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Whether Behçet's patients with large vessel involvement have concurrent small vessel involvement? A case-control Study

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Behçet's disease (BD) is a chronic multisystem disorder with the principal pathological finding of vasculitis, which may involve vessels of different sizes. The concurrence of small and large vessel involvement in BD patients is undetermined. The current study aims to evaluate small vessel involvement in BD patients with large vessel involvement. The study population comprised 35 BD patients with large vessel involvement (cases) and 35 BD patients without large vessel involvement (controls). Small vessel involvement was evaluated in all patients by capillaroscopy. Capillaroscopic findings were compared between the two groups. According to the capillaroscopic findings, all of our BD patients had small vessel involvement. The most prevalent abnormality was tortuosity (87.1%), followed by enlarged loops (58.6%) and avascular areas (51.4%). Capillaroscopy findings between the case and the control groups were not statistically different. There was a significant association between microbleeding and history of erythema nodosum (P-value = 0.015), tortuosity and a history of skin aphthosis (P-value = 0.015), architectural derangement and history of uveitis (P-Value = 0.029), the number of avascular areas and active oral aphthosis (P-value = 0.021), and architectural derangement and increased ESR (P-value = 0.011). There was no difference in nail fold folder involvement between BD patients with and without large vessel involvement; however, some capillaroscopic features were associated with some disease manifestations.

Keywords: Behçet's disease; Vascular involvement; Nail fold capillaroscopy; Vasculitis

Introduction

Behçet's disease (BD) is a chronic disorder characterized by multi-organ involvement [1]. Vasculitis is the principal pathologic finding in this disorder [2]. BD is classified as variable vessel vasculitis [3] and is characterized by oral and genital aphthosis as well as cutaneous, ophthalmic, central nervous system, gastrointestinal, articular, and vascular involvement [1].

Vascular involvement is one of the most important manifestations of Behçet's disease, which causes severe morbidity and mortality [4]. The prevalence of large vessel involvement in BD is 25% to 35% including superficial thrombophlebitis, deep vein thrombosis (DVT), cerebral venous thrombosis, aortic and peripheral artery aneurysms, pulmonary artery occlusion and aneurysm, coronary artery aneurysm, and abdominal veins thrombosis [5, 6]. Small vessel involvement occurs in 48% to 90% of BD patients [7, 8, 9, 10, 11]. Moreover, vasculitis and phlebitis, lymphocytic vasculitis, and leukocytoclastic vasculitis have been reported in 48%, 31%, and 17% of skin biopsies in BD patients, respectively [12]. There is no data about the concurrence of large and small vessels

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involvement in BD patients. The current study aims to evaluate the involvement of small vessels in BD patients who have large vessel involvement.

Materials and Methods

Enrolled in this study were 35 BD patients with vascular involvement (cases) and 35 BD patients without vascular involvement (controls), who were referred to the Behçet's Disease Clinic of Shariati Hospital in Tehran, Iran, from 2017 to 2018. All participants fulfilled the International Study Group criteria for BD. Diagnosis of vascular involvement in the case group was based on previous imaging findings, including the presence of superficial thrombophlebitis or deep vein thrombosis in duplex ultrasound, pulmonary embolism in CT angiography, cerebral venous thrombosis in MR venography, abdominal vein thrombosis in CT angiography, and arterial aneurysm in CT or MR angiography.

Demographic findings (including age, sex, and ethnicity), BD manifestations, BD activity according to Behçet's Disease Dynamic Activity Measurement (IBDDAM) criteria, The Behçet's Disease Current Activity Form (BDCAF) criteria and physician global assessment, Pathergy test, para clinical results (including CBC, ESR, CRP, HLAB5 and, HLAB51), and drug history at the time of capillaroscopy were recorded in all patients. Nailfoldcapillaroscopy was conducted by a video capillaroscope (Optilia, model op120021, *200 magnification, Sweden). Before the capillaroscopy, all patients rested for 15-20 minutes in an examination room with a temperature of 25 ℃. Patients consumed no tea or coffee for 4 to 6 hours before the capillaroscopy. Eight nails (2nd to 4th fingers) were evaluated in each patient, and 4 consecutive pictures were taken from the center of each nailfold except for those with a recent trauma. An expert rheumatologist who was blinded to the patients' conditions evaluated the nailfold capillaries in terms of capillary density, number of avascular areas, architectural derangement, micro-bleeding, enlarged loops, giant capillaries, and tortuosity of capillaries. All associations between capillaroscopic changes and demographic results, disease manifestation, disease activity, paraclinical tests, and drug history were evaluated.

Statistical Analysis

After assessing normality assumption using the Kolmogorov–Smirnov test, the continuous and categorical variables were described as mean ± SD and frequency (%), respectively. Chi-Square, Fisher Exact tests, the Monte Carlo Method, and Independent t-test were used to compare demographic characteristics, disease manifestation, drug consumption, and capillaroscopic findings in patients with and those without large vessel involvement. All statistical analyses were performed with SPSS software, version 17.0. A P value of < 0.05 was considered statistically significant.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (IRB 1398.397, 8/13/2019). All subjects were informed of the study's goal and methods and were enrolled after providing their written informed consent.

Results

Seventy patients were evaluated (35 cases and 35 controls). The mean age was 41.26 (SD = 14) years in the case group and 46.63 (SD = 9) years in the control group. There was no significant difference in age between cohorts (P-*value* = 0.062). Men comprised 71.4% of patients in the case group and 40% in the control group. In the case group, 34.4% were of Turk ethnicity, and 65.6% were of Fars ethnicity. In the control group, 22.9% and 77.1% of participants were of Turk and Fars ethnicity, respectively. Hypertension affected 5.7% of the patients in the case group and 2.9% in the control group. None of the patients in either the case or control group had diabetes, and 7% and 5% of patients in the case and control group, respectively, were smokers (Table 1). In this study, 69 patients (98.5%) had nonspecific changes in their nailfoldcapillaroscopy, and one patient had a scleroderma pattern. The most frequently noted abnormality was tortuosity of the capillaries (87.1%), followed by enlarged loops (58.6%) and avascular areas (51.4%) (Table 2). Although these abnormalities were more common in the case group, they did not differ between cohorts (P-value = 0.999, P-value = 0.467, and P-value = 0.056, respectively). Ramification,

Table 1: Demographic characteristics, disease manifestation, and drug consumption in the case and control groups

Characteristics		Total	Case group	Control group	*Pvalue*‡
Sex	Female (%)	31 (44.3%)	10 (28.6%)	21 (60%)	**0.008**
	Male (%)	39 (55.7%)	25 (71.4%)	14 (40%)	
Age (years)		43.94 ± 12	41.26 ± 9	46.63 ± 14	0.062
Hypertension (%)		3 (4.3%)	2 (5.7%)	1 (2.9%)	0.999
Smoking (%)		12 (17.1%)	7 (20%)	5 (14.3%)	0.526
Disease duration (years)		15 ± 9	13 ± 9	18 ± 8	**0.025**
Oral aphtosis (%)		69 (98.6%)	35 (100%)	34 (97.1%)	0.999
Genital aphtosis (%)		35 (50%)	19 (54.3%)	16 (45.7%)	0.473
Erythema nodusom (%)		17 (24.3%)	12 (34.3%)	5 (14.3%)	**0.051**
Pseudofoliculitis (%)		24 (34.3%)	16 (45.7%)	8 (22.9%)	**0.044**
Cutaneous aphtosis (%)		3 (4.3%)	3 (8.6%)	0 (0%)	0.239
Eye involvement (%)		35 (50%)	11 (31.4%)	24 (68.6%)	**0.002**
CNS involvement (%)		1 (1.4%)	1 (2.9%)	0 (0%)	0.999
Artricular involvement (%)		16 (22.9%)	8 (22.9%)	8 (22.9%)	0.999
Epididimitis (%)	Mild (%)	2 (2.9%)	2 (5.7%)	0 (0%)	0.493
	Moderate (%)	28 (40%)	14 (40%)	14 (40%)	
Physician global assessment					
	Severe ((%))	1 (1.4%)	1 (2.9%)	0 (0%)	0.421
	Inactive (%)	39 (55.7%)	18 (51.4%)	21 (60%)	
Immunosuppressants*(%)		20 (28.6%)	14 (40%)	6 (17.1%)	**0.034**
Corticosteroids (%)		35 (50%)	24 (68.6%)	11 (31.4%)	**0.002**

Categorical and continuous variables described as N (%) and mean ± SD, respectively.

*Immunosuppressive consumption includes cyclophosphamide, cyclosporine, and azathioprine.

‡P-values calculated based on Chi-Square, Fisher Exact tests, the Monte Carlo method, and the Independent t-test.

micro-bleeding, and giant capillaries were observed with the same frequency in the case and control groups. Bushy capillaries were not seen in the capillaroscopy of any of the patients in the case or control groups (Figures 1 and 2).

Discussion

Behçet's disease is a multi-systemic and chroniccondition [1]. Vasculitis is the main pathologic finding in this disorder [2]. Nailfold

Table 2: Capillaroscopic findings in the case and control groups

Capillaroscopic finding	Total	Case group	Control group	*P value*‡
Tortuosity (%)	61 (87.1%)	31 (88.5%)	30 (85.7%)	0.999
Enlarged loops (%)	41 (58.6%)	22 (62.9%)	19 (54.3%)	0.467
Avascular areas (%)	36 (51.4%)	22 (62.9%)	14 (40%)	0.056
Decreased capillary density (%)	31 (44.3%)	19 (54.3%)	12 (34.3%)	0.092
Architectural derangement (%)	16 (22.9%)	10 (28.5%)	6 (17.1%)	0.255
Ramification (%)	13 (18.6%)	7 (20.0%)	6 (17.1%)	0.759
Micro-bleeding (%)	9 (12.9%)	5 (14.3%)	4 (11.4%)	0.999
Giant capillaries (%)	5 (7.1%)	3 (8.6%)	2 (5.7%)	0.999

Categorical variables described as N (%). P-values calculated based on Chi-Square and Fisher Exact tests.

Figure 1. Tortuosity in a patient with BD

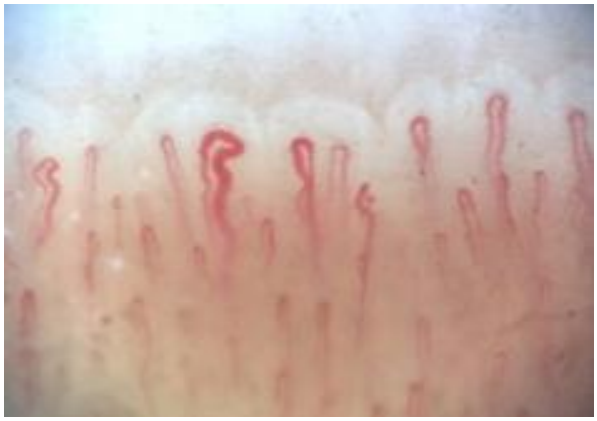

Figure 2. Avascular areas and decreased capillary density in patient with BD

capillar- oscopy is a noninvasive and accessible procedure for evaluating microvascular abnormalities have already been described in some rheumatologic conditions [13], including systemic lupus erythematosus, dermatomyositis, polymyositis, rheumatoid arthritis, primary Sjogren's syndrome, and familial Mediterranean fever [14, 15, 16]. Moreover, nailfold capillary abnormality is shown to be associated with stage, severity, and pulmonary hypertension in scleroderma [17]. Nailfold changes in capillaroscopy are also valuable for identifying patients in the early phase of connective tissue disorder [14, 15].

BD is characterized by variable vessel vasculitis [3]; as a result, nailfold abnormality can be expected. In this study, all BD patients (cases and controls) had abnormal capillaroscopic findings; however, small vessel involvement did not differ between cohorts. It seems that small vessel involvement is a unique finding in BD with any presentation, but some patterns may be more common in some unique manifestations. Tortuosity of capillaries, enlarged loops, and avascular areas were the most common nailfold findings in the capillaroscopy of the studied patients. Various morphological changes, such as megacapillaries, microaneurysms, and hemorrhages, have been reported in previous studies on BD patients [7, 8, 9, 10, 11]. Wechsler et al. reported 22 abnormal nailfold capillaroscopies among 30 evaluated patients. Decreased density of capillaries was not found in their study [7]. Vaiopoulos et al. reported abnormal capillaroscopic changes in most BD patients [8]. Movasat et al. reported abnormal capillaroscopies in 40% of patients, with enlarged loops and microhemorrhage being the most common findings [9]. Enlarged capillaries were reported as a shared finding in patients with BD in a study by Aytekin et al. [10]. Therefore, nailfold capillaroscopic changes seem to be a common presentation in BD patients. Although the frequency of avascular areas, enlarged loops, and tortuosity of capillaries were more common in BD patients with large vessel involvements compared with the others, the difference was not statistically significant. The present findings revealed a significant association between capillaroscopic changes and some BD manifestations during the disease course, including erythema nodosum, skin aphthosis, uveitis, and active mucosal aphthosis at the time of capillaroscopy. It seems that capillaroscopic changes correlate with some manifestations of Behçet's disease; however, Aytekin et al. did not find any association between capillaroscopic changes and dermatologic expressions [10]. Vaiopoulos et al., however, reported a significant correlation between abnormal capillary changes, skin manifestations, and arthritis/arthralgia [8]. Movasat et al. found a correlation between microhemorrhage and articular manifestations [9]. The current findings showed no association between capillaroscopic abnormality and systemic immunosuppressive drugs or corticosteroid usage. Similarly, Aytekin et al. found no correlation

between capillaroscopic alterations and systemic drug usage [10].

The present study is the first to compare nailfold capillaroscopic changes in Behcet's disease patients with vascular involvement and those with no vascular involvement. The first limitation of this study seems to be an inadequate sample size. Moreover, drug usage was not matched betweenthe two groups, which may affect the final results. Unspecific capillaroscopic changes seem to occur in nearly all patients with BD and are associated with some disease manifestations, including skin, ocular, and vascular involvement.

Although no specific pattern for capillaroscopic changes in Behçet's disease has been described to date, such changes may be used for diagnostic and prognostic purposes in the future.

Conclusion

All patients in the current study had small vessel involvement according to the capillaroscopic findings. We found no difference in nailfold capillary involvement between BD patients with and those without large vessel involvement.

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Conflict of interests

The authors declare that they have no conflict of interests.

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