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Recurrent Aphthous Stomatitis and Related Factors in Turkish Adult Population: A Striking Outcome of Cappadocia Chronic Diseases Epidemiological Study

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ABSTRACT

Background: Recurrent aphthous stomatitis (RAS) is a common painful lesion affecting millions of people. This population-based epidemiological study aimed to determine the frequency of recurrent aphthous stomatitis in the population and associated diseases and factors.

Methods: In 2013, by the Turkish Society of Internal Medicine, a cohort for chronic diseases and related risk factors was initiated in the Central Anatolia Region of Turkey (Cappadocia region). 90% of the whole adult population was included and photos of oral aphthae were used during the questionnaire for chronic diseases.

Results: 10 992 participants, aged ≥18 years included. The mean age were 44.6± 16.4 years; 56.1% were males. RAS history was present in 13.2%, more frequent in females (17.1%). Female gender (OR: 1.441, CI: 1.253-1.656, p<0.001), presence of any rheumatic disease (OR: 2.364, CI: 1.408-3.968, p:0.001), history of joint swelling (OR: 1.755, CI: 1.527-2.016, p<0.001), low back pain history (OR: 1.727, CI:1.529-1.952, p<0.001) were independent risk factors for RAS. Age (OR: 0.994, CI: 0.990-0.997, p:0.001), alcohol usage (OR: 0.744, CI: 0.566-0.977, p: 0.033) and smoking (OR: 0.651, CI: 0.555-0.763, p<0.001) were protective for RAS.

Conclusions: RAS prevalence was 13.2% in our population-based cohort. Underlying inflammatory rheumatic diseases must be searched in the case of RAS. Alcohol may have a reducing effect on RAS, needs further evaluation.

Keywords: Recurrent aphthous stomatitis, inflammatory rheumatic diseases, low back pain

Türk Erişkin Popülasyonunda Tekrarlayan Aftöz Stomatit ve İlişkili Faktörler: Kapadokya Kronik Hastalıkları Epidemiyolojik Çalışmasının Çarpıcı Bir Sonucu

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ÖZ

Amaç: Tekrarlayan (rekürren) aftöz stomatit (RAS), milyonlarca insanı etkileyen yaygın ağrılı bir lezyondur. Bu popülasyona dayalı epidemiyolojik çalışma, toplumda tekrarlayan aftöz stomatit sıklığını ve ilişkili hastalıkları ve faktörleri belirlemeyi amaçlamıştır.

Yöntem: 2013 yılında Türk İç Hastalıkları Uzmanlık Derneği tarafından Türkiye'nin İç Anadolu Bölgesi'nde (Kapadokya bölgesi) kronik hastalıklar ve ilişkili risk faktörleri kohortu başlatılmıştır. Tüm yetişkin popülasyonun %90'ı dahil edilmiş ve kronik hastalıklar anketi sırasında oral aft fotoğrafları kullanılmıştır.

Bulgular: 18 yaş ve üzerinde 10 992 katılımcı dahil edildi. Ortalama yaş 44.6± 16.4 yıl; %56.1'i erkekti. RAS öyküsü %13.2 idi, kadınlarda daha sıktı (%17.1). Kadın cinsiyet (OR: 1.441, CI: 1.253-1.656, p<0.001), herhangi bir romatizmal hastalık varlığı (OR: 2.364, CI: 1.408-3.968, p:0.001), eklem şişmesi öyküsü (OR: 1.755, CI: 1.527-2.016, p<0.001), bel ağrısı öyküsü (OR: 1.727, CI:1.529-1.952, p<0.001) RAS için bağımsız risk faktörleriydi. Yaş (OR: 0.994, CI: 0.990-0.997, p:0.001), alkol kullanımı (OR: 0.744, GA: 0.566-0.977, p: 0.033) ve sigara kullanımı (OR: 0.651, CI: 0.555-0.763, p<0.001) RAS için koruyucu idi.

Sonuç: Populasyon temelli kohortumuzda RAS prevalansı %13.2 idi. RAS varlığında altta yatan inflamatuar romatizmal hastalıklar araştırılmalıdır. Alkolün RAS üzerinde azaltıcı bir etkisi olabilir, daha fazla araştırmaya ihtiyaç vardır.

Anahtar sözcükler: Tekrarlayan aftöz stomatit, inflamatuar romatizmal hastalıklar, bel ağrısı

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Introduction

Aphthae are painful, localized, shallow, round to oval oral ulcers with a yellowish adherent exudate centrally[1]. Recurrent aphthous stomatitis (RAS, also called canker sores) is the most common cause of mouth ulcers characterized by painful, round, or oval-shaped ulcers with an inflammatory halo [2]. Typically starts in childhood and diminishes in adulthood, by the third decades and family history is present. RAS is more common in women, younger than 40 years of age, nonsmokers, and people with high socioeconomic status [3,4,5]. RAS can affect up to 25% of the general population. The exact etiology is unknown. Vitamin B12, folate, or iron deficiencies have been reported in patients with aphthous stomatitis [6,7,8]. Treatment or supplementation with iron or vitamin failed to show clear benefits on this disease [9.] Oral trauma, cessation of smoking, anxiety or stress, food sensitivities, and hormonal changes during the menstrual cycle have been suggested as precipitating factors for RAS but not proven clearly [2].

We aimed to determine the prevalence of RAS and associated factors in the Turkish population.

Materials and Methods

This is a population-based epidemiological study. In 2013, a Turkish cohort was initiated by the Turkish Society of Internal Medicine aiming to investigate the prevalence and incidence of chronic diseases along with related factors. For this purpose, Avanos and Gülşehir districts in the Central Anatolia Region of Turkey, popular as Cappadocia Region, were selected due to a 5-year migration rate of less than 10%. The cohort included all subjects aged 18 years and higher, living in these districts. The main target was to reach the whole adult population. Informed consents were obtained from adults and 90% of the whole adult population agreed to participate in the study. A questionnaire about chronic diseases including inflammatory rheumatic diseases was applied to all participants with a face-to-face interviews. Demographic data, data about chronic diseases, and lifestyle were collected. Alcohol consumption was defined as at least one drink per month for the cohort since alcohol use per capita is very low in Turkey.

During interviews, oral aphthae photographs were shown to participants, and the presence of aphthae history was questioned. Participants with and without oral aphthous ulcers were compared in terms of demographic and medical characteristics.

Statistical analysis

Descriptive statistics were given as mean±standart deviation for normally distributed numerical data, median (minimum-maximum) for non-normally distributed numerical data, and percentages for ordinal data. For categorical variables, a chi-square test was used in two group comparisons when the chi-square condition was met. When comparing two independent groups, the Mann-Whitney U test was used for non-normally distributed numerical variables. Relative risks were estimated among genders in terms of behavioral risk factors and disease prevalence within the stratum of each town. A Wald chi-square test was used for testing the homogeneity of relative risks between the towns and a Cochran Mantel-Haenszel test was used to evaluate the association beyond chance between gender and risk factors. The probability of a type I error was set at 0.05.

Results

In this population-based epidemiologic survey, the target population was 12.187 adults, aged ≥18 years old, living in Gülşehir and Avanos. A total of 10 992 (90%) resident adults participated in the study; 5150/5262 (95%) from Gülşehir, 5842/6925 (87%) from Avanos. The mean age of the participants was 44.6 ± 17.4 years and 56.5% were female [10]. RAS history was positive in 1462 participants and the overall prevalence was 13.3%. Participants with and without RAS were compared in the means of sociodemographic and clinical characteristics and results were given in Table 1.

RAS were more prevalent in females than males, 1063 (17.1%) vs. 399 (8.2%), respectively (OR:1.44, CI: 1.253-1.656, p<0.001). There was no significant difference in the median age of the participants with or without RAS, 45.07±16.51 vs 44.55±17.52 years, respectively (p=0.131). 262 (17.9%) of subjects with RAS was an active smoker and 72 (4.9 %) were consuming alcohol.

According to body mass index (BMI), 526 (36.2%) of the participants with RAS were obese, whereas 30.7 % of the participants without RAS were obese (p<0.001).

Any inflammatory rheumatic disease was more frequent in subjects with RAS compared to subjects without RAS (118 [8.1%] vs. 0%, p<0.001). History of joint swelling, low back pain, low back pain lasting more than 3 months, recurrent diarrhea were more prevalent in subjects with RAS (33%, 59.7%, 35.4%, and 35.4% respectively, p<0.001 for all).

Female gender, presence of any inflammatory rheumatic disease, history of joint swelling, and history of low back pain were found to be the risk factors for RAS (Table 2). Age, smoking, and alcohol intake were found to be protective factors for RAS (Table 2).

Table 1. Clinical Characteristics of subjects with and without RAS.

	Subjects with RAS (n=1462)	Subjects without RAS (n=9530)	P value
Gender (female), %	72.8	53.9	**<0.001**
Age, year (mean+SD)	45.1 ±16.5	44.6±17.5	0.131
Smoking, %	17.9	30	**<0.001**
Alcohol consuming,%	4.9	9.6	**<0.001**
Body mass index (BMI, kg/m2)			**<0.001**
• **<25,%**	31.4	32.6	
• **25-30,%**	32.4	34.1	
• **≥30,%**	36.2	29.5	
Any inflammatory rheumatic disease, %	8.1	0	**<0.001**
History of joint swelling, %	33.0	17.7	**<0.001**
History of low back pain, %	59.7	41.5	**<0.001**
Low back pain lasting >3 months, %	35.4	20.7	**<0.001**
History of recurrent diarrheal illness, %	9.4	3.1	**<0.001**
Rheumatological drug use, %	12.2	10.1	0.116
Presence of any chronic illness, %	59.4	45.5	**<0.001**
Any medicine use, %	45.6	33.4	**<0.001**
Values are labelled mean (SD) or median (min-max)			

Table 2. Risk and protective factors for RAS.

	Odds ratio	Confidence interval (CI)
Gender, female	1.441	1.253-1.656
Any inflammatory rheumatic disease	2.364	1.408-3.968
History of joint swelling	1.755	1.527-2.016
History of low back pain	1.727	1.529-1.952
Age	0.994	0.990-0.997
Smoking	0.651	0.555-0.763
Alcohol	0.744	0.566-0.977

Discussion

Face-to-face interviews of over 10.000 subjects revealed the prevalence of RAS in Turkey as 13.3% according to Cappadocia Chronic Diseases Epidemiological Study. Any inflammatory rheumatic disease, history of joint swelling and history of low back pain were more frequent subjects with RAS. Age, smoking, and alcohol use, were protective factors for RAS (OR: 0.9, 0.6, and 0.7, respectively).

Previous reports have a wide range for the prevalence of RAS changing between different countries and also different populations: In the US population, the prevalence was 0.89% in adults, and 1.64% in children [12]. On the other hand, a much higher prevalence was reported for Asian countries. This extreme difference in the prevalence of RAS can be due to genetic variations between ethnic populations, the age range of the study samples, and due to sampling features of the study population. Davatchi et al reported a 25.2% prevalence of oral apthae in the normal population in Tehran [13]. Safedi et al reported that 78% of dental patients had a history of RAS in Jordan [14]. Patil et al found 21.1% of dental patients had RAS history in India [15]. There are numerous studies about the prevalence of oral aphthae in dental patients or Behçet's diseases in Turkey. Overall RAS frequency as 25.5 % in 10-50 years old patients admitting a University Dental Hospital for various dental conditions whereas in another study RAS prevalence was 2.9% in 40 years and older individuals [16, 17]. Baş et al reported an annual prevalence of 10.8% for RAS in Tokat, representing the Northern Anatolia region, among 2325 volunteers that are comparable with our results [18]. Our study population was selected due to the very low migration rate and thought to be representative of the Turkish population, not only a region, and reached more than 10 000 subjects. So we believe that this is the largest population-based study on the frequency of RAS in Turkey. We collected the aphthae information from subjects by showing an aphthae picture, thereby we reached more accurate information, and reduced the risk of reporting other oral lesions that could be mistaken for oral aphthae.

Although the exact etiology and pathogenesis of RAS remain unclear, they may have a wide variety of

underlying systemic cause and autoinflammatory syndromes: Behçet's disease, periodic fever with adenitis, pharyngitis, and aphthae (PFAPA) syndrome, Crohn's disease, genital ulcers with inflamed cartilage (MAGIC) syndrome, and immunodeficiency states, including nutritional defects (such as celiac disease and other gastrointestinal disorders), immune defects (such as human immunodeficiency virus infection/acquired immune deficiency syndrome) and neutrophil defects (such as cyclic neutropenia) [11,19]. Also, a positive family history, food hypersensitivity/allergy, smoking cessation, psychological stress, and immune disturbance, non-specific viral and bacterial infections, vitamin and microelement deficiencies, hormonal imbalance, mechanical injuries had been associated with RAS [20,21]. The results of previous studies indicate that genetically mediated disturbances of innate and acquired immunity play an important role in RAS development. Immune dysregulation linked to several triggers may facilitate the development of RAS. The roles of the immune system and inflammatory processes have been confirmed in recent large-scale bioinformatics analyses [14,15]: a Th1-type hyperimmune response favors the appearance of inflammatory reactions that precede ulcerations [16,22]. Genetic risk factors can determine individual susceptibility. NOD-like receptor 3, toll-like receptor 4, interleukin (IL)-6, E-selectin, IL-1β and TNF-α genes [17, 20-24]. However, despite a large number of factors examined, the underlying cause triggering the episodes of ulcers remains to be elucidated. Therefore, clinically, the emergence of new lesions cannot be avoided at present.

RAS is the most important diagnostic criteria for Behçet's Disease [25]. Livneh et al described 17/64 patients with RAS had a rheumatic diagnosis as Reiter's syndrome, Behçet's diseases, and familial Mediterranean fever, 13/23 patients with undiagnosable extra-oral manifestations had arthritis and low back pain more than control subjects [26]. In our study, low back pain lasting more than 3 months and joint swelling were found in nearly one-third of the subjects with RAS, and significantly more frequent than subjects without RAS. Also, we found that the presence of any rheumatic diseases, the presence of low back pain lasting more than 3 months, and joint swelling history were the risk factors for the presence of RAS. As our study had a cross-sectional design, it is difficult to distinguish if the ulcers are a component of a systemic disease or not.

Also in our study participants with RAS significantly have more chronic illnesses, drug usage other than rheumatological drugs, and higher body mass index. Slebloda et al reported recently that the most common systemic conditions in RAS patients were hypertension, allergies, and anemia [27]. Hypertension (22.3%), hyperlipidemia (16.8%), diabetes mellitus (10.6%), rheumatoid arthritis (1.2%), ankylosing spondylitis (0.8), systemic lupus erythematosus (0.3%) were statistically more frequent in patients with RAS than patients without RAS [28]. We did not determine the chronic non-rheumatological diseases in detail for participants with RAS, but in whole the study, hypertension was the most prevalent chronic disease affecting 18.8% of the study population [10].

In this epidemiological survey, smoking and alcohol consumption were related to low RAS rates. Patients with vitamin B12 deficiency, positive family history, and nonsmoking status reported having the highest risk for having RAS [29]. In a study, it has been presented that smoking cessation results with occurrence of RAS mostly in the first week after cessation, even in subjects without aphthae history [30]. This diminishing effect of smoking can be explained by the keratinization effect of combustible products of smoking of oral lining mucosa. The keratin layer may block the ingress of antigens and prevent the occurrence of RAS on the keratinized masticatory mucosa [31]. Also, nicotine or its metabolites can result in a decrease of the pro-inflammatory cytokines like TNF-α, IL-1, and IL-6, and an increase of anti-inflammatory cytokine IL- 10. Consequently, there is a reduced susceptibility to RAS due to immunosuppression and/or reduction in the inflammatory response [31].

In our study, alcohol-consuming was also found as a protective factor from RAS. Matranga et al reported 4.8% of 103 subjects with RAS were drinkers [32]. But there is no clear relationship between RAS and the protective role of alcohol consumption in the literature. In this survey, alcohol-consuming is defined as at least one drink/month which is very low compared to other studies in the literature. Further research to document any protective role of alcohol on RAS is needed.

The limitations of this study were mostly due to the cross-sectional design of the survey. So, it is difficult to establish a definite causal relationship between RAS and risk factors. Oral aphthae history was taken from individuals' statements, not proven by physicians' examinations. But to improve the confidentiality of data, the subjects were informed about oral aphthae with oral aphthae pictures.

On the other hand, this is the largest population-based epidemiological data presenting the Turkish population defining the people with RAS, demographics, and concomitant diseases. We reached 90% of the total target population, and participants defined their lesions after showing a picture of oral aphthae. The sample size and the way used for data collection make our results more powerful when compared to literature.

Conclusions

In conclusion, RAS affects over 1/10 Turkish population and can be a sign of systemic disease. Further research to find out the mechanisms, and reasons underlying RAS are needed. Prevention of recurrence and accurate treatments are the gaps in this painful, discomfortable lesion. We, the clinicians facing

patients with RAS should keep in mind to investigate possible chronic and rheumatic diseases, especially for Behçet diseases.

Declaration:

Ethics approval and consent to participate: The study protocol was approved by the Committee on Human Research Ethics of Hacettepe University. A well written informed consent and consent to publish was obtained from all the partipicants included in this study

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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