Original Article

Association Between Initial Findings Leading to Behçet's Disease Diagnosis and Further Organ Involvements

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Abstract

Objectives: Studies show that the symptoms are clustered in certain ways in Behçet's disease (BD), which causes involvement of multiple organs. We aimed to investigate the association between clinical findings at onset and further organ involvements, which may occur during follow-up. **Materials and Methods:** A total of 363 patients diagnosed with BD in accordance with the International Criteria for BD (ICBD) between 2003 and 2019 at the Inonu University were included in the study, and all the first findings were compared with further organ involvements. **Results:** A statistical significance was detected between erythema nodosum like lesions and both pulmonary (P = 0.002) and vascular (P = 0.022) involvements. The frequency of neurological involvement was higher in patients with papulopustular/pseudo-follicular lesions (P = 0.043). Gastrointestinal involvement was detected in 33.3% of the patients with herpetiform aphthae. The frequency of ocular involvement was significantly higher in patients with a negative pathergy test result (P = 0.013). **Conclusion:** The clinical clusters in BD may provide a predictive value about the disease course for clinicians. Although it has been shown that there is an association between some clinical findings and involvements which are mentioned before, this is one of the most comprehensive studies according to us. The clinical clusters in BD may provide a predictive value about the disease course for clinicians. Although it has been shown that there is an association between some clinical findings and involvements in the literature, this is one of the most comprehensive studies as far as we know.

Keywords: Gastrointestinal, neuro-Behçet, ocular, pulmonary, vascular

Introduction

Behçet's disease (BD) is a chronic, systemic inflammatory vasculitis characterized by episodes of exacerbations and remissions.[1] BD often occurs in the third decade. Although it is seen equally frequently in men and women, studies show that organ involvements occur at different frequencies between genders.[2,3] As it involves both arteries and venous vessels along with large, medium, and small vessels, it is called "variable vessel vasculitis."[1,4] This wide range of vessel involvements affecting vascular, ocular, articular, gastrointestinal, neurological, and pulmonary systems leads to various clinical findings.[5] BD may cause blindness, physical disability, and cognitive impairment.[3]

There are studies in the literature showing that different organ and system involvements cause phenotypic clustering in patients. Tascilar *et al.*[6] manifested that dural sinus thrombosis, pulmonary artery aneurysm, and vena cava involvements clustered in a group of patients. Diri *et al.*[7] presented an association with papulopustular lesions and arthritis. Based on these data, we may interpret that certain clinical findings are associated with specific organ involvements.

We retrospectively have analyzed the data of 459 patients who have been followed up in our clinic since 2003. We

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aimed to assess the association between clinical signs, which enabled us to diagnose in accordance with the International Criteria for Behçet's Disease (ICBD), and organ involvements. Besides, we assessed the association between the clinical presentation at the time of diagnosis (aphthae type, skin manifestations, etc.) and these organ involvements.

Materials and Methods

The study included 459 patients who were diagnosed with BD according to the ICBD between 2003 and 2019 years at the Inonu University. We got ethics approval from the local Institutional Ethics Committee. The patients with BD aged between 18 and 65 were retrospectively included in the study. The patients with incomplete BD, pediatric BD, and patients who have not come for follow-up after the first diagnosis were excluded from the study. Patients with inflammatory bowel disease and connective tissue disease were excluded. Considering the inclusion and exclusion criteria, 49 patients with incomplete BD, 27 patients with pediatric BD, and 20 patients who have not been followed up were left out of the study, and the data of the remaining 363 patients have been analyzed.

All patients have been questioned for systemic symptoms in the first visit and during follow-up every 2–6 months by dermatologists. Patients have been questioned for symptoms such as headache, blurry vision, redness on the eye, abdominal pain, diarrhea, chest pain and cough, erythema, pain, and tenderness on extremities. Patients with complaints were consulted to the relevant specialty. All patients were consulted regularly with the Department of Ophthalmology. Appropriate diagnostic tests such as magnetic resonance imaging of the brain and magnetic resonance angiography, endoscopy-colonoscopy, histopathological examination, computed tomography of the chest, ultrasonography, and blood tests have been done for patients who have symptoms.

The pathergy test has done by a needle prick on three different points on the front face of the forearm. Attention was paid to perform the test on patients without immunosuppressive treatment. Patients with parenchymal (brainstem, hemispheric, spinal) and non-parenchymal (cerebral venous sinus thrombosis, arterial involvement) central nervous system findings compatible with neuro-BD were accepted as neurological involvement by a neurologist. Gastrointestinal involvement was accepted among the patients with BD who have gastrointestinal ulcer compatible with BD endoscopically or histopathologically.[8] Patients with venous thrombosis such as superficial vein thrombosis, lower extremity vein thrombosis, vena cava inferior thrombosis without any evidence of thrombotic disease, and arterial aneurysms were excepted as vascular involvement.[3] Patients who have pulmonary artery aneurysms or pulmonary artery thrombosis were accepted as pulmonary involvement.[9] Patients with anterior and/or posterior uveitis, relapsing and remitting panuveitis, and retinal vasculitis were accepted as ocular involvement by the exclusion of other inflammatory and infectious diseases.[10]

The herpes simplex virus-polymerase chain reaction test was done in patients with clustering of small aphthous lesions in one area to exclude herpes infection. In the case of any clinical suspicion for deep vein thrombosis and erythema nodosum-like lesions (ENLLs), a Doppler ultrasonography was done.

According to these criteria, patients who have been diagnosed by a relevant specialist were considered to have organ involvement. Patients were investigated in terms of they have any organ involvements at the beginning of the diagnosis or during the follow-up. The presence of an association between clinical findings included in the criteria ICBD and organ involvements was analyzed. The presence of an association between relevant complaints and organ involvements (such as headache and neurological involvement) was also analyzed. The study was performed retrospectively and the Declaration of Helsinki was followed.

Statistical analysis

The data of the study have been analyzed by using SPSS version 17 for Windows software (SPSS, Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test has been used to assess the conformity of the data to the normal distribution, and the χ^2 test and Mann–Whitney *U*-test have been used for the analysis of categorical variables and numerical variables, respectively. All significant levels were two-tailed and set at the level of 0.05.

Results

Demographic data of the patients

A total of 363 patients were included in the study: 155 (42.7%) females and 208 (57.3%) males. The mean age of the patients at the time of diagnosis was 29.2 ± 1.21 years in the females and 30.5 ± 0.94 years in the males ($P = 0.803$). The average length of follow-up was 13 years. About 43.4% of the patients had BD or recurrent aphthous stomatitis (RAS) in their family history. Patients who had BD ($P = 0.774$) or RAS ($P = 0.067$) in the family history were compared with those who did not have and there was not any significant association with the BD. The frequency of the first manifestation of the diagnostic criteria and demographic data according to gender is shown in Table 1.

Involvements by gender

When involvements of BD were investigated according to gender, vascular ($P = 0.001$) and gastrointestinal system (GIS) ($P = 0.043$) involvements were found higher in the male group when compared with females. However, no significant

differences were detected between these two groups in terms of genital ulcer, pathergy test, skin manifestations, ocular involvement [Table 1], neurological involvement, arthritis, pulmonary involvement, central nervous system symptoms, and GIS symptoms. Involvement frequencies according to the gender and *P*-values are outlined in Table 2.

Relationships between organ involvement and diagnostic criteria

Oral aphthae

GIS involvement was detected in 33.3% of the patients who had herpetiform aphthae. There was a statistically significant association between GIS involvement and herpetiform aphthae ($P = 0.000$) [Table 3].

Skin findings

There was no significant association between the presence of skin manifestations and organ involvement. However, when the skin manifestations were classified as ENLLs and papulopustular/pseudo-follicular (PPL-PSF), a statistical significance was detected between ENLL and both pulmonary ($P = 0.002$) and vascular ($P = 0.022$) involvements. It has been observed that the frequency of neurological involvement disease was higher in patients with PPL-PSF ($P = 0.043$) [Table 3].

Pathergy test—genital ulcer

The frequency of ocular involvement was higher in patients with a negative pathergy test result, which was found to be statistically significant ($P = 0.013$). It was seen that ocular involvement was infrequent in patients who had genital ulcers ($P = 0.005$). However, 74.8% of the patients with ocular lesions were accompanied also by genital ulcers ($P = 0.005$). The incidence of vascular ($P = 0.034$) and ocular ($P = 0.005$) involvements was lower in patients with genital involvement [Table 3].

Ocular involvement

There was no statistical increase in terms of neurological, vascular, gastrointestinal, pulmonary, and joint involvements in patients with ocular involvement [Table 3].

Organ involvements and symptoms

It was shown that there was no increase in the development of neurological disease or GIS involvement ($P = 0.553$ and 0.470) in patients who had neurologic or gastrointestinal complaints such as headache, dizziness, abdominal pain, diarrhea, and constipation at the time of diagnosis. Yet, ocular involvement was higher in patients who had neurological complaints ($P = 0.000$).

Table 1: Frequency of the initial findings for the diagnosis and demographic data according to gender

	Female *N* (%)	Male *n* (%)	Total *n* (%)	*P*-value
Number	155 (42.7)	208 (57.3)	363 (100)	
Age	29.2 (mean)	30.5 (mean)		0.803
Behçet's disease in the family	20 (12.9)	29 (13.9)	49 (13.5)	0.774
RAS* in the family	54 (34.8)	54 (26)	108 (29.8)	0.067
Genital ulcer	132 (85.2)	167 (80.3)	299 (82.4)	0.228
Pathergy phenomenon	70 (45.2)	111 (53.4)	181 (49.9)	0.122
Skin findings	28 (18.1)	176 (84.6)	303 (83.5)	0.497
EN† like lesions	61 (39.4)	64 (30.8)	125 (34.4)	0.101
Papulopustular/pseudo-follicular lesions	66 (42.6)	112 (53.8)	178 (49.0)	0.101
Ocular inv.	49 (31.6)	82 (39.4)	131 (36.1)	0.125

*RAS = recurrent aphthous stomatitis

†EN = erythema nodosum

Table 2: Involvement rates and *P*-values according to the gender

	Female *n* (%)	Male *n* (%)	Total *n* (%)	*P*-value
Neurologic inv.	11 (7.1)	14 (6.7)	25 (6.9)	0.892
Vascular inv.	9 (5.8)	36 (17.3)	45 (12.4)	**0.001**
Arthritis	13 (8.4)	21 (10.1)	34 (9.4)	0.580
GIS* inv.	2 (1.3)	11 (5.3)	13 (3.6)	**0.043**
Pulmonary inv.	4 (2.6)	12 (5.8)	16 (4.4)	0.143
CNS† complaint	115 (74.2)	142 (68.3)	257 (70.8)	0.219
GIS complaint	72 (46.5)	88 (42.3)	160 (44.1)	0.432

*GIS = gastrointestinal system

†CNS = central nervous system

Table 3: Components of the diagnostic criteria and relations between systemic involvements

	Ocular inv. *n* (%), *P*	Neurologic inv. *n* (%), *P*	Vascular inv. *n* (%), *P*	Pulmonary inv. *n* (%), *P*	Gastrointestinal inv. *n* (%), *P*	Arthritis *n* (%), *P*
Aphthae types						
Major aphthae	53 (35.6), 0.864	10 (6.7), 0.912	22 (14.8), 0.253	10 (6.7), 0.074	7 (4.7), 0.339	16 (10.7), 0.454
Minor aphthae	122 (36.2), 0.871	22 (6.5), 0.331	41 (12.2), 0.631	14 (4.2), 0.397	12 (3.6), 0.940	31 (9.2), 0.693
Herpetiform aphthae	3 (50), 0.474	0 (0), 0.502	0 (0), 0.353	1 (16.7), 0.140	**2 (33.3), 0.000**	1 (16.7), 0.536
Skin findings	110 (36.3), 0.848	24 (7.9), 0.081	42 (13.9), 0.057	16 (5.3), 0.069	12 (4), 0.382	28 (9.2), 0.854
EN-like lesions	50 (40), 0.523	6 (4.8), 0.043	**23 (18.4), 0.022**	**12 (9.6), 0.002**	4 (3.2), 0.571	11 (8.8), 0.959
Papulop.-pseudof.	60 (33.7), 0.523	**18 (10.1), 0.043**	19 (10.7), 0.022	4 (2.2), 0.002	8 (4.5), 0.571	17 (9.6), 0.959
Pathergy phenomenon	**54 (29.8), 0.013***	11 (6.1), 0.544	22 (12.2), 0.889	6 (3.3), 0.312	7 (3.9), 0.770	15 (8.3), 0.482
Genital ulcer	**98 (32.8), 0.005****	18 (6), 0.159	**32 (10.7), 0.034**	13 (4.3), 0.904	12 (4), 0.338	26 (8.7), 0.343
Ocular inv.		10 (7.6), 0.673	13 (9.9), 0.283	4 (3.1), 0.345	3 (2.3), 0.320	9 (6.9), 0.220

EN = erythema nodosum

*In the patients with a negative pathergy test result, ocular involvement was more common in patients with negative pathergy test than patients with positive pathergy test

**In the patients without genital ulcer, ocular involvement was more common in genital ulcer-negative patients than that in genital ulcer-positive patients

Significant values are indicated by in bold.

Discussion

Studies which show that ENLLs are associated with ocular involvement and GIS involvement have been published in the literature.[11,12] Studies show the association of papulopustular lesions and arthritis and the relationship of pathergy positivity with ocular involvement.[7,13] Suwa *et al.*[14] reported a negative relationship between genital ulcers and ocular involvement. We, like Suwa *et al.*, found an inverse relationship between genital ulcer and ocular involvement. Additionally, we statistically detected more frequent pulmonary involvement in patients with ENLL. We showed a significant association between GIS involvement and the presence of herpetiform aphthae and PPL with neurological involvement. We think that the clinical clusters in BD show that such variation is due to the close relationship of the disease with race, genetics, and geography. This interesting cluster of findings in BD may provide a predictive value about the disease course for clinicians. Although it has been shown that there is an association between some clinical findings and involvements which are mentioned earlier, this is one of the most comprehensive studies according to us.

Skin manifestations occupy an important place in BD. Particularly, ENLL may precede severe organ involvements. ENLL was determined as a skin finding which is seen in one-third of the patients, more often in women.[5] Although erythema nodosum is panniculitis, ENLL is a venulitis-type vasculitis histopathologically.[11]

It was emphasized in the studies that the patients who have ENLLs could have vascular involvement more frequently. It was also emphasized that young male patients who have ENLLs, in particular, may have accompanying deep vein thrombosis.[12] It was defended that ENLLs may be a sign of severe phlebitis in another study.[11] ENLL was found in 34.4% of the patients in our study. Vascular involvement was found to be higher in patients with ENLL, similar to the literature. Unlike other vasculitides, Behçet progresses with venous vascular involvement. As BD is a vasculitis with venous vascular involvement predominantly (lower extremity veins, hepatic veins, and cerebral veins),[3] we think that the presence of ENLL which is showing venulitis-type vasculitis may be an indicator of severe vascular involvement in patients. We have not encountered any studies which show the relation between ENLL and pulmonary involvement as we found. A number of previous studies have shown that pulmonary involvement commonly coexists with systemic vascular involvement, particularly deep vein thrombosis.[9] Therefore, associations of ENLL with both the involvements seem reasonable.

The PPL which is seen in BD is similar to acne-like lesions and/or folliculitis which occurs in the form of sterile erythematous papule and usually becomes pustule in 24–48 h. These lesions were found in 28–96% of the patients. There is evidence that PPL is seen in patients with positive pathergy and patients with arthritis.[5,7] The more frequent presence of arthritis in females and in patients who have PPL was indicated in the studies. In our study, we did not detect any significant differences between them.[6] PPL was found in 49% of the patients. Besides, we statistically established that neurological involvement is higher in patients with PPL, and we have not encountered any studies which report these interesting relations.

Gastrointestinal involvement varies between 2.8% and 60% according to geography. Gastrointestinal involvement may cause abdominal pain, nausea, gastrointestinal ulcer formation, and bleeding. It has been suggested that mucosal inflammation due to neutrophilic phlebitis leads to ulcer formation.[15] Histopathologically, infiltration consisting of perivascular neutrophils, lymphocytes, and macrophages is dominant in neutrophilic phlebitis

and aphthous lesions.[16,17] As the oropharynx area is anatomically and embryologically a part of the GIS, aphthous lesions can be considered as a part of gastrointestinal involvement as in Crohn's disease. To the best of our knowledge, there is no study investigating the relationship between the type of aphthous lesions and GIS involvement. In our study, 33% of the patients with herpetiform-type aphthae have GIS involvement. This was found to be statistically significant. Despite the small number of patients with herpetiform-type aphthae, a *P*-value of 0.000 indicates that the significance is strong. That is why we think that there is a significant association between variables rather than a random relationship.

Herpetiform aphthae are caused by the clustering of small aphthous lesions in one area. It has been shown that Behçet's intestinal ulcers tend to be seen as focal (middle or distal third of the esophagus and ileocecal region). We think that the herpetiform aphthae association may be related to this. Intestinal ulcers include 67% of localized single and 27% of localized multiple ulcers. Although we could not show this in our study, there may be a relation between herpetiform aphthae and multiple intestinal ulcers. Turkey is one of the countries in which Behçet's gastrointestinal involvement is seen the least frequently. Further researches should be done with a more comprehensive case series to show it precisely.[8]

Oculary involvement was reported to range from 29% to 100%.[5] It was shown that oculary involvement is higher in young male patients compared with females.[18] There were no significant differences between genders regarding ocular involvement. Nevertheless, we statistically showed that patients who had genital ulcer had ocular involvement less frequently, as it was mentioned in the literature by a couple of authors. Additionally, we found that ocular involvement was higher in frequency and severity in patients without systemic vasculitis. A study conducted by Hussein *et al.* showed that patients who do not have genital ulcers have ocular involvement more frequently and patients who do not have systemic vasculitis have ocular involvement more frequently, similar to our results. Suwa *et al.*[14] have reported that patients with ocular involvement have a lower rate of accompanying genital ulcer history during the disease. This interesting condition was called "reverse immunological targeting" by various authors. Hussein *et al.*[19] attributed this inverse relationship to the fact that pericytes that form the eye vessels are originated from the pericytes of the central nervous system embryologically.

The pathergy phenomenon is known as hyperreactivity or hyperirritability that is formed by minor trauma. All around the world, pathergy test positivity is included in most of the criteria which are used for diagnosing the disease. The rate of positivity differs by country. Positivity is seen most frequently in Turkey, Japan, and East Mediterranean countries which are located in Silkroad.[20] We detected a positive pathergy test in 49.9% of the patients. There was not any significant difference between both disease severity and organ involvement regarding pathergy results in a study about the comparison between pathergy positivity and disease severity and organ involvement.[21] It was detected that ocular involvement is higher in patients with positive pathergy test.[13] But it was not the same with our patients. Ocular involvement was seen less frequently in patients who have a positive pathergy test. We think that this can be explained by the "reverse immunological targeting" theory. There was not any significant difference between other organ involvements and pathergy test results.

It has been reported that neurological involvement is ranging between 5% and 15% in BD. Neurological involvement has been accepted as a poor prognostic factor, and higher incidence has been shown in male patients. In the literature, the most frequent symptom is a headache in patients with neurological involvement.[5,22] There was neurological involvement in 6.9% of our patients. Neurologic or gastrointestinal complaints such as headache, dizziness, abdominal pain, diarrhea, and constipation were not found to be related to neurological involvement disease or GIS involvement in our study. Interestingly, ocular involvement was higher in patients who had neurological complaints. This may be due to the embryological relation between eye and neurologic systems.

The limitations of the study are as follows: in some patients group such as herpetiform aphthae, we had a small number of patients. Further researches with a more comprehensive case series are needed to reveal any possible association. Also one of the most important limitations is that the study is retrospective.

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Conflicts of interest

There are no conflicts of interest.

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