

## The oral and skin pathergy test

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### INTRODUCTION

Pathergy phenomenon is defined as a state of altered tissue reactivity that occurs in response to minor trauma.<sup>[1]</sup> Pathergy test (PT) is an easy to perform skin test to look for the pathergy phenomenon.<sup>[1]</sup> This test is used as a criterion in most diagnostic criteria for Behcet's disease e.g., Dilsen criteria,<sup>[2]</sup> Japan revised criteria,<sup>[3,4]</sup> International criteria,<sup>[5]</sup> Iran traditional format criteria,<sup>[6]</sup> and the Classification Tree.<sup>[7]</sup>

### HISTORY

Blobner first described pathergy in Behcet's disease in 1937 and Katzenellenbogen further investigated the phenomenon in 1960. The latter observed that the reaction that resulted 24 h after the insertion of a needle prick remained sterile and named it as non-allergic pathergy.<sup>[8,9]</sup>

### EPIDEMIOLOGY:

Pathergy positivity is most prevalent around the silk route, which extends from the Far East to the Mediterranean Basin, including the Gulf area. The sensitivity of pathergy test was 83% in Russia,<sup>[10]</sup> 77%

in Morocco,<sup>[11]</sup> 71% in Iraq,<sup>[12]</sup> 62% in China<sup>[13]</sup> and Egypt,<sup>[14]</sup> 61.5% in Iran,<sup>[15]</sup> 55% in Germany,<sup>[16]</sup> 44% in Japan,<sup>[17]</sup> and 18% in Saudi Arabia.<sup>[18]</sup> The sensitivity of pathergy test is declining over time.<sup>[19]</sup>

### Pathogenesis of pathergy phenomenon

Although the exact mechanisms underlying pathergy phenomenon are unknown, skin injury caused by needle prick apparently triggers a cutaneous inflammatory response which is much more prominent and extensive than that seen in normal skin and suggests an increased or aberrant release of cytokines from keratinocytes or other cells in the epidermis or dermis resulting in a perivascular infiltration observed on skin biopsy.<sup>[20]</sup>

A study conducted by Serhat Inaloz *et al.*<sup>[21]</sup> on the significance of immunohistochemistry in the skin pathergy reaction (SPR) of patients with Behcet's syndrome suggested that cell adhesion molecule interactions (E-selectin, P-selectin, and endoglin) together with endothelial proliferation may play an important role in the formation of skin pathergy reaction.

Types of pathergy tests:

1. Oral pathergy test<sup>[22]</sup>
  - a. Site: lower lip.
  - b. Procedure of oral pathergy test : prick the mucous membrane of the lower lip to the submucosa using a 20 gauge blunt disposable needle [Figure 1].
  - c. Assessment: Readings are taken after 48 h, and the test is considered positive if a pustule or ulcer is seen [Figure 2].
  - d. Sensitivity: The sensitivity of the oral PT is lower than that of the ordinary skin pathergy test.
  - e. Advantage over the skin pathergy test: The oral PT is easier to assess than the skin PT as there is no need to measure the size of the lesion: a pustule or ulcer of any size is considered positive.

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**Figure 1: Oral pathergy test: mucous membrane of the lower lip is pricked using a 20 gauge blunt disposable needle**



**Figure 2: Reading taken after 48 h shows an ulcer: positive Oral pathergy test**

## 2. Skin pathergy test

- a. Site: A hairless area on the flexor aspect of the forearms is usually chosen as the test site.<sup>[23]</sup> Ozdemir *et al.*<sup>[23]</sup> analyzed the skin pathergy test in different hairless body areas which included the flexor surfaces of the forearms, the lateral aspect of the tibial area, the scapular areas of the back, and the lumbar areas of the abdominal region. They concluded that the forearm is the region with the most frequently positive skin pathergy test and the abdomen the least. They suggested that variations in positivity of different body segments may result from variation in the structure, thickness and vascularity of the skin on these areas.<sup>[23]</sup>
- b. Various routes for skin pathergy testing: Intradermal (ID), intravenous (IV) and subcutaneous methods have been used.<sup>[24]</sup> In a study conducted by Ozlem Akmaz *et al.*,<sup>[24]</sup> the positivity rate yielded by intradermal needles was statistically higher than that by IV application in Behcet's patients during both the active and remission periods.<sup>[24]</sup>
- c. Procedure of skin pathergy test: There is no standardized pathergy test. It can be performed using 1–16 needle pricks.<sup>[23,25,26]</sup> In a study conducted by Ozdemir *et al.*<sup>[23]</sup> on the use of multiple needle pricks for skin pathergy test (SPT), they concluded that the positive pathergy reaction rates were 19%, 24%, 28%, 30%, and 33% for two, three, four, five and six needle pricks, respectively. The greatest increase in the mean percentage of positive pathergy reaction rates was detected for the application of two needle prick combination.<sup>[23]</sup> That is when two

needle pricks were performed, there was a 46% increase in the positive pathergy reaction rate relative to that found with one needle prick. The percentage increase in the positive pathergy reaction rate for the three and four needle prick combinations were 26% and 17%, respectively. They concluded that two needle pricks are sufficient for SPT.<sup>[23]</sup>

In most studies investigators have used either a sterile needle (20 gauge) prick or an intradermal injection of normal saline,<sup>[27]</sup> monosodium urate (MSU) crystals<sup>[28]</sup> or streptococcal antigens<sup>[7]</sup> to perform the test. The procedure is performed on a hairless part of the volar forearm. Generally, the needle is inserted vertically or diagonally at an angle of 45° to a depth of 3–5 mm. The needle should reach the dermis for a proper response.<sup>[7,29]</sup>

- d. Assessment of SPT:
  1. Clinical evaluation: Readings are taken after 48 hrs of the needle prick. A 1-2mm papule that is usually felt by palpation and which is surrounded by an erythematous halo is formed on the skin. The papule may remain as a papule or transform into a 1–5mm pustule. The pustule becomes prominent in 24 h, becomes maximum in size in 48 h, and disappears in 45 days. Erythema without induration is interpreted as a negative result.<sup>[30]</sup>
  2. Histopathological evaluation: Histopathological studies have been performed on the skin pathergy test induced by various methods and evaluated after different

time periods. Different results have been reported in various studies. They range from mononuclear cell infiltration of varying densities in perivascular and periadnexal locations with increased numbers of mast cells to leukocytoclastic vasculitis or Sweet-like vasculitis.<sup>[27]</sup> It has been suggested that the variability of the reported histopathologic features of SPT may be related to the individual differences in immune responses to inciting agents or to the different stages of skin response.<sup>[31]</sup> A more recent study compared histopathologic and clinical evaluations of the skin pathergy test and concluded that histopathological investigation was no more sensitive than clinical evaluation.<sup>[24]</sup>

3. Photographic evaluation: This method was found to have increased variability and decreased sensitivity.<sup>[32]</sup>
- e. Factors affecting the sensitivity and specificity of skin pathergy test:
  1. The specificity of skin pathergy reaction is very high, especially when it is positive at 48 h,<sup>[33]</sup> although it cannot be reproduced consistently even in the same patient. Because of its specificity, the skin pathergy reaction was included in the diagnostic criteria proposed by the International Study Group for Behçet's disease.<sup>[5]</sup> The low sensitivity of pathergy test prevents it from being used as a screening test.<sup>[34]</sup>
  2. Studies have demonstrated that use of a blunt (reusable, sterilized) needle increases the frequency and intensity of a positive skin pathergy test.<sup>[25]</sup> It is proposed that the reusable needles that are repeatedly sterilized in boiling water become rough due to the collection of calcium on the bent parts of the needles making them more traumatic than disposable ones.<sup>[35]</sup> However, the use of disposable needles for the prevention of diseases such as AIDS and Hepatitis B and the lesser amount of trauma initiated by these seem to decrease the rate of pathergy positivity.<sup>[35]</sup>
  3. The positivity rate of pathergy test in Behçet's disease was found to vary from country to country (It is most prevalent around the silk route, which extends

from the Far East to the Mediterranean Basin, including the Gulf area than in comparison to its western counterparts, especially in Europe and the USA).<sup>[24]</sup>

4. Another method of increasing the rate of positivity consists of resting the needle in the dermis for 90 seconds before taking it out.<sup>[36]</sup>
5. Males who were affected by Behçet's disease were found to have a higher positivity rate than in comparison to females.<sup>[34,37]</sup>
6. Pathergy positivity is further related to the diameter of the needle.<sup>[38]</sup> A 20G disposable needle gave a positive skin pathergy test in 62.5% of cases. This figure fell to 35.8% when 26 gauge needles were used.<sup>[35]</sup> It appears that a fine needle causes insufficient trauma to induce pathergy in the dermis.
7. It was shown that surgical cleaning of the skin surface before application of the needle reduced the test positivity. Some substances, bacteria, or skin products, eliminated by surgical cleaning, might play a role in the development of skin pathergy reaction.<sup>[39]</sup>

#### Conditions with positive pathergy phenomenon:

1. Behçet's disease<sup>[40]</sup>
2. Pyoderma gangrenosum (PG): The pathergy test positivity at a rate of 25% has been reported in the literature in PG patients.<sup>[41]</sup> Aggressive surgical debridement or skin grafting is discouraged in these patients because of the risk of a pathergic response.
3. Interferon alpha-treated chronic myeloid leukemia patients<sup>[42]</sup>
4. Sweets syndrome<sup>[43,44]</sup>
5. Eosinophilic pustular folliculitis<sup>[45]</sup>
6. Inflammatory bowel disease<sup>[46]</sup>
7. Healthy individuals<sup>[47]</sup>
8. Rarely in spondyloarthropathies<sup>[48]</sup>

#### Uses of pathergy testing:

1. Positive pathergy reaction is very important for the diagnosis of Behçet's disease in patients with only recurrent oral ulceration plus one of the other criteria (recurrent genital ulceration, eye lesions, skin lesions).<sup>[49,50]</sup>
2. The test has also been used as an indicator of disease activity in patients with Behçet's disease.<sup>[41]</sup>

3. To determine the etiological factor in a case of recurrent aphthous stomatitis.<sup>[49,50]</sup>
4. Positive pathergy test is an independent risk factor for occurrence of postoperative complications in patients with Behcet's disease. In clinical practice, the presence of ischemia from thromboembolism, an impending vessel wall or aneurysm rupture, and bowel perforation all mandate urgent surgical intervention. In these cases, pathergy test results can be helpful to identify subgroups of patients at particular risk for postoperative complications and can guide initiation of immunosuppressive treatment in these patients.<sup>[51]</sup>

### Sites of pathergy other than the skin

The pathergy phenomenon is not only restricted to the skin. In fact, any disruption of tissue integrity is potentially associated with an exaggerated inflammatory response in Behcet's disease. In particular, the posttraumatic arterial thrombus and/or aneurysm formation following conventional angiographic interventions,<sup>[52]</sup> vascular surgery,<sup>[52,54]</sup> superficial thrombophlebitis induced by venipuncture, eye inflammation after intraocular corticosteroid injections<sup>[55]</sup> and anastomotic ulcers following surgical treatment of intestinal ulcer<sup>[56]</sup> are well known examples of pathergy reactions triggered at different tissue sites.

### CONCLUSION

Although the pathergy test has lost some of its sensitivity during the past 35 years, it has not lost its value as a diagnostic test. In a practical view, the chances of getting a positive test have decreased over the time. However, a positive test is rather a synonym of Behcet's disease, with a probability of 98.4% specificity.<sup>[19]</sup>

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