SEASONAL VARIATIONS AND BEHÇET'S DISEASE ACTIVITY

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Abstract
Behçet's disease (BD) is a systemic vasculitis with mucocutaneous manifestations such as recurrent oral ulcers and genital ulcers in addition to major organ involvements including the vascular and central nervous systems. Many studies have found that the prevalence of clinical symptoms of BD varies by geographical region. The course of BD is characterized by relapses and remissions. Infectious agents and altered microbiomes have been blamed for exacerbations of the disease. Stress, physical exhaustion, mechanical oral trauma, and hormonal effects have been specifically associated with flare-ups. A seasonal pattern in the activation of certain diseases, such as rheumatoid arthritis and systemic lupus erythematosus, has been reported. However, the relationship, if any, between the seasonal changes and the symptoms and organ involvements of BD has yet to be determined. In this review, we discussed whether clinical findings in BD patients are related to the seasons in terms of activation.

Keywords: Behçet's disease, Seasons, Weather, Exacerbation

INTRODUCTION
Behçet’s disease (BD) is a multisystemic vasculitis which may cause mucocutaneous symptoms such as recurrent oral ulcers and genital ulcers as well as ocular, articular, vascular, gastrointestinal, and nervous system involvements. Men typically have a more severe course of disease than women, and disease severity tends to lessen over time. Both innate and acquired immunity play a role in the pathogenesis of BD [1]. BD is a multifactorial condition of an uncertain etiopathogenesis. Aside from HLA and non-HLA genetic predisposing elements and epigenetic factors, environmental factors such as infectious agents (both bacterial and viral) and specific microbiome alterations play a significant role in BD pathogenesis [2]. BD is characterized by exacerbations and remissions. Many factors may trigger the disease activation. Infections not only play a role in BD pathogenesis, but also cause BD symptoms. In BD patients, there is a well-known link between disease relapse, particularly oral ulcers, and stress, physical exhaustion, nutrient intake, and smoking [2,3].

There is a long-held and widespread belief that certain rheumatic diseases are influenced by the weather conditions (e.g., temperature and humidity). The severity of rheumatic diseases may change by seasons [4]. Activation of rheumatic diseases across the seasons has been well studied among patients with rheumatoid
arthritis and systemic lupus erythematosus [5-9]. Studies on gout disease and Sjogren's syndrome are also available, albeit to a lesser extent [10-12]. Although the above-mentioned classical triggering factors governing BD are widely recognized, studies to assess the role of seasons on disease activation are scarce [8,13-17].

In this article, we reviewed the relationship between the seasons and the activation of basic clinical symptoms in BD patients. We also discussed whether seasonal changes have any effect on the activation of oral ulcers, the disease component that has the greatest impact on life quality.

SEARCH STRATEGY
The search strategy of the current review was based on review strategies [18]. We have searched the databases of Web of Science, Scopus, and MEDLINE/PubMed using the keywords “Behçet’s Disease” or “Behçet’s Syndrome” [AND] “Season” or “Seasonal” or “Weather” from database inception to November 2021. Original articles, case series, and reviews written in English were selected for this review. Articles written in languages other than English were not included in the study. Two authors (DUC and CK) independently screened all relevant articles' titles, abstracts, and full texts. The studies on seasonal association of any organ involvement of BD were included. The studies investigating the seasonal association of oral ulcers were analyzed separately.

For the purpose of clarity, we will first briefly review the classical triggering causes of BD and then concentrate on the activation of skin, joint, eye, and gut involvements and of oral ulcers through seasonal changes.

DISCUSSION

BEHÇET’S DISEASE – THE CLASSICAL TRIGGERING FACTORS
Several environmental factors may lead to epigenetic modifications, and this may be the reason why BD has a higher prevalence in certain geographic regions. The HLA class I antigen HLA-B51 has been described as the predominant genetic susceptibility factor in BD etiopathogenesis in many populations particularly along the ancient Silk Road spanning from the Eastern Asia to the Middle East and the Mediterranean basin [2].

Furthermore, environmental factors such as infections and other triggering factors cause disease exacerbation in the course of BD. Mechanical oral traumas, hormonal factors, ingestion of certain food, and psychological stress are recognized as classical triggering factors. Dental intervention and toothbrushing are exemplary mechanical oral traumas featuring salient factors that trigger oral ulcers [2,19]. In the majority of BD patients, relapse of oral ulcer has a reported association with stress and fatigue [3,19]. In a study evaluating 200 BD patients, it was revealed that mucocutaneous lesions exacerbate especially with menstruation [20]. Hormonal fluctuations have been associated with disease activity. Reports have implicated that diet-related factors might result in exacerbation of BD, specifically the mucocutaneous lesions. The varying ranges of cultural factors and socioeconomic characteristics among the studies have consequences on the dietary composition and thus its effect on disease exacerbation. Indeed, the set of offending food listed in a Turkish study composed of eggplant, walnut, carbonated beverages, tomato, hot pepper, spices, sunflower, peanut, almond, and zucchini, whereas a different set of dietary ingredients such as nut, pineapple, citrus fruits, cheese, strawberry, tomato, spice, banana, dried fruits, and kiwi was responsible for the exacerbation of oral ulcers in the case of French patients [3,21]. Smoking has a well-established impact on oral ulcers of BD. Oral ulcers have been shown in studies to reactivate after patients stop smoking [22].

The impact of seasons on the course of rheumatic disease has long been questioned, particularly by the patients. The effect of various seasonal factors such as weather, temperature, humidity, sunlight, and atmospheric pressure on the activation of certain rheumatic diseases has been shown [6,23].

In addition to the well-established proven triggers causing exacerbation of certain BD symptoms, it is found, although rarely, that some BD symptoms exacerbate upon seasonal changes. From this point on, we will explain the seasonal association with BD exacerbation in terms of symptoms or organ involvement of BD.

BEHÇET’S DISEASE AND SEASONAL ASSOCIATION

Behçet’s Disease – Skin Involvement and Seasonal Exacerbation
In BD, the most well-known and common skin lesions are erythema nodosum, pseudofolliculitis, papulopustular, or acneiform lesions [1]. In a study using BD-checklist 92, the skin involvement rate was 85.4%, and the patients with skin involvement experienced worse symptoms induced by the changes in climate and season compared
with the patients without any skin involvement [OR 3.57 (95% CI 1.21-10.54 p = 0.022)] [24]. Another study has enrolled 410 patients of whom 73.4% had skin involvement and 22.9% had an association of BD symptoms with seasonal changes. In the latter study, it was not specified on which organ involvement(s) exacerbations had occurred, but it was indicated that exacerbations occurred during the spring, summer, and winter seasons [14]. In another study encompassing 1155 BD patients, 11.2% of the patients had skin involvement and symptom flare-ups have been associated with season in 21.3% of patients. Similarly, this study lacks information on which organ involvement(s) exacerbations occurred, and it was indicated that exacerbations occurred during the spring, summer, and winter seasons [13].

**Behçet’s Disease – Joint Involvement and Seasonal Exacerbation**

Typically, arthritis in BD is in the form of repetitive, non-deforming monoarthritis or oligoarthritis. In approximately 5% of the patients, involvement of small joints may be predominant [1]. Evaluating 16 patients, of whom 11 had BD (69%), seasonal exacerbation of joint pain was reported specifically in the autumn (50%) and/or spring (38%) period (some being in more than one season) [8]. In the study with 1155 BD patients, joint involvement was detected in 24.2% of patients and an association between the symptom exacerbations and the seasons was determined in 21.3% of the cohort. In that study, again, no information was provided regarding which organ involvement(s) had exacerbated, yet they had taken place during the spring, summer, and winter seasons [13].

**Behçet’s Disease – Intestinal Involvement and Seasonal Exacerbation**

Gastrointestinal involvement of BD is more common in Eastern Asia including Korea and Japan (5%-25%) than in the Mediterranean and other western countries (0%-3%). The leading findings in the intestinal involvement of BD are change of bowel movements, weight loss, abdominal pain, diarrhea, and gastrointestinal bleeding. Gastrointestinal BD is characterized by recurrent disease exacerbations [1]. In a cohort of 268 patients with gastrointestinal BD, 339 relapses experienced by 142 patients were evaluated and the seasons with the most frequent relapses were spring and autumn, more specifically the months of May and September. In comparison to winter, spring and autumn were found to have higher rates of exacerbations (HR 1.92 and 1.91, p-value =0.001, respectively) [15].

**Behçet’s Disease – Uveitis and Seasonal Exacerbation**

Ocular findings are the most challenging symptom of BD, considering their prevalence and morbidity. Uveitis and neuro-ophtalmic manifestations of BD remain to be a potential threat of vision loss [1]. A total of 200 uveitis patients including 142 BD-related cases were recruited in a study which pointed out that uveitis was most often encountered during autumn to winter transmission with higher incidence rates in October and November. The authors have commented that the incidence of uveitis is related to seasonal changes [16]. In the study of 1155 BD patients, 28.5% of the patients had ocular involvement. In that study, seasonal association was sought not for the onset but for exacerbations of BD. Although there is no information about specific organ involvement(s) of the patients that had exacerbated, it is stated that the exacerbations occurred during the spring, summer, and winter seasons [13].

**Behçet’s Disease – Oral Ulcers and Seasonal Exacerbation**

Oral ulcers feature out as the most common symptom at onset and in overall BD at a rate of 97%-99%. Moreover, outpatient visits related to BD are most frequently due to oral ulcers which is one of the most active symptoms with consecutive remissions and recurrences [25]. Therefore, oral ulcer developed in BD patients is one of the far most studied symptoms. Nevertheless, our knowledge pertaining to the impact of seasonal variations on BD remains limited. There are only a few studies which have investigated the relationship between BD-induced oral ulcers and seasons [8,17]. Only in one study, exacerbation of oral ulcers was associated with seasons. In that study, the investigators have applied a self-reported questionnaire to assess the oral ulcer-season relationship and the characteristics of oral ulcers in BD patients. In their 90-patient cohort, the exacerbation of oral ulcers was due to stress in 92%, infection in 16.7%, oral trauma in 7.8%, certain food in 12.2%, and seasons in 33.3%. Of the patients, 60% stated that the winter months worsen their oral ulcers, whereas 20% indicated that their oral ulcers worsened during the autumn months [17]. In another study, the exacerbation of oral ulcers was not related to the weather conditions [8]. Two other studies from Korea found seasonal differences in the degree of severity of BD symptoms. However, neither of them has precisely delineated which symptoms aggravated in relation to seasons [13,14]. Consequently, the controversial and different results from studies on activation of oral ulcers in BD upon seasonal changes might be driven by the patient origin and/or geographic variation in the studies which have reported an association.
CONCLUSIONS

There has been a small number of studies that have clarified the relationship between seasonal variations and activation of cutaneous, articular, bowel involvements, oral ulcers, and the overall disease in BD. These studies were mostly conducted in Korea, at the first place Japan, China, and Turkey. Altogether, these studies conducted in different geographic areas suggest a role for seasonal factors in the exacerbation of certain symptoms and organ involvements of BD. Along with the classical triggering factors, such a possible effect should also be kept in mind by medical practitioners, particularly by those working in geographic areas with a higher BD prevalence. In the future, larger studies including seasonal variations such as air, temperature, humidity, sunlight, and atmospheric pressure will more clearly reveal the effect of seasonal variations on the BD exacerbation, both in general and on organs.

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AUTHOR CONTRIBUTIONS

Both authors substantively contributed to the drafting of the initial and revised versions of this review. They take full responsibility for the integrity of all aspects of the work.

CONFLICTS OF INTERESTS

Both authors have completed the ICMJE Disclosure Form (http://www.icmje.org/disclosure-of-interest/; available on request from the corresponding author). Both authors declare that there are no potential conflicts of interest.

DISCLAIMER

No part of this review is copied or published elsewhere in whole or in part.

REFERENCES

Болезнь Бехчета (ББ) представляет собой системный васкулит, который поражает сердечно-сосудистую и нервную системы, а также характеризуется кожно-слизистыми проявлениями, такими как рецидивирующие язвы в полости рта и генитальные язвы. Имеющиеся исследования показали, что распространенность клинических симптомов ББ варьируется в зависимости от географического региона. Течение ББ характеризуется рецидивами и ремиссиями. Обострение болезни связывают с инфекционными агентами и измененными микробиомами. Стресс, физическое истощение, механические травмы полости рта и гормональные нарушения также провоцируют обострения. Имеются данные о сезонном характере обострений некоторых заболеваний, таких как ревматоидный артрит (РА) и системная красная волчанка (СКВ), но взаимосвязь, если таковая имеется, между сезонными изменениями и проявлениями, поражением органов при ББ на данный момент не установлена. В данном обзоре мы рассмотрели, связаны ли клинические данные у пациентов, страдающих ББ, с сезонами с точки зрения развития обострений.

**Ключевые слова:** Болезнь Бехчета, время года, погода, обострение