Major vessel thrombosis in Behçet's disease: the dilemma of anticoagulant therapy – the approach of rheumatologists from different countries

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Abstract

Objectives

The best treatment for patients with Behçet's disease (BD) with major vessel thrombosis has not been fully determined. Our objective was to raise this therapeutic dilemma and to call for controlled studies to help establish guidelines to address this problem.

Methods

Three patients with BD and major vessel thrombosis whom we recently encountered are described. Their cases were presented to rheumatologists from Turkey, Israel and the USA. The physicians were asked about the kind of treatment they would give each patient at diagnosis of thrombosis and if they chose to give anticoagulation and for long.

Results

Fifty-five Turkish, 33 Israeli and 25 American rheumatologists responded to the questionnaire. More than 87% of the Israeli and American rheumatologists would give anticoagulation at the time of diagnosis for the cases of venous thrombosis compared with only 40-44% of the Turkish physicians. In these cases 56% of the American and 45% of the Israeli rheumatologists would give warfarin for life compared with only 5-18% of the Turkish physicians. Regarding a case with intra-cardiac thrombus, 96% of American, 94% of Israeli, and 60% of Turkish rheumatologists would start anticoagulation at diagnosis while 70%, 39% and 33%, respectively would give this treatment for life.

Conclusion

The therapeutic approach towards thrombosis in Behçet's disease differs significantly among rheumatologists from different countries. The different prevalence of the disease in these countries may explain this difference. A randomised controlled prospective trial is needed in order to determine the exact role of anticoagulant treatment in BD.

Key words

Behçet's disease, thrombosis, anticoagulants

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Introduction

Behçet's disease (BD) is a systemic autoinflammatory disease characterised by recurrent oral and genital ulcers with ocular involvement (1). The disease can also affect the joints, nervous system, gastrointestinal tract and the blood vessels. Large-vessel involvement occurs in approximately one-third of patients with BD (2), and may lead to haemorrhage, vascular stenosis, aneurysm formation with bleeding or thrombosis in arteries, veins, and varices (3, 4). Venous disease is more common than arterial involvement. Venous thrombosis may be the first presentation of the disease but usually appears 4-5 years after the onset of BD (5). Patients with BD have a 14-fold increased risk of venous thrombosis compared with healthy controls. Males with BD have a 6-fold increased risk compared with females (6). A retrospective analysis of 2319 Turkish patients with BD found a prevalence of vascular disease of 14.3%; 29.8% of them suffered from deep venous thrombosis (7). Treatment modalities for thrombosis in BD include immunosuppressive agents (steroids, azathioprine etc.), anticoagulation and antiplatelet agents (8). However, there are no large controlled studies available regarding the best approach to BD patients complicated by thrombosis and the exact role of long-term anticoagulation in these cases.

Recently, we encountered three BD patients whose main problem was thrombosis in a major vein or the heart. We present these cases in order to raise the serious dilemma of whether to initiate anticoagulant treatment in major vessel thrombosis in BD patients and when to stop the treatment. In order to gain some idea about the approach to this dilemma we conducted a survey regarding anticoagulant treatment in the above cases among rheumatologists from Turkey, Israel and the USA. We report these results as well.

Patients and methods

Three patients with major vessel thrombosis were interviewed and examined in our Department of Medicine. A diagnosis of Behçet's disease was made based upon the international study group for BD (9).

Rheumatologists' survey

A short description of the three patients was presented to rheumatologists from Turkey (a country with a relatively high prevalence of BD), USA (low BD prevalence) and Israel (intermediate BD prevalence). The physicians were asked to respond to the following 2 questions for each case:

1. Following the diagnosis of the thrombotic event in BD, which medications would you choose to treat the patient?
   a. Steroids and azathioprine only
   b. Warfarin only
   c. Steroids, azathioprine and warfarin
   d. None of the above
2. If you choose treatment with warfarin (with or without steroids and azathioprine) when would you stop this medication?
   a. Following clinical improvement of the thrombotic event
   b. Following disappearance of inflammatory parameters of BD
   c. Treatment with warfarin should be taken for life
   d. None of the above

The questionnaire was distributed by e-mail and the response was anonymous. Our main goal was to see how many physicians would give anticoagulation treatment upon diagnosis of a thrombotic event in BD and how many would continue this treatment for life.

Statistical method

The data were compared between rheumatologists from different countries. First, the χ^2 test was applied to test the null hypothesis that there are no differences between the groups. To correct for multiple comparisons, the significance level was adjusted using the Bonferroni correction, corresponding to a critical *p*-value of 0.008. Significant tables were followed up by multiple pair-wise comparisons that were tested using Fisher's exact test, with significance level adjusted by Bonferroni correction (*p*-value <0.017 was considered significant).

Case presentations

Case 1: A 17-year-old male was hospitalised due to headache, diplopia, with

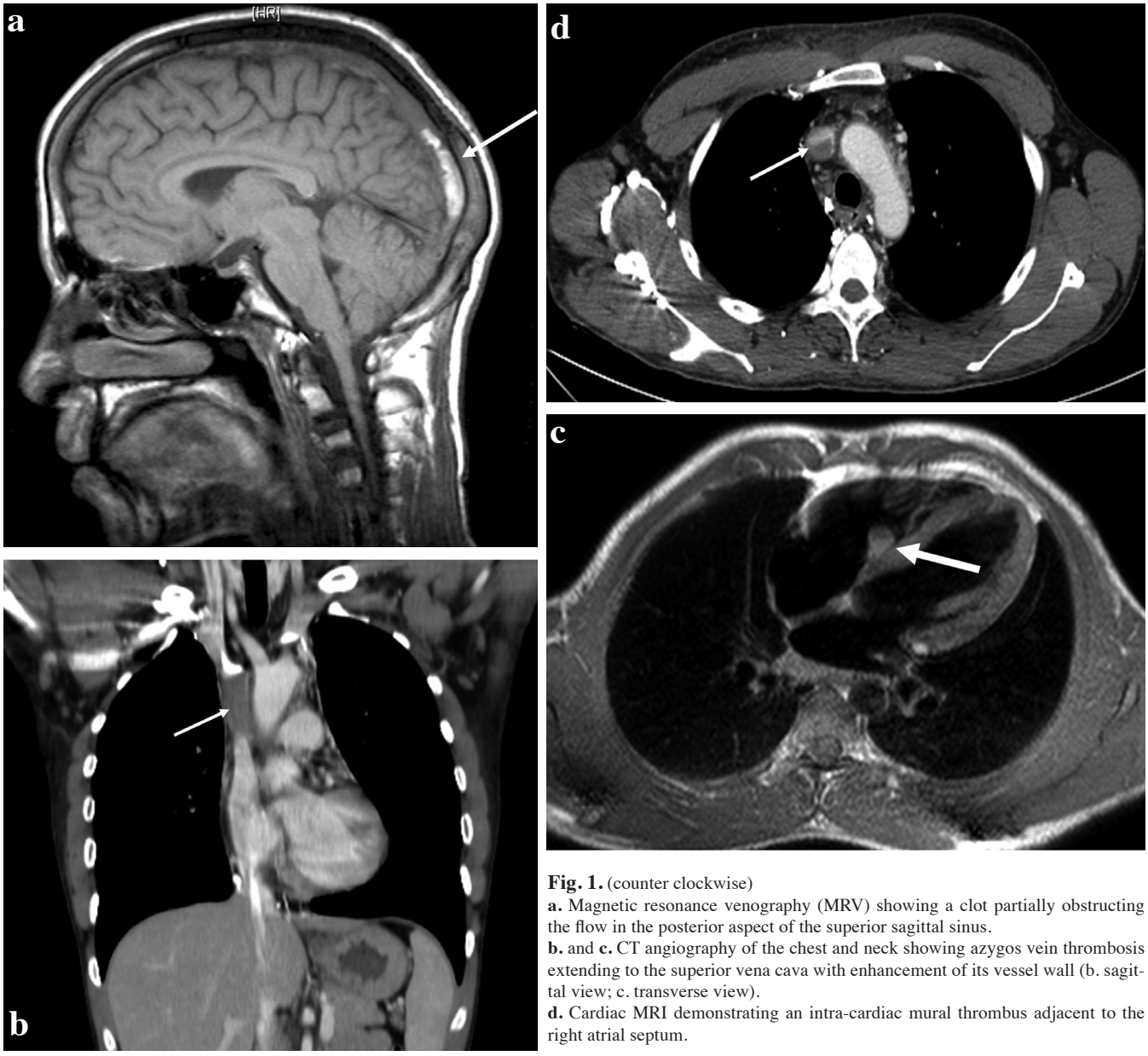

Fig. 1. (counter clockwise)
a. Magnetic resonance venography (MRV) showing a clot partially obstructing the flow in the posterior aspect of the superior sagittal sinus.
b. and **c.** CT angiography of the chest and neck showing azygos vein thrombosis extending to the superior vena cava with enhancement of its vessel wall (b. sagittal view; c. transverse view).
d. Cardiac MRI demonstrating an intra-cardiac mural thrombus adjacent to the right atrial septum.

bilateral papiledema and left 6th cranial nerve paralysis. Head and orbits computed tomography (CT) disclosed sagittal sinus thrombosis. Magnetic resonance venography (MRV) showed a clot in the superior sagittal sinus extending into the left transverse sinus (Fig. 1a). Electrocardiogram, chest x-rays, echocardiography and CT angiography of the chest were normal. Treatment with enoxaparin followed by warfarin was initiated. Three months later, the patient came again with left arm superficial vein thrombosis. At this time he admitted having recurrent oral aphthosis and 2 episodes of scrotal ulcers seen previously by his family physician. Physical examination revealed left arm thrombophlebitis, pseudofollicular rash on both legs, and mild left 6th nerve palsy. Laboratory tests disclosed elevated erythrocyte sedimentation rate (ESR) 60mm/hour, C-reactive protein (CRP) 1.03 mg% (normal 0–1), leukocytes 15,100/mm^3, and platelets 419,000/mm^3. The international normalised ratio (INR) was 2.18. Anticardiolipin antibodies, lupus anticoagulant, protein C, protein S, activated protein C resistance, antithrombin 3, factor v-Leiden, C-ANCA, P-ANCA were all negative. A diagnosis of BD was made. The patient started treatment with colchicine 1.0 mg daily, prednisone 50 mg/day and azathioprine 100 mg daily. During the following 3 years, the patient continued treatment with low-dose steroids, azathioprine, colchicine and warfarin.

Case 2: A 27-year-old man was hospitalised with suspected bacterial meningitis. CSF analysis contained few lymphocytes and the culture was sterile. He was treated with antibiotics with complete recovery. Two months later, he was re-hospitalised due to neck swelling of one week's duration. The patient reported that 6 months before he experienced two episodes of scrotal ulcers. Physical examination disclosed a patient with high fever (38.6°C), severe

acne over his back and face, oral aphthous ulcers and jugular venous congestion. Laboratory tests revealed elevated ESR 88mm/hour and CRP 16.14 mg%. Chest x-ray showed widened mediastinum. CT angiography showed azygos vein thrombosis extending to the superior vena cava (Fig. 1b,1c). Further investigation revealed HLA B51 positivity while anticardiolipin antibodies, anti β2 glycoprotein1 were negative. A diagnosis of BD was made and treatment with prednisone 50 mg/day, colchicine 1.0 mg daily and subcutaneous enoxaparin was initiated followed by warfarin. Three weeks after discharge he was readmitted due to recurrence of neck and face swelling despite therapeutic INR levels. The patient discontinued prednisone on his own. Treatment with pulse methyl prednisolone 1 gram daily for 3 successive days led to impressive clinical improvement. The patient was discharged with prednisone 60 mg/day, azathioprine 100 mg/day, colchicine and warfarin.

Case 3: A 33-year-old man was referred to our hospital for further evaluation of fever up to 40.6°C of 5 months' duration. His past medical history included two episodes of scrotal swelling, recurrent events of oral aphthosis and a single episode of epidydimitis 10 years prior to the present admission. Physical examination disclosed oral aphthous ulcers and a left sternal border systolic murmur 2/6. Pseudofolliculitis was evident over his back and thighs. Laboratory tests showed elevated ESR (90mm/hour) and CRP 22.7 mg%. Blood, sputum and urine cultures, and viral and bacterial serology were all negative. Bone marrow biopsy was normal. Trans-esophageal echocardiogram and MRI revealed an intracardiac mural thrombus of 2 cm diameter adjacent to the right atrial septum (Fig. 1d). Chest CT angiography showed pulmonary embolus in the right lower lobe. A diagnosis of BD was made. Treatment with subcutaneous enoxaparin and high-dose intravenous hydrocortisone was initiated with immediate disappearance of the fever. Subsequently, the patient was prescribed oral prednisone (60 mg daily), azathioprine (100 mg daily) and warfarin. Complete investigation for thrombophilia was negative. HLA B51 was positive. A year following the diagnosis of BD, the patient continued treatment with low-dose prednisone (5 mg daily), azathioprine (100 mg daily), colchicine 1.0 mg daily and warfarin. In a recent echocardiogram the cardiac thrombus has completely disappeared.

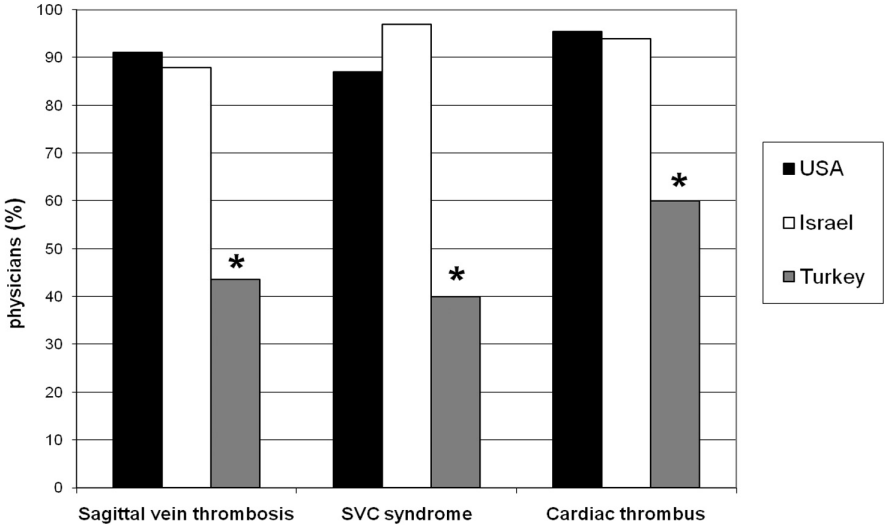

Fig. 2. Distribution of the three groups of physicians according to their therapeutic approach (giving anticoagulants) at the diagnosis of thrombotic event in the 3 BD patients. (55 Turkish, 33 Israeli and 25 American rheumatologists).
*denotes significant difference between the Turkish group and both Israeli and American rheumatologists.

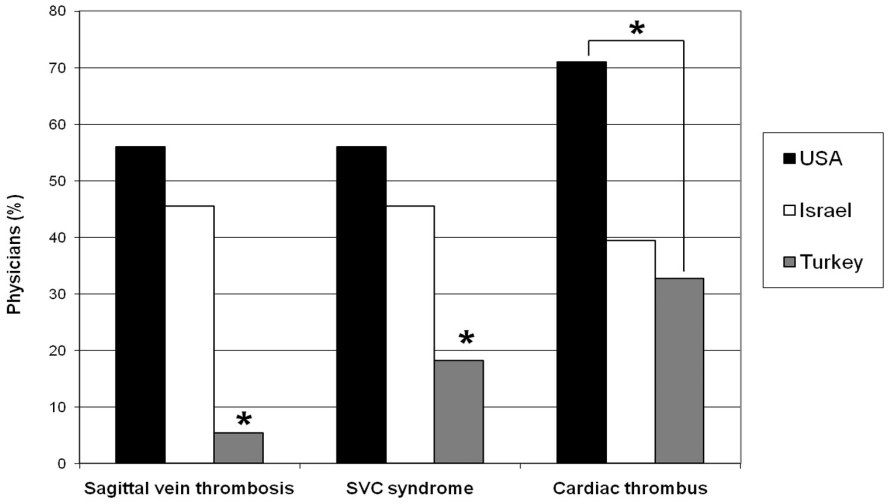

Fig. 3. Distribution of the three groups of physicians according to their therapeutic approach (giving anticoagulants for life) in 3 BD patients.
*denotes significant difference between the Turkish group and both Israeli and American rheumatologists. In case 3 (cardiac thrombus) the difference was significant only between the Turkish and American rheumatologists.

Results

Fifty-five Turkish, 33 Israeli and 25 American rheumatologists responded to the questionnaire. The response rate in the Turkish group was almost 100%, in the Israeli group 70% while among the American group only 25%. All the responders were specialists in Rheumatology. Results of the survey are depicted in Figures 2 and 3. The first finding is that the rheumatologists in Turkey approached the three cases differently. Most (60%) considered the case with cardiac thrombus (case 3) to be more severe than the other two with venous thrombosis and initiated anticoagulation treatment at the time of diagnosis (Fig. 2). For the Israeli and American rheumatologists, the three cases looked

quite similar with respect to the therapeutic approach at diagnosis. The second interesting finding was that while 97% and 87% of the American and Israeli rheumatologists respectively, would give anticoagulation at diagnosis of venous thrombosis (cases 1 and 2) only 40-44% of the Turkish physicians would do so. As for the duration of anticoagulant treatment, 56% of the American and 45% of the Israeli rheumatologists would give warfarin for life in the cases with venous thrombosis compared with only 5-18% of the Turkish physicians (Fig. 3). Regarding case number 3 with intra-cardiac thrombus, 96% of the Americans and 94% of the Israelis would start anticoagulation at diagnosis compared with 60% of the Turkish rheumatologists. In addition, 39% of the Israeli and 33% of the Turkish rheumatologists would give this treatment for life compared with 70% of the Americans (Figs. 2, 3).

Discussion

The pathogenesis of thrombosis in BD is not fully understood. As yet, no consistent primary abnormality of the coagulation, anticoagulation, or fibrinolytic system has been identified (3, 10-11). As the likely cause of thrombosis in BD patients is vessel wall inflammation, immunosuppressive therapy is quite reasonable. Nevertheless, there are no firm guidelines for the management of major vessel thrombosis in BD (12).

Anticoagulation treatment is more problematic in BD patients due to the increased risk of arterial aneurysms mainly involving the large pulmonary arteries (13). These aneurysms are one of the life-threatening complications of BD and patients may bleed to death under anticoagulant therapy.

In 2008, the European League Against Rheumatism (EULAR) published recommendations for the management of thrombosis in BD (14). For acute deep vein thrombosis, immunosuppressive agents such as corticosteroids, azathioprine, cyclophosphamide are recommended. However, anticoagulants, antiplatelet and antifibrinolytic agents are not recommended due to the increased risk of fatal bleeding. These guidelines relied partially on an abstract presented at the 2003 ACR meeting (15) which indicated that the risk for recurrent DVT and post-thrombotic syndrome was significantly lower in patients receiving immunosuppressants while anticoagulants did not reduce this risk. Furthermore, a randomised placebo-controlled double-blind trial of azathioprine showed that the number of BD patients who developed DVT was significantly lower in the azathioprine group regardless of anticoagulation (16).

In a review of 10 papers describing 2319 patients with BD, 32 had thrombosis. Following administration of warfarin or heparin therapy, recurrence of thrombotic events or even progression in thrombus size was still documented (7).

A retrospective study of 37 patients with venous thrombosis in BD compared treatment with immunosuppressants, anticoagulants and a combination of immunosuppressants and anticoagulants (17). No difference was found between the immunosuppressant group and the combination therapy group regarding thrombosis recurrence rates, suggesting that anticoagulation therapy might be unnecessary in these patients.

In our patients, the course of their diseases with their major vessel thrombosis supports these observations. The first patient with saggital vein thrombosis was re-hospitalised with arm thrombophlebitis despite full anticoagulant. The second patient with superior vena cava syndrome returned with facial swelling due to steroid discontinuation despite full anticoagulant therapy.

In a study of 657 BD patients in the United Kingdom, 62 had a history of thrombosis (18). Among these patients, 55 were treated with warfarin at the time of thrombosis (before diagnosis of BD) and discontinued in only two patients due to complications (haemoptysis secondary to pulmonary aneurysms and upper gastrointestinal bleeding). Seventeen were considered to have had a pulmonary embolus. The authors claimed that initial warfarin treatment is appropriate in the acute management of thrombosis in BD given the rarity of this disease in the UK, the lack of familiarity of most acute physicians with the condition and the chances of thrombosis in an undiagnosed patient being due to more common causes. Regarding long-term anticoagulation, they recommend systematic arterial imaging with CT angiography or MRA at the time of thrombosis for screening the vasculature for aneurysms. In case of a negative screen for aneurysms, they suggest continuing anticoagulation until there is clinical evidence of response to immunosuppression, guided by improvement in other manifestations such as orogenital ulceration, skin lesions or ocular disease, as well as a fall in acute-phase reactants. These guidelines seem reasonable for non-endemic regions for BD. That is why they differ from the above guidelines issued by EULAR which are probably more appropriate for countries endemic for BD (14).

As a matter of fact, our survey showed that most Turkish physicians do not give anticoagulants at diagnosis of venous thrombosis in BD, while being more aggressive with immunosuppressant treatment. On the other hand, physicians in Israel and the USA give anticoagulants to BD patients with thrombosis, many of whom continue this treatment for life. In countries where BD is rare, most probably the therapeutic approach to thrombosis derives from the physicians' experience in parallel cases, such as antiphospholipid syndrome, with which they are more familiar.

Based on a review of the literature and the survey analysis, it seems that we need a large randomised controlled prospective trial comparing immunosuppressive treatment with and without anticoagulation in BD thrombosis. Furthermore, the duration of anticoagulant therapy should also be determined.

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