# Postprint of a Case Report of Behçet' s Disease with Progressive Central Nervous System Involvement

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**Date:** 2017-12-21T00:00:00+00:00

## Abstract

Behçet' s disease is a systemic vasculitis that is prone to vascular thrombosis and can involve both brain parenchyma and blood vessels. This article reviews a case of a Behçet' s disease patient who neglected "tertiary prevention" — preventing disease progression after onset—resulting in rapid central nervous system involvement following discharge. We summarize the lessons learned and emphasize that timely intervention is required for Behçet' s disease patients with high-risk factors for vascular thrombosis.

## Full Text

### 1. Clinical Case Report

A 36-year-old man presented with a four-year history of recurrent oral ulcers without apparent precipitating factors, characterized by frequent relapses shortly after improvement or healing. Two months prior to admission, he developed genital ulcers triggered by seafood consumption, with two subsequent episodes involving scrotal skin lesions measuring 10 mm in diameter, accompanied by left knee joint pain. He had not received formal treatment with poor outcomes. He was admitted to our rheumatology department with a diagnosis of Behçet' s disease.

On admission, physical examination revealed a conscious patient with five painful oral ulcers distributed on the tongue, lips, and buccal mucosa, each approximately 5 mm in diameter. Cardiopulmonary and abdominal examinations were unremarkable, and neurological examination showed no abnormalities. Laboratory tests showed mild iron deficiency anemia on complete blood count, erythrocyte sedimentation rate (ESR) of 90 mm/h, and C-reactive protein (CRP) of 4.1 mg/L. Biochemical tests showed normal liver and kidney function and blood glucose. Coagulation studies revealed prothrombin time (PT) of

13.1 seconds (normal reference: 9–13), PT normalized ratio of 1.1 (normal reference: 2–4), while activity, activated partial thromboplastin time (APTT), APTT ratio, fibrinogen, thrombin time (TT), and D-dimer were all normal. Rheumatoid factor (RF) was elevated at 56.1 IU/ml (normal reference: 0–15), while various autoimmune antibodies and anti-streptolysin O were normal. Brain MRI showed no obvious abnormalities. Colonoscopy revealed a 0.6 cm × 0.6 cm polyp in the descending colon, which was not removed due to the patient' s prolonged PT. Color Doppler echocardiography showed mild mitral regurgitation without segmental wall motion abnormalities.

During hospitalization, comprehensive examinations revealed no evidence of involvement of vital organs. The patient received immunomodulatory therapy with corticosteroids, thalidomide, and hydroxychloroquine sulfate, along with supportive care, resulting in resolution of oral ulcers and normalization of ESR before discharge.

However, one week after discharge, the patient presented to a local tertiary hospital with sudden bilateral lower limb weakness and dysarthria. Brain MRI revealed cerebral infarction lesions [Figure 1: see original paper]. Details of diagnosis and treatment at that hospital were unavailable, but he improved and was discharged after more than one month of hospitalization.

Retrospective analysis of the patient's medical history revealed several abnormal findings at the time of admission to our hospital: high-density lipoprotein cholesterol (HDL-C) was 1.07 mmol/L (low, normal reference: 1.16–1.42), apolipoprotein B was 0.92 g/L, apolipoprotein A1 was 0.91 g/L (normal reference: 1.0–1.6), lipoprotein(a) was 1074 mg/L (normal reference: <300), and platelet aggregation was 93.2% (normal reference: 35–75%). Color Doppler ultrasound of the carotid and vertebral arteries showed no abnormalities, while ultrasound of the extremity vessels revealed multiple hyperechoic lesions at the bifurcation of the right femoral artery, the largest measuring 3.7 mm × 4.0 mm, indicating multiple arteriosclerotic plaques [Figure 2: see original paper].

## Discussion

Behçet's disease is a chronic, relapsing systemic vasculitis characterized by recurrent oral-genital ulcers, uveitis, and skin lesions, with potential involvement of joints, blood vessels, gastrointestinal tract, and nervous system [1]. The disease course typically involves alternating periods of relapse and remission. Vascular involvement, which may affect veins or arteries, represents a critical factor for disability and mortality in Behçet' s disease. Vascular inflammation is closely associated with thrombosis, as endothelial inflammatory injury promotes thrombus formation and correlates with disease activity [2]. Platelet aggregation at sites of vascular injury plays an important role in coagulation and thrombogenesis.

Soluble receptor agonists at sites of vascular injury initiate platelet aggregation and thrombus formation. Carberry et al. [3] found that hemodynamic changes

represent an important factor affecting platelet aggregation. Under conditions of vascular inflammatory injury, platelet aggregation progressively stabilizes thrombi, with platelets more readily adhering to low shear regions downstream of thrombi.

Venous involvement is common in Behçet' s disease and may serve as a diagnostic criterion or even the initial manifestation, particularly in younger patients. Superficial vascular involvement is often permanent. Venous involvement also underlies the pathogenesis of non-specific hypersensitivity reactions, erythema nodosum, and uveitis. Veins at all levels may be affected, especially those prone to thrombosis such as the superior and inferior vena cava and iliac-femoral veins. Less common sites include the hepatic portal vein and intracranial veins [4].

Elevated expression of pro-inflammatory cytokines such as TNF- and IL-6 in Behçet's disease patients is associated with insulin resistance, resulting in various manifestations of metabolic syndrome. Metabolic disturbances in BD patients may constitute risk factors for vascular endothelial dysfunction, while altered glucose metabolism and insulin resistance promote the development of metabolic syndrome.

Neuro-Behçet' s disease (NBD) is generally considered to have a relatively low incidence but poor prognosis. NBD is more common in males, with a reported incidence of 5%–30%. It can involve parenchymal or non-parenchymal structures. Parenchymal NBD, including venous sinus thrombosis, predominantly affects the brainstem, diencephalon, cerebral hemispheres, and spinal cord, manifesting as meningoencephalitis associated with small vessel vasculitis. Cerebrospinal fluid analysis may reveal lymphocytic pleocytosis and elevated protein. Non-parenchymal NBD includes venous sinus thrombosis, arterial embolism, or aneurysm; intracranial venous sinus thrombosis, a vasculitis of large veins, represents the main form of vascular NBD. MRI is the preferred diagnostic modality for NBD, typically showing iso- or hypointense signals on T1-weighted images and hyperintense signals on T2-weighted images [5].

For parenchymal NBD, treatment with corticosteroids combined with immunosuppressants is recommended, while for venous sinus thrombosis, corticosteroids combined with anticoagulants are advised. NBD management can be divided into two phases: treatment of acute attacks and prevention of relapse. High-dose intravenous corticosteroids may be used during acute attacks, followed by oral maintenance therapy for 6–12 months depending on type and severity. Immunosuppressants such as azathioprine, mycophenolate mofetil, and methotrexate are commonly used for relapse prevention [6]. For refractory cases or patients intolerant to standard therapy, cyclophosphamide, interferon- , or anti-TNF- monoclonal antibodies (infliximab, etanercept, or adalimumab) may be employed. Recent studies have shown that newer agents such as tocilizumab, canakinumab, and anakinra, which exert biological effects by inhibiting IL-1 and IL-6 pathways, may serve as alternative options for patients with progressive or relapsing disease [7].

The use of anticoagulation therapy for BD patients with large vessel thrombosis remains controversial. Over 87% of Israeli and American rheumatology experts, compared with 40%–44% of Turkish specialists, administer anticoagulants at diagnosis for patients with venous thrombosis. Warfarin is prescribed by 56% of American physicians and 45% of Israeli physicians, but only by 5%–18% of Turkish doctors. For intracardiac thrombosis, 96% of American, 94% of Israeli, and 60% of Turkish rheumatology experts prescribe warfarin at diagnosis, with 70%, 39%, and 33% of these physicians, respectively, recommending lifelong therapy [8].

In clinical practice, we have encountered NBD patients not infrequently and have accumulated considerable experience in NBD management. In this case, comprehensive evaluation during hospitalization revealed markedly elevated platelet aggregation rate, decreased HDL-C, mildly reduced apolipoprotein A1, significantly elevated lipoprotein(a), and multiple arteriosclerotic plaques at the right femoral artery bifurcation. Consequently, aspirin was briefly administered. However, due to slightly prolonged PT (13.1 seconds) during colonoscopy, polypectomy was not performed, aspirin was discontinued, and the issue was not emphasized at discharge. One week after discharge, the patient developed sudden speech disturbances and mild limb paralysis; MRI revealed cerebral vascular embolism, suggesting neuro-Behçet' s disease. If low-dose aspirin had been continued, it would not only have served as therapy for Behçet' s disease and prevention of thrombosis or neuro-Behçet' s disease, but would also have been beneficial for the patient' s colonic polyps and arthralgia. Had greater attention been paid to tertiary prevention— "preventing disease progression after onset" —this adverse event might have been avoided to some extent.

Figure 1. MRI of the case with Behçet' s disease before (A1-D1) and after (A2-D2) brain involvement. A1-D1: T1WI showed complete structure of brain without lesions; A2-D2: T2Flair array shows multiple spots or flake foci with increased signal intensity.

Figure 2. Arteriosclerosis in the bifurcate orifice of the right femoral artery.

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*Note: Figure translations are in progress. See original paper for figures.*