

# Pathergy reaction in Behçet's disease: Lack of correlation with mucocutaneous manifestations and systemic disease expression

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Behçet's disease, pathergy, disease  
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## ABSTRACT

### Objective

*The pathergy reaction is a unique feature of Behçet's disease (BD) and, according to the International Study Group (ISG), is among the major criteria required for the diagnosis. Different positive pathergy reaction rates in BD have been reported worldwide. We evaluated the prevalence of the pathergy reaction in Israeli BD patients, and its relation to mucocutaneous and systemic manifestations of the disease.*

### Methods

*Forty-three patients were studied, all of whom fulfilled the ISG criteria for BD. The mucocutaneous and systemic disease manifestations were analyzed with respect to the presence of the pathergy reaction, and a systemic severity score for BD was calculated according to the potential morbidity and mortality associated with various clinical features.*

### Results

*Nineteen patients (44.2%) had a positive pathergy test. The pathergy-positive and pathergy-negative BD groups showed a similar male:female ratio, age at disease onset, and mean disease duration. They also exhibited similar HLA-B5 levels and a similar frequency of oral ulcerations in close family members. The mucocutaneous manifestations, systemic disease expression, and severity score were similar in patients with and without the pathergy reaction.*

### Conclusion

*The presence of a positive pathergy reaction, although common in Israeli BD patients, is not associated with an increased risk for specific mucocutaneous or systemic manifestations of the disease, and probably does not predict a more severe disease course.*

### Introduction

The pathergy reaction, i.e. the formation of a papule or pustule 24 to 48 hours after a simple needle prick, is considered a highly specific feature of Behçet's disease (BD) (1). According to the Interna-

tional Study Group criteria for BD, a positive pathergy test is among the major criteria required for the diagnosis of BD (2). Different rates of positive pathergy reaction in BD have been reported worldwide. While pathergy is considered highly sensitive and specific for BD in patients from Turkey and Japan (3), it is frequently negative in Western patients (4, 5). Up until now, the clinical significance of the pathergy reaction and its possible association with other clinical features of BD has not been fully elucidated. The present study was undertaken to evaluate the incidence of the pathergy reaction in a group of Israeli BD patients, and its relation to the mucocutaneous as well as the systemic manifestations of the disease.

### Patients and methods

Forty-three BD patients were studied, all of whom fulfilled the International Study Group criteria for BD as follows: recurrent oral ulcers (at least 3 times in one year) plus two of the major features of the disease (i.e., recurrent genital ulcers, uveitis, typical skin lesions or positive pathergy test) (2). The pathergy test was performed by an intradermal 21-gauge needle puncture on the skin of the forearm previously cleaned with alcohol, with the injection of 1 drop of sterile normal saline. The results were evaluated after 48 hours. The formation of a round palpable erythema or pustule was considered a positive reaction.

The pathergy test was performed at least once for each patient; 18 patients were evaluated several times during their follow-up. Patients were considered positive for pathergy if they showed at least one positive result. Data from medical files and patient interviews, relating to mucocutaneous and systemic disease manifestations, the mode of and the age at disease onset, and any family history of oral ulcers or BD, was collected. Most patients were followed sequentially for several years; some of the patients were referred for consultation and were interviewed once. The data used for our analysis consisted of a summation of all manifestations which had ever occurred in a given patient.

Disease duration was calculated as the time interval between the disease onset

(i.e., appearance of the first disease manifestation) and the last visit of the patient to the clinic.

The severity score was calculated by summing the points for all disease manifestations, as follows: 1 point for each mild symptom; 2 points for each moderate symptom; and 3 points for each severe disease manifestation, according to Table I (6).

Major oral ulcers (MaOU) were defined as oral ulcers which were larger than 1 cm in diameter and/or which healed with scarring. Minor oral ulcers (MiOU) were defined as those smaller than 1 cm, which healed without scar formation (7, 8). Determination of the type of oral ulcer was made according to the results of an oral examination by a physician.

Statistical analysis was performed using Student's t-test for mean values, and  $\chi^2$  for table analysis.

## Results

The clinical characteristics of the patients are presented in Table II. Nineteen patients (44.2%) had a positive pathergy test. The pathergy-positive and pathergy-negative patients showed a similar male:female ratio, age at disease-onset, and mean disease duration. They also exhibited similar HLA-B5 levels and a similar frequency of oral ulcerations in close family members. Ten patients were treated with either corticosteroids or cyclosporine A; 5 of these had a positive pathergy test and 5 a negative test. Colchicine and/or NSAID were given at some time during the disease course in 20 patients; 8 of these were positive and 12 were negative for the pathergy reaction. Table III summarises the mucocutaneous manifestations in the two groups of patients. No significant difference was found between the pathergy-positive and pathergy-negative BD patients with respect to the prevalence of MaOU versus MiOU (examined in 23 patients), genital ulcers, typical skin lesions, or superficial venous thrombosis.

The systemic manifestations of the disease are presented in Table IV. Analogous to the mucocutaneous manifestations, the prevalences of the systemic features of the disease (i.e., uveitis, deep venous thrombosis, joint disease, gastrointestinal complaints, and CNS involve-

**Table I.** Severity of Behçet's disease (6, 20).

Mild	Oral aphthosis
	Genital ulcers
	Typical skin lesions (erythema nodosum, papulopustular lesions, folliculitis)
	Arthralgia
	Recurrent headaches
	Epididymitis
	Mild gastrointestinal symptoms (chronic diarrhea, chronic abdominal pain)
Moderate	Pleuritic pains
	Superficial vein thrombosis
	Arthritis
	Deep vein thrombosis of the legs
Severe	Anterior uveitis
	Gastrointestinal bleeding
	Posterior/pan uveitis, retinal vasculitis
	Arterial thrombosis or aneurysms
	Major vein (vena cava, hepatic) thrombosis
Neuro-Behçet's	
Bowel perforation	

**Table II.** Characteristics of the BD patients with a positive or negative pathergy test [number of patients (%)].

	Pathergy positive (n = 19)	Pathergy negative (n = 24)	p value
Male: Female ratio	0.9: 1	0.7: 1	NS
Age	34.2 ± 18.4	32.1 ± 19.8	NS
Age of onset of BD (years)	17.6 ± 14.9	19.8 ± 14.3	NS
Disease duration (years)	16.7 ± 7.2	12.4 ± 12.1	NS
HLA-B5 positive	12/17 (70.6)	13/20 (65.0)	NS
Oral ulcers in family	7 (36.8)	9 (37.5)	NS

**Table III.** Mucocutaneous manifestations of the pathergy-positive and pathergy-negative BD patients [number of patients (%)].

	Pathergy positive (n = 19)	Pathergy negative (n = 24)	p value
Major oral ulcers	3/12 (25)	5/11 (45.5)	NS
Minor oral ulcers	9/12 (75)	6/11 (54.5)	NS
Genital ulcers	12 (63.1)	15 (62.5)	NS
Erythema nodosum	7 (36.8)	11 (45.8)	NS
Folliculitis	9 (47.4)	7 (29.2)	NS
Papulopustular rash	5 (26.3)	4 (16.7)	NS
Superficial vein thrombosis	6 (31.6)	5 (20.8)	NS

**Table IV.** Systemic manifestations of the BD patients [number of patients (%)].

	Pathergy positive (n = 19)	Pathergy negative (n = 24)	p value
Uveitis	9 (47.4)	15 (62.5)	NS
Deep vein thrombosis	5 (26.3)	2 (8.3)	NS
Arthritis	12 (63.1)	14 (58.3)	NS
Gastrointestinal complaints	4 (21.1)	5 (20.8)	NS
Headaches	9 (47.4)	8 (33.3)	NS
Neuro-Behçet's	4 (21.1)	3 (12.5)	NS
Disease severity (see Table I)	7.0 ± 3.2	6.8 ± 1.9	NS

ment) were similar in the patients with and without the pathergy reaction. Furthermore, the disease severity score, in which we assigned relative weights to the various manifestations of the disease based on the expected outcome and potential morbidity, was similar in the two groups of patients.

### Discussion

The applicability of the pathergy test to BD has been the subject of ongoing debate. Much of the controversy is related to the lack of standardization in performing the test. It has been shown that the results of the pathergy test can be influenced by the size and type of needles used, the sharpness of the needles, the number of pricks, and whether or not an antiseptic is used to clean the skin (1, 9). Furthermore, the results may fluctuate over time, being positive at one point and negative at another (10, 11).

In the present study we tested the pathergy reaction, using previously described and accepted methods (12, 13). Some patients were tested for pathergy more than once during their disease course, and were considered as positive if they ever had a positive reaction. Our results confirm that the pathergy reaction is common in Israeli BD patients, although not to the extent reported by Friedman-Birnbaum *et al.* (14), who found a prevalence of 98% among 46 Israeli patients with BD. The different rates might have resulted from a dissimilar definition of BD (we used the ISG criteria, whereas Friedman-Birnbaum *et al.* utilised earlier criteria), as well as from differences in the technique of pathergy testing.

The occurrence of positive pathergy in our study population (44%) is in line with rates reported from the Mediterranean basin, the Middle East, and Japan (30-77%) (3, 5), and is in contrast to the considerably lower prevalences reported for other parts of the world, such as Brazil (8%) (15), India (9%) (16), Britain (5%) (4), and North America (17). Yazici *et al.* (10) reported a stronger pathergy reaction in male BD patients compared to females, although the prevalences were similar in males and females. While we did not test for the severity of the pathergy reaction, like Yazici *et al.* we found a similar male:female ratio in patients

with and without pathergy. We did not detect a genetic tendency to pathergy in our BD population, since the prevalences of both HLA-B5 and oral ulcers in close family members were similar in the 2 groups of patients.

The group with a positive pathergy test and those with a negative reaction were similarly treated with immunosuppressive drugs and colchicine/NSAID. Although we can not exclude an influence of drugs upon the pathergy reaction, the similarity of treatment between the two groups probably argues against a significant impact of medications on the results of the pathergy test.

The relationship between the pathergy test and other manifestations of BD has not yet been sufficiently studied. Mansoori *et al.* (18) found slightly higher rates of genital ulcers, erythema nodosum, arthralgia and HLA-B5 among pathergy-positive Iranian BD patients. However, their study included a high percentage of patients with incomplete BD, making it difficult to compare their data with the results of our study.

Koc *et al.* (19) reported a significantly higher rate of positive reactions among a group of BD patients with vascular involvement, 88% of whom had venous thrombosis and 12% arterial lesions. In our study we found similar rates of venous thrombosis in patients with and those without pathergy. A regional variability in BD expression could account for this difference, but since our patients had no arterial involvement, we cannot exclude a possible association between arterial lesions and the pathergy reaction. Davies *et al.* (4) employed cluster analysis to compare disease expression in 19 British and 42 Turkish BD patients. It was found that, although the pathergy reaction was nearly absent in the British patients and very common in the Turkish patients, the two groups showed no differences in the other clinical features, implying that the presence of a positive pathergy test was not associated with other clinical manifestations of the disease. The results of our study are in line with those of Davies *et al.*, showing that the presence of the pathergy reaction is not linked to other clinical manifestations of BD (whether mucocutaneous or systemic).

Furthermore, in order to correlate the pathergy phenomenon with the severity of BD, we used a scale in which relative weights were assigned to the whole spectrum of clinical manifestations in BD, according to the expected outcome and potential morbidity and mortality (6, 20). We found the severity score to be the same in patients with and without the pathergy reaction. Thus, it is conceivable that the presence of pathergy does not pose an increased risk for a more severe prognosis in BD. Although our study was performed in a limited number of patients, the similarity of the clinical manifestations in the patients with and without pathergy leads us to conclude that, at least in our geographical area, the pathergy phenomenon is not associated with a specific clinical presentation.

A possible association of local trauma with the initiation of ulceration in BD has been previously postulated. Pathergy has been demonstrated in the oral mucosa by the injection of physiological saline or the application of a needle prick. The clinical course of these experimentally-induced oral ulcerations was similar to those occurring spontaneously (21); it was also suggested that coitus might precipitate genital lesions (21). In our study we found no difference in the rate of genital ulcers nor in the severity of oral ulcers between pathergy-positive and pathergy-negative patients. It appears therefore that pathergy is not a risk factor for genital involvement or for a more severe oral disease. Nevertheless, since the appearance of the pathergy reaction may be episodic and associated with BD activity (10,11), administration of the pathergy test during the course of genital or oral flare-ups may yield different results.

In conclusion, our results indicate that the presence of a positive pathergy reaction, although common in Israeli BD patients, is not associated with an increased risk for specific mucocutaneous or systemic manifestations of the disease, and probably does not predict a more severe disease course.

### References

1. DILSEN N, KONICE M, ARAL O *et al.*: Comparative study of the skin pathergy test with blunt and sharp needles in Behçet's disease: Confirmed specificity but decreased sensitiv-

- ity with sharp needles. *Ann Rheum Dis* 1993; 52: 823-5.
2. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990; 335: 1078-80.
  3. KAKLAMANI VG, VAIPOULOS G, KAKLAMANI PG: Behçet's disease. *Semin Arthritis Rheum* 1998; 27: 197-217.
  4. DAVIES PG, FORDHAM JN, KIRWAN JR, BARNES CG, DINNING WJ: The pathergy test and Behçet's syndrome in Britain. *Ann Rheum Dis* 1984; 43: 70-3.
  5. O'DUFFY JD: Behçet's disease. *Curr Opin Rheumatol* 1994; 6: 39-43.
  6. KRAUSE I, UZIEL Y, GUEDJ D *et al.*: Childhood Behçet's disease: Clinical features and comparison with adult-onset disease. *Rheumatology (Oxford)* 1999; 38: 457-62.
  7. LEHNER T: Oral ulceration and Behçet's syndrome. *Gut* 1977; 18: 491-511.
  8. REES TD, BINNIE WH: Recurrent aphthous stomatitis. *Dermatol Clin* 1996; 14: 243-56.
  9. FRESKO I, YAZICI H, BAYRAMICLI M, YURDAKUL S, MAT C: Effect of surgical cleaning of the skin on the pathergy phenomenon in Behçet's syndrome. *Ann Rheum Dis* 1993; 52: 619-20.
  10. YAZICI H, TUZUN Y, TANMAN AB *et al.*: Male patients with Behçet's syndrome have stronger pathergy reactions. *Clin Exp Rheumatol* 1985; 3: 137-41.
  11. JORIZZO JL, SOLOMON AR, CAVALLO T: Behçet's syndrome. Immunopathologic and histopathologic assessment of pathergy lesions is useful in diagnosis and follow-up. *Arch Pathol Lab Med* 1985; 109: 747-51.
  12. TUZUN Y, YAZICI H, PAZARLI H *et al.*: The usefulness of the nonspecific skin hyper-reactivity (the pathergy test) in Behçet's disease in Turkey. *Acta Derm Venereol* 1979; 59: 77-9.
  13. YAZICI H, CHAMBERLAIN MA, TUZUN Y, YURDAKUL S, MUFTUOGLU A: A comparative study of the pathergy reaction among Turkish and British patients with Behçet's disease. *Ann Rheum Dis* 1984; 43: 74-5.
  14. FRIEDMAN BIRNBAUM R, BERGMAN R, AIZEN E: Sensitivity and specificity of pathergy test results in Israeli patients with Behçet's disease. *Cutis* 1990; 40: 261-4.
  15. SCHERRER MA, VITRAL N, BAMBIRRA E, OREFICE F: Histologic and clinical study of pathergy in Behçet's disease in Brazil. In: WECHSLER B and GODEAU P (Eds.): *Behçet's Disease, Proceedings of the 6th International Conference on Behçet's disease*. Amsterdam, Excerpta Medica 1993: 363-6.
  16. PANDE I, UPPAL SS, KAILASH S, KUMAR A, MALAVIYA AN: Behçet's disease in India: A clinical, immunological, immunogenetic and outcome study. *Br J Rheumatol* 1995; 34: 825-30.
  17. O'DUFFY JD, LEHNER T, BARNES CG: Summary of the Third International Conference on Behçet's Disease, Tokyo, Japan, October 23-24, 1981. *J Rheumatol* 1983; 10: 154-8.
  18. MANSOORI P, CHAMS C, DAVATCHI F *et al.*: Relationship of pathergy phenomenon and Behçet's disease manifestations. In: WECHSLER B and GODEAU P (Eds.): *Behçet's Disease, Proceedings of the 6th International Conference on Behçet's Disease*. Amsterdam, Excerpta Medica 1993: 367-9.
  19. KOC Y, GULLU I, AKPEK G *et al.*: Vascular involvement in Behçet's disease. *J Rheumatol* 1992; 19: 402-10.
  20. KRAUSE I, ROSEN Y, KAPLAN I, *et al.*: Recurrent aphthous stomatitis in Behçet's disease: Clinical features and correlation with systemic disease expression and severity. *J Oral Pathol Med* 1999; 28: 193-6.
  21. NAZZARO P: Cutaneous manifestations of Behçet's disease. Clinical and histopathological findings. In: MONACELLI M and NAZZARO P (Eds.): *Behçet's Disease, International Symposium on Behçet's Disease, Rome, 1964*, Basel, S. Karger, 1966: 15-41.