

Cerebral venous thrombosis in Behçet's disease: A study of 17 cases

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Citation: Snoussi M, Chatti A, Ben Hmad M, Feki W, Mnif Z, Frikha F, Marzouk S, Bahloul Z. Cerebral venous thrombosis in Behçet's disease: A study of 17 cases. *Electron J Gen Med.* 2025;22(2):em639. <https://doi.org/10.29333/ejgm/16061>

ARTICLE INFO

Received: 13 Aug. 2024

Accepted: 22 Jan. 2025

ABSTRACT

Introduction: Cerebral sinus thrombosis is an uncommon neurologic condition caused by many etiologies. Behçet's disease (BD) is one of the leading causes in Mediterranean and Middle Eastern countries. The aim of our study was to summarize the clinical manifestation, the therapeutic strategies and the prognosis of cerebral sinus thrombosis of BD in southern Tunisia.

Patients and methods: This is a descriptive study of patients followed for BD complicated with cerebral sinus thrombosis in the department of internal medicine of Hedi Chaker Hospital in Tunisia. The study was conducted during a period of 24 years (January 1996 to December 2021). Statistical study was performed with SPSS 2022.

Results: 17 patients were enrolled with a mean age of 28 years and male predominance noted in 88% of cases. The most common mode of onset was subacute in 41% of cases. 53% of patients had intracranial hypertension. Transverse sinus and longitudinal sinus were the most affected in 59% and 47% of cases. Anticoagulation was the basis of the treatment in all patients. The specific treatment was based on colchicine in all patients, corticotherapy in 14 patients and cyclophosphamide was administered in four patients with ocular manifestation. Outcome was good in all patients with no relapses or death.

Conclusion: In southern Tunisia cerebral sinus thrombosis in BD is predominant in male young patients. It has a subacute presentation dominated by intracranial hypertension and the prognosis is good under anticoagulation and etiological treatment.

Keywords: Behçet's disease, cerebral venous thrombosis, anticoagulation

INTRODUCTION

Cerebral venous thrombosis (CVT) is an uncommon neurologic condition that accounts for 0.5 to 1% of all strokes in the adult population. It has various symptoms and it is caused by several etiologies [1, 2].

Behçet's disease (BD) is a significant cause of CVT, especially in certain Middle East and Mediterranean countries. In fact, in these regions BD is seen with a prevalence varying from 20 in 100,000 inhabitants in Saudi Arabia, Iraq 17, Italy 15.9, Egypt 7.6, Spain 7.5, and France 7.1 [3, 4].

BD is a chronic inflammatory multisystemic vasculitis characterized by recurrent oral and genital ulcerations, uveitis, arthritis, and central nervous system (CNS) involvements. It usually affects young male patients [4, 5]. The main symptoms of BD-related CVT are intracranial hypertension syndrome and a progressive headache [6]. The diagnosis of CVT is currently based on neuroimaging techniques: cerebral magnetic resonance imaging (MRI) with venous time angio-MRI are the gold standard means of diagnosis [1].

BD-related CVT has a favorable prognosis if it is well treated. Treatment is based primarily on early and appropriate anticoagulation and also includes symptomatic and etiological

management [3]. There are a few studies in the literature focusing on clinical presentation, therapeutic strategies and prognosis of CVT related to BD mainly in North Africa. In this paper, we aim to summarize the clinical manifestation, treatment and outcome of CVT caused by BD in the southern of Tunisia.

MATERIALS AND METHODS

Study Design

This is a monocentric retrospective descriptive study of patients followed for BD complicated by CVT in the department of internal medicine at the Hedi Chaker Hospital of Sfax (Tunisia). The study was conducted over a period of 24 years from January 1996 to December 2021.

Population

17 patients included in the study fulfilled the diagnosis criteria of the international study group for BD and the new international criteria for BD [7].

The diagnosis of CVT was based on the clinical features and radiological techniques findings including brain computed tomography scan (CT) and MRI.

Data Collection

For each patient the following data were collected:

1. Age.
2. Gender.
3. Clinical features including acute or progressive headache, nausea, vomiting, intracranial hypertension, altered consciousness, generalized or partial seizure, focal neurological deficit, visual disturbances, and extra neurological signs.
4. The interval between the onset of BD and initial thrombotic event.
5. Onset symptoms:
 - a. Acute onset: CVT diagnosed within 48 hours (after clinical onset).
 - b. Sub-acute: CVT diagnosed between 48 hours and 30 days (after the onset of clinical signs).
 - c. Chronic: CVT diagnosed beyond 30 days.
6. Neuroimaging findings: The diagnosis of CVT was confirmed by neuroimaging: Cerebral CT scan and cerebral MRI.
7. Treatment:
 - a. Anticoagulant treatment: Unfractionated heparin (UFH), low molecular weight heparin (LMWH), and anti-vitamin K.
 - b. Etiological treatment: Corticosteroid therapy, colchicine, and immunosuppressants therapies.
8. Prognosis: We classified patients as having a favorable or unfavorable outcome according to clinical and radiological control criteria we noted also cases of death and relapse.

Statistical Analysis

Statistical analysis was performed using SPSS software in its 22nd version. We conducted a descriptive study to calculate the qualitative variables simple and relative frequencies (percentages). We also calculated means and standard deviations, medians and determined the range (extreme values: minimum and maximum) for the quantitative variables.

RESULTS

Demographic Characteristics

Our study included seventeen patients with CVT. There are 15 men and 2 women with a sex ratio of 7.5. The mean age of our patients was 28 years (range: 12-56).

Disease Onset

Fourteen patients were diagnosed with BD after the CVT onset with an average interval of 34 months (range: 2-108 months).

Clinical Features

The mode of onset was acute in 24% of cases, subacute in 41% and chronic in 35%. The most common symptom was headache (100%) followed by papilledema (41%), nausea /vomiting (35%), diplopia (24%) and cranial nerve palsies (24%). However, seizure and focal deficits were uncommon symptoms in our study. The different symptoms are summarized in **Table 1**.

Table 1. Clinical characteristics of BD patients with CVT (n = 17)

Characteristics	Number of patients (n) (%)
Mode of onset	
Acute	4 (24%)
Subacute	7 (41%)
Chronic	6 (35%)
Clinical symptoms and signs	
Headache	17 (100%)
Nausea and vomiting	6 (35%)
Papilledema	7 (41%)
Diplopia	4 (24%)
Intracranial hypertension	9 (53%)
Cranial nerve palsies	4 (24%)
Focal deficits	3 (18%)
Seizure	1 (6%)

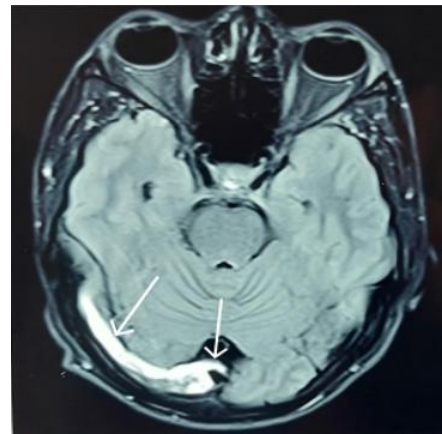


Figure 1. FLAIR MRI in axial plane FLAIR sequence showing hyperintensity in the right transverse sinus and superior sagittal sinus (arrow) (Reprinted with permission of patient)

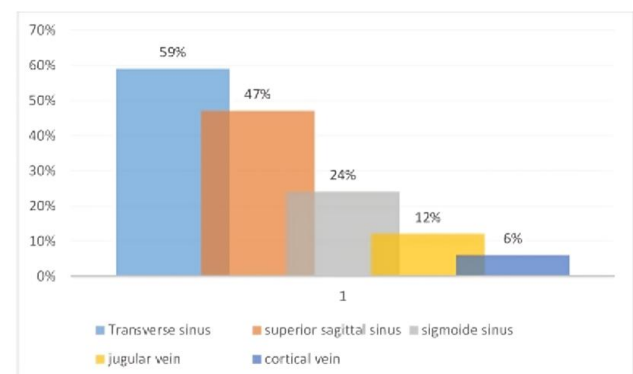


Figure 2. Locations of CVT in patients with BD

Neuroimaging Finding

MRI or CTscan confirmed CVT in all our patients. CT scans were performed in seven patients (41%). It allowed the diagnosis to be made in 12% of cases (2 patients). Two direct signs were reported: the “dense triangle sign” was found in one patient (6%) and “the cord sign” was found in one patient (6%). A diffuse brain edema (indirect sign) was seen in four patients (23%). Cerebral MRI with injection of contrast medium (gadolinium) explored all patients (**Figure1**). The transverse sinus was the most common site of thrombosis (59%) followed by the superior sagittal sinus (47%). The sigmoid sinus was thrombosed in 24% of cases. Besides, the exception of jugular vein and cortical vein were reported, respectively in (12%) and (6%) (**Figure 2**).

Table 2. Distribution of BD patients with CVT according to radiological control results

Radiological control results	Number of patients (n) (%)
Total recanalization	3 (30%)
Partial recanalization	4 (40%)
No recanalization	3 (30%)

Treatment

All patients in our study received anticoagulation with LMWH relayed by vitamin K antagonist (VKA) with an average interval of 43 months (ranges 6-168 months).

The specific treatment of BD was based on corticosteroid therapy in fourteen patients (82%), all patients were treated by colchicine and cyclophosphamide was administered in 4 patients (24%) because of the severity of the condition with ocular involvement.

Prognosis

In our study, all patients had a favorable outcome, relapses were documented in two patients (6%) and no death was reported. Ten patients (59%) had radiological control within an average of 40 months. MRI evaluated nine patients, while CT scanner controlled the tenth. The results of radiological control are summarized in **Table 2**.

DISCUSSION

BD is a chronic inflammatory disorder classified as one of the systemic vasculitis, which can affect the articular, cutaneous, vascular, neurological, and gastrointestinal systems. The onset of BD is usually in the third decade of life and is characterized by a relapsing and remitting course [8, 9]. Although BD is a vasculitis disorder, it differs from other vasculitis diseases due to increased thrombotic events [10]. Moreover vascular events affect 15-50% of patients with BD. neurological manifestations in BD is reported in 2.9-44% and affect CNS [3,4]. There are two categories of CNS involvement: parenchymal or neurovascular neuro-BD. Non-parenchymal syndromes include nonvascular etiologies such intracranial hypertension and acute meningitis syndrome but are assumed to be predominantly related to vascular processes such as cerebral venous sinus thrombosis, acute arterial infarct, and aneurysms [11]. CVT is the most frequent type of neurovascular involvement in BD. This latter manifestation accounted for 10 to 30% of extra-axial neuro-BD and is more common in young male patients [6, 9].

In our study, the main age of our patients was 28 years with male predominance with a sex ratio of 7.5. This epidemiological data was concordant to the largest multicenter VENOST study. It noticed that BD was the first etiologic factor among men aged 18-36 years with CVT [13]. Moreover a recent German meta-analysis found a significant relationship between the male gender and vascular involvement in BD patients [14]. This may be explained by the increased hypercoagulable state in men compared with women [10].

The most common mode of onset of CVT in our study was subacute in 41% of cases, the chronic mode was found in 35% and the acute mode was in 24% of cases, similar to two other series, which reported that the onset of neurologic symptoms was mostly subacute/chronic mode. These studies suggested

that the progressive onset differentiated BD-induced CVT from those other etiologies [3, 15-17].

In our study symptoms related to intracranial hypertension were frequently seen in (53%). They included headache (100%), papilledema (41%), and nausea/vomiting (35%), these results were compatible with those found in the literature [3, 15-17].

It was compared CVT in BD to those in other etiologies, they reported that intracranial hypertension is more frequent in BD patients [3].

Furthermore, headaches are the most commonly reported neurological symptom of BD. The majority of studies conclude that overall headache prevalence is higher in the BD population than in the general population and CVT has been identified as the most frequent secondary cause of headache in BD. In paediatrics, it is the most common neurological presentation [11].

In fact, CVT-related headaches have no specific characteristics, they are generally progressive than abrupt, they can be localized, diffuse or migraine type. Generally, they worsen after Valsalva's manoeuvres and recumbence but it remains an irrelevant diagnostic feature. However, there is no correlation between the localization of headache and the seat of thrombosis [18, 19].

In addition, it's important to take note of additional headache-causing diseases such CNS involvement, uveitis, and primary headaches such as migraine and tension headache [15].

On the other hand, cranial nerve palsies, seizure, and altered consciousness were uncommon in CVT related to BD and might lead to problem of differential diagnosis [15].

Similar to our study, it was reported that seizure or localized deficits were not frequent in BD patients (6%) [3].

Neuroimaging has a crucial role in the diagnosis of CVT. Radiological images are diverse and can provide direct and/or indirect signs of CVT [2].

In our series, all patients had a radiological examination that confirmed the diagnosis.

Unenhanced CT scan is the first line imaging technique performed when CVT is suspected.

In our study, CT scans were performed in seven patients. It allowed the diagnosis to be made formally in 12% of cases.

In the acute phase and without injection of contrast product, two specific radiological signs are described according to the localization of the thrombosis: the "dense triangle sign" when thrombosis is located in the superior sagittal sinus and the "dense cord sign" when it is located in a cortical or deep vein. But these signs are only observed in acute and subacute cases, since the thrombus becomes iso-attenuating after the first two weeks [20].

In the presence of the contrast agent, a specific radiological sign is the "empty delta sign", a filling defect within a dural sinus. This sign is the most common direct sign but it is present only in 29 to 35% of cases [1, 20] and it can occur at any time from the subacute to the chronic phase, most often between the fifth day and two months after the onset of the disease. It is important to consider that in the majority of cases CT scan will only show indirect signs of CVT such as diffuse brain edema or intracerebral hemorrhage. However, false positives could be found due to normal sinus hypoplasia or arachnoid granulations [20].

In our study, the dense triangle sign and the cord sign were found in only one patient and the diffuse brain edema was seen in 23% of cases.

Currently, cerebral MRI and angio MRI are the gold standard imaging techniques for diagnosis of CVT. It is the most specific and sensitive imaging technique that allowed the visualization of the thrombus, to follow its evolution and sometimes to recognize its cause. MRI is also the best technique to assess parenchymal involvement (ischaemia, haemorrhages, and oedema) [21].

The clinical symptoms and signs of CVT depend on the location of the thrombosis [21]. Our study reported that the most involved sites of CVT were the transverse sinus and superior sagittal sinus. This finding is similar to other studies [15, 17].

Previous research reported that BD patients often developed multiple sites of thrombosis and patients with CVT had a considerably greater incidence of extracranial vascular lesions than individuals without CVT [22, 23]. It was noted that extracranial thrombosis accounted for two thirds of cases in which the veins in the lower limbs were most involved [15].

Also, it was reported that there was a significant association between main vessel involvement and CVT in BD [24].

As a result, BD patients who have been identified with CVT should have additional testing for vascular involvement at other sites.

Recent studies showed that there was a correlation between inflammation and thrombosis. Moreover, inflammatory reactions provoke thrombotic events through endothelial disorder, platelets hyper activation, and increased tissue factor expression [22, 25].

Considering that vasculitis-induced endothelial dysfunction and aberrant activation as the primary causes of thrombosis in BD, vigorous treatment of vascular inflammation is crucial for the CVT of BD. A combination of corticosteroids with immunosuppressants is the mainstay of the control of vasculitis, which is helpful for treating and preventing venous thrombosis [26, 27].

In our study, all the patients were treated with LMWH relayed by VKA and no patient needed endovascular procedure.

The meta-analysis of these two trials confirms the efficiency of anticoagulation with a 54% reduction in the risk of death or dependency [28].

Two randomized controlled trials compared LMWH and UFH. In the first, the death rate in the LMWH group was significantly lower (0% vs. 18.8%) [29], whereas in the second, there were no differences in mortality (3.8% vs. 5.6%) or new symptomatic cerebral hemorrhage (none in either group) [30]. In unstable patients or those needing invasive treatments, UFH may be recommended due to its shorter half-life and reversibility [31].

However, on the basis of the outcomes of more recent trials, it is reasonable to expect that many more patients will be treated with direct oral anticoagulants (DOAC): Rivaroxaban and dabigatran. Studies confirmed their safety. The ideal timing for initiation of DOAC after diagnosis of CVT, and the ideal DOAC to use for CVT, are remaining questions. The results of future studies may help to establish guidelines if no adverse

safety signaled and a similar efficacy to standard therapy is seen [32-34].

CVT associated with BD has a good prognosis if it is well treated. In our study, we noted that our patients improved after treatment. Headache disappeared in all patients. Control neuroimaging showed partial or total repermeabilization of CVT in a number of patients. There was no severe neurologic outcome during the follow-up period. Through studies of literature, CVT due to BD has a favorable outcome with suitable treatment compared to other etiologies. The risk of recurrence of CVT is low [3, 15]. No death reported in our study.

The limitations of our study are its retrospective nature and it was a monocentric trial with a limited number of cases. A larger, prospective, multicenter studies would be of great help to better understand the specificities of CVT in patients with BD in the Tunisian population.

CONCLUSION

BD is chronic multisystem disorder and it is a significant cause of CVT, especially in certain Middle East and Mediterranean countries. According to our study, it affects a young men with a progressive onset and revealed by intracranial hypertension and headache. Cerebral MRI with angio-MRI is mandatory to do the diagnosis showing mainly thrombosis of transverse and superior sagittal sinuses in BD. CVT associated with BD has a good prognosis with curative anticoagulation, corticotherapy, and even immunosuppressant in severe cases.

Author contributions: MS & AC: collection of data and redaction of the manuscript; MBH, FF, SM, & ZB: validation of the manuscript; & WF & ZM: radiological investigations. All authors have agreed with the results and conclusions.

Funding: No funding source is reported for this study.

Ethical statement: The authors stated that the study does not require any ethical approval since the study is retrospective and it is a non interventional study.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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