Interleukin-1,8 and Psychological Factors in Patients with Benign Migratory Glossitis

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Abstract

Objective: Benign migratory glossitis is a immunologic-psychologic disease with unknown etiology.Aim of this study is evaluation of salivary IL-1 and Il-8 levels in these patients. Study Design: A case-control study was performed on 170 participants (85 with BMG, 85 controls). Unstimulated whole saliva was collected, and interleukin 8 (IL-8) and interleukin 1(IL-1) concentrations were measured. Anxiety level was measured using psychologic and physiologic testing instruments. An independent t test and a Pearson correlation analysis were performed with SPSS. Results: There was a significant difference between the 2 groups regarding the salivary concentrations of IL8 ($P \le .006$) and IL-1 ($P \le .002$). The concentration of salivary cortisol and state and trait anxiety levels in the BMG group were significantly higher than those in the control group ($P \le .001$). Conclusions: Immunologic and psychologic parameters appear associated with BMG and may constitute risk factors of this condition.

Introduction

Benign migratory glossitis (BMG) is usually an asymptomatic inflammatory disorder of multiple sites on the tongue found mostly on its dorsal surface [1]. This condition is characterized by migratory erythematous patches, representing atrophy of the filiform papillae of tongue that sometimes includes raised whitish peripheral margins that recover spontaneously [2]. Although BMG is generally asymptomatic, some patients complain of a burning sensation associated with cigarette smoke, spicy foods, and fruits [3]. Some studies have proposed possible associations between BMG and pustular psoriasis [4,5], allergy [6,7], hormonal disturbances [8,9], juvenile diabetes [10], nutritional deficiencies [8], psychologic disorders [7,11], and fissured tongue [3,12]. Other studies, in contrast, reported no associations between hormonal changes, diabetes mellitus, allergy, or psychologic or dermatologic conditions and BMG [1]. The etiology of this disease is not clear [2]. It is suggested that BMG is more prevalent in patients who have a tendency to develop immunologic diseases such as psoriasis and Reiter syndrome [13-15]. It is well known that functional interleukin 1 (IL-1) and 8(IL-8) polymorphisms and associated plasma levels are related to the pathogenesis of different immunologic diseases [16,17]. Therefore, we speculate that there might be an association between BMG and levels of IL-1 and IL-8 in other biofluids such as saliva. However, to date, this association has not been investigated [18]. Although researchers have proposed various inputs of immunologic and psychologic backgrounds with BMG [14,18] salivary levels of inflammatory cytokines in patients with BMG or the possible association between anxiety and BMG as measured by both a psychologic testing instrument (State-Trait Anxiety Inventory [STAI]) and a physiologic testing instrument (salivarycortisol levels) have not been investigated. The aim of the present study was to investigate the possible association between BMG and some immunologic factors and psychologic parameters.

Material and method

The present observational, case-control study was performed in the Oral Disease Department of Isfahan University of Medical Sciences in Iran. Case and control samples were selected from consecutive patients who visited this department for routine dental examination between March and July 2015. This study was approved by the Ethics Committee of the Isfahan University. Informed consent to participate in the study was obtained from all participants. The study included 170 participants divided into 2 groups of 85 individuals. The case group comprised 85 patients diagnosed with BMG after clinical examination by 2 calibrated independent oral medicine specialists. The diagnosis was based on guided clinical diagnostic criteria described by Kramer et al. [19]. Although the diagnosis of BMG has readily demonstrable clinical features, intra and inter examiner calibration for this study was 0.84 and 0.81, respectively. The control group comprised 85 healthy individuals, age- and sex matched with the study group, with no evidence of any systemic diseases or history of drug consumption during the past 2 weeks. Patients who had a history of immunologic and dermatologic diseases such as psoriasis, *Lupus erythematosus*, *Lichen planus*, and asthma were not included in this study. Patients with any inflammatory lesions of the oral cavity that were noted after clinical examination by an oral disease specialist were also not included in the study. Individuals with a history of smoking, alcohol consumption, lithium consumption or vitamin deficiency were excluded, as were women who reported a history of oral contraceptive pill use or individuals who had taken steroids. Because salivary and serum concentration of proinflammatory cytokines may be increased as a result of various oral cavity inflammatory conditions [13], the present case and control groups were matched for gingival condition using a modified gingival index [20]. The data collected were based on saliva sampling and anxiety assessment. For saliva sampling, participants were asked not to eat, drink, or use saliva stimulators (such as chewing gum or mint) for at least 1 hour before the evaluation. Unstimulated whole saliva was collected between 9 AM and 9:30 AM using standard technique [21]. Participants were asked first to swallow the

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whole content of saliva in their mouth, then tilt their head forward and expectorate all saliva into 50-mL centrifuge tubes for 5 minutes without swallowing. The saliva samples were frozen at _70_C until analysis. All samples were centrifuged at 4500 g for 15 minutes. IL-1 and IL-8 concentrations were measured using human IL-1 (sensitivity, <0.3 pg/mL) and IL-8 (sensitivity, <1 pg/mL) enzyme-linked immunosorbent assay (ELISA) kits (Boster Biological Technology Co, Pleasanton, CA, USA) according to the manufacturer's recommendation. All samples were analyzed in duplicate, and the mean analysis result was reported. Salivary cortisol was also measured using an ELISA kit (UBI-MAGIWEL; United Biotech Inc, USA), according to the manufacturer's instructions. The levels of cortisol were determined as the total amount per site (nmol/L). To minimize the effect of diurnal variations in salivary cortisol, all collection of salivary samples was performed between 9 AM and 9:30 AM. The anxiety levels were measured using the STAI, which measures both trait anxiety as a general aspect of personality (STAI-T) and state anxiety as a response to a specific situation (STAI-S) [22]. STAI consists of 40 statements, of which 20 measure trait anxiety and 20 measure state anxieties. Items are scored on 4-point scales. For both levels, the STAI scoring ranges from 20 to 80; and the higher the score, the greater the intensity of anxiety. The instrument was translated into Persian and then back-translated into the original language. We submitted the translated version of the STAI to 5 specialists, including 2 psychologists, 2 oral disease specialists, and a health education professional to evaluate the understandability and the extent to which the items adequately measured what we were setting out to measure. The validity and reliability of this questionnaire were previously verified for the Iranian population by Shahmansouri et al. [23]. SPSS (version 18; SPSS Inc) was used to analyze the data. Distribution of the variables was examined for normality using the Kolmogorov-Smirnov test. Because the data were normally distributed, a parametric independent t test was used. A Pearson correlation analysis was used to study the correlation among variables. The threshold of statistical significance was set at P <.05.

Results

A total of 85 patients diagnosed with BMG (43 men, 42 women) and 85 controls (43 men, 42 women) were enrolled in the study. The mean ages in the study and control groups were 32 ± 5.6 and 34.5 ± 6.8 years respectively. The gender and age differences between the 2 groups were non-significant. Also, there was no significant difference between the 2 groups with regard to the salivary flow rate. The mean amounts of IL-1 and IL-8 in both case and control groups are summarized in *(Table 1)* .ELISA analysis of unstimulated whole saliva found that the mean levels of IL-1 and IL-8 were significantly higher in the BMG group than in the control group($P \leq .002$ and $\leq .006$, respectively). The cortisol level and STAI questionnaire were used to evaluate the anxiety level of participants. The mean concentrations of salivary cortisol in the case and control groups were 4.22 nmol/L and 2.56 nmol/L, respectively. The salivary cortisol and state and trait anxiety levels in the study group were significantly higher than those in the control group ($P \leq .001$) *(Table2)*. There was a positive correlation between STAI-S and STAI-T scores ($r \leq 0.738$; P

$\leq .001$). Correlation was also found between saliva cortisol levels and either STAI-S ($r \leq 0.815$) or STAI-T ($r \leq 0.718$). There were positive significant associations between salivary cortisol level ($r \leq 0.318$), STAI-S ($r \leq 0.362$), STAI-T($r \leq 0.353$), and the presence of BMG ($P \leq .001$).

Table 1. Mean amounts (pg/mL) of IL-1 and IL-8 in BMG and control groups.

Salivary cytokine	BMG group	Control group	P
IL-1	$6.32 \pm .75$	$4.48 \pm .32$	0.002
1L-8	$8.34 \pm .32$	$6.94 \pm .71$	0.006

Table 2. Mean amount of salivary cortisol (nmol/L) and mean score of STAI.

Variable	BMG group	Control group	P
Salivary cortisol	4.22 ± 1.9	$2.56 \pm .87$	0.001
Trait anxiety	40.95 ± 13.24	25 ± 9.93	0.001
State anxiety	41 ± 9.70	27 ± 10.8	0.001

Discussion

BMG was first reported in 1,831 patients as a wandering rash of the tongue. However, studies hava specific etiology for BMG. Some reports indicated that BMG may relate to hormonal disturbances [9], psychologic findings [24], and diabetes mellitus [10]. Our hypothesis was that we would find significant differences in salivary levels of IL-1 and IL-8 in patients with BMG compared with those of the control group. The results of this study provide support for our hypothesis. In the present study, saliva was used to assess the level of inflammatory cytokines. Saliva is a safe and low-cost alternative and, as a biofluid, it has several advantages over blood supporting its use in diagnosis and assessment of diseases [25]. Studies have found that levels of some serum markers, such as IL-8, IL-1, and TNF-α, can correlate with those in saliva [26]. Some oral diseases, including oral cancer, *Lichen planus*, and periodontal diseases, have been associated with IL-1 deregulation [27]. In the present study, the mean salivary level of IL-1 in BMG was significantly higher than in the control group. The present results may suggest a possible association (although it is unsubstantiated) between *Lichen planus* and BMG representing inflammatory conditions [28]. However, such possible association may be related simply to the fact that both conditions represent inflammatory responses rather than a cause-and-effect outcome related to levels of IL-1. The literature demonstrates IL-1 as a genetic marker for periodontitis [27]. The periodontal condition of patients with oral lichen planus is significantly worse than that found in healthy control groups [29]. An increased incidence of periodontal disease was also noted in patients with ectopic BMG [30]. Therefore, it is possible that elevated salivary levels of inflammatory cytokines associated with BMG lesions may not be identified contribute to the increased incidence of periodontal disease among patients with BMG. However, the complex relationship between interleukins and different oral inflammatory conditions requires further investigation to better understand the biologic and clinical

associations between these conditions. Stress has been regarded as an important etiologic factor in BMG [7,8]. However, it may represent also an outcome, resulting from BMG. The present study was probably a pioneer in assessing the possible association between anxiety and BMG by using both a psychologic testing instrument (STAI) and a physiologic testing instrument (salivary cortisol level). Our study found a positive correlation between BMG and either psychologic factors or physiologic factors of anxiety. However, Shulman and Carpenter [1] found no significant relationship between stress and BMG. This discrepancy may be explained by the fact that in their study Shulman and Carpenter did not use physiologic measures of stress (such as serum cortisol levels) or questionnaires directly addressing stress. It should be pointed out that the clinical appearance or possible burning sensation of BMG may sometimes resemble cancer or sexually transmitted diseases, which can increase the anxiety level in those patients [31]. Therefore, the salivary cortisol levels and the state and trait anxiety levels (which reflect response to stress) are clinical parameters that play an important role in the investigation of BMG's possible etiology or Because immunologic and psychologic parameters may eventually represent risk factors that could influence the frequency of recurrence of BMG, some patients with BMG may benefit from behavioral evaluations and interventions to increase their ability to cope with stress in conjunction with symptomatic BMG.

Acknowledgement

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