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Activity Criteria in Behçet's Disease

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Abstract

Behçet's disease is a complex disease characterized by remission and activation periods of unknown duration. It has an unpredictable course. Behçet's disease shows a heterogeneous pattern of organ involvement that occurs in recurrent episodes of acute inflammation throughout the course of the disease. Disease activity in Behçet's disease is difficult to define because of its fluctuating course, lack of laboratory tests reflecting overall disease activity, absence of a standardized form to report the severity of Behçet's disease manifestations and also trying to develop new diagnostic criteria. This led to the development of standardized disease activity index. To be useful, a measurement of disease activity must be valid, reliable, and simple enough to use in routine clinical practice. We will try to explain what the situation is in terms of Behçet's disease activity index.

Keywords: Behçet, activity, disease, criteria, remission, activation

1. Introduction

As with many inflammatory diseases, Behçet's disease has a course including periods of remissions and exacerbations. Exacerbation periods are unknown, and it is difficult to predict the duration of attacks. In addition, the severity of disease varies from one patient to another, and for a given patient, it varies from one period to another [1]. The disease has an unpredictable course.

There are no laboratory markers compliant with the clinical findings in Behçet's disease. Therefore, disease activity is evaluated based on the clinical history. The reliability of the patients' answers to retrospective questions decreases as the time interval increases. Since the disease characteristics such as exacerbation, remission, severity of the attack, and

duration of the attack are not known, the disease is refractory. It is also difficult to identify whether the remission in disease findings is due to the response to treatment or to the disease course. Therefore, during the treatment period, clinicians frequently rely on clinical findings of exacerbation and quality of life scales. However, since these parameters have not been standardized yet, they are not reliable in the evaluation of the response to treatment. In addition, clinical drug researches are far from measuring the treatment efficacy with sufficient sensitivity. In conclusion, it is difficult to define the disease activity in Behçet's disease, as:

- (1) the disease has a fluctuant course;
- (2) there is not an established laboratory test which would represent all the disease findings;
- (3) there is not a standard test to explain the severity of disease symptoms; and
- (4) new diagnosis criteria are being developed, which cause diagnostic difficulties [2].

Activity scales and laboratory findings in the evaluation of Behçet's disease are, however, important in understanding the treatment and course of the disease. An ideal activity scale for Behçet's disease should have the following properties:

- (1) It should be sensitive to clinical changes.
- (2) It should be authentic.
- (3) It should be able to evaluate all the organs and systems involved.
- (4) It should be sensitive to different effects on morbidity and life quality caused by different organ and system involvements.
- (5) It should be able to evaluate the fluctuations in the natural course of the disease.
- (6) It should be understandable and easily applicable.
- (7) It should not be time consuming.
- (8) It should be valid for different communities.
- (9) It should not be affected by the differences in practitioners [3].

In addition, there are two kinds of activity scales in Behçet's disease. While the first one evaluates the specific organ activity, the other one is a general activity scale.

The Composite Index for the oral ulcer activity, which is used for aphthous stomatitis, measures the pain intensity and functional response. In the Composite Index, the presence of active oral aphthous stomatitis within the past month, pain caused by the lesion and, in addition, eating, masticatory, gustatory, and speech disorders are scored. However, it is not specific to Behçet's disease and can be used in other diseases with a course of aphthous stomatitis [4]. The Disease Activity Index for Behçet's disease has been developed to evaluate the intestinal activity of Behçet's disease, although its use is limited, except in Korea where it was developed [3, 5].

Yazici et al. developed Turkish Behçet's Disease Activity Index, and later performed activity index studies for Iranian Behçet's Disease and European Behçet's Disease [6, 7]. Finally, in Behçet's Disease meeting in Leeds, UK in 1994, both studies were combined, redefined, and evaluated as Behçet's disease current activity form by Bhakta [8].

First activation criteria were defined by Yazici et al. in Turkey. The body parts affected by Behçet's disease were classified into five groups and scored based on the level of the impact. Based on these criteria, the eyes, the skin, involvement of the vascular bed, arthritis, and neurological involvement were considered. This form evaluates the findings at the time of patient's admission, and retrospective evaluation cannot be performed (**Table 1**) [6].

The Iranian Behçet's Disease Activation Form (IBDDAM) was defined by Davatchi et al. in 1991. It evaluates 18 clinical symptoms and pathergy test within the past 4 months [7]. Activity within the past 12 months can be evaluated and a mean activity score is obtained. Each 5 aphthous stomatitides, each 1 of the genital ulcers, each 10 folliculitis, each 1 of the erythema nodosum, superficial thrombophlebitis, and positive pathergy test gets 1 point. Eye involvement is evaluated based on the severities of anterior and posterior uveitis and retinal vasculitis, and uveitis is multiplied by the constant 2 and retinal vasculitis is multiplied by the constant 3. Gastrointestinal system is scored between 3 and 6, central nervous system between 1 and 6, and arthritis between 1 and 3. An additional 2 points is added for deep veins, 6 for large veins, and 2 for the presence of epididymitis. If these findings are being observed for more than 1 month, scores equivalent to the total sum of scores are added for each month (**Table 2**).

Involvement	Evaluation
Eye	0 – normal 1 – only vitreous or anterior chamber inflammation 2 – visual acuity 0.5 3 – visual acuity 0.3 4 – a few meters finger count 5 – blindness
Skin	1 – oral ulcer 1 – erythema nodosum 1 – genital ulcer
Vascular involvement	5 – vena cava superior or inferior thrombosis and/or arterial occlusion 4 – vena cava superior or inferior thrombosis 3 – calf vein thrombosis or superficial thrombophlebitis requiring rest 2 – bilateral calf vein thrombosis and/or superficial thrombophlebitis 1 – unilateral calf vein thrombosis and/or superficial thrombophlebitis
Arthritis	1 – each joint
Neurological involvement	2 – intracranial hypertension 3 – multiple sclerosis like syndrome 4 – pyramidal and/or cerebellar involvement

Table 1. Turkish Behçet activity criteria.

Oral ulcer	Every 5 ulcer 1 point
Genital ulcer	Each lesion 1 point
Skin lesion	Every 10 papulopustulosis 1 point, every 5 erythema nodosum 1 point
Eye	Anterior uveitis: 1–4 points (cell, hypopyon, precipitate) Posterior uveitis: 1–4 points (posterior cell, snowball, snowbank) Retinal vasculitis: 1–4 points (papil edema, macular edema, papillitis, arthritis)
Arthritis	Arthralgia 1 point (irrespective of the number of joints) Monoarthritis 2 points Polyarthritis 3 points
Central nervous system	Isolated lesion 1 point Mild involvement 3 points Severe involvement 6 points
Thrombosis	Superficial thrombophlebitis 1 point Thrombophlebitis in deep venules 2 points Large vein involvement 6 points
Gastrointestinal involvement	Mild symptom 3 points (chronic diarrhea, rectal hemorrhage) Severe symptom 6 points
Epididymitis	2 points
Pathergy test (+)	1 point

Table 2. Iranian’s Behçet activity criteria.

The European Behçet’s Disease Index was defined in 1993. Oral ulcer, genital ulcer, skin, and joint symptoms are evaluated based on the past month. In the eye, gastrointestinal system, central nervous system involvement, scoring is based on symptoms and findings. Eye involvement is scored between 0 and 47, involvement of any other organs except the eye is scored between 0 and 5 [9].

The aforementioned indices were found insufficient due to their inability to evaluate all organs and systems, not being easily applicable, and inability to be tested for validity for different communities. Following the consensus meeting in 1994, Behçet’s disease current activity index was defined to eliminate the disadvantages in other indices. Ten symptoms frequently observed in Behçet’s disease were evaluated. Among these symptoms, fatigue, headache, oral ulcers, genital ulcers, erythema nodosum or superficial thrombophlebitis, papulopustular eruption, arthralgia, arthritis, nausea, vomiting or abdominal pain, and bloody diarrhea are evaluated for the past 4 weeks with scores between 0 and 4. The eye, large veins, and central nervous system, the other three organ systems, are evaluated with two different variables. The patient’s feelings about the disease activity within the past 4 weeks are questioned and marked on two visual Likert-type scales with seven different facial expressions. Similar visual score is used by the clinician to evaluate total disease activity. The patient does not have a self-evaluation form and clinical appointment and the decision of the clinician are required (**Table 3**).

Japanese Behçet's disease activity phase classification was performed in 2003 [10]. In the active phase, presence of subcutaneous venous thrombosis, skin findings (i.e., erythema nodosum and genital ulcer), arthralgia, gastrointestinal ulcer, central nervous system lesions, vasculitis, or epididymitis, and serum CRP, cerebrospinal fluid, colonoscopy in the clinical examination including ophthalmologic examination, and other clinical laboratory findings are evaluated. In this evaluation, presence of a score of two or more for oral aphthous stomatitis, genital ulcer, skin and eye symptoms, or presence of the defined symptoms of Behçet's disease, are defined as active phase. In addition, for the activation phase, there are some information which are advised to be taken into consideration:



BEHÇET'S DISEASE CURRENT ACTIVITY FORM 2006

Date: _____ Name: _____ Sex: M/F
Centre: _____ Telephone: _____ Date of birth: _____
Country: _____
Clinician: _____ Address: _____

All scoring depends on the symptoms present over the **4 weeks** prior to assessment.
Only clinical features that the **clinician feels are due to Behçet's Disease** should be scored.

PATIENT'S PERCEPTION OF DISEASE ACTIVITY

(Ask the patient the following question:)

"Thinking about your Behçet's disease only, which of these faces expresses how you have been feeling over the last four weeks?" (Tick one face)



HEADACHE, MOUTH ULCERS, GENITAL ULCERS, SKIN LESIONS, JOINT INVOLVEMENT AND GASTROINTESTINAL SYMPTOMS

Ask the patient the following questions and fill in the related boxes "Over the past 4 weeks have you had?"

(please tick one box per line)

	not at all	Present for up to 4 weeks
Headache	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Mouth Ulceration	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Genital Ulceration	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Erythema	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Skin Pustules	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Joints - Arthralgia	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Joints - Arthritis	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Nausea/vomiting/abdominal pain	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Diarrhoea+altered/frank blood per rectum	<input type="checkbox"/>	<input checked="" type="checkbox"/>

EYE INVOLVEMENT

(Ask questions below)

"Over the last 4 weeks have you had?"

a red eye
a painful eye
blurred or reduced vision

(please circle)
Right Eye Left Eye
No Yes No Yes
No Yes No Yes
No Yes No Yes

If any of the above is present: "Is this new?"
(circle the correct answer)

No Yes

NERVOUS SYSTEM INVOLVEMENT (include intracranial vascular disease)

New Symptoms in nervous system and major vessel involvement are defined as those not previously documented or reported by the patient
(Ask questions below)

Over the last 4 weeks have you had any of the following?

blackouts

difficulty with speech

difficulty with hearing

blurring of/double vision

weakness/loss of feeling of face

weakness/loss of feeling of arm

weakness/loss of feeling of leg

memory loss

loss of balance

please circle

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

tick if new

Is there any evidence of new active nervous system involvement?

No

Yes

MAJOR VESSEL INVOLVEMENT(exclude intracranial vascular disease)

(Ask question below)

"Over the last 4 weeks have you had any of the following?"

had chest pain

had breathlessness

coughed up blood

had pain/swelling/dischouration of the face

had pain/swelling/dischouration of the arm

had pain/swelling/dischouration of the leg

please circle

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

No

Yes

tick if new

Is there evidence of new active major vessel inflammation?

No

Yes

CLINICIAN'S OVERALL PERCEPTION OF DISEASE ACTIVITY

Tick one face that expresses how you feel the patient's disease has been over the last 4 weeks.



BEHÇET'S DISEASE ACTIVITY INDEX

Add up all the scores which are highlighted in blue (front page items, one tick = score of 1 on index, all other items score 'yes' = 1. You should now have a score out of 12 which is the patient's Behçet's Disease Activity Index Score.

	SCORE												
Patients index score	0	1	2	3	4	5	6	7	8	9	10	11	12
Transformed index score on interval scale	0	3	5	7	8	9	10	11	12	13	15	17	20

Table 3. Behçet's disease current activity form.

- (1)

Increasing the drug dose, changes in or addition to the medication must be done, if the findings are indicating the active phase.
- (2)

Since they are not good criteria for the disease activity, only in the presence of oral aphthous stomatitis and papulopustular eruption, other suggested symptoms and past findings should be considered (number, width, changes in the frequency, and length of the recovery).
- (3)

In cases with distinct attacks, such as uveitis, active phase is concordant with the attack duration and usually regresses within 2 weeks. However, if distinct inflammatory findings last longer than 2 weeks, it is assumed that active phase continues.

- (4) Cases in inactive phase can suddenly become active.
- (5) Inactive phase, which is defined as the stable phase (remission), means 0 activity index for more than 1 year [10].

The activity index is presented in **Table 4**.

Other than these activity indices, there are indices mostly used in their country of development and have a more limited use. The Behçet's Disease Activity Index by Yossipovitch in 1993 (**Tables 5 and 6**), the index prepared by Krause et al. to measure the activity of Behçet's disease in their publication in 1999 (**Table 7**), clinical activity scoring defined by Chang et al. in 2002 (**Table 8**), and the index defined in Korea in 2003 can be used to measure the activity of Behçet's disease [11–14].

Behçet's disease does not have any parameters or tests which may be indicative of specific activity. However, there are some laboratory parameters that can lead to further investigation in the clinically relevant area.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels have been shown to be unrelated to disease activity [15]. ESR and CRP levels may be elevated when the disease is inactive, or there may be no elevation of specific organ involvement in the active phase. Higher levels are considered a clue for further research [8]. Human leukocyte antigen (HLA)-B51 is still known as the strongest genetic susceptibility factor. The T-helper 17 and interleukin (IL)-17 pathways are active, as well as play an important role, particularly in acute attacks of Behçet's disease. Neutrophil activity is increased in Behçet's disease, and the affected organs show a significant neutrophil and lymphocyte infiltration. HLA-B51 association and increased IL-17 response are thought to play a role in neutrophil activation [16]. Human mitochondrial heat shock protein (HSP) is highly homologous with microbial HSP and provokes proliferation of autologous T cells in Behçet's disease patients [10]. The HSP 60/65 plays an important role in Behçet's disease mucocutaneous lesions [10]. The Serum IL-12 levels correlate with disease activity and higher levels of soluble TNFR-75 are presented in active Behçet's disease [17].

In the active phase of Behçet's disease, oxidation protein products which can be considered as acute phase proteins, such as neopterin, anti-streptolysin, rheumatoid factor, amyloid-A, α 1-antitrypsin, β 2-microglobulin, myeloperoxidase, and malondialdehyde levels, were found to increase [18–21]. On the other hand, a decreasing tendency in antioxidant enzyme levels, such as superoxide dismutase, catalase, and glutathione peroxidase, can be detected [22]. There was an increment in the presence of IgA, IgM, sometimes IgD, IgG-containing immunocomplexes in patients with Behçet's disease [23]. It has been also shown that an increase is observed in salivary IgA levels during oral aft activation [24]. P-selectin, I-selectin, and L-selectin among the adhesion molecules during the activation period in Behçet's disease and increases in the expression of sICAM-1 during uveitis episodes have been detected [25–27]. The increased E-selectin levels were associated with Behçet's disease particularly the eye, central nervous system involvement, and thrombosis activation [28]. Increases in homocysteine levels have been demonstrated in Behçet's disease patients in which thrombosis has developed, and it has been suggested that the level is more related to endothelin and nitric oxide [29, 30]. Plasminogen activator inhibitor-1 levels were increased in thrombosis and arthritis attacks in Behçet's disease [31].

Active phase	<p>One of the following symptoms is found: uveitis, subcutaneous venous thrombosis, skin lesion such as erythema nodosum, genital ulcers (those relating to the female sexual cycle should be excluded), arthralgia, intestinal ulceration, progressive central nervous system lesions, progressive vasculitis, and epididymitis</p> <p>Inflammatory findings are also evident from clinical examination (including ophthalmological findings) and/or clinical laboratory findings (serum CRP, findings in cerebral fluid, findings by colonic fiberscopy, and others)</p> <p>As for oral aphthous ulcers, skin/genital ulcers, and ocular symptoms, cases with a score of 2 or above are defined as BD in the active phase</p>
Non-active phase	<p>Cases excluded by the above definition for active phase</p> <p>1 – Dosage up, change or addition of therapeutic reagents is generally required in the active phase</p> <p>2 – As for cases with only oral aphthous ulcers or follicular papules, careful diagnosis is recommended taking into account other symptoms or past symptoms, since these symptoms are not good criteria for disease activity</p> <p>3 – In cases of lesions in which attack is obvious, for example, uveitis, active phase corresponds to the attack phase and the lesions continue for no longer than 2 weeks in general. However, if obvious inflammatory findings continue for more than 2 weeks, cases can be diagnosed as in the active phase at present</p> <p>4 – One should consider that it is possible that cases in the inactive phase suddenly move into the active phase</p> <p>5 – Stable phase (remission) is defined as the inactive phase with the activity index of 0 for more than 1 year</p>
Oral ulcer	<p>0 – none</p> <p>1 – less than 2 weeks in the last 4 weeks</p> <p>2 – more than 2 weeks or more than 2 weeks in the last 4 weeks</p> <p>3 – lesion last 4 weeks</p>
Skin lesion	<p>0 – none</p> <p>1 – less than 2 weeks in the last 4 weeks</p> <p>2 – more than 2 weeks or more than 2 weeks in the last 4 weeks</p> <p>3 – lesion last 4 weeks</p>
Eye	<p>0 – none</p> <p>1 – 1 episode in the last 4 weeks</p> <p>2 – 2 episodes in the last 4 weeks</p> <p>3 – 3 episodes in the last 4 weeks</p>
Arthritis	Arthritis, walking difficulty, deformity
Gastrointestinal involvement	Acute/chronic abdominal pain, melena
Epididymitis	Pain, swelling
Vascular involvement	Cardiac/aortic disease, middle or small vein occlusion, thrombophlebitis
Central nervous system involvement	Headache, dizziness, paralysis

Table 4. Japan's Behçet activity criteria.

Mild involvement	Minor oral aphthous and genital ulcer Skin symptoms Arthritis less than two joints
Severe involvement	Major oral ulcer and genital ulcer Arthritis more than two joints Eye symptoms Neurological symptoms Big vessels involvement

Table 5. Yossipovitch's activity form.

Mild involvement	Oral ulcer Genital ulcer Skin symptoms
Moderate involvement	Arthritis less than three joints Recurrent genital ulcers Mild anterior uveitis
Severe involvement	Anterior and posterior uveitis Big vessel involvement Arterial aneurysm Arthritis more than three joints

Table 6. Yossipovitch's activity form.

Mild (each one 1 point)	Oral ulcer Genital ulcer Skin lesion Arthritis Recurrent headache Epididymitis Mild gastrointestinal disease (chronic diarrhea, abdominal pain, etc.) Superficial vein thrombosis Chest pain
Moderate (each one 2 points)	Arthritis Deep vein thrombosis Anterior uveitis Gastrointestinal bleeding
Severe (each one 3 points)	Posterior or panuveitis, retinal vasculitis Arterial thrombosis or aneurysm Big vein thrombosis (vena cava, hepatic vein, etc.) Neurological involvement Bowel perforation

Table 7. Krause's activity form.

1 point	Oral ulcer
	Genital ulcer
	Skin lesion (erythema nodosum-like lesion, pp eruption)
	Superficial thrombophlebitis
2 points	Arthritis more than two joints
	Gastrointestinal ulcer with complication
	Small or medium diameter vascular involvement is not related to the vital organ
3 points	Uveitis
	Gastrointestinal tract involvement with perforation or bleeding
	Big vessels involvement
	Vital organ involvement (brain, lung, heart, etc.)

Table 8. Chang’s activity form.

2. Pathergy test

The skin pathergy reaction is highly specific for Behçet’s disease; there is considerable variation in the rate of positivity in patients from different geographical areas, which limits its clinical usefulness. A positive pathergy reaction is common in patients from Iran, Turkey, and Japan, but rare in those from the UK, the USA, and France [8].

Correlation studies with the disease activity of the pathergy test are insufficient. It has also been suggested that the pathergy test may be a positive relationship for the formation of oral aphthae, genital ulcer, arthritis, papulopustular eruption, and erythema nodosum, and a negative relationship to the presence of uveitis and venous thrombosis [32, 33]. Generally, there was no correlation between the severity of the disease and the pathergy test and it was stated that the positivity ratio could be increased by using nondisposable blunt needle [34]. It has been reported that the group defining the IBDDAM criteria may be able to detect positivity when the pathergy test is used periodically and that negative and positive phases may be detected during the disease. Pathergy test is one of the IBDDAM criteria. It has been reported that the pathergy test can be used to assess drug treatment efficacy [7].

3. Conclusion

Behçet’s disease is a chronic inflammatory disease. Behçet’s disease is characterized by remissions and exacerbations. The determination of whether the disease is in the active phase is important in terms of treatment and prognosis. Therefore, the parameters that determine the active phase are important. Although a change in laboratory parameters was detected during the course of Behçet’s disease, no specific marker was detected. For this reason, disease activity index have been started to be developed on the basis of clinical history in order to detect disease activity. The activity index based on the story of clinical features appears to be more useful following the disease activity and treatment.

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