agents, that could change immune reactivity and therefore to predispose the person to the disease. The role of viral infections, including Human immunodeficiency virus (HIV) is well known and evaluated previously. The analysis of health-insurance and clinic-epidemiological status of 102,070 patients in Taiwan showed, that HIV infection was an independent risk factor, as a gender, age and comorbidity for development of psoriasis (adjusted HR, 1.80; 95% CI 1.38-2.36). (20)

The bacterial infections, associated with initiation of psoriasis are mainly caused by streptococcus acute forms of guttate psoriasis in young persons. The relationship between

streptococcal tonsillopharyngitis and the debut of psoriatic disease is comparatively well studied. According to Weisenseel P.et al (2002) (21), the streptococcal infection is related to distinctive subtype of pustular psoriasis, appears in young patients up to 40-year-age, which have a family history for psoriasis, as well as with presence of HLA-Cw6, HLA-B13 or HLA-B57. (89). This pattern suggests a certain type of immune response to streptococcal antigens, that may trigger psoriatic disease. (21)

Psycho emotional disturbances and psoriasis

The psycho emotional stress is a part of factors, that may provoke or aggravate the clinical manifestations of the psoriatic disease. A high frequency of psoriasis, as well as associated with psoriasis diseases (defined by metabolic syndrome) is assessed in cohorts exposed to stress situations, like a war, disasters, continuous psychological tension. (22,23)

The psoriatic disease changes life and general appearance of affected patients. It can worsen the self-confidence of the person, with further decrease in a life quality, defined by several questionnaires for self-assessment, as the most popular in the moment Dermatology Life Quality Index (DLQI). The negative impact on quality of life of suffering from psoriasis patients often leads to alcohol or drug abuse (with tranquilents, relaxants, antidepressants) and intensive smoking. An association between the clinical severity of the symptoms and the experienced emotional discomfort is found: the spread and severity of lesions is proportional to the decrease of life quality, assessed with DLQI. (24) The study of Kurd S.et al (2010) shows that in United Kingdom every year is diagnosed and registered 10,400 depressing episodes, 7,100 cases with mood disturbances and 350 suicidal attempts in persons with psoriasis. (25) Women and young patients, particularly are more severe affected by depression, related to manifestation of psoriatic disease. Generally, women are prone to be interested in their appearance more than men, so the level of depression is probably higher. The same reason exists and describes emotional disorders in young persons, because their physical form is strictly related to the self-assessment. (26)

The investigations and discussion on psycho emotional disorders in patients with psoriasis are necessary to improve the perspectives of treatments and to lower the financial burden of therapy. A good cooperation between dermatologist and psychiatrist is a baseline of patient's management, in order to improve their quality of life.

Smoking and psoriasis

The smoking could influence the clinical course of psoriasis, as well as the severity of confounding diseases, part of metabolic syndrome. It is established that the frequency of smoking is higher between the patients with psoriasis, compared to the whole population or to the patients in dermatology clinic without psoriatic disease. (27,28)

Perspective for the treatment of psoriasis

The therapy of psoriasis corresponds to close cooperation of physicians from several specialities, due to complex and systemic pattern of disease. Particularly, dermatologist must insist on this association, because for obvious reasons the patients are firstly referred to them. The skin changes are easily recognizable part of the disease, but psoriasis can affect also joints, may be associated with disturbed lipids and carbohydrates metabolism as well as with cardio-vascular diseases. Both atherosclerotic plaques of vessels and psoriatic plaques on skin have common inflammatory pathogenesis. The association is based on the genetic code of psoriatic disease, generating the comorbidities with Th1/Th17 cytokines profile. (29,30) The treatment, that targets engaged in the pathogenesis of psoriasis interleukins has great perspective for controlling the recurrence and complications of the disease. During the studies on development of even more and more precision and specific effect of the biological agents a detail evaluation of the generation and development of psoriasis on the sub-cellular level is achieved. A modern, new approach is initiated, that incorporates the current knowledge of inflammatory and systemic pattern of psoriasis with established role of diverse spectrum of triggers, like mechanical trauma, drugs, infectious agents, smoking and emotional stress. The special attention is put on investigations of antimicrobial peptides. It is established, that concentration of antimicrobial peptides in psoriatic plaques is related to the clinical severity of the disease and is significantly decreased after the successful treatment with systemic medications. (31) The antimicrobial peptides are acting like mediators of inflammation process. Their role is also to attract immune cells, in order to produce active cytokines, like IL-6 and IL-10 and chemokines, like IL-8 (CXCL8) and CXCL10. The mentioned pro-inflammatory molecules can further attract the neutrophils and macrophages. Antimicrobial peptide cathelicidin LL-37 is an important “player” in the pathogenesis of the psoriatic disease. Its synthesis is regulated by the vitamin D, the former activates human hCAMP-gene to produce this peptide. (32) Otherwise, vitamin D is a promoter for synthesis of the cathelicidin molecule, that may initiate inflammatory sequence, eventually leading to the development of the psoriatic plaques. In the initiation of this inflammatory cascade is a human antimicrobial peptide cathelicidin LL-37, regulated by a vitamin D. The final steps leading to psoriatic disease are the disturbed proliferation and differentiation of the keratinocytes. The ability of the cathelicidin to connect the derived DNAs and RNAs in the cytosol from the damaged epithelial cells and to present them to the dendritic cells is a subject of further studies aimed to found a factor, that consolidate all other triggers of disease.

Lande R.et al (2014) even go further; using experimental in vitro and in vivo models of the T-cell activation they concluded that, antimicrobial peptide cathelicidin LL-37 is a T-cell autoantigen in psoriasis. (33) Thus, LL-37 alone, without an association with the nucleic acids from apoptotic keratinocytes, could activate the inflammatory cascade. To prove this hypothesis, further experimental and clinical studies are warranted.

The evolution of science leads to new data on immune pathogenesis of the psoriasis. The translational studies on fundamental genetic investigations, like GWAS (genome-wide association study) may further elucidate the genetic features of the disease. Several fast-acting and potent biological agents without significant side-effects are developed. Their high specificity diminishes a chance to disturb the native immune defence of the organism against pathogens that is an important risk during current therapy with anti-TNF-alpha antagonists. (34)

However, a careful monitoring of efficacy and tolerability of the investigated and new-registered biological agents is necessary. Data for analysis should be gathered from specialized referral centres. A detailed information on the genotype and phenotype features of psoriasis, studied in large cohorts of patients included in clinical trials will help to identify the individual biomarkers of the disease.

The future belongs to the development and application of the specific biological medications, as a step towards personalized medicine, based also on the genetic profile of the patient.

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