

# Clinical study of 200 patients with recurrent aphthous stomatitis

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## Abstract

**Introduction:** Recurrent aphthous stomatitis (RAS) affects approximately 20% of the general population. Its etiology is still unknown. **Objective:** To analyze this entity's clinical features. **Method:** Data such as age, gender, family history of RAS, age at first episode onset, prodromal symptoms, number, size, morphology and localization of lesions, RAS clinical form, annual rate of recurrence, predisposing factors, symptoms and time for symptoms and lesions disappearance were assessed in 200 patients with RAS. **Results:** Patients had RAS minor forms. Main clinical characteristics were family history of RAS (89%), first episode at  $\geq 10$  years of age (69%), prodromal symptoms (66%), one lesion per episode (63%),  $< 0.5$  cm lesions (64%), rounded morphology (55%), localization at the tongue (27%), 3 recurrent episodes per year (36%), stress as predisposing factor (34%), symptom disappearance in 2 days (54%) and healing of lesions in 8 days (40%). **Conclusion:** Even when RAS is a common disorder of the oral mucosa, there is no curative treatment available. Therapeutic measures seek to reduce the pain and size of lesions, accelerate the time of recovery and decrease the rate of relapses.

**KEY WORDS:** Mouth diseases. Recurrent aphthous stomatitis. Oral mucosa.

## Introduction

Recurrent aphthous stomatitis (RAS) remains oral mucosa most common ulcerative disease.<sup>1</sup> RAS is characterized by the appearance of one or several painful ulcers (aphthae), which initially are necrotic, covered by a white or greyish pseudomembrane and surrounded by a well-defined erythematous halo. The lesions usually affect non-keratinized oral mucosa, can persist for days or weeks and subsequently recur after highly variable periods.<sup>2,3</sup>

RAS affects approximately 20 % of the general population, although some studies indicate from 5 to 60 %, depending on ethnic and socioeconomic group.<sup>3,4</sup> These lesions are common in patients between 10 and 40 years of age, and have a predilection for the female gender and for high socioeconomic status individuals.<sup>5,6</sup>

RAS is considered to be a multifactorial process where different triggering factors and an underlying

immune alteration are combined.<sup>7</sup> Currently, RAS etiopathogenesis is not fully understood, although its onset has been associated with diverse factors, with genetic factors such as a family history related to this condition standing out.<sup>8</sup> Other related factors are food allergy, local trauma, hormonal changes (such as those of the menstrual cycle), stress and anxiety, nutritional deficits, infectious agents and different systemic diseases.<sup>4,6,9,10</sup> Aphthae are less common in smokers, which suggests that tobacco plays a possible protective role.<sup>11</sup>

Immune response in RAS is characterized by keratinocyte antigenic stimulation, which favors T cell<sup>12,13</sup> activation and immunoglobulins,<sup>14</sup> circulating immunocomplexes,<sup>15</sup> cytokines and adhesion molecules<sup>16-18</sup> participation. This results in lymphocyte accumulation and in the development of a cytotoxic response that induces the appearance of ulcers in the oral mucosa.<sup>6,9,19</sup>

According to the lesions' size, three clinical forms of RAS have been described: minor aphthae, major aphthae and herpetiform aphthae.<sup>4,20</sup>

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Minor aphthae are the most common (> 85 % of cases), and are characterized by superficial lesions of less than 1 cm in diameter, which normally appear in non-keratinized oral mucosa and heal in one to two weeks without leaving a scar.<sup>4,20</sup>

Major aphthae are less common (10 % of cases) and produce lesions > 1 cm in diameter, deeper and very painful. They can appear in non-keratinized and keratinized mucosa. They require more than 2 weeks to heal, and often do it leaving a scar.

Herpetiform aphthae (5 % of cases) are characterized by episodes of multiple, small (2 to 3 mm), superficial lesions, grouped in the form of clusters and distributed throughout non-keratinized mucosa. The lesions tend to coalesce and to form larger irregular ulcers. They usually heal in 7 to 10 days without leaving a scar. Clinically, they can be mixed up with recurrent intraoral herpes.<sup>4,20</sup>

RAS diagnosis is based on patient history and clinical findings, but there are no specific diagnostic tests. Its association with some systemic diseases such as Behçet's disease, cyclic neutropenia, celiac disease, periodic fever, adenitis, pharyngitis and aphthae (PFA-PA) syndrome, oral and genital ulcers with inflamed cartilage (MAGIC) syndrome, Sweet's syndrome, Reiter's disease or some immunodeficiencies should be taken into account.<sup>21-23</sup>

RAS is of unknown origin, and specific treatment is therefore not available; therapeutic measures are basically aimed at minimizing symptoms and preventing recurrences. The choice of topical or systemic treatment depends on symptom severity, lesion size and number and on the frequency of recurrent episodes.<sup>4</sup>

The purpose of this study was to analyze RAS clinical characteristics in a series of patients who attended a dentistry practice to receive treatment.

## Method

Two hundred patients who attended a dental practice in Tétouan, Morocco, to receive dental care between January 2013 and January 2015 were included. The detection of lesions was a casual finding during oral examination. All subjects were provided the necessary information about the purposes of this work with the purpose to obtain their consent. The information was incorporated to a clinical record especially designed for this purpose. The study protocol was approved by the Human Research Ethics Committee of the Faculty of Dentistry, University of Granada (registry FOD-UGR-054/2012).

Patients who refused to participate in the investigation, who didn't sign the informed consent, with the smoking habit, who consumed alcohol regularly, and those with systemic diseases related to the appearance of mouth ulcers were excluded. All patients were diagnosed on the first day of lesions' appearance.

Each patient was applied a questionnaire that included age, gender, family history of RAS, age at first episode appearance, prodromal symptoms, number, size, morphology and site of lesions at each episode, RAS clinical presentation, recurrence rate (number of episodes/year), predisposing factors, symptoms of the process and time to symptoms and lesions disappearance.

Descriptive statistics (arithmetical mean, standard deviation and averages) and analytical statistics were used for comparison of variables, by means of parametric (Student's t-test, ANOVA) and non-parametric tests (Mann-Whitney U-test, Kruskal-Wallis test, chi-square test and Fisher's test, as required). Lowest significance level was considered at a p-value < 0.05. Data were processed with the statistical program SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

## Results

Of the 200 included patients, 120 were females (60 %) and 80 were males (40 %), with a mean age of  $34.20 \pm 13.77$  years and a range of 10 to 74 years. No statistically significant differences were found between both population groups in terms of age and gender.

Table 1 shows the clinical characteristics of the 200 patients with RAS. The patients referred a previous family history of RAS, had their first episode at  $\geq 10$  years of age, had prodromal symptoms, one single lesion per episode, lesions of < 0.5 cm in diameter, of rounded morphology, and the majority located at the tongue. All subjects had minor aphthae, with a recurrence rate of 3 episodes per year; stress was the most commonly referred predisposing factor. The lesions were painful, and in 20 % of patients there was associated functional impairment coexisting; symptoms disappeared in two days, and most lesions healed at eight days of their appearance.

When the age was compared with some clinical parameters of the study (Table 2), a mean older age was observed in those patients who had their first RAS episode at  $\geq 10$  years of age ( $p < 0.001$ ), with lesions > 0.5 cm in diameter ( $p < 0.01$ ), of irregular morphology

**Table 1. Main clinical characteristics in 200 individuals with recurrent aphthous stomatitis**

Parameter	n	%	Parameter	n	%
Family history of RAS			Recurrence rate/year		
Yes	178	89	1 time	4	2
No	22	11	2 times	32	16
First RAS episode			3 times	72	36
< 10 years	62	31	4 times	26	13
≥ 10 years	138	69	5 times	50	25
Prodromal symptoms			≥ 6 times	8	4
Yes	132	66	Continuous	8	4
No	68	34	Predisposing factors		
Number of lesions			None	26	13
1	126	63	Stress	68	34
2	56	28	Food allergy	34	17
3	18	9	Bowel disorders	30	15
Lesion diameter			Local trauma	28	14
< 0.5 cm	128	64	Hormonal changes	14	7
0.5-1 cm	72	36	Other allergies	0	0
Lesion morphology			Symptoms		
Rounded	110	55	Pain	160	80
Oval-shaped	64	32	Pain + functional impairment	40	20
Irregular	26	13	Symptoms disappearance		
Lesion site			1 day after	76	38
Tongue	54	27	2 days after	108	54
Floor of mouth	28	14	3 days after	16	8
Upper lip mucosa	14	7	Healing of lesions		
Lower lip mucosa	16	8	6 days after	36	18
Buccal mucosa	10	5	7 days after	62	31
Soft palate	0	0	8 days after	80	40
Hard palate	0	0	9 days after	0	0
Gums	0	0	10 days after	22	11
Several sites	78	39	> 10 days after	0	0
RAS clinical form					
Minor	200	100			
Major	0	0			
Herpetiform	0	0			

RAS, recurrent aphthous stomatitis

( $p < 0.01$ ), located at the floor of mouth ( $p < 0.001$ ), and with an annual recurrence rate of  $\geq 6$  episodes ( $p < 0.001$ ), as well as in those who referred food allergy as a predisposing factor ( $p < 0.05$ ). For the remaining factors (family history of RAS, prodromal symptoms, number of lesions, symptomatology, disappearance of symptoms or lesions), comparisons with age were not statistically significant.

When the influence of gender on some clinical parameters was analyzed (Table 3), more females than males were found to have experienced their first RAS episode at  $< 10$  years of age ( $p < 0.001$ ) and to have lesions  $< 0.5$  cm in diameter ( $p < 0.05$ ). Conversely, more males than females were found to refer stress, bowel disorders or food allergy as predisposing factors ( $p < 0.01$ ). The remaining comparisons were not statistically significant.

A direct relationship was observed between prodromal symptoms experienced by the patients and a higher number of lesions per episode ( $p < 0.001$ ) or with lesions located at lower lip mucosa ( $p < 0.001$ ).

Regarding the comparison between the number of lesions per RAS episode and some clinical parameters (Table 4), a higher mean number of lesions was found in males ( $p < 0.05$ ), in patients who had the first RAS episode at  $\geq 10$  years of age ( $p < 0.001$ ), with lesions  $< 0.5$  cm in diameter ( $p < 0.05$ ) and with continuous annual recurrence rate ( $p < 0.05$ ). For the remaining parameters, the comparisons with the mean number of lesions per episode were not statistically significant.

The relationship between lesion size and some studied clinical parameters is shown in Table 5. Among the small lesions ( $< 0.5$  cm in diameter),

**Table 2. Influence of age on clinical parameters in 200 individuals with recurrent aphthous stomatitis**

Parameter	Patients (n)	Age ( $\bar{x} \pm SD$ )	p
Age at first episode (years)			
< 10	62	27.65 ± 9.88	< 0.001
≥ 10	138	37.14 ± 14.27	
Lesion size			
Small (< 0.5 cm)	128	32.27 ± 12.80	< 0.01
Large (0.5-1 cm)	72	37.64 ± 14.82	
Lesion morphology			
Round-oval-shaped	174	32.84 ± 13.43	< 0.01
Irregular	26	43.31 ± 12.70	
Lesion site			
Floor of mouth	28	47.43 ± 13.97	< 0.001
Rest of sites	172	32.05 ± 12.51	
Annual recurrence rate			
1 time	4	18.50 ± 8.66	< 0.05
Other	196	34.52 ± 13.68	
Predisposing factors			
Food allergy	34	38.65 ± 15.27	< 0.05
Other factors	166	33.29 ± 13.31	

**Table 3. Clinical parameters association with gender in 200 individuals with recurrent aphthous stomatitis**

Parameter	Gender				p
	Male		Female		
	n	%	n	%	
Age at first episode (years)					
< 10	16	20.0	46	38.3	< 0.01
≥ 10	64	80.0	74	61.7	
Lesion size (diameter)					
Small (< 0.5 cm)	44	55.0	84	70.0	< 0.05
Large (0.5-1 cm)	36	45.0	36	30.0	
Predisposing factors					
None	8	10.0	18	15.0	< 0.01
Stress	30	37.5	38	31.7	
Bowel disorders	16	20.0	14	11.6	
Local trauma	8	10.0	20	16.7	
Food allergy	18	22.5	16	13.3	
Hormonal changes	0	0.0	14	11.7	

rounded lesions ( $p < 0.001$ ), located at the tongue ( $p < 0.001$ ) and that healed 6 days after their appearance ( $p < 0.01$ ) stood out. In contrast, among the large lesions (0.5 to 1 cm in diameter), oval-shaped lesions ( $p < 0.001$ ), located on the floor of mouth ( $p < 0.001$ ) and those that healed 10 days after their appearance ( $p < 0.01$ ) stood out.

When the influence of predisposing factors on the time to symptoms or lesions disappearance was analyzed, symptoms were observed to have

**Table 4. Relationship between mean number of lesions and some clinical parameters in 200 individuals with recurrent aphthous stomatitis**

Parameter	n	Number of lesions (mean)	p
Gender			
Male	80	1.58 ± 0.70	< 0.05
Female	120	1.38 ± 0.61	
Age at first episode (years)			
< 10	62	1.26 ± 0.51	< 0.01
≥ 10 years	138	1.55 ± 0.69	
Lesion size			
Small (< 0.5 cm)	128	1.53 ± 0.68	< 0.05
Large (0.5-1 cm)	72	1.33 ± 0.58	
Recurrence rate			
Continuous	8	2.00 ± 1.07	< 0.05
Other rates	192	1.44 ± 0.63	

disappeared at 3 days in half of the patients who referred food allergy as a predisposing factor, with statistically significant association being found ( $p < 0.01$ ). The lesions healed after 10 days in 72.5 % of patients in whom stress was the predisposing factor, with a statistically significant relationship ( $p < 0.001$ ).

## Discussion

Even though RAS is the most common ulcerative disease of the oral mucosa, its etiology is not entirely understood and there is no fully curative treatment.<sup>1</sup>

The population with RAS of the present study had a mean age of  $34.20 \pm 13.77$  years, with a range between 10 and 74 years, which is consistent with the information obtained by Chattopadhyay et al.<sup>24</sup> in a large study in a large study in 20,050 North American adults with RAS, in whom mean age was  $36.10 \pm 1.92$  years. In Jordan, patients included in the work by Safadi<sup>25</sup> had a mean age of 37.5 years, with a range from 13 to 68. In turn, Brailo et al.<sup>26</sup> recorded a mean age of 38.8 years, ranging from 5 to 73, in 68 Croatian patients. Oh et al.<sup>27</sup> found a mean age of 40.75 years in 1643 Chinese patients. Other studies have recorded mean ages of  $41.77 \pm 20.71$  years, ranging from 21 to 65 years;<sup>28</sup>  $43.08 \pm 8.37$  years, ranging from 21 to 65;<sup>29</sup>  $42.80 \pm 14.30$  years, ranging from 17 to 79.<sup>30</sup> Although RAS is more common in young than in adult individuals,<sup>4,24</sup> in this study it was the opposite: 27 % of patients were within the range of 20 to 30 years, while 17 % were within the range of 10 to 20 years.

Table 5. Relationship between lesion size of and some parameters in 200 individuals with recurrent aphthous stomatitis

Parámetro	Lesion size				p
	Small (< 0.5 cm)		Large (0.5-1 cm)		
	n	%	n	%	
Lesion morphology					
Rounded	84	65.6	26	36.1	< 0.001
Oval-shaped	34	26.6	30	41.7	
Irregular	10	7.8	16	22.2	
Lesion site					
Tongue	40	31.3	14	19.4	< 0.001
Floor of mouth	4	3.1	24	33.3	
Upper lip mucosa	12	9.4	2	2.8	
Lower lip mucosa	10	7.8	6	8.3	
Buccal mucosa	6	4.7	4	5.6	
Several sites	56	43.8	22	30.6	
Lesion healing (days after)					
6	30	83.3	6	8.3	< 0.01
7	36	58.1	26	41.9	
8	54	67.5	26	32.5	
10	8	36.4	14	63.6	

Most authors<sup>3,7,25,27-29,31</sup> agree on pointing out that RAS affects females more often; however, in some studies,<sup>2,32</sup> the prevalence was the same for both genders, as in the study by Majorana et al.<sup>33</sup> in Italian children < 12 years, with a slight predominance of the male gender being observed. Consistently with findings in our work, RAS was more common in females (60 %).

A conditioning factor for the development of RAS is the existence of a family history thereof.<sup>25,31,34</sup> In fact, patients with a family history of the condition had 90 % probabilities for developing RAS, in contrast with 20 % of patients without a family history.<sup>4</sup> In the presented research, 89 % of patients referred a family history of RAS.

Some investigations<sup>3,7,35</sup> place the first RAS episode at the second decade of life, in coincidence with the onset of puberty, which is consistent with the obtained results: 69 % of patients had their first episode at between 10 and 20 years of age versus 31% in whom the first episode occurred before 10 years of age.

As for the number of lesions, different authors<sup>1,2,36-38</sup> indicate that RAS episodes occur with less than 3 lesions in most occasions. In this work, 63 % of patients had episodes with one single lesion. Safadi,<sup>25</sup> in his study on 561 patients, observed 49.2 % of patients with one single lesion per episode. The number of lesions per episode was conditioned by gender, age

at onset of first episode, lesion size and annual recurrence rate.

Nearly all investigations coincide in associating lesion size with RAS clinical form,<sup>1,2,4,7,19,20,35</sup> differentiating between minor (diameter < 1 cm), major (diameter > 1 cm) and herpetiform (2 to 3 mm) forms. In this study, all RAS lesions were minor, which in general terms are the most common (85 % of cases).<sup>4,20</sup>

With regard to lesion form, most authors<sup>2,3,7,19,32,36,37,39</sup> distinguish between irregular and regular (oval or round-shaped) lesions, with the latter being the most common and associated with RAS minor forms. The results of the present work (87 % of lesions with regular and 13 % with irregular morphology) are consistent with those published by other investigators. The records carried out by Safadi<sup>25</sup> indicate 34.3 % of irregular and 65.7 % of regular lesions, which disagrees with our findings, although more than 15 % of his patients had RAS major forms.

Numerous studies<sup>1-7,9,19,32,35</sup> concur in indicating a predilection of RAS lesions to be located on areas of non-keratinized oral mucosa. Similarly, the most common lesion site in this study was the tongue, with 27 % of cases, followed by internal lip mucosa (15 %), floor of mouth (14 %) and buccal mucosa (5 %). No case was located on the soft palate or keratinized oral mucosa (hard palate, gums). The tongue is also referred to as the most common site of RAS lesions in the works by Salafi<sup>25</sup> in Jordan, Oh et al.<sup>27</sup> in China or



López-Jornet et al.<sup>28</sup> in Spain. In contrast, others<sup>1,2,31,40</sup> refer to internal lip mucosa as the most common lesion site, before the tongue.

In the present work, annual recurrence rate was 3 episodes (36 %), followed by 5 episodes (25 %), 2 episodes (16 %) and only 4 % of patients had aphthae continuously. In concordance with these results, Axell and Henricsson,<sup>40</sup> in a study about 3500 patients, only found 1 % of continuous recurrence, 15 % of frequent occurrence and 84 % of intermittent clinical signs and symptoms, i.e., patients who experienced less than 6 episodes per year. Contrariwise, Bagán et al.,<sup>38</sup> when analyzing a series of 93 patients, observed that 53.8 % had an annual recurrence rate of 5 to 8 episodes, which is higher than that found in our study. The apparent discrepancies between different authors regarding annual RAS recurrence rate could be attributed to differences in sample size and to the establishment of different recurrent intervals in the studies' methodological design.

Different RAS-associated predisposing factors have been analyzed. In the present study, the 3 most important were stress (34 %), food allergy (17 %) and bowel disorders (15 %). Stress as a relevant predisposing factor for RAS has been widely suggested in investigations that consider oral mucosa as a target organ in certain emotional disorders.<sup>2,3,19,25,30,32,38,41</sup>

The disparity of results around this factor probably lies in the studied sample sizes, type of population and in differences in the investigations' methodological design.

Food allergy as a RAS precipitating factor has also been mentioned.<sup>25,42,43</sup> There are analyses where it even is the most important predisposing factor: 50 or 75 % of cases.<sup>41,43</sup> Given the small sample size of those investigations, the results should be regarded as being poorly representative. Furthermore, other particular factors that act with unknown mechanisms should be considered in each patient. Larger studies that delve into this issue and enable discrepancies to be clarified are required.

Bowel disorders, either due to nutritional deficits or gastrointestinal pathology, have also been referred to as triggering causes in different works.<sup>1,25,28,44</sup>

Hormonal changes were the least common predisposing factor (7 %), which is consistent with reports by Axell et al.<sup>40</sup> (8 %) and Lotufo et al.<sup>41</sup> (2.5 %). In a systematic review carried out by McCartan and Sullivan<sup>45</sup>, no relationship was found between RAS onset and menstrual cycle, pregnancy, menopause or hormone replacement therapy; conversely, some

authors<sup>3,7,27,39</sup> have given much higher relevance to this factor. The differences in this issue could be due to different sample sizes, differences in gender distribution and research approaches.

In this study in patients with RAS minor forms, the majority had a family history of RAS, single-lesion episodes, regular morphology (oval-shaped or rounded) lesions, located mainly on the tongue or internal labial mucosa and with an annual recurrence rate of 3 episodes. The most commonly related triggering factor was stress, time to symptoms disappearance was 2 days and time to remission was 8 days after the bout.

Even though RAS is one of the most common disorders of the oral mucosa and its clinical characteristics are well defined, its specific etiology and pathogenesis remain unclear and, therefore, there is no curative treatment available. Therapeutic measures are aimed at reducing pain, accelerating the healing period and decreasing the frequency of relapse, and new works delving into the study of the etiopathogenic mechanisms of this condition and its triggering factors are therefore required, in order to find an entirely effective treatment.

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