World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 4.223

ROLE OF GENETICS AND IMMUNOLOGICAL ASPECTS IN RECURRENT APTHOUS STOMATITIS

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Article Received on 15/11/2017 **Article Revised on 06/12/2017** **Article Accepted on 27/12/2017**

ABSTRACT

Recurrent apthous stomatitis (RAS) is a chronic inflammatory, ulcerative condition of the oral mucosa. The etiopathogenesis of the disease is considered to be multifactorial, but remains still not fully understood. In patients with RAS, an enhanced immunologic response occurs to some trigger factors including mechanical injury, stress or bacterial and viral antigens. Higher prevalence of apthae in relatives may also indicate the genetic background of the condition. The inheritance of some specific gene polymorphism, especially those encoding proinflammatory cytokines that plays a role in formation of apthous ulcer, may also predispose family members to RAS. The results of currently performed studies indicate that genetically mediated disturbances of the innate and acquired immunity play an important role in disease development. The aim of this paper is to emphasize on the involvement of genetics and immunological factors as one of the important but least discussed etiology of apthous.

KEYWORDS: Family History, Genetics, Immunology, Interleukins, Oral ulcers.

INTRODUCTION

Recuurent apthous stomatitis (RAS) belongs to a group of chronic, inflammatory, ulcerative diseases of the oral mucosa,[1,2] initially described by a Polish Surgeon, Johann Von Mikulicz Radecki in 1898.[1] RAS occurs worldwide although it appears most common in developed countries. Studies have reported that globally 20% of world population is affected by the condition, with prevalence as high as 66% in certain population.[3]The aetiology of RAS is not entirely clear, and apthae are therefore considered idiopathic. It may be the manifestation of group of disorders of quite different aetiology, rather than a single entity. Factors that commonly contribute to pathogensis of RAS includes stress, immunological factors, gastric disturbances (celiac disease, Crohn's disease, ulcerative colitis),[4] local traumas, hormonal stress, hereditary and genetic factors, microbial factors, food hypersensitivity,[5] drug allergy, smoking cessation[6] and hematinic deficiencies. Despite extensive investigations, the exact cause for RAS is still unknown. However, most patients who suffer from this order are usually healthy individuals.[1,3] Despite many studies trying to identify casual microorganisms, RAS does not appear to be infectious, contagious or sexually transmitted.[3]

Clinical description and Classification of RAS

Typically RAS lesions involve self-limited, painful, clearly defined shallow round or oval 1-3 mm ulcers. The pain lasts 3-4 days until formation of thick fibrinous cover or early epithelization. The second decade of life is considered as a peak period of occurrence of RAS with the first episode in childhood or in later life stages.[2,3]

"Cooke" classified RAS in to minor apthous ulcers (MiAU) that are recurrent crops of 1 to 5 punched-out ulcers usually affecting the movable or nonkeratinized oral mucosa (lips, buccal mucosa, mucobuccal and mucolabial sulci and tongue), less than 10 mm, exquisitively painful covered with grayish-white to yellow pseudomembrane with bright red erythematous halo. It tends to heal within 10-14 days without scarring. Major apthous ulcers (MjAU) are larger than 10 mm, recurrent, large chronic and usually solitary ulcers that begin as nodules, destroy deep tissue and heal with scarring lasting for weeks to several months affecting posterior mucosal surfaces along with movable oral mucosa. Herpetiform ulcers are recurrent, multiple, shallow, pinpoint ulcers that can affect any part of oral mucosa.[3,4,7] Many syndromes have been associated with RAS including MAGIC (mouth and genital ulcers with

inflamed cartilage) syndrome, FAPA (periodic fever, apthous ulcers, pharyngitis and cervical adenitis) syndrome and Sweet's syndrome.[6,8]

Stages of Recurrent Apthous Stomatitis

The stages of natural evolution of lesions of RAS are divided into the following 4 stages: premonitory, preulcerative, ulcerative, and healing. Stage 1, the premonitory stage, lasts for up to 24 hours. This stage is characterized by tingling, tense, burning, painful, raw, or hyperesthetic sensations in the absence of any clinical changes. Some patients do not report a premonitory stage. Stage 2, the preulcerative stage, lasts for 18 hours to 3 days. The painful sensation varies in intensity but is usually moderately severe. Clinically, the aphthae begin as erythematous macules or papules with slight induration. They are single or multiple, or circular or oval, depending on their location. The aphthae are surrounded by an erythematous halo and range from 2 to 20 or 40 mm in diameter. On the cheeks or lips, lesions are circular, whereas in the buccal or labial sulci or vestibule, oval lesions occur. Lesions overlying fibromuscular bands such as the frenum are exceptionally painful. Stage 3, the ulcerative stage, lasts from 1 to 16 days. Early, these lesions are usually severely painful. Clinically, the papule or macule, which had begun to erode in the second stage, enlarges and ulcerates but remains a discrete lesion. The maximum size is usually attained 4 to 6 days after the onset; following this an indolent period sets in which persists until stage 4. The aphthae are gradually covered by a gray or yellow membrane and are surrounded by a dusky, red halo. Two or 3 days later, there is an abrupt cessation of pain, leaving residual discomfort that correlates clinically with the appearance of the covering fibromembranous slough. Stage 4, the healing stage, lasts from 4 to 35 days. The lesions usually heal without scarring in 10 to 21 days. Scarring occurs most commonly with MjAU and correlates with the depth of necrosis.[3,7]

Association of Genetics and Immunological background with recurrent apthous stomatitis

The role of genetic predisposition in recurrent aphthous stomatitis was for the first time suggested by Miller *et al*. in 1977 and Ship in 1965, who assumed the autosomal recessive or multigene mode of inheritance with the modulating influence of the environment.[1] In the epidemiologic studies, the positive family history of the disease has been reported in 24% to 46% of RAS subjects.[9] The presence of aphthae in parents influences significantly the risk of RAS development and the course of the disease in their offspring. The risk of RAS in a child with both parents with aphthae reaches 90%, while in children with healthy parents it was estimated at 20%. People with a positive family history are prone to develop a more severe type of the disease with more frequent recurrences than the subjects with no history of RAS in the family. Family and twin studies confirmed the role of genetic predispositions in the development of RAS. Moreover, similarly to Behçet's syndrome, the risk of the disease occurrence is higher in monozygotic twins than in dizygotic ones.[1]

The genetic risk factors that may determine the individual susceptibility to recurrent aphthous stomatitis includes various DNA polymorphisms distributed in the human genome. A special attention should be paid to the alterations in the metabolism of cytokines, which include: interleukins (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12), inter- feron γ (IFN-γ) and tumour necrosis factor-α (TNF-α), serotonin transporter gene and endothelial nitric oxide synthase gene. Buno *et al* analysed the expression of selected genes in oral cavity in patients with RAS. The elevated concentration of mRNA corresponding with IL-2, IFN-γ and TNF-α and the decreased mRNA level corresponding with IL-10 was detected in the examined subjects with aphthae in comparison to healthy controls.[10]

Akman *et al*. observed a higher frequency of TNF-α-1031C allele, corresponding with the increased number of mononuclear cells that produce IFN-γ and TNF-α in peripheral blood of patients with Behçet's syndrome in comparison to healthy controls.[11] Different results were demonstrated by Bazrafshani *et al*., who in contrast to Akman *et al*., did not observe the increased frequency of IL-1α-889C in RAS patients when compared to the control group. Meanwhile, they demonstrated a statistically significant increment in IL-1β-511T and IL-6-174G frequencies in diseased subjects. Based on the obtained results the authors claimed that interleukin 1β, and not interleukin 1α was a cytokine that played a crucial role in the RAS etiopathogenesis. Although both cytokines manifest similar biologic activity, an unequal receptor distribution and affinity in the oral mucosa may be a very important issue in this process. In another study Bazrafshani *et al*. did not reveal any correlation between IL-10 (–592 and –1082) and IL-12 (1188) polymorphisms and the increased risk of RAS development. Possibly, the decreased basal IL-10 concentration in people with recurrent aphthae, described by Buno *et al*. and cited above, is caused by the other, not yet determined polymorphism of IL-10 gene cluster.[12]

In genetically predisposed patients, the effect of certain trigger factors initiates the cascade of proinflammatory cytokines, directed against selected regions of the oral mucosa. The microscopic observation of the aphtha region reveals a massive leukocytic infiltration, which varies depending on the disease duration and severity. In the initial phase that precedes the ulcer formation, monocytes and lymphocytes (mainly of the T type) together with single mast and plasmatic cells accumulate under the basal cell layer. In more advanced stages, polynuclear leukocytes dominates in the center of the ulcer, while on the lesion border the abundant mononuclear cell infiltration can be observed.[2]

The role of genetic factors in the etiopathogenesis of recurrent aphthae was confirmed in further studies of relatives and twins with RAS, where the positive family history of the disease was reported in 24–46 % of cases. The disease in parents significantly influences the risk of RAS and the course of the condition in their children—patients with a positive family history of RAS suffer more frequent recurrences and more severe course of the disease comparing to those with a negative RAS family history.[13] The genetic risk factors that modify the individual susceptibility to RAS include various DNA polymorphisms distributed in the human genome, especially those related with the alterations in the metabolism of interleukins (IL- 1b, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12), interferon (IFN)-c and tumor necrosis factor (TNF)-a.4 Th1 type cytokines, which include: IL-2, IL-12, IFN-c and TNF-a, determine the predisposition towards autoimmunisation, induce the cellular type response and stimulate the secretion of IgG. Th2 type cytokines, including: IL-4, IL-5, IL-10 and IL-13, manifest anti-inflammatory properties, stimulate the humoral immune response and the secretion of IgE. Strong anti-inflammatory effect is contributed also to another cytokine called transforming growth factor (TGF)-b, secreted mainly by the T-regulator lymphocytes. It was found that aphthous ulcer develops in response to the enhanced immunologic reaction against particular regions of the oral mucosa. This reaction occurs in a result of improperly initiated cascade of cytokines, which activate certain immune responses.[2]

It is has been suggested that RAS pathogenesis is modulated via a local cell-mediated immune response mechanisms that involve cytotoxic CD8+ T cells, natural killer cells, macrophages, and mast cells, as well as increased intralesional expression of TNF-a and IL-2. In addition, a number of systemic immunologic abnormalities have been found in patients with RAS including increased plasma levels of TNF-a, IL-2, IL-8, and IL-6 (produced by peripheral blood mononuclear cells) and decreased IL-10 mRNA levels, he latter suggesting a failure of the immune system to suppress inflammatory reaction to oral mucosa. IL-1b and IL-6 gene polymorphisms have been associated with increased risk for RAS development. Of note, periodic increased serum IL-6 expression (via IL-1b overproduction) is typically seen in individuals with oral mucosal ulceration within the context of hereditary autoinflammatory syndromes that include periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA), TNF receptor-associated periodic syndrome, and Familial Mediterranean Fever among many others.[6,14]

Niels Salles Willo et al conducted a prospective, cross-sectional study on 31 Brazilian patients with RAS to typify class I and II HLA molecules by matching DNA from those patients who matched the inclusion criteria and typified their HLA by PCR, and found statistically significant occurrences of HLA-A33 and HLAA-B35.[15]

Thus, the heterogeneity of RAS is beginning to be appreciated, and subpopulations are being defined which may allow a more efficacious therapeutic approach to RAS. Clinical studies purporting to demonstrate therapeutic efficacy will be difficult to conduct because of the variable duration and frequency of lesions and the pain reduction that naturally attends the covering of the ulcer by the fibromembranous slough. The evidence for an immunopathogenesis for RAS is based on clinical and pathologic observations that lend credence to the thesis. These observations are becoming better founded as the associated diseases are studied more intensively and the subpopulations of RAS sufferers are better defined. Evidence for a lymphocyte-epithelial cell inter- action that may have pathogenetic significance can be gleaned from the pathologic features of early lesions, the evidence by lymphocyte trans- formation tests, lymphocytotoxicity tests, and leukocyte migration tests for sensitization of the lymphocyte (or the target cell), and the presence of antimucosal antibodies as an indication of immunologic reaction to epithelial tissue damage. Specific immunopathologic mechanisms can be better defined by utilizing the sophisticated immunologic techniques that have been developed in recent years. Further elucidation of these mechanisms and their role in the pathogenesis of RAS may provide a more rational approach to therapy for this common disorder.3.

CONCLUSION

Conclusions from the genetic research support the thesis that the immune system's hyper-reactivity in response to some trigger factors in patients with RAS is at least partially related with a genetic predisposition of certain polymorphisms in the cytokine encoding genes implicate a higher predisposition to RAS. As the etiopathogenesis of the condition has not been clearly defined, the treatment is mainly symptomatic and not very effective. Discovering the direct etiopathogenetic factors in RAS may in future help to predict the risk of the disease occurrence and to develop the effective, causative management.

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