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ORIGINAL PAPER

Behçet disease: treatment of vascular involvement in children

Seza Ozen · Yelda Bilginer · Nesrin Besbas · Nuray Aktay Ayaz · Aysin Bakkaloglu

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Abstract Behçet disease is the only primary vasculitis that affects both arteries and veins of any size. We present our treatment protocol in disease with vascular involvement in seven pediatric patients. All seven patients met the international criteria for the disease before the age of 16 years. Only one was a girl. The vascular involvement was as follows: Two patients had superficial vein thrombosis, two patients had atrial or ventricular thrombosis, one had arterial involvement with pulmonary aneurysms, and two had thrombosis of the venous sinuses in the central nervous system. The median duration of vascular involvement was 4 months (range 3–24 months) after the diagnosis of BD and was concomitant with diagnosis in three patients. All received colchicine and steroids. The ones with thrombosis in the venous system received additional azathioprine, whereas those with pulmonary arterial or cardiac involvement initially received cyclophosphamide for 150–180 mg/kg total dose (IV or oral) and then were switched to azathioprine for a further 6 months. All except the patient with pulmonary arterial involvement received a course of anticoagulation treatment as well. These patients have been followed up for a period of at least 18 months and so far are free of vascular relapses. One has developed a severe uveitis necessitating further therapy. In conclusion, features of vascular involvement should be carefully sought for in patients with Behçet disease. Effective management has enabled disease-free survival in the presented patients.

Keywords Behçet disease · Vascular involvement · Treatment

S. Ozen (✉) · Y. Bilginer · N. Besbas · N. A. Ayaz · A. Bakkaloglu
Department of Pediatrics, Nephrology and Rheumatology Unit, Hacettepe University School of Medicine, Ankara, Turkey
e-mail: sezaozen@hacettepe.edu.tr

Y. Bilginer
e-mail: yeldabilginer@yahoo.com

Introduction

Behçet's disease (BD) is a chronic multisystemic disease characterized by recurrent oral and genital ulcerations, uveitis, and skin lesions and is first defined by "Hulusi Behçet" in 1937 [3]. Vasculitis accounts for much of the pathologic process in Behçet's syndrome and can affect both veins and arteries of all sizes [11]. Although the specific cause of vascular thrombosis seen in BD cases is not yet known, endothelial cell injury and a pathological activation due to vasculitis are known to be characteristics of BD [12].Venous involvement exceeds the rate of arterial involvement as reported in different studies [10, 13].

Since vascular manifestations are the main predictors of mortality and morbidity, treatment of these children should be a main concern. However, we lack firm evidence for the best treatment of vascular involvement in Behçet disease.

Whether immunosuppressive therapy alone is sufficient or anticoagulation should be added to the regimen for the thrombosis is still controversial. However, many continue to use anticoagulation for active thrombosis. It is agreed on that the mainstay of the treatment should be effective anti-inflammatory and immunosuppressive therapy [1, 4, 5, 9].

In this paper, we reviewed our experience in the treatment of patients with vascular disease. We report the clinical characteristics, immunosuppressive and anticoagulation therapy, and outcomes of seven pediatric patients.

Patients

Among the 20 patients with Behçet disease followed in our center, seven of them (six male and one female) had either arterial or venous involvement. All patients met the criteria of the International Study Group for the diagnosis of BD [6]. All had recurrent oral ulcers. Four had skin involvement in the form of erythema nodosum, and one in the form of folliculitis; two had typical genital ulcers, three had uveitis (Table 1), and four had a positive pathergy test. The median age at the onset of the first symptoms was 14 years (8–16 years). Clinical features of the patients are listed below:

Patient 1 A 14-year-old boy presented with painful nodules on his leg. He had recurrent oral and genital ulcers. He was human leukocyte antigen (HLA) B5 positive and was put on colchicine treatment. On his fourth year follow-up, he was admitted to our hospital due to hemoptysis. Thoracal computerized tomography angiography showed pulmonary artery aneurysm (PAA). Successful embolization of a giant PAA was performed. He responded to pulse and oral steroid therapy and six pulses of i.v. cyclophosphamide.

Patient 2 An 11-year-old male was admitted to our hospital with the complaints of swelling and sensitivity in the left arm and leg. The patient had a history of recurrent aphthous oral ulcerations and erythema nodosum. Pathergy test was positive. Epididymo-orchitis developed on the third day of his admission to the hospital. He responded to colchicine and oral prednisone therapy. After 2 months, the patient presented with acute calf pain, and Doppler ultrasonography confirmed a thrombophlebitis. He was given i.v. heparinization followed by oral warfarin for 6 months. Azathioprine was also started.

Patient 3 A 16-year-old boy who had an operation due to tetralogy of Fallot was referred to our department because of erythema nodosum. He had congestive heart failure, and echocardiogram showed right atrial and ventricular thromboses. A detailed review of the history revealed an episode of anterior uveitis 3 years ago. He also gave a history of recurrent oral ulcerations three to four times in a year. Pathergy test was positive. He was put on oral cyclophosphamide and steroid therapy. He was started on i.v. heparin followed by warfarin for 6 months.

Patient 4 A 15-year-old boy presented with dyspnea to the emergency department. Echocardiogram was performed, and ventricular thrombus was found. His history revealed erythema nodosum and recurrent oral aphthous lesions. Both HLA B5 and pathergy tests were positive. He was given cyclophosphamide and steroid therapy. Tissue plasminogen activator was also administered. He was started on i.v. heparin followed by warfarin for 6 months. After 3 months, cyclophosphamide was switched to azathioprine on clinical remission.

Patient 5 A 10-year-old boy was referred to our emergency department due to headache, diplopia, and generalized tonic-clonic convulsion. Magnetic resonance imaging angiography revealed sinus vein thromboses. The patient had a history of recurrent oral aphthous lesions, genital ulcers, and HLA B5 was positive. He was given pulse methylprednisolone followed by oral steroids along with azathioprine. After i.v. heparinization, low molecular weight heparin (LMWH) was introduced. On discharge, his physical examination was normal.

Patient 6 An 8-year-old boy was admitted because of left leg pain with swelling and redness. Doppler ultrasonography was performed and confirmed the diagnosis of popliteal vein thromboses. He had arthralgia, abdominal pain, oral aphthous lesions, and uveitis. HLA B5 and pathergy test was positive. He was put on colchicine, oral prednisone, and azathioprine along with i.v. heparinization followed by oral warfarin.

Patient 7 A 15-year-old girl was referred to our emergency department due to severe headache and vomiting. She had been followed as Behçet disease in another center due to recurrent oral and genital ulcers, uveitis, and put on colchicine treatment. Magnetic resonance imaging angiography revealed sinus vein thromboses. Ventriculoperitoneal shunt was inserted due to uncontrolled increased intracranial pressure. She was given oral steroid and azathioprine. After i.v. heparinization, LMWH was introduced. She was still on low dose oral steroid therapy, and cyclosporine is added to the refractory uveitis.

The vascular involvement was as follows: Two patients had superficial vein thrombosis, two patients had atrial or ventricular thrombosis, two had sinus vein thrombosis, and one had arterial involvement with pulmonary aneurysms. The disease was diagnosed 4 months (range 3–24 months) before the vascular involvement in four patients and concomitant with diagnosis in three patients.

Table 1 Clinical characteristics of the patients

Features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years) at BDDX	14	10	16	15	10	8	15
BD duration (months)	126	41	30	23	18	19	40
ESR (mm/h; 0–20)	92	78	82	96	67	46	72
CRP (mg/dl; 0–0.5)	7.6	5.4	6.4	8.2	4.6	2.4	3.6
HLA B5	+	+	+	+	+	+	–
Oral ulcer	+	+	+	+	+	+	+
Genital ulcer	+	–	–	–	+	–	+
Erythema nodosum	+	+	+	+	–	–	–
Ocular lesions uveitis	–	–	+	–	–	+	+
Vascular involvement	Pulmoner artery aneurysms	Left gastrocinemus vein thrombosis	Right atrial and ventricular thrombosis	Right ventricular thrombosis	Sinus vein thrombosis	Left popliteal vein thrombosis	Sinus vein thrombosis
Immunosuppression	Pulse MP (i.v.), prednisone (po), CP (po)	AZA (po), prednisone (po)	CP (po), prednisone (po)	Pulse MP (i.v.), prednisone (po), CP (po), AZA	Pulse MP (i.v.), prednisone (po), AZA (po)	Prednisone (po), AZA (po)	Prednisone (po), AZA (po)
Anticoagulation	–	i.v. heparinization followed by oral warfarin for 6 months	i.v. heparinization followed by warfarin for 6 months	i.v. heparinization followed by oral warfarin for 6 months	i.v. heparinization followed by LMWH for 6 months	i.v. heparinization followed by oral warfarin for 6 months	i.v. heparinization followed by LMWH for 6 months

MP methylprednisolone, *CP* cyclophosphamide, *AZA* azathioprine, *LMWH* low molecular weight heparin

All received colchicine for mucocutaneous involvement and/or arthritis and/or erythema nodosum. Steroids were given for the vasculitis, tapered rapidly after disease control, and continued for 1 year. The ones with thrombosis in the venous system received additional azathioprine, whereas those with pulmonary arterial or cardiac involvement initially received cyclophosphamide for 150–180 mg/kg total dose (i.v. or oral) and then were switched to azathioprine for a further 6 months.

These seven patients were investigated for a prothrombotic state: protein C, protein S, factor V leiden R506Q mutation, prothrombin G20210A mutation, methylenetetrahydrofolate reductase gene mutation, plasma homocysteine level, anti-cardiolipin, and antiphospholipid antibodies. Only one of them had methylenetetrahydrofolate reductase heterozygote mutation. The remaining patients were free of any additional prothrombotic risk factors.

Only two of the patients who had sinus vein thrombosis were given LMWH. Anticoagulation was given to all except for the patient with pulmonary artery involvement and was continued for 6 months.

These patients have been followed up for a period of at least 18 months. At present, they are free of vascular relapses and have had no recurrences of thrombosis.

Discussion

The vasculitis of Behçet's disease has unique features. It is the only vasculitis that affects both arteries and veins of any size. The aneurysms are characterized by neutrophilic infiltrate around the vasa vasorum [7]. That may also be reflecting the abnormalities in neutrophil and vascular cell interactions. On the level of capillaries, BD may affect the glomeruli as well, albeit rare [2]. Overall, vascular involvement in BD is not rare. In a multicenter study of children, arterial and venous involvement was present in 7% and 12% of the patients, respectively, not including dural sinus thrombosis [8]. When disease affects the veins, it is in the form of thrombosis; when it affects the arteries, it results in aneurysms, thrombosis, or stenosis. Dural sinus thrombosis has been classified in this paper as "venous involvement" to unify our treatment approach.

A recent review has highlighted the lack of grade I evidence for the treatment of vascular disease in BD [5]. Pulmonary arterial and cardiac involvement is associated with high morbidity and mortality, and thus it is treated no different than a severe small-sized vessel vasculitis. Thus, we have treated these patients similar to severe systemic vasculitides.

On the other hand, BD is one of the rare vasculitides that would also affect the venous system. The thrombi in the veins that is characteristic for the disease is rather

unique in that they adhere to the vessel wall. The veins that are most commonly affected are the femoral and popliteal veins, axillary veins, renal veins, hepatic vein, vena cava superior and vena cava inferior, dural sinuses, and central retinal veins [12]. The treatment of the venous inflammation is with azathioprine, which is mainly based on adult experience.

Dural sinus involvement may also be regarded as a neurological involvement. In fact, in BD, the central nervous system is involved in the form of dural sinus thrombosis or parenchymal involvement, the latter is rare in children. Since the sinus also is a part of the venous system, the patients with dural venous thrombosis were included in this cohort.

In this small cohort, we show that patients with severe arterial involvement treated with a regime similar to severe small vessel vasculitides and venous disease treated with azathioprine was successful in inducing remission. Furthermore, we show that a duration of 6 months of azathioprine seemed to prevent relapses in the median 18 months of follow-up in the presented group of patients. None of them required further biological treatment.

There is no consensus and no evidence for the benefit of anticoagulation treatment in the vasculitis of BD. Although in the aforementioned paper it was concluded that there was not enough evidence to recommend anticoagulation therapy, the bedside decision is not so easy [5]. The only contraindication of anticoagulation would be the presence of PAA because of the risk of rupture. We have used short-term anticoagulation in our patients. However, we need controlled studies for the final conclusions on the subject.

We suggest that pediatricians should monitor their patients with BD for arterial and venous vascular disease. The families should be informed about the possible features of peripheral venous involvement, signs of sinus thrombi, and cautioned against chest pain. In the presence of relevant symptoms, the imaging modalities should be performed urgently. Effective management and the judicious use of immunosuppressives are successful in disease control and avoidance of biological agents. Carefully planned controlled studies will provide evidence for the need of anticoagulation in these patients.

Conflict of interest The authors do not have a financial relationship.

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