Can nailfold capillaroscopy findings be a marker for uveitis in Behçet's syndrome?

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Abstract

Objective

To evaluate the differences between BS patients with uveitis and BS patients without uveitis and healthy controls in terms of nailfold capillaroscopic examination.

Methods

The study was performed on patients with a definite diagnosis of BS according to the International Criteria for Behçet's Disease, and healthy controls without BS. The participants were divided into three groups: BS patients with uveitis, BS patients without uveitis and healthy controls. All volunteers were examined by nailfold capillaroscopy for microvascular changes.

Results

A sample size of 90 participants, including 32 patients with BS with uveitis, 29 patients with BS without uveitis and 29 healthy controls, were included in our study. Fourteen (15.6%) BS patients with uveitis, 14 (15.6%) BS patients without uveitis and 16 (17.8%) healthy controls were female. In our study, we found microhaemorrhage occurrence to be significantly higher in BS patients with uveitis compared to the healthy control group (p=0.028). Although there was no significant difference compared to the BS without uveitis group, microhaemorrhage was approximately 2.5 times more common in the BS with uveitis group. The crossing medians were determined as 2.0 (0.8–3.3) in the BS with uveitis group, 1.3 (0.6–2.7) in the BS without uveitis group and 1.2 (0–3.2) in the healthy control group, showing a statistically significant difference across groups (p<0.001). In the post hoc crossing analysis, a significant difference was detected in the BS with uveitis group compared to the other two groups. A giant capillary was detected in one of the patients with uveitis, but no giant capillary was detected in the volunteers in the other groups.

Conclusion

Our findings show that microhemorrhage and crossing are associated with uveitis in BS patients.

Key words

Behçet's syndrome, uveitis, nailfold capillaroscopy

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Received on December 18, 2024; accepted in revised form on April 4, 2025.

Competing interests: none declared.

Introduction

Behçet's syndrome (BS) is classified as a systemic vasculitis involving the skin, mucosa, joints, eyes, arteries, veins, and nervous and gastrointestinal systems (1). Unlike other systemic vasculitis, BS may affect both arteries and veins of any size (2). BS is a multifactorial disease, with infectious, genetic, epigenetic and immunological factors contributing to its pathogenesis. Although HLA-B*51, located in the major histocompatibility complex class I region, is the strongest genetic susceptibility factor of BS, it accounts for less than 20% of the genetic risk for this syndrome (3). Since there are no specific laboratory tests to determine BS cases, the syndrome's diagnosis is based on clinical criteria; differential diagnosis with other inflammatory diseases may be difficult as well (4).

The uveal layer of the eye consists of a dense network of small vessels (5). Uveitis, one of the most important involvements of BS, is inflammation of the uveal layer (6). Ocular involvement is the most common vital organ involvement and has poor prognosis, potentially culminating in blindness, despite many advances in diagnosis and treatment (7). Young males are especially at risk of developing uveitis (8). In BS, ocular inflammation is the first symptom in 20% of cases and may involve the entire uveal tract. Uveitis may be categorised as anterior (11%), posterior (28.8%) or panuveitis (60.2%) (9). Posterior uveitis, a frequent and serious symptom of BS, refers to inflammation of the retina, choroid, retinal vessels and posterior vitreous (10). Ischemia, vascular occlusions, preretinal neovascularisation, microaneurysms, macroaneurysms and teleangiectasia may also be observed in posterior uveitis cases due to retinal vasculitis (11). The gold standard for diagnosis of Behçet's uveitis remains clinical examination based on ocular findings observed through slit-lamp evaluation, following Standardisation of Uveitis Nomenclature criteria. However, due to the subjectivity and limited sensitivity of Behçet's uveitis, objective diagnostic tools, including fundus fluorescein angiography (FFA) and retinal imaging techniques, have been proposed to complement clinical assessment, as they provide operator-independent assessments and generate quantitative data, making them valuable adjuncts, rather than replacements, for clinical evaluation (8).

Nailfold capillaroscopy (NFC) is a highly sensitive, inexpensive, simple, safe and non-invasive imaging technique used for in vivo morphological analysis of the nourishing capillaries in the nailfold region of fingernails (12). Capillaroscopic study is usually performed in patients with suspected microcirculatory problems, such as Raynaud's phenomenon, which is the main indication for NFC. Capillaroscopic findings based on microcirculation studies may provide helpful information in the areas of pathophysiology, differential diagnosis and treatment monitoring (13). Notably, clinically significant changes have already been found between complications related to systemic sclerosis and capillary changes in NFC (14). However, with regard to BS, several studies have analysed microcirculation with inconsistent results (15).

We suggest that inflammation in the uveal layer, which is rich in vascular structures, may be associated with capillary changes in the nailfold as well. In BS uveitis, similar to small vessel findings on FFA, peripheral capillary structures may be disrupted in NFC and may contribute to the diagnosis. The aim of this study was thus to evaluate the differences between the NFC findings of patients with BS with and without uveitis, considering that uveitis is a serious manifestation of small vessel involvement in BS cases.

Methods

The study was performed on patients with a definite diagnosis of BS according to the International Criteria for Behçet's Disease, and healthy controls without BS (16). The participants were divided into three groups: BS patients with uveitis, BS patients without uveitis and healthy controls. Before the study took place ethics committee approval was obtained and written informed consent was obtained from all participants. Participants aged 18–65 years were included in the study. Patients

with another inflammatory rheumatic disease, who had professions requiring intensive use of the hands (farming, tailoring, etc.), pregnant women and breastfeeding women were excluded. In addition, BS patients with a history of anterior uveitis only were not included in the study.

The participants were retrospectively screened for a history of oral aphthae, genital ulcers, skin presentations, uveitis, central nervous system involvement, joint involvement and vascular involvement. Age, gender, smoking, body mass index (BMI) and systemic chronic diseases other than BS were recorded, as were the medications, sedimentation and CRP values of the patients with BS. Disease activity of the patients with BS was also determined using the Behçet's Disease Current Activity Form. Patients with a history of uveitis were evaluated for uveitis activity by an ophthalmologist on the same day.

NFC was performed with a capillaroscopy device (Dino-Lite Pro Capillary Scope 200 Digital Microscope, Taiwan) with a × 00 magnification lens. The NFC applications were performed by the same operator. The images obtained were independently evaluated by two rheumatologists; as there were no obvious differences of opinion, a third assessor was not required. The images were recorded and evaluated with Dino Capture 2.0 software. Each patient was kept in the examination room at a temperature of 20–24°C for at least 15 minutes before analysis. Immersion oil was carefully dripped into the nailfold to improve image quality. Patients with fingers affected by recent acute local trauma were excluded. The second to fifth fingers of both hands were examined. The number of capillaries was determined by counting consecutive distal capillaries at a distance of 1 mm. Capillary diameter between >20 μm and <50 μm was considered indicative of a dilated capillary, while that which was >50 μm was considered indicative of a giant capillary.

The capillary patterns described by Cutolo *et al*. (17) used to conduct a qualitative analysis. Distal haemosiderin deposits were defined as microhaemorrhages; tortuosity was defined as tortuous capillaries without crossing; and branched, bizarre, bushy, irregular or branched capillaries were indicative of neoangiogenesis. The presence of aneurysm and subpapillary plexus visibility were also evaluated.

Statistical analysis

The minimum sample size required to find a significant difference while using the test was 29 participants per group, totalling 87 participants. The type error (alpha) was 0.05, the power of the test (1-beta) was 0.8 and the effect size was 0.86 (18).

Data were statistically analysed using SPSS 17.0 (Statistical Program for the Social Sciences). Quantitative data were given as mean ± standard deviation or median (minimum-maximum), while qualitative data were recorded as numbers and percentages. Normal distribution of the data was investigated with the Kolmogorov-Smirnov normality test. Chi-square analysis was used to compare the groups' categorical data. ANOVA was used to compare numerical data showing normal distribution, while the Mann-Whitney U-test and Kruskall-Wallis analysis were used to compare numerical data without normal distribution. p-values <0.05 were accepted as statistically significant.

Results

A sample size of 90 participants, including 32 patients with BS with uveitis, 29 patients with BS without uveitis and 29 healthy controls, were included in our study. Fourteen (15.6%) BS patients with uveitis, 14 (15.6%) BS patients without uveitis and 16 (17.8%) healthy controls were female. The median ages were 46 (23–64) in the BS with uveitis group, 40 (20–58) in the BS without uveitis group and 40 (22–50) in the healthy control group. There was no significant difference in disease activity scores between the BS patient groups. Only one of the patients in the uveitis group had active uveitis findings. Among BS patients with uveitis, 23 (71.9%) had panuveitis and 9 (28.1%) had posterior uveitis. None of the patients had only anterior uveitis. Table I presents the BMI, comorbidities that may be associated with vasculopathy, smoking, BS treatment and disease activity status of the patients and healthy controls. There was no difference between the groups in terms of BS presentation other than uveitis. Table II outlines the clinical presentations of the patients with BS.

Capillary density per NFC was 9.7±0.1 in the BS with uveitis group, 9.3±0.6 in the BS without uveitis group and 9.84±0.89 in the healthy control group, and was found to be statistically similar across groups. The most common nonspecific anomalies were tortuosity in 68 participants (75.5%) and dilated capillaries in 64 participants (71.1%). Microhaemorrhage was detected in 9 (10%) BS patients with uveitis, 4 (4.4%) BS patients without uveitis and 1 (1.1%) healthy control, indicating a significant difference across results. Post-hoc analysis of microhaemorrhage cases revealed a significant difference between BS patients with uveitis and healthy controls. Dilated capillaries, aneurysms, neoangiogenesis, tortuosity and abnormally shaped capillaries were detected more commonly in the BS with uveitis group but were not statistically significant. A giant capillary was detected in one of the BS patients with uveitis, but no giant capillaries were detected in the other groups. No avascular area was detected in any of the participants. The crossing medians were determined as 2.0 (0.8–3.3) in the BS with uveitis group, 1.3 (0.6–2.7) in the BS without uveitis group and 1.2 (0–3.2) in the healthy control group, showing a statistically significant difference across groups. In the post hoc crossing analysis, a significant difference was detected in the BS with uveitis group compared to the other two groups. No significant difference was observed between the BS without uveitis group and the healthy control group. Table III summarises the participants' capillaroscopic findings.

Discussion

In this study, we investigated whether nailfold capillaroscopic findings are associated with the presence of uveitis in BS cases. Microhaemorrhage incidence was found to be significantly higher in BS patients with uveitis compared to

Table I. Descriptive characteristics of patients.

Characteristic		BS (with uveitis)	BS (without uveitis)	Healthy controls	χ^2	*p*-value
Age, years; median (min-max)		46 (23-64)	40 (20-58)	40 (22-50)	-	0.072 [a]
Sex, n (%)	Female	14 (15.6)	14 (15.6)	16 (17.8)	0.801	0.670 [b]
	Male	18 (20.0)	15 (16.7)	13 (14.4)		
Body mass index, kg/m^2 median (min-max)		25.9 (17.5-38.0)	26.4 (18.3-36.1)	24.0 (17.3-35.4)	–	0.201 [a]
Comorbidity, n (%)	Yes	7 (7.8)	5 (5.6)	3 (3.3)	1.466	0.480 [b]
	No	25 (27.8)	24 (26.7)	26 (28.9)		
Smoking status, n (%)	Yes	13 (14.4)	7 (7.8)	9 (10.0)	1.921	0.383 [b]
	No	19 (21.1)	22 (24.4)	20 (22.2)		
BS treatment, n (%)	Colchicine	21 (34.4)	25 (41.0)	–	3.475	0.062 [b]
	Steroid	13 (21.3)	11 (18.0)	–	0.046	0.830 [b]
	Azathioprine	14 (23.0)	12 (19.7)	–	0.035	0.852 [b]
	Cyclosporine	6 (9.8)	0 (0)	–	6.031	0.014 [b]
	Anti-TNF	5 (8.2)	4 (6.6)	–	0.041	0.840 [b]
					Z	*p*-value
BSDA median (min-max)		1 (0-7)	3 (0-5)	–	-1,649	0,099[c]

BS: Behçet's syndrome; BSDA: Behçet Syndrome Disease Activity; [a] Kruskal-Wallis test; [b] χ^2 test; [c] Mann-Whitney U-test.

Table II. Clinical presentation of the patients.

Characteristic		BS (with uveitis) n (%)	BS (without uveitis) n (%)	χ^2	*p*-value
Oral ulcers	Yes	32 (52.5)	29 (47.5)	–	1.000
	No	0 (0)	0 (0)		
Genital ulcers	Yes	27 (42.6)	26 (44.3)	0.372	0.542
	No	5 (8.2)	3 (4.9)		
Cutaneous manifestations	Yes	23 (37.7)	25 (41.0)	1.863	0.172
	No	9 (14.8)	4 (6.6)		
Vascular manifestations	Thrombosis	6 (9.8)	5 (8.2)	3.484	0.175
	Aneurysm	0 (0)	3 (4.9)		
Neurological manifestations	Vascular	2 (3.3)	3 (4.9)	2.726	0.256
	Parenchymal	0 (0)	2 (3.3)		
Arthritis	Yes	3 (4.9)	2 (3.3)	0.124	0.725
	No	29 (47.5)	27 (44.3)		

BS: Behçet's syndrome.

healthy controls. However, there was no significant difference between the BS with uveitis and BS without uveitis groups. Crossing was significantly higher in BS patients with uveitis as well, compared to BS patients without uveitis and healthy controls. Among the patients included in this study, only one from the BS with uveitis group had NFC findings with an early scleroderma pattern. However, uveitis was not active in this patient. No significant difference was found across groups in terms of enlarged capillary, aneurysm, neoangiogenesis, tortuosity and abnormally shaped capillary incidence.

Capillaroscopic examination is an accepted method used for the differential diagnosis of Raynaud's phenomenon and the early diagnosis of systemic sclerosis (14). In addition, abnormal capillaroscopic findings have been reported in other connective tissue diseases, including systemic lupus erythematosus, Sjögren's syndrome and mixed connective tissue disease (19-21). One study reported that scleroderma pattern is more frequent in some connective tissue diseases compared to healthy controls (21). In vasculitis group diseases, such as Wegener's disease, Takayasu's arteritis and Henoch-Schönlein purpura, capillaroscopy studies have also reported abnormal capillaroscopic findings (22-24).

BS, itself a vasculitis group disease, boasts few NFC-based studies in the literature. These studies feature general capillaroscopic evaluation of BS patients or BS patients with vascular involvement (15, 25-28). However, we did not find any NFC study evaluating the occurrence of Behçet's uveitis one-to-one.

In a study using ultrawide-field FFA in patients with Behçet's uveitis, fluorescein leakage from retinal capillaries was found in 84.8% of patients and peripheral capillary non-perfusion in 66.7%, even in the absence of significant visual loss or fundus abnormalities (29). Furthermore, a meta-analysis comparing OCT-A findings in patients with BS and healthy subjects showed that parafoveal capillary density was significantly reduced and the foveal avascular zone was significantly enlarged in patients with BS (30). Similar to these changes in BS uveitis, changes in NFC may be a sign of capillary involvement of BS.

In a study of 128 BS patients, enlarged capillary (26%) was reported as the most common abnormal finding. However, tortuosity rates were not given (26). In one of two more recent studies, the most common findings were found to be dilated capillaries (45.2%)

Table III. Capillaroscopic examination findings of volunteers.

Characteristic	BS (with uveitis)	BS (without uveitis)	Healthy controls	F	*p*-value
Capillary density, mean ± SD	9.7 ± 0.1	9.3 ± 0.6	9.8 ± 0.8	3.084	0.051
				χ^2	*p*-value
Enlarged/dilated capillaries, n (%)	26 (28.9)	22 (24.4)	16 (17.8)	5.506	0.064
Microhaemorrhage, n (%)	9 (10.0)[a]	4 (4.4)[a,b]	1 (1.1)[b]	7.154	0.028
Aneurysm, n (%)	5 (5.6)	1 (1.1)	2 (2.2)	2.995	0.224
Neoangiogenesis, n (%)	17 (19.5)	9 (10.3)	11 (12.6)	2.525	0.283
Capillary tortuosity, n (%)	26 (28.9)	22 (24.4)	20 (22.2)	1.245	0.537
Subpapillary plexus, n (%)	14 (15.6)	10 (11.1)	15 (16.7)	1.759	0.415
Abnormal shapes, n (%)	11 (12.2)	8 (8.9)	7 (7.8)	0.811	0.667
Crossing, n (%)	2.0 (0.8-3.3) [a]	1.3 (0.6-2.7) [b]	1.2 (0-3.2) [b]	-	<0.001

BS: Behçet's syndrome. The letters [a] and [b] indicate the difference between the groups.

and tortuosity (31%). In contrast, the number of patients with dilated capillaries was relatively low (7.7%) in the other study. Neither of these studies included a healthy control group (15, 27). In our study, the most common findings in both BS groups and the healthy control group, at no significant difference, were dilated capillaries and tortuosity. In one study with a healthy control group, the number of dilated capillaries was found to be significantly higher in patients with BS. However, younger participants were included in this study compared to ours (25). Demographic factors, including age and gender, may affect capillaroscopic findings (31).

One study in which patients with BS were evaluated via ocular videocapillaroscopy, reported a high percentage of microaneurysms (32). However, no evaluation of aneurysm occurrence has been reported in NFC studies, nor has the presence of abnormally shaped capillaries. Subpapillary plexus visibility was reported as 0% in one study conducted in Egypt (33). In our study, however, subpapillary plexus visibility was a common finding, occurring in 43.3% of all participants. We argue that the reason for these very different results may be related to ethnicity. In general, however, there was no statistically significant relationship between Behçet's uveitis and microaneurysm, neoangiogenesis, subpapillary plexus visibility or the presence of an abnormally shaped capillary in our study.

Microhaemorrhage is one of the basic parameters in the evaluation of NFC. Notably, BS may cause intraretinal haemorrhages (34). Microhaemorrhage is one of the parameters frequently reported in NFC studies performed on patients with BS (15, 25-27). In two previous studies, microhaemorrhage was reported to be significantly higher in patients with BS compared with healthy controls (25, 33). However, there was no control group in other studies that assessed microhaemorrhage (26, 27). In our study, we found microhaemorrhage occurrence to be significantly higher in BS patients with uveitis compared to the healthy control group (p=0.028). Although there was no significant difference compared to the BS without uveitis group, microhaemorrhage was approximately 2.5 times more common in the BS with uveitis group. The lack of significant difference may be due to the patients' uveitis being inactive. The presence of microhemorrhage may be an indicator of the presence or risk of Behçet's uveitis. Accordingly, we argue that more care should be taken to assess uveitis in those with microhaemorrhage.

Crossing is one of the changes considered a non-specific variation in NFC. The frequency of crossing has been reported to increase in patients with diabetic retinopathy in whom vasculopathy plays an important role (35). In our study, crossing was significantly higher in the BS with uveitis group (p<0.001). According to these results, we believe that patients with BS who have intense crossing NFC findings should be carefully evaluated for uveitis.

The strength of our study lies in that it is the first to evaluate the capillaroscopic features of patients with Behçet's uveitis. Another strength is the presence of a healthy control group. The most important limitations of our study, however, are that the patients in the BS with uveitis group had inactive uveitis, and the cross-sectional structure of the study. Considering these limitations, it would not be correct to draw conclusions about causality from this study alone.

Prospective studies can provide more robust and meaningful results by evaluating BS patients and controls with intermittent capillaroscopy, then following up with patients with worsening capillaroscopy findings to monitor the development of uveitis or major organ involvement. This may help establish clearer connections between BS and uveitis concurrence. Another limitation is the lack of a control group consisting of BS patients with vascular involvement without uveitis.

In conclusion, NFC is an easily accessible, non-invasive imaging technique to identify the nailfold capillaroscopic changes common in BS cases. Our NFC findings show that microhaemorrhage and crossing are associated with uveitis in BS patients, though only one patient's NFC results fit the early scleroderma pattern. Prospective studies that include BS patients with active uveitis are needed to confirm our results.

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