

Diagnosis/Classification Criteria, Pathergy Test, Activity and Life Quality Scales of Behçet's Disease

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ABSTRACT

Behçet's disease (**BD**) is a multi systemic, auto inflammatory disorder with a relapsing and remitting course. The etiology of BD is still unclear. Clinical manifestations include recurrent oral aphthosis, genital ulcerations and skin eruptions; ocular involvement; arthritis; vasculitis and involvement in different systems such as neurological and large vessels. There is no diagnostic tool in diagnosis out of clinical examination. Different diagnostic criteria have been identified in diagnosis and activity score of BD. To be aware of significant impact of BD on life quality of the affected patients would improve the life quality of the patients and decrease the morbidity ratios in BD.

Keywords: Aphthous stomatitis, Behçet's disease, Life quality, Uveitis

INTRODUCTION

Behçet's disease (**BD**), which is recently denominated as Behçet's syndrome, is a complex, multisystem, autoinflammatory disorder which may represent with heterogenous clinical and systemic manifestations including recurrent oral aphthous ulcers, genital ulcers, the pathergy test positivity, skin diseases including papulopustular lesions and erythema nodosum, ocular

inflammation, gastrointestinal and neurologic involvement, fever, and arthritis without autoantibody production [1-3]. These symptoms may present concurrently or may present in a long time duration and exhibit relapses and remissions. Vasculitis is the major pathogenic mechanism in clinical symptoms of BD which can affect all sizes and types of vessels [4]. Eyes, vascular, gastrointestinal and nervous system are the major organ involvements in BD and the vascular and nervous system involvements are also the most common causes of mortality in BD [4].

BD was first described as a distinct clinical entity by Turkish dermatologist Hulusi Behçet in three patients who have a triad of symptoms including oral aphthous ulcers, genital ulcers, and hypopyoniritis in 1937 [5]. Although the etiology of BD remains unclear, the pathogenesis is simply clearer that both genetic factors and immunological reactions to the external triggering factors such as infections are leading to vasculitis in patients with BD [6].

Behçet's disease is more common along the ancient "Silk Route" from eastern Asia to the Mediterranean; however it may affect any ethnic origin [7]. The prevalence of BD is reported to be highest in Turkey (80 to 370 cases per 100,000), and the prevalence of BD is much lower in Northern European and North American populations (1 per 15,000 to 1 per 500,000) [7,8].

DIAGNOSIS OF BEHÇET'S SYNDROME

Recently there is no currently available specific laboratory, biological or radiological tests in diagnosis of BD, and the diagnosis of BD is based mainly on clinical findings. After observations about involvement of different systems in BD, different diagnostic and classification criteria were identified for BD. The first classification/diagnosis criteria was created by Curth in 1946 and different classifications were followed by different authors and recently revised by International Study Group (**ISG**) as International Criteria for Behçet's Disease (**ICBD**) in 2014 [9-11].

In first classification criteria, the diagnosis of BD was made with the presence of two of the clinical findings in addition to recurrent oral aphthous ulcers: genital ulcers, ocular involvement, and pathergy test positivity concurrently [12]. This classification was revised in 2006 by ISG and vascular involvement was included to the diagnostic criteria [13]. In this classification, while genital ulcers and ocular involvement score two points each, recurrent oral aphthous ulcers, other skin lesions, vascular involvement and pathergy test positivity score one point each. BD can be diagnosed if the patient has three or more points. In 2014 the ISG evaluated the validity of the 2006 ICBD diagnostic criterias. As compared to the earlier ISG criteria, both vascular and neurological features were identified in diagnostic criteria list and assigned more points for the presence of oral or genital aphthosis and ocular findings in the ICBD 2014 criteria. According to the revised ICBD, recurrent oral aphthous ulcers, genital ulcers and ocular disease are evaluated as two points each and skin lesions, vascular involvement and neurological findings are evaluated as one point each. The patient is diagnosed as BD with four or more points. Recent version of ICBD criteria has higher sensitivity as compared to the older widely accepted ISG criteria. While

the sensitivity of ISG criteria was reported as 77.9% and in ICBBD the sensitivity was reported as 97.9 % [7].

The pathergy test positivity is another diagnostic test which is recently accepted as optional in diagnosis of BD in newly revised criteria because of the varying clinical results and differences in the application and evaluation of the test [12].

Kaneko et al reported that skin prick with self-saliva may be a new diagnostic way for BD but the validation of this technique has not been proven yet [14]. Tzanck smear, serologic tests, endoscopic examination are other tests that can be useful for the diagnosis and differential diagnosis of BD. Histopathologic, immunohistochemical evaluation of tissue samples and immunofluorescence tests may also be helpful in the exclusion of malignancy, autoimmune blistering disorders, inflammatory bowel diseases, erosive lichen planus which are also important in differential diagnosis of BD [15]. Chun et al investigated the histopathologic findings of cutaneous lesions in BD and reported leukocytoclastic vasculitis in majority of oral ulcers and lymphocytic vasculitis in genital ulcers [16]. These findings were also supported by Kalkan et al and Ozluk et in which vasculitis was reported in papulopustular lesions and pathergy reaction of BD [3,15].

PATHERGY TEST

Pathergy phenomenon is a nonspecific, cutaneous hypersensitive response, which is characterized by formation of erythematous in duration at the site of trauma with a papule or sterile pustule formation at its centre, 24-48 hours after 20-26G syringe needle stick in BD [17]. This diagnostic test was first described by Blobner in 1937 and several further investigations about its epidemiology, pathogenesis, and histological findings have been reported since 1937 [15,18].

Pathergy test is applied to a hairless area on skin such as flexural surface of the forearm, the scapular areas on back, lateral surface of the tibia, and the lumbar area on the abdominal region after cleaning with alcohol or can also be applied to mucosa of the lower lip into the sub mucosa using a 20-26 gauge blunt disposable needle alternatively [19,20]. While the sensitivity of the oral pathergy test is reported to be lower than classical skin pathergy test, it is easier to assess according to skin pathergy test as clinician do not need to measure the size of the lesion, a pustule or ulcer of any size is accepted to be positive [19].

There is no standardized method while performing skin pathergy test, three oblique punctures (intravenous, intramuscular, and intra dermal) at an angle of 45 degrees to the forearm flexor surface can be used and none of these methods has been accepted to have a higher positivity [21]. Dermoscopy can also be helpful in evaluation of pathergy test positivity [22].

Pathergy test is an important indicator in diagnosis of BD and the incidence of positivity of the test may change according to gender (male > female), genetic factors (HLA B5 positive individuals), age and geographic regions, where the disease is more commonly seen such as

Mediterranean and Middle East countries [23]. Beside these factors the thickness and type of the needles, number of punctures, application method, disease activity, and cleaning the application area with an antiseptic can also change pathergy positivity [24,25].

The positivity of skin pathergy test is increased by performing pathergy test with a reusable, sterilized blunt needle. Also keeping and turning the needle in the dermis for 90 seconds before taking it out is another factor that increases the pathergy test positivity [25,26].

The relationship of pathergy test positivity with systemic involvement is a controversial topic. In the literature, there are conflicting results whether the positivity of pathergy test is more commonly associated with skin disorders, vascular or ocular involvement or whether it is a sign of more severe clinical course [27].

ACTIVITY AND LIFE QUALITY SCALES OF BEHÇET'S DISEASE

Measurement of disease activity in BD is critical to assess the efficacy of the treatments and disease management. Because of the heterogenous, multi systemic, relapsing and remitting course of the disease it is difficult to assess the disease activity for a clinician. There are various clinical indexes to assess BD activity in the literature [28,29]. Recently, the most commonly used instrument is the Behçet's Disease Current Activity Form which evaluates oral ulcers, genital ulcers, erythema nodosum/superficial thrombophlebitis, headache, fatigue, joint involvement, oculopathy index, gastrointestinal involvement, patient's impression of disease activity and doctor's impression of disease activity [30]. Although this instrument is the most widely used index for disease activity, the only validated score for measuring specific organ involvement is the Oral Ulcer Composite Index which was developed by Mumcu et al. in 2006 [29]. Eye activity can also be measured by ophthalmologist via Behçet's disease oculopathy index about presence of blurring of vision, pain or redness in any eye [31]. Additionally genital ulcer severity score was described by Senusi et al, including six different parameters of number, size, duration, ulcer free period, pain and site [32]. These specific scores can be used in the management and in assessment of treatment efficacy of BD patients and can reduce morbidity.

The etiopathogenesis of Behçet's disease is still unclear, and the chronic, relapsing-remitting course of the disease and especially complex pattern of signs and symptoms, severe organ involvements notably effect the life quality of the patients and life satisfaction. In the literature, there are several clinical trials about the effect of clinical symptoms, given systemic therapies on life quality, sexual and/or sleep disorders in patients with BD. Several instruments have been used to assess this impact in the literature. The first clinical trial about the association of life quality and BD was reported in 1997 and the questionnaire consisted of the Dermatology life Quality Index (**DLQI**) [33]. It was shown that skin manifestations especially genital ulcers are significantly effecting life quality of the patients with BD [33]. As reported in this study although the clinical manifestations of BD are not visible the severe pain and ulceration are

mainly effecting the personal relationships and daily activities which are responsible from high scores in DLQI [32]. Nottingham Health Profile (**NHP**) is another scale which is widely used in assessment of the subjective perception of physical, emotional, and social aspects of the chronic diseases. The Turkish validation of this scale has been also used in assessment of life quality in BD that is evaluating patients in six parts including energy, pain, physical mobility, emotional reactions, sleep and social isolation [34,35]. Life satisfaction index (**LSI**) is a multidimensional scale which can also be used to assess psychological well-being in evaluating the life, mood tone and difference between desired and achieved goals in BD [34]. The genital ulcers, articular involvement and fatigue are reported as the most related clinical symptoms with QoL, reflecting disease activity and causing marked disability, emotional problems pain and sexual dysfunction. Beside the studies mainly focused on the effect of impairment on life quality in BD, Gilworth et al investigated the impact of the disease on individual's lifestyle and called this scale as BD-quality of life (**QoL**) which is based on needs [34].

The impact of different organ involvements such as oral aphthous ulcers, uveitis, arthritis, genital ulcers, deep vein thrombosis and on life quality have been also separately investigated [30,36-38]. Different questionnaire have been used including SF-36 Health survey, State-Trait Anxiety Inventory (**STAI-T**), Beck depression Inventory and Beck Anxiety Inventory in these trials.

Without any association with specific organ involvement, clinical symptoms of BD are significantly affecting life quality of the patients. The lower QoL, marked disability, low sleep quality and chronic pain in BD are also major risk factors for higher incidence of major depression and suicidal thoughts in patients with BD [39,40]. Clinicians should be aware of this effect during the management of BD.

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