Nailfold videocapillaroscopy abnormalities and vascular manifestations in Behçet's syndrome

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Abstract

Objective

To evaluate microcirculation abnormalities and their clinical association in patients with BS, especially with vascular manifestations.

Methods

A cross-sectional study was carried out using nailfold videocapillaroscopy (NVC) to evaluate the microcirculation in patients with BS.

Results

A total of 65 patients were included in the study. Thirty-four (52.3%) were men, and 84.6% were European Caucasian. Vascular involvement was present in 24 (36.9%) patients. Qualitative abnormalities in NVC were observed in 47.7% of patients. The most frequent were tortuous and branched capillaries (21.5%), followed by microhaemorrhage (12.3%), enlarged capillary (7.7%) and giant capillary (3.1%). We found a significant relationship between the presence of tortuous and branched capillaries and previous superficial thrombophlebitis (ST) (p=0.025). The presence of ≥2 qualitative abnormalities in NVC was associated with vascular involvement (p=0.031), mainly with venous thrombotic events (p=0.024) and particularly with ST (p=0.003). No specific Cutolo's pattern was observed. No association was observed between NVC and Raynaud's phenomenon or ANA, although patients with positive ANA presented more frequent non-specific capillaroscopic abnormalities (p=0.003).

Conclusion

The presence of ≥2 qualitative abnormalities in NVC is associated with Vasculo-Behçet. NVC might be a potential tool for early detection of patients at risk of vascular events.

Key words

Behçet's syndrome, nailfold videocapillaroscopy, microvascular abnormalities, vascular involvement

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Introduction

Behçet's syndrome (BS) is a systemic inflammatory disease, characterised by recurrent flares of oral and genital ulcers, although the disease can involve the skin, joints, eyes, and vascular, nervous and gastrointestinal systems. First described in 1937, by Hulusi Behçet (1), BS is classified as a variable vessel inflammatory vasculitis (2). The absence of a known specific antibody and a course of self-limited and recurrent flares without a trigger, has raised over the last years the hypothesis that it could actually be a polygenic autoinflammatory disease (3).

BS has a characteristic geographic distribution, with a high prevalence along the ancient silk route, between latitudes 30º and 45º North (4). The estimated global prevalence of BS is 10.3 cases per 100,000 habitants (5), although rates of up to 60 cases per 10,000 habitants have been described (6, 7). Environmental factors are hypothesised to act as triggers in genetic predisposed people. The most strongly correlated genetic factor is the presence of HLA-B*51, although association with other HLA subtypes and single nucleotide mutations has been observed (8-11).

Initial symptoms usually appear in the third or fourth decade of life. Familial aggregation of BS has been reported in 1-18% of patients, with earlier ages of onset (12). Although more symptomatic forms predominate in men, there is a women predominance in BS (4). Orogenital ulcers are the main manifestation, followed by cutaneous and ophthalmological involvement (12-14).

Vascular involvement has been described in up to 40% of patients with BS (15). The rupture of arterial aneurysms and thrombotic events are the main cause of mortality (16). Vascular involvement is more frequent in young men at the disease onset, and recurrence is common despite immunosuppressive treatment (16-18). Venous involvement predominates (3:1) over arterial (19). Superficial venous thrombosis (ST) and deep venous thrombosis (DVT) are the most frequent vascular manifestations (20-22). Arterial manifestations are rare (3-5% of patients) (4), being aneurysms in the pulmonary arterial system the main manifestation. Less frequent are aneurysms in other arterial territories, and cardiac involvement (19).

Diagnosis of BS can be challenging due to the absence of a specific serological marker, and relay on clinical criteria after ruling out other similar diseases. The most commonly used criteria are the Criteria for diagnosis of Behçet's disease (ISGBD) from 1990 (23), and the International Criteria for Behçet's Disease (ICBD) from 2014 (24), useful for diagnosis and classification. Nevertheless, new tools are needed to improve diagnostic approach to BS and to differentiate clinical phenotypes of the disease.

Nailfold videocapillaroscopy (NVC) is a non-invasive method for evaluating microvascular abnormalities in the nail fold. It is mandatory in the study of Raynaud's phenomenon and in the evaluation of patients with systemic sclerosis (25-27). However, the role of NVC in systemic vasculitis has been not elucidated (28). Recently, NVC has been described as a useful tool for assessing the disease activity and treatment response in ANCA associated vasculitis (29). Regarding BS, few studies have analysed microcirculation with inconsistent results.

The aim of the present study was to investigate NVC abnormalities in patients with BS and to evaluate possible relationships between NVC findings and clinical features, especially with vascular manifestations.

Patients and methods

NVC was performed in a cohort of patients with BS from a national referral centre in Barcelona that fulfilled the ICBD of 2014 (24), with other diseases having been ruled out. Local Ethics Committee approved the study, and all patients gave written informed consent. Demographic and clinical data were retrospectively collected from medical records. Cardiovascular, gastrointestinal, and neurological involvement was confirmed by imaging tests, and when possible, by histology. The presence of Raynaud's phenomenon was also investigated. All patients were examined by an ophthalmologist at diagnosis of the disease and during the follow-up.

HLA-B*51 and anti-nuclear antibody (ANA) titres were also recorded. ANA was considered positive if >1/80.

Nailfold videocapillaroscopy

NVC was performed using an Optilia Digital Videocapillaroscope (Optilia Instruments AB, Sollentuna, Sweden), with a 200x magnification lens and a LED lamp by the same operator who was blinded to clinical patient's conditions. Patients were acclimated for at least 20 minutes at room temperature of 20-24°C before the examination. NVC was made with an immersion oil dropper and contact adapter and the second to fifth fingers of both hands were examined. Optipix Lite software (Optilia Instruments AB) was used for the visualisation of 1-mm-wide consecutive images of first-line capillaries.

Qualitative NVC was carried out according to the following definitions: capillary loss, defined as the existence of avascular areas; enlarged capillary, when there was an increase in capillary diameter >20 μm; giant capillary, when a capillary dilation >50 μm was present; microhaemorrhage, when distal haemosiderin deposits were observed; tortuous capillaries, when curled capillaries without a cross were present; and neoangiogenesis, when branched, bizarre, bushy, disorganised, or arborised capillaries were observed. For qualitative analysis we used the capillary patterns described by Cutolo *et al*. (normal, early, active and late) (30), that are correlated with microangiopathy in scleroderma (31).

Statistical analysis

Qualitative variables were expressed as a proportion, while continuous variables were expressed as mean and standard deviation if they presented a normal distribution or as median and interquartile range otherwise. For the analysis of the categorical variables, the Fisher's exact or Chi-square test was used. Confidence intervals of 95% were calculated. Statistical analysis was performed using SPSS Statistics 28.0.1.1 (Inc., Chicago, USA). *p*-value <0.05 were considered statistically significant.

Results

Sixty-five patients with BS were included in the study. The mean age at diagnostic was 30.37 years, while the mean age at the study entry was 45.25 (SD ± 14.01) years. There were 34 (52.3%) men and 31 (47.7%) women. A total of 55 (84.6%) patients were European Caucasian, 7 (10.8%) North African, 2 (3.1%) Asian, and 1 (1.5%) Hispanic. Cardiovascular risk factors were present in 15 (23.1%) patients. Only 3 (4.6%) had diabetes mellitus. One patient had a family history of BS. The baseline demographic characteristics are shown in Table I.

Table I. Demographic characteristics of patients with BS.

Age at diagnosis, years	30.37 (±10.05)
Delay in diagnosis, years	2.73 (±4.85)
Age at inclusion	45.25 (±14.01)
Sex	
Men	34 (52.3%)
Women	31 (47.7%)
Ethnicity	
Caucasian	55 (84.6%)
North African	7 (10.8%)
Asian	2 (3.1%)
Latin	1 (1.5%)
Cardiovascular risk factors	15 (23.1%)
Arterial hypertension	10 (15.4%)
Diabetes mellitus	3 (4.6%)
Dyslipidaemia	10 (15.4%)
Smoking	
Never	38 (59.3%)
Former smoker	12 (18.8%)
Active smoker	14 (21.9%)
Family history	
BS	1 (1.5%)
Systemic autoimmune disease related to connective tissue	4 (6.2%)

Quantitative variables are presented in mean and standard deviation.

Clinical and immunological characteristics

Sixty-four (98.5%) patients had history of mucosal ulcers and 45 (69.2%) of oral and genital ulcers. Up to 81.5% of the subjects had presented skin manifestations. Previous ophthalmologic, gastrointestinal, and neurologic manifestations were present in 41.5%, 12.3%, and 27.7% of patients, respectively. Additionally, up to 29.2% of the patients presented infrequent manifestations related to BS (recurrent orchitis, pericarditis, mononeuritis and IgA nephropathy). Table II summarises the main clinical manifestations of our cohort.

Regarding vascular manifestations, 24 (36.9%) patients had a previous history of vascular involvement. ST was present in 13 (20%) patients and DVT in the extremities in 9 (13.8%), being the most frequent vascular manifestations. Less prevalent were aneurysms of the pulmonary arterial system and large vessel vasculitis, present in 2 (3.1%) patients in both cases.

Up to 35 (53.8%) of patients showed positive ANA at some point during follow-up, and 8 (12.3%) patients presented Raynaud's phenomenon.

Table II. Prevalence of clinical manifestations of patients with BS.

Clinical manifestations	n (%)
Mucocutaneous ulcers	64 (98.5%)
Oral ulcers	19 (29.2%)
Oral and genital ulcers	45 (69.2%)
Ulcers in other locations	10 (15.4%)
Cutaneous manifestations	53 (81.5%)
Erythema nodosum	29 (44.6%)
Pseudofolliculitis	43 (66.2%)
Cutaneous vasculitis	4 (6.2%)
Ophthalmologic manifestations	27 (41.5%)
Anterior uveitis	14 (21.5%)
Posterior uveitis	7 (10.8%)
Panuveitis	12 (18.5%)
Retinal vasculitis	11 (16.9%)
Articular manifestations	44 (67.7%)
Monoarthritis	16 (24.6%)
Oligoarthritis	10 (15.4%)
Polyarthritis	5 (7.7%)
Arthralgia	31 (47.7%)
Neurological manifestations	18 (27.7%)
Aseptic meningoencephalitis	5 (7.7%)
Demyelinating lesion	8 (12.3%)
Intracranial hypertension	4 (6.2%)
VST	3 (4.6%)
Vascular manifestations	24 (36.9%)
ST	13 (20%)
DVT in extremities	9 (13.8%)
DVT in other locations[¶]	7 (10.8%)
PE	5 (7.7%)
Pulmonary artery aneurysms	2 (3.1%)
Large vessel vasculitis	2 (3.1%)
Digestive manifestations	8 (12.3%)
Oesophageal involvement	1 (1.5%)
Small intestine involvement	6 (9.2%)
Colon involvement	5 (7.7%)
HLA-B*51	32 (49.2%)

[¶]Deep vein thrombosis in any location except extremities and PE (including central venous sinus thrombosis).
DVT: deep vein thrombosis; PE: pulmonary embolism; ST: superficial thrombophlebitis; VST: venous sinus thrombosis.

Association between NVC findings and BS manifestations

A total of 31 (47.7%) patients presented at least one qualitative abnormality in the microcirculation and 10 (15.4%)

Table III. Prevalence of qualitative abnormalities and patterns of Cutolo in NVC of patients with BS.

Abnormalities in NVC	
At least 1 abnormality	31 (47.7%)
≥2 abnormalities	10 (15.4%)
Qualitative abnormalities	
Enlarged capillary	5 (7.7%)
Giant capillary	2 (3.1%)
Microhaemorrhage	8 (12.3%)
Tortuous capillary	14 (21.5%)
Branched capillary	14 (21.5%)
Capillary disorganisation	0
Capillary loss	0
Pattern	
Normal	51 (78.5%)
Unspecific NVC pattern	14 (21.5%)

Table IV. Association between vascular manifestations and ≥2 abnormalities in the NVC.

Vascular manifestations	≥2 abnormalities in NVC		*p*
	Yes (n=10)	No (n=55)	
Thrombotic event (arterial o venous)	7 (70%)	15 (27.3%)	0.024
Venous thrombotic event	7 (70%)	14 (25.4%)	0.01
ST	6 (60%)	7 (12.7%)	0.003
DVT in extremities	2 (20%)	7 (12.7%)	0.61
PE	0	5 (9%)	
Venous thrombosis in other locations[¶]	2 (20%)	5 (9%)	0.29
Pulmonary aneurysm	0	2 (3.6%)	
Vasculitis without thrombosis	0	2 (3.6%)	

[¶]DVT in any location other than extremities and PE (including venous sinus thrombosis).
DVT: deep vein thrombosis; PE: pulmonary embolism; ST: superficial thrombophlebitis.

subjects presented ≥2 abnormalities. The most prevalent abnormalities observed were tortuous and branched capillaries, present in 14 (21.5%) patients each one. It should be noticed that only 4 (28.6%) patients presented both abnormalities concomitantly. Microhaemorrhages were observed in 8 patients and giant capillaries in 2. Capillary loss was not observed. No association between non-specific NVC abnormalities and Raynaud's phenomenon was found. No patient met criteria for other systemic autoimmune disease. A total of 14 (21.5%) patients presented an unspecific altered pattern, characterised by the presence of tortuous capillaries, neoangiogenesis and/or microhaemorrhage, without capillary loss and enlarged capillary. The remaining 51 (78.5%) patients had a normal NVC pattern. We did not observe any of the capillaroscopic patterns described by Cutolo *et al*. Qualitative abnormalities present in NVC are summarized in Table III.

No statistical relationships between microcirculation abnormalities observed in NVC and demographic characteristics of patients were found.

When we analysed possible relationships between clinical manifestations and non-specific NVC abnormalities, we only found a statistical relationship between vascular manifestations and the presence of ≥2 qualitative abnormalities in NVC (OR de 5.21, IC 95%: 1.2 – 22.64, p=0.031).

Analysis of vascular manifestations revealed a significant association between the presence of ≥2 abnormalities in NVC and thrombotic events (OR 6.22, IC 95%: 1.42–27.25, p=0.024), especially with venous thrombosis (OR 6.83, IC 95%: 1.55–30.08, p=0.01), as summarised in Table IV. The most significant association was found between ST and the presence of ≥2 qualitative abnormalities in NVC (OR 10.28, IC 95%: 2.31–45.87, p=0.003).

Analysis of non-specific qualitative NVC abnormalities revealed a significant association between branched and tortuosity capillary and ST (OR 4.71, IC 95%: 1.25–17.74, p=0.025, both). No other associations between different qualitative anomalies observed in NVC and vascular features were found.

We did not observe correlation between Raynaud's phenomenon and qualitative abnormalities in NVC. Similarly, we did not found association between positive titres of ANA and the presence of ≥2 non-specific qualitative abnormalities or altered pattern, although patients with BS and some morphological abnormality in the microcirculation presented more frequently positive ANA (OR 5.03, IC 95%: 1.72–14.7, p=0.003). Finally, we did not observe an association between Raynaud's phenomenon and positive ANA.

Discussion

BS is a chronic multisystemic disease with variable vessel vasculitis, which affects arteries, veins and/or capillaries of different organs. NVC is a non-invasive technique that enables to study the nail fold microcirculation. NVC findings have been correlated with diagnosis and evolution of microangiopathy in scleroderma (31), but microcirculation abnormalities are present in other rheumatic or systemic autoimmune diseases (32–35).

In our study, we observed that 31 (47.7%) patients had at least one non-specific qualitative abnormality in NVC, and up to 10 (15.4%) patients had concomitantly ≥2 non-specific qualitative anomalies. The most prevalent non-specific anomalies observed were tortuous and branched capillaries, present in 14 (21.5%) patients in both cases. However, both findings were only present in 28.6% of patients simultaneously. We also observed haemorrhages (12.3%), capillary loop dilation (7.7%), and giant capillary (3.1%). No capillary loss was observed in any patient. We found a significant association between the presence of tortuous and branched capillaries in NVC and superficial thrombosis and no association between non-specific NVC abnormalities and baseline demographic characteristics or cardiovascular risk factors.

When we analysed possible relationships between the presence of ≥2 non-specific qualitative abnormalities in NVC and clinical manifestations of the disease, we only found a significant association with vascular manifestations. Indeed, the presence of ≥2 non-specific qualitative anomalies in NVC was significantly associated with thrombotic events (arterial or venous), especially with venous thrombosis. Regarding the different vascular symptoms, only ST was associated with the simultaneous presence of ≥2 non-specific abnormalities in NVC. Finally, we did not observe

any of the capillaroscopic patterns described by Cutolo *et al*., and a non-specific NVC pattern was present in 14 (21.5%) patients.

Additionally, we reported 8 (12.3%) patients with Raynaud's phenomenon. We did not find association between Raynaud's phenomenon and NVC abnormalities. Thirty-five (53.8%) patients showed positive ANA. ANA were more frequent in patients with at least one qualitative non-specific abnormality in NVC. However, the presence of ANA was not associated with any qualitative anomaly or specific pattern in NVC, or the presence of Raynaud's phenomenon. No association between the presence of ANA and the simultaneously presence of ≥2 non-specific qualitative abnormalities in NVC was found.

To date, few studies have analysed nail fold anomalies in BS, with heterogeneous results. Wechsler *et al*. (36) were the first to assess microcirculation in patients with BS, describing frequent abnormalities on capillaroscopy, that have been later reported in subsequent studies with rates ranging from 40-75% (37, 38). In addition, anomalies of the microcirculation have also been described in oral mucosa and retina (39-41). These data confirm that abnormalities of the microcirculation in NVC are more frequent in patients with BS than in general population, detected in 10-34% of healthy subjects (27, 42). Nonetheless, our data differ from most recent studies that used similar morphological criteria, and found that capillary dilations and microhaemorrhages were predominant (38, 43, 44). We also observed less frequently haemorrhages, capillary loop dilation, and giant capillary than previously reported, and we did not observe capillary loss, in contrast to previous studies (36-38, 40, 43).

In the largest study with NVC and BS, Movasat *et al*. (38) described association between enlarged capillaries in NVC and an earlier onset of the disease and hypertension, and between haemorrhages and joint involvement, in contrast to our data, which did not observe an association between non-specific NVC abnormalities and baseline demographic characteristics or cardiovascular risk factors. They also found a correlation between superficial thrombosis and giant capillaries in NVC, which was not observed in our study that correlated with the presence of tortuous and branched capillaries.

As for Raynaud's phenomenon, only Movasat *et al*. and del Peral-Fanjul *et al*. reported prevalences of 7% and 23.8%, respectively (38, 44). The remaining studies did not mention the presence of Raynaud's phenomenon (36, 37, 40, 43). These rates are similar to those observed in our cohort. Likewise, both studies have not reported association between Raynaud's phenomenon and non-specific NVC abnormalities. Furthermore, no previous capillaroscopy study in BS evaluated the presence of ANA. We reported a prevalence of 53.8%, which was more frequent in patients with at least one qualitative abnormality in NVC, but without any other correlation.

The present study has some limitations. First, most patients were white, mainly European Caucasians, so it remains unknown whether our findings are applicable to other ethnicities. Second, the study was conducted on a small number of patients from a single tertiary centre and there may be a bias. Thus, more studies are needed to confirm these results. Finally, this was a cross-sectional study, so we could not evaluate if observed anomalies of the microcirculation were present at diagnosis or appeared during the disease evolution.

In conclusion, non-specific abnormalities of microcirculation are common in patients with BS. No specific NVC Cutolo's pattern is observed. The presence of ≥2 non-specific qualitative abnormalities in NVC is associated with vascular manifestations, especially with thrombotic events, and particularly with superficial venous thrombosis. Our findings suggest that changes in the NVC are related to the vascular manifestations of BS. Further prospective studies are needed to confirm these results and to clarify the prognostic value of NVC in patients with BS.

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