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Skin prick test with self saliva as a diagnostic test for Behçet's disease

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ABSTRACT

Aim of the work: To determine the reliability of skin prick test using self-saliva, which mostly contains streptococci, for in vivo diagnosis of Behçet's disease (BD) in comparison to the usual pathergy test.
Patients and methods: Thirty patients diagnosed with BD of matched age and sex to 30 with undiagnosed recurrent aphthous stomatitis (RAS) and 30 healthy controls were enrolled into this study. Skin pathergy test and skin test with self saliva before and after being filtered with a micro filter paper was performed on forearm of all subjects participated in this study. The skin reaction was observed at 48 h after pricking.
Results: The mean age of the BD patients was 30.1 ± 7.1 years and were 22 males and 8 females (M:F 2.75:1). The mean disease duration of the BD patients was 10.13 ± 7.47 months. In BD patients, mucocutaneous and ocular manifestations were significantly increased. Positive tests were more frequent in BD patients. SPT-NSS showed a significantly higher accuracy more than pathergy and SPT-FSS in discriminating BD from non BD and from RAS. Diagnostic accuracy of skin prick test with neat self saliva (SPT–NSS) in discriminating BD from non BD was significant with sensitivity 80%, specificity 100% while the ability of the test to discriminate between BD and RAS was 83% sensitivity and 63% Specificity more than pathergy test and skin prick test with filtered saliva respectively.
Conclusion: Skin prick test with neat self-saliva could be considered as a simple, cost accessible and accurate diagnostic test for BD.

1. Introduction

Behçet's disease (BD) is a multisystem vasculitic disorder characterized by recurrent oral ulcers, genital ulcers and ocular affection [1]. It spreads geographically along the silk road countries [2], with male predominance as presented in a recent nationwide survey in Egypt (males: females was 2.6:1) [3]. Clinical presentation of BD involve recurrent aphthous stomatitis starting at childhood or early adolescence, genital ulcers affecting >50% of the patients [4], ocular affection especially the retina and uvea, with high morbidity despite the aggressive corticosteroids treatment [5]. Neuro Behçet affects 5–10% of patients with involvement of central nervous system more than the peripheral [6]. Different sizes blood vessels are affected in BD especially veins, starting from superior and inferior vena cava to the smallest venules causing deep venous thrombosis and superficial thrombophlebitis in 30–40% of patients [7]. The exact etiology of BD is still not fully understood but genetic and epigenetic factors may be key triggers of its development [8], through the induction of T Helper 1 (Th1) response with secretion of cytokines causing systemic inflammation. Histopathology shows non-specific vasculitis with neutrophils, lymphocytes and plasma cells infiltration [9]. A link between the development of BD and human leukocyte antigen (HLA)-B51, HLA-B 27, may lead to spontaneous or induced Th1 immune response [10].

Infections including viruses and bacteria are also thought to trigger BD [11] possibly through the production of heat shock proteins (HSP). HSP are unique proteins that are produced via cells in response to stressful events and are able to induce Th1 and B cell responses. One of these HSP is 60-kD HSP (HSP60) which can be recognized by toll like receptors (TLR) with induction of Th1 response leading to systemic inflammation [12]. Streptococcus sanguinis (S. Sanguinis), normally found as commensals in the oral cavity [13], were the most common isolated type of bacterial flora from the oral cavity of BD patients [14]. HSP65 produced in response. S. sanguinis has a similar structure as human HSP60 with emerging cross reactivity reaction [15]. After recognition of HSP65

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by the TLR, secretion of pro inflammatory cytokines such as IL-6, IL-12, IL-15 and tumor necrosis factor-alpha (TNF-α) results in formation of auto reactive T-cell clones specific to human HSP60 [16,17].

The relation assumed between S. sanguinis and BD developments was proved and a high positivity of pathergy test was found when done using the killed bacteria or the streptococcal antigens than the usual technique. Moreover S. sanguinis DNA was expressed in the cytoplasm of inflammatory cells from BD mucocutaneous biopsies [18]. Diagnosis of BD depends mainly on the clinical presentation plus a positive pathergy test [19].

The aim of the present work was to introduce a new diagnostic test for BD using skin prick test with self saliva, as a source of S. sanguinis antigen and to determine its reliability in comparison to the usual pathergy test.

2. Patients and methods

Thirty adult BD patients with a confirmed diagnosis according to the international Study Group for BD criteria updated in 2013 [20,21], who attended the immunology clinic at Ain Shams University, BD patients had controlled disease (inactive BD) and were not receiving steroids or immune suppressive drugs that might interfere with tests results [22] two weeks prior to the study were enrolled in this work. 30 patients with undiagnosed recurrent aphthous stomatitis (RAS) and another 30 healthy controls of matched age and sex were also included. The current study excluded patients with other rheumatic diseases, inflammatory bowel disease or malignancy, patients with active BD were also excluded, BD activity was assessed according to the presence of any clinically active symptoms including; oral and genital ulcers (recurrence/year, being painful or painless), skin, ocular, vascular, rheumatological, gastrointestinal or neurological involvement [23], exclusion of disease activity was done for the capability of stopping immunosuppressive drugs, moreover the presence of active mucocutaneous lesions at the time of study might induce ulceration by the prick [4]. Written consent was taken from all the participants; Ethical approval was taken from the Human Research Ethics Committee of Ain Shams University Hospitals.

A detailed medical history was taken; complete physical examination was performed including oral and genital ulcers as regard edge and floor. Laboratory investigations were assessed including complete blood count (CBC), erythrocyte sedimentation rate (ESR) and antinuclear antibodies (ANA) done with immunofloresecence technique.

2.1. Pathergy test

Needle was inserted into skin intradermally at forearm before and after sterilization of the forearm with alcohol. The area where the needle was inserted was circled. Area of the skin was then inspected after 24 and 48 h following the test. The results are interpreted as follows: 0 = needle mark or simple erythema; 1 = papule; 2 = pustule [24].

2.2. Skin prick test with self saliva

A clinical immunologist performed the test three times for each subject using neat self-saliva, filtered self-saliva and saline as control, a sample of freshly obtained saliva was diluted with 2 cm of sterilized water, and then mixing was done. Filter paper of 0.2 μm pores and 47 mm diameter was used to have a sterilized self-saliva. The forearm skin of the subjects was pricked using a Prick Lancetter. The skin prick test with neat self-saliva was repeated after sterilization of the forearm with alcohol. Popular and erythematous skin reactions were measured in diameter (mm) after 48 h. The test was considered positive if erythema develops >10 mm in BD patients or >5 mm in those with RAS or the control and if pustules develop >2 mm after 24 h in BD patients [25].

2.3. Statistical methods:

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY) and JMP® Version 13.2.1 (SAS© Institute Inc., Cary, NC). Continuous numerical variables were presented as mean and standard deviation and compared using the *t*-test. Skewed numerical data were presented as median and interquartile range and 2 groups were compared using the Mann-Whitney *U* test. Categorical data were presented as number and percentage and compared using Fisher's exact test. Receiver-operating characteristic (ROC) curve examined the diagnostic value of the tests. $p < 0.05$ were considered significant.

3. Results

The mean age of the BD patients was 30.1 ± 7.1 years and were 22 males and 8 females (M:F 2.75:1). The group with RAS mean age was 28.3 ± 6.8 years and M:F was 0.57:1 while the control age was 31.17 ± 5.62 years and M:F was 0.87: 1 and were of matching age and sex to the BD patients ($p = 0.284$, $p = 1.473$). The mean disease duration of the BD patients was 10.13 ± 7.47 months. Clinical features and laboratory characteristics of the BD and RAS patients are presented in Table 1. Mucocutaneous manifestations including genital ulcers, erythema nodosum, pustules in the scalp and folliculitis as well as ocular were significantly more frequent in the BD patients. The total leucocytic count (TLC) and ESR were also significantly increased in the BD cases.

Diagnostic accuracy of skin prick test with self saliva vs pathergy test for discrimination between BD and non BD subjects are presented in Table 2. SPT NSS was repeated after sterilization of the skin of the hand with alcohol and the number of positive reacting patients decreased to 21/30 (70%). Positive tests were more frequent in BD patients. SPT-NSS showed a significantly higher accuracy more than pathergy and SPT-FSS in discriminating BD from non BD (Table 3, Fig. 1) and in discriminating BD from RAS (Table 4). Comparing the ROC curves between the 3 groups for discrimination between the patients with BD and RAS there was a significant difference in the area under the curve (AUC) between SPT-NSS with pathergy test ($p = 0.019$) and with SPT-FSS ($p < 0.0001$). The diagnostic accuracy of SPT-NSS to discriminate between BD and RAS showed a sensitivity of 83%, specificity 63%, positive predictive value (PPV) 69% and negative predictive value (NPV) 79%.

Table 1
Clinical features and laboratory characteristics of the Behcets' disease (BD) and recurrent aphthous stomatitis (RAS) patients.

Parameter	BD (n = 30)	RAS (n = 30)	p
Arthritis	5 (16.7)	4 (13.3)	1
Vasculitis	8 (26.7)	4 (13.3)	0.33
Mucocutaneous	29 (96.7)	4 (13.3)	**<0.001**
Neurological	7 (23.3)	1 (3.3)	0.052
Ocular	14 (46.7)	0 (0)	**–**
TLC ($x10^3/mm^3$)	8.4 ± 2.4	6.3 ± 2	**0.001**
Hb (g/dl)	13.0 ± 1.6	12.5 ± 2.1	0.25
Pl ($x10^3/mm^3$)	255.6 ± 58.6	282.3 ± 65.1	0.1
ESR (mm/h)	32 (12–40)	15 (5–25)	**0.02**

BD: Behçet's disease, RAS: recurrent aphthous stomatitis, TLC: total leucocytic count; Hb: haemoglobin, Pl: platelets, ESR: erythrocyte sedimentation rate, ANA: antinuclear antibody. Values are presented as mean ± SD, median (range) or n(%). Bold values are significant at $p < 0.05$

Table 2
Comparison between pathergy test and skin prick test with self saliva for discrimination of Behcets' disease (BD) from recurrent aphthous stomatitis (RAS) and control.

Test n (%)		BD (n = 30)		RAS (n = 30)		Controls (n = 30)		p
Pathergy	–	15	(50)	27	(90)	28	(93.3)	**<0.001**
	+	15	(50)	3	(10)	2	(6.7)	
NSS SPT	–	5	(16.7)	19	(63.3)	28	(93.3)	**<0.001**
	+	25	(83.3)	11	(36.7)	2	(6.7)	
FSS SPT	–	19	(63.3)	27	(90)	30	(100)	**<0.001**
	+	11	(36.7)	3	(10)	0	(0)	

BD: Behçet's disease, RAS: recurrent aphthous stomatitis, NSSSPT: skin prick test with neat self saliva; FSSSPT: skin prick test with filtered self saliva. Bold values are significant at p < 0.05.

Table 3
Receiver-operating characteristic (ROC) curve discrimination between subjects with and without Behcets' disease (BD) using quantitative pathergy test and skin prick test with neat and filtered self saliva.

ROC metric	Pathergy	SPT NSS	SPT FSS
AUC	0.71	0.91	0.65
95% CI	0.6–0.8	0.83–0.96	0.55–0.75
p	**<0.0001**	**<0.0001**	**0.001**
Cut off	>0 mm	>2 mm	>0.5 mm
Sensitivity	50%	80%	36.7%
Specificity	91.7%	100%	95%

ROC: Receiver-operating characteristic; AUC: area under the curve; CI: confidence interval; SPT NSS: skin prick test with neat self saliva; SPT FSS: skin prick test with filtered self saliva. Bold values are significant at p < 0.05.

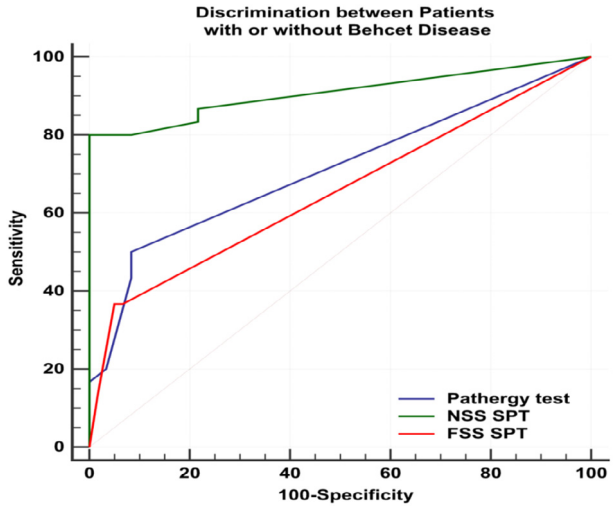

Fig. 1. Receiver-operating characteristic (ROC) curves for discrimination between subjects with and without Behcets' disease (BD) using quantitative pathergy test, skin prick test (SPT) with neat (NSS) and filtered (FSS) self saliva.

Table 4
Receiver-operating characteristic (ROC) curve discrimination between patients with Behcets' disease (BD) and recurrent aphthous stomatitis (RAS) using quantitative pathergy test and skin prick test with neat and filtered self saliva.

ROC metric	Pathergy	SPT NSS	SPT FSS
AUC	0.71	0.89	0.62
95% CI	0.58–0.82	0.78–0.96	0.49–0.75
p	**0.0001**	**<0.0001**	**0.025**
Cut off	>0 mm	>2 mm	>0.5 mm
Sensitivity	50%	80%	36.7%
Specificity	90%	100%	90%

ROC: Receiver-operating characteristic; AUC: area under the curve; CI: confidence interval; SPT NSS: skin prick test with neat self saliva; SPT FSS: skin prick test with filtered self saliva. Bold values are significant at p < 0.05.

4. Discussion

Behçet's disease is a chronic inflammatory disease of immunological based etiology thought to be induced through microbial agents in genetically susceptible patients [26]. BD patients have a high frequency of oral unhygienic conditions mostly due to streptococcal infections, especially S. sanguinis, suggesting a relation between the disease etiology and infections [13].

The current study showed that the number of patients with positive SPT NSS were 25/30 (83.3%), which decreased to only 11 patients after filtration of saliva, suggesting that the positive reaction might be a cutaneous response to some bacteria in the oral cavity which was eliminated by the filtration. In parallel the SPTNSS was repeated after sterilization of the skin of the hand with alcohol and we observed that the number of positive reacting patients decreased to be 70% which also suggest that the positive reaction might be a cutaneous response to some bacteria living on the surface of the skin of BD patients.

As regard diagnostic accuracy of SPT NSS to discriminate between BD and non BD, an excellent accuracy was present more than the pathergy and SPT FSS tests. The current findings were in agreement with *Togashi et al,* who tested ten BD patients and 9 of them demonstrated positive skin prick specific for their own oral microorganism (s), while 3/5 patients with recurrent oral ulcers had a week positive tests and negative results in healthy controls [27]. Furthermore, *Kaneko et al*, revealed that >90% of BD patients had a positive reaction to salivary prick test [25]. While comparing the test sensitivity and specificity with previous studies and our study it is appropriate to mention that after taking a new cut off 2 mm depending on the size of popular reaction not the erthyma, the sensitivity of the test slightly declined but the test specificity was 100%.

Antibodies against the HSP peptides obtained from bacteria including S. sanguinis are found in aphthous ulceration and serum of BD patients [28], yet HSP specific antibodies and T cells are thought to exert a complex role in the pathogenesis of human autoimmune diseases [29]. It is speculated that HSPs trigger both innate and adaptive immune mechanisms in BD.

In the current study, the ability of SPT NSS to discriminate between patients with BD and patient with undiagnosed RAS, there was a significant difference as regards the AUC. The sensitivity of SPT NSS was 80%, specificity 100%, positive (PPV) 69% and negative (NPV) predicted value 79% higher than pathergy test and SPT FSS. Pathergy test is considered the only test used for diagnosis of BD [27] however the current study revealed that SPT NSS was superior to pathergy in BD diagnosis. To the best of our knowledge, this is the first research to compare the diagnostic accuracy of SPT with self-saliva to pathergy in BD patients.

A positive pathergy test in 50% of BD patients was able to discriminate between BD and non-Behçet's patients at a sensitivity of 50%, specificity of 92%, PPV of 75% and NPV of 79%. These results were similar to the study of *Davatchi et al,* comparing the results of pathergy test recently and 35 years ago and showed that the sensitivity of pathergy test decreased from 64.2% to 35.8%; specificity improved from 86.6% to 98.4%; PPV improved from 82.7% to 95.7%

and NPV decreased from 82.7% to 60.5% [30]. Close to the current results, *Chang and Cheon* observed positive pathergy reactions in 23/64 BD patients with 35.9% positivity rate and specificity of 98.9% among Korean BD patients [31]. *Sequeira and Daryani* assessed the positivity of pathergy test in different countries, according to the area involved especially around ancient the silk route. The study showed that the sensitivity of pathergy test was 61.5% in Egypt, 83% in Russia, 77% in Morocco, 71% in Iraq, 62% in China and, in Iran, 55% in Germany, 44% in Japan and 18% in Saudi Arabia [32]. *Srisuttiyakorn and Aunhachoke* held a study to access the sensitivity and specificity of pathergy test with correlation between clinical criteria and histopathological findings, the study showed that the sensitivity, specificity and accuracy of the test were 30.3%, 64%, and 44.8% respectively and increased to 100%, 16%, and 63.8%, respectively after histopathological assessment was added [33].

It is of interest that the surgical cleaning of the forearm before needle prick reduced the prevalence of the pathergy reaction, assuming that the positive pathergy test was due to a cutaneous response to normal flora living on the skin surface [4]. In corresponding to the previous theory the current study noticed that 15/30 patients with BD had positive pathergy test and after sterilization of the skin of the forearm with alcohol, the number of the positive patients decreased to be only 10.

Because of the relatively small sample size, these results require to be confirmed by further studies with larger number of cases, also on patients with other autoimmune diseases. Moreover, we did not correlate the test results with the diseases activity nor HLA B51 typing, so we recommend further studies are needed to correlation the obtained results with disease activity. Also to further highlight our results, histopathology examination of skin biopsy could be obtained and examined.

In conclusion, skin prick test with neat self-saliva was superior to pathergy test and skin prick test with filtered saliva in diagnosis of BD. Skin prick test with neat self-saliva can be considered as a diagnostic test for BD, which is accurate and cheap; moreover it is considered a valuable test for differentiating BD from other mimicking mucocutaneous diseases.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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