

# Paediatric Behçet's disease with sinus venous thrombosis: experience from three centres in Turkey

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## ABSTRACT

**Objective.** To report our experiences of the juvenile Behçet's disease (BD) patients with cerebral venous sinus thrombosis (CVST) and to review previous studies reporting the clinical characteristics and outcomes of juvenile BD with CVST.

**Methods.** Clinical characteristics and outcomes of paediatric patients with CVST who met the Paediatric Behçet's Disease (PEDBD) classification criteria for juvenile BD from 3 referral centres in Turkey were reviewed retrospectively. A systematic review of literature of all published data was conducted.

**Results.** The study group consisted of 12 juvenile BD patients with CVST. At the time of CVST diagnosis, the most common symptom was headache (100%), followed by vomiting (25%), blurred vision (16.7%), and disturbances in eye movements (16.7%). Six (50%) patients presented with CVST. Transverse sinus was the most frequently affected sinus (9/12, 75%) followed by superior sagittal sinus. The mean ( $\pm 2SD$ ) BDCAF at the CVST diagnosis was 6 ( $\pm 3.8$ ). Four children (33.3%) had another venous thrombosis apart from CVST. All patients received pulse methylprednisolone for three consecutive days continued with oral prednisolone. Steroid treatment was tapered and discontinued minimum in six months. Eleven patients received azathioprine concomitant to steroid treatment at the time of CVST. All the patients received anticoagulant therapy concomitantly. Only one patient who did not receive azathioprine relapsed. Median follow-up period was 4 years (IQR: 2-5.4). In the literature review, we identified nine articles, describing 35 paediatric CVST patients associated with BD. Thirty patients achieved remission, while five

patients had residual neurologic deficit.

**Conclusion.** Neuroimaging is very important in the diagnosis of NBD. We suggest that treatment with immunosuppressants and steroid treatment is essential to decrease the adverse events of corticosteroids in the paediatric population and decrease relapses. Further multicentre studies with prospective follow-up may guide us in better management of these patients.

## Introduction

Behçet's disease (BD) is a heterogeneous disease that was first described by the Turkish dermatologist Hulusi Behçet in 1937 (1). It is a multisystemic disease and is characterised by recurrent mucocutaneous, ocular, musculoskeletal, vascular, gastrointestinal, and central nervous system (CNS) manifestations. BD may involve any size of vessel in both the arterial and venous systems, thus it has been classified in 2012 International Chapel Hill Consensus Conference as 'variable vessel vasculitis' (2).

CNS involvement is potentially one of the most serious manifestations of BD that occurs in 2.9–44% of adult patients with a male predominance. In adults, neuro-BD (NBD) mostly presents in a parenchymal form that includes a wide variety of clinical features from isolated headaches, benign raised intracranial pressure, cerebellar signs, pyramidal syndrome to myelomeningoencephalitis which can be life-threatening (3). However, non-parenchymal forms, usually presenting with cerebral venous sinus thrombosis (CVST), are more common among paediatric BD patients (4). NBD may be the initial symptom of BD. Since BD is very rare in childhood, neurological symptoms in children and adolescents can be confused with many

other disorders. Therefore, neuroimaging is very crucial to diagnose NBD in a child with neurologic signs and symptoms and to distinguish the parenchymal form from the CVST. In this study, we aimed to evaluate the clinical and imaging characteristics, treatment responses, and outcomes of the juvenile BD patients with CVST seen in 3 main centres along with a literature review.

## Patients and methods

### Patient selection

Paediatric NBD patients from 3 main referral centres in Turkey were included into the study. The paediatric patients (<16 years of age at disease onset and diagnosis) were classified as having BD according to the Paediatric Behçet's Disease (PEDBD) classification criteria (5). Demographic data, clinical manifestations, laboratory, radiological findings, treatments, and outcomes were documented from patient charts between January 2010 and November 2018 retrospectively. The neurological symptoms and the magnetic resonance imaging (MRI) results were also recorded. Remission was defined by the disappearance of all neurological symptoms and improvement (more than >50% decrease in the thrombosis) of radiological abnormalities at the six months. Disease activity was assessed by BD current activity form (BDCAF) (6). Relapse was defined by the recurrence of a new neurological symptom and/or a new lesion on cranial MRI.

### Systematic review of the literature

We comprehensively searched PubMed and Medline for articles published before November 1<sup>st</sup>, 2018. The following search keywords were used in all databases: "Behçet disease; OR BD OR Behçet syndrome; AND cerebral venous sinus thrombosis; OR CVST; AND neuroBehçet". Both searches were limited to English language and paediatric patients. Randomised and non-randomised controlled trials, observational studies (case-control, cohort studies, and case series) and single case reports involving the paediatric BD patients with CVST were included. The references of these studies and review articles for additional publica-

tions were also reviewed. One author (SD) searched the literature and manually screened titles and abstracts for relevance. Inconsistencies were resolved by discussion with authors YB and SO.

### Statistical analyses

Statistical analyses were performed using the SPSS software v. 21 (SPSS, Inc., Chicago, IL). The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. Descriptive analyses were presented using means and standard deviations (SD) for normally distributed variables and medians and interquartile range (IQR) for the non-normally distributed and ordinal variables.

## Results

### Clinical and laboratory findings of our patients

Totally 12 children from three main paediatric rheumatology centres [Hacettepe University (n=7), Dokuz Eylül University (n=3), and Ankara Child Health and Disease Haematology Oncology Training and Research Hospital (n=2)] were included in the study. All of the patients were from Turkish ancestry. Fifty eight percent of them were female. The median (IQR) age of diagnosis of BD and of cerebral venous sinus thrombosis were 13 (IQR: 11.8–14.3) and 13.2 (IQR: 12.3–14.3) years, respectively. The median delay time between the first symptom and BD diagnosis was 4.4 (IQR: 0.3–12) months. All patients had oral ulcers. Pathergy test was positive in one patient. HLA-B51 allele was carried by ten patients. Three children had family history of BD. The mean ( $\pm 2$ SD) BDCAF at the BD diagnosis was 5.1 ( $\pm 3.4$ ). The main clinical and laboratory findings at the diagnosis are summarised in Table I. At the time of CVST diagnosis, the most common symptom was headache (100%), followed by vomiting (25%), blurred vision (16.7%), and disturbances in eye movements (16.7%). Six (50%) patients presented with CVST. CVST was confirmed by magnetic resonance venography (MRV) in all

**Table I.** The clinical and laboratory findings of patients at the diagnosis.

Clinical findings	n=12
Oral aphthosis, n (%)	12 (100)
Genital aphthosis, n (%)	7 (58.4)
Skin involvement, n (%)	2 (16.7)
Eye involvement, n (%)	6 (50)
Retinal vasculitis, n (%)	1 (8.3)
Arthralgia, n (%)	3 (25)
Arthritis, n (%)	1 (8.3)
Other vascular involvement, n (%)	4 (33.3)
Gastrointestinal involvement, n (%)	0 (0)
Laboratory findings	Mean ( $\pm 2$ SD) <sup>a</sup>
WBC, $\times 10^3/\text{mm}^3$	11.4 ( $\pm 6.800$ )
PLT, $\times 10^3/\text{mm}^3$	350 ( $\pm 226$ )
CRP, mg/dl	1.9 ( $\pm 2.5$ )
ESR, mm/h	35.8 ( $\pm 36.27$ -59)

BD: Behçet's disease; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; PLT: platelet; WBC: white blood cell.  
<sup>a</sup>These values are at the time of cerebral venous sinus thrombosis.

patients. Transverse sinus was the most frequently affected sinus (9/12, 75%) followed by superior sagittal sinus (8/12, 66.6%) and sigmoid sinus (1/12, 8.3%). Presence of multiple sinus occlusions (n=6, 50%) and single sinus involvement (n=6, 50%) were equal. Parenchymal involvement was observed in one patient (8.3%). The mean ( $\pm 2$ SD) BDCAF at the CVST diagnosis was 6 ( $\pm 3.8$ ).

Four children (33.3%) had venous thrombosis elsewhere along with the CVST. Four patients had lower extremity vein thrombosis (LEVT), two had thrombosis in vena cava inferior, one had thrombosis in vena hepatica and one had cardiac thrombosis. Apart from venous involvement, one patient (8.3%) had pulmonary arterial thrombosis and one had pulmonary arterial aneurysms. Thrombophilia tests were screened however none of the patients had any mutations.

### Treatment, outcome, and safety

Colchicine was started to all the patients at the diagnosis. All patients received pulse methylprednisolone (10-30 mg/kg/day for three consecutive days) and continued with oral prednisolone (1 mg/kg, maximum 60 mg/day) for the CVST. Steroid treatment was tapered to 0.8 mg/kg/day by month one, and

**Table II.** Summary of reported cases who had CVST associated with juvenile Behçet's disease.

First author, year of publication (reference number)	n	Gender	Age at diagnosis	Age at neurologic involvement	Symptoms	Neurologic involvement	Treatment before neurologic involvement	Treatment after neurologic involvement	Anticoagulation	Relapse	Outcome	Follow-up
Cakar <i>et al.</i> , 2014 (7)	1	F	13	14.5	Headache and vomiting	1 CSVT	Colchicine	Pulse steroid	Enoxaparin	None	Improvement	NA
Uluduz <i>et al.</i> , 2011 (4)	23	2F/21M	13 (7-16)	14 (10-16)	NA	23 CSVT	NA	NA	NA	None	2 residual defect/ 21 improvement	6 (1-19)
Yılmaz <i>et al.</i> , 2010, (8)	1	F	12	12	Headache, vomiting and diplopia	CSVT	None	Pulse steroid, colchicine, AZA	Enoxaparin and warfarin	Yes	Improvement	NA
Panicker <i>et al.</i> , 2007 (9)	1	M	12	12	Blurred vision, weakness	CSVT	None	Antiepileptic	Heparin	Yes	Improvement	NA
Wechsler <i>et al.</i> , 1992 (10)	1	F	13	13	NA	CSVT	None	CS	None	None	Improvement	1 year
Stern <i>et al.</i> , 1989 (11)	1	M	NA	16	Diplopia headache and vomiting	CSVT	NA	NA	NA	NA	NA	NA,
Alper <i>et al.</i> , 2001 (12)	1	F	15	15	Headache and vomiting	CSVT	None	Acetazolamide, methylprednisolone, colchicine	None	None	Improvement	1 year
Can <i>et al.</i> , 2006 (13)	1	M	12	12	Headache, dizziness and vomiting	CSVT	None	prednisolone, colchicine, and AZA	None	None	Improvement	NA
Metreau-Vastel <i>et al.</i> , 2010 (14)	5	2F/3M	9 (5-15)	8 (6-15)	NA	CSVT	NA	NA	Yes in three	None	Improvement in two, residual defect in three	8.5 (2.5-17) years

Cvst: cerebral venous sinus thrombosis; CS: corticosteroids; AZA: azathioprine; NA: not available.

then by 0.1-0.2 mg/kg/day each month and discontinued in about six months. Eleven patients received azathioprine concomitant to steroid treatment at the time of CVST. Azathioprine treatment was continued at least one year. Enoxaparin sodium (1 mg/kg SC q12hr) was administered to 11 patients and one patient received warfarin sodium (adjusting the daily dose to maintain INR between 2.0 and 3.0). None of the patients had cranial haemorrhage. All patients achieved remission. The median BDCAF at the last visit was 1 (IQR: 0-2.75). None of the patients had neurologic deficit. There was only one patient who relapsed. This patient was initially treated with steroids only at the time of CVST. Subsequently, he relapsed after 2 years and azathioprine was started concomitant to steroid treatment. He was stable without relapse for the subsequent 36 months.

Adverse events such as cytopenia, elevated liver enzymes were not observed

during the azathioprine treatment. Median follow-up period was 4 years (IQR: 2-5.4).

#### *Paediatric BD patients with CVST in the literature*

We found 35 related articles. The number was reduced to 11 when we restricted the search to 'children' and 'English language'. Finally, after the title and abstract review, we identified nine articles, including 35 cases (Table II) (4, 7-14). The treatment data of 29 patients was not available (4, 11, 14). Among the remaining six patients, all of them received anticoagulant therapy, five patients were treated with steroids, and three patients used colchicine and one patient received azathioprine concomitant to steroid therapy. One patient was treated with only anti-epileptic drugs since he refused to use immunosuppressants. Thirty patients achieved remission, while five patients had residual neurologic deficit (4, 14). Two patients

had relapse (8, 9). Of them, one was treated with azathioprine after relapse and achieved remission (8), and the other patient did not receive any immunosuppressant and had three relapses (9).

#### **Discussion**

The clinical spectrum of juvenile BD mainly resembles the adult disease however the prevalence of some clinical features differs between children and adults. Adult patients with CNS findings usually present with parenchymal involvement while non-parenchymal involvement constitutes 88.5% of paediatric BD patients with CNS involvement in the Turkish population (4). On the other hand in France, Israel, Saudi Arabia and Italy parenchymal involvement is more dominant in paediatric BD patients (15-18). Additionally, there is no standard approach in the management of CNS involvement in the paediatric population. All information is confined to case reports and

small series with a short follow-up (19). In the presented study, we demonstrated the clinical findings, treatments and outcomes of BD patients with CVST with a rather long follow-up.

The diagnosis of BD in children is difficult because of the rarity of the disease. All of the criteria for BD diagnosis may not be fulfilled before 16 years of age. The most common initial systemic manifestation in paediatric patients with BD is mucocutaneous symptoms (20). Although most of the major vascular events in BD occur within 5 years from the disease onset (21), CVST may be the initial feature in 20% of patients with BD (22). The clinicians should keep in mind that patients with BD might present with CVST as an initial symptom without fulfilling any of the available diagnostic and classification criteria for BD. In fact our data showed that 50% of children (n=6) initially presented with CVST. When their medical histories were evaluated retrospectively, other features supporting BD (recurrent oral and genital ulcerations, uveitis) were also identified. The possible differential diagnosis of CVST other than BD in children includes meningitis, thrombophilic syndromes causing hypercoagulability (antithrombin deficiency, protein C or protein S deficiency, Factor V Leiden mutation, G20210 A prothrombin gene mutation, hyperhomocysteinaemia), malignancies, and antiphospholipid syndrome. A detailed diagnostic work-up, for thrombophilia along with imaging methods excluded other causes in these children. It is important to avoid diagnostic delay and start appropriate treatment.

Tunc *et al.* (23) have demonstrated a strong association between CVST and thrombosis in large-vessel disease. Therefore, BD patients diagnosed with CVST should be screened for early and occult vascular lesions. In the presented study, 4 patients (33.3%) with CVST had new major vascular events within median 12 months.

Since the prognosis and outcomes are different in parenchymal and non-parenchymal forms of NBD, neuroimaging is very important to decide on the management of the patient. MRI and MR venography are crucial to detect

NBD and CVST (24). Similar to previous reports, neuroimaging features of CVST in patients with BD in our series had no discriminating feature from those of patients with CVST of other aetiology (3). Transvers sinus and superior sagittal sinus were the most common involved sinuses of CVST in children compatible with the literature (25). On the other hand BD patients presenting with intracranial hypertension without any demonstrable neuroimaging abnormality have also been reported (26).

There is no prospective placebo-controlled studies for the treatment in paediatric BD patients with CVST. The main aim of the treatment of CVST is to reduce the inflammation. In 2018 an international group of experts published the European League against Rheumatism (EULAR) endorsed recommendations for the management of BD (27). According to these recommendations, the first episode of CVST should be treated with high dose glucocorticoids. These recommendations do not specifically suggest adding an immunosuppressive since relapses are rare in CVST. However, 11 of our patients received azathioprine concomitant to steroid. In the presented cohort, only one of our patients relapsed and he was not receiving azathioprine. At the time of his first CVST attack he had received steroid and enoxaparin sodium and after 2 years he had a second CVST attack. In fact azathioprine was shown to prevent thrombotic attacks in a double blind randomised (28) and, in its subsequent extension study (29). Since our cohort is small we cannot conclude that azathioprine prevented the relapses. However, paediatric patients may be more prone to relapses. Furthermore we suggest that adding an immunosuppressant is essential to decrease the adverse events of corticosteroids including osteoporosis, hyperglycaemia, and adrenal suppression and especially in the paediatric population, growth suppression. We also lack consensus on the duration of steroid treatment for NBD. The use of anticoagulant agents in CVST is also controversial. In the 2018 EULAR recommendations it was concluded that there was not enough evidence to recommend anticoagula-

tion therapy, and anticoagulants may be added especially in patients who had an additional prothrombotic tendency (27). In a recent multicentre retrospective study, the relapse rate in vascular BD was found at 29.1% and 22.4% in patients using only immunosuppressive treatment and immunosuppressive combined anticoagulation therapy, respectively (30). Saadoun *et al.* (22) showed in a retrospective study that anticoagulation was a safe and effective therapy in BD. Up to 90% of patients were treated with anticoagulant treatment together with immunosuppressive treatment without severe haemorrhagic complications. On the other hand Sorgun *et al.* (31) reported 21 patients with BD were treated with intravenous high dose prednisolone for acute CVST without anticoagulation and all patients improved. These data suggest the clear need for randomised controlled studies for the need of anticoagulation in these patients. Despite the lack of evidence-based studies, we prefer to use anticoagulation in CVST on an expert-based approach in BD.

Our study is limited by retrospective design and small sample size. However, this study reports the outcome of paediatric BD with CVST with a long follow-up.

In conclusion, imaging modalities should be performed to make a differential diagnosis in a child with the suspicion of NBD and to avoid diagnostic delay and start appropriate treatment. We suggest that adding an immunosuppressant to glucocorticoid treatment is essential to decrease the adverse events of corticosteroids in the paediatric population and maybe to decrease relapses. Further multicentre studies and prospective follow-up may help us to understand the whole spectrum in these patients.

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