



Difference between Behcet's Disease Oral Aphthosis and Idiopathic Recurrent Aphthous Stomatitis

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Abstract

Introduction: The aim of this study was to look if any clinical characteristics of oral aphthosis (OA) could discriminate Behcet's Disease (BD) from Recurrent Aphthous Stomatitis (RAS), at the patient's first visit.

Materials and Methods: In a prospective study, patients were enrolled in a case-control study as consecutive patients. BD was diagnosed by the International Criteria for Behcet's Disease (ICBD). RAS were people who had recurrent OA for four years or more, but not any other manifestations of BD. The following parameters were checked: age, age of onset, number of attacks, number of aphthosis per attack, healing time, and diameter of aphthosis, the most common sites and pain on a Likert scale, Pathergy test, and HLA-B51. Comparisons were made by Mann-Whitney U test (Z) and Pearson's chi square test (Chi2).

Results: Selected patients for the study were 200 BD and 194 RAS patients. The starting mean age, BD versus RAS was (23.0 vs. 21.9, $p=0.32$), First visit mean age (31.4 vs. 33.2, $p=0.08$). Males were (60% vs. 48%, $p=0.02$). Pathergy test was (33% vs. 7%, $p<0.0001$). There was no significant difference in the number of attacks, mean number of aphthosis per attack, and aphthosis diameters between the two groups by Mann-Whitney test. The healing time was longer in controls than in BD ($Z=-3.129$, $p=0.002$). For HLA-B51 it was 36.8% vs. 21.7%, $p=0.001$.

Conclusion: Not enough differences were found in clinical findings to differentiate BD-OA from RAS-OA. The main differences were gender, positive Pathergy, and HLA-B51.

Keywords: Behcet's disease; Oral aphthosis; Aphthous stomatitis

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Received Date: 11 Sep 2016

Accepted Date: 20 Oct 2016

Published Date: 03 Nov 2016

Citation:

Abdollahi BS, Davatchi F, Chams-Davatchi C, Ghodsi Z, Shahram F, Nadji A, et al. Difference between Behcet's Disease Oral Aphthosis and Idiopathic Recurrent Aphthous Stomatitis. *J Dent Oral Biol.* 2016; 1(2): 1007.

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Introduction

Oral aphthosis of Behcet's Disease (BD) is characterized by a round to oval ulceration, with a white yellowish necrotic base, surrounded by a local inflammatory reaction, like a red areola [1]. OA is painful, but will heal spontaneously in 1 to 2 weeks, most usually without sequela. In each attack there will be from one to several aphthous lesions. The diameter will vary from 1 to 20 millimeters. Although the lesions heal spontaneously, they recur frequently, but the rate differs from one patient to another, or in the same patient, and goes from a few days to few weeks, months, or even longer [2]. They may be seen on every part of the oral mucosa. The most frequent is on lips, then on cheeks, tongue, gingiva, palate, and tonsils. The least frequent location is the pharynx [2].

Recurrent Aphthous Stomatitis (RAS) is characterized by recurring oral aphthous. The etiology of RAS is not clear. Much research has been done to elucidate the causes of RAS. Recent works on RAS shows that many factors may play a role in its advent. Hematological Factors, especially deficiency of hemoglobin, iron, vitamin B12, and folic acid from one part, and elevation of homocysteine levels have significant association with RAS [3,4]. Zinc deficiency has also been implicated [5]. Oxidative stress was also found to favors the attack of RAS [6]. Recently it has been shown that higher levels of Serum interleukin-1, interleukin-13, interleukin-17, interleukin-18, interferon gamma were found in RAS compared to normal controls [7]. Recently, it was shown that IL10 GA genotype at position -1082 ($p=0.007$), CA genotype at position -592 ($p=0.001$), and CT genotype at position -819 ($p=0.001$) were significantly higher in the RAS patients than in controls [8]. A meta-analysis showed that infection with *Helicobacter Pylori* increased the risk of RAS and its eradication may relief the symptoms and help the healing of oral aphthous [9]. A higher correlation between anxiety, depression, and psychological stress with symptoms of RAS has been observed [10]. Other factors like trauma, certain foods hypersensitivity, and infectious agents are some of the other causes [11].

Table 1: Age Distribution (Mean).

	Beginning Age		First Visit Age		Age at Diagnosis
	BD	RAS	BD	RAS	BD
Diagnosis					
Number	200	194	199	194	197
Mean	23.0	21.9	31.4	33.2	31.4
Standard Deviation	9.5	11.1	8.1	11.4	8.3
Standard Error of Mean	0.67	0.80	0.57	0.82	0.59
Leven's test (F)	4.287		17.758		-
Comparison (p Value)	0.32		0.08		-

BD: Behcet's Disease; RAS: Recurrent Aphthous Stomatitis

Table 2: Gender.

	Total No.	Male			Female		
		No.	%	95%CI	No.	%	95%CI
Behcet's Disease	199	119	59.8	52.9 - 66.4	80	40.2	33.6 - 47.1
Recurrent Aphthous Stomatitis	194	93	47.9	41.0 - 54.9	101	52.1	45.1 - 59.0
Pearson's Chi Square Test χ^2	-	5.562					
Comparison (p value)	-	0.018					

95%CI: 95% Confidence Interval

Table 3: Characteristics of the Aphthous Ulcer at the first visit and the last visit.

	Number of Attacks Mean Per Month		Number of Aphthae Mean Per Attack		Diameter of Aphthae Mean (millimeter)		Duration of Aphthae Mean (days)	
	Onset of Disease	First Seen	Onset of Disease	First Seen	Onset of Disease	First Seen	Onset of Disease	First Seen
BD	1.3	1.9	2.1	2.9	3.3	4.2	7.6	8.6
*SD	1.5	2.0	1.5	3.1	1.7	2.7	4.3	5.2
RAS	1.1	1.9	2.1	3.0	3.5	4.7	8.1	10.9
*SD	1.4	1.6	1.7	2.1	2.2	3.3	4.3	7.6
Z	-1.742	-1.380	-0.885	-1.	-0.401	-1.684	-0.828	-3.465
P value	0.08	0.17	0.38	0.08	0.69	0.09	0.41	0.001

BD: Behcet's Disease; RAS: Recurrent Aphthous Stomatitis; Z: Mann-Whitney U test

In a previous study in the year 2003 on Behcet's Disease (BD) and Recurrent Aphthous Stomatitis (RAS), we showed that there was no significant difference between BD and RAS except for positive Pathergy test, HLA-B5 and HLA B51 [12]. The aim of this study was to evaluate in a larger group of BD and RAS patients, selected consecutively, if any clinical characteristics of oral aphthous could differentiate the two and permit to suspect an aphthous of BD and follow them more closely.

Materials and Methods

In a prospective study, patients were enrolled in a case-control study. Cases were diagnosed when fulfilling the International Criteria for Behcet's Disease (ICBD) [13]. Controls were people who had recurrent OA for four years or more, but no other manifestations of BD. Both groups were selected as consecutive patients. The age at the time of inclusion in the study, age the onset of the symptoms, first visit mean age, average number of attacks per month, average number of aphthosis per attack, mean healing time, mean diameter of aphthosis, the most common sites, and the pain on a likert scale were checked for all subjects. To have an estimation of the diameter of the aphthous at the beginning of disease we showed four circles with different diameters (2.5 mm, 5 mm, 10 mm and 15 mm) to the patients and asked them to show the diameter of the aphthous at the beginning and at the present time. The Pathergy test was done by 3 needle pricks on the forearm, after disinfection of the skin with povidone-iodine. Needles were inserted in the skin as for doing an

intradermal injection. The first needle was a 21 gauge needle, just inserted under the skin and then withdrawn. The second needle was a 25 gauge needle, inserted under the skin and then withdrawn like the first needle. The third needle was a 25 gauge needle, inserted under the skin with injection of one drop of normal saline. HLA typing for B5, B51, and B27 was done for all patients and controls.

Statistical Calculations; for percentages, a 95% confidence interval (95% CI) was calculated. For continuous variables, a mean and standard deviation were calculated. Comparisons were done by Mann-Whitney U test (Z) and Pearson's chi square test (Chi2). As a secondary aim a Pearson correlation coefficient was computed to assess the relationship between the age of onset of the OA with the age at the diagnosis of BD and the age at the first visit of BD patients respectively.

Results

We enrolled 200 BD patients and 194 RAS consecutive patients. One BD patient did not give complete information and was discarded from the cohort of BD patients.

In the BD group, the mean age at the beginning of the OA (the first attack) was 23.0 years with a standard deviation (SD) of 9.5 years. In the RAS group, it was 21.9 years and an SD of 11.1 years. The difference was not statistically significant (p=0.32). At the first visit (inclusion in the study), in the BD group, the mean age was 31.4 years (SD: 8.1), while in the RAS group it was 33.2 years (SD: 11.4). The

Table 4: Pathergy test and HLA typing.

		Total Test	Positive			Pearson's Chi2	P value
			No.	%	95%CI		
Pathergy Test	BD	178	60	33.7	27.2 – 41.0	40.197	<0.0001
	RAS	183	13	7.1	4.1 – 11.9		
HLA-B5	BD	191	88	46.1	39.2 - 53.2	14.613	<0.0001
	RAS	191	52	27.2	21.4 – 34.0		
HLA-B51	BD	190	70	36.8	30.3 – 43.9	10.499	0.001
	RAS	189	41	21.7	16.4 – 28.2		
HLA-B27	BD	193	11	5.7	3.1 – 10.1	4.337	0.04
	RAS	188	22	11.7	7.8 – 17.2		

BD: Behcet's Disease; RAS: Recurrent Aphthous Stomatitis

Table 5: The effect of disease duration as a risk factor for RAS.

Disease Duration (year)	BD			Control		
	Number	%	Cumulative %	Number	%	Cumulative %
0-10	142	71.7	71.7	109	56.2	56.2
20-Nov	43	21.7	93.4	62	32	88.1
21-30	9	4.5	98	18	9.3	97.4
31-40	4	2	100	3	1.5	99
41-50	0	0	100	2	1	100

OR (Control/BD): 1.524 (1.148-2.024) p = 0.004

difference was not statistically significant (p=0.82). In the BD group, the mean age at the diagnosis of BD 31.4 years (SD: 8.3), which for the majority of the patients at the time of their inclusion in the study. The details of the age distribution are given in Table 1.

The gender distribution was males 59.8% in the BD group with a 95% confidence interval (95% CI) of 52.9% to 66.4%. It was 47.9% in the RAS group (95% CI: 41.0% - 54.9%). The difference was statistically significant with p=0.018 (Table 2).

We calculated the clinical characteristics of the aphthous as follow: the number of attacks as their mean per month at their first visit and then at their last visit. For BD, at their first visit, the mean number of attack per month was 1.3 (SD: 1.5) and for RAS 1.1 (SD: 1.4). The difference was not statistically significant (p=0.08). The difference was also not statistically significant at the last visit (p=0.17). The mean number of aphthous per attack was 2.1 for BD at the first visit (SD: 1.5), and 2.1 for RAS (SD: 1.7) [14-18]. The difference was not statistically significant (p=.38), as at the last visit (p=0.08). The mean diameter of aphthous in millimeter (per attack) for BD at the first visit was 3.3 (SD: 1.7) and for RAS 3.5 (SD: 2.2). The difference was not statistically significant (p=0.69) as for the last visit (p=0.09). Finally, the mean duration of aphthous per attack, for BD, at the first visit was 7.6 days (SD: 4.3), while it was 8.1 days for RAS (SD: 4.3). Again, the difference was not statistically significant, while this time and for this item, the difference was statistically highly significant (p=0.001) at the last visit. All details are given in Table 3.

The Pathergy test was positive in 33.7% of BD patients (95% CI: 27.2% - 41.0%), while it was positive in only 7.1% of RAS patients. The difference was statistically significant with p< 0.0001. HLA-B5 was present in 46.1% of BD (95%CI: 39.2% - 53.2) while in RAS it was 27.2% (95%CI: 21.4% - 34.0%) with p< 0.0001. HLA-B51 was present in 36.8% of BD (95%CI: 30.3% - 43.9%) and in 21.7% of RAS (95%CI: 16.4% - 28.2%), and p=0.001. HLA-B27 was seen, on the contrary, more frequently in RAS (11.7%, 95%CI: 7.8% - 17.2%) than in BD

(5.7%, 95%CI: 3.1% - 10.1%) with a significant p value of 0.04. Details are given in Table 4.

We used binary logistic regression to eliminate the effect of those variables that can be thought of as confounders. The effect of male sex as a risk factor for BD and the protective effect of HLA B27 were omitted. Pathergy (OR: 3.84, p=0.000) and HLA B5 (OR: 2.33, p=0.001) remained the risk factors for BD. More pain (OR: 0.735, p=0.008, longer duration of spontaneous healing (OR: 0.94, p=0.027) and longer disease duration (OR: 0.94, p=0.001) were more in favor of RAS than BD. We calculated the effect of “decades of disease duration” on risk of BD. More decades of disease duration, less chance to have BD. The Odds Ratio (RAS/BD) was 1.52 and p value = 0.004 (Table 5).

Discussion

To summarize the results obtained in the new study, we didn't find any statistically significant difference between clinical characteristics of aphthous in BD and RAS patients, except for duration of aphthous in their last visit, and for lab tests (Pathergy test, HLA-B5, B51, and B27). However, regarding the mean duration of aphthous, they were 8.6 days for BD and 10.9 days for RAS. Looking at their confidence intervals, they were 5.2 days and 7.6 days. It is obvious that the majority of patients were in the same range of duration. Therefore, although statistically the difference was significant, clinically it is not easy to differentiate them, except for very extreme values, being larger than 2 standard deviations.

However, such values, theoretically, will be seen very rarely, and will give just some clues, not high evidences. Positive Pathergy test was seen in 33.7% of BD patients and 7.1% of RAS patients. The difference was highly significant; however, a positive Pathergy test will not refute the diagnosis of RAS, while a negative value will not refute the diagnosis of BD. The same is valid for HLA-B51. As for HLA-B27, the difference is too small and the above discussion more

relevant.

Comparisons of our new results with those obtained in 2003, although the patients were not the same, showed the same results, which were no difference was found between clinical characteristics of aphthous in BD and RAS [12].

Other studies have also announced a clinical resemblance between oral aphthous of BD and RAS, while declaring that other manifestations of Behcet's disease will help to differentiate the two entities 14-18. However, Gunduz in 2012 [19] showed that immunofluorescence of lesions may differentiate the two lesions; OA of BD from OA of RAS. In BD, the direct immunofluorescence of lesions will show deposition of IgM and C3 in perivascular region with or without granular deposit of C3 at the dermoepidermal junction in the perilesional skin of aphthous oral ulcer. The same deposit was not found in the lesions of RAS [20].

Conclusion

Clinical characteristics of aphthous, in both Behcet's disease and recurrent Aphthous Stomatitis, as defined by the mean age of patients, the mean number of attacks in months, the mean number of lesions in each attack, the diameter of lesions, and the duration of spontaneous healing were near the same. Only the existence of other manifestations of BD could differentiate it from RAS. However, it seems that direct immunofluorescence of lesions can be of help to differentiate the two.

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