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Research Article

Behcet's Disease: Change of Clinical Picture during the Time

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Abstract

Introduction: In a study presented 15 years ago, we showed that the clinical picture of the disease was changing toward milder forms. The aim of this study was to repeat the study in a larger group of 7140 patients.

Patients & Methods: patients were divided into four quartiles of 1785 each (Q1 to Q4), according to their first visit. Eighty symptoms/signs were compared by chi2 test and Odd Ratios (OR) in whole patients and in those having a disease duration of 6 to 20 years (893 in Q1 versus 1075 in Q4). Figures of OR≥2.5 or ≤0.4 were taken as differences clinically relevant.

Results: There was no clinically relevant difference in male/female ratio between Q1/Q4. Oral aphthosis was seen less frequently in selected patients in Q1 (OR=0.20), while the following were seen more frequently: pseudofolliculitis (OR=4.93), Gastrointestinal manifestations (OR=2.45), Gastroduodenitis (OR=5.39), peptic ulcer (OR=6.13), cardiac manifestations (OR=3.65) epididymitis (OR=3.93), overlap/association (autoimmune diseases, cancer, etc., OR=11.99), ESR>100 (R=2.30), Positive Pathergy test (OR=2.38), Proteinuria (OR=3.28), cast (OR=3.63), and positive VDRL/RPR (OR=14.18).

Conclusion: Oral aphthosis was seen less frequently in Q1, perhaps due to less sensitive criteria. While, several other manifestations were seen more frequently, a sign of more multisymptom disease in Q1.

Keywords: Behcet's Disease; Vasculitis; Change of clinical picture

Introduction

Behcet's Disease (BD) is classified among vasculitides, and is seen essentially in countries along the *Silk Road* [1]. The clinical picture is very distinctive from other vasculitides, making the differential diagnosis rather easy [2]. Iran has one of the highest prevalence of BD in the world [3-4]. In 2000, we found that BD was gradually changing its clinical picture, and the newer patients seemed to have milder forms of the disease [5]. In that study, we analyzed a cohort of 4130 patients, seen from 1975 till 2000. Patients seen from 1975 until March 1991 (1777 patients) were compared to those seen since March 1993 until December 1999 (1655 patients). A gap of two years was put between the two groups to enhance the difference. The male to female ratio and the mean age at the onset did not change. The male to the female ratio was 1.25 to 1 in the older group versus 1.15 to 1 in the new group. The mean age at the onset was 25.9 ± 9.7 years in the older group versus 25.9 ± 9.2 years in the new group. The mean disease duration (DD) was 4.2 ± 4.4 years in the old group versus 1.2 ± 1.4 years in the new group. The mean follow-up was 10.3 ± 7.4 years in the old group and 7.5 ± 5.8 years in the new group. Oral aphthosis, as presenting manifestation (first symptom), was seen less frequently in the older group; 71.4% with 95% confidence interval (95%CI) of 69.3% to 73.5%. In the newer group, it was seen more frequently with 86.5% (95%CI: 84.9% to 88.1%). The difference was statistically significant (p<0.0001). The incidence of oral aphthosis increased gradually during the follow-up, but it remained less frequently in the old group when compared to the new group. The incidence of oral aphthosis reached 95.1% (95%CI: 94.1% to 96.1%) in the older group versus 97.9% (95%CI: 97.2% to 98.6%) in the new group. The difference between the two groups remained statistically significant (p<0.0001). However, for the majority of other manifestations, they were seen more frequently in the older group when compared to the newer group. They were uveitis and joint manifestations as presenting symptoms. During the follow-up time, skin lesions, especially pseudo-folliculitis, ocular lesions (anterior and posterior uveitis, retinal vasculitis), Joint manifestations, gastrointestinal manifestations, vascular lesions, neurologic involvement, pulmonary and cardiac manifestations, were seen less frequently in the new group. It was concluded that BD was progressing toward milder forms of the disease as the years passed. The progression toward milder forms was explained as 1- A real change in the form of the disease. The pathergy phenomenon is seen less frequently compared to older times [6-9]. 2- Better recognition of milder forms of the disease. 3- Late involvement of major organs, appearing later in the course of the disease [10-11]. 4- The impact of the treatment on the course of the disease may give milder progression of the disease, while inhibiting the onset of some late major organ symptoms [12-13].

The aim of this study was to repeat the same analysis to see if the same results of 2005 will be found, but this time in a cohort of 7140 patients, and several years later. To check the supposition 3 and 4 of the preceding paragraph, patients with a minimum of 6 years DD and not more than 20 years, were also analyzed.

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Table 1: Gender and first manifestations of the disease: All versus selected patients (Disease Duration 6-20 years).

All Patients	First Quartile (1785 patients)		Forth Quartile (1785 patients)		Difference		Odds Ratio	
Item	%	95%CI	%	95%CI	χ^2	p	OR	CI
Male	55.2	52.9-57.5	57.9	55.6-60.2	3.418	0.06	0.90	0.79-1.03
Female	44.8	42.5-47.1	42.1	39.8-44.4	2.58	0.11	1.12	0.98-1.27
Oral Aphthosis	71.5	69.4-73.6	87.6	86.1-89.1	140	0.000	0.4	0.30-0.42
Genital Aphthosis	10.2	8.8-11.6	8.5	7.2-9.8	2.973	0.08	1.2	0.97-1.53
Uveitis	13.2	11.6-14.8	5.9	4.8-7.0	19.96	0.000	2.4	1.9-3.1
Retinal vasculitis	0.4	0.1-0.7	0.3	0.0-0.6	0.085	0.77	1.4	0.44-4.42
Joint manifestations	9.6	8.2-11.0	1.6	1.0-2.2	108	0.000	6.46	4.3-9.6
Other lesions	8.5	7.2-9.8	4.3	3.4-5.2	26.46	0.000	2.08	1.6-2.8
Selected Patients	First Quartile (893 patients)		Forth Quartile (1076 patients)		Difference		Odds Ratio	
Item	%	95%CI	%	95%CI	χ^2	p	OR	CI
Male	56.3	53.0-59.6	58.2	55.3-61.1	0.724	0.39	0.93	0.77-1.11
Female	43.7	40.4-47.0	41.7	38.8-44.6	0.724	0.39	1.08	0.80-1.29
Oral Aphthosis	72.7	69.8-75.6	88.1	86.2-90.0	76.70	0.000	0.36	0.28-0.45
Genital Aphthosis	11.0	8.9-13.1	7.6	6.0-9.2	6.573	0.01	1.49	1.10-2.03
Uveitis	10.5	8.5-12.5	4.9	3.6-6.2	22.10	0.000	2.27	1.60-3.22
Retinal vasculitis	0.1	0.1-0.3	0.1	0.1-0.3	0.335	0.56	1.20	0.08-19.3
Joint manifestations	10.8	8.8-12.8	1.5	0.8-2.2	77.96	0.000	7.97	4.7-13.6
Other lesions	8.4	6.6-10.2	3.5	2.4-4.6	21.32	0.000	2.50	1.68-3.74

Materials and Methods

The whole registry of Behcet's Disease patients was used for this study. The diagnosis of BD was on "Expert Opinion", when another disease could not explain the clinical manifestations. However, 99.87% of the patients in the registry were classified as BD with one or more of the known classification/diagnosis criteria for BD. The International criteria for Behcet's Disease (ICBD) classified 98.3% of patients [14] and the revised ICBD (2013) 96.7% of patients [15].

To accentuate the presumable change in the clinical picture of the disease by the time, the gap between the two groups to analyze were increased compared to the first analysis of year 2000. On the other hand, it was decided to have approximately the same number of patients in each group. Therefore, patients were divided into 4 equal groups of 1785 patients (total: 7140 patients). The first quartile (Q1), from 1975 to 1991, was compared to the fourth quartile (Q4), from 2003 to 2014. All the data from consecutive follow-ups were included in the analysis. The comparison was made by the t test for continuous data and the Pearson's chi square test (χ^2) for dichotomous data. To investigate the conclusion 3 and 4 (main paragraph of the Introduction), patients with a DD of 6 to 20 years were analyzed separately and the results will be given altogether with the complete data.

Due to the great number of cases, differences as small as 2% in very low or very high percentages become statistically significant while they are not clinically relevant. Even in the middle percentages, at 50%, a difference of 3.5% becomes statistically significant. Therefore, with χ^2, the difference between near all symptoms will become statistically significant between the 2 groups (Q1/Q4). Therefore, in those with a significant p value, we will compare the two samples by Odds ratio (OR) too, and will accept a difference as clinically relevant if OR ≥ 2.5 or ≤ 0.4, with confidence intervals not attaining or passing the level of 1.

Results

The mean age (all patients) of the first quartile (Q1) was 25.9 with standard error (SE) of 0.23 and standard deviation (SD) of 9.7. For the fourth quartile (Q4), it was 25.1 (SE: 0.24, SD: 10.6). The difference by the independent t test was statistically significant (t= 2.071, p=0.04). In selected patients (DD of 6 to 20 years), the mean age of Q1 was 25.8±9.1 versus 24.5±10.5 in Q4. The t was 2.902 (p=0.004).

The mean disease duration of Q1/Q4 was 13.0 vs 10.2 years with SD 10.1 vs 7.4. The difference was highly significant (t= 9.445, p<0.001). In selected patients (DD of 6 to 20 years), the mean of Q1 was 11.5±4.1 versus 11.4±4.0 in Q4. The t was 0.076 (p=0.94).

The mean follow-up of Q1/Q4 was 7.0 vs 2.3 years with SD 8.3 vs 3.0. The difference was highly significant (t= 22.5, p<0.001). In selected patients (DD of 6 to 20 years), the mean Q1 was 5.3±4.8 versus 2.9±3.4 in Q4. The t was 12.94 (p<0.001).

The mean delay between the first symptom and the diagnosis of Q1/Q4 was 6.0 vs 8.0 years with SD 6.0 vs 7.1. The difference was highly significant (t= 9.088, p<0.001). In selected patients (DD of 6 to 20 years), the mean DD of Q1 was 6.2±4.3 versus 8.4±4.8 in Q4. The t was 10.61 (p<0.001).

Complete details of the data are given in 5 different tables. In this section, only data having a significant OR will be given.

Table 2: Major manifestations of the disease: All versus selected patients (Disease Duration 6-20 years).

All Patients	First Quartile (1785 patients)		Forth Quartile (1785 patients)		Difference		Odds Ratio	
Item	%	95%CI	%	95%CI	χ^2	p	OR	CI
MUCOUS MEMBRANE	95.6	94.6-96.6	98.9	98.4-99.4	35.3	0.000	0.25	0.15-0.41
Oral Aphthosis	95.2	94.2-96.2	98.8	98.3-99.3	39.8	0.000	0.24	0.15-0.39
Genital aphthosis	65.0	62.8-67.2	62.4	60.2-64.6	2.677	0.10	1.12	0.98-1.28
SKIN MANIFESTATIONS	78.5	76.6-80.4	48.3	46.0-50.6	352	0.000	3.92	3.39-4.54
Pseudo Folliculitis	71.2	69.1-73.3	31.5	29.3-33.7	562	0.000	5.37	4.65-6.19
Erythema Nodosum	24.0	22.0-26.0	23.0	21.0-25.0	0.505	0.48	1.6	0.91-1.23
Other Lesions	6.6	5.4-7.8	8.7	7.4-10.0	5.708	0.017	0.74	0.58-0.95
OCULAR LESIONS	67.3	65.1-69.5	56.9	54.6-59.2	41.18	0.000	1.56	1.36-1.79
Uveitis (ant.)	53.8	51.5-56.1	40.7	38.4-43.0	61.54	0.000	1.70	1.49-1.94
Uveitis (post.)	51.9	49.6-54.2	44.8	42.5-47.1	18.09	0.000	1.33	1.17-1.52
Retinal Vasculitis	36.6	34.4-38.8	35.1	32.9-37.3	0.955	0.33	1.07	0.93-1.23
Cataract	20.5	18.6-22.4	27.8	25.7-29.9	26.22	0.000	0.67	0.57-0.78
Conjunctivitis	9.4	8.0-10.8	4.6	3.6-5.6	30.35	0.000	2.12	1.62-2.78
Selected Patients	First Quartile (893 patients)		Forth Quartile (1076 patients)		Difference		Odds Ratio	
Item	%	95%CI	%	95%CI	χ^2	p	OR	CI
MUCOUS MEMBRANE	96.8	95.6-98.	99.2	98.7-99.7	17.95	0.000	0.22	0.10-0.49
Oral Aphthosis	96.4	95.2-97.6	99.2	98.7-99.7	21.20	0.000	0.20	0.09-0.44
Genital aphthosis	66.5	634-69.6	64.1	61.2-67.0	1.169	0.28	1.11	0.92-1.34
SKIN MANIFESTATIONS	79.6	77.0-82.2	49.8	46.8-52.8	186	0.000	3.93	3.21-4.81
Pseudo Folliculitis	71.6	68.6-74.6	33.7	30.9-36.5	279	0.000	4.93	4.07-5.98
Erythema Nodosum	25.4	22.5-28.3	22.7	20.2-25.2	1.986	0.16	1.16	0.94-1.43
Other Lesions	5.6	4.1-7.1	8.8	7.1-10.5	7.494	0.006	0.61	0.43-0.87
OCULAR LESIONS	65.8	62.7-68.9	56.4	53.4-59.4	18.00	0.000	1.49	1.24-1.79
Uveitis (ant.)	52.9	49.6-56.2	40.8	37.9-43.7	29.34	0.000	1.62	1.36-1.94
Uveitis (post.)	51.6	48.3-54.9	44.1	41.1-47.1	10.82	0.001	1.35	1.13-1.61
Retinal Vasculitis	35.5	32.4-38.6	35.6	32.7-38.5	0.004	0.95	0.99	0.83-1.20
Cataract	14.4	12.1-16.7	30.2	27.5-32.9	68.50	0.000	0.39	0.31-0.49
Conjunctivitis	9.6	7.7-11.5	5.4	4.0-6.8	12.90	0.000	1.87	1.32-2.64

The male and female incidence

There were no statistically significant differences between Q1 and Q4 series, in whole patients (male and females: p= 0.06 and 0.11) and selected patients (0.39 and 0.39).

First Manifestation's difference between Q1/Q4 were clinically significant for oral aphthosis in whole patients, 71.5% versus (vs) 87.6%, p< 0.001, and OR 0.4. The difference remained significant in selected patients (72.7% vs 88.1%, p<0.001, OR 0.36). Joint manifestations were (9.6% vs 1.6%, p<0.001, and OR 6.5) in whole patients, and (10.8% vs 1.5%, p<0.001, and OR 8.0) in selected patients. The difference between the remaining was not clinically significant (Table 1).

Major manifestations

Oral aphthosis was seen less frequently in Q1 than Q4 (95.2% vs 98.8%, p<0.001, OR 0.24) and more frequently for pseudofolliculitis (71.2% vs 31.5%, p<0.001, OR 5.37), with clinically significant differences, in the group of whole patients. In the group of selected patients, for oral aphthosis, the figures remained near the same (96.4% vs 99.2%, p<0.001, OR 0.20). It was for pseudofolliculitis (71.6% vs 33.7%, p<0.001, OR 4.93). No significant clinical differences were found for genital aphthosis and ocular lesions (Table 2).

Minor manifestations

In the whole group of patients, a clinically significant difference was found for gastrointestinal manifestations, which were more frequent in Q1 than in Q4 (12.0% vs 4.6%, p<0.001, OR 2.81), and its subgroups of gastroduodenitis (4.5% vs 0.8%, p<0.001, OR 6.01) and peptic ulcer (2.5% vs 0.4%, p<0.001, OR 5.74). Epididymitis was also more frequent in Q1 than Q4 (6.2% vs 1.8%, p<0.001, OR 3.52) as was overlap or association with other autoimmune diseases and malignancies (3.2% vs 0.5%, p<0.001, OR 6.62). Cardiac manifestations were seen more frequently in the Q1 group than the Q4 group (1.1% vs 0.4%, p=0.02, OR 2.88). Pulmonary vasculitis was seen more frequently in the Q1 group than the Q4 (0.5% vs 0.1%, p= 0.03, OR 9.04), but not other pulmonary manifestations

Table 3: Minor Manifestations of the disease: All Patients.

All Patients	First Quartile (1785 patients)		Forth Quartile (1785 patients)		Difference		Odds Ratio	
Item	%	95%CI	%	95%CI	χ^2	p	OR	CI
JOINT MANIFESTATIONS	53.5	51.2-55.8	41.6	39.3-43.9	50.48	0.000	1.61	1.41-1.84
Arthralgia	30.2	28.1-32.3	20.0	18.1-21.9	49.36	0.000	1.73	1.48-2.02
Monoarthritis	13.2	11.6-14.8	9.9	8.5-11.3	9.230	0.002	1.38	1.12-1.69
Oligoarthritis	24.5	2205-26.5	16.3	14.6-18.0	36.78	0.000	1.66	1.41-1.96
SPA	2.0	1.4-2.6	2.4	1.7-3.1	0.634	0.43	0.83	0.53-1.30
GASTRO-INTESTINAL	12.0	10.5-13.5	4.6	3.6-5.6	63.79	0.000	2.81	2.16-3.65
Gastroduodenitis	4.5	3.5-5.5	0.8	0.4-1.2	48.54	0.000	6.01	3.40-10.6
Peptic Ulcers	2.5	1.8-3.2	0.4	0.1-0.7	24.82	0.000	5.74	2.70-12.2
Diarrhea	2.7	1.9-3.5	2.0	1.4-2.6	1.756	0.19	1.34	0.87-2.08
Rectorrhagia	1.4	0.9-1.9	0.7	0.3-1.1	4.615	0.32	2.10	1.05-4.19
Abdominal pain-nausea	3.1	2.3-3.9	2.0	1.4-2.6	4.559	0.03	1.59	1.04-2.44
VESSEL INVOLVEMENT	12.9	11.3-14.5	7.2	6.0-8.4	32.3	0.000	1.91	1.53-2.40
Superficial Phlebitis	2.9	2.1-3.7	1.7	1.1-2.3	6.029	0.014	1.75	1.11-2.76
Phlebitis	9.9	8.5-11.3	5.3	4.3-6.3	27.51	0.000	1.98	1.53-2.57
LARGE VESSEL	2.0	1.4-2.6	1.6	1.0-2.2	0.788	0.37	1.25	0.76-2.07
Arterial Thrombosis	0.1	0.0-0.2	0.3	0.0-0.6	4.176	0.04	1.20	0.02-1.71
Aneurism	0.7	0.3-1.1	0.3	0.0-0.6	1.393	0.24	2.01	0.75-5.36
Pulse Weakness	0.1	0.0-0.2	0.0	0.0	0.5	0.48	7.39	0.46-1.18
Large Vein Thrombosis	1.3	0.8-1.8	1.1	0.6-1.6	0.586	0.44	1.27	0.69-2.32
EPIDIDYMITIS	6.2	5.1-7.3	1.8	1.2-2.4	44.03	0.000	3.52	2.37-5.22
NEUROLOGICAL MANIF.	15.3	13.6-17.0	9.4	8.0-10.8	29.13	0.000	1.75	1.43-2.15
Peripheral	0.4	0.1-0.7	0.3	0.0-0.6	0.0	1.0	1.17	0.39-3.48
Central	4.3	3.4—5.2	4.1	3.2-5.0	0.111	0.74	1.06	0.76-1.47
Cephalea	12.0	10.5-13.5	6.2	5.1-7.3	36.51	0.000	2.07	1.63-2.62
PULMONARY MANIF.	1.3	0.8-1.8	0.8	0.4-1.2	2.207	0.14	1.65	0.85-3.22
Vasculitis	0.5	0.2-0.8	0.1	0-0.2	4.914	0.03	9.04	1.14-71.43
Fibrosis	0.2	0.0-0.4	0.0	0.0	1.333	0.25	-	-
Infection	0.5	0.2-0.8	0.3	0.0-0.6	0.644	0.42	1.80	0.60-5.39
Pleurisy	0.3	0.0-0.6	0.1	0.0-0.2	0.571	0.45	2.52	0.48-12.92
Embolism	0.0	0.0	0.2	0.0-0.4	6.260	0.012	-	-
Others	0.2	0.0-0.4	0.1	0-0.2	0.166	0.68	2.00	0.37-10.94
CARDIAC MANIF.	1.1	0.6-1.6	0.4	0.1-0.7	5.367	0.02	2.88	1.21-6.82
Myocardial Infarction	0.3	0.0-0.6	0.2	0.0-0.4	0.125	0.72	1.67	0.40-6.99
Angina Pectoris	0.3	0.0-0.6	0.0	0.0	4.171	0.04	-	-
Murmur	0.3	0.0-0.6	0.0	0.0	3.202	0.07	-	-
Heart Failure	0.1	0.0-0.2	0.1	0.0-0.2	0.0	1	-	-
Pericarditis	0.2	0.0-0.4	0.1	0.0-0.2	0.250	0.62	-	-
PRIMARY LIMB EDEMA	0.5	0.2-0.8	0.2	0.0-0.4	2.088	0.15	3.01	0.81-11.13
HEPATO-SPENOMEGALIA	0.6	0.2-1.0	0.1	0.0-0.2	6.922	0.009	11.25	1.45-87.20
OVERLAP / ASSOCIATION	3.2	2.4-4.0	0.5	0.2-0.8	35.02	0.000	6.62	3.27-13.41

(fibrosis, infection, pleurisy, and embolism). Hepatosplenomegaly was also seen more frequently in Q1 than Q4 (0.6% vs 0.1%, p=0.009, OR 11.25). Joint manifestations, Vessel involvement (arterial and venous), Neurological manifestations, and subgroups of cardiac manifestations were not significantly different from Q1 to Q4 (Clinical significance). Details are given in Table 3. In the selected

Table 4: Minor Manifestations of the disease - Selected Patients (Disease Duration 6-20 years).

Selected Patients	First Quartile (893 patients)		Forth Quartile (1076 patients)		Difference		Odds Ratio	
Item	%	95%CI	%	95%CI	χ^2	p	OR	CI
JOINT MANIFESTATIONS	51.2	47.9-54.5	45.8	42.8-48.8	5.519	0.019	1.07	0.89-1.28
Arthralgia	28.1	25.2-31.0	22.6	20.1-25.1	7.857	0.005	1.34	1.09-1.64
Monoarthritis	12.4	10.2-14.6	10.7	8.9-12.5	1.440	0.23	1.18	090-1.56
Oligoarthritis	24.4	21.6-27.2	18.0	15.7-20.3	11.94	0.000	1.47	1.18-1.82
SPA	2.1	1.2-3.0	2.7	1.7-3.7	0.666	0.41	0.78	0.4-1.41
GASTRO-INTESTINAL	11.9	9.8-14.0	5.2	3.9-6.5	28.65	0.000	2.45	1.75-3.43
Gastroduodenitis	4.8	3.4-6.2	0.9	0.3-1.5	28.09	0.000	5.39	2.69-10.78
Peptic Ulcers	2.2	1.2-3.2	0.4	0.0-0.8	12.61	0.000	6.13	2.09-18.01
Diarrhea	3.1	2.0-4.2	2.1	1.2-3.0	2.021	0.16	1.50	0.86-2.62
Rectorrhagia	1.1	0.4-1.8	0.7	0.2-1.2	0.764	0.38	1.73	066-4.56
Abdominal pain-nausea	2.8	1.7-3.9	2.4	1.5-3.3	0.280	0.60	1.16	067-2.03
VESSEL INVOLVEMENT	5.5	4.4-6.6	4.3	3.4-5.2	9.260	0.002	1.62	1.18-2.21
Superficial Phlebitis	2.4	1.4-3.4	1.6	0.9-2.3	1.528	0.220	1.50	0.79-2.86
Phlebitis	9.0	7.1-10.9	5.6	4.2-7.0	8.420	0.004	1.66	1.18-2.36
LARGE VESSEL	1.3	0.6-2.0	1.7	0.9-2.5	0.309	0.58	0.81	0.39-1.69
Arterial Thrombosis	0.0	0.0	0.2	0.1-0.5	4.000	0.045	-	-
Aneurism	0.2	0.0-0.5	0.6	0.1-1.1	2.298	0.13	0.40	0.08-1.99
Pulse Weakness	0.2	0.0-0.5	0.0	0.0	0.709	0.40	-	-
Large Vein Thrombosis	1.1	0.4-1.8	1.1	0.5-1.7	0.0	0.99	1.00	0.43-2.33
EPIDIDYMITIS	6.6	5.0-8.2	1.8	1.0-2.6	30.01	0.000	3.93	2.33-6.65
NEUROLOGICAL MANIF.	15.0	12.7-17.3	11.2	9.3-13.1	6.081	0.014	1.39	1.07-1.81
Peripheral	0.2	0.1-0.5	0.6	0.1-1.1	2.298	0.13	0.40	008-1.99
Central	4.4	3.1-5.7	4.5	3.3-5.7	0.011	0.92	0.98	0.6-1.51
Cephalea	11.8	9.7-13.9	7.7	6.1-9.3	9.202	0.002	1.59	1.18-2.16
PULMONARY MANIF.	1.6	0.8-2.4	0.9	0.3-1.5	1.646	0.20	1.70	0.75-3.84
Vasculitis	0.7	0.2-1.2	0.1	0-0.3	3.128	0.08	7.26	0.87-60.46
Fibrosis	0.2	0.0-0.5	0.0	0.0	0.709	0.40	-	-
Infection	0.6	0.1-1.1	0.3	0.0-0.6	0.383	0.54	2.01	0.48-8.44
Pleurisy	0.3	0.0-0.7	0.1	0.0-0.3	0.474	0.49	3.62	0.38-34.87
Embolism	0.0	0.0	0.4	0.0-0.8	5.417	0.020	-	-
Others	0.3	0.0-0.7	0.2	0-0.5	0.043	0.84	1.81	0.30-10.85
CARDIAC MANIF.	1.3	0.6-2.0	0.4	0.0-0.8	4.570	0.033	3.65	1.17-11.35
Myocardial Infarction	0.1	0.0-0.3	0.3	0.0-0.6	1.748	0.19	0.40	0.04-3.86
Angina Pectoris	0.4	0.0-0.8	0.0	0.0	2.869	0.09	-	-
Murmur	0.4	0.0-0.8	0.0	0.0	2.869	0.09	-	-
Heart Failure	0.1	0.0-0.3	0.1	0.0-0.3	0.335	0.56	1.20	0.08-19.28
Pericarditis	0.3	0.0-0.7	0.0	0.0	1.746	0.19	-	-
PRIMARY LIMB EDEMA	0.4	0.0-0.8	0.3	0.0-0.6	0.061	0.81	1.61	0.36-7.20
HEPATO-SPENOMEGALIA	0.4	0.0-0.8	0.1	0.0-0.3	1.226	0.27	4.830	054-43.31
OVERLAP / ASSOCIATION	3.2	2.0-4.4	0.3	0.0-0.6	25.05	0.000	11.99	3.64-39.51

group of patients, the same items were seen more frequently in Q1 than Q4, except gastrointestinal manifestations, where the OR went below the limit of clinical significance, the pulmonary vasculitis and the heapatosplenomegaly where the p value became non-significant: gastroduodenitis (4.8% vs 0.9%, p<0.001, OR 5.39), peptic ulcer (2.2% vs 0.4%, p<0.001, OR 6.13), (epididymitis 6.6% vs 1.8%, p<0.001,

Table 5: Lab data: All patients versus selected patients (Disease Duration 6-20 years).

All Patients	First Quartile (1785)		Forth Quartile (1785)		Difference		Odds Ratio	
Item	%	95%CI	%	95%CI	χ^2	p	OR	CI
Positive Pathergy Test	63.7	61.4–66.0	35.8	33.6-38.0	234	0.000	2.85	2.49-3.27
Positive HLA-B5	54.1	51.7-56.5	54.0	51.7-56.3	1.620	0.20	0.92	0.81-1.05
Positive HLA-B27	10.4	8.8-12.0	7.3	6.1-8.5	1.432	0.23	1.16	0.91-1.49
ESR ≤ 20	38.2	35.9-40.5	58.3	56.0-60.6	144	0.000	0.44	0.39-0.51
ESR 21- 50	31.5	29.-33.7	28.8	26.7-30.9	3.065	0.08	1.14	0.98-1.31
ESR 51 - 100	17.9	16.1-19.7	9.4	8.0-10.8	54.84	0.000	2.10	1.72-2.57
ESR > 100	2.3	1.6-3.0	0.7	0.3-1.1	14.74	0.000	3.20	1.71-6.00
URINALYSIS								
Proteinuria	4.3	3.4-5.2	1.3	0.8-1.8	27.82	0.000	3.26	2.05-5.19
Hematuria	8.5	7.2-9.8	9.7	8.3-11.1	1.493	0.22	0.87	0.69-1.09
Leukocyturia	6.1	5.0-7.2	5.7	4.6-6.8	0.182	0.67	1.06	0.80-1.40
Cast	0.5	0.2-0.8	0.2	0.0-0.4	1.235	0.27	2.26	0.69-7.34
Positive VDRL/RPR	3.0	2.1-3.9	0.1	0.0-0.3	36.01	0.000	22.01	5.32-90.98
Selected Patients	First Quartile (893)		Forth Quartile (1076)		Difference		Odds Ratio	
Item	%	95%CI	%	95%CI	χ^2	p	OR	CI
Positive Pathergy Test	62.9	59.7-66.1	37.6	34.7-40.5	90.45	0.000	2.38	1.99-2.84
Positive HLA-B5	53.4	50.1-56.7	53.7	50.7-56.7	0.681	0.41	0.93	0.78-1.11
Positive HLA-B27	10.4	8.2-12.6	6.1	4.7-7.5	10.77	0.001	1.78	1.26-2.52
ESR ≤ 20	39.4	36.2-42.	56.9	53.9-59.9	59.86	0.000	0.49	0.41-0.59
ESR 21- 50	31.4	28.4-34.4	29.8	27.1-32.5	0.514	0.47	1.07	0.88-1.30
ESR 51 - 100	17.2	14.7-19.7	9.9	8.1-11.7	22.55	0.000	1.89	1.45-2.46
ESR > 100	1.9	1.0-2.8	0.8	0.3-1.3	3.477	0.06	2.30	1.02-5.18
URINALYSIS								
Proteinuria	4.1	2.8-5.4	1.3	0.6-2.0	15.60	0.000	3.28	1.76-6.10
Hematuria	8.0	6.2-9.8	10.8	8.9-12.7	4.575	0.032	0.71	0.52-0.97
Leukocyturia	5.4	3.9-6.9	6.7	5.2-8.2	1.629	0.20	0.78	0.54-1.14
Cast	0.7	0.2-1.2	0.2	0.0-0.5	1.771	0.18	3.63	0.73-18.03
Positive VDRL/RPR	3.1	1.8-4.4	0.2	0.0-0.5	20.34	0.000	14.18	3.33-60.33

OR 3.93), overlap or association with other autoimmune diseases and malignancies (3.2% vs 0.3%, p<0.001, OR 11.99), and Cardiac manifestations (1.3% vs 0.4%, p=0.033, OR 3.65). Details are given in Table 4.

Laboratory investigations

In the group of whole patients, HLA-B5 and HLA-B27 were not different in Q1 and Q4. HLA-B51 was not checked during the Q1 period. The Positive Pathergy test was seen more frequently in Q1 than Q4. The difference was very large (64.1% vs 34.6%, p<0.001, OR 0.3). For ESR, only the small gap of ESR superior to 100 was seen more frequently in Q1 than Q4 (2.3% vs 0.7, p<0.001, OR 3.2). For urinalysis, proteinuria was seen more frequently in Q1 (4.3% vs 1.3%, p<0.001, OR 3.26). False positive reaction for syphilis (VDRL or RPR) was also seen more frequently in Q1 (3.0% vs 0.1%, p<0.001, OR 22.01). Detailed figures are given in Table 5. In the selected patients' group, the positive Pathergy test lost its clinically significant OR, while ESR superior to 100 lost both the significant p value and the clinically significant OR (Table 5).

Adult versus childhood Behcet's disease

There was no clinically relevant difference between the Q1 and Q4 group (Table 6).

Discussion

The gender and the mean age of onset remained the same from the first to the fourth quartile (Table 1). This was the same as in the previous study [5]. The same was seen for the genetic predisposition of the disease as seen in HLA typing (Table 4).

Oral aphthosis was absent in a minority of BD patients (4.8%) in the first quartile (seen from 1975 to 1991). In the second quartile it became 3.5%, in the third quartile 1%, and in the fourth again 1%. The difference between the Q1 and Q3-Q4 may be explained by the improvement in diagnostic methods. The major diagnostic criteria used until 1991 were essentially Mason and Barnes criteria [16], Japan criteria [17], Hubault and Hamza criteria [18], O'Duffy

Table 6: Type of Behcet's Disease (BD): All patients versus selected patients (Disease Duration 6-20 years).

All Patients	First Quartile (1785)		Forth Quartile (1785)		Difference		Odds Ratio	
Item	%	95%CI	%	95%CI	χ^2	p	OR	CI
Adult BD	85.3	83.7-86.9	80.6	78.8-82.4	14.04	0.000	1.40	1.17-1.67
Childhood BD (≤ 16 years)	14.7	13.1-16.3	19.0	17.2-20.8	11.91	0.000	0.73	0.61-0.87
* Childhood Completed	1.4	0.9-1.9	2.8	2.0-3.6	8.527	0.004	0.49	0.30-0.80
* Diagnosed in Childhood	3.4	2.6-4.2	1.6	1.0-2.2	11.06	0.000	2.10	1.34-3.30
* Adult Completed	9.9	8.5-11.3	14.5	12.9-16.1	17.62	0.000	0.65	0.53-0.79
Adult BD + Adult Completed	95.2	94.3-96.1	95.1	94.1-96.1	0.055	0.82	1.04	0.76-1.41
Selected Patients	First Quartile (893)		Forth Quartile (1076)		Difference		Odds Ratio	
Item	%	95%CI	%	95%CI	χ^2	p	OR	CI
Adult BD	85.9	83.6-88.2	79.3	76.9-81.7	14.34	0.000	1.58	1.25-2.01
Childhood BD (≤ 16 years)	14.1	11.8-16.4	20.5	18.5-22.9	13.97	0.000	0.63	0.50-0.81
* Childhood Completed	1.8	0.9-2.7	3.4	2.3-4.5	5.609	0.024	0.51	0.28-0.93
* Diagnosed in Childhood	2.1	1.2-3.0	1.7	0.9-2.5	0.543	0.46	1.28	0.67-2.45
* Adult Completed	10.2	8.2-12.2	15.3	13.1-17.5	11.47	0.000	0.63	0.48-0.82
Adult BD + Adult Completed	96.1	94.8-97.4	94.6	93.2-96.9	2.346	0.13	1.40	0.91-2.15

criteria [19], and Dilsen criteria [20]. They all needed the presence of more complete or aggressive forms of the disease to be classified as BD. In 1993, the advent of Classification Tree for Classification/Diagnosis of BD opened the door for recognition of milder forms of BD, mainly the forms with bipolar aphthosis [21]. The improvement of sensitivity and accuracy ("percent agreement") over the other criteria sets, especially the young International study group criteria [22], was evident in the same data set from Iran [23], Russia [24], and USA [25], and in India [26], Singapore [26], China [26], and Korea [26]. The difference seen for oral aphthosis as inaugural manifestation can be explained by the same phenomenon.

Skin manifestations have been seen much less frequently in Q4 than Q1. Perhaps a part of it can be explained by the possibility to diagnose milder forms of the disease (as for oral aphthosis). However, the difference is too large to explain all of it by the inclusion of milder forms. In the previous study [5], the difference between the groups for cutaneous manifestations was 9%, while in the new study the difference had increased to 31%. The difference for pseudo folliculitis was 11% in the old study; it increased to 40% in the new study. Treatment also may not be the cause of such difference, because the first line treatment for these patients was colchicines [27] when no major organ involvement was present. It became cytotoxic drugs when CNS or eye lesions were present. The treatment protocol, as for the first line treatment, has not much changed during these years.

Among minor manifestations, gastrointestinal, cardiac, pulmonary vasculitis, epididymitis, and overlap were more frequent in the Q1 than Q4. Two explanations may be given. 1- Milder diagnosed forms as explained for Oral aphthosis. 2- Longer follow-up and longer disease duration, which will give the time to other manifestations to appear [28]. However, for laboratory tests, the most prominent difference is the Pathergy test, which was seen, much less frequently in Q4 than Q1, exactly like skin manifestations. It was the same in the older study [5], where these manifestations decreased during the time, except for vascular manifestations. However, the difference was the same for gastrointestinal, cardiac, and pulmonary manifestations, on the contrary of skin manifestations.

A later study from 2003 [29], having 574 newer patients (a total 4704 patients), showed the same results as the older one [5]. It is interesting to note that if in the new study, the comparison of Q1 to Q4 is done by Pearson's chi square test, as it was done in the elder studies [5,29], the results will show the same as in the old studies, except for the magnitude of the differences, especially in skin manifestations.

Comparing the results of the entire group of patients, to those of the selected patients (in Q1 and Q4), having a disease duration (DD) of 6 years to 20 years, showed the same results. These results are in contradiction of the difference in disease duration, to explain the milder forms of the disease in recent decades.

A comparative analysis was done in Lebanon [30]. They analyzed patients seen from 1977 to 1989, and patients seen from 1990 to 2003. They found, like us, no difference in male to female ratio. The severity of the disease was increased in the new group, but the difference did not reach statistical significance. However, the number of their patients was low, 40 in the old group and 50 in the new group. The lack of statistical significance may be due to the low number of patients. If the number of BD patients in each group were twice, the difference would become significant with a p value around 0.03. In their patients, the incidence of genital ulcers decreased as in our new study, while the incidence of neurologic manifestations increased (not in our study). The difference was not significant for the remaining of clinical manifestations.

A new study (2014) was done in Korea [31]. They found a decrease in genital aphthosis, eye lesions, and skin lesions. They found on the hand an increase in joint, gastrointestinal, and neurological manifestations. Their results differed greatly from ours and the study from Lebanon [30].

Conclusion

The most prominent change in Behcet's Disease picture during the past decades was the skin manifestation and the Pathergy phenomenon, which is also a skin manifestation. Longer duration of the disease and longer follow-up may not explain the observed differences.

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