

Nagihan Bilal^{1*}, M Fatih Karakus²,
Mihriban Dalkiran Varkal³, Osman
Fatih Boztepe⁴, Bora Bilal⁵ and Selman
Sarica¹

¹Department of Otorhinolaryngology, Faculty of
Medicine Kahramanmaraş Sutcu Imam University,
Turkey

²Ankara Golbasi Hasvak State Hospital,
Otorhinolaryngology Clinic, Turkey

³Istanbul Sisli Hamidiye Etfal Training and Research
Hospital, Psychiatry Clinic, Turkey

⁴Antalya Medikal Park Hospital,
Otorhinolaryngology Clinic, Turkey

⁵Department of Anesthesiology and Reanimation,
Faculty of medicine Kahramanmaraş Sutcu Imam
University, Turkey

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***Corresponding author:** Nagihan Bilal, Haydar
bey mah, 32120, Sok. Beytepe sitesi 4. Blok no: 13
Kahramanmaraş, Turkey, Tel: +90 505 251 36 18;
E-mail: nagihanyazan@gmail.com

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Research Article

An Assessment of the Levels of Anxiety and Depression in Patients with Recurrent Aphthous Stomatitis

Abstract

Backgrounds: There is a lack of valid and reliable studies in literature on both the distinctive and ambiguous relationship between the psychological profile and the occurrence of recurrent aphthous ulcers in the individual.

Objectives: The etiology of recurrent aphthous ulceration (RAU) is not well understood. This study analyzes the psychological treatment of patients with recurrent aphthous using valid, confidential and effective psychological measures.

Materials: In this study we included 50 patients with recurrent aphthous stomatitis who were undergoing no psychiatric treatment, as well as 50 age and gender matched healthy individuals as the control group. The study utilized the Beck Depression Inventory and STAI-S and STAI-T tests, which have been evaluated as valid sources for assessment.

Results: A comparison of the aphthous ulcer group with the control group revealed no significant difference in STAI-S psychiatric scores ($p > 0.05$). In contrast, the scores of the STAI-T of the patients with aphthous ulcers were found to be increased when compared to the control group ($p < 0.05$).

Conclusion: This study proposes a different overview for this area of etiologic research on this disease, based on the significant differences revealed by the STAI-T, which discovered increased anxiety levels in patients. Accordingly, there is need for more investigation into comorbid anxiety disorder and depression in patients with recurrent aphthous stomatitis, and an assessment of treatment with psychological traits, implying that further comparative studies are required to understand the issue.

Introduction

Recurrent aphthous ulceration (RAU) is one of the most prevalent oral mucosal human diseases. The most comprehensive and largest RAU study performed to date involved a sample of more than 10,000 young adult patients from 21 different countries. The said study demonstrated that 38.7% of male patients and 49.7% of female patients suffered from more than one RAU episode throughout their lives. In addition, nearly 25% of the patients included into the study described experiencing an episode (or episodes) in the 12 months preceding the study [1-3]. However, studies conducted in recent years, suggest a ratio of 40% [4]. It is clinically diagnosed with recurrent, painful yellowish white or grey, single or multiple, and round or oval ulcers with erythematous margins that are mainly confined to non-keratinized oral mucosa [5-8]. RAU lesions can be categorized into three groups on the basis of size, the number of ulcers and the features of the healing process: minor, major and herpetiform ulcerations [9]. The precise etiology and pathogenesis of RAU remains unclear, although several factors are generally considered as crucial in the development of RAU, such as nutrition, drugs, food hypersensitivity, hormones, infections, trauma, tobacco and psychological stress [10,11]. Many local and systemic factors have been associated with the condition, and there is also evidence of a genetic and immunopathogenic basis of RAU [12]. It is also generally

accepted that acute psychological disorders (e.g. stress and anxiety) play a role in the development of recurrent aphthous ulcers [2,13-16]. Stressful situations are thought to cause a transitory increase in salivary cortisol and/or provoke immunoregulatory activity in cases of inflammation by raising the number and the activity of leukocytes [2,15,17].

There is a lack of valid and reliable studies in literature on both the distinctive and ambiguous relationship between the psychological profile and the occurrence of recurrent aphthous ulcers in the individual. This study investigates and compares the psychological traits of patients with recurrent aphthous ulcers with healthy controls and their potential role in the occurrence of recurrent aphthous ulcers using valid, reliable and comprehensive psychological measurement methods.

Materials and Methods

In accordance with the Helsinki II Declaration, prior to the beginning of this study all of the study subjects signed an informed consent form obtained from the Ethical Committee of the University of Kahramanmaraş, Turkey.

In this study we included 50 sequential subjects suffering from both minor or major forms of RAU and 50 healthy volunteers. The

study subjects were volunteers recruited from the Ear, Nose and Throat (ENT) Department of Kahramanmaraş City State Hospital. Both the experimental and control groups were resident in the same geographical area, had the same socioeconomic status, and were matched for age and gender.

Non-smoker patients with a minimum two years history of minor, major and herpetiform RAU were included into the study. RAU was diagnosed based on clinical findings, and the patients were grouped depending on the severity of their RAU episodes and their ulcer types. All patients in the study were aged 18 or above, ensuring that they could understand and score the questionnaires correctly. Patients with medical conditions that would negatively affect their ability to understand or complete the study questionnaires (such as psychological disorders and mental problems) were not included into the study. The control group comprised persons with no RAU history who had been referred to our clinic for ENT treatment; in all other respects, these controls shared the same characteristics as the study group (or RAU) patients.

Patients who were less than 18 years of age; pregnant patients; patients with relatives taking part in the study; patients who received systemic steroids in the one month preceding the study; patients with a history of gastric bypass surgery or gastrectomy; patients who mistook their perioral lesions for RAU; and patients unwilling or unable to give informed consent were excluded from the study (Patients mistaking their perioral lesions for RAU were excluded to avoid the overrepresentation of herpetic lesions among the controls). Patients with the following systemic diseases were also excluded. Behçet's syndrome, celiac disease, cyclic neutropenia, periodic fever, mouth and genital ulcers with inflamed cartilage syndrome, pharyngitis and adenitis syndrome, aphthous stomatitis, low white blood cell counts, Sweet's syndrome, inflammatory bowel disease, Reiter's disease, HIV/AIDS, Systemic lupus Erythematosus and severe immunodeficiency.

Each patient was assessed, and a record made of the number, position, duration and frequency of their ulcers. The assessment also asked for dental and medical histories and disorders, and personal information regarding age, gender, education, occupation, address and marital status. Moreover, an assessment was made of the pain experienced by the patient when the ulcers came into contact with oral structures or food. The patients were exposed to an extensive medical assessment, including a detailed history, a full examination and laboratory checks, including hematological and tuberculin skin tests.

The fifty control participants included in the study had all referred to the ENT clinic for routine examinations, but had never experienced recurrent aphthous ulcers. To be included in the study, the controls had to be free of systemic diseases, allergic conditions or unfavorable habits related to tobacco and drug abuse. Complete physical examination and laboratory assessments (including hematological assessments) were performed for all study subjects.

Psychological assessments

Anxiety levels were measured using Spielberger's STAI (1983) which evaluates both trait anxiety as a general aspect of personality

(STAI-T) and state anxiety as a response to a specific situation (STAI-S). The sensitivity of the STAI-S and STAI-T scale to general stress has been shown consistently in researches of emotional reactions. STAI-T is unique in its measurement of anxiety independently of depression, and includes 40 questions for the assessment of both trait anxiety (20 questions) and state anxiety (20 questions). Each item is scored on a four-point scale, with response categories varying according to the nature of the question. For both levels, the range of values falls 20 and 80, with a high score indicating a higher level of anxiety. The questionnaire has been tested extensively for reliability and validity.

The second test, the Beck Depression Inventory (BDI) is commonly used as a self-report scale to assess the severity of depression. The BDI was developed to determine the type and the degree of depression based on symptoms [18], and takes the form of a questionnaire containing 21 items rating emotional, cognitive, motivational and physiological symptoms, among others. Each item consists of four expressions on a scale of 0 to 3 rating the intensity of depression as a reflection of the participants' feelings over the previous week. Possible scores range from 0 to 63, with a higher score indicating a more severe depression. The Turkish version of the BDI was standardized, and has been found to be reliable and valid.

Statistical analysis

The statistical analyses were performed using the Statistical Package for Social Sciences Statistical Software, release 21 (SPSS Windows Version 21, SPSS, Inc., Chicago, IL, USA), while a t-test was used to determine the average of the basic data. For the purpose of the study, $p < 0.05$ was considered statistically significant.

Results

The present study consisted of 50 participants with recurrent ulcers and 50 healthy controls (participants without recurrent ulcers). The study group was 54% (27) female and 46% (23) male, aged between 18 and 65 years (mean 36.9 ± 13.2). The control group was matched with the study group with respect to the number of patients and the ratio of males and females. The age average in the control group was 36.7 ± 12.7 , while the age range was between 18 and 63 (Table 1).

We determined that 56% (28) of the patients had good dental hygiene while 44% (22) had lower/reduced dental hygiene. Aphthous ulcers were determined to be minor in 88% (44) of the patients, major in 8% (4) and herpetiform in 4% (2). Food allergies, determined by patient histories, were present in 14% (7) of the patients. In a

Table 1: Patients characteristics and Serum levels of Ig E, Ig A, Ig G, C3, C4 in the control and patient with aphthous ulceration.

	Aphthous stomatitis	Control
Mean age	36.9 ± 13.2	36.7 ± 12.7
Female	27	23
Male	27	23
Ig E	8	6
Ig A	5	5
Ig G	4	2
C3	2	2
C4	0	2

determination of the increasing rate of Ig in patients, elevations of IgE, IgA, and IgG levels were evaluated as 14% (8), 10% (5) and 8% (4), respectively. C3 levels were assessed as positive at the rate of 4% (2), while none of the patients had increased C4 levels. In the control group, the increase in IgE, IgA and IgG levels was determined as 12% (6), 10% (5) and 4% (2), respectively. In addition, C3 and C4 levels were positive in 2% (1) and 2% (1) of the control group patients, respectively (Table 2).

A comparison of the aphthous ulcer group with the control group revealed no significant difference between the two in terms of the STAI-S psychiatric score (State-Trait Anxiety Inventory-State form) ($p>0.05$), with an average score of 43 in the patient group and 40.8 in the control group (Table 2).

In contrast, a significant difference was identified between the two groups in terms of the STAI-T scores ($p<0.05$), which were 49.9 in the patient group and 46.5 in the control group. No significant difference was determined between the male patients and the control group ($p>0.05$), while there was a statistically significant difference between the women ($p<0.05$) (Table 3).

The results of the Beck Depression Inventory revealed no significant difference between the two groups (Figure 1).

Discussion

It has been reported that the etiopathogenesis of RAU becomes complex when interactions with nutritional, hematologic and genetic factors [19,20], are included. For a long period, certain medical disorders were thought to be correlated with stressful situations. For example, Santos et al. reported that patients with Graves' disease had

experienced significantly more negative events and greater negative impacts prior to the onset of the disease [21].

One case-control study found that the stressful episodes occurred more often in the group of patients with *lichen planus* when compared to the control group, who had other dermatological diseases but not ones associated with psychosomatic causes [22].

In another case-control study of life events in patients with an onset/recurrence of psoriasis, it was found that more than 54% of cases had experienced at least one stressful event (47.36% for onset, and 63.51% for recurrence/extension) when compared with 19.52% in the controls, and a significant difference was identified in the mean number of stressful events between the patients and controls ($p<0.0001$) [23].

According to the correlation mentioned in the studies above, we sought to determine if stress played a role in the development of RAU, thereby contributing to the etiology.

The mechanisms of stress that result in RAU episodes are still unclear, although it has been suggested that elevated levels of salivary cortisol [2,15], or reactive oxygen species in the saliva, may initiate the onset of ulcers. That said, both myeloperoxidase levels and the status of reactive oxygen species were found to be unaltered in patients with RAU [24]. Due to stress, patients may bite their cheeks or lips, or engage in actions that may injure their oral mucosa, thus causing an episode [2,25]. A genetic variation in the pathways linked to stressful reactions may also be involved. For example, a polymorphism in the serotonin transporter gene, which is common in patients with depression, was significantly higher in the group of RAU patients when compared with the general population [9].

In the present study, it was reported that the patients with recurrent aphthous ulcers showed higher levels of anxiety than the controls, confirming the findings of the previous study [13-16]. It has been well documented that stress affects multiple immune system mediators, including phagocytosis, the production of cytokines and antibodies, and the distribution, proliferation and also activity of lymphocytes and natural killer cells [26]. Stressful transient and episodic situations may trigger the pathways of the recurrent ulcer histopathogenesis, bringing about a temporary increase of salivary cortisol and stimulation of immunoregulatory activity through the elevated number of leukocytes, due to inflammation.

Oral ulcers may cause painful lesions that can disrupt speaking, eating, drinking and even participating in daily activities. It is assumed that stress activates the mechanisms that are involved in the development of recurrent aphthous ulcers, leading to pain and negative impacts on daily activities, causing further stress. This can lead to a cycle of stress-ulcer-stress, where stress leads to ulcers, and ulcers lead to stress [14].

Most of the published data on psychological status and RAU report a correlation between the two. It has been stated that subjects with RAU are more anxious than healthy controls [13], while Victoria et al. found that 69 RAU patients had more variants in the promoter region 5-HHT (5HTTLPR), which is responsible for the serotonin expression, when compared to the control group. From

Table 2: Tested differences in average scores of the results.

	Study group	Control Group
STAI-S	43	40,8
STAI-T	49,9	46,5
BDI	16,5	13,7

Table 3: Terms of STAI-T (female patients and males patients average scores).

	STAI-T Study Group	STAI-T Control Group
Females	51,07	46,9
Males	42,9	40,8

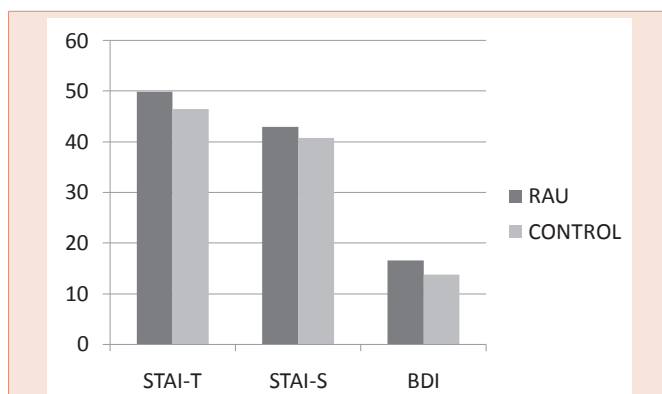


Figure 1: Tested differences in average scores of the results.

this they concluded that RAU patients tend to be more anxious than the controls [9]. Pedersen evaluated psychological stress in patients with RAU by means of a social readjustment rating scale and a visual analogue scale during the acute phase and the remission period, but could find no differences in the aforementioned scores between the two phases of the disease, concluding that there was no relationship between psychological life stress and repetitive RAU [27]. In contrast to the results of Pederson, the present study revealed significant differences in the anxiety trait scores of patients with RAU, which amplified the hypothesis regarding the role of anxiety.

Although the trait anxiety scores of the patients were higher than the control group in our study, Mahmoud K. Al-Omiri et al., demonstrated that no psychological profile or trait was related to the presence of recurrent oral ulcers [28].

Additionally, Albanidou-Farmaki et al. came up with similar findings to our research, claiming that anxiety, as both a trait and state, could play a role in patients with RAU, reporting significant differences between patients with RAU and the controls [2]. In this regard, they suggested that stress might be involved in the pathogenesis of RAU, as hypothesized in the present study.

Picek et al., found no significant differences in the anxiety treatment and state scores, or the depression scores, of the control group and patients with RAU during the acute phase. In contrast, there were significant differences in the anxiety state scores between the control group and the patients with acute RAU and patients with RAU during the remission period [12]. Soto-Araya et al. reported that anxiety and stress were significantly connected with RAU, unlike depression [16]. Cohen and Shafer also found a high incidence of RAU in patients under stressful situations [29,16]. McCartan et al. distinguished between RAU produced by known organic causes and stressful situations, expressed with significant rates of anxiety which cause a transitory increase of salivary cortisol [15].

We could find no significant difference in the depression scores of the patients with RAU and the controls, and so it can be assumed that depression does not play an important role in RAU in patients. Further assessment and careful scientific-based evidence is required to explore whether the psychological traits of a patient can predict their predisposition to recurrent oral ulcers.

Conclusion

Recurrent aphthous stomatitis is a common disease with an etiology that cannot be precisely identified. Our study introduces a different perspective to the etiologic research of this disease; a significant difference (assessed by STAI-T) revealed that anxiety levels were increased in patients, as a trait feature of their personality, suggesting that trait anxiety may play a role in its etiology. Although high levels of anxiety were found in the patient group, a relationship between depression and individuals with recurrent aphthous stomatitis was not determined. As such there is a need to investigate further comorbid anxiety disorder and depression in patients with recurrent aphthous stomatitis, and the assessment of treatment with psychological traits, requiring further comparative studies. Additionally research in this area may lead to the development

of strategies to predict and/or prevent RAU episodes based on identification of causative stressors.

Author Contribution

Nagihan Bilal and M. Fatih Karakus developed the original idea and the protocol, abstracted and analyzed data, wrote the manuscript, and is guarantor. Mihriban Dalkılıç Varkal contributed to the development of the protocol, abstracted data, and prepared the manuscript. Bora Bilal acquired data, statistical assistance, approved version to be published. Fatih Boztepe acquired data, proved version to be published. Selman Sarıca acquired data, proved version to be published.

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