

VALIDITY OF PATHERGY TEST IN PATIENTS WITH BEHÇET'S DISEASE

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ABSTRACT

Background and objectives Behçet's disease is a chronic relapsing multi-system disease with a high prevalent rate and of severe form in countries along the silk route. For diagnosis, a set of criteria has been adopted. Pathergy test, a unique skin lesion of disease, is an important criterion for diagnosis and classification of it. The aim of study was to assess pathergy test in patients diagnosed as Behçet's disease according to the International Study Group criteria.

Methods The study was conducted in two years between October 2005 and October 2007. Cases were diagnosed as having Behçet's disease based on the International Study Group criteria for the diagnosis of Behçet's disease. All cases were patients attending Duhok Center for Rheumatic Diseases and Rehabilitation. Controls were volunteers and persons who attended the center for consultation of non specific mechanical strain or sprain and with no history of orogenital ulceration.

Results Majority of patients were in the fourth decade of life and in most of them the disease had started in the third decade. The male to female ratio was 1.12:1. History of oral ulcer has been reported by 84.3 % at disease onset and the percentage was 100% at diagnosis. Statistically significant difference in the rate of positive pathergy test during exacerbation and remission of disease was obtained and of high specificity for disease. Gender played no role in the positive rate during phases of disease. Age extremities and disease duration less than 10 years were associated with a drop in the positive rate during remission.

Conclusion Pathergy phenomenon occurred in about one half of patients with Behçet's disease and it is recommended to be performed in every patients of Behçet's disease especially those with incomplete manifestations for diagnosis as it is one of criteria required diagnostic set.

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Key words: Validity, Behçet's disease, Pathergy test

Behçet's disease is a chronic systemic disease which consists of varying combinations of mucocutaneous, ocular, neurologic, cardiovascular, pulmonary, gastrointestinal, and other manifestations.¹ The disease tends to wax and wane, the frequency and duration of exacerbations being unpredictable.² The disease generally runs an improving or stable course after the first five years with clinical complications generally recurring

at longer intervals.³ Hence the prognosis of patients with Behçet's disease is generally favorable, once the initial insult abates.⁴ However, central nervous system involvement and mojar vessels disease are exception, since their onset may occur 5-10 years in to the course of the disease .

Several aspects of the immunopathogenesis are considered but its accurate etiology and pathogenesis are still unknown.¹ An autoimmune reaction

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triggered by an infectious or environmental agents (possibly local to a geographic region) in a genetically predisposed individual seems most likely.²

Behçet's disease is most frequent in countries along the ancient silk route from Japan to the Middle East and Mediterranean basin.⁵ The highest prevalence of the disease is reported for Turks living in Anatolia with 370 patients per 100 000 inhabitants.⁶ In Iraq the prevalence is 17: 100 000,⁷ and in Iran the prevalence is 16.7: 100000.⁸

Diagnosis has always depended on the grouping together of sufficient features in the individual patient to satisfy the physician that a secure diagnosis can be made,⁹ so sets of criteria are used to diagnose the disease depending on disease manifestations. Pathergy test, which is one of the unique skin lesions in Behçet's disease, is an important criterion for the modern diagnosis and classification criteria of Behçet's disease.¹⁰ And pathergy phenomenon is a non specific neutrophil hyperactivity reaction in response to minor cutaneous trauma in Behçet's disease.² It is manifested as the development of a papulo-pustular lesion around a puncture site on the skin, 24-48 hours after the injection of a sterile substance.¹¹ Pathergy reaction is considered highly sensitive and specific for Behçet's disease in patients originating from Turkey, the Middle East, Japan and Korea.¹² It is positive in 57-65 % of patients from the Middle East and Turkey.¹³⁻¹⁵ A positive skin test for pathergy reaction is considered an important criterion of International Study Group for the Diagnosis of Behçet's Disease.^{16,17}

The aim of this study was to assess pathergy reaction in patients diagnosed as having Behçet's disease according to the International Study Group criteria among those with recurrent oral ulcerations. Also, the study aimed at comparing the rate of positivity of pathergy test among patients with Behçet's disease during exacerbation and remission phases and examining the

relationship of age, gender and duration of the disease to the difference in positivity of pathergy test.

METHODS

The study was conducted between October 2005 and October 2007. Cases were diagnosed according to the international study group criteria for diagnosis of Behçet's disease. This included patients with a history of recurrent oral ulceration on three or more occasions for more than one year plus two of recurrent genital ulcerations, eye lesions and/or skin lesions.¹⁸ All cases were patients attending Duhok Center for Rheumatic Diseases and Rehabilitation. This center is the only specialized center in Duhok governorate which is responsible for dealing with rheumatologic problems. Controls were volunteers and persons who attended the center for consultation of non specific mechanical strain or sprain and with no history of orogenital ulceration. Controls were matched with cases for age (± 2 years) and sex. A total of 70 cases with a similar number of controls were included in the study.

Consent of each patient and control was taken followed by data collection. Data were collected using a questionnaire form that included demographic and clinical information. Clinical data included history of first presentation of the disease and its duration; history of orogenital ulceration, eye lesions, Also, smoking and diet history including spicy food and family history of recurrent oral ulcers and/or Behçet's disease were taken. Pathergy test was done for the participants during exacerbation and remission phases .

Pathergy test was performed by first cleaning the puncture site by 0.9% normal saline then using a sterile, sharp, 23 gauge disposable needle that was inserted perpendicularly to the skin and subcutaneous tissue of volar aspect of forearm to the depth of 0.5 cm, rotated briefly on its axis, and then removed.

Then, the site of puncture in encircled by a pen mark and after 24-48 hours, the skin lesion that appeared at the site of the puncture was measured using a tape measure. The appearance of an erythematous papule, pustule, or erythema of more than 2mm was considered positive.²

Categorical data were presented as count (%). Z test for two proportions was used to test for difference in the proportions. Level of significance was set at 0.05. For purpose of avoiding cells with zero frequencies, 0.1 was added to all cells.¹⁹

RESULTS

During the period of two years study, 70 patients were registered, 37 males and 33 female, and the male to female ratio was 1.12:1. Their ages were ranged from 4-61 years and the mean age was 35 years at presentation. Figure 1 shows age and gender distribution of the patients. Fifteen out of 37 (40.5%) of male patients were aged 30-39 years compared to 11 out of 33 (33.3%) of female patients.

The duration of the disease or the

symptoms since the onset of disease was varied between patients from one year to more than 25 years and the mean duration was 8.4 years. Thirty (42.9%) patients had the disease for 1-4 years and 19 (27.1%) patients had symptoms for 5-9 years.

At the onset of disease the first presentation was oral ulcer in 59 (84.3%) patients while 7.1% presented with genital ulcer. Thrombophlebitis, arthritis, and uveitis each accounted for 2.9% of first presentations.

When cases and controls were tested for pathergy reaction, all the controls were negatives for pathergy reaction, while it was positive in 48 of cases during the disease flare, but the positive rate of test dropped to 27 of cases when the test was repeated during remission of disease (Table 1). When Z test applied, a statistically significant difference in positivity of pathergy test between the cases in exacerbation and remission was obtained at p value of < 0.001.

There was no significant difference in the positivity of test between males and females during exacerbation and remission (Table 2).

Figure 2 shows that patients with

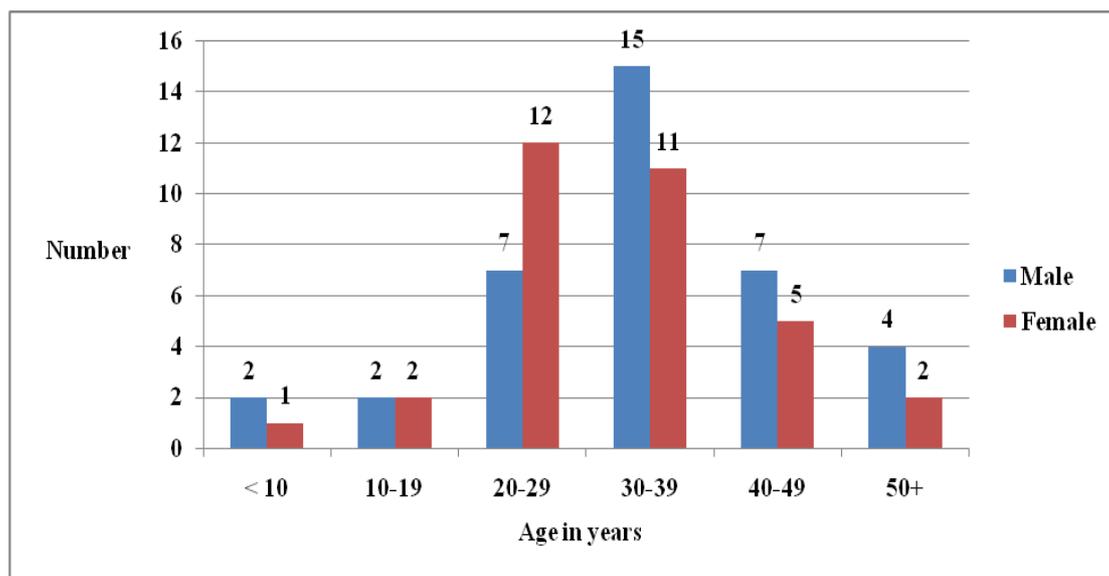


Figure 1. Age-gender distribution of patients with Behçet's disease in Dohuk province, 2005-2007

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Table 1. Pathergy test outcome in cases of Behçet's disease during exacerbation and remission of disease, and in control in Dohuk province, 2005-2007

Pathergy test outcome during phases of disease	Exacerbation		Remission	
	Cases	Control	Cases	Control
Positive	48	0	27	0
Negative	22	70	43	70

Table 2. Gender distribution of pathergy test during exacerbation and remission in patients with Behçet's disease in Dohuk province, 2005-2007

	Male (n = 37)	Female (n = 33)	p value*
Positive pathergy test during exacerbation	25 (67.6)	23 (69.7)	> 0.05
Positive pathergy test during remission	14 (37.8)	13 (39.4)	> 0.05

* Z test for two proportions was used

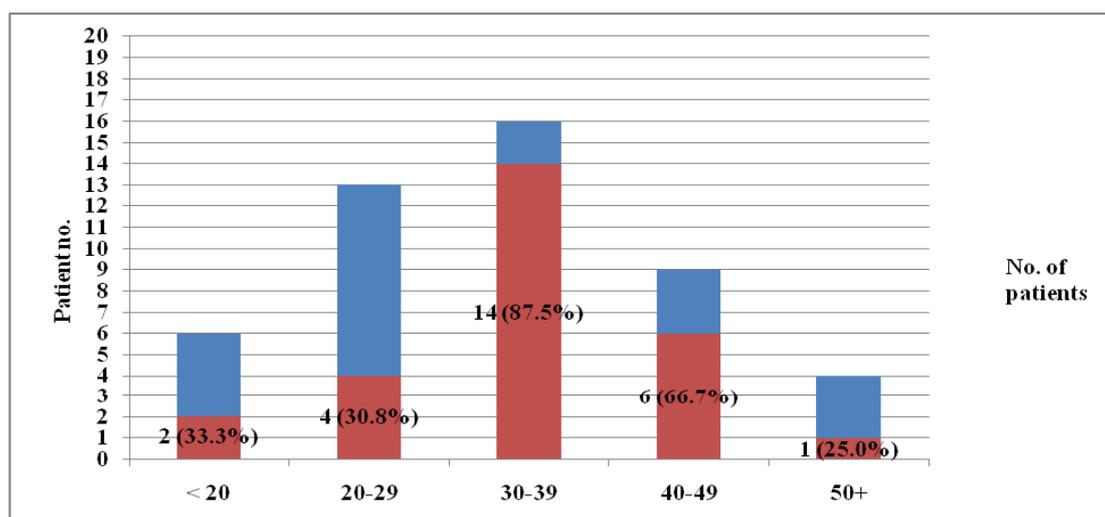
positive pathergy test during the exacerbation period in age group of 30-39 and 40-49 were still positive for the test during the remission period (87.5% and 66.7%, respectively).

Most patients affected by the differences in positive pathergy reaction rate during exacerbation and remission were those who had disease duration of less than 10 years (Table 3).

The test shows its great specificity in patients with Behçet's disease and during both exacerbation and remission whiles the

sensitivity, though was abed variable during phases of disease but was reliable to be applied specially during exacerbation.

The specificity of the test was 99.9% during exacerbation and remission. The positive predictive value was 99.8% and 99.6% during exacerbation and remission, respectively. The sensitivity and negative predictive value were 68.5% and 76% respectively during exacerbation and were 38.6% and 61.9% respectively during remission (Table 4 A and B).



Percentage indicate rate of positivity of pathergy test during the remission period among patients who were positive also during the exacerbation period.

Figure 2. Rate of positivity of pathergy test during the remission period among patients with Behçet's disease who were positive also during the exacerbation period in Dohuk province, 2005-2007

Table 3. Distribution of years since onset of disease to positive pathergy test during exacerbation and remission in patients with Behçet's disease in Dohuk province, 2005-2007

Duration in years No. (%)	Positive pathergy test		Total
	During exacerbation	During remission	
1-4	19 (39.6)	6 (22.2)	30 (42.9)
5-9	13 (27.1)	9 (33.3)	19 (27.1)
10-14	3 (6.3)	3 (11.1)	5 (7.1)
15-19	3 (6.3)	2 (7.4)	3 (4.3)
20-24	7 (14.6)	6 (22.2)	9 (12.9)
25+	3 (6.3)	1 (3.7)	4 (5.7)
Total	48 (100.0)	27 (100.0)	70 (100.0)

Table 4 A and B. Sensitivity, Specificity, positive predictive value and negative predictive value during exacerbation and remission*

A. During exacerbation				B. During remission			
Pathergy test	Cases	Control	Total	Pathergy test	Cases	Control	Total
+ve	48.1	0.1	48.2	+ve	27.1	0.1	27.2
-ve	22.1	70.1	92.2	-ve	43.1	70.1	113.2
Total	70.2	70.2		Total	70.2	70.2	
Sensitivity 68.5%, Specificity 99.9%, positive predictive value 99.8%, negative predictive value 76%.				Sensitivity 38.6%, Specificity 99.9 positive predictive value 99.6%, negative predictive value 61.9%.			
For purpose of avoiding cells with zero frequencies, 0.1 was added to all cells.				For purpose of avoiding cells with zero frequencies, 0.1 was added to all cells.			

DISCUSSION

From the list of manifestations it can be seen that patients may be referred from primary care, or may present, to about a dozen different medical or surgical specialties, so that not only is this a multi-system condition, but it also requires multi-disciplinary co-operation.

Nevertheless, the most common feature is recurrent oral ulceration. Therefore, although oral aphthous ulceration has been shown to occur in up to 20 % of the normal Western population, its presence may be considered to be an essential enquiry in history intake.^{9,20} But the unique feature of Behçet's disease is the pathergy reaction which is listed among the major manifestations of Behçet's disease and according to the International Study Group is among the

major criteria required for the diagnosis of the disease. However, different positive pathergy reaction rates and intensity in Behçet's disease have been reported worldwide.²¹ And North of Iraq is among the countries of high expected prevalence and high expected rate of positive pathergy reaction recording as it is among the countries along the silk route and without much informations about the disease and pathergy reaction. So we conducted this study to evaluate the prevalence of pathergy reaction among patients of Behçet's disease in Dohuk province and its relation to the flare and remission of the disease. Although, pathergy test has often proved to be a problem in terms of the way in which it is performed, its specificity and its geographical variability, it is now recommended internationally that the test should be performed by insertion of a 20

gauge needle through the skin under sterile conditions, without injection of saline. The high rate of positive test is reported in countries along the silk route and this rate becomes low outside this geographic basin. During distribution of positive pathergy rates in both phases of the disease according to the sex, age and duration, we were unable to find such conducted studies for comparing with this study for the differences or similarity between them.

According to gender distribution, the percentage and the rate of positive test of each gender were affected similarly by the drop during remission or there was no difference in the drop rate between male and female during the phases of disease apart from a higher rate of a positive test among male than female and in both phases of disease but not to a significant difference. In one study conducted by Yazici et al concluded that the male patients have a stronger pathergy reaction than matched age and duration of disease female patients and to a significant difference²² but not comments on the rate of positive test in either gender.

In regard to the relation of a positive test in both phases of disease to the age of patients, the study revealed that all age groups are affected by drop in positive test during remission and to different rates among age groups. Although the high rate of positive reaction and in both exacerbation and remission were observed among the age groups between 20-29 years and those between age of 30-39 years, this might reflect that the bulk of the sample were those age groups. But the most age groups affected by the drop rate of positive test when disease remits were in age extremities. The explanation of this drop in test in early age onset of disease is that the patients may have a more severe disease in early age onset than adult patients.²² But this not explained in adult who have more stable course of disease.

Patients with history of disease duration less than 10 years have higher rate of positive reaction during phases of

disease and most period of disease affected by drop in the rate of positive reaction during remission, which might be due to that the disease is more severe in the first 5-10 years and the disease tend to improve or become more stable over time.⁴

Pathergy phenomenon is an important feature of Behçet's disease that occur in about one half of patients with Behçet's disease and it is recommended to be performed in every patients with Behçet's disease and especially those with incomplete manifestations for diagnosis as it is one of criteria required diagnostic set. The sensitivity of the test is decreased when the disease remits and it is important to be performed and repeated for every patient with Behçet's disease during flare of disease as many patients become positive for reaction during this period and especially in extreme ages and those of less than 10 years duration. Further extended studies required for more assessment and evaluation of other aspects of the disease and its management as we are in a locality with a high prevalence for Behçet's disease.

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پوخته

ههلسانگاندا تاقیکرنا بشارجی لسره نه خوشییین به هجته

پیشهکی و نارمانج: نه خوشیا به هجته ئیک ژ نه ساخییین دومدریژه و کاتیکرنی ل هه موو کوئه ندامین له شی دکهت. ئه فه نه خوشیه کا بهر به لافه ل وان دهوله تین کو دکه فنه لسره ریکا هریری کو نه خوشییین ژ جورئ دژوارتر په پیدا دهن-جوندین سالوخهت دهینه بکارئینان. تاقیکرنا بشارجی ئیک ژ ریکین گرنکه ژ بو دهستنیشانکرنا نه خوشیا به هجته. نارمانج ژ فی فه کولینی ههلسانگاندا کارلیکرنا بشارجی ل نه خوشیین کو تووشی نه خوشیا به هجته بووین.

ریکین فه کولینی: ئه فه کولینه هاته کرن ل پاریزگه ها دهوکی ژ کانینا دووی 2005 تا کانینا دووی 2007. د فی ماوهی دا ههفتی نه خوشیین کو تووشی نه خوشیا به هجته بووین هاتنه وهرگرتن. هه رورسا ههفتی که سین کو تووشی نه خوشیا به هجته نه بووین کو سهردانا سهنته ری فه ژاندا ههستیکا ل دهوکی کرین هاتنه وهرگرتن.

ئه نجام: د فه کولینی دا دیاربوو کو ریژا رهگه زی نیر به رامبه ر می 1.12:1 بوو. پرانیا نه خوشا د ژیی 40 سالیدا بوون. کولک ل ده فی 84.3% ژ نه خوشا هه بوون ل دهستیپیکا نه خوشیی. ههروه سا دیاربوو کو کارلیکرنا بشارجی یا بوزه تیف بوول ژ نه خوشا د ده می فه گه ریا نا نه خوشیی و ل ده می نه مانا نه خوشیی. ژیی نه خوشی و ماوی نه خوشیی کیتمتر ژ 10 سالان رول هه بوو د کیتمکرنا ریژا بوزه تیف یا کارلیکرنا بشارجی به لی رهگه ز هبج رول نه بوو.

دهرئه نجام: کارلیکرنا بشارجی یا گرنکه د دهستنیشانکرنا نه خوشیا به هجته و لده فه نیفه ک ژ نه خوشا په پیدا دبیت. و ئه م پشنیاردکه یین کو بهیته کرن لسره هه می نه خوشا تایبته ئه گهر هه می سالوخه تین نه خوشیی په پیدا نه بن.

الخلاصة

تقييم اختبار بئارجي للمرضى المصابين بمرض بهجت

خلفية واهداف البحث: مرض بهجت من الأمراض المزمنة ذات انتكاسات على أعضاء الجسم المتعددة. و يكثر انتشارها في المناطق التي تقع على الطريق الحريري القديم. من السمات الفريدة للمرض هو ظهور بثور جلدي أو قيجي أو احمرار جلدي في موقع الحقن و تدعى تفاعل بئارجي. الهدف من الدراسة هو تقييم ايجابية اختبار بئارجي لدى المرضى المصابين بمرض بهجت.

طرق البحث: أجريت الدراسة في محافظة دهوك خلال فترة زمنية امتدت من كانون الثاني 2005 و الى كانون الثاني 2007. حيث تم جمع 70 حالة من المصابين بمرض بهجت و 70 من المتطوعين الذين ليس لديهم مرض بهجت. وتم اجراء اختبار بئارجي عليهم.

النتائج: تبين من الدراسة أن نسبة الذكور الى الاناث هي 1:1.12. معظم المرضى كانوا في العقد الرابع. كانت لدى 84.3% من المرضى تقرحات فموية و شفوية منذ بداية المرض. كما أظهرت الدراسة سلبية اختبار بئارجي لدى جميع المتطوعين. كان هناك اختلاف في نسبة ايجابية بئارجي خلال فترة الانتكاس و الركود. الجنس لم يكن له دور في تقليل نسبة الايجابية لاختبار بئارجي اثناء فترة الركود. من جانب آخر، كانت لطرفي العمر وفترة مراضة أقل من 10 سنوات دور في تقليل نسبة الايجابية أثناء فترة الركود.

الاستنتاج: اختبار بئارجي مهم في تشخيص مرض بهجت حيث تظهر في حوالي نصف المرضى. لذا نقترح اجراء اختبار بئارجي لكافة المرضى الذين لديهم مرض بهجت و خاصة المرضى الذين تكون أعراضهم غير كافية للتشخيص.