# Behçet's disease and cerebral sinus vein thrombosis in children: a case study and review of the literature

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## ABSTRACT

**Objective.** *Central nervous system (CNS) involvement, one of the most severe manifestations of Behçet's disease (BD), is uncommon in children. Because it is rare, the clinical features of this disease in children are not well characterised. Here we describe a teenager with BD which was disclosed following an episode of cerebral sinus vein thrombosis (CSVT) and review the available literature on children with CSVT associated with BD.*

**Methods.** *A 12-year-old boy who presented with CSVT is described and the relevant literature, based on a Medline search from 1966 to January 2015 is reviewed.*

**Results.** *Twenty-three well-documented reports of children with CSVT and BD are described. This manifestation affected mainly males (61%) with a mean age of 12 years (range 4–18). BD was first diagnosed simultaneously or following CSVT in the majority of cases (75%). Multiple sinuses were involved in 30% of the cases. Thrombosis of additional large vessel was identified in 5 of the 23 children. The most common presenting symptom and signs were headache (91%), lasting more than 3 days in most cases (75%), followed by papilledema (43%), seizures (17%), and personality changes (9%). A mixed pattern of CNS involvement including both parenchymal involvement and CSVT, was demonstrated in only two patients (9%). Management of CSVT differed between reports.*

**Conclusion.** *CSVT in children is a rarely reported manifestation of BD and has a characteristic clinical picture of a teenage boy presenting with prolonged headache, with no previous diagnosis of BD. A therapeutic approach has not been established yet.*

## Introduction

Behçet's disease (BD) is a chronic inflammatory disorder with polygenetic background, characterised by recurrent oral and genital ulcers, uveitis, and skin lesions. It is classified as a variable vessel vasculitis, mainly involving small vessels, with protean clinical manifestations (1). The mean age of disease onset is in the third or fourth decade of life. Onset of disease in childhood is uncommon (2).

Central nervous system (CNS) involvement, one of the most severe and life threatening manifestations of BD, is reported at variable rates in adults (2.2–50%) (3). CNS disease is caused either by primary inflammatory parenchymal lesions, present in the majority of adult BD patients with CNS disease, or by vascular involvement, mainly due to cerebral sinus vein thrombosis (CSVT), the latter form carrying a better prognosis (4). CSVT is an infrequently recognised condition with nonspecific and variable manifestations, mimicking nearly any other acute cerebral disorders, and thus often presents a diagnostic challenge. There are relatively few reports of CNS involvement in childhood Behçet's disease (3). Since only case studies and small series of paediatric Behçet patients with CSVT have been reported, the clinical course of patients with this type of disease involvement has not been well characterised. In the present study, we present an unusual case of a child with a BD and CSVT. We also review the current literature concerning the clinical course of children with BD and CSVT.

## Methods

We present a child with BD and CSVT. A PubMed search of the literature

(www.ncbi.nlm.nih.gov/pubmed, 1966 to January 2015) was performed to identify all previously reported cases, using the terms "cerebral venous thrombosis" or "sinus thrombosis" and "Behçet's disease". The references of the studies obtained were then examined to identify additional reports. We included only paediatric cases (age 16 years and less) that were sufficiently detailed to be individually analysed. In the study by Uluduz *et al*., who described 26 children with neuro-Behçet's syndrome (NBS), there were 23 cases of CSVT (20). However, as data regarding clinical presentation, laboratory results, immunosuppressive and anticoagulant therapy and follow up were missing, their results were not included in the table presented. Demographic, epidemiological and developmental information noted in Uluduz paper (20) were added in the discussion when applicable.

## Results

*Case report*

A 12-year-old boy presented with dehydration, after experiencing difficulty drinking because of numerous painful oral ulcers. His past medical history was remarkable for a several previous episodes of oral ulcers and skin rash during the two years preceding his hospitalisation. The family medical history was not contributory.

On admission, he was mildly dehydrated and had multiple large oral ulcers. A papulopustular rash was present on his extremities. The physical examination was otherwise unremarkable. Laboratory investigations were notable for elevated C-reactive protein (150 mg/dL). Chest x-ray showed mild perihilar and lingular infiltrates with a small left pleural effusion. During treatment with intravenous cefuroxime and fluids, a severe headache and recurrent vomiting appeared. Fundoscopic examination showed bilateral papilledema without uveitis. On neurologic examination, neither focal deficits nor other abnormal findings were observed. Cranial computed tomography imaging revealed venous thrombosis involving the superior sagittal sinus and left jugular vein. There were no cerebral parenchyma or brainstem lesions. MR venography performed later confirmed these findings, and in addition, revealed thrombosis of the left transverse and left sigmoid sinuses. A lumbar puncture was not performed. Pathergy test, performed following observation of pustules and erythematous papules at venipuncture sites, was read positive. Based on the findings of recurrent oral ulcers, papulopustular skin rash, positive pathergy test and CSVT, Behçet's disease was diagnosed based on the International Study Group (ISG) criteria (5).

Further laboratory examinations revealed normal values of PT, aPTT, lipid profiles, factors 8, 9 and 11, protein C, S, homocysteine, prothrombin 20210-A, anti-neutrophil cytoplasmic antibodies (C, P and atypical), anticardiolipin and anti beta-2-glycoprotein antibodies (both IgG and IgM) and complement C3 and C4. Antinuclear antibodies were positive +2 by immune-fluorescence. Anti-thrombin III levels were slightly elevated. The patient was heterozygous for factor V Leiden and MTHFR mutations.

Treatment was initiated using low-molecular weight heparin, high dose corticosteroids, and colchicine, and acetazolamide was given to reduce intracranial pressure. While on this treatment, left leg swelling appeared, and thrombosis of the left femoral vein was demonstrated by Duplex Doppler sonography. IV heparin treatment was later switched to warfarin. Under this treatment, his manifestations resolved, and he was discharged from hospitalisation without headache, skin rash or oral ulcers. He was maintained on low dose steroids, colchicine and azathioprine and long-term anticoagulation.

On follow-up examination 6 months later, he reported normal daily functioning. Neurologic examination was normal, with no signs of papilledema. Follow up MRI revealed completely patent cerebral venous sinuses, without brain parenchymal abnormalities.

*Literature review*

In addition to our case, we identified 22 reports of CSVT in children with BD, which are summarised in Table I. Of the 23 patients, 14 (61%) were boys. The median age of the patients was 12 years (range 4–16). BD was diagnosed simultaneously or following CSVT in 9 out of 12 in whom data was available (75%). Recurrent oral ulcerations were the most common manifestation, occurring in 18 cases (78%), followed by genital ulcers in 11 (48%), skin involvement in 8 (35%) and uveitis in 5 (22%). The pathergy test was positive in 7 patients out of 17 (41%) in whom it was performed. Less common disease manifestations were retinal vasculitis observed in 4 patients, femoral vein thrombosis in 2, and thrombosis of the inferior vena cava, common iliac artery and pulmonary artery, each in 1. HLA-B51 was reported positive in seven of 11 patients (64%) in whom it was studied. Three patients (13%) had a family history of BD. CSVT was diagnosed using magnetic resonance imaging (MRI) (14 cases, 82%), computed tomography scans (3 cases, 18%) or digital subtraction angiography (3 cases, 18%). Data concerning imaging was not available in 6 patients.

The superior sagittal and lateral sinuses were the most commonly involved veins, occurring in 12 cases each (52%). Other cranial veins affected were the sigmoid sinus and internal jugular veins (2 cases each), and cavernous and straight sinuses (1 case each). In seven cases including our patient (30%), multiple sinuses were involved.

Symptoms were present for at least three days in most cases prior to establishing the diagnosis of CVST in most cases (75%). The most common signs and symptoms were headache (91%) followed by papilledema (43%) and seizures (17%). Interestingly, two patients exhibited personality changes as part of their presentation. While in the present case dehydration might have triggered CSVT, it is not mentioned in other reports. Mixed pattern of CNS involvement- parenchymal alongside CSVT, was demonstrated on MRI scans in only 2 patients (9%). However, none of the patients displayed focal neurological deficits.

Elevated white blood cell count was reported in 22% of cases, and increased erythrocyte sedimentation rate and C-reactive protein were found in 15 (65%) and 13 (57%) patients, respec-

**Table I.** Clinical characteristics of reported cases of cerebral vein sinus thrombosis associated with paediatric Behçet's disease.

| Reference | Age (years) Sex (M/F) | Known BD | Age at first BD symptom (years) | Headache | Papille-dema | Involved sinuses | Additional vascular involve-ment | Parenchy-mal involve-ment | Elevated inflam-matory markers | Follow up duration years | Anti-coagulation | Other treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 Our case | 12, M | No | 10 | Yes | Yes | SSS, LS, SiS, IJV | FVT | None | Yes | 0.5 | Yes | S,C,A |
| 2 Hacihamdioglu (7) | 4, M | No | 4 | None | Yes | SSS, LS | None | None | Yes | 0.1 | Yes | S,C,A,I |
| 3 Yilmaz (8) | 12, F | No | 10 | Yes | Yes | LS | None | None | Yes | 0.25 | Yes | S,C |
| 4 Metreau-Vastel (6) | 11, M | No | NA | Yes | None | SSS, LS | IVCT | None | Yes | 5.3 | Yes | C |
| 5 Metreau-Vastel (6) | 6, F | No | NA | Yes | Yes | LS | None | Yes | Yes | 8.5 | Yes | C |
| 6 Metreau-Vastel (6) | 5, M | No | NA | Yes | None | IJV | RV | None | Yes | 4 | Yes | C |
| 7 Metreau-Vastel (6) | 9, M | No | NA | Yes | None | SSS | RV | Yes | Yes | 16.5 | None | C |
| 8 Metreau-Vastel (6) | 15, F | No | NA | Yes | None | SSS | RV | None | Yes | 15 | None | C |
| 9 Can (18) | 12, M | No | 12 | Yes | Yes | LS | None | None | Yes | 0.3 | NA | NA |
| 10 Yesilot (10) | 15, F | No | NA | Yes | None | SSS | None | None | NA | NA | None | S |
| 11 Yesilot (10) | 13, M | No | NA | Yes | None | LS | None | None | NA | NA | None | S |
| 12 Yesilot (10) | 14, M | No | NA | Yes | None | NA | None | None | NA | NA | None | S |
| 13 Yesilot (10) | 11, M | No | NA | Yes | None | LS, SiS | None | None | NA | NA | None | S |
| 14 Stern (13) | 16, M | No | 16 | Yes | Yes | SSS | SVT | None | Yes | NA | None | S |
| 15 Panicker (9) | 12, M | No | 6 | Yes | Yes | SSS | None | None | NA | NA | Yes | None |
| 16 Alper (11) | 15, F | No | 13 | Yes | Yes | LS | None | None | NA | 1 | None | S,C |
| 17 Besbas (12) | 13, M | No | 11.5 | Yes | None | SSS, SS | AA, IAT | None | Yes | 0.5 | Yes | CY,C |
| 18 Ozen (15) | 15, F | Yes | NA | Yes | None | NA | None | None | Yes | 1.5 | Yes | S,C,A |
| 19 Ozen (15) | 10, M | Yes | NA | Yes | None | NA | None | None | Yes | 1.5 | Yes | S,C,A |
| 20 Emad (17) | 16, M | No | NA | None | None | SSS | PAT, FVT | None | NA | 0.2 | Yes | S,A |
| 21 Saatci (14) | 11, F | No | 8 | Yes | Yes | SSS, LS | None | None | Yes | NA | None | CH |
| 22 Wechsler (16) | 13, F | No | NA | Yes | None | SSS, LS, CS | None | None | NA | 1 | None | None |
| 23 Cakar (19) | 15, F | Yes | 13 | Yes | Yes | LS | RV | None | Yes | 0.25 | Yes | S,C |

M: male; F: female; BD: Behçet's's disease; NPD: Not previously diagnosed; PD: Previously diagnosed; NA: not available; SSS: superior sagittal sinus; LS: longitudinal sinus; IJV: internal jugular vein; SiS: sigmoid sinus; SS: straight sinus; CS: cavernous sinus; IVC: inferior vena cava; FVT: femoral vein thrombosis; IVCT: Inferior vena cava thrombosis; RV: retinal vasculitis; SVT: superficial vein thrombosis; AA: aortic aneurysm; IAT: iliac artery thrombosis; PAT: pulmonary artery thrombosis; S: steroids; C: colchicine; A: azathioprine; I: infliximab; CY: cyclosporine; CH: chlorambucil.

tively. Results of cerebrospinal fluid (CSF) analysis were available in 11 patients (48%). Five patients had elevated opening pressure during lumbar puncture. In 9, CSF was normal and in 2, lymphocytic pleocytosis and elevated protein were observed. Hypercoagulability testing, performed after the diagnosis of CSVT in 12 patients (52%), detected a thrombophilic risk factor in 4 patients (33%). Factor V leiden and MTHFR mutations were found alone in one patient each and together in another patient. Lupus anticoagulant antibodies were repeatedly positive in one patient, which led the clinicians to recommend long-term anticoagulation. Elevated lipoprotein (a) levels were detected in one patient.

Information regarding treatment was available in 22 patients. Management of CSVT differed between cases 14 patients (64%) were treated with corticosteroids, and 12 patients (55%) received colchicine. Immunomodulating agents including azathioprine, infliximab, chlorambucil and cyclosporine, were prescribed in 7 patients (32%). Anticoagulation was used in 12 cases (55%), 4 (18%) of whom did not receive any immunosuppressive therapy. Immunosuppressants were used as a sole therapy in only 8 patients (36%).

Follow up ranging from 1 month up to 16.5 years was reported in 16 cases. Three patients suffered from recurrence of CSVT that occurred in 1 to 4 months after the initial event, two of whom had a thrombophilic risk factor. All other patients had full resolution of their symptoms.

## Discussion

Behçet's disease is rare in children (2). CNS disease occurs in 2.2–50% of adult BD patients and is one of the most serious disease manifestations (3). Overall, children comprise less than 4% of BD patients with CNS disease (20). Because of the rarity of this condition, the clinical features of CNS disease in paediatric BD are not well described, and CSVT is even less characterised. Herein we present a 12 year old child and summarise all informative 22 paediatric cases of CSVT reported during a period between 1966 and 2015 in 14 articles. Our study provides information about this rare and important disease. As per this study and the study by Uluduz *et al*. (20), the typical patient is a teenager boy, presenting with prolonged headache, without previous diagnosis of BD. In contrast to other thrombophilic conditions in which unprovoked thrombosis forms the minority of cases, BD associated CSVT usually develops without noticeable precipitating factors, suggesting a distinct pathogenesis for this entity.

In addition to the rarity of CSVT, the paucity of cases reported during such a long period may be partly explained by the difficulty of BD diagnosis in the paediatric age, as some of the children do not meet yet the ISG criteria, which were not validated in children (21). Moreover, the ISG criteria do not include neurological and gastrointestinal manifestations or vascular thrombosis, which are common presenting signs

of paediatric BD. Only 13 cases in our review (57%) fulfilled the ISG criteria. Five of the remaining cases could receive a diagnosis of incomplete BD, and in the other 5 the data was insufficient. In the report by Uluzud *et al*. data regarding the ISG criteria was not presented.

In most cases in our series in which data were available (75%), the diagnosis of BD was established only after the occurrence of CSVT. In accordance with our results, in the study of Uluduz et al, the diagnosis of BD was made concurrently or after the appearance of neurological manifestations in 50% of the cases (20). This differs from adult-onset NBS that usually occurs later in BD course and in previously diagnosed BD patients (22). Taken together, these findings should encourage paediatricians to consider BD as an underlying cause in a teenagers presenting with persistent headache and papilledema, especially in endemic countries.

In our report, only 2 children (9%) with BD-associated CVST had parenchymal CNS involvement as well. In adult-onset NBS parenchymal involvement is more frequent than vascular NBS, with rates of 5.2% and 0.6% respectively (23). Conversely, most children (88%) with NBS present with CSVT (20). It has also been noted that concurrent parenchymal CNS involvement and CSVT is uncommon (4, 20). We observed that in BD, the mode of presentation of CSVT is usually indolent in most cases, and symptoms were reported to last more than 1 month prior to presentation in more than fifth of cases reviewed, which is another feature that distinguishes BD-CSVT from CSVT caused by other aetiologies. Our main finding is that the predominant presentation of CSVT in BD in our review was headache, probably caused by slowly growing intracranial pressure. However, since headache is a common and non-specific complain, diagnosis may be delayed in patients not displaying other clinical signs of BD.

In our review and the report of Uluduz *et al*. (20), the superior sagittal and transverse sinuses were the most frequent sites involved, which is in agreement with previous series (24). An important finding is the high frequency (30%) of multiple sinuses occlusion. Interestingly, only large vessels of the venous system were involved, a finding that may explain why neither neurologic deficits nor focal signs were noted in this series. Venous thrombosis, including CSVT in BD patients was hypothesised to reflect mainly endothelial disease, which usually takes longer time to evolve, allowing resolution of the thrombus to occur before drainage of the cortical veins is affected (10). Thus, the spreading of thrombus to smaller cortical veins is delayed, and cortical venous infarction and the resulting focal neurological deficits are prevented.

CT with CT angiography are available and very useful technique that enable diagnosis CSVT diagnosis in most cases. Magnetic resonance venography in combination with T1 and T2-weighted images is the preferred and the most sensitive study to diagnose CSVT and to assess parenchymal damage in BD (4, 20).

Lumbar puncture in patients with CSVT may reveal increased pressure, but the cellular and chemical composition of the CSF is usually normal, reflecting the sparing of parenchyma in most cases (25). However, CSF examination is still recommended in cases when it is considered safe, as it may be necessary to exclude meningitis, to monitor intracranial pressure and as a therapeutic measure to reduce intracranial pressure (26).

In the International Study of Cerebral Venous Thrombosis, at least one prothrombotic risk factor was present in 44% of cases, which may act together with endothelial dysfunction to promote thrombosis. Acquired and genetic thrombophilia were diagnosed in 22% and 15% of patients, respectively (27). Von Willebrand factor, homocysteine and lipoprotein (a) levels were found to be increased in BD (8). In addition, factor V Leiden mutation was found to be more frequent in BD patients who developed thrombosis (28). Decreased fibrinolytic activity has also been reported in patients with BD (29). It is currently recommended that a diagnostic work-up for hypercoagulable states should be done after diagnosis of CSVT (30). In our review, any prothrombotic factor was found in 4 patients out of 12 (33%) in whom studies to detect thrombophilia were carried out. This underscores vasculitis as the underlying mechanism of CSVT, rather than any hereditary or acquired thrombophilia.

One of the patients in our study had consistently high levels of lupus anticoagulant and was given long-term anticoagulation. Of note, elevated levels of anti-phospholipid antibodies are common (40%) in adult patients with BD with or without thrombosis. This finding and the conflicting reports, which could not display increased prothrombotic serum factors in BD, questions the role of anti-phospholipid antibodies as a risk factor for thrombosis in BD (31-32). Some authors consider HLAB51 to be associated with a higher risk of cerebral thrombosis in BD (33), and others found that carriage of the MEFV M694V mutation may be associated with venous thrombosis (34).

The relatively low frequency of positive pathergy test found (41%) may reflect the low rate of pathergy among BD patient is non-endemic regions, from where a significant portion of cases in this series were reported (35).

Treatment of CSVT in BD is controversial. In order to reduce inflammation, the use of corticosteroids with or without colchicine and/or azathioprine, is generally recommended, and usually leads to the resolution of CSVT (20). TNF-inhibitors have been utilised in cases refractory to standard treatment (7). Reviews of the randomised, placebo-controlled trials in CSVT from other causes support the use of anticoagulants (4). However, because the pathophysiologic mechanisms in BD may differ from other forms of CSVD, appropriate treatment remains the subject of debate. Some authors remain cautious in recommending the use of anticoagulants, due to the fear of hemorrhage from an undetected aneurysm of a large vessel (4, 36-37). Nevertheless, serious hemorrhagic complications due to anticoagulation have rarely been described in this setting (38). Moreover, compared to anticoagulation alone, immunosuppressants did not improve neurologic outcome or thrombosis recurrence rate, which led

to the conclusion that anticoagulation is safe and effective and should be the mainstay of therapy (40). In our review, combined immunosuppression with anticoagulation were used in only 36% of the cases. Immunosuppression and anticoagulants, were used in 36% and 18%, respectively. This discrepancy in treatment highlights the need for randomised controlled trials to examine the best therapeutic approach.

Almost a third of adult patients with BD and CSVT experience a relapse of thrombosis, which was CSVT in 35% of the cases. This led some authors to advocate long-term anticoagulation, especially when prothrombotic risk factors are present (39). In our review, CSVT thrombosis recurrence was reported in three patients within 1 to 4 months interval after discharge, with thrombophilic risk factor detected in two of them. Despite the lack of data to support anticoagulation, we support short-term anticoagulation, until more data are obtained, especially in children with detected thrombophilic risk factors.

Although CSVT has a better neurologic outcome compared with parenchymal CNS involvement, sequelae may appear in up to 20% of patients-mainly optic nerve atrophy (21, 25). On multivariate analysis, papilledema and concurrent prothrombotic risk factors were reported to correlate with the development of neurologic sequelae (39). Despite the good neurologic outcome in most children with CSVT, due to increased prevalence of systemic vasculitis overall morbidity and mortality may be affected (36).

## Conclusions

CSVT associated with BD is very rare in children, and can occasionally be its presenting manifestation. The typical patient is male teenager without previous diagnosis of BD, presenting with prolonged headache due to intracranial hypertension and without focal neurologic deficits. Assessment of thrombosis in additional large vessel is recommended. Immunosuppression usually leads to resolution of the thrombus. The use of anticoagulants is controversial and should be further assessed in randomised controlled trials.

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