

# The frequency and etiology of recurrent aphthous stomatitis in helicobacter pylori positive patients

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**Abstract:** Objective: Recurrent aphthous ulcerations (RAU) is a disease characterized by recurrent painful ulcerations of the oral mucosa. The etiopathogenesis of the disease still unknown, and recently the role of Helicobacter pylori (HP) is overlooked. RAU frequency and etiologic factors of HP positive patients have been investigated in this study. Materials and Methods: 64 patients who attended to Mustafa Kemal University Department of Nuclear Medicine and presented with positive HP were included in the study. A questionnaire about sociodemographic characteristics and etiologies for RAU was administered to the patients. Results: The mean age of 64 patients determined a HP infection with C- 14 urea breath test was  $54.1 \pm 19.3$ . 35(54.7%) of 64 patients were females, 29(45.3%) of 64 patients were males. Smoking prevalence rate were 65.6%. 43.8% of patients had RAU 1-3 times per year, 35.9% more than 3 times. 35.9% of the patients had RAU in tongue, 28.1% of the patients had RAU on lips, tongue and cheek. 42% of the patients had minor, 51.6% of patients had major, 6.4% of patients had herpetiform ulcers. The average degree of pain (score out of ten) were found  $7.39 \pm 1.54$ . There was correlation between the number of aphthae in the past year and the degree of pain. The degree of pain in herpetiform ulcers were higher. Familial history was found to be 32.8%. 68.7% of the patients had reflux. 51.6% of the patients declared hoarseness. Conclusion: High incidence of RAU in HP positive patients and patients with reflux may cause the idea that HP may be suspected to be an etiologic factor of RAU.

**Keywords:** Helicobacter Pylori, Recurrent Aphthous Ulcers, Aphthae

## 1. Introduction

RAU is the most common ulcerative disease which affecting 10-25% of population. Some researchers claims that prevalence in certain populations are up to 50% (1). RAU, can be seen at any age from childhood or adolescence and is characterized by recurrent episodes of painful ulcers which can last about 1-4 weeks.

As regards the clinical manifestations, the basic lesion is a recurrent, painful, rounded or oval ulcer with a necrotic base. Three clinical subtypes of RAU have been established according to the magnitude, number and duration of the

outbreaks (2):

- Minor RAU: This is the most common presentation of the disease, representing 70-85% of all cases. It manifests as small rounded or oval lesions covered by a grayish-white pseudomembrane and surrounded by an erythematous halo. Each minor RAU episode usually involves the appearance of 1-5 ulcers measuring under 1 cm in diameter. These episodes are self-limiting and resolve within 4-14 days without leaving scars (3-6).

- Major RAU: This is the most severe presentation of the disease, representing 10% of all cases. In this subtype the ulcers measure over 1 cm in size and tend to appear on the

lips, soft palate and pharynx. The lesions persist for over 6 weeks and can leave scars.

- Herpetiform RAU: This subtype accounts for 1-10% of all cases and is characterized by recurrent outbreaks of small, deep and painful ulcers. Up to 100 aphthae can develop simultaneously, measuring 2-3 mm in size, though they tend to merge to form larger ulcerations with an irregular contour. This presentation is more often seen in women and in patients of older age, in contrast to the other two clinical subtypes of the disease (2,3,6,7).

The diagnosis of RAU is based on the patient anamnesis and clinical manifestations. There is no specific diagnostic test, though it is essential to discard possible underlying systemic causes particularly in the case of adults who suffer sudden outbreaks of RAU. It is advisable to request a complete series of laboratory tests. A biopsy of the lesions is only recommended in the case of diagnostic uncertainty, since the findings only indicate a simple nonspecific inflammatory lesion (2,3,7).

RAU is a non-infectious disease beginning at the oral mucosa and usually the first line of immunological and mechanical defense against infectious agents and physical injuries. Characteristic histological features of RAU are vascular dilatation, inflammatory cell infiltration and epithelial ulceration (8,9). Non-vascular infiltration of erythrocytes on the side of ulcers, may indicate that the disorder is in the vessel wall.

The etiopathogenesis of RAU so far remains not fully understood. The potential factors are: genetic predisposition, viral and bacterial infections, food allergies, vitamin and microelement deficiencies, systemic diseases (e.g., celiac disease, Crohn's disease, ulcerative colitis, AIDS), increased oxidative stress, hormonal defects, mechanical injuries and anxiety (10-12,2). Recently, also the atopic background of the condition has been suggested (13). In genetically predisposed patients, the effect of certain 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 which 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 (14).

Among the potential factors some authors mention bacterial (*Streptococcus oralis*, *Helicobacter pylori*) and viral (herpes simplex virus, varicella-zoster virus, cytomegalovirus, adenoviruses) antigens. The studies results, however, are ambiguous and conflicting (15,16). The elevated serum level of antibodies against some streptococcal strains in RAS patients reported in the 1960s was not confirmed in latter studies, similarly in the case of antibodies against *H. pylori* (17,19). Tas et al. (20) proved the beneficial effect of *H. pylori* eradication in patients with RAS. The underlying mechanism, however, is rather related with the increase in serum vitamin B12 levels after the eradication than with the direct action of the bacteria. The

attempts to isolate herpes simplex, cytomegalovirus, varicella-zoster and Epstein-Barr viral DNA from the biologic material collected from aphthae and mononuclear peripheral blood cells were successful only in single case of RAS, which also does not confirm the direct role of viruses in the etiopathogenesis of the condition (15).

Tobacco use is reported to cause an increase in keratinization in the oral mucosa. Although there are controversial results it has been reported that tobacco use causes decrease in the frequency of occurrence of aphthae (21,22).

*Helicobacter pylori* (HP) is a microaerophilic, gram negative bacteria which has affinity to gastric mucosa. Infection with this organism is serious, transmissible and connected with peptic and duodenal ulcers (23-27). Based on the statistics, 20-30% of adult people in the developed countries and more than 90% of them in the developing countries are probably infected by this bacterium (26). Being infected with this pathogen is basically asymptomatic and the person will be a carrier through his life, till the time when eradication therapy is done (28,29). The exact mechanism by which *H. pylori* induces tissue injury is not clear. Some immune-mediated mechanisms are suggested.

The way this bacterium is transmitted is not yet quite clear. However, they are mostly found in contaminated foods, feces, saliva and the dental plaque of healthy individuals and also in patients with upper digestive system disease (30). Thus, the infection can be caused via oral-oral, fecal-oral or gastro-oral through gastrointestinal refluxes (23,28,29,31-34). Specialists believe that, dental plaque might be a bed of *H. pylori* and possibly cause re-infection of gastric mucosa, and that it is transient in the oral cavity or is mixed with normal oral microflora (23,25,28,35-38).

Different studies have revealed that *H. pylori* can be isolated from the oral cavity, dental plaque (supragingival and subgingival plaque), dorsum of the tongue and salivary secretions (39-42). Wide variations in the prevalence of *H. pylori* in the oral cavity are partly due to employing different detection methods. For example, in a study by Butt et al, using urease test and cytology, *H. pylori* was detected in 100% and 88% of dental plaque samples, respectively (42). In another study, *H. pylori* was detected in the saliva of 54.1% and in dental pockets in 48.3% of examined cases (41) and was considered a resident of the oral cavity. However, Chitsaziet al detected *H. pylori* in 34.1% of dental plaque samples (43).

Because of similarities in the histological characteristics of gastric ulcers and oral aphthous ulcers which respond to treatment with broad-spectrum antibiotics, it seems logical to assume that *H. pylori* could play a role in the development of recurrent aphthous ulcers. The data regarding the potential relation between RAS and *H. pylori* infection are limited and controversial. Accordingly, the aim of the present study was to determine the association between *H. pylori* and RAS. For these reasons, in our study, the C-14 urea breath test determined HP infection in

patients and we investigated the relationship between HP and RAU frequency, etiology and cigarette.

## 2. Materials and Methods

### 2.1. Working Groups and Work Plan

The study population included HP C-14 urea breath test positive 92 patients of Mustafa Kemal University Faculty of Medicine Hospital in the Department of Nuclear Medicine. Those with systemic disease (Ulcerative Colitis, Crohn, Behçet Disease) and those applied in the previous month dental surgery were excluded from the study. To determine sociodemographic characteristics, the incidence and etiology of RAU in patients a questionnaire was administered. In questionnaire age, gender, smoking history were asked. 64 patients with RAU was assessed of the incidence of apht, apht settlement, type of apht, subjective complaints, in association with a history of reflux, in association with a history of hoarseness.

### 2.2. Statistical Analysis

Data was entered in SPSS 15.0 package program. The mean of descriptive data, standard deviation, percentages were calculated. In the comparison between groups who have normal distribution parametric data Student t test, Pearson's correlation test was used. Comparison of nonparametric data Mann-Whitney U test, Spearman correlation test and Chi-square test was used. p-value less than 0.05 was considered as significant ones.

## 3. Results

Demographic data: 64 (69.56%) of 92 patients had a history of RAU and mean was  $54.1 \pm 19.3$ . 35 (54.7%) patients were female, 29 (45.3%) were men. 34.4% of were regular smokers, 65% of nonsmoker.

The frequency of RAU: 20.3% of patients once a year, 43.8% of patients 1-3 times per year, 35.9% of patients described RAU more than 3 times per year.

Settlement of RAU: 20.3% of patients had RAU in the lips, 15.6% of the patients in the cheek, 35.9% of patients in the tongue, 28.1% of the patients in lips, cheeks and tongue were found to occur together. None of the patients had aphthae in the tonsils and gums.

Type of RAU: 42% of patients had minor aphthae, 51.6% patients major aphthae, 6.4% patients herpetiformis aphthae.

Complaints caused by RAU: Pain, swallowing difficulty, eating difficulty was present in 40.6% of patients. In addition, lack of appetite and difficulty in speaking was both present in 46.9% patients. Who described pain in patients, average degree of pain (score out of ten) was found to be  $7.39 \pm 1.54$ .

In the past year apht number was found statistically significant with the degree of pain ( $p = 0.0001$ ). it was observed that according to type of apht the degree of pain changes, patients pain degree was higher in herpetiformis

aphthae ( $p = 0.0001$ ). Minor and major aphthae when we look at the degree of pain were not statistically different ( $p = 0.779$ ).

20.3% of patients were found to have no changes in sense of taste. Taste changes were in 35.9% of patients at sometimes, in 28.1% of the patients mostly, in 15.6% of patients were seen at all times.

Relationship with a family history of RAU: RAU family history was positive in 32.8% of patients. 67.2% of perceived any family history.

RAU relationship with reflux: 68.7% of patients were complaining of reflux. Hoarseness or sound bifurcation was in 51.6% of patients.

RAU relationship with smoking: Smoking reduces the formation of aphthae by increasing mucosal keratinization. It is reported that of starting smoking again with reduced prevalence of aphthae (6,7). In our study, this result was not significant ( $p > 0.05$ ). Major and herpetiform aphthae of those were smoking amnesty. But it was not statistically significant ( $p > 0.05$ ).

## 4. Discussion

Immunodeficiency, hematological problems, microbial factors such reasons known to have a role in the etiology of RAU, but none yet to be fully elucidated (44). It have been reported that in the etiology of RAU genetic factors may play a role and also suggested that in patients with a positive family history disease becomes earlier with high ratio (45). In the literature there are many studies available about genetic, nevertheless the presence of genetic transmission has not been certainly established (46,47).

1/3 of RAU patients has the family history. In these people, the disease developing at an earlier age and is with more severe symptoms (45). In our study consistent with the literature, those patients with a family apht history had numerous aphthae in the past year and this was significant ( $p < 0.05$ ).

In some of patients with duodenal ulcer there is HP in saliva and suggested that it comes from the stomach to the mouth with reflux or acid regurgitation. Even if there is HP inside the mouth it is an indicator of HP gastritis. It is also suggested that HP comes into the mouth from external sources at HP positive or negative person (48,49). Especially gastric colonization and mucosal involvement exposure in individuals HP, recurrent oral aphthous ulcers. It is suggested to play a role in the pathogenesis (48).

In our study, relation was found between patients with reflux and the incidence of aphthous stomatitis. There was no difference between the types of aphtae. HP-positive patients with reflux there was significant relationship between the occurrence of hoarseness.

In a study on oral ulcers, *H. pylori* was detected in six (20.7%) out of 29 cases, and all the positive samples were located in the buccal mucosa (50). In another study on recurrent aphthous ulcers, 71.9% of cases were positive for *H. Pylori* (48). Fritscher et al, studying 105 children and

adolescents, found that 9.4% of 53 patients with recurrent aphthous stomatitis were positive for *H. Pylori*, and in the control group only 3.8% were positive. They did not find any statistically significant relationship between the presence of *H. Pylori* and recurrent aphthous stomatitis (18).

Rubin et al, working on 61 samples from head and neck malignant and premalignant conditions, detected *H. pylori* positivity in 16.3% of oral cavity samples (51).

*H. pylori* usually spreads via the fecal-oral route, and possibly by the oral-oral route and the spread of contaminated secretions (52-56). An investigation of *H. pylori* genotypes in saliva, dental plaques, stools and gastric biopsy samples from 300 patients found that the fecal-oral route was the main method of *H. pylori* transmission. Furthermore, the oral cavity might serve as a reservoir for *H. pylori* because the genotypes of *H. pylori* isolates from saliva, stomach and stool are similar (57-60). Debate continues regarding whether or not the oral cavity is the major reservoir of *H. pylori* for gastric re-infection (61-69). Although some investigators have reported that the oral cavity is the reservoir for *H. Pylori* (70-81), insufficient evidence supports the notion that dental treatment can prevent recurrent gastric *H. pylori* infection (24).

A relationship with *H. pylori* has been investigated among various oral disorders including periodontal disease (82-85), glossitis, burning mouth syndrome (86), halitosis (87-89), Behçet's syndrome (90), lichen planus (91,92), and taste perception (93). Combining periodontal with systemic therapy might be a promising approach to improving therapeutic effects and decreasing the risk of recurrent gastric infection (94). However, an association between *H. pylori* and various periodontal disorders has not been established.

*H. pylori* might comprise part of the normal oral microflora (95). *H. pylori* in dental plaque might not be associated with brushing frequency and oral health status and one study of 161 patients concluded that *H. pylori* is not pathogenic in the oral cavity (96-98). But most studies suggest that whether or not *H. pylori* in the oral cavity plays a pathogenic role remains debatable. Nonetheless, dentists and dental professionals are at increased risk of exposure to *H. pylori* through contact with the oral cavities of infected patients (99,100).

It can be hypothesized that, if *H. pylori* has a role in the development of RAS, we can decrease the frequency and the severity of the RAS lesions, by omitting the organism through chlorhexidine mouth rinses or irrigation and developing oral hygiene via mechanical plaque removal parallel to the triple therapy (a therapeutic period by antibiotics for digestive infections), (24) which itself results in patient's comfort and a better quality of life. The idea that, after eradication of *H. pylori*, the severity and recurrence frequency of RAS is decreased has been supported by Karaca et al. and Farmaki et al (101).

As a result; oral cavity is a gastric reservoir for HP and we think that gastric HP settles through the oral mucosa by reflux due to gastric HP may play a role in the pathogenesis of RAU.

[Note: For I have seen in the research literature; research often built on recurrent aphthous ulcers in patients with *Helicobacter pylori* detection. But in our study of *Helicobacter pylori*-positive people with recurrent aphthous ulcers were evaluated.]

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