

## The Clinical Significance of a Pathergy Reaction in Patients with Behçet's Disease

This study was done to evaluate the frequency, intensity, and specificity of a positive pathergy reaction (PR) in Behçet's disease (BD) patients, to clarify an association between the PR and the clinical features or disease severity, and to assess whether patients with pustule formation at the venous puncture site (PFVPS) without positive PR could be regarded as a positive reaction. The PR was tested in 64 BD patients, 74 disease controls, and 20 healthy controls. Venous PR was performed in 8 BD patients with PFVPS. Follow-up PR was done in 14 patients with positive reaction during inactive phase. The PR was positive in 35.9% of BD patients, in 1 patient among disease controls, and in none of healthy controls. The pustule formation was observed in one BD patient. There was no statistical significance between positive PR and the clinical variables. The mean clinical activity score of BD patients with positive PR was similar to patients with negative reaction. Venous PR was positive in 7 patients. The follow-up PR was positive in 2 patients during inactive phase. Conclusively the positive PR appeared to be specific for BD, and was not associated with the clinical variables or disease severity, but was usually found during active phase in cases with positive reaction. The PFVPS in patients with negative PR might be considered to be positive.

**Key Words :** *Pathergy Reaction; Behçet's Syndrome*

**Hyun Kyu Chang, Kyeong Soo Cheon\***

Division of Rheumatology, Department of Internal Medicine, Dankook University Hospital, Cheonan; Family Medicine\*, Ulsan University Asan Kangnung Hospital, Kangnung, Korea

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### Address for correspondence

Hyun Kyu Chang, M.D.  
Department of Internal Medicine, Dankook University Hospital, 16-5 Anseo-dong, Cheonan 330-715, Korea  
Tel : +82.41-550-3919, Fax : +82.41-556-3256  
E-mail : hanks22@dankook.ac.kr

## INTRODUCTION

Behçet's disease (BD) is a multisystemic disorder characterized by oral ulcerations, genital ulcerations, uveitis, and skin lesions, most likely occurring due to underlying vasculitis. There are also other organ involvements, including joints, heart, lungs, neurological involvement, and gastrointestinal involvement. Because the pathognomonic diagnostic tools are lacking, the diagnosis mainly depends upon the thorough history taking and clinical features. Pathergy reaction (PR), a nonspecific hypersensitivity of the skin to a needleprick, has been known to be a curious and unique phenomenon occurring in patients with BD, and proposed as a useful adjunct to diagnosis. This phenomenon has been accepted as one among the major criteria of International Study Group (ISG) (1).

The prevalence of a positive PR varies according to countries or investigators. The high positive rate of PR has been described in some ethnic areas such as Turkey (2, 3), Iran (4), Japan (5), and Israel (6), but this was not the case in other countries (7, 8). After the introduction of a disposable needle, the prevalence and intensity of a positive PR in BD patients has been described to decrease, when compared to non-disposable needle used in pre-AIDS era (9). On the other hand, there have been conflicting results between the PR

and the clinical features of BD. Information about the relationship between PR and the disease activity is limited. In addition, some investigators (10) and we noticed that a few patients with BD with a negative PR developed a pustule formation at the venous puncture site (PFVPS) for the intravenous fluid infusion or blood draw.

Therefore, this study was undertaken to evaluate the frequency of a positive PR, the intensity and disease specificity of this reaction in patients with BD when a disposable needle is used, to clarify the clinical association between the PR and the clinical features of BD or its disease activity, and to assess whether the patients with PFVPS without a positive PR could be regarded as a positive reaction.

## MATERIALS AND METHODS

The study subjects included 64 patients with BD (25 males and 39 females) who fulfilled the ISG criteria, 74 patients without BD (24 males and 50 females) consisting of 24 patients with recurrent aphthous stomatitis, 19 patients with systemic lupus erythematosus (SLE), 13 patients with Sjogren syndrome, 15 patients with spondyloarthropathy (SpA) and 3 patients with ulcerative colitis, along with 20 age and sex-

**Table 1.** The clinical activity score for Behçet's disease

1	Oral ulceration Genital ulceration Skin lesions: EN-like lesions, pseudofolliculitis/PPL Monoarticular arthritis Superficial thrombophlebitis
2	Arthritis involving two joints or more Gastrointestinal ulceration without complications Small or medium-sized vessel involvement not related to vital organ
3	Uveitis Gastrointestinal ulceration with bleeding or perforation Major vessel involvement Major organ involvement such as brain, lungs, or heart

EN: erythema nodosum, PPL: papulopustular lesion.

**Table 2.** The clinical characteristics of patients with BD

	No. of patients	Percent
Early disease	24	37.5
Late disease	40	62.5
Erythema nodosum	32	50.0
PPL/pseudofolliculitis	38	59.4
Gastrointestinal involvement	10	15.6
Genital ulcer	48	75.0
Arthritis	18	28.1
Uveitis	14	21.9
Positive HLA-B51	33	51.6

**Table 3.** The relationship of disease onset of age or sex and a pathergy reaction in patients with Behçet's disease

	Pathergy positive (n=23)	Pathergy negative (n=41)	p-value
Early disease	7 (30.4%)	17 (41.5%)	0.431
Late disease	16 (69.6%)	24 (58.5%)	
Male	12 (52.2%)	13 (31.7%)	0.120
Female	11 (47.8%)	28 (68.3%)	

matched healthy controls (7 males and 13 females) consisting of hospital personnel. The other demographic features of BD patients were as follows: mean age at presentation  $40.2 \pm 10.3$  yr, mean age at onset  $35.8 \pm 9.5$  yr, and mean period of follow-up  $14.6 \pm 8.4$  months. The mean ages of patients without BD and healthy controls were  $40.6 \pm 12.8$  yr and  $39.5 \pm 10.6$  yr, respectively. The age at onset was defined at the time the patient historically fulfilled the ISG criteria. Patients who were under 29 yr were considered as having the early disease and those over 30 yr as the late disease.

For the PR, the skin on the flexor aspect of the forearm was cleaned with 70% isopropyl alcohol and pricked intradermally with a disposable 21-gauge needle. The results were read at 48 hr by the same physician, and were graded as follows: grade 0, needle mark or erythema only; grade 1, papule; and grade 2, pustule. A grade over 1 was considered as a positive reaction (2, 11). The PR was retested in a few BD patients with

**Table 4.** The relationship of clinical features and a pathergy reaction in patients with Behçet's disease

	Pathergy positive (n=23)	Pathergy negative (n=41)	p-value
Erythema nodosum	11 (47.8%)	21 (51.2%)	1.0
PPL/pseudofolliculitis	15 (65.2%)	23 (56.1%)	0.598
Genital ulcer	14 (60.9%)	34 (82.9%)	0.072
Uveitis	3 (13.0%)	11 (26.8%)	0.345
Gastrointestinal involvement	5 (21.7%)	5 (12.2%)	0.474
Arthritis	9 (39.1%)	9 (22.0%)	0.160
HLA-B51	12 (52.2%)	21 (51.2%)	1.0

initially negative PR whose disease flared up during the follow-up period. If these results were positive, they were also considered to have a positive reaction.

Venous PR was performed in 8 patients with BD having a PFVPS, and in 10 patients without BD (5 patients with SLE, 3 patients with SpA, and 2 patients with Sjogren syndrome) after obtaining informed consents. Five percent dextrose (500 mL) was infused using a disposable 21-gauge needle for 3 hr at the forearm. The results were also evaluated at 48 hr. Only the pustule formation was regarded as a positive venous PR.

Follow-up PR was done in 11 patients with a positive PR, and follow-up venous PR was done in 3 patients with a positive venous PR, during the relatively quiescent phase of their disease.

The clinical activity score (Table 1) was calculated by summing each clinical manifestation present when a PR was performed. This score was established with reference to the study of Yazici et al. (3) and in view of the morbidity and the disease severity of the BD (12).

For statistical analysis, Student t-test and Fisher's exact test were used.

## RESULTS

The clinical characteristics of patients with BD are presented in Table 2. A positive PR was observed in 23 out of 64 BD patients with a positive rate of 35.9%. However, this reaction was positive in only one patient with SLE among 74 patients without BD, and none had a positive reaction in healthy controls. In addition, a grade 2 reaction with a pustule formation was only found in one patient with BD. The PR in patients with BD was not associated with age at onset of the disease, sex, the clinical features, and the presence of HLA-B51 (Table 3 and 4). The mean clinical activity score of BD patients with a positive PR was  $2.91 \pm 1.31$ , and that of BD patients with a negative PR was  $2.85 \pm 1.17$  ( $p=0.853$ ).

Venous PR was positive in 7 among 8 BD patients with a PFVPS, and the PR was positive only in 3 among these 8 patients. However, venous PR was negative in all ten patients without BD.

**Table 5.** The results of pathergy reaction according to the clinical activity score of Behçet's disease

Patients	Initial pathergy reaction		Follow-up pathergy reaction	
	CAS	Pathergy	CAS	Pathergy
1	3	+*	0	-*
2	3	+	0	-
3	3	+	1	-
4	4	+	0	-
5	2	+	0	-
6	5	+ <sup>†</sup>	0	+
7	3	+*	1	-*
8	4	+	0	-
9	4	+	1	-
10	2	+	0	-
11	4	+	0	-
12	1	+	0	-
13	3	+	1	+
14	2	+*	0	-*

CAS: clinical activity score.

\*: Venous pathergy reaction, <sup>†</sup>: Grade 2 pathergy reaction.

Among 11 patients on the follow-up PR, 2 patients had a positive reaction during inactive phase of the disease, and 1 patient having a pustule formation in initial PR was observed a papule without the pustule formation. The follow-up results of all 3 patients with a positive venous PR were negative during inactive phase of the disease (Table 5).

## DISCUSSION

Since the PR, which was first described in 1937 by Blobner (13), has been proven to be helpful for the diagnosis of BD, it has become one of the ISG criteria. However, after the introduction of the disposable needle, which is less traumatic than the non-disposable needle, the prevalence and intensity of positive PR has been known to decrease. This study also reconfirmed the specificity of the PR in Korean BD, revealing the positive rate of 35.9% and specificity of 98.9%. The formal reports on the prevalence of the PR performed in the pre-AIDS era in Korea have been rare, and one study in 1984 showed a positive rate of 47.3% (14). In addition, contrary to a Turkish study on the PR done in the pre-AIDS era that described a pustule formation in 58% of patients with BD (15), our study showed that the pustule formation was observed only in one among 23 patients with a positive reaction. This may be due to the use of a disposable needle or the ethnic difference.

There have been no controlled studies to determine whether medications can exert an influence on the results of PR. Some authors suggested that medications might affect the results of PR (16), while others might not (17). In the current study, the PR was done in most cases before initiation of any treatment, or at least one week after discontinuation of treatment. However, in a few inevitable cases due to the clinical status, the test was performed with minimum medications. So, we

could not reveal an impact of medications on the results of the PR.

Up to date, conflicting studies have been reported on the association between the PR and the clinical features of BD. Some investigators found that the presence of a positive reaction was not related to the clinical manifestations of the disease (8, 17). However, the PR was reported to be significantly associated with vascular involvement (18). Yazici et al. described that male patients had a stronger PR (19). In addition, it is plausible that this phenomenon might be associated with the presence of HLA-B51 in BD, because most patients in a Turkish study simultaneously had HLA-B51 and a positive reaction (20). In our study the PR was not associated with age at onset of the disease, sex, other clinical features, and the presence of HLA-B51. However, we could not assess the clinical association between the PR and the vascular involvement due to the small number of patients with vascular involvement in our study group.

It remains unclear whether the presence of a PR reflects the disease severity. Yurdakul et al. described that the PR was less commonly positive in patients with milder BD such as those in the community than in hospital-based patients (21). However, other investigators claimed that the PR was not associated with the disease severity (17, 19). On the other hand, although the rate of a positive reaction could be influenced by the disease activity when the test has been performed (6, 16), formal studies have been limited. In the current study, it appeared that the PR was not related to the disease severity, but was usually encountered during the active phase of the disease in individual case with a positive reaction.

Since the sensitivity of the PR has decreased with the introduction of the disposable needle, it was noticed that the PFVPS had been found in some BD patients with a negative PR. Even though the standardized method of a PR has been lacking at present, these patients group have not been considered to be a positive reaction according to the ISG criteria (22). The current study suggests that it may be a positive PR, especially in patients having the clinical features of BD until a more sensitive and standardized tool for PR becomes available.

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