

# Musculoskeletal System Involvement in Behçet's Disease

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## INTRODUCTION

Hulusi Behçet reported that 'rheumatoid pain' could be seen in patients with Behçet's disease (**BD**) only a year after he defined the three symptom complex as a chronic inflammatory disease [1]. The frequency of arthropathy ranges between 11-93% according to the department (dermatology-rheumatology-ophthalmology) in which the patients are seen [2,3]. Nearly half of the patients indeed have arthritis or arthralgia [4,5].

Usually, oral ulcers or genital ulcers are the first symptom in patients with BD whereas 9-23% of them have articular involvement on their first visit to a physician. If arthropathy is the first presentation of BD; it is hard to differentiate from other rheumatologic diseases. Chronic arthritis of the wrists or elbows can mimic seronegative rheumatoid arthritis (**RA**) [4].

Arthritis seen in BD is characterized by attacks of exacerbations and remissions. Involvement of the joints is usually monoarticular. Oligoarticular and polyarticular involvements are commonly symmetric in order but asymmetric involvement was also noted in some series [6,7]. Arthritis attacks are usually resolved in a few months and are non-erosive. However, in a small group of patients, deformity of the elbows and ankles has been reported [7-9]. The most commonly affected joints are the knees, ankles, and wrists, respectively [1]. Swollen and warm arthritis without redness is typical in BD; rarely, if arthritis coexists with erythema nodosum, redness can be seen [1,4].

Although BD arthritis is known as non-erosive and non-deforming; it was reported in a study that overall functional impairment and pain is similar to those seen in RA patients [10].

Asymmetric, non-erosive arthritis can be seen in BD which is usually seen in systemic lupus erythematosus (**SLE**), reactive arthritis, ankylosing spondylitis (**AS**), juvenile idiopathic arthritis (**JIA**), psoriatic arthritis (**PsA**), vasculitis, sarcoidosis or inflammatory bowel disease [11].

The duration of attacks does not often exceed a few months, but chronic arthritis can last for months if it develops. In the literature, one case lasted for 4 years. Morning stiffness can be observed in some patients [4].

A good correlation between joint involvement and bone scintigraphy was reported in a study with 211 BD patients by Korean dermatologists. Ninety-one percent of cases were confirmed by the rheumatologists as arthritis. Therefore, it can be said that scintigraphy is a good diagnostic tool for detecting joint involvement in BD patients [12,13]. The extent to which Behçet's disease has been associated with various groups of rheumatic diseases has varied over the years. Although BD was thought of as a seronegative spondylitis just a few decades ago, recent results have shown exactly the opposite [14]. Then it was assumed that BD was a member of the vasculitis spectrum; the common features of auto inflammatory diseases finally came to the attention of researchers in the last decade.

BD carries the common properties of both autoimmune and auto inflammatory diseases. There have also been some cases of two rare autoimmune diseases coexisting in one patient. This can be seen as a proof of the common pathway of similar diseases [15].

Different conclusions have been drawn regarding the relationship between BD and sacroiliac joint involvement. In a study by Yazıcı et al. comparing healthy controls and BD patients, there was no difference between the two groups in terms of the incidence of sacroiliitis. They therefore stated that there is no evidence that BD increased the incidence of sacroiliitis [16]. However, in some studies, it has been claimed that BD caused an increase in sacroiliitis frequency [17-20]. In a community based epidemiological study in Iran, AS was seen in 1.5% of patients with BD. It is stated that BD is one of the causes of secondary AS because its frequency is 2.4 times higher than in the general population [21].

One of the parameters examined in sacroiliitis studies is HLA B27. Chamberlain and colleagues found that the frequency of HLA-B27 increases in BD [22]; in contrast, this increase was not observed in another publication [17].

Most cases are sporadic, but it was reported that there were some families in whom more than one member has been diagnosed as having BD. These are called familial clusters. One of the risk factors for the disease is having a first degree relative with BD [23,24].

Studies showed that some of the symptoms of BD make a cluster. Acneiform lesions such as papules and pustules seem to be more frequent in BD patients with arthritis and it is possible that BD arthritis is related to acne associated arthritis [25].

Enthesopathy is more common in Behçet's disease patients with arthritis and papulopustular lesions than in patients without acneiform rashes. In this case, acne associated arthritis or the papulopustular lesion/arthritis subset can be mentioned [25,26]. Karaca et al. found that this clustering is more prominent in familial BD [27]. It is difficult for acneiform eruptions to be distinguished from ordinary acne and papules/pustules. However, pustular lesions are not sterile; microbiological examinations showed *Staphylococcus aureus* and *Prevotella species* in the pustules [28,29].

Acute phase reactants such as erythrocyte sedimentation rate (**ESR**) and C-reactive protein (**CRP**) usually increase during arthritis attacks [1,6,8,30]. Rheumatoid factor, anti-nuclear antibody (**ANA**) and anti-cyclic citrulline peptide (**anti-CCP**) were found to be negative in patients.

Yurdakul and colleagues found that the frequency of HLA-B5 increases in patients with joint involvement of BD [1].

In Behçet's disease, the synovial fluid has an inflammatory fluid type which contains polymorphonuclear leukocytes. Glucose level is normal in the synovial fluid of patients with BD [8,31]. Ertenli et al. reported the comparison of cytokine levels such as IL-1 $\beta$ , TNF- $\alpha$ , TNF- $\beta$ , IL-1 receptor antagonist (**IL-1ra**), soluble IL-2 receptor (**sIL-2R**) and IL-8 levels in synovial fluid between BD and rheumatoid arthritis and osteoarthritis. IL-1 $\beta$  and TNF- $\alpha$  levels were higher in the synovial fluid of patients with rheumatoid arthritis. IL-1 $\beta$  levels were higher in the synovial fluid of patients with BD than in patients with osteoarthritis. IL-1ra and TGF- $\beta$  levels were found to be higher in the synovial fluid of patients with BD than in patients with osteoarthritis, similar to patients with rheumatoid arthritis. sIL-2r and IL-8 levels were found to be high in patients with BD and in patients with rheumatoid arthritis [32].

As a result, the arthritis seen in BD is not erosive, and arthritis seen in rheumatoid arthritis with cartilage destruction involves high levels of IL-1 $\beta$  and TNF- $\alpha$  cytokines in the synovial fluid. IL-1ra and TGF-beta cytokines play a protective role in inflammatory joints. High levels of sIL-2r and IL-8 reflect a non-specific inflammatory process [32].

Extensive findings had reported in the synovitis of Behçet's disease [33]. Pannus formation is seen in BD, comprising a wide variety of conditions, including the formation of erosive changes. Vernon-Roberts et al. reported on eight synovium samples taken from Behçet's patients and they showed that only the superficial zones of the synovium were found to be affected. Seven of the eight pathology samples had lymphocytes, macrophages, vascular elements, fibroblasts, neutrophils, and dense, inflamed granulation tissue in the synovium superficial zone. Pannus and erosive changes were seen in three cases [33].

## RADIOLOGICAL FINDINGS

Radiological findings are not specific in arthritis seen in patients with BD. However, in patients with chronic arthritis, peripheral joint erosions are not frequent. Large BD series reported either

no radiological changes [30,34,35] or erosions in only a few patients [1,7-9]. Controversially, there are case reports of atypical involvements and different patterns of erosions eg. 'pencil in cup' or reversible osteolytic lesions in BD patients [36-40].

## Fibromyalgia

Fibromyalgia syndrome (**FMS**) is a soft tissue rheumatism type that can cause long term pain and sensitivity in the body, which can be long lasting in the musculoskeletal system. Among the syndromes that cause long term pain and disability, FMS is the first in terms of work loss and drug cost. As with other rheumatic diseases, the incidence with Behcet's disease is also high [41].

In a study conducted in Turkey, the relationship between the prevalence of fibromyalgia and disease activity in Behcet's patients was examined. A total of 100 patients, 60 female and 40 male, were included in the study. Eighteen patients were diagnosed with fibromyalgia (18%). FMS was seen more frequently in women ( $p<0.001$ ). There was no significant difference in age, gender, disease duration, sedimentation rate and CRP levels in patients with and without fibromyalgia. Likewise, symptoms such as fatigue, headache, and joint pain were more common in patients who were diagnosed with fibromyalgia while there was no difference in uveitis, central nervous system involvement, gastrointestinal system involvement or serious organ involvement. In conclusion, fibromyalgia is a widespread and important clinical picture that worsens pain and physical limitations in Behcet's patients [42]. In another study of 70 Behcet's patients, it was reported that FMS was found to be associated with anxiety and depression; but it was not affected by disease activity [43].

## Osteonecrosis

Osteonecrosis can be defined as death due to impaired bone feeding. One of the most common causes is the use of corticosteroids. Early diagnosis is very important because it is irreversible and crippling. Osteonecrosis can also be caused by BD because it can be triggered by any kind of vascular involvement. Rare cases of BD and osteonecrosis have been reported in the literature [31,44,45]. The relationship between anticardiolipin antibodies and bone infarction was mentioned in two BD patients [31]. Magnetic resonance imaging (**MRI**) or bone scintigraphy can be performed for diagnosis.

## Myositis

Myositis is a rare finding that is local or diffuse in BD. Myositis mainly affects the bilateral lower extremities. The local form is more common [46,47]. Common forms may include symptoms such as elevated muscle enzyme, and severe muscle weakness. Muscle biopsy shows significant inflammatory cell infiltration and muscle fiber changes typical for myositis. These findings are similar to the changes seen in polymyositis or dermatomyositis [48]. MR imaging is helpful in showing the affected muscle region [49].

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