

# Risk Factors Associated with Minor Recurrent Aphthous Ulcers in Adult Population of Semnan City in Iran: An Epidemiological Study

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## ABSTRACT

**Background:** Recurrent aphthous stomatitis (RAS) is a common oral mucosal disease, characterized by painful ulcerations. Several hereditary, nutritional, infectious and psychological factors have been reported that are associated with RAS. The aim of this epidemiological study was to evaluate the clinical characteristics and some possible related risk factors in patients with minor RAS in local population of Semnan in Iran.

**Material and Methods:** Thirty-eight patients with minor RAS and forty-five control subjects were included in this study. For all participants a questionnaire was completed, and complete blood count was performed. The RAS patients were visited and interviewed during an active episode in clinic of infectious diseases of Fatemeh Hospital of Semnan University of Medical Science.

**Results:** Significant correlation was observed between diagnosis of minor RAS (mRAS) and positive family history ( $P < 0.001$ ). Disease was more common in those above the age of 30 years (52.3%). There was not

statistically significant association between minor RAS and smoking ( $P = 0.683$ ) and anemia ( $P = 0.405$ ). Sublingual and lateral margins of the tongue were the commonest sites of ulcerations (66.7%). In 22.2% of female patients attacks were associated with menstruation.

**Conclusion:** RAS is a multifactorial disease. Positive family history is among the important predisposing factors. Anemia and smoking status may be less important predisposing factors in patients with mRAS.

**Keywords:** Adults, Clinical feature, Minor ulcers, Recurrent aphthous ulcers

## INTRODUCTION

Recurrent aphthous stomatitis (RAS) is an inflammatory condition of unknown etiology characterized by painful recurrent, solitary or multiple ulcerations of the oral mucosa<sup>1</sup>. It is one of the most common oral diseases worldwide. The prevalence ranges from 2% to 66% in different populations.<sup>2</sup>

The ulcers usually appear first in childhood. In the adult population, the first ulceration appears before the age of 30 years in 60–85% of cases.<sup>3</sup> The lesions recur at varying frequencies from every few years to almost constantly.<sup>4</sup> Aphthous ulcers are painful and shallow ulcers, usually covered with a grayish white pseudomembrane that is surrounded by an erythematous margin. Ulcers arise on nonkeratinized oral mucosa such as lateral margins of the tongue and buccal and labial mucosa.<sup>5</sup>

Aphthous ulcers are classified on the basis of ulcer size into minor, major or herpetiform. Minor ulcer is the most common, and affects about 80% of patients with RAS. These ulcers are small (up to 1 cm in diameter), shallow, painful, well-circumscribed, and round-shaped. These affect labial and buccal mucosa and floor of the mouth or the ventral surface of the tongue and heal spontaneously in 10 to 14 days. Much less common type is major aphthous ulcers. Major ulcers are larger than 1 cm in diameter, last several weeks, and can affect the dorsum of the tongue and the hard palate. The herpetiform aphthous stomatitis, the least common type, presents itself



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as multiple clusters of pinpoint lesions that may give rise to large irregular ulcers lasting 7 to 10 days.<sup>6</sup>

Studies suggest that RAS is more common in women, in people under the age of 40 years, in whites, in nonsmokers, and in people of high socioeconomic status.<sup>7</sup> The etiology of recurrent aphthous ulceration is not fully understood. Many factors have been implicated in the promotion and/or exacerbation of RAS including oral trauma, anxiety or stress, microorganism, the cessation of smoking, food hypersensitivity, and hormonal changes. Also attacks may be associated with vitamin and trace element deficiency.<sup>3</sup> Some conditions including genetic predisposition, immune dysregulation, and family history might play a role in RAS in some patients.<sup>8</sup> The diagnosis of RAS rests mainly on two features: a history of recurrent ulcers and the presence of the typical solitary or multiple round or ovoid ulcers on labial mucosa on clinical examination.<sup>9</sup>

Although there are many factors accused in the etiology of RAS, there is still need to seek for more accurate and strong statements regarding the etiology because of the contradictory literature. The aim of this epidemiological study was to investigate demographic feature, diverse clinical characteristics and possible roles of some predisposing factors in patients' with minor RAS in local population of Semnan city of Iran.

**MATERIALS AND METHODS**


In the present study thirty eight adult patients (18 years) with a diagnosis of minor RAS were included. They attended the clinics of the university affiliated hospitals of Semnan, Iran between 2007 and 2009. Forty-five healthy age- and gender-matched individuals without clinical evidence and history of recurrent aphthosis living in the same geographical area enrolled as the control group. Controls were selected from subjects receiving routine preventive health examinations at the same hospitals during the same period. The study was approved by Research Committee of Semnan University of Medical Science.

The following exclusion criteria were considered: history of anemia, use of any pharmacological therapies and / or drugs containing iron or vitamins, and any systemic disorders.

After obtaining a written informed consent from both the groups, a questionnaire for each individual was completed (Table 1). The RAS patients were visited and interviewed during an active RAS episode in the clinic of Infectious diseases of Fatemieh Hospital of Semnan university of Medical Science. Questionnaire included questions about the age, sex, duration of disease, duration of each attack, interval between attacks, size and number of ulcers, location of ulcers, smoking status and family history.

Full oral examination was done for all patients by a single

**Table 1: Patient questionnaire for the study.**



**Semnan University of Medical Science**

**Aphthous ulcer questionnaire**

**Patient code:** \_\_\_\_\_

**Age:** \_\_\_\_\_ **Gender:** \_\_\_\_\_

**Age of first attack:** \_\_\_\_\_

**Attack interval:** <2 weeks       2-4 weeks       >4 weeks

**Duration of attack:** <1 weeks       1-2 weeks       >2 weeks

**Number of ulcers:** <2       2-5       >5

**Size of ulcers:** <5mm       ?5mm

**Location of ulcers:** \_\_\_\_\_

**Family history:** Positive       Negative

**Smoke:** No       Yes

**Number**      **Duration**

**Association with menstruation:** Yes       No

**Lab test:**

WBC: \_\_\_\_\_ platelet: \_\_\_\_\_

Hemoglobin: \_\_\_\_\_ Hematocrit: \_\_\_\_\_

MCV: \_\_\_\_\_ MCHC: \_\_\_\_\_ MCH: \_\_\_\_\_

clinician. Diagnosis of minor RAS was based on clinical criteria found at the time of examination.<sup>3</sup> Family history was considered positive when recurrent aphthosis was present in at least one first-degree relative. Patients who smoked more than 5 cigarettes per day for at least 3 months were accepted as active smokers. For both the groups venous blood samples were taken and complete blood count including hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular hemoglobin (MCH) were determined. After inspecting, all patients were treated for symptomatically to facilitate healing. Data were analyzed by Kolmogorov-Smirnov, t test and Chi Square test using SPSS 18.0. P-values of less than 0.05 were considered statistically significant.

**RESULTS**

Patient group was composed of 38 (20 male and 18 female), and the control group was composed of 45 (24 male and 21 female) individuals. Mean (±SD) age of patients was 37.1(±14.8) years and control 40.4(±17.4) years. Gender distribution (P=0.949) and mean age (P=0.346) in two groups

were not significantly different. Mean ( $\pm$  SD) age of onset of disease was  $30.8 \pm 14.6$  years. 52.6% of patients reported that they experienced the first attack of RAS in age above thirty. Others characteristics of patients are shown in table 2.

Family history was positive in 50% of cases and 8.3% of control group. In the presence of family history, we found a statistically significant risk for having RAS ( $P < 0.001$ ). According to our laboratory's normal range, 10.5% of patients and 4.4% of control had anemia that all were microcytic. Also anemia was more common in patients than control group, but this difference was not statistically significant ( $P=0.405$ ). Leukocyte and platelet number was normal in both the groups. Two patients (5.3%) and four controls (8.9%) were smoker. Analysis showed no significant relationship concerning minor RAS and smoking status ( $P=0.683$ ). Sublingual and lateral margins of the tongue were the commonest sites of ulcerations (66.7%). Other locations of ulcer were as follow; labial mucosa (55.7%), buccal mucosa (44.4%) and gingivae (22.2%). In 22.2% of female patients attacks were associated with menstruation.

**Table 2: Clinical characteristics of patients with minor recurrent aphthous stomatitis.**

Variable	N (%)	P
Age		
<30 years	14(36.8)	0.346
$\geq 30$ years	24(63.2)	
Gender		
Male	20(52.6)	0.949
Female	18(57.4)	
Duration of Disease		
<5 years	17(44.7)	
5-10 years	13(34.2)	
>10 years	8(21.1)	
Attack interval		
<2 weeks	13(34.2)	
2-4 weeks	9(23.7)	
>4 weeks	16(42.1)	
Duration of attack		
<1 weeks	15(39.5)	
1-2 weeks	20(52.6)	
>2 weeks	3(7.9)	
Number of ulcers		
<2	12(35.7)	
2-5	16(45.7)	
>5	10(28.6)	
Size of ulcers		
<5mm	27(71.1)	
$\geq 5$ mm	11(28.9)	

## DISCUSSION

RAS is quite common condition affecting the oral cavity. Morbidity is quite high in RAS. It interferes with normal life

activities by affecting eating and swallowing of sufferers. Despite extensive investigations, studies have failed to find the exact etiology and pathophysiology of RAS.<sup>10</sup>

This disease can affect people of any age group. In about 80% of cases, the first episodes appear before the age of thirty and in particular during childhood.<sup>2,3</sup> In contrast, most of our patients were older than thirty (52.3%). Similarly Complito *et al.*<sup>11</sup> in their study on adult patients reported that RAS was more common under the age of 38.5 years.

Most studies showed that family history might play a role in the RAS. Patients with a positive family history of RAS develop oral ulcers at an earlier age and have more severe symptoms than individuals with no family history of RAS.<sup>3</sup> In our study family history was positive in 50% of the patients and have the strongest correlation with mRAS ( $P < 0.001$ ), as suggested by previous studies. In agreement with our results, in the study done by Koybasi *et al.*,<sup>12</sup> the rate of positive family history in patients and control group were 54.2% and 9% with significant difference. Shohat-Zabarski<sup>13</sup> reported that more than 42% of RAS patients had first-degree relatives with RAS. 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.

Many studies suggest that RAS is more common in women. Also there is a female predisposition in affected children.<sup>6,7</sup> In our study, however, both the genders were affected almost equally. In accordance with our finding two other studies did not show any significant influence of sex on RAS.<sup>12, 14</sup> In a study in USA, males were at greater risk for RAS.<sup>15</sup> In another study, patients with a clinical diagnosis of RAS were significantly more often males ( $P = 0.001$ ).<sup>16</sup>

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.<sup>3</sup> Components of tobacco that is systemically absorbed (such as nicotine) might be responsible for this protection.<sup>17</sup> The result of present study showed 5.3% active smokers in patients versus 8.9% in the control group. Although a smaller number of patients were smoker than control but, there was not statistically significant relationship between smoking and minor RAS ( $P = 0.386$ ). Similarly, in study on 22 patients and 29 control, they found a smaller number of smokers (9.4% vs. 27.6%) in the test group than controls but, without statistically significant differences ( $P = 0.13$ ).<sup>11</sup> In another study on 34 patients with minor RAS, eight (20%) patients were smokers compared with 14 smokers (43.7%) in the control group; with no significance difference ( $P = 0.052$ ).<sup>12</sup> In contrast with our finding, most other studies have showed statistically significant relationship between smoking and RAS.<sup>18,19</sup> We studied only patients with minor RAS whereas, most other studies evaluated all form of RAS. Effect of smoking may be less prominent in patients with minor RAS.

Minor ulcer usually heals before two weeks but, three (7.9%) of our patients reported that duration of attacks were more than two weeks. 35.7% of patients reported single ulcer in attacks. Interval of attacks in most of patients (42.1%) was more than 4 weeks. In Safadi study, approximately half of participants reported that ulcerations were single.<sup>20</sup>

In the present studied patients ulcers occurred in the lower half of the oral cavity, mostly in sublingual and lateral margins of the tongue (66.7%) which supports the general notion about the site of RAS occurrence. In a study of the 209 patients with RAS, ulceration usually occurred on the labial mucosa (39%), buccal mucosa (30%) or the floor of mouth (29%).<sup>16</sup> In another study, lips and buccal mucosa were the commonest sites of ulcerations (55%).<sup>20</sup>

Several studies have demonstrated that anemia and hematinic deficiency (iron, folic acid, or vitamin B<sub>12</sub>) are more common in RAS patients than in controls.<sup>21-23</sup> According to our normal laboratory values 10.5% of patients and 4.4% of control had anemia. There was no statistically significant difference between two groups (P=0.405). Anemia in both groups was microcytic that means probably are due to iron deficiency. In agreement with this result, in Burgan *et al.*<sup>24</sup> study, 14% of patients and 10.5% of control group were anemic with no significant difference (P=0.37). The USA study did not show any hematinic problem.<sup>15</sup> Also, Olson *et al.*<sup>25</sup> found that vitamin B<sub>12</sub>, folate and iron deficiencies were not significantly different between patients with RAS and controls. In contrast, in a study by Compilato *et al.*,<sup>11</sup> patients with recurrent aphthous were significantly anemic (34.4%) compared with (6.9%) controls.

A minority of women with RAS have cyclical oral ulceration related to the onset of the menstruation. In our study 22.2% of women pointed that menstruation was trigger for attack. Axéll *et al.*<sup>26</sup> in their study reported that one of the factors thought by patients to trigger RAS was menstruation. In other study, female patients who related the onset of their oral ulceration to their menstrual cycle were significantly more often diagnosed with RAS.<sup>16</sup> Nevertheless, a detailed review of all pertinent literature failed to find any association between RAS and menstruation.<sup>27</sup>

One of the limitations of our study is small sample size. We did not evaluate the serum hematinic parameter that is another limitation. More studies on patients with mRAS especially with larger sample size are recommended.

## CONCLUSION

Taking these findings into consideration, we can conclude that minor RAS in adult is more common above 30 years old, affects both sex equally and positive family history is among the possible etiologic factors for RAS. Anemia and smoking

status are less important etiologic factors in patients with minor RAS.

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