Review paper

Recurrent aphthous stomatitis: genetic aspects of etiology

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Abstract

Recurrent aphthous stomatitis (RAS; recurrent aphthous ulcers – RAU; canker sores) is a chronic inflammatory, ulcerative condition of the oral mucosa. Its prevalence in the general population ranges between 5% and 20%, depending on the method and group studied. 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 that may include: mechanical injury, stress or bacterial and viral antigens. Higher prevalence of aphthae in relatives may also indicate the genetic background of the condition. The inheritance of some specific gene polymorphisms, especially those encoding proinflammatory cytokines, which play a role in the formation of aphthous ulcer, may predispose family members to RAS. The purpose of this paper was to present the main clinical features of recurrent aphthous stomatitis, epidemiologic data and crucial etiopathogenetic factors with a special emphasis on genetic background of the condition.

Key words: recurrent aphthous stomatitis, genetic background, etiology.

Introduction

Recurrent aphthous stomatitis (RAS; recurrent aphthous ulcers – RAU; canker sores) belongs to a group of chronic, inflammatory, ulcerative diseases of the oral mucosa [1-4]. The condition was initially described by a superb surgeon of Polish origin, Johann von Mikulicz-Radecki, in 1898 [5]. To honor the author, a great professor and scientist, a pioneer in many surgical techniques, small aphthae are traditionally called the Mikulicz's aphthae [5, 6]. Multifactorial etiopathogenesis of RAS remains still not fully understood. The genetic background and the disturbed immunologic mechanisms of this condition have not been clearly defined so far [7-10]. In the course of RAS, a recurrent onset of single or multiple painful erosions and ulcers in various regions of the oral mucosa is observed. These eruptions are surrounded by erythematous halo, while the other regions of the oral mucosa remain unchanged. Most common locations of the lesions include the areas covered with non-keratinized oral mucosa: the lips, cheeks, floor and vestibule of the mouth, palatal arches and soft palate [2, 7, 8, 10, 11]. Severe pain, which often disturbs speaking and swallowing, may accompany the development of the lesions. The treatment of the disease is not very effective and mainly symptomatic. Aphthous ulcers occur as a result of enhanced immunologic response and the activation of pro-inflammatory cytokines' cascade, directed against the selected regions of the oral mucosa [12, 13]. Histologic observations of the oral mucosa affected by RAS revealed the presence of massive, leukocytic infiltration, which evolves with time. In the initial stage of the disease, before the ulcer is formed, monocytes, lymphocytes (mainly T type) with single mast and plasmatic cells accumulate under the basal layer. In the advanced stages, polynuclear lymphocytes dominate in the center of the ulcer, while the massive infiltrate of mononuclear cells surrounds the aphtha [14, 15]. Considering the clinical features, three main types of recurrent aphthous stomatitis can be defined: minor aphthae (Mikulicz's aphthae; MiRAS), major aphthae (Sutton's aphthae; MaRAS) and herpetiform aphthae (HeRAS) [1, 2, 16].

The most common type of RAS is the minor aphtha, which can be described as an erosion smaller than 1 cm in diameter, surrounded by erythematous halo. It heals

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with no scar formation and lasts no longer than 2 weeks. Mikulicz's aphtha on the upper lip in a female patient of the Department of Oral Mucosa Diseases, Poznan University of Medical Sciences is presented in Figure 1.

Sutton's aphthae are typical ulcers – they are observed less frequently than MiRAS, larger and extend deeper. They are very painful and may significantly disturb speaking and swallowing. Lesions heal slowly (they may last up to 1 month) and very often with scaring. Herpetiform aphthae are very small and multiple – up to 100 lesions may be observed simultaneously during one episode of the disease. In no type of aphthae, vesicles or gingivitis – typical symptoms of viral infections – can be observed [1-3, 16]. The most crucial clinical signs of aphthae are presented in Table 1.

Recurrent aphthous stomatitis may be also one of the symptoms of the Behçet's syndrome – a systemic, inflammatory disease, where, apart from oral and genital lesions, various general symptoms may occur. They include anterior or posterior uveitis, retinal vasculitis, erythema nodosum, cutaneous vasculitis and arthralgia and less commonly – dysfunction of the gastrointestinal tract, nervous system and kidneys [9, 17-20].

The occurrence of RAS varies in patients' populations depending on their ethnic origin and on the diagnostic criteria system accepted in different research centers. The occurrence of aphthae in general population ranges between 5% and 20% [2, 7-9]. In two independent North-American studies recurrent aphthous stomatitis directly during the dental examination was observed in 0.89% and in 1.03% of randomly chosen subjects, respectively [21, 22], while in the cross-sectional study in Turkey, aphthae were observed in 1.2% of the examined patients [23]. In Reichart study performed on 1997 in Germany, among 655 volunteers aged 35-44 years the frequency of the disease directly during the examination was described as 1.4%, while it reached 18.3% when the data from the patient's history were also included (RAS in the history) [24]. Similar results were observed by Gorska in a study from 1994, performed on 1537 high-school students from Warsaw, Poland. Recurrent aphthae during the examination appeared in 2% of students, while the RAS occurrence increased up to 27.3% after the inclusion of the past episodes of the disease from the history [25]. In the 10-year retrospective observations of the Department of Oral Mucosa Diseases, Poznan University of Medical Sciences, subjects with RAS accounted for 7.6% of a total number of admitted patients [26].

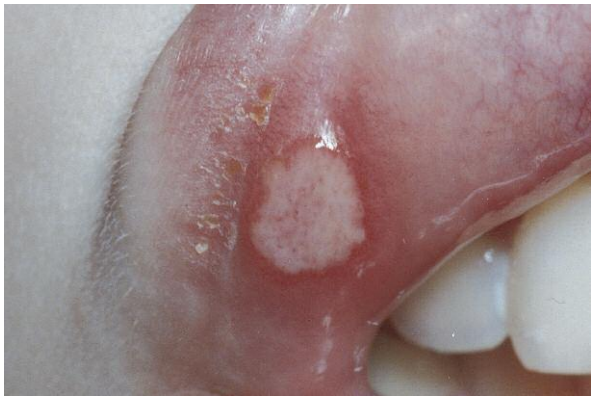

Figure 1. Mikulicz's aphtha on the upper lip in female patient of the Department of Oral Mucosa Diseases, Poznan University of Medical Sciences

Many epidemiologic studies and our own observations confirmed the higher incidence of RAS in people with a higher socio-economic status. Also females seem to be at a higher risk of the disease development in comparison to males [4, 21, 22, 26]. In the North-American population, aphthae appear 3 times more often in Caucasians than in Afro-Americans, the condition affects also more often non-smokers in comparison to smokers [21, 22]. Aphthae may appear for the first time in childhood or at later life stages. The second life decade is considered as a peak period of the RAS occurrence. The severity and frequency of the episodes vary on a case-by-case basis, however, it usually decreases with age [2, 21, 26].

Genetic background of recurrent aphthous stomatitis

The etiology of recurrent aphthous stomatitis still remains not clearly understood. The possible trigger factors include immunologic and hormonal disturbances, genetic background, infections, food allergies, vitamin and microelement deficiencies, gastrointestinal diseases (celiac disease, Crohn's disease, ulcerative colitis), mechanical injuries and stress [7, 8, 17, 27, 28].

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

Table 1. Clinical features of aphthae depending on type

	Feature of the lesion					
	Size [mm]	Depth	Scar	Number	Duration [days]	Frequency in comparison to other types [%]
Minor aphthae (MiRAS)	5-10	Shallow	No	< 10	10-14	75-90
Major aphthae (MaRAS)	> 10	Deep	Yes	< 10	> 14	10-15
Herpetiform aphthae (HeRAS)	< 5	Shallow	No	> 10	10-14	5-10

autosomal recessive or multigene mode of inheritance with the modulating influence of the environment [29, 30].

In the epidemiologic studies, the positive family history of the disease has been reported in 24% to 46% of RAS subjects [1, 7]. According to Safadi, a positive family history was found in 66.4% of the examined 684 Jordanian patients with RAS [31]. 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% [8]. 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 [29, 30]. Family and twin studies confirmed the role of genetic predispositions in the development of RAS [31, 32]. Moreover, similarly to Behçet's syndrome, the risk of the disease occurrence is higher in monozygotic twins than in dizygotic ones [31, 32]. An interesting case of monozygotic twins with RAS was presented by Kobayashi *et al*., while Yilmaz and Cimen described the disease occurrence in 4 members of the same family [19, 32].

The genetic risk factors which may determine the individual susceptibility to recurrent aphthous stomatitis include 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), interferon γ (IFN-γ) and tumour necrosis factor-α (TNF-α) [12, 35-38], serotonin transporter gene and endothelial nitric oxide synthase gene [39-41]. The analysis of the expression of selected genes in the oral cavity in patients with RAS was performed by Buño *et al*. 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 [35]. The results of the observations on the role of DNA polymorphisms in RAS and Behçet's disease development using the genetic associations presented in Table 2 still remains ambiguous and equivocal.

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 [12]. In Guimarães *et al*.'s study, a correlation between the TNF-α gene polymorphism and the increased RAS risk was observed, which remains consistent with previously cited Buño *et al*.'s results [35, 36]. The elevated concentration of the described proinflammatory cytokines supports the thesis that the Th1-type cellular immune response plays a crucial role in the development of RAS and Behçet's syndrome. In their further studies Guimarães *et al*. observed also a correlation between one of the IL-1β gene polymorphisms, related with the enhanced IL-1β production, and the risk of RAS development [36]. That sort of association was not detected for IL-6 and IL-10 genes' polymorphisms [37]. Also Akman *et al*. investigated the role of particular IL-1α and IL-1β encoding gene polymorphisms in the etiopathogenesis of RAS and Behçet's syndrome. A significantly increased frequency of IL-1α- 889C allele was found in both examined groups when compared to healthy controls. Moreover, the IL-1β+3962T and IL-1β-511T alleles were detected more often in RAS patients than in the other study groups [38].

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 which 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 [42]. 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 [43]. Possibly, the decreased basal IL-10 concentration in people with recurrent aphthae, described by Buño *et al*. and cited above, is caused by the other, not yet determined polymorphism of IL-10 gene cluster [35].

Borra *et al*. found the increased expression of the Th1 gene cluster in comparison to the Th2 cluster in patients with RAS, which may confirm the thesis that the Th1-mediated immune response is the key mechanism related with the development of the disease. The increased activity of Th1-type immune response was also described in other autoimmune-mediated diseases, including Crohn's disease, celiac disease and PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical lymphadenopathy) syndrome [44].

The serotoninergic system participates in the development of some psycho-somatic conditions and disorders, including stress and depression. Taking into consideration the suggested influence of some psychogenic factors on the course and severity of the recurrent aphthous stomatitis, Victoria *et al*. decided to determine whether the polymorphism in the 5-HTTLPR gene promoter region, observed in subjects with depression, was also more frequent in RAS patients than in healthy controls. In RAS patients, an increased frequency of S allele was found, which corresponds with the decreased ability of serotonin expression and uptake. Such a correlation may help to understand the increased occurrence of recurrent aphthae in people with psycho-somatic disturbances [39].

Some reports suggest also the role of endothelial nitric oxide synthase (eNOS) gene polymorphisms in the development of RAS and Behçet's syndrome. Nitric oxide medi-

Table 2. The role of DNA polymorphisms in development of RAS and Behçet's syndrome

Gene	DNA polymorphism	Number of examined subjects (*n*)	Association present (+), not present (–)	Authors
TNF-α	–1031 T>C –308 G>A	Behçet's syndrome (99), Turkey	+	Akman *et al.*, 2006 [12]
		RAS (66), Brazil	+	Guimarães *et al.*, 2007 [36]
IL-1α	–889C C>T	Behçet's syndrome (57), Turkey	+	Akman *et al.*, 2007 [38]
		RAS (41), Turkey	+	Akman *et al.*, 2007 [38]
		RAS (91), UK	–	Bazrafshani *et al.*, 2002 [42]
	+4845	RAS (91), UK	–	Bazrafshani *et al.*, 2002 [42]
IL-1β	+3954 C>T	RAS (66), Brazil	+	Guimarães *et al.*, 2007 [36]
		RAS (91), UK	–	Bazrafshani *et al.*, 2002 [42]
	+3962 T>C	RAS (41), Turkey	+	Akman *et al.*, 2007 [38]
	–511G	RAS (91), UK	+	Bazrafshani *et al.*, 2002 [42]
IL-6	–174 G>C	RAS (66), Brazil	–	Guimarães *et al.*, 2007 [36]
		RAS (91), UK	+	Bazrafshani *et al.*, 2002 [42]
IL-10	–1082 G>A	RAS (66), Brazil	–	Guimarães *et al.*, 2007 [36]
	–592	RAS (100), UK	–	Bazrafshani *et al.*, 2003 [43]
	–1082	RAS (100), UK	–	Bazrafshani *et al.*, 2003 [43]
IL-12	+1188	RAS (100), UK	–	Bazrafshani *et al.*, 2003 [43]
5-HTTLPR	5-HTTLPR S>L	RAS (69), Brazil	+	Victoria *et al.*, 2005 [39]
eNOS	–786 T>C	RAS (91), UK	–	Karasneh *et al.*, 2009 [47]
		Behçet's syndrome (193), Turkey	+	Karasneh *et al.*, 2005 [20]
	+894 G>T	RAS (91), UK	–	Karasneh *et al.*, 2009 [47]
		Behçet's syndrome (193), Turkey	+	Karasneh *et al.*, 2005 [20]
		Behçet's syndrome (132), Turkey	+	Oksel *et al.*, 2006 [45]
		Behçet's syndrome (73), Italy	+	Salvarani *et al.*, 2002 [40]
		Behçet's syndrome (65), Italy	+	Kim *et al.*, 2003 [41]
	VNTR	RAS (91), UK	–	Karasneh *et al.*, 2009 [47]
		Behçet's syndrome (193), Turkey	–	Karasneh *et al.*, 2005 [20]

Table 3. Selected HLA frequency in patients with recurrent aphthous stomatitis (RAS), Behçet's disease (BD) and generally healthy (C)

Number of patients (*n*)	HLA	Allele frequency [%]		Significance level (*p*)	Authors
		Study group	Control group		
RAS (31) C (961) Brazil	A33 B35 B81	19.4* 48.4* 6.5*	6.5* 21.2* 0.8*	0.016* < 0.001* 0.036*	Wilhelmsen *et al.*, 2009 [48]
RAS (101) C (97) Turkey	B51	45.5	46.3	0.905	Özdemir *et al.*, 2009 [49]
BD (100) C (97) Turkey		63.0*	46.3*	0.019*	
BD (32) C (310) China	DRw8	37.5*	9.7*	< 0.0001*	Sun *et al.*, 2001 [18]
RAS (20) Finland	B12	25.0	–	–	Malmström *et al.*, 1983 [51]
RAS (20) C (100) UK		45.0*	22.0*	< 0.05*	Lehner *et al.*, 1982 [52]
BD (60) C (100) UK		46.6*	22.0*	< 0.01*	
RAS (17) C (70) UK	DR7	11.8	17.1	NS	
BD (51) C (70) UK		39.2*	17.1*	< 0.01*	
RAS (26) C (84) Italy	DR7 B5	61.5* 0*	21.4* 27.3*	< 0.0025* < 0.04*	Gallina *et al.*, 1985 [53]

**Statistically significant differences*

ates various biological reactions. It participates in the conversion of GTP into cGMP – a compound required in smooth muscle relaxation and in vasodilatation, it inhibits blood platelets and monocytes adhesion [45, 46]. Oksel *et al*. and Karasneh *et al*. demonstrated an increased frequency of Glu298Asp eNOS gene polymorphism in Turkish patients with Behçet's syndrome when compared to healthy controls [20, 45]. Similar results were presented also by Salvarani *et al*. in Italy and by Kim *et al*. in Korea [40, 41]. Meanwhile, Karasneh *et al*. did not demonstrate the correlation between the discussed eNOS gene polymorphism and aphthae occurrence in the Turkish population, which may suggest that those two diseases have unrelated genetic background [20, 47].

Apart from the analysis of particular proinflammatory cytokines encoding gene polymorphisms in the development of RAS, many researches were also focused on the evaluation of the role of some human histocompatibility antigens in the disease etiopathogenesis. The basic function of the main histocompatibility complex (MHC) is to present antigen to the T lymphocytes. In order to be recognized by T cell and to stimulate the cellular immune response, an antigen needs to be conjugated with a presenting cell, therefore the frequency of particular HLA molecule types may significantly influence the immune response severity and character also in patients with recurrent aphthae. The results of the international studies of MHC in RAS patients remain inconsistent, which may suggest the ethnic background of the condition, but also may be a consequence of unequal patients' qualification criteria and different methodology used in various studies. Table 3 illustrates correlations between the selected HLA allele and the increased risk of RAS and Behçet's syndrome development.

In patients with recurrent aphthous stomatitis, a higher incidence of HLA-A33, HLA-B35 and HLA-B81 [48], HLA-B12 [45, 51, 52], HLA-DR7 and HLA DR5 [53, 54] and lower incidence of HLA-B5 and HLA-DR4 [53, 54] was observed when compared to healthy controls. In patients with Behçet's syndrome, HLA-B51 [44] and HLA-DRw8 [20] were detected more often than in RAS patients and in healthy controls. Moreover, HLA-B12 was found more frequently in subjects with cutaneous and arthral type of Behçet's syndrome than in healthy people [52]. Albanidou-Farmaki *et al*. tried to determine the influence of the inheritance mode of some particular HLA haplotypes on familial RAS occurrence. They failed to demonstrate the correlation between the individual HLA alleles and RAS in the examined subjects, although it was proved that RAS susceptibility was inherited in concordance with HLA haplotypes [55].

Summary

The results of the cited studies confirm that the genetic factors play a crucial role in the etiopathogenesis of recurrent aphthous stomatitis. Some of the detected gene polymorphisms (proinflammatory cytokine encoding genes) explain the increased susceptibility to develop enhanced immune response to some antigens in their carriers, which leads to the formation of aphthous erosions and ulcers. A correlation between the serotonin transcriptase encoding gene polymorphisms and RAS also seem to be very interesting and helps to understand the role of stress and psychogenic stimuli as the trigger factors in recurrent aphthous stomatitis. Variations in the endothelial nitric oxide synthase gene expression was found in studies on subjects with circulatory system diseases, e.g. with hypertension, stroke and heart infarction. Polymorphisms in eNOS gene detected in some studies in patients with Beh et's syndrome may indicate that the endothelial disorders and thromboembolic complications also play a role in the etiopathogenesis of this disease, although so far in none of the studies the correlation between the eNOS gene polymorphism and recurrent aphthous stomatitis was found. More profound research on a large sample of RAS patients is definitely required also in this area.

Recurrent aphthous stomatitis remains a challenge for the clinicians of various specialties. Due to unclear etiopathogenesis of the disease, the treatment is mainly symptomatic, not very effective and does not prevent the recurrences. Defining the RAS etiologic factors also in genetic studies may in future help to determine the risk of the disease onset and to develop the effective treatment. Inconsistent international genetic studies' results and the lack of that type of studies in the Polish population suggest the necessity of such an analysis in Poland.

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