



## ARAŞTIRMA / RESEARCH

### Are mucocutaneous lesions seasonal in Behçet's disease?

Behçet hastalığında mukokutanöz lezyonlar mevsimsel midir?

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#### Abstract

**Purpose:** Although it is worth to investigate seasonality in a disease that has a recurrent course, this issue has not been dealt with sufficiently for Behçet's disease. The aim of the study was to evaluate whether or not frequencies of its mucocutaneous attacks varied between months of the year.

**Materials and Methods:** One hundred eight patients with Behçet's disease were retrospectively evaluated in terms of attacks of oral aphthae, genital ulcers, and erythema nodosum. For their each visit, a four-week period preceded this visit and dates of attack onsets in this period were taken into consideration. Then, by using them, mean monthly attack numbers were calculated for time series analysis.

**Results:** Although mean monthly attack numbers were higher in May and October for oral aphthae and in August for genital ulcers, seasonalities were not verified by time series analysis.

**Conclusion:** After a literature search on PubMed, there is only one study that detected no seasonality for mucocutaneous lesions of Behçet's disease, and only one study detected a seasonality for oral aphthae. However, it is worth noting that time series analysis is not utilized in these studies. Since the present study is retrospective, its results should be verified by diary-based prospective studies that include time series analysis.

**Keywords:** Behçet disease, Behçet's syndrome, oral ulcers, genital ulcers, seasonal variations

#### Öz

**Amaç:** Tekrarlayan seyir gösteren bir hastalıkta mevsimsellik araştırılmaya değer olmakla birlikte Behçet hastalığında yeterince ele alınmamıştır. Çalışmanın amacı, mukokutanöz atakların sıklığının aylar arasında farklılık gösterip göstermediğini değerlendirmektir.

**Gereç ve Yöntem:** Behçet hastalığı olan 108 hasta oral aft, genital ülser ve eritema nodosum atakları açısından retrospektif olarak değerlendirildi. Hastaların her ziyaretinde, bu ziyaret öncesindeki dört haftalık süre ve bu sürede atakların başlangıç günleri dikkate alındı. Daha sonra bunları kullanarak, zaman serisi analizi için, aylık ortalama atak sayıları hesaplandı.

**Bulgular:** Oral aftlar için Mayıs ve Ekim aylarında, genital ülseler için Ağustos ayında ortalama atak sayıları daha yüksek olmasına rağmen, zaman serisi analizi ile mevsimsellik doğrulanamadı.

**Sonuç:** Pubmed'de yapılan literatür taramasının ardından, Behçet Hastalığının mukokutanöz lezyonları için mevsimsellik tespit etmeyen sadece bir çalışma ve oral aft için mevsimsellik tespit eden sadece bir çalışma bulundu. Ancak bu çalışmalarda zaman serisi analizinin kullanılmadığını belirtmekte fayda vardır. Bu çalışma retrospektif olduğu için sonuçları zaman serisi analizini kullanılarak, günlük-tabanlı prospektif çalışmalarla doğrulanmalıdır.

**Anahtar kelimeler:** Behçet hastalığı, Behçet sendromu, oral ülseler, genital ülseler, mevsimsel değişimler

## INTRODUCTION

Since the first description of Behçet's disease by Hulusi Behçet in 1937, its clinical spectrum has widened. However, it has kept its recurrent nature. If a disease shows a recurrent course, a question arises

spontaneously that whether or not its course is periodic, particularly whether or not it possesses seasonality. Since some of triggering factors in Behçet's disease such as infections and food consumption may exhibit seasonal variations in incidence or in pattern, severity of symptoms in

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Behçet's disease may also increase in particular seasons<sup>1</sup>. However, there are only several studies aimed to answer the question about seasonality in Behçet's disease. While some studies were not on mucocutaneous symptoms<sup>2,3</sup>, some did not specifically deal with individual mucocutaneous symptoms<sup>4,6</sup>. One of the studies evaluated skin manifestations, oral ulcers, and genital ulcers in terms of seasonality, but involved only 16 patients<sup>7</sup>. Finally, only one of the studies examined the relationship between oral ulcers and seasons in a sufficiently large group of patients<sup>8</sup>. However, their findings were based on patients' beliefs. Since the current literature is not sufficient to make precise conclusions, in the present study, the hypothesis of seasonality of mucocutaneous attacks was investigated with time series analysis by evaluating records of patients with Behçet's disease, whom were questioned at each visit about how many and when did they suffered attacks in the last four weeks. By taking into account that the main goal of treatment in Behçet's disease is to suppress attacks<sup>9</sup>, results of the present study may guide seasonal adjustments in the treatment protocols.

## MATERIALS AND METHODS

### Patients and data collection

Records of 170 patients with Behçet's disease were reviewed, who had fulfilled The International Study Group Criteria<sup>10</sup> and who had been followed up by a single dermatologists in the Department of Dermatology in Medical School of Çukurova University. Sixtytwo patients with only one visit within a period of two and a half years were excluded, so only 108 patients with at least two visits within this period were included. In these visits, the patients were asked about numbers and dates of attacks of oral aphthae, genital ulcers, and erythema nodosum within the last four weeks. Such information had not been collected for papulopustular lesions, given that the onset and end of their attacks are not as clear as those of oral aphthae, genital ulcers, and erythema nodosum, although papulopustular lesions of Behçet's disease also follow a waxing and waning course.

### Main outcome

Mean monthly attack numbers for oral aphthae, genital ulcers, and erythema nodosum were based on number of attacks per patient-days. For each month,

patient-days were calculated by summing number of that month's days belonging to 4-week periods ending with visits. For each month, number of attacks was calculated by summing number of attacks reported by the patients to be occurred in that month. To find mean monthly attack numbers, number of attacks was divided by patient-days, and then multiplied by lengths of months in days.

### Statistical analysis

The variables "mean monthly attack numbers" for oral aphthae, genital ulcers, and erythema nodosum were converted into time series objects and analyzed by R (R Core Team, 2018) and its "seastests" library. First, the time series objects were decomposed into seasonal, trend, and irregular components using loess (locally estimated scatterplot smoothing) regression. Then, the Webel-Ollech overall seasonality test (WO-test) was performed to verify seasonalities. This study was approved by the Clinical Researches Ethics Committee of the Medical Faculty of Çukurova University (Date: 11.06.2021, Number: 112/06).

## RESULTS

Of 108 patients, 71 were male; and 37, female (Table 1). Their ages ranged from 15 to 51 years, and the mean age was 33.7 years (SD  $\pm 8.2$ ) at the first visit. All patients suffered from oral aphthae at any time in their disease course; 88.9%, genital ulcers; 84.3%, papulopustular lesions; 56.5%, erythema nodosum; and 17.6%, thrombophlebitis. The pathergy test was conducted on 99 patients, and returned positive in 50.5% of the cases. As for systemic involvements, articular disease was found in 73.1% of the patients; ocular, 36.1%; vascular, 19.4%, neurological, 4.6%; and intestinal, 1.9%. In almost 90% of the visits, the patients were under treatment with systemic drugs, mostly with colchicine. Only four patients were followed without treatment.

Only patients with at least two visits were considered for this study. Its maximum was fifteen; and its mean, 4.4. Since the review involved a period of two and a half years, there were 30 months. For oral aphthae, the mean monthly attack number ranged from 1.13 to 2.67, and was averagely 1.97 (SD  $\pm 0.38$ ). For genital ulcers, the mean monthly attack number ranged from 0 to 0.62, and was averagely 0.27 (SD  $\pm 0.16$ ). For erythema nodosum, the mean monthly attack number ranged from 0 to 0.46, and was averagely 0.18 (SD  $\pm 0.12$ ).

Table 1. Descriptive characteristics of the patients (N=108).

Variable	Group / Finding	Number (n)	Percentage (%)
Gender	Female	37	34.3
	Male	71	65.7
Age	11-20 years	5	4.6
	21-30 years	35	32.4
	31-40 years	42	38.9
	41-50 years	25	23.1
	51-60 years	1	0.9
Mucocutaneous lesion	Oral aphthae	108	100.0
	Genital ulcers	97	89.9
	Papulopustular lesions	91	84.3
	Erythema nodosum	61	56.5
	Thrombophelebitis	19	17.6
Pathergy	Positive	50	46.3
	Negative	49	45.4
Systemic involvement	Articular	79	73.1
	Ocular	39	36.1
	Vascular	21	19.4
	Neurological	5	4.6
	Intestinal	2	1.9

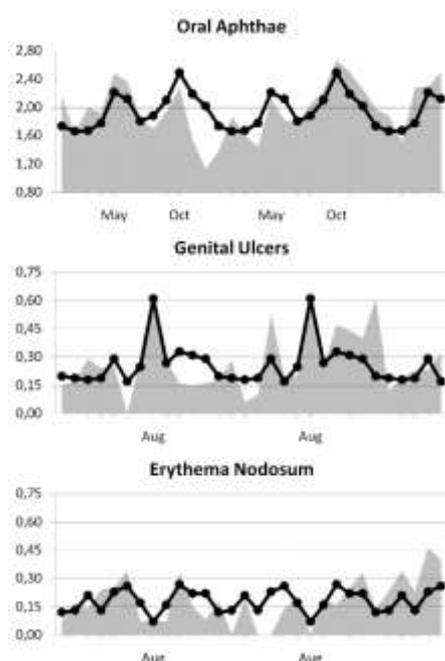


Figure 1. The mean monthly attack numbers (gray areas) and their seasonal components (black lines) for oral aphthae (top), genital ulcers (middle), and erythema nodosum (bottom).

The top of Figure 1 illustrates the mean monthly attack numbers for oral aphthae and their seasonal

components, which were obtained from the decomposition done by using the former numbers as a time series. According to these components, it seemed that attacks of oral aphthae showed peaks in May and October. However, the WO-test denied seasonality.

The middle of Figure 1 illustrates the mean monthly attack numbers for genital ulcers and their seasonal components. According to these components, it seemed that attacks of genital ulcers peaked in August. However, the WO-test denied seasonality once again. The bottom of Figure 1 illustrates the mean monthly attack numbers for erythema nodosum and their seasonal components. According to these components, no obvious peak was visible for attacks of erythema nodosum, while a slight nadir could be seen in August. The WO-test again denied seasonality.

## DISCUSSION

On October 14th 2021, a search was carried out in PubMed for seasonality in Behçet's disease, using all possible spelling formats, including: "Behçet's disease", "Behçet disease", "Behçet's syndrome", and "Behçet syndrome". For a comprehensive search, the word "season" was followed by an asterisk: "season\*". So, only seven relevant studies were found. In a study on patients with rheumatic inflammatory autoimmune diseases including

Behçet's disease, no significant seasonal distribution was found for episodes of uveitis<sup>2</sup>. In a study that involved 268 patients with intestinal Behçet's disease, a biphasic pattern (peaks in spring and autumn) was observed in exacerbations of the disease<sup>3</sup>. Two studies from Korea, reported in 1988 and 1997, included 410 and 1155 patients with Behçet's disease, respectively<sup>4,5</sup>. Slightly over 20% of these patients showed seasonal aggravations, especially in summer and spring. However, the status of individual symptoms in these seasonal aggravations was not mentioned in these reports. A study from Japan, reported in 2019, dealt with mucocutaneous symptoms of Behçet's disease as only three categories, namely oral aphthous ulcers, genital ulcers, and skin involvement<sup>6</sup>. Patients with skin involvement reported worse symptoms based on climate, as compared with patients without skin involvement.

Only two studies are investigating a relationship between seasons and individual mucocutaneous symptoms of Behçet's disease. The first study was from Israel and involved 16 patients<sup>7</sup>. According to answers to a telephone questionnaire, exacerbations of joint pains were more common in autumn and spring. However, oral ulcers, genital ulcers, and skin manifestations had no seasonal pattern. The second study was from Turkey and involved 100 patients<sup>8</sup>. A self-reported questionnaire was used in this study. The patients were asked to answer the following questions: "Do you believe that seasons have a part for the occurrence of oral ulcer? If you believe that there is a relationship between oral aphthous ulcer and seasons, which season aggravates the occurrence of oral ulcer?" Thirty patients believed that there was such a relationship. Eighteen patients reported winter as the aggravating season; 6 patients, autumn; 5 patients, summer; and 1 patient, spring.

Seasonality is a subject of time series analysis which is a statistical technique. While the aforementioned two studies did not use such an analysis, in the present study, it was used in order to explore a seasonality for individual mucocutaneous symptoms of Behçet's disease. However, no significant seasonality for oral aphthae, genital ulcers, and erythema nodosum was found. On the other hand, there are four main limitations of the present study. First, it has a retrospective design. Second, for none of the studied patients, a complete information comprising all months in the study's period of two and a half years was present. Third, the patients were

almost exclusively were under treatment with systemic drugs, so the results of the present study could not explore the natural course of Behçet's disease. Fourth, because of the retrospective nature, it was not possible to evaluate effects of triggering factors, such as infections, on seasonality. Another limitation is that a power analysis was not done to calculate the sample size.

It is recommended for future studies exploring seasonality effects in Behçet's disease, to utilize a prospective design, meaning the study should ask patients to individually record their future attacks, and potential triggering factors, in a diary. It is also recommended to include a time series analysis for statistical evaluation. Since it is not ethical to leave patients without treatment, exploration of seasonality in the natural course of Behçet's disease is somewhat impossible. Instead, one may try to follow a standardized treatment protocol for patients included in such a study.

**Yazar Katkıları:** Çalışma konsepti/Tasarımı: BFK; Veri toplama: BFK; Veri analizi ve yorumlama: BFK; Yazı taslağı: BFK; İçeriğin eleştirel incelenmesi: BFK; Son onay ve sorumluluk: BFK; Teknik ve malzeme desteği: BFK; Süpervizyon: BFK; Fon sağlama (mevcut ise): yok.

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**Conflict of Interest:** Authors declared no conflict of interest.

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