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Cerebral venous sinus thrombosis in Behçet's disease: A retrospective single-centre study

Behçet hastalığında serebral venöz sinüs trombozu: Retrospektif tek merkezli bir çalışma

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Abstract

Objective: This study aims to analyze the clinical, laboratory findings, treatments and prognosis of Behçet's disease (BD)-associated cerebral venous sinus thrombosis (CVST) and to compare the clinical features of BD patients with and without CVST.

Methods: In this single-center retrospective study, we reported a series of 24 consecutive CVST patients (20 males and 4 females; mean age 34±12 years) were diagnosed with BD according to international study group criteria. The control group included 36 (24 males and 12 females; mean age 32±8 years) consecutive patients with BD without CVST from the same center.

Results: Headache (n=20, 83.3%) was the most common complaint at admission in patients with BD-associated CVST. In comparison between BD cases with and without CVST, extracranial vascular involvement was more frequent in the BD-associated CVST patients (p=0.03). Twenty-three (95.8%) patients received corticosteroid (CS) treatment. A total of 8 BD-associated CVST patients received anti-tumor necrosis factor-alpha (anti TNF-α) treatment. There was no significant difference in the rate of CS use before and after anti-tumor necrosis factor-α (TNF-α) treatment (p=0.345) but CS dose was significantly reduced after treatment (p=0.018). When patients with BD- associated CVST who receive or did not receive anti-TNF-α treatment compared, on cranial imaging, thrombosis was significantly less in patients received anti TNF-α treatment than who did not (p=0.02).

Conclusion: When the CVST was detected in young men patients with headache, BD should come to mind and patients should also be evaluated in this respect. As the risk of extracranial vascular involvement increases in such patients, they should be systematically evaluated in terms of vascular involvement. Although CS treatment could not be stopped completely with anti TNF-α drugs, it could be reduced. Significant radiological improvement was observed with anti-TNF-α treatment.

Keywords: Behçet's disease, cerebral venous sinus thrombosis, anti-tumor necrosis factor-α, treatment, neurobehçet

Öz

Amaç: Bu çalışmanın amacı, Behçet hastalığı (BH) ile ilişkili serebral venöz sinüs trombozunun (SVST) klinik, laboratuvar bulgularını, tedavilerini ve prognozunu analiz etmek ve SVST olan ve olmayan BH hastalarının klinik özelliklerini karşılaştırmaktır.

Yöntem: Bu tek merkezli retrospektif çalışmaya, uluslararası çalışma grubu kriterlerelerine göre BH tanısı konan 24 ardışık SVST hastası (20 erkek ve 4 kadın; ortalama yaş 34±12 yıl) dahil edildi. Kontrol grubu aynı merkezden 36 (24 erkek ve 12 kadın; ortalama yaş 32±8 yıl) SVST'si olmayan ardışık BH hastasıydı.

Bulgular: Baş ağrısı (n=20, %83,3) BH ile ilişkili SVST'li hastalarda başvuru sırasında en sık görülen şikayetti. SVST olan ve olmayan BH olguları karşılaştırıldığında, BH ile ilişkili SVST hastalarında ekstrakraniyal vasküler tutulum daha sıktı (p=0,03). Yirmi üç (%95,8) hasta kortikosteroid (KS) tedavisi aldı. Toplam 8 BH ile ilişkili SVST hastası, anti-tümör nekroz faktör (TNF-α) tedavisi aldı. TNF-α tedavisi öncesi ve sonrası KS kullanım oranında anlamlı fark bulunmadı (p=0,345), ancak tedavi sonrası KS dozu anlamlı olarak azalmıştı (p=0,018). BH ile ilişkili SVST olan ve anti-TNF-α tedavisi alan ve almayan hastalar karşılaştırıldığında, kraniyal görüntülemede, anti TNF-α tedavisi alan hastalarda tromboz, almayanlara göre anlamlı olarak daha azdı (p=0,02).

Sonuç: Baş ağrısı olan genç erkek hastalarda SVST saptandığında akla BH gelmeli ve hastalar bu açıdan değerlendirilmelidir. Bu hastalarda ekstrakraniyal vasküler tutulumu riski arttığından, vasküler tutulum açısından sistemik olarak değerlendirilmelidirler. Anti TNF-α ilaç tedavisi ile KS tedavisi tamamen kesilesemese de, dozu azaltılabilir. Anti-TNF-α tedavi ile belirgin radyolojik iyileşme gözlendi.

Anahtar Kelimeler: Behçet hastalığı, serebral venöz sinüs trombozu, anti-tümör nekroz faktör-α, tedavi, nörobehçet

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Introduction

Behçet's disease (BD) is a systemic vasculitis that can involve many tissues; patients often develop oral and genital ulcers.[1,2] Although many organs and systems can be affected, neurological involvement (neuro-BD) is uncommon. Both the central and peripheral nervous systems may be affected in such patients. The central nervous system (CNS) involvement may be parenchymal or non-parenchymal; the latter includes cerebral venous sinus thrombosis (CVST), arterial occlusion, and/or aneurysms. Although CVST is a major manifestation of non-parenchymal involvement, only a few case reports and few retrospective clinical series have described the treatment and long-term outcomes thereof. Primary treatment of neurological involvement in BD undoubtedly requires immunosuppression with or without corticosteroid (CS). Anti-tumor necrosis factor-α (anti-TNF-α) agents are now used for BD complications but experience on their effect on CVST is limited.[1,3,4]

Since data on the clinical features, disease course and outcome of BD-related CVST is limited, we tried analyzing the clinical, laboratory findings, treatments and outcomes of BD-associated CVST and compare the clinical features of patients with BD with and without CVST who were followed up in a single centre.

Materials and Methods

Patients

Between June 2014 and January 2018, patients diagnosed with BD according to the 1990 guidelines of the International Study Group or the International Criteria for Behçet's disease were included. CVST was diagnosed based on typical clinical features, magnetic resonance venography (MRV), cranial magnetic resonance imaging (MRI) features, and neurologist opinion. Patients with comorbidities (trauma, infection, malignancy, or oral contraceptive use) were excluded. The control group included thirty-six consecutive patients with BD without CVST from the same period. CVST patients were compared as patients who received and did not receive anti TNF-α treatment.

Methods

Data on 24 patients with BD-associated CVST and the 36 controls were retrieved from our electronic database and retrospectively reviewed. We recorded age at the onset of problems, and at diagnosis, along with disease duration, laboratory parameters, the cranial and extracranial locations of thromboses as revealed by imaging, and the course of cranial imaging over the years. The clinical findings were compared to those of the controls. Immunosuppressant (IS) and anticoagulant treatments prescribed at diagnosis, along with treatment duration and changes therein during follow-up, were recorded. Patients receiving anti-TNF-α treatment were examined in detail in terms of previous and ongoing treatments, treatment duration, and long-term results. The disease activity was evaluated by measuring the levels of clinical and acute phase reactants, imaging results and, patients on anti-TNF treatment, Behçet Disease Current Activity Form (BDCAF) scores. We contacted all patients by telephone.

The remission criteria were an absence of BD-related symptoms, no new vascular involvement or progression of existing vascular involvement, normal levels of acute phase reactants, and a methylprednisolone dose ≤10 mg/day for 3 months. Recurrence was defined as the development of new symptoms and/or sufficient progression of a pre-existing BD-related symptom to necessitate an increase or change in treatment. Infliximab was intravenously administered at an induction dose of 5 mg/kg during weeks 0, 2, and 6, and every 8 weeks thereafter. Adalimumab was given subcutaneously (40 mg every 2 weeks) along with etanercept (50 mg weekly).

The approval of the institutional ethical committee was obtained (University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, approval number: 541, date: 11.09.2020).

Statistical Analysis

Histograms and probability plots were generated. We used the Kolmogorov-Smirnov or Shapiro-Wilk test to determine whether variables were normally distributed. Continuous variables with normal distributions are expressed as mean ± standard deviation (SD); all other variables are expressed as median values (range). Categorical variables were compared using the chi-squared or Fisher's exact test. Continuous variables were compared using Student's t-test. Non-normally distributed continuous variables were compared using the Mann-Whitney U test and the Wilcoxon test. A p-value <0.05 was considered statistically significant. All tests were performed using SPSS for Windows software (ver. 22.0; IBM Corp., Armonk, NY, USA).

Results

Demographic Characteristics and Clinical Features

In total, 24 (20 males and 4 females) of 571 patients with BD (4.2%) were diagnosed with BD-associated CVST; 54

exhibited neurological involvement (9.4%), and headache [n=20 (83.3%) patients] was the most common complaint at admission. Three (12.5%) patients presented with oral aphthae and 1 (4.2%) patient with hemoptysis due to pulmonary artery aneurysm at admission.

Of the patients with CVST, the most common BD-related symptoms were oral aphthae in 24 (100%) and genital ulcers in 21 (87.5%) (Table 1).

Neurological Imaging

CVST was diagnosed using MRV and cranial MRI. A neuroradiologist (K.A.; 8 years of experience) reviewed all brain MRI scans while blinded to the clinical and laboratory data, and treatments. Multiple sinus involvement (19, 79.2%) was more common than single sinus involvement (5, 20.8%). No patient had a cerebral infarction, bleeding, or permanent neurological damage. The parenchymal involvement was observed in 32 (5.6%) patients and 2 (0.3%) exhibited both parenchymal involvement and CVST. All patients had control imaging including brain MRI and MR venography. In 10 of 23 patients at their final visit, CVST was continuing on MR venography and brain MRI.

Extracranial Thrombosis

In total, 16 (66.7%) patients exhibited extracranial vascular involvement; lower extremity deep vein thrombosis was seen in 8 (33.3%) patients, jugular vein thrombi in 7 (29.2%), and pulmonary thromboembolism in 6 (25.0%) (Table 1).

Laboratory Findings

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level were elevated in 20 (83%) patients at admission. The mean ESR at presentation was 54.08 (0-20) mm/h, and the mean CRP level 66.7 (0-5) mg/dL. After 1 year, the ESR was higher in nine (39%) patients and the CRP level was higher in six (26%); the mean ESR and CRP level were 19.04 mm/h and 9.26 mg/dL, respectively. Compared to baseline, the values decreased significantly after 1 year (both $p<0.01$). Antinuclear antibody status was negative in 15 patients and weakly positive (≤1:160) in 2 patients. Anti-extracted nuclear antigen antibody status was negative in all patients. Of the 16 patients evaluated, all were negative for antiphospholipid antibodies (anticardiolipin antibody immunoglobulin G (IgG)/IgM, lupus anticoagulant, and anti-beta-2 glycoprotein (anti-ß2GPI) IgG/IgM]. HLA B51 analysis was performed in six (25%) patients; four (16.7%) were positive.

Table 1. Clinical and demographic characteristics of Behçet-associated CVST patients

Parameter	Values, n (%)
Age, mean ± SD (years)	34±12
Onset of symptoms, mean ± SD (years)	27.2±10.8
Age at diagnosis, mean ± SD (years)	27.9±10.8
Duration of the disease, mean ± SD (months)	80.7±59.1
Gender	
Male	20 (83.3)
Female	4 (16.7)
Localizations of Sinus Vein Thrombosis	
Transverse sinus	20 (83.3)
Superior sagittal sinus	18 (75.0)
Sigmoid sinus	16 (66.7)
Cavernous sinus	3 (12.5)
Symptoms	
Headache	20 (83.3)
Oral aphthae	3 (12.5)
Hemoptysis	1 (4.2)
BD-Related Clinical Findings	
Oral aphthae	24 (100)
Papuloustular lesion	14 (58.3)
Superficial thrombophlebitis	7 (29.2)
Erythema nodosum	3 (12.5)
Genital ulcer	21 (87.5)
Ocular involvement	8 (33.3)
Positive Pathergy test	6 (25)
Arthralgia	8 (33.3)
Arthritis	2 (8.3)
Localizations of Extracranial Vascular Involvement	**16 (66.7)**
Deep vein thrombosis	8 (33.3)
Jugular vein thrombosis	7 (29.2)
Pulmonary thromboembolism	6 (25.0)
Vena cava thrombosis	5 (20.8)
Iliac vein thrombosis	3 (12.5)
Pulmonary artery aneurysm	2 (8.3)
Cardiac thrombus	1 (4.2)
Treatments on CVST diagnosis	
Colchicine	16 (66.7)
Azathioprine	14 (58.3)
Corticosteroid (all)	23 (95.8)
Pulse corticosteroid	18 (75.0)
Cyclophosphamide (intravenous)	11 (45.8)
Anti TNF-α	1 (4.2)
Anticoagulant	19 (79.2)
Warfarin	16 (66.7)
Enoxaparin	19 (79.2)

BD: Behçet's disease, CVST: Cerebral venous sinus thrombosis, TNF-α: Tumor necrosis factor-alpha

Treatments and Outcomes

Treatments on CVST Diagnosis

Previous treatments included ISs and anticoagulants. In total, 16 (66.7%) patients with BD-associated CVST were prescribed colchicine and 14 (58.3%) were prescribed azathioprine. Twenty-three (95.8%) patients received CS (methylprednisolone or an equivalent) treatment. Eighteen (75%) patients received pulsed CSs and five (20.8%) received CS at a starting dose of 1 mg/kg/day, which that was gradually tapered and stopped. The pulsed protocol was methylprednisolone or an equivalent at 1 g/day for 3-5 days (induction), followed by 1 mg/kg/day (maintenance); the CS was then tapered or stopped. Eleven patients (45.8%) received pulsed cyclophosphamide (CYC) treatment (1 g per month, intravenously for 6 months, or 500 mg every 15 days). Anti-TNF-α (adalimumab) therapy was prescribed for one (4.2%) patient (40 mg subcutaneously every 2 weeks). Low-molecular-weight heparin (enoxaparin, 100 IU/kg x 2) was given during the acute period and then replaced with warfarin (used only for maintenance treatment). Before anticoagulant treatment, all patients were evaluated in terms of pulmonary artery aneurysms. Anticoagulant treatment was prescribed for 19 (79.2%) patients. All patients received enoxaparin (Table 1).

Treatment During Follow-up

Patients who received current treatments were evaluated at outpatient clinic visits every 1-3 months according to their clinical status after discharge. Ten of 16 (66.7%) patients who received colchicine treatment was switched to azathioprine and/or anti TNF-α treatment after one year because they were colchicine-resistant.

Initially, 18 (75%) patients received pulsed CS treatment. Two (8%) patients received repeat-pulsed treatments because of recurrence during follow-up. Of 23 (95.8%) patients prescribed CSs, the doses were reduced and ultimately discontinued in 16 (69.5%). At the last visit, 7 of 23 patients were receiving low dose (<10 mg/day) CS treatment.

Initially, 19 (79.2%) patients were prescribed anticoagulants, of whom 16 (66.7%) were followed up with warfarin only; 10 (43.5%) continued on both anticoagulants and warfarin. None of the 11 (45.8%) CYC-treated patients received a second CYC treatment after 6 months; all were switched to maintenance azathioprine. At the beginning, 14 (58.3%) patients received azathioprine treatment. Number of patients who were treated with azathioprine increased to 16 (66%) after one year. No patient who received colchicine, azathioprine, CYC and CS treatment developed any drug-related complications. Seven (29%) patients were switched to anti-TNF-α treatment because they were resistant to other treatments.

Analysis of CVST Patients Receiving Anti TNF-α Treatment

The mean age of eight patients (five males and three females) who received anti-TNF-α treatments was 30.6±8.3

Table 2. Clinical characteristics of Behçet's disease-associated CVST patients who received anti TNF-α treatment

Patient	Anti TNF-α treatment	Age	Previous treatment	The period before anti TNF-α treatment	The period of anti TNF-α treatment	Concomitant IS	Anti TNF-α related complication	Response at third month	Treatment at last visit
1	IFX	33	CS (pulse and maintenance) CYP, AC	5 months	64 months	CS, AZA	No	CR	IFX, AZA
2	IFX	25	CS (not pulse) CYP, AC	12 months	58 months	CS, AZA	No	CR	IFX, AZA
3	ADA	29	CS (pulse and maintenance) Colchicine, AC	4 months	70 months	CS, AZA	No	CR	ADA, AZA
4	IFX	38	Colchicine, AC	60 months	10 months	No	No	CR	IFX
5	ETN	21	CS (pulse and maintenance) Colchicine, AC	4 months	45 months	CS, colchicine	No	CR	ETA, CS, colchicine
6	IFX	21	CS (not pulse), Colchicine	108 months	24 months	CS, colchicine	No	CR	IFX, CS colchicine
7	IFX	45	CS (pulse and maintenance), Colchicine, AZA, AC	1 months	16 months	CS, AZA	No	CR	IFX, AZA
8	IFX	33	CS (pulse and maintenance), Colchicine, AZA, AC	12 months	60 months	CS, AZA	No	CR	IFX, AZA, AC

AC: Anticoagulation, ADA: Aadalimumab, AZA: Azathioprine, CR: Complete response, CS: Corticosteroid, CYC: Cyclophosphamide, ETN: Etanercept, IFX: Infliximab, IS: Immunosuppressant, TNF-α: Tumor necrosis factor-alpha

years; six of these patients were prescribed infliximab; one each received adalimumab and etanercept. The mean disease duration, which was 8.5 [minimum-maximum (min-max: 1-108)] months before anti-TNF-α treatment, increased to 51 (min-max: 10-70) months after anti-TNF-α treatment. The mean duration of CS use before anti-TNF-α treatment was 4 (min-max: 0-12) months and that after TNF-α treatment 2.5 (min-max: 0-45) months. There was no significant difference in the rate of CS use before and after anti-TNF-α treatment (p=0.345). The mean dose of CS before anti-TNF-α treatment was 34.1±22.2 mg/day, and that after anti-TNF-α treatment was 2.7±1.7 mg/day; the CS dose was significantly reduced after treatment (p=0.018). Although seven patients had received anticoagulants for an average of 3 months before anti-TNF-α treatment, this was then discontinued in six; only one patient received anticoagulants for 60 months (Table 2).

Seven of 8 CVST patients received anti TNF-α treatment had received CS treatment before anti TNF-α. At the last visit, 2 patients were continuing to receive CS treatment. When the patients received and did not receive anti TNF treatment were compared in terms of CS and anticoagulant use, there was no significant difference (p=0.679 and p=0.101, respectively) (Table 3).

During the follow-up period, all 23 patients were evaluated for CVST by MR venography and brain MRI. It was found that thrombosis continued in 10 patients. At the last visit of anti-TNF-α treatment, the cerebral venous thrombosis evident on cranial MRV disappeared in seven of the eight patients and did not recur (Figures 1 and 2). The thrombosis decreased in the other patient (Figure 3). On cranial imaging, thrombosis was significantly less in patients received anti TNF-α treatment than who did not (p=0.02)

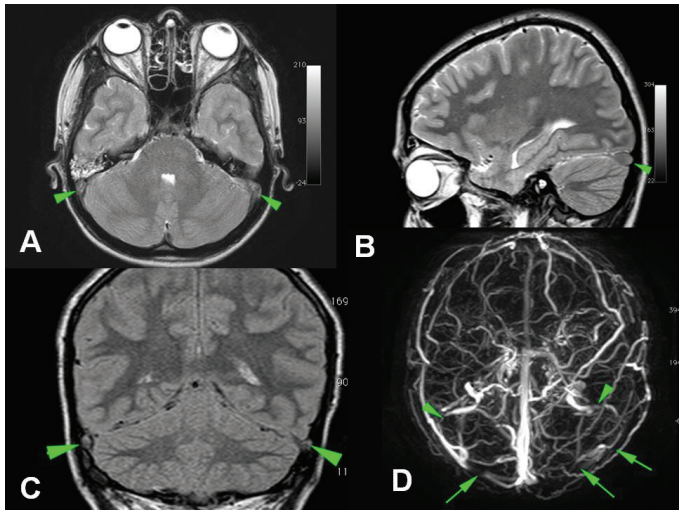

Figure 1. Magnetic resonance imaging before anti-TNF (A-D) of a 21-year-old female patient with dural venous sinus thrombus diagnosed with Behçet's. Axial T2-weighted MR (A), sagittal T2-weighted MR (B), and coronal FLAIR (C) images show thrombus in bilateral transverse sinuses (arrowhead). A magnetic resonance venography (D) shows thrombus in bilateral transverse sinuses (arrow) and sigmoid sinuses (arrowhead)

TNF: Tumor necrosis factor, MR: Magnetic resonance

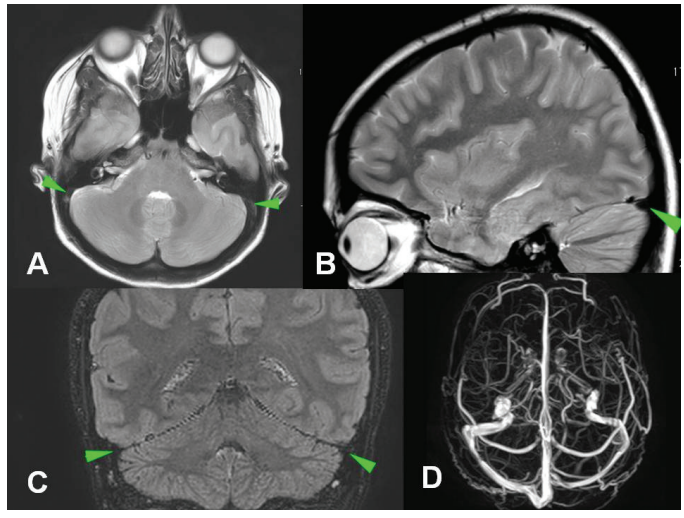

Figure 2. Magnetic resonance imaging after anti-TNF (A-D) of a 21-year-old female patient with dural venous sinus thrombus diagnosed with Behçet's. Axial T2-weighted MR (A), sagittal T2-weighted MR (B), and coronal FLAIR (C) images show no thrombus in bilateral transverse sinuses (arrowhead). A magnetic resonance venography (D) shows no thrombus in bilateral transverse sinuses (arrow) and sigmoid sinuses (arrowhead)

TNF: Tumor necrosis factor, MR: Magnetic resonance

Table 3. Comparison of the characteristics of BD-associated CVST patients in terms of anti TNF-α treatment

	BD-CVST received anti TNF treatment n, (%)	BD-CVST did not receive anti TNF treatment n, (%)	p-value
Age, mean ± SD (years)	30.6±8.3	37.2±13.5	0.222
Gender (male)	5 (62.5)	14 (93.3)	0.06
Duration of disease, mean ± SD (months)	65.3±32.6	94±67	0.271
On corticosteroid at last visit	2 (25)	5 (33.3)	0.679
On anticougulants at last visit	1 (12.5)	7 (46.7)	0.101
Thrombosis at the last cranial imaging	1 (12.5)	9 (60)	0.02
ESR (mm/h) at last visit (mean ± SD)	11±10	23.3±20	0.133
CRP (mg/dL) at last visit (mean ± SD)	3.8±3.6	12.1±20	0.267

BD: Behçet's disease, CRP: C-reactive protein, CVST: Cerebral venous sinus thrombosis, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, TNF-α: Tumor necrosis factor-alpha

(Table 3). No patient who received anti-TNF-α treatment developed any permanent neurological sequelae or drug-related complications.

Comparison Between BD Cases with and without CVST

The control group included thirty-six consecutive patients with BD without CVST from the same period; they all had oral aphthae. Skin involvement was more common in the controls, while the extracranial vascular involvement was more frequent in the patients with BD with CVST (p=0.03 and p=0.03, respectively) (Table 4).

Discussion

Of all patients with BD, 9.4% showed neurological involvement. The incidence rates of CVST were 4.2% in BD and 44% in neuro-BD patients. Anti-TNF-α treatment was relatively safe and effective in patients with BD-associated CVST; most patients exhibited no recurrence. The frequency of neuro-BD ranges from 5% to 35%.[5] In an autopsy series, 20% of 170 patients with BD exhibited neurological involvement.[6] Bolek et al.[7] reported a neuro-BD rate of 18.4%. Among a cohort of 820 patients with BD, 64 (7.8%) had CVST. The prevalence of CVST in neuro-BD patients varies from 10% to 20%.[8,9] In this study, the rate of neurological involvement among all patients with BD was 9.4%. The incidence of CVST in patients with BD was 4.2%, compared to 44% in neuro-BD patients. Although some studies found that CVST was more common in males (65.6% and 68.5% of all patients), others reported no gender difference.[4,8,10] We found that the disease was significantly more common in young males (83.3%). The CVST disease duration was approximately 6.5 years. The most common initial complaint was headache; most patients presented to the neurology clinic. BD is the most common cause of CVST in some Middle Eastern countries.[11,12] The most common findings of BD-associated CVST are headache, focal neurological deficits, and changes in consciousness, which are mainly attributed to intracranial hypertension. Saadoun et al.[8] found that the initial complaint was often a severe headache that had developed a few days earlier, followed by fever and focal deficit. In an Italian study, the most common presentation of neuro-BD was an acute attack with motor symptoms and cognitive changes.[13] In contrast, most of our patients complained of sub-acute chronic and progressive headache, although some also showed behavioral changes. The parenchymal involvement was seen in only two CVST patients. No patient exhibited permanent neurological deficits, either at admission or during long-term follow-up. The headache improved in most patients. CVST patients may develop visual problems caused by neurological involvement or uveitis.[14] Eight of our CVST patients had uveitis, but none suffered permanent

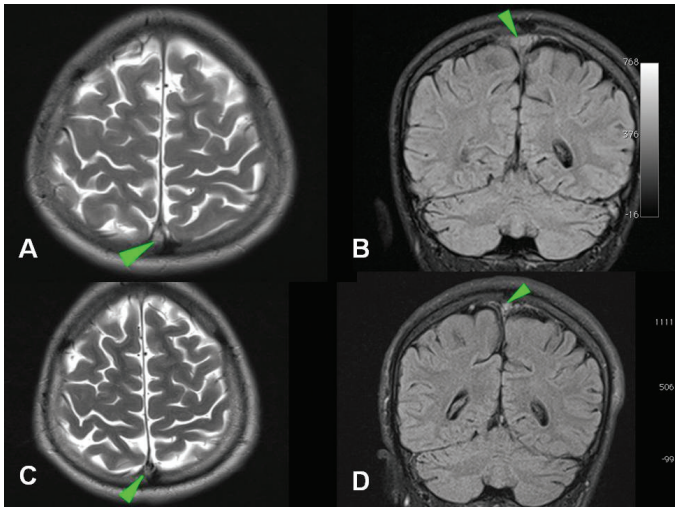

Figure 3. Magnetic resonance imaging before (A, B) and after (C, D) anti-TNF of a 21-year-old male patient with dural venous sinus thrombus diagnosed with Behçet's. Axial T2-weighted MR (A), and coronal FLAIR (B) images show thrombus in superior sagittal sinus (arrowhead). Axial T2-weighted MR (C), and coronal FLAIR (D) images show partial thrombus in superior sagittal sinus (arrowhead)

TNF: Tumor necrosis factor, MR: Magnetic resonance

Table 4. Demographics of patients with BD patients with and without CVST

	Behçet's with CVST n, (%)	Behçet's without CVST n, (%)	p-value
Age mean ± SD years	34±12	32±8	0.373
Gender (male)	20 (83.3)	24 (66.7)	0.144
Duration of the disease, mean ± SD (months)	80.7±59.1	74±40.7	0.265
Skin involvement	18 (75)	34 (94)	**0.03**
Genital ulcer	21 (87.5)	26 (72.2)	0.148
Ocular involvement	8 (33)	10 (27.8)	0.646
Positive Pathergy test	6 (25)	7 (19.4)	0.611
Arthritis	2 (8.3)	8 (22.2)	0.142
Extracranial vascular involvement	16 (66.7)	14 (38.9)	**0.03**
Gastrointestinal system involvement	0 (0)	1 (2.8)	0.309

BD: Behçet's disease, CVST: Cerebral venous sinus thrombosis, SD: Standard deviation

vision loss. As the gold standard imaging modalities, MRV and cranial MRI, which were used in this study, play critical roles in CVST diagnosis. Approximately 80% of our patients exhibited involvement of more than one sinus. The transverse sinus was the most commonly involved, followed by the superior sagittal sinus, consistent with the literature.[4,15] Two-thirds of patients exhibited extracranial vascular involvement: arterial involvement (pulmonary artery aneurysms and thrombi) was seen in eight patients, while venous and cardiac thromboses were observed in all other patients (mostly deep vein thromboses in the lower extremities). Compared to the patients with BD without CVST, extracranial vascular involvement was more common in CVST patients. As reported by Shi et al.,[4] among others, when BD is complicated by thrombosis, any vascular thrombus increases the risk of other thromboses.[16] Tunc et al.[17] found that, in BD patients with CVST, the risk of extracranial vascular involvement was high. Therefore, after the diagnosis of BD-associated CVST, all patients should be thoroughly evaluated for possible vascular involvement of other organs (including the heart). Although CSs are the cornerstone of treatment for neuro-BD, colchicine, azathioprine, and CYC serve as steroid-sparing agents that prevent relapse.[18] High-dose CS and CYC treatments are recommended for patients with BD exhibiting major organ involvement, but long-term use is limited by toxicity. In our study, five (20%) patients received high-dose CSs and 2 (8%) were given CYC before anti-TNF-α treatment.

TNF-α is a major proinflammatory cytokine that plays a critical role in the pathogenesis of BD. It is widely accepted (including by the European League Against Rheumatism) that anti-TNF-α agents (usually infliximab, adalimumab, and etanercept) are effective for treating BD.[19-21] In our study, six (25%) patients received infliximab, while one (4%) received adalimumab and another (4%) etanercept. There was no recurrence in any patient during 43 months of anti-TNF-α treatment. Significant clinical and laboratory improvements were evident by 3 months. Seven patients had received CSs for an average of 4 months before anti-TNF-α treatment, and initially remained on the CSs. However, these were discontinued after 3 months in four patients, and after 24 months in the remaining patient.

At the final follow-up, only two patients were taking ≤4 mg/day methylprednisolone or equivalent. Although the duration of CS use before and after anti-TNF-α treatment did not differ between the patients (p=0.345), the CS dose decreased significantly after anti-TNF-α treatment (mean ± SD, 34.1±22.2 to 2.7±1.7 mg/day, p=0.018). In patients with BD-associated CVST and vascular BD, it is unclear how long anti-TNF-α treatments should be given. Aksoy et al.[22] reported recurrence in two of three patients with vascular BD who discontinued anti-TNF-α treatment. Our patients were followed up for an average of 43 months; all entered remission during month 3 and none suffered recurrence. The mean BDCAF score was 2.2±1.4 at baseline and decreased significantly to 0.5±0.9 at month 3, and 0.3±0.5 at the last follow-up (both p=0.01). Cranial MRI revealed complete resolution of the thromboses of seven patients, but significant recanalization was seen in one case. No patient had any treatment-related complications. In a series of neuro-BD patients, the mortality rate was reported to be around 10%. Neuro-BD patients with CVST have better prognoses than those with parenchymal involvement.[23,24] Saadoun et al.[8] reported only 4 deaths (6%) among 64 patients followed up for a mean of 8 years; diseases other than BD (e.g. myocardial failure) or parenchymal neurological involvement attributable to BD caused the deaths. The mortality rate was similar to that of patients with CVST unrelated to BD.[25] In our study, one (4%) patient died of myocardial infarction outside the hospital. Our findings are consistent with the literature. Although the use of anti-TNF-α drugs to treat parenchymal neuro-BD has received some attention,[7,26] their use in neuro-BD patients with CVST is limited and the studies were retrospective. Although the number of patients is small, we found that long-term anti-TNF-α agents can be safely used to treat CVST, which is the best-known form of non-parenchymal neuro-BD. Although CS treatment could not be stopped completely with anti TNF-α drugs, it could be reduced.

Study Limitations

Our study was retrospective and no disease activity index was universally applied to evaluate neuro-BD activity. Therefore, we used the BDCAF index adopted in other studies to evaluate anti-TNF-α treatment efficacy. Other patients were evaluated according to the absence of CVST-related disease activity, the laboratory and imaging results, and the CS doses required.

Conclusion

As the risk of extracranial vascular involvement increases in BD-CVST patients, they should be systematically evaluated in terms of vascular involvement. Although the number of patients is small, we found that long-term anti-TNF-α treatment was safe and effective. Although CS treatment could not be stopped completely with anti TNF-α drugs, it could be reduced. Significant radiological improvement was observed with anti-TNF-α treatment.

Ethics

Ethics Committee Approval: The approval of the institutional ethical committee was obtained (University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital, approval number: 541, date: 11.09.2020).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: L.A., M.S., Design: L.A., Data Collection or Processing: L.A., K.A., C.G., Analysis or Interpretation: L.A., K.A., M.Ö., M.S., Literature Search: L.A., Writing: L.A.

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References

1. Hatemi G, Seyahi E, Fresko I, Talarico R, Hamuryudan V. One year in review 2018: Behçet's syndrome. Clin Exp Rheumatol 2018;36(6 Suppl 115):13-27.
2. Esatoglu SN, Kutlubay Z, Hatemi G. Highlights of the 18th International Conference on Behçet's syndrome. Clin Exp Rheumatol 2018;36(6 Suppl 115):3-12.
3. Aydin AE, Gunduz O, Sari I, Saatci AO, Yilmaz E, Akkoc N. Papilledema Caused by Cerebral Venous Sinus Thrombosis in a Patient With Behcet Disease. Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases 2013;19:52.
4. Shi J, Huang X, Li G, et al. Cerebral venous sinus thrombosis in Behçet's disease: a retrospective case-control study. Clin Rheumatol 2018;37:51-7.
5. Wechsler B, Sbaï A, Du-Boutin LT, Duhaut P, Dormont D, Piette JC. [Neurological manifestations of Behçet's disease]. Rev Neurol (Paris) 2002;158(10 Pt 1):926-33.
6. Lakhanpal S, Tani K, Lie JT, Katoh K, Ishigatsubo Y, Ohokubo T. Pathologic features of Behçet's syndrome: a review of Japanese autopsy registry data. Hum Pathol 1985;16:790-5.
7. Bolek EC, Sari A, Kilic L, et al. Clinical features and disease course of neurological involvement in Behcet's disease: HUVAC experience. Mult Scler Relat Disord 2020;38:101512.
8. Saadoun D, Wechsler B, Resche-Rigon M, et al. Cerebral venous thrombosis in Behçet's disease. Arthritis Rheum 2009;61:518-26.
9. Saip S, Akman-Demir G, Siva A. Neuro-Behçet syndrome. Handb Clin Neurol 2014;121:1703-23.
10. Uluduz D, Midi I, Duman T, et al. Behçet's disease as a causative factor of cerebral venous sinus thrombosis: subgroup analysis of data from the VENOST study. Rheumatology (Oxford) 2019;58:600-8.
11. Wechsler B, Vidailhet M, Piette JC, et al. Cerebral venous thrombosis in Behçet's disease: clinical study and long-term follow-up of 25 cases. Neurology 1992;42(3 Pt 1):614-8.
12. Bank I, Weart C. Dural sinus thrombosis in Behçet's disease. Arthritis Rheum 1984;27:816-8.
13. Lo Monaco A, La Corte R, Caniatti L, Borrelli M, Trotta F. Neurological involvement in North Italian patients with Behçet disease. Rheumatol Int 2006;26:1113-9.
14. Ksiaa I, Abroug N, Kechida M, et al. [Eye and Behçet's disease]. J Fr Ophtalmol 2019;42:626-41.
15. Aguiar de Sousa D, Mestre T, Ferro JM. Cerebral venous thrombosis in Behçet's disease: a systematic review. J Neurol 2011;258:719-27.
16. Wu X, Li G, Huang X, et al. Behçet's disease complicated with thrombosis: a report of 93 Chinese cases. Medicine (Baltimore) 2014;93:e263.
17. Tunc R, Saip S, Siva A, Yazici H. Cerebral venous thrombosis is associated with major vessel disease in Behçet's syndrome. Ann Rheum Dis 2004;63:1693-4.
18. Esatoglu SN, Hatemi G. Update on the treatment of Behçet's syndrome. Intern Emerg Med 2019;14:661-75.
19. Tatlican S. Behçet Hastalığı Tedavisinde Anti-TNF Ajanlar. Turk J Rheumatol 2009;24:27-38.
20. Kehribar DY, Ozgen M. Infliximab treatment in refractory vascular Behcet's disease: A single-center experience. Vascular 2020;28:829-33.
21. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis 2018;77:808-18.
22. Aksoy A, Yazici A, Omma A, et al. Efficacy of TNFα inhibitors for refractory vascular Behçet's disease: A multicenter observational study of 27 patients and a review of the literature. Int J Rheum Dis 2020;23:256-61.
23. Kidd D, Steuer A, Denman AM, Rudge P. Neurological complications in Behçet's syndrome. Brain 1999;122(Pt 11):2183-94.
24. Akman-Demir G, Serdaroglu P, Tasçi B. Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. The Neuro-Behçet Study Group. Brain 1999;122(Pt 11):2171-82.
25. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). Stroke 2004;35:664-70.
26. Desbois AC, Addimanda O, Bertrand A, et al. Efficacy of Anti-TNFα in Severe and Refractory Neuro-Behcet Disease: An Observational Study. Medicine (Baltimore) 2016;95:e3550.