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Effect of Stressful Life Events on the Onset and Duration of Recurrent Aphthous Stomatitis

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Abstract

Background—Recurrent Aphthous Stomatitis (RAS) is a common and painful oral mucosal disease. Possible etiologies include genetics, vitamin deficiencies, trauma, immune dysfunction and stress. The goal of the present study was to examine the relationship between the occurrence, type, and magnitude of stressful events and the onset and duration of RAS episodes.

Methods—160 subjects with a history of RAS completed a weekly phone survey for up to one year, providing data on the occurrence of RAS episodes and details of any stressful events they experienced during the previous week. During RAS episodes, subjects also completed daily paper diaries that recorded incidence and duration of the RAS episode. Stressful events were quantified using the validated Recent Life Changes Questionnaire (RLCQ), and were classified as mental or physical stressors.

Results—Stressful life events were significantly associated with the onset of RAS episodes ($p<0.001$), however not with duration of the RAS episodes. Experiencing a stressful life event increased the odds of an RAS episode by almost three times (OR=2.72; 95% CI 2.04-3.62). When controlled for each other, mental stressors had a larger effect (OR=3.46, 95% CI=2.54-4.72) than physical stressors (OR=1.44; 95% CI 1.04-1.99) on the occurrence of RAS episodes. RAS episodes did not occur more frequently or last longer with increasing stress severity.

Conclusions—In patients with a history of RAS, stressful events may mediate changes involved in initiation of new RAS episodes. Mental stressors are more strongly associated with RAS episodes than physical stressors.

Introduction and Background

Recurrent Aphthous Stomatitis (RAS), also known as canker sores, is one of the most common oral mucosal diseases. In the largest study on RAS, involving a sample of over 10,000 young adults in 21 countries, 38.7% of men and 49.7% of women had suffered from at least 2 episodes of RAS in their lifetime. Approximately 25% of the study population reported that an episode had occurred in the year prior to the study (1).

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Minor RAS is the most common form of the disease and makes up approximately 80% of reported RAS episodes. The episodes are characterized by round or oval-shaped ulcers, less than 1 cm in diameter, with erythematous margins and necrotic centers (2, 3). Although they usually heal within 10-21 days, these ulcers are often accompanied by significant pain, disproportionate to the size of the lesions. The painful nature of these ulcers leads to a negative impact on the patient's quality of life. One study reported that among oral health diseases, RAS patients scored the lowest on a quality of life questionnaire (4). The ulcers may prevent the patient from eating certain foods and compromise proper oral hygiene, which in turn can lead to other oral diseases such as caries and periodontal disease (2). Therefore, RAS does present a public health burden due to its high prevalence and associated pain and quality of life issues experienced by affected individuals. RAS morbidity is even higher in the major form, characterized by excruciatingly painful ulcers larger than 1 cm in diameter and lasting several weeks.

The exact cause of RAS is still unknown; however, genetics, vitamin deficiencies, trauma and immune dysfunction have been cited as possible etiologies (3, 5). Additionally, many studies have examined stress as a causative factor (3, 6, 7). Patients frequently report that they believe their RAS episodes are due to stress (6, 7). The research literature, however, yields contradictory results on the association of RAS with stress. For example, in one study of a group of RAS patients, there was no difference in stress scores from the previous 1-2 weeks, when measured during an active RAS episode as compared to when measured in the absence of a RAS lesion (6). On the other hand, another study reported that a significantly increased proportion of RAS patients had anxiety, as compared to a control group. Furthermore, salivary cortisol levels were also elevated in RAS patients as compared to controls (8).

One possible reason for these conflicting findings is that previous studies have not examined the effects of magnitude or specific type of stress on RAS. Further, most studies have focused on incidence of RAS, with little or no research on the effects of stress on the duration of RAS episodes. The aims of the current study were to study the effect of occurrence, magnitude, and type of stressful life events on the onset and duration of RAS episodes experienced by study subjects. We also examined the effects of age, gender, and a history of depressive or anxiety disorders on the onset and duration of RAS episodes.

Subjects and Methods

Study Overview

This study used data collected during a randomized, double-blind, placebo-controlled clinical trial to determine the effect of daily multivitamin supplementation on the incidence and duration of RAS episodes over a 12-month period. The primary outcomes of that trial are being reported separately (9). This study and the parent clinical trial were approved by the Institutional Review Board (IRB) at the University of Connecticut Health Center. All research subjects provided written informed consent.

Inclusion/exclusion criteria were identical for the parent clinical trial and this substudy survey for evaluation of stress. Inclusion criteria included a history of at least three episodes of minor RAS within the past year and age of 18 years or older. Patients were excluded if they had used multivitamins within 90 days prior to enrollment in the study, if they were pregnant or a current smoker, if they regularly used oral antimicrobial rinses or topical anti-inflammatory agents, or if they had any systemic condition, or took any medication, known to be associated with oral ulceration. Subjects with psychological and stress issues were not excluded. Detailed inclusion/exclusion criteria are available at www.clinicaltrials.gov, where the parent study is registered under identifier number NCT00527306. Subjects were

recruited from the local population using flyers, paycheck inserts and newspaper advertisements. The enrolled study population consisted of 160 subjects with a mean age of 36.03 (range 18-73) years, with 65% being female. Subjects were randomized to daily multivitamin supplement or placebo for a one year period. The placebo was identical to the multivitamin supplement except that it lacked the active ingredients. Participants and researchers administering the treatment and collecting data were blinded to treatment allocation. All subjects completed a standardized baseline medical history form, from which data on age, gender, and history of anxiety/depression was abstracted.

Collection of Data on Incidence and Duration of RAS Episodes

All subjects were asked to complete paper diaries that captured data on onset, duration, and healing of each RAS episode experienced during study participation. In addition, subjects were asked to complete a weekly telephone survey by calling an automated interactive voice response (IVR) system which recorded their responses. Subjects who did not call by Thursday evening of a given week received up to two reminder calls, which allowed subjects to take the survey at that time or call in later. Subjects were compensated US $5 for each weekly telephone survey completed. The survey asked subjects if they had experienced any mouth sores since the last (weekly) call. Subjects responded by pressing numbers on the telephone keypad (1 for yes and 0 for no). All subjects reporting mouth sores were asked to come in for a study visit so that the mouth sores could be clinically verified as RAS or not.

Collection of Data on Occurrence and Type of Stressful Events

The weekly telephone survey also asked subjects if they had experienced any illness or unusual stress since their last IVR call. Subjects responded by pressing numbers on the telephone keypad (1 for yes and 0 for no). Subjects who responded “yes” were further asked to verbally describe the illness or unusual stress and when it happened. This information was securely recorded and later transcribed.

Assessment of Magnitude and Type of Stressful Events

The magnitude of each stressful event reported by subjects was scored by two independent investigators, blinded to participants’ RAS status, using the Recent Life Changes Questionnaire (RLCQ) (10, 11,12). This validated scale lists 91 different life events that can lead to stress and assigns a numerical value (ranging from 18 to 123) to the level of stress the event causes. For example, if a subject reported a recent vacation, that event would have been scored 24, but the death of a spouse would have been scored 119. The score assigned for each reported stressful event was recorded as the magnitude of that event. Stressful events reported by subjects were also broadly classified as either “Physical Stressors” or “Mental Stressors”, based on the description provided. For example, if a subject had been involved in a physically traumatic accident or experienced a recent physical illness, those events would have been classified as physical stressors. Death of a family member would have been classified as a mental stressor. The responses of the two independent reviewers were compared to determine inter-rater reliability. Differences between the two investigators were resolved by discussion and consensus.

Statistical Analyses

Generalized estimating equations with a binary logistic model were used to model the odds of experiencing RAS episodes with stressful life event as the main predictor variable. An RAS episode was considered related to a stressful event if the stress was reported within 7 days before the reported start date of an RAS episode. Further models included age, gender, multivitamin supplementation, and history of depression or anxiety as covariates, to determine if these factors interacted with stress on the number of RAS events. For duration

of RAS episodes, a linear mixed model was used to examine if stressful events led to longer RAS episodes. Similar analyses were also conducted to test for the effect of specific types of stress (mental v/s physical stressors) on onset/duration of RAS episodes. In additional models, we assessed potential confounding effects of age, gender, multivitamin supplementation and history of depression/anxiety. All analyses were conducted in SPSS v17.

Results

A total of 160 subjects participated in the RAS stress study, 79 in the multivitamin arm and 81 in the placebo arm. The mean duration of study participation across all 160 subjects was 315 days. Of these, 114 subjects completed the full one year on study (58 in the active drug/multivitamin supplement arm and 56 in the placebo arm). Most of the subjects who did not complete the study were lost to follow-up despite multiple phone and mail reminders. The 160 subjects collectively reported a total of 784 stressful events and 660 RAS episodes.

Inter-Rater Reliability

The 784 stressful events were assigned an event description in the RLCQ by two independent investigators, blinded to RAS status. The inter-rater reliability of the two investigators was 80.4%. Stressful events on which the investigators initially differed were discussed and a consensus assignment reached; the consensus assignments were used for further analyses.

Occurrence and Magnitude of Stressful Events

Experiencing a stressful life event significantly increased the odds of having an RAS episode within 7 days (OR=2.72, 95% CI=2.04-3.62, $p<0.001$). However, stressful life events did not have an effect on the duration of RAS episodes ($p=0.73$). Among individuals with a stressful event, the degree of stress severity was not associated with RAS onset ($p=0.09$) or duration ($p=0.25$). Age, gender, treatment allocation, and history of anxiety or depression, did not change the association between stress and RAS onset or duration.

Type of Stress

When considering different types of stress, both mental and physical stressors significantly increased the odds of an RAS episode, but not the duration of an episode (mental stressors: $p=0.54$; physical stressors: $p=0.95$). When controlled for each other, mental stressors had a larger effect (OR=3.46, 95% CI=2.54-4.72, $p<0.001$) than physical stressors (OR=1.44, 95% CI=1.04-1.99, $p=0.03$) on the odds of having an RAS episode.

Discussion

Stressful events have been linked to the onset of certain medical illnesses for many years. For example, 80% of psoriasis patients reported the occurrence of a stressful life event before disease onset as compared to a significantly lower proportion of controls with fungal infections (13). A case-control study found that stressful episodes occurred significantly more often in a group of patients with lichen planus compared with controls who had other dermatological diseases not associated with psychosomatic causes (14).

The mechanisms whereby stress may result in RAS episodes are not well-understood. It has been suggested that increased levels of salivary cortisol (7, 8), or of reactive oxygen species (15) in the saliva, may lead to the onset of lesions. However, myeloperoxidase levels, as well as reactive oxygen species status (a possible determinant of stress level in the subject), were found to be unchanged in subjects with RAS (15). Due to stress, patients may begin to

chew their lips or perform other coping habits that cause trauma to the area, thus leading to an episode (7). A genetic alteration of pathways linked to stressful responses may also be involved. For example, a polymorphism in a serotonin transporter gene that is commonly found in patients with depression was significantly more prevalent in a sample of RAS patients compared with the general population (16). Stress has been reported to affect multiple immune system components including the distribution, proliferation and activity of lymphocytes and natural killer cells, phagocytosis, and production of cytokines and antibodies (17). Since RAS has also been linked to immune system alterations (3), this may at least partly explain the relationship of stress and RAS.

Our finding that stressful life events were significantly associated with onset but not duration of RAS episodes indicates that stress is involved with the initiation of an RAS episode but not necessarily its maintenance. Interestingly, the magnitude of stressful events was not associated with either RAS onset or duration. This suggests that RAS onset in different patients may occur at different stress threshold levels or that the stress threshold is low.

Both mental and physical stressors were significantly associated with the development of RAS episodes; however, mental stressors had a much more pronounced effect. This finding supports a systemic relationship of stress to RAS, such as via immune system changes. Among oral mucosal diseases, RAS has been found to have the highest proportion of patients with psychological problems (4). Another study, which quantified stress, anxiety and depression in a group of RAS patients, found that patients with RAS were significantly more stressed and had higher anxiety than a control group (18). In this study, we did not find any impact of a history of depression or anxiety on the relationship of stress with onset and duration of RAS episodes. However, it should be noted that only 25 of the 160 RAS subjects in this study reported such a history and this finding should therefore be interpreted with caution.

Data on stressful life events was collected prospectively on a weekly basis; therefore, recall bias was minimized. This was made possible by the IVR system. However, reporting bias may have occurred if subjects experiencing an RAS episode were more likely to report a recent stressful event as compared to those not experiencing an episode. Data on onset and duration of episodes was also collected prospectively using daily paper records (for incidence and duration) and IVR (for incidence). This close to real-time prospective collection of data was a strength of the study. A limitation of the study was that stressful events reported by subjects were retrospectively quantified by investigators via assignment to event descriptions in the RLCQ. While the high inter-rater reliability indicates that this quantification was done consistently, direct quantification of each stressful event by the subject experiencing it would have been preferable. The RLCQ is a validated scale that includes both major life events (e.g. death of a spouse) and minor stressful events (e.g. change in social activities). The literature indicates that such scales that incorporate minor events (hassles) in addition to major life events are better measures of life stress than those that evaluate major events only (19).

In conclusion, this study further clarifies the relationship between RAS and stress by reporting the effects of occurrence, magnitude, and type of stressful events on onset and duration of RAS episodes. Further research in this area may lead to the development of strategies to predict and/or prevent RAS episodes based on identification of causative stressors.

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