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Pathergy testing: prospective comparison of dermatoscopic evaluation and naked eye examination

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Abstract

Pathergy phenomenon is a non-specific tissue hyperreactivity reaction due to trauma and is a minor diagnostic criterion of Behcet's disease. In this study, 100 patients with a suspicion of Behcet's disease who were referred to Cerrahpasa Medical Faculty Dermatology department between 01.11.2014 and 31.01.2015 are included. Skin pathergy tests were applied to all the patients and results were evaluated by two dermatologists separately at 48th hour, each with naked eye and with dermatoscopy. Test results were scored on a scale of 0–6. At the end of the study, score results of naked eye and dermatoscopy for doctor number 1 were statistically similar. Same results applied for doctor number 2. However, naked eye results of doctor number 1 and 2 for the same patients were significantly different from each other (p 0.0372) and with dermatoscopy examination this difference was eliminated ($p > 0.05$). This study revealed that naked eye evaluation of pathergy test results can yield different results among different interpreters. Use of dermatoscopy during the evaluation process decreases interobserver variation and subjectivity of the test.

Keywords Pathergy test · Pathergy phenomenon · Behcet's disease · Dermatoscopy

Introduction

Behcet's disease (BD) is an inflammatory vasculitis, affecting vessels of all kinds and sizes. Every organ of the human body can theoretically be involved in the disease process. The exact pathophysiological mechanism of the disease remains unknown. The populations along the 'Silk Road', in the Mediterranean basin and Far East regions, have the highest disease prevalence, but it can be observed in almost every country of the world. This geographical tendency of the disease may implicate the effect of environmental factors, as well as the genetic background. Disease expression can vary depending on ethnic origin and geographical distribution, but there are a number of common clinical hallmarks defined by the International Study Group for BD including recurrent mucocutaneous lesions, skin lesions, ocular findings and reactivity of the skin to needle prick or injection, namely pathergy test (PT) [1]. The disease can also present with systemic involvement, including joints, heart, lungs, neurological and gastrointestinal system. There is no single laboratory finding or pathognomonic diagnostic tool for BD, and the diagnosis mainly depends on thorough history-taking and clinical examination. Due to the lack of a universally recognized test, BD diagnosis is primarily based on a set of clinical criteria, including PT [2].

Pathergy phenomenon is simply a hypersensitivity reaction of skin, in response to trauma. PT is a diagnostic tool used for the diagnosis of BD. It was first described by Blobner in 1937 [3]. It is an important criterion of many classification and diagnostic criteria of BD, as well as a possible indicator of disease activity. According to many studies in the literature, PT has lost some of its sensitivity recently [4], but it is still a powerful and objective diagnostic element for BD. Positivity rates for PT may fluctuate throughout the different geographical locations and due to the differences in the application or evaluation processes. Even

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the stage of the disease or medication use can affect the positivity rates. Positive PT is less frequently observed in non-endemic countries, and lately there have been a global decrease in both intensity of the reaction and positivity rates, most probably due to the use of disposable needles [5]. But still, pathergy is a unique diagnostic test, principally with regard to its positive predictive value. A positive PT result is rather a synonym of BD, with a probability of 98.4% [6]. Thus, an accurate PT is highly critical in BD diagnosis. To detect true-positive results more effectively and minimize false positivity in PT, an advanced evaluation technique may be incorporated into routine clinical use. With this regard, we propose the use of dermatoscopy for the evaluation of PT results, in addition to naked eye examination. Dermatoscopy is a non-invasive technique enabling direct microscopic examination of diagnostic features that are not seen by the naked eye in case of pigmented skin lesions and many other skin conditions. There is lack of standardization for the performance and as well as the evaluation of PT with methodological discrepancies, limiting the strength of this test on diagnostic process of BD. The overall objective of this study is to incorporate a new but yet simple and convenient method for the assessment of PT in daily practice, to increase the accuracy of the PT procedure.

Methods

This is a prospective and double-blind study conducted in Cerrahpasa Medical Faculty, Department of Dermatology and Venereology. Patients with suspected BD who were referred from Cerrahpasa Medical Faculty Rheumatology Department between 01.11.2014 and 31.01.2015 were enrolled in the study. When the number of patients reached 100, the study was terminated. Sociodemographic characteristics, systemic diseases and comorbidities with family histories, medications and results of ophthalmological examination are registered for the patient population in the study. Total body dermatological examination was made for each patient and the presence or history of skin lesions specific for BD such as oral aphthae, genital ulceration, acneiform eruptions, folliculitis, erythema nodosum and superficial thrombophlebitis was notetd.

For each patient, PT was performed on the hairless and avascular flexor surfaces of the both left and right forearms. On each forearm, three needle pricks with 2 cm inter-needle distance were performed, giving a total number of six needle pricks with six disposable needles. After asepsis of skin with 100% alcohol, 20-G needle tips were blunted using the cap and pricked intradermally at a 45°–90° angle. Prick sites were evaluated at 48th hour. Two dermatologists evaluated each patient via naked eye physical examination and Heine Delta 20 dermatoscopy device. Development of only crusts or needle mark due to the trauma or minimal erythema without papule formation was considered negative. For naked eye examination, papules of >2 mm in diameter and pustules with or without erythematous halo at any prick site was accepted as positive result. With dermatoscopy, evaluations for the measurement of the pathergy reaction were made with 10× magnification and papules of >1 mm in diameter and pustules were considered positive. Both observers graded the test results blindly within a grade range from 0 to 6. The grade for each test is equal to the sum of the positive results observed in six prick sites. If there is no positive reaction in any prick site, it is scored as 0 whereas positive reactions at all the six prick sites would yield a score of 6. The same grading methodology was applied to both naked eye and dermatoscopy examinations. A group of patients were initially evaluated via naked eye by the first observer and afterwards dermatoscopical evaluations were made blindly by the same observer, without knowing the results of the naked eye examination. Same approach was followed for the second observer. At the end of the study, each patient has four different evaluations, graded between 0 and 6.

Statistical analyzes were made by SAS Enterprise Guide V0.7.1. Paired *t* test and Wilcoxon paired sample tests were used. In these tests, p values below 0.05 are accepted as statistically significant.

Results

One hundred patients were enrolled in this study, between 01.11.2014 and 31.01.2015. Male to female ratio was 1.43 (59% vs 41%). Mean age of the patients was 33.03, ranging between 12 and 61. Most common comorbidities included hypertension, uveitis, rheumatoid arthritis, inflammatory bowel disease, major depression and familial Mediterranean fever. Four patients were on systemic corticosteroid treatment and other commonly used systemic medications were anti-hypertensives, nonsteroidal anti-inflammatory drugs, anti-diabetics and antidepressants. There was no statistically significant relation between age, gender, existence of comorbidities or medication use and pathergy positivity rates. Fourteen patients had a history of recurrent aphthous stomatitis, 10 of whom had active oral lesions. (7 minor aphthae and 3 major aphthae) Seven patients had history of genital ulceration and one of them had active genital lesion while four of them had genital scar tissue. Five patients had history of erythema nodosum, and none of them had lesions at the time of examination. Ten patients had acneiform lesions on the back and facial area. Fourteen patients had arthritis of small joints and four patients had previous diagnosis of uveitis. No significant relationship was found between these clinical findings and pathergy positivity rates.

PT results were evaluated separately by two dermatologists, both with naked eye and via dermatoscopical examination. Examples of positive and negative test results can be seen in Figs. 1, 2, and 3.

At the end of the study, we had four different sets of PT results for each and every patient; naked eye examination result of the first observer, dermatoscopical examination result of the first observer, naked eye examination result of the second observer and dermatoscopical examination result of the second observer. For the first observer, 19 and 21 patients showed positive pathergy testing with naked eye and dermatoscopy, respectively. For the second observer, 22 and 24 patients showed positive pathergy testing with naked eye and dermatoscopy, respectively. To test the normality of the data sets, Kolmogorov–Smirnov normality test was applied and it shows that the four sample data sets were not

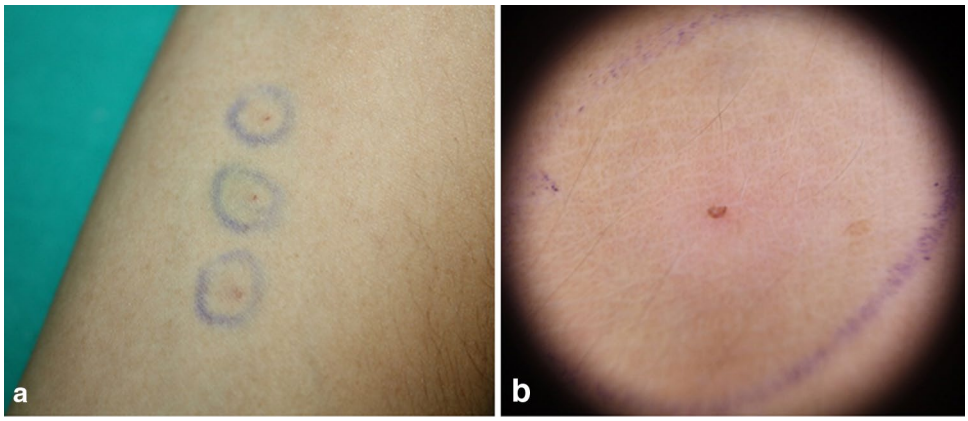

Fig. 1 **a** Negative PT result, with naked eye. **b** Negative PT result with dermatoscopy

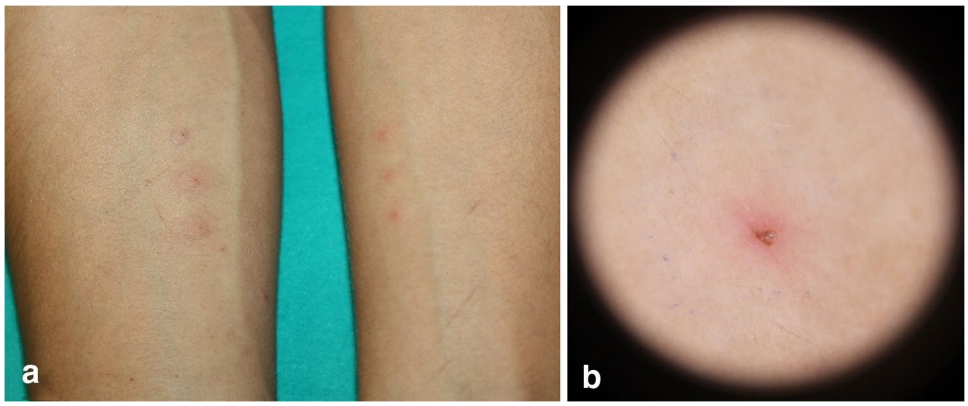

Fig. 2 **a** Papules of positive PT, with naked eye. **b** Dermatoscopic appearance of papules for positive PT

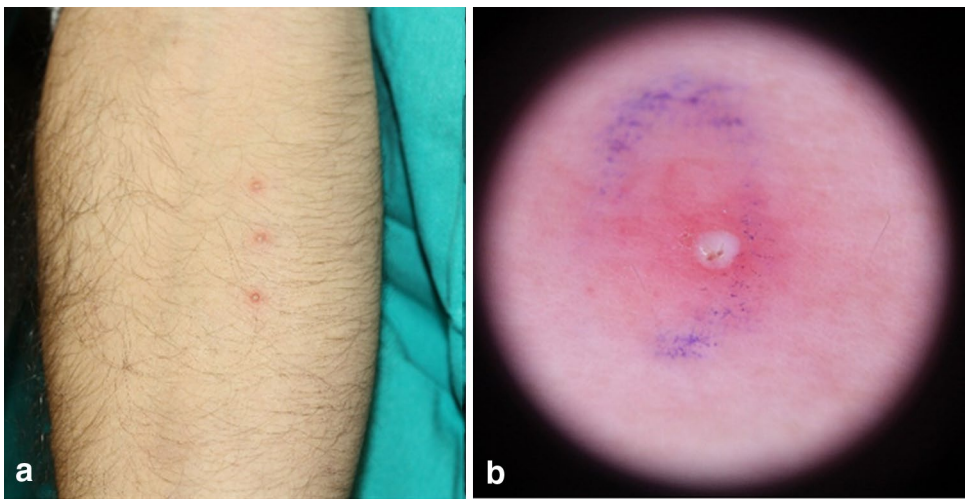

Fig. 3 **a** Pustules of positive PT, with naked eye. **b** Dermatoscopic appearance of pustules for positive PT

normally distributed. Paired sample *t* test requires the data to be normally distributed. Therefore, all the comparisons in this study were made with Wilcoxon paired sample test that does not assume normality of the data.

For the first observer, PT scores of the naked eye and dermatoscopical examination were compared and statistical analysis reveals that there is no significant difference between these two data sets (p 0.0703). Same results were observed for the second observer (*p* 0.6072). However, when naked eye examinations of the two observers are compared, PT scores are significantly different for the same patients (*p* 0.0372). More interestingly, the difference between dermatoscopical PT scores of the first and second observer are not statistically significant (*p* 0.7539). The inter-observer variation disappears when dermatoscopy is put into use, contrary to the naked eye examination.

Discussion

Pathergy is a non-specific hypersensitivity reaction of the skin to trauma, commonly a needle prick in clinical practice. This reaction is accepted as one of the minor criteria of International Study Group for BD. It is pathognomonic for BD, and has also been used as an indicator of disease activity. Positivity rates increase during the active phase of critical disease, with major vessel involvement. In clinical practice, effective use of PT may contribute to the guidance of treatment approaches such as dose arrangements of immunosuppressive treatments and determination of morbidity and mortality rates. Positive PT itself is also an independent risk factor for postoperative complications in BD patients. Although the reaction is considered pathognomonic for BD, it can be observed in cases of inflammatory bowel disease, pyoderma gangrenosum, erythema elevatum diutinum and other neutrophilic dermatoses, such as Sweet syndrome and blind loop syndrome [7–9].

In some patient groups with BD, positive PT is related to the presence of genital ulcers and papulopustular lesions [10]. However, for our patient population, no relationship was observed between pathergy positivity rates and clinical findings such as oral aphthae, genital ulcers or scars, erythema nodosum and acneiform lesions or the presence of uveitis or arthritis. According to other clinical studies, mucocutaneous findings, systemic involvement, age, gender and duration of the disease are not significantly related to positivity rates of PT [6, 11]. Parallel to that, our study does not find any relationship between gender, age, medication use or coexistence of any chronic illness and pathergy positivity rates, either. However, unlike these studies conducted on BD patients, our study group consists of patients with a suspicion of BD, which may possibly explain the lack of relationship between pathergy and other factors.

There has been a continuous debate about lack of standardization for the application and the evaluation process of PT. Nevertheless, according to the vast majority of the studies in the literature, application procedures are similar to a certain extent among different physicians from all over the world. Hence, different positivity rates from different countries and recent global decrease of positive results may be attributed to human error. Despite its high specificity, the pathogenic cutaneous response has variable sensitivity and inconsistent reproducibility, which limits its use. This study primarily focuses on the evaluation process of PT, existence of inter-observer variability and how this variability can be decreased to minimize the subjectivity of the test.

During routine clinical practice, assessments of PT are made via naked eye examination. Here, we propose the use of dermatoscopy with the intention to standardize the methods of evaluation. Dermatoscopy (epiluminescence microscopy, in vivo cutaneous surface microscopy) is a non-invasive technique for advanced investigation of all kinds of skin lesions, which cannot be visualized adequately with the naked eye. A dermatoscope consists of a magnifier (typically ×10), cross-polarized light source, a transparent plate and a liquid medium between the instrument and keratin layer of the skin, allowing the epidermis to become translucent and permitting the visualization of structures in the epidermis and superficial dermis.

In our study, dermatoscopy is used as an additional method for PT evaluation. In case of negative results, the device reveals only the impression of needle mark at the entry site together with minimal erythema and in some cases crust formation, of which may form exaggerated pseudo-papule-like appearance during naked eye examination and yield false-positive test results. In case of positive PT, papules and pustules surrounded with areas of edematous erythema and minimal ulcerated regions with crusts were more clearly visible, enabling faster and more accurate diagnosis. Cutoff values for papule sizes in case of positive reaction (2 mm for naked eye examination and 1 mm for dermatoscopy) are based on both our clinical experience and previous studies in the literature [5, 12]. According to one of these studies [12], histopathological examination of papules measuring 1–2 mm and even ≤1 mm in diameter reveals properties of positive reaction. However, naked eye examination may miss these lesions, leading to false-negative test results.

In the literature, there is only one study about the use of dermatoscopy for PT in clinical setting, which verifies dermatoscopical examination using histopathology and encourages the use of both the dermatoscopic and histopathological examinations, but the results are not compared with the naked eye examination in this study [12]. In our study, for the same observer, naked eye and dermatoscopy scores are similar. With solely this finding, it may be stated that dermatoscopy is not superior to naked eye. However, in case of

naked eye examination, for the same patients, PT scores of the two observers are significantly different, supporting our hypothesis of personal differences between observers and consequently subjectivity of the test. When dermatoscopical evaluation is involved, this difference disappears and PT grading of the two observers are statistically indifferent. When we further analyze the results, the difference between two observers is more prominent in case of moderately positive results. Thus, dermatoscopy is notably supportive for intermediate positivity, whereas clearly positive results such as formation of multiple pustules or erythematous and edematous papules of ≥2 mm can be easily and correctly detected via naked eye. In addition, in case of plain negative results, naked eye examination may be sufficient. Role of dermatoscopy is critical for moderately positive PT results, and for those cases, use of dermatoscopy in addition to naked eye examination significantly decreases the subjectivity of the results that enhances the diagnostic strength of the PT.

Pathergy reaction is an objective finding, universally applicable, cost effective and reproducible, therefore, a well-established diagnostic tool throughout the complex investigational process of BD. Apart from racial, geographical or gender factors, there has been a prominent decline in the positivity rates in the last decades. Nevertheless, it is an important component of many of the classification and diagnostic criteria for BD, increasing diagnostic sensitivity significantly [13]. Dermatoscopical evaluation of PT results has significantly decreased inter-observer variations. Based on this finding, we suggest the use of dermatoscopy in addition to naked eye examination for the evaluation of PT in routine practice. The aim of this study is also to constitute a basis and example for future studies to be conducted in clinical settings in search for further evidence for a gain in BD diagnostic accuracy of PT through dermatoscopy.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Statements on human and animal rights This study was approved by the ethical committee of Cerrahpasa Medical Faculty.

Informed consent Written informed consents of all patients were obtained before the study.

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