REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br

SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Brief communication

The dermatoscopy in the skin pathergy testing: case series in patients with suspected Behçet's Disease

Maria Antonieta Rios Scherrer[a], *Lúcia Porto Fonseca de Castro*[b], *Vanessa Barreto Rocha*[a,*], *Leonardo Pacheco*[a]

[a] *Ambulatório de Dermatologia, Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*
[b] *Departamento de Anatomia Patológica e Medicina Legal, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*

ARTICLE INFO

Article history:
Received 9 November 2013
Accepted 12 June 2014

Keywords:
Behçet disease
Diagnostic techniques and procedures
Vasculitis

ABSTRACT

Behçet's disease is a multisystemic disease consisting of a varying combination of ocular, mucocutaneous, neurologic, cardiovascular, gastrointestinal and other manifestations. Its diagnosis is based on clinical criteria, in which a positive pathergy test scores 1. A case series with 26 suspected patients is presented, and the skin pathergy test was performed in 23. The results were read in 48 hours, and they were considered negative when without papule, and positive with a papule or pustule. Positive results were divided by papule size, and dermatoscopy was done to measure and observe its clinical aspects. After the readings, a biopsy was performed, with annotation of histopathological aspects. The test was negative in 2 (8.7%) and positive in 21 (91.3%) patients. The results and the literature review are presented.

Dermatoscopia no teste cutâneo da patergia: série de casos de pacientes com suspeita de Doença de Behçet

Palavras-chave:
Doença de Behçet
Técnicas e procedimentos diagnósticos
Vasculite

RESUMO

A doença de Behçet é uma doença multissistêmica que consiste de diferentes combinações de manifestações oculares, mucocutâneas, neurológicas, cardiovasculares, gastrintestinais e outras. Seu diagnóstico se fundamenta em critérios clínicos, em que o teste da patergia positivo recebe um ponto. Apresenta-se uma série de casos com 26 pacientes suspeitos, tendo o teste da patergia da pele sido realizado em 23 deles. Os resultados foram avaliados em 48 horas, tendo sido considerados como negativos diante da ausência de pápula e positivos na presença de pápula ou pústula. Os resultados positivos foram divididos pelo tamanho da pápula, efetuou-se uma dermatoscopia para medir e observar seus aspectos clínicos. Após as leituras, foi realizada uma biópsia, com anotação dos

DOI of original article: http://dx.doi.org/10.1016/j.rbr.2014.06.003.
* *Corresponding author.*
E-mail: vanessabarreto@oi.com.br (V.B. Rocha).
http://dx.doi.org/10.1016/j.rbre.2014.06.005

aspectos histopatológicos. O teste foi negativo em 2 (8,7%) e positivo em 21 (91,3%) pacientes. Apresentam-se os resultados e a revisão da literatura.

Introduction

Behçet's disease (BD) is classified among vasculitides.[1] It was first defined as a triad of recurrent aphtous stomatitis, genital aphtae and relapsing uveitis in 1937 by Hulusi Behçet. It is considered a multisystemic disease consisting of varying combination of ocular, mucocutaneous, neurologic, cardiovascular, gastrointestinal and other manifestations.[2–7]

Its diagnosis is based on clinical criteria. The New International Criteria for Behçet's Disease are one of the most recently revised diagnostic criteria. A diagnosis of BD consists of a sum of three or more points according to a score system. Positive pathergy test scores 1 point (Table 1).[8]

Pathergy is a hyper reactivity of the skin after a needle trauma. It was first described in 1937 and it is considered pathognomonic, although it can be seen in pyoderma gangrenosum, erythema elevatum diutinum and other neutrophilic dermatoses, including Sweet syndrome and the blind loop syndrome.[9] It is reported that about 8% of inflammatory bowel disease patients show this phenomenon.[10]

In spite of its high specificity, the skin pathergy response has variable sensitivity and inconstant reproducibility, which limit its use. Regardless of this, it is used in many sets of classification/diagnosis criteria.[1,9,11,12]

Methods

A case series study was done with twenty-six suspected BD patients (23 women and three men) referred to a private clinic to be tested for pathergy phenomenon.

Out of 26 patients, the pathergy test was performed in 23 patients, as three of them (two men and one woman), which already fulfilled the diagnosis of BD did not agree to be tested. Eight patients did not present disease activity (presence of symptoms or signs) during the test, contrasting to 15 who did. Five patients were in treatment (taking less than 20 mg of prednisone) when it was performed.

Six needle pricks using 21 gauge disposable needles were done intradermally at the same point on the skin of the forearm, after cleaning the site with 70% ethanol swabs. Results were read by the same observer 48 hours later.

They were considered negative if without papule and only needle mark or erythema and positive if with papule or pustule surrounded by an erythema. Dermatoscopy was done to measure the reaction and observe its clinical aspects.

After the readings a biopsy was performed and stained with hematoxylin and eosin (HE). In some cases more than 1 point of multiple punctures were performed (two prick tests) to choose the biggest papule to biopsy.

Table 1 – Revised international criteria for Behçet's disease.

Criterion	Score (point)
Oral aphtosis	1
Skin manifestations (erythema nodosum-like lesions, papulopustular lesions or pseudofoliculitis, acneiform nodules)	1
Vascular lesions (arterial and venous thrombosis, aneurysm)	1
Pathergy phenomenon (test)	1
Genital aphtosis	2
Ocular lesions	2

Behçet's Disease, three or more points.

Results

Among the patients, 23 were women and 3 men. The age ranged from 11 to 72 years and the average age was 33.11, with standard deviation 14.73.

The oral lesions were present in all patients (100%), followed by genital lesions, observed in 12 (46.1%), ocular lesions in 10 (38,5%), skin lesions in 10 (38.5%), and joint and neurological involvement in 13 (50%) and two (7.7%), respectively (Table 2).

The pathergy test was negative in two BD patients (8.7%) and positive in 21 (91.3%). Among the positive tests, four (17.4%) were less than 1 mm, 16 (69.5%) were between 1-2 mm and one (4.3%) more than 2 mm. These results were not correlated with the disease activity or treatment. Dermatoscopy showed needle marks and mild erythema in the negative tests (2 patients) and erythematous papule/pustule or exulcerocrostous lesions surrounded by erythematous and/or edematous area in the positives (21 patients) (Table 3). It was a good tool especially to measure and examine the inflammatory aspects of the small lesions (less than 2 mm). Figure 1 shows the dermatoscopic aspect of a pathergy test.

The main histopathologic findings of the 23 biopsed patients were: perivascular inflammatory infiltration in 19

Table 2 – Clinical manifestations in 26 patients with suspected BD.

Clinical manifestation	Absolute number (%)
oral	26 (100)
genital	12 (46)
ocular	10 (38)
cutaneous	12 (46)
arthritis	13 (50)
neurological	2 (7,6)

Table 3 – Variants analysed in the SPT performed in 23 patients: size, dermatoscopy, histopathology, presence of treatment at the moment of the test.

Pathergy							Histopathology				Treatment at the test	
Negative	Positive - Papule size			Dermatoscopy								
Nd mark	<1mm	1-2mm	>2mm	Pap/pus	Pap/crust	Nd mark	Perivasc inf	Fibrina	Erytr extr	Interst inf	Others	With	Without
2	4	16	1	15	6	2	19	16	13	10	43	5	18

Pap/pust, papule/pustule; Pap/crust, papule crust; Nd mark, needle mark; Perivasc inf, perivascular inflammatory infiltration; Fibrina: deposition of fibrinoid material; Erytr extr, extravasation of erythrocytes; Interst inf, interstitial inflammatory infiltration.
Presence of neutrophils or eosinophils, microabscesses, leucocytoclasis, edema, necrosis,nuclear debris, vasculitis and damage of vessels.

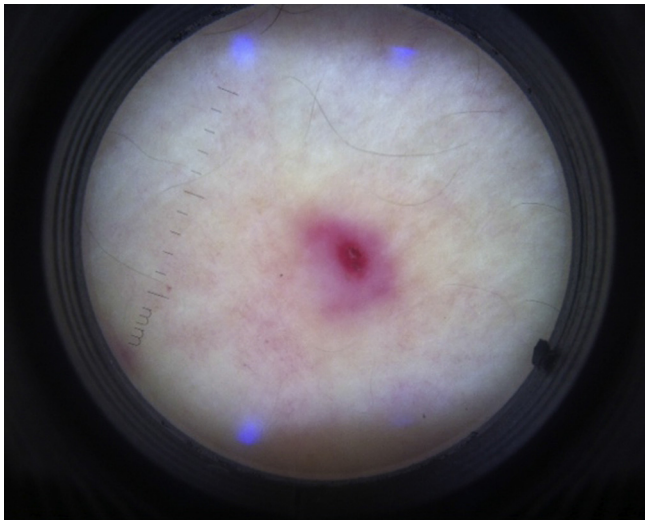

Figure 1 – The dermatoscopic aspect of a pathergy test.

(82.6%), deposition of fibrinoid material in 16 (69.5%), extravasation of erytrocytes in 13 (56.5%), interstitial inflammatory infiltration in 10 (43.5%). Other detected alterations were: presence of neutrophils or eosinophils, micorabscesses, leucocytoclasis, edema, necrosis, nuclear debris, vasculitis and damage of vessel walls (Table 3).

After testing, the final diagnosis was: 20 patients (77%) fulfilled the International Study Group (ISG) criteria for the diagnosis of BD (Table 1), and 6 (23%), who did not, were classified as having suspected BD.

Discussion

Positive pathergy is amongst the criteria for a diagnosis of BD. Therefore, the study of this phenomenon is important not only to make the diagnosis but also to understand the disease.

Although its aetiology is still unknown, endothelial dysfunction is a prominent feature in BD. Thrombomodulin (TM) is a membrane-bound receptor of thrombin on vascular endothelial cells, which activates protein C and inactivates thrombin. It is downregulated by inflammatory cytoquines, leading to a procoagulant state of the endothelium. TM is also expressed by spinous keratinocytes. High blood levels of TM were strongly correlated with positive skin pathergy test (SPT), suggesting that this test could be an alternative to the SPT.[8,11]

Positive SPT has been reported with high frequency from most countries along the Silk Road but the sensitivity is declining over the time.[1,9] In a recent study, the sensitivity of the pathergy phenomenon decreased gradually in Iranian patients from 64.2% to 35.8%, and the reason remains obscure; however, the specificity increased from 86.6% to 98.4%. Therefore, the chances of getting a positive test have decreased, and a positive test is rather synonymous with BD, with a probability of 98.4% (specificity).[9] A recent study about the impact of the positive SPT on the performance of the sets of classification/diagnosis criteria for BD showed that, without it, the sensitivity of the majority of these sets decreases by 1.9 to 35%. On the contrary, the specificity improves by 0.1-4.7%. Overall,

the sets of criteria show a loss of accuracy, demonstrating that this parameter is necessary to improve the power of existing classification/diagnosis criteria.[12]

The mechanisms underlying pathergy are unknown. The skin injury caused by the needle prick in the patient's skin apparently triggers a cutaneous inflammatory response which is more prominent and extensive than that seen in normal skin. It is suggested that an increased and aberrant release of cytokines from keratinocytes or other cells in the epidermis or dermis results in a perivascular infiltration observed on skin biopsy.[8]

Pathergy phenomenon was detected more frequently in HLA-B51 patients especially in some countries.[1,8]

The forearm is the most frequently positive site and it is often chosen to perform the test.[6,8,9,12]

Studies have demonstrated that the use of a blunt, re-usable, sterilized needle increases the frequency and intensity of SPT. The introduction of disposable needles caused its decrease. Pathergy is further related to the diameter of the needle. A 20-gauge disposable needle gave a positive SPT in 62.5% but the result fell to 35.8% when 26-gauge needles were used. Other authors recommend the test with a 25 or 21-gauge needle inserted intradermally, perpendicular or diagonally to the skin.[1,6,8,9,12–14]

Therefore, the intensity of the reaction was more prominent with thicker needles (20-gauge). The intracutaneous physiological injections, a method used by some investigators, was the least sensitive.[8]

There is no consensus about the number of the needle pricks required. Some studies used multiple pricks, which is considered important to increase the positive rate of a SPT and others, one or two.[1,3,8,9,13,14]

Most investigators have read 24-48 h after the test, and it is considered positive if an erythematous papule > 2 mm in diameter or a pustule is observed. Others have reported positive results in the presence of a papule or pustule not mentioning its size. Therefore, the percentage of positive tests differs from one report to another not only because of ethnic factors but also for this reason.[1,3,5,6,8,9,13,14]

In order to investigate the reactions, the SPT results were divided based on the size of the papule and a biopsy was taken even if the papule was smaller than 2 mm.

The higher frequency was found between 1-2 mm, and the tests bigger than 2 mm were detected in a low frequency (4.3%).

On the other hand, the histologic exams showed prominent aspects even when the sizes were smaller than 1 mm and for that reason all the results with the presence of a papule were considered positive. In a study reported in Brazil, 91.6% of 24 patients had SPT negative, but the histopathology on the site of the pathergy test showed inflammatory aspects in 83.3% of them.[13]

Although some authors do not recommend the biopsy of the SPT, we performed the histopathologic exam because, according to our results, it confirmed the inflammatory process showing important findings to complement the test.[8,13]

The pathergy phenomenon is not constant during the course of the disease. The degree of positivity may occasionally correlate with disease activity.[1,2,12] Reports do not confirm the relation between pathergy and clinic manifestations, being necessary longitudinal studies to establish it.[2,12]

There are apparent controversies about the histopathologic findings of the SPT, since its methodology is variable and evaluated after different time periods. In addition to this, a study compared histopathologic and clinical evaluations and concluded that histopathologic investigation was no more sensitive than clinical observation, but in this series the test was considered positive if > 2 mm.[2,8,13]

In our series a variety of histopathologic findings were described but perivascular infiltration and deposition of fibrinoid material were the most frequent, confirming the literature.

The expression pattern of adhesion molecules in pathergy reaction suggested a direct epidermal injury as the cause of the cutaneous inflammation. An intense antigen-independent induction phase of cutaneous inflammation might be developed by increasing the release of cytoquines from keratinocytes, which might later be amplified by the effect of infiltrating activated mononuclear cells.

In addition, the immunohistologic picture of the pathergy reaction suggested a cell-mediated immune response.

Ethnic factors and the cross-sectional methodology of the various studies performed in several countries may also influence the reported histopathologic findings.[2,8,13]

Sometimes, the cutaneous inflammation due to the epidermal injury caused by the pricking is so light that the SPT is considered negative. However, when the reactions are better observed by both dermatoscopy and histopathology, and, consequently, even the tiny ones are considered positive, as described in our report, the frequency of positive SPT increases. Therefore, this high frequency was detected because of the methodology applied which valued the size and histopathologic findings of the reactions.

Despite the controversies in the methodology of the SPT, it is necessary to establish guidelines to perform it, since it is an important key for the diagnosis of the BD.

Reports using dermatoscopy in the SPT were not found.

In conclusion, the dermatoscopy and histopathologic study on the site of the punctures, performed 48 hours after the pricking test, are strongly recommended for the investigation of suspected BD patients, since they can reveal evidence of inflammation even in the small lesions.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, et al. Behçet's disease: from east to west. Clin Rheumatol. 2010;29:823–33.
2. Lee S, Bang D, Lee ES, Sohn S. Behçet's Disease: A guide to its Clinical Understanding textbook and atlas. Berlin: Springer-Verlag; 2001.
3. Ozdemir M, Bodur S, Engin B, Baysal I. Evaluation of application of multiple needle pricks on the pathergy reaction. Int J Dermatol. 2008;47:335–8.

4. Vaiopoulos G, Konstantopoulou P, Evangelatos N, Kaklamanis Ph. The spectrum of mucocutaneous manifestations in Adamantiades-Behçet's disease in Greece. J Eur Acad Dermatol Venereol. 2010;24:434–8.
5. Gul U, Gonul M. Oral and genital pathergy in Behçet's Disease. Dermatology. 2007;215:80–1.
6. Ozdemir M, Balevi S, Deniz F, Mevlitoglu I. Pathergy reaction in different body areas in Behçet's disease. Clin Exp Dermatol. 2006;32:85–7.
7. Yalçindag NF, Batioglu F. Pathergy-like reaction following intravitreal triamcinolone acetonide injection in a patient with Behçet's Disease. Ocul Immunol Inflamm. 2008;16: 181–3.
8. Varol A, Seifert O, Anderson CD. The skin pathergy test: innately useful? Arch Dermatol Res. 2010;302:155–68.
9. Davatchi F, Chams-Davatchi C, Godhsi Z, Shahram F, Nadji A, Hormoz S, et al. Diagnostic value of pathergy test in Behçet's disease according to the change of incidence over the time. Clin Rheumatol. 2011;30:1151–5.
10. Hatemi H, Hatemi G, Celik AF, Melikoglu M, Arzuhal N, Mat C, et al. Frequency of pathergy phenomenon and other features of Behçet's syndrome among patients with inflammatory bowel disease. Clin Exp Rheumatol. 2008;26 Suppl 50:S91–5.
11. Menashi S, Tribout B, Dosquet C, Toumelin Pl, Piette JC, Wechsler B, et al. Strong association between plasma trombomodulin and pathergy test in Behçet disease. Ann Rheum Dis. 2008;67:892–3.
12. Davatchi F, Abdollahib BS, Davatchi CC, Shahram F, Ghodsi Z, Nadji A, et al. Impact of the pathergy test on the performance of classification/diagnosis criteria for Behçet's disease. Mod Rheumatol. 2013;23:125–32.
13. Scherrer MAR, Vitral N, Bambirra E, Orefice F. Estudo clínico e histopatológico da patergia na Doença de Behçet. Ann Bras Dermatol. 1994;69:267–71.
14. Ozden MG, Bek Y, Aydin F, Senturk N, Canturk T, Turanli AY. Different application techniques of pathergy testing among dermatologists. J Eur Acad Dermatol Venereol. 2010;24:1235–46.