Children With Behçet Disease–associated Thrombosis: A Single-Center Experience

Zeliha Guzelkucuk, MD, Dilek Gurlek Gokcebay, MD,* Ozlem Arman Bilir, MD,* Ozge Basaran, MD,† Banu Celikel Acar, MD,† Namik Y. Ozbek, MD,* and Nese Yarali, MD‡*

Summary: Behçet disease (BD) is a systemic vasculitis that can be complicated with thrombosis, which is an important cause of mortality and morbidity. The course of BD is more severe, and the diagnosis is usually delayed. In children, thrombosis associated with BD is very rare. In this study, we aimed to evaluate the characteristics of children with BD complicated with thrombosis. Forty-six patients with BD who were followed-up at a pediatric rheumatology department between January 2012 and September 2019 were evaluated retrospectively. Thrombosis was detected in 10 patients (21.7%), and it was the first sign of BD in 7 patients. Four patients had cerebral sinus venous thrombosis, 4 patients had deep-vein thrombosis, 1 patient had renal vein thrombosis, 1 had pulmonary artery thrombosis, and 1 had intracardiac thrombosis. None of the patients had arterial thrombosis. All patients had received anticoagulant therapy with immunosuppressive treatment. Any complication due to anticoagulant therapy was not detected. One patient had recurrent thrombosis, and none of the patients died during follow-up. Vasculitic diseases such as BD may cause a predisposition to thrombosis, and thrombosis might be the first sign of BD. Therefore, in children presenting with unprovoked thrombosis, BD should also be investigated.

Key Words: Behçet disease, thrombosis, children

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Behçet disease (BD), which was described by Hulusi Behçet in 1937, is a multisystemic vasculitic disease of unknown etiology.[1] The disease is common in young adults, but can also occur in childhood.[2] Gastrointestinal, neurologic, musculoskeletal, and vascular systems could be affected in patients with BD.[1–3] It can affect a vessel of any size.[4] As there are no pathognomonic laboratory findings, clinical symptoms play an important role for the diagnosis.[2] There are established diagnostic criteria for adult patients. However, these criteria are not validated in the pediatric population.[5] Therefore, it is more difficult to recognize BD in childhood. The diagnosis is usually delayed, and the disease course is more severe in children than in adults.[1]

Mucocutaneous involvement is the most common manifestation of the disease.[6,7] Eye, neurologic, and vascular involvements are among the most serious involvements.[8] Vascular involvement in BD may occur as thrombosis, aneurysm, or stenosis.[9] Thrombosis of the lower extremity veins is the most common form of vascular involvement.[4,5,10] Vena cava, pulmonary artery, hepatic artery, dural sinus thrombosis, and abdominal aortic and peripheral artery aneurysms are the other affected vessels.[10] In childhood BD, the frequency of vascular involvements is relatively rare.[9]

In this study, we aimed to investigate the characteristics of children with BD-associated thrombosis.

MATERIALS AND METHODS

All patients with BD who were followed-up at the University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital Pediatric Rheumatology Department between January 2012 and September 2019 were evaluated retrospectively. Demographic features, age at the time of diagnosis, family history, initial presentation, clinical findings such as oral aphthae, genital ulcer, papulopustular lesions, erythema nodosum, eye, joint, vascular, gastrointestinal, and central nervous system (CNS) findings at diagnosis, pathergy test and HLAB51 results, presence of thrombosis, side of thrombosis, imaging methods, treatment protocols, treatment duration, and follow-up duration were recorded.

Informed consents were obtained from all patients' parents, and institutional review board approval was obtained.

Statistical Methods

Analysis of data was primarily descriptive, using SDs, ranges, and mean and median values. Categorical variables were analyzed using the χ^2 test, and continuous variables were analyzed using the Student t test. All analyses were performed using SPSS 18 for Windows (SPSS Inc., Chicago, IL). When $P \leq 0.05$, it was considered statistically significant.

RESULTS

All patients who were diagnosed with both BD and thrombosis according to the ICD-10 codes were reviewed. Forty-six patients were followed-up with BD. Seventeen patients were male individuals (36.9%). The mean age at diagnosis of BD was 14.2 years (min-max range, 4 to 18 y).

A total of 10 patients (21.7%) with BD had thrombosis. Seven of them were male individuals, and mean age at the time of thrombosis was 13.4 years (range, 5 to 17.5 y). Male patients with BD were more likely to have thrombosis (7/17, 41.1%) than were female patients (3/29, 10.3%). All patients were of Turkish nationality. The mean follow-up period from thromboembolic event was 31.5 months (range, 6 to 82 mo). A family history of BD was present in 3 patients. Moreover, 1 patient's mother died due to myocardial infarction before the age of 40. Recurrent oral aphthae in 7 patients, genital ulcer in 2 patients, scar secondary to genital ulcer in 1 patient, acneiform skin lesions in 1 patient, eye involvement in 4 patients, and neurologic findings in 2

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From the Departments of *Pediatric Hematology and Oncology; †Pediatric Rheumatology, Ankara City Hospital, University of Health Sciences; and ‡Department of Pediatric Hematology and Oncology, Ankara City Hospital, Yıldırım Beyazıt University, Ankara, Turkey.

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Reprints: Zeliha Guzelkucuk, MD, Faculty of Medicine Research and Training Hospital, Ahi Evran University, Kervansaray Mah. 2019. Sok. No:1 Kırşehir 40200, Turkey
(e-mail: drguzelkucuk@hotmail.com).

TABLE 1. Clinical and Laboratory Features of Patients With Behçet Disease With TE

Patient	Sex	Age BD/ TE	BD Diagnostic Criteria	Clinical Presentation of TE	Localization of Thrombosis	Hereditary Thrombophilia	AC* Treatment	Duration of AC Treatment (mo)	Follow-up Time (mo)
1	F	11/11	Recurrent oral aphthae +HLAB51+pathergy test+eye finding+	Headache	Sagittal and transverse sinus	MTHFR 1298*	LMWH	6	46
2	M	17/17,5	Recurrent oral aphthae +genital ulcer +pathergy test +HLAB51+	Swelling and pain of the leg	Vena saphena magna	High Lp(a) and hyperhomocysteinemia factor V Leiden* MTHFR C677T*	LMWH	3	22
3	M	15/15	Pathergy test+HLAB51+	Abdominal pain	Renal vein	PAI 4G/5G MTHFR C677T*	LMWH	3	15
4	M	11/11	Recurrent oral aphthae +pathergy test+eye finding+	Headache	Sagittal and transverse sinus	—	LMWH	3	13
5	M	5/5	Arthralgia+pathergy test +HLAB51	Abdominal pain	Right femoral, popliteal iliac vein, right renal vein	PAI 4G/5G	LMWH	6	16
6	F	15/15	Recurrent oral aphthae +eye finding+	Headache	Transverse sinus	MTHFR C677T*	LMWH	6	70
7	M	15/15	Recurrent oral aphthae +HLAB51+	Swelling and pain of the leg, tachypnea	Right femoral, popliteal vein, pulmonary artery	Factor V Leiden* MTHFR C677T*	LMWH	6	19
8	M	14/15	Arthralgia pathergy test+	Swelling of the leg	Right femoral vein	—	LMWH	3	26
9	F	13/14	Recurrent oral aphthae +genital ulcer +HLAB51+ eye finding+	Headache	Recurrent transverse sinus (same place)	Factor V Leiden* MTHFR C677T*	LMWH, coumadin	3	82
10	M	16/16	Recurrent oral aphthae+ genital scar+acneiform skin lesion	Fever	Intracardiac (right ventricular apex)	—	LMWH	6	6

*Heterozygous.
AC indicates anticoagulant; F, female; LMWH, low–molecular-weight heparin; Lp(a), lipoprotein a; M, Male.

patients except isolated headache were detected. Pathergy test was positive in 6 patients with thrombosis. HLAB51 was positive in 6 patients. The characteristics of the patients are summarized in Table 1.

Thrombosis was the presenting sign of BD in 7 patients. None of the patients had a history of catheterization. All thrombotic events were unprovoked and had developed in the venous system. Arterial thrombosis was not detected in any patient. Four patients presented with headache. Cranial magnetic resonance imaging and cranial angiography revealed sagittal sinus and transverse sinus thrombosis in these patients. One patient with abdominal pain had renal vein thrombosis. In another patient presenting with abdominal pain, popliteal, femoral, iliac, and renal vein thromboses were detected. Another patient had swelling of the left leg, and vena saphena magna thrombosis was detected on the lower extremity by Doppler ultrasonography. The other patient presented with swelling of the right leg, and deep venous thrombosis of the lower extremity was detected with Doppler ultrasonography. Pulmonary computerized tomography angiography was performed in this patient due to chest pain, and pulmonary embolism was detected. One patient had intracardiac thrombosis, which was located in the right ventricular apex, and the size was 21×11 mm.

Thrombophilia was evaluated in all patients with thrombosis. Factor V Leiden heterozygote mutation was detected in 3 patients, and PAI 4G/5G was detected in 2 patients. Lipoprotein(a) elevation and homocysteine elevation were detected in a patient. Hyperlipidemia was detected in 1, and MTHFR C677T heterozygote mutation was detected in 5 patients.

All patients received colchicine, and immunosuppressive treatment consisted of corticosteroids, azathioprine, or cyclophosphamide, and low–molecular-weight heparin as well. The duration of anticoagulant therapy ranged from 3 to 6 months. A 13-year-old girl with transverse sinus thrombosis with both factor V Leiden and MTHFR C677T heterozygosity was treated first with low–molecular-weight heparin, and, later, coumadin treatment was given. Thrombosis recurrence was detected in this patient 6 months after discontinuation of anticoagulant therapy, and lifelong anticoagulant therapy was planned. Another patient with sagittal sinus thrombosis had neurologic sequel. Any mortality associated with the thrombosis was not detected.

DISCUSSION

The etiopathology of BD-associated thrombosis is still uncertain.[1,2] Instead of hypercoagulability, endothelial damage and dysfunction and/or the inflammatory process are considered predisposing factors for thrombosis.[1,2,4] Depending on the genetic and environmental factors, monocytes, NK cells, and T helper-17 cells are activated. Cytokines such as IFN-y, IL-17 and CXCL8 initiate neutrophil activation.[10,11] Neutrophil hyperactivity is assumed to play a major role in hyperinflammation in BD.[12] Inflammation is thought to promote thrombotic events through endothelial dysfunction, platelet hyperactivity, and increased tissue factor expression.[11]

BD is common in adults in the second and fourth decades; however, it is very rare in childhood. Prevalence varies according to the ethnic origin.[1–3] The frequency of family history is higher in children compared with adult patients.[7] Three of our patients had a positive family history for BD. Moreover, the mother of one of our patients died due to myocardial infarction before the age of 40. It might be in consequence of a vascular disease that could be attributed to genetic factors affecting the clinic of BD.

According to the International Study Group criteria, the presence of at least 2 of the following findings is considered as BD: recurring oral aphthous ulcers, genital ulcers, ophthalmologic findings, cutaneous findings, and a positive pathergy test.[5,13] Mucocutaneous involvement is the most common manifestation of the disease.[6,7] The most common finding in BD is recurrent oral aphthae, similar to our patients.

Vascular involvement in BD is associated with the severity of the disease.[14,15] Vascular involvement is thought to affect 25% of patients, and male individuals predominated.[9] Similar to previous studies, vascular involvement was more common in male patients in our study. Vascular involvement in BD may occur as thrombosis, aneurysm, or stenosis.[9] The venous system is mostly affected.[10,14] Thrombosis as an initial manifestation of BD is very rare in children.[15] However, in most of our patients who had thrombosis, the presenting signs were related to unprovoked thrombosis.

Superficial venous thrombosis (SVT) and deep-vein thrombosis (DVT) are the most common vascular involvements in BD. Deep veins of the lower extremity are the most common venous thrombosis sites, accounting for 15% to 40% of patients with BD.[10] Thrombosis of atypical sites including the inferior and superior vena cava, suprahepatic veins, portal vein, cerebral sinuses, and right ventricle is an important clinical feature of BD.[10] Sinus vein thrombosis was the most common site in our cases. Renal vein thrombosis, intracardiac, and inferior vena cava thrombosis were also detected in our patients.

CNS involvement is a serious condition and occurs in 5% to 10% of children.[16,17] It is either a parenchymal lesion or thrombotic phenomenon. Headache is frequently seen as a result of increased intracranial pressure due to cerebral sinus venous thrombosis (CSVT).[17] Therefore, magnetic resonance imaging is useful in children with BD with unexplained headache.[18] In our study, patients who presented with headache and in whom CSVT was detected were diagnosed as suffering from BD. One patient had both parenchymal and vascular involvement. The other 3 patients had cranial sinus thrombosis. Cerebral sinus vein thrombosis is the most common clinical entity in juvenile BD. The mean age of our patients with CSVT was 12 years, compatible with published studies.[19]

The effect of genetic thrombophilia on thrombosis in patients with BD is controversial.[4,20,21] Factor V gene G1691A mutation (factor V Leiden) is reported to contribute to the development of venous thrombosis in BD.[22] However, the current data suggest that the pathogenesis of thrombosis in BD is not due to coagulation abnormality, and genetic studies may be insufficient to guide the patient's treatment.[20] In our study, hereditary thrombophilia was detected in 5 patients (50%). Recurrence was detected in a patient who had both factor V Leiden and MTHFR C677T heterozygosity. The frequency of MTHFR C677T has been reported as 42.9% in our country,[23] and 50% of our patients had MTHFR C677T polymorphism. As only homozygotes for MTHFR have mild hyperhomocysteinemia, and the MTHFR gene mutation is not a direct risk factor for atherosclerosis and thrombosis, the relationship with MTHFR variants and VTE development in BD has not been considered. In a meta-analysis examining thrombophilia and thrombosis in BD, it was also reported that there was no association between MTHFR variants and thrombosis in BD.[21] In another study, triglyceride concentration was found to be the

best predictor of thrombosis in BD.[4] Hyperlipidemia and elevated lipoprotein(a) and homocysteine levels were observed in 1 patient. The parameters that provoke the development or recurrence of thrombosis were not compared with nonthrombotic patients.

Understanding the contribution of inflammatory and coagulation components to the pathogenesis of BD vascular events is critical to identifying the most effective therapeutic strategy.[11] Treatment of vascular disease in BD requires immunosuppressive agents.[3,9] All our patients received colchicine and other immunosuppressive treatment. There is no consensus in terms of the need for anticoagulant therapy and the effect of anticoagulant therapy on recurrence of thrombosis in patients with BD. In particular, unlike the usual DVT that occurs in association with a hypercoagulable condition, the requirement of anticoagulation therapy in DVT associated with BD is debatable. Anticoagulation therapy alone is not effective at treating DVT associated with BD.[24] Immunosuppressive treatment is essential in preventing the attacks and increasing survival.[25] However, there are studies in which the use of anticoagulant therapy was necessary, especially in the treatment of patients with CSVT and intracardiac thrombosis.[10] The only contraindication of anticoagulant therapy has been reported to be pulmonary artery aneurysm due to the risk of rupture.[9] Our patients received anticoagulants because of CNS, pulmonary, cardiac, and renal vein thromboses. No complication due to anticoagulant therapy was seen.

Thrombosis recurrence is ~20% in adult BD patients.[25] In a study in which pediatric patients were evaluated, 21% of recurrent attacks were reported.[5] There was no difference in relapse rate between patients who received immunosuppressant therapy alone and those who received anticoagulant therapy with immunosuppressant therapy.[24] In our study, thrombosis recurrence was detected in a patient 6 months after discontinuation of anticoagulant therapy. Whether anticoagulants should be added to prevent relapses should be discussed and individualized on the basis of the location of thrombosis and presence of comorbidity.

In this study, which examined the characteristics of childhood BD-associated thrombosis, it was determined that BD could be diagnosed after the development of thrombosis. Although not included in the diagnostic criteria, thrombosis might be the main clinical feature of BD. In most of our patients, there were no apparent features other than the findings of thrombosis. In children presenting with unprovoked thrombosis, BD should be considered, vague oral or genital lesions should be investigated carefully, and BD should be questioned in family history. Prospective studies with more patients and longer follow-up period are needed to determine the factors affecting morbidity and thrombosis recurrence in BD.

REFERENCES

1. Karincaoglu Y, Borlu M, Toker SC, et al. Demographic and clinical properties of juvenile-onset Behçet's disease: a controlled multicenter study. *J Am Acad Dermatol*. 2008;58:579–584.
2. Koné-Paut I. Behçet's disease in children, an overview. *Pediatr Rheumatol Online J*. 2016;18:10.
3. Ozen S, Eroglu FK. Pediatric-onset Behçet disease. *Curr Opin Rheumatol*. 2013;25:636–642.
4. Leiba M, Seligsohn U, Sidi Y, et al. Thrombophilic factors are not the leading cause of thrombosis in Behçet's disease. *Ann Rheum Dis*. 2004;63:1445–1449.
5. Krupa B, Cimaz R, Ozen S, et al. Pediatric Behcet's disease and thromboses. *J Rheumatol*. 2011;38:387–390.
6. Davatchi F, Shahram F, Chams-Davatchi C, et al. Behcet's disease in Iran: analysis of 6500 cases. *Int J Rheum Dis*. 2010;13:367–373.
7. Borlu M, Ukşal U, Ferahbaş A, et al. Clinical features of Behçet's disease in children. *Int J Dermatol*. 2006;45:713–716.
8. Krause I, Uziel Y, Guedj D, et al. Childhood Behçet's disease: clinical features and comparison with adult-onset disease. *Rheumatology (Oxford)*. 1999;38:457–462.
9. Ozen S, Bilginer Y, Besbas N, et al. Behçet disease: treatment of vascular involvement in children. *Eur J Pediatr*. 2010;169:427–430.
10. Emmi G, Bettiol A, Silvestri E, et al. Vascular Behçet's syndrome: an update. *Intern Emerg Med*. 2019;14:645–652.
11. Becatti M, Emmi G, Bettiol A, et al. Behçet's syndrome as a tool to dissect the mechanisms of thrombo-inflammation: clinical and pathogenetic aspects. *Clin Exp Immunol*. 2019;195:322–333.
12. Emmi G, Becatti M, Bettiol A, et al. Behçet's syndrome as a model of thrombo-inflammation: the role of neutrophils. *Front Immunol*. 2019;14:1085.
13. Evaluation of diagnostic ('classification') criteria in Behçet's disease—towards internationally agreed criteria. The International Study Group for Behçet's disease. *Br J Rheumatol*. 1992;31:299–308.
14. Çelik G, Yildirm E, Narci H, et al. Diffuse thrombosis secondary to Behçet's disease: a case report. *Am J Emerg Med*. 2013;31:1723.e1–1723.e2.
15. Gurunathan A, Teachey DT, Chikwava KR, et al. Behcet disease initially presenting as deep venous thrombosis: a case report. *J Pediatr Hematol Oncol*. 2017;39:410–412.
16. Hacihamdioglu DO, Demiriz M, Sobaci G, et al. Cerebral vein thrombosis in a four year old with Behçet's disease. *Reumatol Clin*. 2014;10:254–256.
17. Yesilot N, Bahar S, Yilmazer S, et al. Cerebral venous thrombosis in Behçet's disease compared to those associated with other etiologies. *J Neurol*. 2009;256:1134–1142.
18. Shi J, Huang X, Li G, et al. Cerebral venous sinus thrombosis in Behçet's disease: a retrospective case-control study. *Clin Rheumatol*. 2018;37:51–57.
19. Rottenstreich A, Machol K, Eisenstein EM, et al. Behçet's disease and cerebral sinus vein thrombosis in children: a case study and review of the literature. *Clin Exp Rheumatol*. 2015;33(6, suppl 94):S163–S168.
20. Espinosa G, Font J, Tàssies D, et al. Vascular involvement in Behçet's disease: relation with thrombophilic factors, coagulation activation, and thrombomodulin. *Am J Med*. 2002;112:37–43.
21. Chamorro AJ, Marcos M, Hernández-García I, et al. Association of allelic variants of factor V Leiden, prothrombin and methylenetetrahydrofolate reductase with thrombosis or ocular involvement in Behçet's disease: a systematic review and meta-analysis. *Autoimmun Rev*. 2013;12:607–616.
22. Gül A, Ozbek U, Oztürk C, et al. Coagulation factor V gene mutation increases the risk of venous thrombosis in Behçet's disease. *Br J Rheumatol*. 1996;35:1178–1180.
23. Sazci A, Ergul E, Kaya G, et al. Genotype and allele frequencies of the polymorphic methylenetetrahydrofolate reductase gene in Turkey. *Cell Biochem Funct*. 2005;23:51–54.
24. Ahn JK, Lee YS, Jeon CH, et al. Treatment of venous thrombosis associated with Behcet's disease: immunosuppressive therapy alone versus immunosuppressive therapy plus anticoagulation. *Clin Rheumatol*. 2008;27:201–205.
25. Seyahi E. Behçet's disease: how to diagnose and treat vascular involvement. *Best Pract Res Clin Rheumatol*. 2016;30:279–295.