Recurrent aphthous stomatitis: investigation of possible etiologic factors

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Abstract

Objective: To investigate the association of serum vitamin B\textsubscript{12}, folic acid, iron, calcium, magnesium, and phosphorus levels as well as family history and cigarette smoking with recurrent aphthous stomatitis (RAS).

Methods: Thirty-four patients with RAS and 32 control subjects were included in this controlled prospective screening study. Both groups received a questionnaire, and serum screening tests were performed. The collected data were analyzed using \( \chi^2 \) test and binary logistic regression analysis.

Results: Family history was found to be the most significant predisposing factor for RAS among the investigated ones. Regarding the serum tests, only vitamin B\textsubscript{12} was found to have significant correlation with RAS. Patients with vitamin B\textsubscript{12} deficiency, positive family history, and nonsmoking status have been found to have the highest risk for having RAS.

Conclusions: RAS is a multifactorial disease. Positive family history, vitamin B\textsubscript{12} deficiency, and nonsmoking status are among the important predisposing factors.

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1. Introduction

Recurrent aphthous stomatitis (RAS) is one of the most common oral diseases worldwide. The prevalence ranges from 2\% to 66\% in different populations [1,2]. RAS is a disease characterized by recurring ulcers in the oral mucosa without any sign of other diseases. Aphthous ulcers are painful and shallow ulcers, usually covered with a grayish white pseudomembrane that is surrounded by an erythematous margin. Recurrent aphthous ulcers arise on nonkeratinized oral mucosa such as lateral margins of the tongue and buccal and labial mucosa.

RAS is classified according to clinical characteristics of the ulcers as minor ulcers, major ulcers, and herpetiform ulcers. The most common type is RAS with minor ulcers and comprises approximately 80\% of the cases. In this type, the ulcers are less than 1 cm in diameter, round, clearly defined, and painful ulcers and heal within 10 to 14 days without scarring. In major RAS (Sutton disease), painful lesions are more than 1 cm in diameter, may last for weeks, and usually heal with scar formation. The herpetiform aphthous stomatitis, the least common type, presents itself as multiple clusters of pinpoint lesions that may give rise to large irregular ulcers lasting 7 to 10 days [3].

Although there are many factors accused in the etiology of RAS, we still need to seek for more accurate and strong statements regarding the etiology because of the contradictory literature and for patients’ benefit.

In this prospective study, we aimed to investigate possible roles of predisposing factors for RAS. These included family history, cigarette smoking, and serum tests. Serum tests included vitamin B\textsubscript{12}, folic acid, iron (Fe\textsuperscript{+2}), Fe\textsuperscript{+2} saturation levels, total iron-binding capacity (TIBC), ferritin, calcium (Ca\textsuperscript{+2}), magnesium (Mg\textsuperscript{+2}), and phosphorus (P) levels. Complete blood count with hemoglobin and hematocrit levels was also performed.

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2. Materials and methods

Thirty-four patients with a diagnosis of RAS with recurrent minor ulcers were included in this study. The control group was composed of 32 healthy volunteers without oral aphthae history and undergoing preoperative blood tests for septoplasty operation with a diagnosis of nasal septal deviation. After obtaining an informed consent (according to principles outlined in the Declaration of Helsinki), both groups were given a questionnaire about the disease. Questionnaire included age, sex, smoking status, family history, and systemic disorders. Both groups were acknowledged about the disease and asked if any of their family members had the symptoms. In addition, the patient group was asked about the frequency and duration of the disease and the ulcers. Family history was accepted positive in case of the presence of the disease in at least one first-degree relative. Patients who smoked more than 1 cigarette on regular daily basis were accepted as active smokers.

In addition to otolaryngological examination, dermatologic and ophthalmologic examinations were made for exclusion purposes. Pathergy test and antinuclear antibody tests were performed to rule out possible coexisting systemic disease; patients with Behc¸et disease or gastrointestinal symptoms were not included in the study.

Complete blood count and the levels of vitamin B12, folic acid, Ca++, Mg++, P, Fe++, Fe++ saturation level, TIBC, and ferritin were investigated. The tests were performed in serum collected after an overnight fast.

The results were evaluated using $\chi^2$ test and binary logistic regression analysis.

3. Results

Patient group was composed of 34 patients with 17 men and 17 women, and the control group was composed of 32 individuals with 13 men and 19 women. Age ranged between 10 and 66 years with a mean of 36.7 years in the patient group and between 11 and 74 years in the control group with a mean of 34.3 years. We did not show any significant influence of age or sex on RAS (binary logistic regression analysis, $P > .05$).

The most striking result was the influence of family history on RAS. The rates of positive family history in patient and control group were 54.2% and 9%, respectively. In the presence of family history, we found a statistically significant risk for having RAS ($\chi^2 = 16.8, P < .001$).

As far as smoking was considered, 8 (20%) of 34 patients were smokers in the patient group compared with 14 smokers (43.7%) in the control group; $\chi^2$ test revealed a borderline significance level ($\chi^2 = 3.73, P = .052$) concerning RAS and smoking status.

When considered together, the influence of family history, vitamin B12 deficiency, and cigarette smoking on RAS probability was calculated to be statistically significant using binary logistic regression analysis ($P < .001$). This finding was summarized in Fig. 1. The non-smoking patients with positive family history and vitamin B12 deficiency were found to have the grater risk for having RAS.

Folic acid, Ca++, Mg++, P, Fe++, Fe++ saturation level, TIBC, ferritin, hemoglobin, and hematocrit levels were found to have some degree of correlation with RAS, which

![Fig. 1. Summary of the effect of studied predisposing factors for RAS in relation with vitamin B12. As clearly seen, patients with low vitamin B12 level, positive family history, and nonsmoking status had the highest risk for having RAS.](image-url)
were not statistically significant (binary logistic regression analysis, \( P > .05 \)). Results of these evaluations were summarized in Table 1.

We studied the frequency and duration of the aphthous lesions and whether they were related to family history, vitamin B\(_{12}\) deficiency, or cigarette smoking. We could not show any significant relation between these parameters and RAS (binary logistic regression analysis \( P > .05 \)).

4. Discussion

Morbidity is quite high in RAS; quality of life of RAS patients is affected in that the recurrent and painful intraoral mucosal lesions and increased salivaion give discomfort while eating, drinking, and speaking. Because the exact etiology of RAS is still unknown, most patients with RAS are usually given some medications to relieve their pain only, instead of an etiologic screening and curative treatment.

RAS may be associated with several diseases such as Behcet disease, gluten-sensitive enteropathy, pernicious anemia, cyclic neutropenia, inflammatory bowel disease, and FAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis). Despite extensive investigations, studies have failed to find the exact etiology and pathophysiology of RAS. Heredity, hematonic deficiencies, immune dysregulation, some foods, drugs, stress, local trauma, hormonal disturbances, infections, smoking habits, and poor oral hygiene are proposed factors [4-8].

A high incidence of aphthous stomatitis was reported by Miller et al. [8] in identical twins compared with nonidentical twins (90% vs <60%). Miller et al. [9], in their study, indicated an increased susceptibility to RAS among children of RAS-positive parents. Shohat-Zabarski [10] reported that more than 42% of RAS patients had first-degree relatives with RAS. In our series, we found positive family history in 54.2% of the patients. Whether this high degree of association is because of a direct genetic influence or similar social status, traditions, or habits of the family members is not known yet. Among the predisposing factors we could study, we found family history to have the strongest correlation with RAS (\( P < .001 \)).

Serum vitamin status is another proposed predisposing factor for RAS, and it has been shown that up to 20% of RAS patients may have at least one hematonic deficiency [5,11-13]. In our study, we found 12 (35.2%) of 34 patients to be deficient in vitamin B\(_{12}\) according to our laboratory’s normal range comparing with none in the control group (\( P < .05 \)). Palopoli and Waxman [12] proposed that the diseases commonly associated with RAS do this through diminishing intestinal absorption of vitamin B\(_{12}\), resulting in vitamin B\(_{12}\) deficiency. The question is how vitamin B\(_{12}\) deficiency causes RAS. So far, this issue remained unclear, but the dramatic response to vitamin B\(_{12}\) replacement therapy and higher incidence of RAS in cases that have vitamin B\(_{12}\) deficiency suggest a direct role of this vitamin on the pathogenesis of RAS [6,11,14,15].

Cigarette smoking is known to have a protective effect on RAS. This protective effect of smoking may be related to the increased keratinization of the oral mucosa in smokers. Keratin layer may possibly act as a mechanical and chemical barrier of the oral mucosa against minor traumas or microbial agents [16]. Recurrent ulcerations were prevented with the use of 8-mg 7-day Nicorette tablets [17]. In our study, we found 20% active smokers (7 patients) in the RAS group versus 43.7% (14 patients) in the control group (\( P = .052 \)). This finding, although not statistically significant enough, is concurrent with the literature [16,18]. The data about the protective effect of tobacco are limited and need further studies.

Iron deficiency is another proposed predisposing factor for RAS [5]. Porter et al. [19], in their study, have shown a significantly lower serum ferritin level (11.6%) in RAS patients compared with control group (4.9%). However, Wray et al. [15] reported Fe\(^{++}\) deficiency to be very rare among patients with recurrent ulcerations. They also claimed that RAS patients with Fe\(^{++}\) deficiency respond in a longer period to replacement therapy with Fe\(^{++}\), compared with replacement with vitamin B\(_{12}\) and folic acid which they attributed to the difficulty in reconstituting body stores of Fe\(^{++}\). Others failed to demonstrate an association of Fe\(^{++}\) deficiency with RAS [6,20]. Results of our study did not show a direct association of the disease neither with serum Fe\(^{++}\), Fe\(^{--}\) saturation level, ferritin, nor hemoglobin and hematocrit levels, but with TIBC, although statistically not significant (\( P = .074 \)).

The association of RAS with the predisposing factors found to be significant was summarized in Fig. 1. The highest occurrence of RAS was found to be in nonsmoking patients with a positive family history and vitamin B\(_{12}\) deficiency. Obviously, among these 3 factors, only vitamin B\(_{12}\) deficiency might be overcome by replacement therapy as we could not change the family history or encourage patients to smoke.

Previous studies proposed possible etiologic roles of folic acid and minerals [5,15]. However, there are studies that deny such a relationship between RAS and folic acid [20]. Our attempts to find such an association between serum folic acid, Ca\(^{++}\), Mg\(^{++}\), or P levels with RAS have failed. This may be attributed to regional differences of our patients, but we think that this issue should be studied further with a larger multicenter series.

Taking all these findings into consideration, we can clearly state that RAS is a multifactorial disease, and we can conclude that positive family history, vitamin B\(_{12}\) deficiency, and smoking status are among the studied possible etiologic factors.

References


