Vasculitis damage index in Behçet's disease

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Abstract

Background: Vasculitis damage index (VDI) is a validated damage index for systemic vasculitis, and as Behçet's disease is considered one of systemic vascular disease we aimed to study the relationship of the vasculitis damage index to clinical manifestations and comorbidity in patients with Behçet's disease (BD) to determine if VDI could be used to assess damage in patients with BD.

Methods: A total of 109 patients with BD were recruited from the Rheumatology Department (outpatient and inpatient clinic), Cairo University Hospitals. All patients were subjected to full history taking, clinical examination, and routine laboratory investigations. Disease activity was assessed by the BD current activity form, and the VDI was calculated in all patients. The relationship of the VDI to the disease clinical manifestations was studied. Mann–Whitney and Kruskal Wallis tests were used to estimate differences in quantitative variables. Spearman correlation test was used to test for correlation between quantitative variables.

Results: In the current study, the VDI ranged from 1 to 10, with a mean of 3.5 ± 1.8. It was significantly associated with total thrombosis ($P = 0.022$); total neurological manifestations ($P = 0.000$), especially stroke and cranial nerve affection; uveitis ($P = 0.005$); avascular necrosis (AVN) ($P = 0.015$); osteoporosis ($P = 0.01$); impaired vision ($P < 0.0001$); cataract ($P < 0.0001$); and diabetes ($P = 0.012$). Generally, immunosuppressive treatment was significantly associated with VDI ($P = 0.039$), especially cyclophosphamide ($P < 0.0001$), biological agent ($P = 0.008$), chlorambucil ($P = 0.003$), and anticoagulant ($P = 0.02$). VDI was also significantly correlated with age ($P = 0.033$), disease duration ($P = 0.029$), and duration of eye involvement ($P = 0.003$).

Conclusion: VDI is significantly associated with most disease parameters of BD, except for parameters such as mucocutaneous manifestations and uncomplicated venous thrombosis; however, further studies may be needed to establish BD-specific damage index.

Keywords: Vasculitis damage index, Behçet's disease, Egyptian Patients

Background

Behçet's disease (BD) is a multisystem, inflammatory, autoimmune disease with unknown etiology and pathogenesis and unpredictable prognosis [1, 2]. BD is classified among systemic vasculitides [3]. Vascular involvement is a common finding in BD, which is significantly associated with higher morbidity and mortality rates, and may affect up to 40% of patients with BD, mostly in the form of deep venous thrombosis (DVT) and superficial thrombophlebitis [4–6]. Arterial vascular involvement is less frequent

than venous affection in BD; however, the prognosis is poorer in such cases [7]. Furthermore, recent data also verified the presence of accelerated classical subclinical arterial damage, such as arteriosclerosis, even in patients without overt vascular complications and may be complementary to that of vasculitis [1].

The prognosis for a patient with systemic vasculitis has improved with treatment [8, 9]. However, the long-term outlook may be associated with accumulation of damage, from recurrent flares or treatment [9, 10]. Careful differentiation between activity and damage is mandatory to prevent unnecessary exposure to cytotoxic medications. Damage significantly influences both long-

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term prognosis and quality of life, so systemic recording of damage may be helpful in improving treatment decision and predicting disease outcomes [1, 10].

A well-established validated damage index, "vasculitis damage index" (VDI) [11], is currently the most widely used assessment tool for damage in vasculitis. It is based on a score derived from individual items from disease onset and comprises 64 items (grouped into 11 organ-based systems). The items were originally selected by consensus among experienced physicians. Damage was defined by three key characteristics: irreversibility, presence for > 3 months, and attribution of the lesion to vasculitis or its therapy. Each item was not weighted; therefore, all items contribute equally to the score. The VDI has been used to demonstrate that irreversible damage occurs early in the disease course and has a significant effect on subsequent morbidity and mortality. Multi-organ involvement within 2 years is associated with an increased risk of death [12].

The Outcome Measures in Rheumatology (OMER-ACT) has defined the core set domain of outcome measures for BD, and concluded that both measures of disease activity and damage should be included, as separate and complementary entities, into the core outcome set for BD [13]. However, no BD damage index had been developed until 2020, when Piga et al. published the first BD damage index (BODI) and validated it through several steps, one of which was the correlation with VDI, and they concluded that pending further validation still required [14]. Thus, this study aimed to evaluate the relationship of the VDI to clinical manifestations and comorbidities in patients with BD. Our study may be a preliminary study to assess if VDI is suitable tool for damage assessment in patients with BD.

Patients and methods

This cross-sectional study included 109 adult patients with BD (98 men and 11 women [8.9:1]). Patients were recruited consecutively (with exclusion of juvenile onset BD patients), from 2016 to 2018, from the Rheumatology Department (inpatient and outpatient clinic) of Cairo University Hospitals, Egypt. All patients met the criteria of the International Study Group for BD [3]. Patients were subjected to full history taking, thorough clinical examination and all clinical manifestations were assessed if ever happened in the disease course, either acute or chronic or both. Routine laboratory tests and relevant medications used were recorded. The treatment protocol of our patients was generally in accordance with 2008 and 2018 EULAR recommendations [15, 16], with few modifications due to financial issues or special case situations.

In the present study, disease activity was assessed for all patients by BD current activity form (BDCAF) by filling the items of the BDCAF according to the

information provided by the patients and current medical reports [17], while VDI was also calculated for each patient at the time of recruitment [11]. A comparative and correlative study of the VDI of our patients was conducted with respect to different disease parameters. It is to be noted that medical records of Behçet's patients who died during the period of the study were reviewed for the previously mentioned data. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethical committee. Informed consent was obtained from all patients before their enrollment in the study.

Statistical analysis

Data were processed and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 15 for Windows (SPSS Inc., Chicago, Illinois, USA). For quantitative variables, median (minimum, maximum, inter quartile range (IQR), or mean (±SD) were used. Frequency and percentage were presented for qualitative variables. Mann–Whitney and Kruskal Wallis tests were used to estimate differences in quantitative variables. Spearman correlation test was used to test for correlation between quantitative variables. A P-value < 0.05 indicated statistical significance.

Results

In the current study, the age of our patients ranged from 18 to 58 years, with a mean of 35.3 ± 8 years. Moreover, 98 patients were male, and 11 were female (8.9:1). Oral ulcers were reported in 94.5% of patients, genital ulcers in 85.3%, uveitis in 69.7%, skin lesions in 39.4%, and vascular involvement in 50.5%. Demographic and clinical data of our patients are shown in Table 1. Medications received by patients with BD are shown in Table 2.

VDI in the current study ranged from 1 to 10, with a mean of 3.5 ± 1.8, and was significantly associated with major organ damage including; total thrombosis, total neurological manifestations (especially stroke and cranial nerve affection), eye manifestations (uveitis, visual impairment, cataract), and disease-related complications or associated comorbidities (avascular necrosis [AVN], osteoporosis, and diabetes). The use of immunosuppressive drugs in general was significantly associated with VDI, especially cyclophosphamide, biological agent, chlorambucil, and anticoagulant. VDI was also significantly correlated with age, disease duration ($P = 0.029$), and duration of eye involvement. Details of association of VDI to different disease variables are shown in Tables 3 and 4. Correlation of VDI score with clinical variables is shown in Table 5.

Discussion

BD is a chronic autoimmune systemic vasculitis with an obscure pathogenesis [18]. Vasculitis of BD can involve

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Table 1 Demographic and clinical data of patients with BD

Parameter	Patients with BD (*n* = 109)
Age, mean ± SD (range)	35.3 ± 8 (18–58) years
Sex, male:female	98:11 (8.9:1)
Disease duration, median, minimum, maximum, IQR	9,1, 38, 8.5 years
Delay in diagnosis, median, minimum, maximum, IQR	12, 0.2, 216, 48 months
BDCAF grades 0/1/2/3	50/45/11/3
Oral ulcers, n(%)	103 (94.5)
Genital ulcers, n(%)	93 (85.3)
Skin lesions, n(%)	43 (39.4)
Eye (uveitis), n(%)	76(69.7)
Duration of eye affection, mean ± SD (range)	86.7 ± 60.1(2–264) months
Impaired vision, n(%)	62(56.9)
Blindness, n(%)	12(11)
Cataract, n(%)	40(36.7)
Vascular involvement, n(%)	55 (50.5)
DVT, n(%)	29 (26.6)
DVT (no. of attacks), n(%)	Once 9 (8.3) or twice 20 (18.3)
Thrombosis (arterial/venous), n(%)	52 (47.7)
Thrombosis (no. of attacks), n(%)	Once 27 (24.8) or twice 25 (22.9)
Aneurysms, n(%)	14 (12.8)
Neurological involvement, n(%)	19 (17.4)
Cranial nerve affection, n(%)	12 (11)
Ataxia, n(%)	3 (2.8)
Coma, n(%)	1 (0.9)
Stroke, n(%)	9 (8.3)
Arthritis, n(%)	12 (11)
AVN, n(%)	4 (3.7)
Osteoporosis, n(%)	7 (6.4)
Diabetes, n(%)	8 (7.3)
Mortality, n(%)	8 (7.3)
VDI	3.5 ± 1.8 (1–10)

BD Behçet's disease, *BDCAF* BD current activity form, *DVT* Deep venous thrombosis, *AVN* Avascular necrosis, *VDI* Vasculitis damage index

Table 2 Medications received by patients with Behçet's disease

Medications	Patients with BD (n = 109)
Cyclophosphamide, n (%)	61 (56)
Azathioprine, n (%)	62 (56.9)
Cyclosporine A, n (%)	39 (35.8)
Biologic therapy, n (%)	22 (20.2)
Colchicine, n (%)	2 (1.8)
MMF, n (%)	1 (0.9)
Chlorambucil, n (%)	3 (2.8)
Leflunomide, n (%)	1 (0.9)
Anticoagulants, n (%)	40 (36.7)

BD Behçet's disease, *MMF* Mycophenolate mofetil

any type and size of vessels, which explains why the disease has the ability of multi-systemic involvement [19], which could lead to serious morbidity and mortality [18].

In conditions associated with systemic vasculitis, a comprehensive assessment of disease severity should include measurements of disease activity, damage, and functional status. Damage develops as a consequence of recurrent or persistent active disease or its treatment and is defined as the accumulation of non-healing scars

that are unlikely to respond to immunosuppressive therapy [20]. Therefore, a damage index is needed to quantify damage, aid in the separation of damage from disease activity, and rationalize selection of therapy.

In the current study, the male/female ratio was quite high (8.9:1). This may be similar to some previous studies conducted on patients with BD in Egypt [21, 22]. In addition, our university is a tertiary referral hospital, receiving severe cases including vascular involvement, which has a higher frequency of male patients [23].

Thrombosis is the most frequent vascular manifestation in BD and an important factor of poor prognosis [24]. A study performed by Gerco et al. in 2018 revealed that the major causes of morbidity and mortality rates in BD result from ocular, major vascular, and neurological involvement [25].

Amigo et al. reported that thrombotic events that are considered the hallmark of antiphospholipid syndrome may cause irreversible damage from the onset of the disease. In our opinion, this is also applicable for BD and may explain the association of thrombosis and VDI [26].

In addition, most neurological manifestations and part of the total thromboses are caused by arterial affection, which was found to be associated with greater mortality rate (13.5% in patients with BD with arterial lesions compared to 3.6% in those without arterial involvement) [27].

The association of VDI with uveitis and its complication may also be predictable, if we consider that ocular inflammation develops in approximately 70% of patients and refractory ocular inflammation that may lead to blindness is common in those not responding well to systemic corticosteroids combined with other immunosuppressive agents observed in patients with BD [28].

Osteoporosis, AVN and diabetes; these specific damage items are shared by different damage indices as SLICC for lupus [29] and even VDI itself because they commonly result from high cumulative doses of glucocorticoids used for the treatment of different manifestations

Table 3 Comparison of Vasculitis Damage Index (VDI) with respect to demographic and clinical manifestations

	VDI score		
	Minimun-Maximum	Median (IQR)	*P*-value
Sex			
Male	1–10	3 (2)	0.1*
Female	1–7	5 (2)	
Oral ulcers			
Yes	1–10	3 (3)	0.21*
No	1–3	3 (1)	
Genital ulcers			
Yes	1–10	3 (3)	0.487*
No	1–8	3 (2)	
Other skin lesions			
Yes	1–8	3 (3)	0.197*
No	1–10	3 (2)	
Vascular involvement			
Yes	1–10	4 (3)	0.073*
No	1–7	3 (2)	
DVT attacks			
Yes	1–8	4 (3)	0.566*
No	1–10	3 (2)	
Arterial or venous thrombosis			
Yes	1–10	4 (3)	**0.022***
No	1–8	3 (2)	
Aneurysm			
Yes	1–8	3 (2)	0.539*
No	1–10	3 (2)	
Neurological affection			
Yes	3–10	5 (2)	**< 0.0001***
No	1–8	3 (2)	
Cranial nerve affection			
Yes	5–10	6 (3)	**< 0.0001***
No	1–8	3 (2)	
Ataxia			
Yes	4–7	4***	0.102*
No	1–10	5 (2)	
Stroke			
Yes	3–6	4 (1)	**0.014***
No	1–10	3 (2)	
Arthritis			
Yes	1–8	4 (1)	0.741*
No	1–10	3 (2)	
AVN			
Yes	3–10	7 (7)	**0.015***

Table 3 Comparison of Vasculitis Damage Index (VDI) with respect to demographic and clinical manifestations *(Continued)*

	VDI score		
	Minimun-Maximum	Median (IQR)	*P*-value
No	1–8	3 (2)	
Osteoporosis			
Yes	3–10	7 (7)	**0.01***
No	1–8	4 (1)	
Uveitis			
Yes	1–10	4 (3)	**0.005***
No	1–8	3 (2)	
Vision			
Normal	1–8	2 (1)	**< 0.0001****
Impaired	1–7	3 (2)	
Blindness	2–10	5 (5)	
Cataract			
No involvement	1–8	2 (2)	**< 0.0001****
Single eye involvement	3–10	5 (4)	
Both eye involvement	2–7	4 (2)	
Diabetes			
Yes	3–10	4 (4)	**0.012***
No	1–8	3 (2)	

*Mann–Whitney test, **Kruskal–Wallis test, *** no IQR is calculated; as only 3 patients had ataxia. *VDI* Vasculitis damage index, *BD* Behçet's disease, *DVT* Deep venous thrombosis, *AVN* Avascular necrosis

of rheumatic diseases thus it is not surprising to find an association between these damage items and VDI.

Systemic immunosuppressive and biological agents are the standard therapy for severe organ involvement in BD [30–32], and the goal of management is early treatment to avoid recurrences and irreversible damage to the vital organs [33]. As other autoimmune diseases, medications used may be associated with serious side effects and damage [31, 34, 35]. In our study, the use of immuno-suppressive drugs in general was significantly associated with VDI, especially cyclophosphamide, infliximab, and chlorambucil, in addition to anticoagulant, while the use of other medications that may be used in BD for milder presentation, such as colchicine and azathioprine, was not significantly associated with VDI. In our opinion, although such medications may improve survival and disease outcomes, they should be reserved for severe aggressive disease manifestations, as these medications may show some serious side effects, increasing the damage; thus, the association of immunosuppressive drug use and VDI could be expected, also from another point of view such medications may be used to treat active, aggressive disease, which itself may be associated with increased damage.

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Table 4 Comparison of Vasculitis Damage Index (VDI) with respect to the medication received

	VDI score		
	Minimun-Maximum	Median (IQR)	P-value
Immunosuppressive drugs			
Yes	1–10	3 (2)	**0.039***
No	1–4	3.5 (2)	
CYC			
Yes	1–10	4 (3)	**< 0.0001***
No	1–7	2.5 (1)	
AZA			
Yes	1–10	3 (3)	0.294*
No	1–8	3 (2)	
CSA			
Yes	1–10	3 (2)	0.874*
No	1–8	3 (3)	
Biological			
Yes	1–10	4(2)	**0.008***
No	1–8	3 (2)	
Colchicine			
Yes	2–2	2**	0.16*
No	1–10	3 (2)	
Chlorambucil			
Yes	7–10	8**	**0.003***
No	1–8	3 (2)	
Anticoagulant			
Yes	1–10	4(4)	**0.02***
No	1–7	3 (2)	

*Mann–Whitney test, **no IQR is calculated; as the number of patients who recieved the drug was less than 4. *CYC* Cyclophosphamide, *AZA* Azathioprine, *CSA* Cyclosporine A

Table 5 Correlation of the Vasculitis Damage Index (VDI) score with some patients´ demographic and clinical variables

Variable	VDI in patients with BD (n = 109)	
	[a]r	*P
Delay in diagnosis	0.02	0.84
BDCAF	0.15	0.13
Age	0.2	**0.03**
Disease duration	0.21	**0.03**
Stroke score	0.09	0.8
Duration of eye affection	0.34	**0.003**

[a]Spearman correlation coefficient. *P is significant at < 0.05. *VDI* Vasculitis damage index, *BD* Behçet's disease, *BDCAF* BD current activity form

It seems expected that longer disease duration and duration of eye involvement may be associated with increased damage, which is the case in our study, as VDI was significantly correlated with disease duration and eye involvement. However, the correlation between VDI and age ($P = 0.033$), may contradict the decreased mortality rate in patients with BD aged > 35 years reported by Saadoun et al. [36], In our opinion this decline in mortality after age of 35, may raise an important point, that elderly onset BD patients may show milder disease manifestations as some elderly onset lupus, which is a point that may require further studies.

In this study, we found that VDI is correlated with most aggressive disease manifestations of BD. However, some damage found in patients with BD may not be covered by VDI, especially damage related to genital ulcers or venous occlusion, e.g., Budd Chiari syndrome, vena caval thrombosis, and cerebral venous sinus thrombosis. Moreover, the development of venous thrombosis (unless complicated) or recurrent venous thrombosis is excluded in the VDI. In contrast, some items mentioned in VDI may not be of value in patients with BD, such as alopecia and proteinuria. Thus, according to the aforementioned reasons, in our opinion, BD modified specific VDI version as that studied by Piga et al. 2020 and including many modified items of VDI [14], may be needed for better assessment of damage in patients with BD, which must be assessed in further prospective, large scale, longitudinal studies.

Among strengths of our study is that, it is one of the pioneer studies in attempt to evaluate Damage index for BD. On the other hand, study limitations include: we did not assess the inter-rater agreement by evaluating Cohen's kappa and the interclass correlation coefficient (ICC), we also did not correlate VDI with the number of flares, cumulative corticosteroid doses, or delay in immunosuppressive therapy.

Vasculitis is a main pathologic finding in BD, and damage index is required in most rheumatic diseases to quantify damage, aid in the separation of damage from disease activity, and rationalize selection of therapy. Fortunately; a recent damage index for Behçet's disease has been validated "Behçet's syndrome overall damage index (BODI)" most items of which, has been derived from VDI, however further validation is needed for such damage index to be established as concluded by their authors.

Conclusions

VDI is significantly associated with most disease parameters of BD, except for parameters such as mucocutaneous manifestations and uncomplicated venous thrombosis; however, further studies may be needed to establish and validate VDI derived BD-specific damage index.

Declarations

Ethics approval and consent to participate
The study was performed in accordance with the Declaration of Helsinki and approved by the local ethical committee. Informed consent was obtained from the patients.

Consent for publication
All authors gave their consent for publication.

Competing interests
All authors declare no conflicts of interest.

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