

# Prevalence of Chronic Rhinosinusitis in the Setting of Behçet Disease

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**Abstract:** Behçet disease (BD) is a systemic autoimmune/autoinflammatory, T helper 1–mediated condition. It is well known that the prevalence of a T helper 1–mediated disease increases in the presence of another T helper 1–mediated comorbidity. The purpose of this study was to investigate the prevalence of T helper 1–mediated chronic rhinosinusitis without nasal polyposis (CRSsNP) and T helper 2–mediated chronic rhinosinusitis with polyposis in the presence of comorbid BD. Sixty-nine patients and 74 healthy controls were included in the study. Participants were asked to complete a questionnaire for symptoms of rhinosinusitis. Nasal cavities were scored using the Lund-Kennedy endoscopy scores. Paranasal sinus computed tomography imagings were scored according to Lund-Mackay radiology scores. Skin prick tests were carried out for all participants to determine the predisposing role of allergy (T helper 2 disease) in the etiopathogenesis of rhinosinusitis among patients and controls. Patients' endoscopy, radiology, and skin prick testing scores were evaluated with regard to BD activity.

The prevalence of CRSsNP was 23.2 % in BD and 2.7% in normal population. The CRSsNP was more frequently seen in patients than in the healthy controls ( $P = 0.002$ ). The BD patients displayed worse scores on their left sinonasal endoscopy. No statistically significant difference was seen between BD and control groups with regard to Lund-Mackay radiology scores of both sides. The presence of an allergic response to a specific allergen in skin-prick testing were confirmed in 25 patients (36.2%) and 17 controls (23.0%). However, the difference was not statistically significant. There were positive responses to more allergens when BD activity was reduced.

The CRSsNP thought to be of T helper 1–mediated origin was more frequently seen in the presence of comorbid BD.

**Key Words:** Chronic rhinosinusitis, autoinflammatory, autoimmune, Behçet disease, Th1 immunity, Th2 immunity, skin prick test, allergic reaction, Lund-Kennedy scores, Lund-Mackay scores

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Behçet disease (BD) is a chronic, relapsing condition of uncertain etiology affecting small vessels in multiple systems of the body. The disease presents with a large spectrum of clinical manifestations varying from mucocutaneous, ocular, vascular, gastrointestinal, and musculoskeletal to central nervous system involvement.

Despite ongoing debate on the autoinflammatory, autoimmune, or infectious etiology of the disease, various immunologic studies have demonstrated an immune hyperreactivity to streptococci, which is possibly triggered by an infectious agent.<sup>1</sup> Antigens derived from streptococci, staphylococci, mycobacteria, and herpes simplex virus have been thought to be contributory factors in the etiology.<sup>2</sup> The physiology and pathogenic properties of these microorganisms led to the synthesis of specific proteins known as the heat-shock proteins (HSPs). Microbial HSP, which shows significant homology with human mitochondrial HSP, is classified among the endogenous molecules called alarmins that signal tissue and cell damage. They are known to induce the secretion of proinflammatory cytokines leading to T helper 1 (Th1) type cell-mediated inflammatory and immune responses in BD.<sup>3</sup> Th1 immune response is a useful marker of BD activity demonstrating the inflammatory, autoimmune condition of the disease.<sup>4</sup>

The presence of Th1-mediated comorbid autoimmune diseases has recently been shown to impact the prevalence of chronic rhinosinusitis (CRS) without polyp formation (CRSsNP).<sup>5</sup> Reciprocally, CRSsNP, which is characterized by a predominantly neutrophilic inflammation, is known to exhibit Th1 responses.<sup>6,7</sup> Furthermore, in the presence of a Th1 autoimmune disorder, the prevalence of CRSsNP has been observed to be higher than in the general population.<sup>8,9</sup> As in other autoimmune diseases, the intrinsic mucocutaneous barrier that separates host tissues from the external environment is affected in BD as a consequence of poor mucosal perfusion secondary to vasculitis. The injury to the mucosal lining caused by this autoimmune versus autoinflammatory condition makes the sinonasal mucosa susceptible to penetration by bacteria and potential infection.<sup>10,11</sup>

Starting from these observations suggesting that BD may predispose patients to CRSsNP, we aimed to determine the frequency of CRS in BD and to compare the prevalence of CRS between patients and a reference group of healthy individuals.

## MATERIALS AND METHODS

### Study Design

This was a case-control study designed to investigate the prevalence of CRS among patients with BD. The study protocol was approved by the institutional local ethics committee at Bezmialem Vakıf

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Gureba Educational and Research Hospital with study ID #VGEAH 11/19. Informed consent was obtained from each participant.

### Participants and Selection Criteria

Patients who were diagnosed as having BD, according to the criteria described by the International Study Group for Behçet's disease, constituted the study group.<sup>12</sup> Healthy controls were selected from the parents of children who were admitted to the ear nose and throat clinic for tonsillectomy and adenoidectomy and from the spouses of those who were attending the clinic with any otorhinolaryngological symptom. Exclusion criteria were (1) pregnancy or expecting to be pregnant within 6 months or lactating, (2) a known hypersensitivity to skin prick tests (SPTs), and (3) serious systemic diseases. Patients and controls were all evaluated in the same period of the year (November–February) to minimize any inconsistencies that may occur because of seasonal variations.

### Evaluation Parameters

#### Diagnosis and Frequency of Symptoms

Demographics and medical history of all patients and controls were recorded. Participants were questioned for the presence of major and minor symptoms of clinical rhinosinusitis, which are significant for the clinical suspicion of adult rhinosinusitis based on a list developed by the Rhinosinusitis Task Force updated in 2012.<sup>13,14</sup> Facial pain/pressure, nasal obstruction/blockage, nasal discharge/purulence/discholorated postnasal drainage, hyposmia/anosmia, purulence in the nasal cavity on examination, or fever (acute rhinosinusitis only) constituted the group of major symptoms. Minor symptoms were headache, fever (other than acute rhinosinusitis), halitosis, fatigue, dental pain, cough, or ear pain/pressure/fullness. Except for facial pain/pressure and fever symptoms that should be supported by another finding in the major category, participants were suspected to have rhinosinusitis if they presented 2 or more major signs or symptoms, 1 major and 2 or more minor signs or symptoms, or nasal purulence on endoscopic examination.

Rhinosinusitis was categorized in 4 groups with regard to symptoms' duration and recurrence rate per 12 months: never, 0 episode per year (e/y); rare, 1 to 2 e/y with a duration no longer than 10 days (acute rhinosinusitis); frequent, 3 to 4 e/y no longer than 10 days (recurrent acute rhinosinusitis); and CRS symptoms lasting more than 12 weeks.

#### Endoscopic Assessment

Participants all underwent nasal endoscopy after having been studied for the presence of rhinosinusitis symptoms, recurrence rate, and duration of the symptoms per year. Nasal cavities were examined using a 30-degree rigid endoscope and scored using the Lund-Kennedy nasal endoscopy scoring system. This is a system assessing 5 specific items in the sinonasal cavities: polyps, discharge, edema, scars or adhesions, and crusting. Scars and crusting were only used for postoperative outcome assessment. The total endoscopic score for each nasal cavity was calculated by adding the scores of the abovementioned items.<sup>15</sup> Participants with positive rhinosinusitis symptoms and endoscopic findings confirming the diagnosis of rhinosinusitis underwent paranasal sinus computed tomography (CT) to establish the radiologic grading of the disease.

#### Radiologic Assessment

The CT images were scored according to the Lund-Mackay radiologic grading system. Scorings for all sinuses and for the ostiomeatal complex, respectively, were as follows: 0, no abnormalities; 1, partial opacification; 2, total opacification; and 0, not

occluded; 2, occluded.<sup>16</sup> Total scores were recorded for each side and compared between the controls and study group.

### Skin Prick Tests

The SPTs were carried out for all participants to determine the predisposing role of allergy in the etiopathogenesis of rhinosinusitis among patients and controls. In total, 16 aeroallergens including common aeroallergens were used, with positive (histamine hydrochloride) and negative (glycerol with phenol) controls. A positive test was defined as the maximum weal diameter measuring 3 mm or more than the negative control for any of the allergens tested.

### Assessment of Clinical Activity

Patients were evaluated for clinical activity by the rheumatology department according to the BD Current Activity Form validated to be used in our population.<sup>17,18</sup> The patients were considered to be in the active period if a history of clinical features of BD had been present during the previous 4 weeks.

### Statistical Analysis

NCSS 2007&PASS 2008 Statistical Software (NCSS, Kaysville, UT) was used for statistical analysis of the results. Descriptive (mean, SD, frequency, median) and quantitative statistical methods were used in the evaluation of the study data. For quantitative analyses, the Mann-Whitney *U* test was used to compare 2 groups with parameters that did not have a normal distribution, and the Student's *t*-test was used for the mean ages of patients and controls. Qualitative data were evaluated using the Pearson Chi-squared test. Fisher exact test with Yates continuity correction was used to determine groups that were statistically significantly different. Statistical significance was accepted at *P* levels of <0.01 and <0.05.

## RESULTS

A total of 143 (69 BD patients, 74 controls) age- and sex-matched participants were included in the study. The mean (SD) ages of BD patients and controls were 35.41 (10.07) and 37.27 (11.11) years, respectively. Patient demographics are shown in Table 1.

### Rhinosinusitis Frequency and Duration

The types of rhinosinusitis in patients and controls are detailed in Table 2. The prevalence of acute rhinosinusitis at 1 to 2 e/y was 39.1% in BD patients and 59.5% in the normal population. There was a statistically significant difference between BD patients and controls with regard to acute rhinosinusitis prevalence (Fisher exact test, *P* < 0.05). Rhinosinusitis with 1 to 2 e/y was more frequently diagnosed in healthy controls than in BD patients.

However, with regard to a rhinosinusitis lasting more than 3 months, the difference between BD patients and controls was highly statistically significant. This group of BD patients with a rhinosinusitis lasting at least 12 weeks, in association with persistent changes on CT, was accepted to have CRS according to the criteria of the Rhinosinusitis Staging and Therapy group defined

TABLE 1. Patients' and Controls' Demographics

		Groups		<i>P</i>
		BD Patients (N = 69), n (%)	Controls (N = 74), n (%)	
Sex	Female	28 (40.57)	32 (43.24)	<i>P</i> > 0.05
	Male	41 (59.43)	42 (56.76)	
Age, y	Mean (SD)	35.41 (10.07)	37.27 (11.11)	<i>P</i> > 0.05

**TABLE 2.** Prevalence of Acute, Recurrent, and CRS in Patient and Control Groups

		Groups		P
		BD Patients (N = 69), n (%)	Controls (N = 74), n (%)	
Rhinosinusitis	Never	2 (2.9)	7 (9.5)	0.168*
	Acute	27 (39.1)	44 (59.5)	0.015†‡
	Recurrent	24 (34.8)	21 (28.4)	0.520§
	Chronic	16 (23.2)	2 (2.7)	0.002§

Never, 0 e/y; acute, 1 to 2 e/y; recurrent, 3 to 4 e/y; CRS, >12 w/y.

\*Pearson Chi-square.

†Fisher exact test.

‡P < 0.05.

§Yates continuity correction.

||P < 0.01.

in 1995.<sup>19</sup> In the light of these criteria, the prevalence of CRS was 23.2% in BD patients and 2.7% in the normal population.

Patients with BD were significantly more frequently affected by CRS than the healthy controls (Yates continuity correction, P < 0.01).

As for the results with regard to rhinosinusitis frequencies of 0 and 3 to 4 e/y, no statistically significant differences were found between BD patients and controls (Pearson Chi-square, Yates continuity correction, P > 0.05).

### Lund-Kennedy Endoscopy Scores

Endoscopy scores for BD patients and controls are presented in Table 3. There was a statistically significant difference between BD patients and controls with regard to Lund-Kennedy scores for the left sinonasal cavities (Mann-Whitney U test, P < 0.05). However, no statistically significant difference was found between the groups with regard to right sinonasal endoscopy findings (P > 0.05). Thirty-two BD patients (43.2%) demonstrated rhinosinusitis (edema, discharge, and crusting) findings after endoscopy and underwent CT imaging, whereas 20 of the controls (29%) underwent CT with findings of rhinosinusitis on endoscopy. Although no statistically significant difference was seen between the groups (P = 0.07), there was a slight preponderance (43.2%) in favor of BD patients who required imaging because of the severity of their endoscopy scores.

### Lund-Mackay Radiology Scores

Right side Lund-Mackay radiology scores in the BD and control groups were 0 to 6 (median, 1.00) and 0 to 6 (median, 1.00), respectively. Left-side radiology scores in BD patients and control groups were also 0 to 6 (median, 1.00) and 0 to 6 (median, 1.00), respectively. No statistically significant difference was seen

**TABLE 3.** Lund-Kennedy Endoscopy Scores of the Participants

	Groups		P*
	BD Patients	Controls	
	Mean (SD)	Mean (SD)	
Lund-Kennedy scores (left)	1.64 (1.283)	1.18 (0.984)	0.023†
Lund-Kennedy scores (right)	1.46 (1.267)	1.08 (1.017)	0.061

\*Mann-Whitney U test.

†P < 0.05.

**TABLE 4.** Presence of Allergic Response to SPTs According to BD and Control Groups

Response to SPT	Groups			P
	BD (N = 69), n (%)		Controls (N = 74), n (%)	
	Negative	Positive		
Negative	44 (63.8)	57 (77.0)	0.120*	
Positive	25 (36.2)	17 (23.0)		

\*Yates continuity correction test.

†P < 0.05.

between the BD patient and control groups with regard to Lund-Mackay radiology scores for both sides (Mann-Whitney U test, P > 0.05).

### Skin Prick Tests

The presence of an allergic response to a specific allergen in SPT was confirmed in 25 patients (36.2%) and 17 controls (23.0%). However, the difference between BD patient and control groups was not statistically significant (Yates continuity correction, P > 0.05) (Table 4).

The distribution of positive responses to allergens in BD patients and controls is shown in Table 5. There was a very significant statistical difference in the number of positive responses to allergens between BD patient and control groups (Mann-Whitney U test, P < 0.01). Positive responses to allergens were significantly higher in BD patients than in the reference group. The BD patients were sensitive to a much larger size of allergens than the normal population. The BD patients were not more atopic than healthy controls; however, they were more likely to be polysensitized than controls.

### Disease Activity

According to the Behçet Disease Current Activity Form, 48 patients (33.6%) were considered to be in the inactive period, whereas 21 patients (14.7%) were in the active period (Table 6).

No statistically significant difference was found in the Lund-Kennedy and Lund-Mackay scores with regard to disease activity. However, patients in the inactive period were hypersensitive to a higher number of allergens than patients in the active period (Mann-Whitney U test, P < 0.01). It seems that there were positive responses to more allergens when disease activity was reduced. Finally, the prevalence of CRS and the presence of a positive allergic response were compared according to BD activity. No statistically significant difference was seen in CRS prevalence and presence of positive allergic response in BD patients with regard to disease activity (Fisher exact test, Yates continuity correction; P > 0.05) (Table 7).

## DISCUSSION

Despite the abundance of scientific publications on BD with regard to its multisystemic and multifaceted characteristics, there are still only a limited number of studies on the sinonasal morbidities caused by this disease. On the basis of a comprehensive review

**TABLE 5.** Distribution of Allergic Responses to SPT Allergens in BD and Control Groups

	Groups				P*
	BD Patients		Controls		
	Min–Max	Median	Min–Max	Median	
Positive responses to allergens	1–7	3.00	0–7	0.00	0.001†

\*Mann-Whitney U test.

†P < 0.01.

**TABLE 6.** Evaluation of Patients' Endoscopy, Radiology, and SPT Scores With Regard to Disease Activity

	Disease Activity				P*
	Inactive (n = 48)		Active (n = 21)		
	Min–Max	Median	Min–Max	Median	
Lund-Kennedy scores (left)	0–6	2.00	0–6	1.00	0.106
Lund-Kennedy scores (right)	0–6	2.00	0–6	1.00	0.237
Lund-Mackay scores (left)	0–6	1.00	0–4	1.00	0.561
Lund-Mackay scores (right)	0–5	1.00	0–6	1.00	0.789
Prick testing scores	1–7	3.00	0–7	0.00	0.001†

\*Mann-Whitney U test.  
†P < 0.01.

in 2008, the most common clinical features of BD in the ENT area are reported to be oral, laryngeal, and oropharyngeal mucosal ulcerations and morbidities related to scar formation during the healing process.<sup>20</sup> However, regarding the sinonasal presentations of BD, there are only a small number of publications, and they report 2 cases of complicated rhinosinusitis as a consequence of deficient tissue perfusion related to Behçet vasculitis.<sup>11,21</sup>

In a study carried out to evaluate nasal mucosal involvement in BD patients, the prevalence of nasal symptoms (dysosmia, obstruction, pain) was determined to be 7.8%, in association with 2 nasal ulcers of 400 patients.<sup>22</sup> The authors attributed this relatively low frequency to local tissue factors contributing to BD pathogenesis. However, patients with sinonasal diseases were excluded from this study, and the authors recognized that the prevalence of nasal involvement in their patients was probably underestimated because of their limited inclusion criteria. Consequently, we are unable to make a comparison of our results with that study.

Numerous studies have been conducted to determine the prevalence of CRS in the normal population, in different countries. The frequency of CRS in the United States has been estimated to be between 10% and 11%.<sup>23</sup> Only 2.7% of healthy individuals showed evidence of CRS in our study. This was less than the prevalence seen in the United States, and the difference is quite likely due to our stricter criteria for categorizing patients and healthy individuals in the CRS group. It would be erroneous to make the diagnosis of CRS in the absence of nasal polyps, based on a single nasal endoscopy. In fact, 32 BD patients (43.2%) and 20 of the controls (29%) had rhinosinusitis findings (edema, discharge, and crusting) after endoscopy, whereas 16 BD patients (23.2%) and two of the controls (2.7%) were diagnosed to have CRS when evaluated according to symptoms' duration and CT imaging. Quite probably, endoscopic findings were temporary because they were not supported by the evidence for CRS from symptoms and CT imaging. A symptom questionnaire, including the severity and duration of symptoms, as part of the patient's history, and CT scan should support the endoscopy for an accurate diagnosis. Taking these evaluations together, our prevalence of CRS dropped to 2.7% in the healthy population. According to a recent study by Chandra et al,<sup>24</sup> to define the frequency of CRS with nasal polyps and CRSsNP in autoimmune conditions (multiple sclerosis, psoriasis, lupus, rheumatoid arthritis, ankylosing spondylitis), the prevalence of CRS (3.9%) was reported to be similar to that observed in a reference group of patients with hypertension (4.4%). This was lower than that observed in BD patients. However, the prevalence of CRS in patients with BD (23.22%) was lower than that observed in some studies on inflammatory bowel disease and multiple sclerosis and higher than observed in other studies on autoimmune diseases.<sup>8,9,24</sup> These observations suggested that BD, which is a Th1 lymphocyte-mediated immune

disorder, might initiate another comorbidity in the same spectrum (CRSsNP, Th1-mediated subclass).<sup>7</sup> Another explanation for the higher prevalence of CRS among BD patients may be the immunosuppressive medication used in the treatment of the active period of the disease that predisposes patients to more inflammatory conditions. Furthermore, the higher rate of comorbid CRS in BD patients may also be due to the complex mechanism of the disease predisposing the host tissues to bacterial infections.<sup>25</sup> Our results were in line with several earlier studies investigating Th1/Th2 pathologies, which have already concluded that the presence of 1 Th1 pathology is strongly associated with the presence of another Th1 comorbidity.<sup>26</sup> Similarly, Th2-mediated CRS with nasal polyps or its variant chronic hyperplastic eosinophilic sinusitis exhibits a higher prevalence in the presence of a Th2-mediated immune disorder (atopism, asthma).<sup>27</sup>

The opposite is also possible: Th1 predominant pathologies inhibit the occurrence of Th2 comorbidities, or down-regulation of Th1 cell responses induces the expansion of Th2 cell responses. Our statements were in accordance with these suggestions with regard to the relationship of BD activity to the number of allergens to which the patient responded. Although the presence of a positive allergic response among BD patients (36.2%) was not statistically significantly different from the normal controls (23.0%), positive responses to a higher number of allergens were seen in the inactive period (Table 5). In other words, we may suggest that, when the influence of Th1 activity was deemed to be decreased, BD patients may possibly have displayed a higher Th2 activity resulting in polysensitization of the patient to allergens. Further supporting our suggestion is the counterbalance and emergence of Th2 sinusitis when the Th1-dominant Crohn disease is medically controlled, as reported in a recent article by Keating and Perry.<sup>28</sup> However, in our opinion, this needs to be clarified on the basis of further immunologic studies.

The data on the positive response to SPT in healthy controls derived from our study were in agreement with articles that reported systemic allergic reactions between 20% and 43% to the allergens tested in SPT in the normal population.<sup>29</sup> The SPTs provide an objective measure for assessing systemic allergy. However, results should be interpreted with caution if seasonal responses are not eliminated by choosing winter months as was done in our study.

An additional finding that supported the hypothesis that BD may influence the development of comorbid CRSsNP was the significant difference detected between groups with regard to Lund-Kennedy scores for the left sinonasal cavities. In fact, overall endoscopy scores were significantly higher (worse) in BD patients. Although not statistically significant, there was also a slight tendency

**TABLE 7.** Rhinosinusitis Types and Presence of Allergic Response With Regard to Disease Activity

		Activity		P
		Inactive (N = 48),	Active (N = 21),	
		n (%)	n (%)	
Rhinosinusitis	Never	2 (4.2)	0 (0.0)	1.000*
	Acute	20 (41.7)	7 (33.3)	0.701†
	Recurrent	16 (33.3)	8 (38.1)	0.914‡
	Chronic	10 (20.8)	6 (28.6)	0.542*
Allergic response	Negative	31 (64.6)	13 (61.9)	1.000†
	Positive	17 (35.4)	8 (38.1)	

\*Fisher exact test, P < 0.01.

†Yates continuity correction test, P < 0.05.

‡P < 0.05.

§P < 0.01.

toward higher scores in the right sinonasal cavities in the BD group. However, radiology scores were similar in BD patients and the control group suggesting that radiologic involvement in BD patients was no worse than that of the normal population.

The limitation of the present study is its small sample size related to patients' disinclination to attend the clinic. It is quite likely that significant differences in CT scores may be found between BD patients and controls in a study with a larger sample size. In addition, referral bias can occur, with patients having more severe disease-attending specialist centers. Another concern of critics may be the season when the study was performed. However, winter months were specifically preferred to eliminate seasonal allergic responses that might lead to an overestimation of SPT responses.

In our opinion, this is the first prospective study on the prevalence of comorbid CRS in patients with BD. We hope that, in the future, new findings will help explain the development of CRSsNP through further immunologic investigations.

## CONCLUSIONS

The prevalence of CRSsNP was 23.2% in BD patients and 2.7% in the normal population in this study. Lund-Kennedy scores on left-side endoscopy of patients with BD were significantly worse than those of the controls. The frequency of positive allergic responses to prick tests among patients and the normal population was not statistically significantly different. The BD patients were polysensitized to allergens during the inactive period.

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