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CLINICAL & BASIC RESEARCH

Haemostatic Parameters in Patients with Behçet's Disease

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متثابتات المرقئات لدى مرضى مصابين بمرض بهجت

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ABSTRACT: ***Objectives:*** This study aimed to evaluate the cause of thrombosis in Behçet's disease (BD) patients, since abnormalities in coagulation and fibrinolytic parameters have shown contradictory results. ***Methods:*** Haemostatic parameters were retrospectively evaluated in BD patients treated between January 2007 and January 2011 at Sultan Qaboos University Hospital, Oman. The blood samples of 35 Omani BD patients and 30 healthy controls were analysed for factor VIII:C levels, activated protein C resistance (APCR), von Willebrand factor (vWF) antigens (Ag), collagen binding and ristocetin co-factor activity (RiCoF), antithrombin (AT), protein C (chromogenic and clotting), protein S, homocysteine, tissue plasminogen activator, plasminogen activator inhibitor, plasminogen, alpha 2-antiplasmin, lupus anticoagulant and anticardiolipin and beta2-glycoprotein-1 antibodies. ***Results:*** The mean values of factor VIII:C, vWF Ag, AT and protein S were significantly higher in the patient group (P = 0.01, 0.006, 0.04 and 0.01, respectively). There was no deficiency in protein C. Screening for APCR, anticardiolipin antibodies, anti-beta2-glycoprotein-1 antibodies and lupus anticoagulant was negative and there were no differences in homocysteine levels, nor were there differences between patients with and without thrombosis. Six patients had elevated factor VIII:C levels (>150 IU/dL, P <0.02) which normalised on repeat measurements after three months. ***Conclusion:*** The elevation of factors VIII:C, vWF Ag and AT most likely represent an acute phase phenomenon. In this study, thrombophilic factors did not seem to explain thrombotic tendency. Therefore, further mechanistic studies in a larger group of patients are needed to elucidate the basis for thrombosis in BD. We hypothesise that active BD causes vasculitic endothelial perturbation with dysfunction, leading to the observed increased propensity for thrombosis.

Keywords: Behcet Syndrome; Vasculitis; Blood Vessels; Thrombosis; Hemostasis; Oman.

الملخص: **الهدف**: هدفت هذه الدراسة إلى معرفة سبب خثار الدم عند مرضى بهجت، حيث إن دراسات سابقة كانت قد أظهرت نتائج متضاربة في مؤشرات التخثر وانْحِلالُ الفِبْرين. **الطرق**: حللت مؤشرات المرْقِئات استعاديا لمرضى عمانيين مصابين بمرض بهجت بين يناير 2007 و يناير 2011. أخذت عينات من دم 35 مريضا وقورنت بعينات دم من 30 أشخاصا أصحاء وتم قياس المؤشرات الآتية: عامل VIII:C ومقاومة بروتين C المنشط (APCR) ومستضد عامل فون فيلي برانرد (vWF) واتحاد الكولاجين ونشاط تميم عامل ريستوستين (RiCoF) ومضادات الثرمبين (AT) وبروتين C وبروتين S وهوموسيستين و منشطات ومثبطات بلازمنوجين الأنسجة والبلازمونجين و الفا 2 مضاد البلازمين ومضادات تخثر الذئبة ومضادات كارديوليبين وأضداد بيتا 2 غلايكو بروتينات 1. **النتائج**: وجد أن هنالك ارتفاعا في متوسط المؤشرات الآتية: VIII:C، vWFAg، AT، S protein في المرضى مقارنة بالأصحاء (P = 0.01، 0.006، 0.04 and 0.01، بالتتابع) لم يوجد اختلاف في بقية المتثبتات. لم يوجد أيضا اختلاف في مستوى متثبتات التخثر بين المرضى المصابين بالتجلطات وغير المصابين. كان 6 من بين المرضى عندهم قياس مستوى متثابتة FVIII (<150 IU/dL، P <0.02). رجعت متثابتة FVIII إلى المستوى الطبيعي بعد 3 أشهر بعد إعادة قياسه. **الخلاصة**: إن ارتفاع مؤشرات التخثر، VIII:C، vWFAg، AT، S protein ربما كانت نتيجة لزيادة نشاط المرض. لم تثبت هذه الدراسة أن عوامل التخثر تفسر بشكل مباشر قابلية التخثر في هذا المرض. يجب عمل مزيد من الدراسات لتشمل عدد أكبر من المرضى لمعرفة سبب قابلية التخثر في هذا المرض. نعتقد بأن التهاب جدار الأوعية الدموية نتيجة مرض بهجت ربما يكون هو السبب الذي يؤدي الى قابلية التخثر.

مفتاح الكلمات: مرض بهجت؛ التهاب الأوعية الدموية؛ الأوعية الدموية؛ التخثر؛ المرْقِئات؛ عمان.

Advances in Knowledge

- *The study showed that thrombophilia is unlikely to play a role in the thrombosis associated with Behçet's disease.*

Application to Patient Care

- *Anti-inflammatory and immunosuppressive therapies, rather than prolonged anticoagulation treatment, seem to be an appropriate therapeutic approach to Behçet's disease.*

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Behçet's disease (BD) is a multisystem vasculitic, chronic relapsing disorder of unknown aetiology associated with considerable morbidity and mainly occurring with eye involvement.[1] It is also associated with an increase in mortality. Yazici *et al.* reported an overall mortality of 4% among a group of 152 Turkish patients after 10 years of follow-up.[2] However, a long-term outcome survey of Turkish patients showed an even higher mortality rate. Kural-Seyahi *et al.* surveyed the 20-year outcome in a cohort of BD patients and found an overall mortality rate of 9.8%.[3] The standardised mortality rate (SMR) was higher among males and, in particular, younger males (14–24 years), with a SMR reaching 10 times that observed in the general population. A significant proportion of this mortality (40%) was related to vascular thrombosis.[3] In another study by Hamuryudan *et al.,* a 50% mortality rate among 24 young male patients with pulmonary artery aneurysms was observed two years after the onset of the aneurysms.[4]

The vascular involvement in BD varies depending on the ethnic group.[5] A Turkish study reported a 27% rate of vascular events,[6] while a British study showed a prevalence of 32% with vascular thrombosis.[7] A study from Saudi Arabia showed a prevalence of 43%.[8]

The pathogenesis of thrombotic events in BD is unknown. Although vasculitis is the predominant histopathological feature of the disease, it only partially explains the thrombotic phenomenon because endothelial-leukocyte interaction and plasma hypercoaguability both play an important role.[9–19] In fact, in other groups of vasculitic disorders, the frequency of major venous thrombosis is not as common as in BD. The extent of the thrombosis and its predilection for unusual sites suggests the presence of an underlying hypercoaguable state. It is believed that anticoagulant proteins and co-factors in plasma as well as the endothelium regulate the blood coagulation system. Under normal conditions, procoagulant and anticoagulant mechanisms are balanced and any disturbances result in thrombosis or bleeding. Abnormalities in coagulation and fibrinolytic systems have been reported in BD, but previous studies have shown contradictory results and as yet no single abnormality has been identified as the sole leading cause [Table 1].

In this study the coagulation and fibrinolytic factors were investigated in a group of Omani patients with BD and compared with the findings of other studies.

Methods

The subjects for this retrospective cross-sectional study fulfilled the criteria of the International Study Group for Diagnosis of Behçet's Disease and were recruited from patients of the Rheumatology Outpatient Department at Sultan Qaboos University Hospital, Muscat, Oman, treated between January 2007 and January 2011. Informed consent was obtained from the patients and approval was granted from the Medical Research & Ethics Committee of the College of Medicine & Health Sciences at Sultan Qaboos University (MRS/06/04).

Pregnant patients, those with malignancies or those receiving medications known to interfere with haemostasis were excluded, as were those patients unwilling to give informed consent. A total of 35 consecutive patients were thus enrolled along with a control group of 30 subjects matched for age, race and sex. Various clinical data were recorded, including age at onset, disease duration, current disease activity and manifestations of the disease (current and past). These data included vascular involvement, the presence of associated cardiovascular disorders and treatment regimens. Patients were considered to have an active form of the disease if they had shown any of the following criteria within the previous month: oral, gastrointestinal or genital ulcers; eye or vascular lesions; arthritis, or central nervous system (CNS) involvement.

Venous blood samples were collected from all subjects between 9 and 10 am to minimise diurnal variation in the levels of biological, haemostatic and rheological factors. Blood was collected from the antecubital vein and anticoagulated with K_2 ethylene-diamine-tetra-acetic acid (EDTA) and trisodium citrate (0.11 M: 9:1 v:v). Citrated plasma was double-centrifuged the same day within two hours of collection and stored at -70 °C for further studies. Plasma activities of coagulation inhibitors (antithrombins [AT]; proteins C and S; von Willebrand factor (vWF) antigens (Ag); factor VIII:C; tissue plasminogen activators (t-PA) antigens and activity; plasminogen activator inhibitors (PAI-1); plasminogen; alpha 2-antiplasmin, and activated protein C resistance [APCR]) were determined using standard techniques as per the manufacturers' advice. The reagents were obtained from Diagnostica Stago, Inc. (Asnières-sur-Seine, France) and Instrumentation Laboratory (Barcelona, Spain). The reference ranges used were as follows: functional protein S - 77–143 IU/dL for males and 55–123 IU/dL for females; functional chromogenic protein C - 65–110 IU/dL; functional protein C (clotting assay) - 66–131 IU/dL; functional

Table 1: Results of selected previous studies

Author and year of study	N/n*	Parameters studied	Main findings	Conclusion
Hampton *et al.*[9]	18/7	Fibrinogen, vWF, TPA, PAI-1, protein C, protein S, AT, factor VIII, fibrinogen peptides A, plasminogen and alpha 2-antiplasmin.	-Increased fibrinogen, vWF, TPA, PAI-1 and plasminogen activator. -Decreased protein C. -No difference between T+ and T-.	No abnormality of coagulation or fibrinolytic activity.
Guermazi *et al.*[10]	30/16	Protein C, protein S and AT.	Decreased free protein S and protein S activity.	Protein S deficiency may be involved in thrombosis in BD.
Mader *et al.*[11]	25/8	ACA, LA, protein C, protein S, AT and APCR.	Elevated ACA and IgG but no relation to thrombosis.	No association with thrombophilia.
Sengül *et al.*[12]	96/22	Protein C, protein S, AT and fibrinogen.	-Increased AT. -No difference between T+ and T-.	Procoagulant activity.
Demirer *et al.*[13]	127/34	Protein C, protein S, AT, fibrinogen, vWF, TM, prothrombin fragment F 1+2 and TPA.	-Increased vWF and TPA in T+. -Decreased thrombomodulin.	Endothelial damage and no activation of coagulation.
Akarsu *et al.*[14]	30/5	TFPI, ACA, fibrinogen, PAI-1, TPA, vWF, protein C, protein S, plasminogen and lipids.	-Increased TFPI and fibrinogen. -Increased PAI-1 and APL-positive in one subject.	TFPI may contribute to thrombotic tendency.
Ozatli *et al.*[15]	39/7	Factor VII, GFC, protein C, protein S, AT, fibrinogen, lipids, APCR, APTT, PT, TT and ACA.	-Increased factor VII, decreased protein S in one patient, decreased protein C in one subject and APCR in one subject. -No differences between T+ and T-.	Coagulation is activated and there is relative hypofibrinolysis.
Probst *et al.*[16]	24/7	Fibrinogen, vWF, factor VIII, factor XI, protein C, protein S, AT, LA and APCR.	Increased factor VIII, IX, AT, vWF and fibrinogen.	Evidence of hypercoagubility and endothelial dysfunction.
Navarro *et al.*[17]	39/12	Protein C, protein S, AT, APCR, factor VIII, vWF, TM, alpha 1-antitrypsin and fibrinogen.	-Increased protein S, AT, alpha 1-antitrypsin, factor VIII and vWF. -Decreased APCR and TM (also decreased in T+).	Reduced APCR levels.
Lee *et al.*[18]	32/4 24/12	Fibrinogen, AT, protein C, protein S, vWF, ACA, LA, APCR and homocysteine.	-Increased fibrinogen, vWF and homocysteine. -Decreased AT. -aPL positive in one subject and LA positive in four subjects.	-No evidence of activation of coagulation -Hypercysteinaemia may be a risk factor.
Leiba *et al.*[19]	107/33	Factor V, factor VIII, prothrombin G 20210A, MTHFR C 677T, plasma glucosylceramide, homocysteine and lipids.	-Increased factor VIII in T+. -Increased lipids.	-No role for thrombophilia. -Dyslipidaemia may be a risk factor.

n = number of patients with thrombosis; vWf = von Willebrand factor; TPA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor; AT = antithrombin; T+/T- = patients with/without thrombosis; BD = Behçet's disease; ACA = anticardiolipin antibodies; LA = lupus anticogulant; APCR = activated protein C resistance; IgG = immunoglobulin G; TM = thrombomodulin; TFPI = tissue factor pathway inhibitor; aPL = antiphospholipid antibodies; GFC = global fibrinolytic capacity; APTT = activated partial thromboplastin time; PT = prothrombin time; TT = thrombin time; G 20210 A = prothrombin mutation G20210A; MTHFR = methylenetetrahydrofolate reductase.*

AT - 67–109 IU/dL; factor VIII:C levels - 50–150 IU/dL; vWF Ag - 50–158 IU/dL; vWF:ristocetin co-factor activity (RiCoF) - 40–150 IU/dL; vWF:collagen binding activity (CBA) - 50–400 IU/dL; plasminogen - 73–127 IU/dL; alpha 2-antiplasmin - 89–112 IU/dL; t-plasminogen activator - 1–12 ng/mL; plasminogen activator inhibitors (PAI-1) - 4–43 ng/mL plasma, and homocysteine - 5–15 µmol/L. For APCR, if the sample showed an APC ratio of <2.1, then factor V Leiden was considered positive.

Statistical analysis was performed using the Statistical Package for the Social Sciences, Version 10.0 (IBM, Corp. Chicago, Illinois, USA). Data were expressed as mean ± standard deviation (SD). For all

Table 2: Demographic details and clinical manifestations of study patients and controls with Behçet's disease

Variable	Patients (n = 35)	Controls (n = 30)	*P* value	Patients T+ (n = 8)	Patients T- (n = 27)	*P* value
Age in years, mean ± SD	32 ± 8	32 ± 7	0.65	31 ± 8	32 ± 7	0.70
Gender by male:female ratio	23:12	18:12	-	-	-	-
Disease duration in years, mean ± SD	10 ± 6.5	-	-	10 ± 7	9 ± 6	0.40
Clinically active disease	20	-	-	5	15	0.90

T+ = patients with thrombosis; T- = patients without thrombosis; SD = standard deviation.

tests, values of $P < 0.05$ (two-tailed) were considered statistically significant. Fisher's exact test, the Mann-Whitney (MW) test and Spearman's correlation test were used.

Results

The male to female ratio was approximately 2:1. The mean age ± SD of the patients and controls were 32 ± 8 and 32 ± 7 years, respectively. The mean ± SD disease duration was 10 ± 6.5 years. The demographic details of all subject and the clinical manifestations of the patients are summarised in Tables 2 and 3. Eight patients with BD had thrombotic events. Of those patients, four had current vascular events: one had deep vein thrombosis (DVT); two had pulmonary artery aneurysms; one had a concomitant stroke, and one a stroke. The other four BD patients had a previous history of thrombosis (stroke = 1; DVT = 2; pulmonary artery aneurysms =1). The mean age of patients with thrombosis was 24 years (range 15–37 years). The mean time-lag between blood tests and vascular events in patients with a past history of thrombosis was seven years (range 2–15 years).

The blood samples showed significantly elevated factor VIII:C, vWF Ag, AT and protein S function in BD patients compared with the controls [Figure 1]. Six patients with a raised factor VIII of >150 IU/dL had an active form of the disease. One of these patients had a vascular event at the time of measurement. There were no deficiencies in protein C or APCR. Furthermore, no differences in anticardiolipin antibodies, anti-beta2-glycoprotein-1 antibodies, lupus anticoagulant, TPA, PAI-1, plasminogen, alpha 2-antiplasmin, homocysteine, total cholesterol, triglycerides or blood glucose levels were found in BD patients compared to the controls. There were no differences in the thrombophilic or fibrinolytic factors studied between patients with and without thrombosis. Elevated factor VIII levels normalised on repeating the measurements after three months and once the disease became inactive. Figure 1 and Table 4 summarise the haemostatic results.

There was no difference between erythrocyte sedimentation rates or C-reactive protein levels between patients and controls. However, the 20 patients with clinically active forms of the disease had raised levels of factor VIII:C ($P = 0.01$); vWF Ag ($P = 0.02$); vWF:RiCoF ($P = 0.04$), and vWF:CBA ($P = 0.01$), as compared to the 15 patients with the inactive form of the disease. Positive correlations were found between factor VIII:C and vWF Ag levels ($r = 0.63$, $P = 0.001$); factor VIII:C and vWF:RiCoF levels ($r = 0.64$, $P = 0.001$); factor VIII:C, and vWF:CBA levels ($r = 0.7$, $P = 0.001$) after performing the different blood tests in the patient group.

Discussion

The vascular complications of BD represent a challenging aspect of the disease in terms of determining the aetiopathogenesis and, more importantly, considering management options. Moreover, there is still no clear or adequate explanation for the thrombotic tendency.

Table 3: Clinical manifestations of study patients with Behçet's disease

Clinical manifestations	%
Oral ulcers	100
Genital ulcers	91
Skin	91
Eye	91
Articular	40
GI*	23
CNS**	21
Epididymo-orchitis	23

GI = gastrointestinal: CNS = central nervous sustem.

**Abdominal pain, constipation or ulcer; **Headache, numbness, paresis and without imaging evidence of thrombosis.*

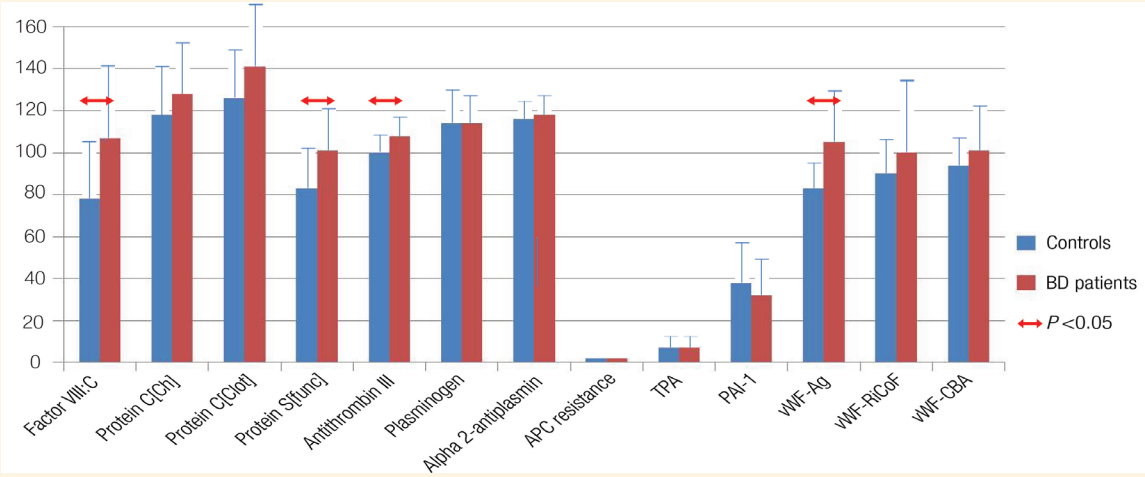

Figure 1: Haemostatic parameters in Behçet's disease patients and controls.
BD = Behçet's disease; [Ch] = chromogenic; [func] = functional; APC = activated protein C; TPA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor; vWF-Ag = von Willebrand factor antigen; RiCoF = ristocetin co-factor activity; CBA = collagen binding activity.

High levels of factor VIII were associated with an increased risk of vascular thrombosis in the Leiden Thrombophilia Study.[20] Individuals with factor VIII activity levels ≥150 IU/dL are associated with a five- to six-fold increased risk of venous thrombosis compared to levels <100 IU/dL. Significantly higher levels of factor VIII were found in BD patients compared to controls as has also been reported by other investigators as well as in some case series associated with thrombosis;[16,17,19,21,22] however, other studies have shown normal results.[9] Nonetheless, in contrast to other studies, follow-up studies found that the level of factor VIII normalised on repeated measurements which suggests that this elevation was merely due to an acute phase reaction.[23] This might explain the lack of association of thrombosis and raised factor VIII levels in the patients of the current study, as well as other studies. This is because the level of factor VIII concentration varies with disease activity; an acute phase reactant may not necessarily predict a thrombotic risk unless follow-up studies show persistently elevated levels. In support of this, the current study clearly shows that all patients with raised factor VIII levels had an active form of the disease and that once their disease status/activity was under control, the factor VIII levels returned to within normal laboratory reference ranges. Furthermore, studies which investigated factor VIII level as a risk factor for venous thrombosis in the general population with idiopathic DVT found that high levels of factor VIII usually persisted over time—up to five years in some cases—and were independent of acute phase proteins.[23] Thus, the reported differences in factor VIII levels could be partially explained by the inherently different disease activity statuses in different series in the reported literature.

Table 4: Haemostatic parameters in Behçet's disease patients with and without thrombosis (n = 35)

Variable	T+ (n = 8)	T- (n = 27)	*P* value
Factor VIII:C in IU/dL	120 ± 30	102 ± 52	0.10
Protein C [Ch] in IU/dL	199 ± 21	127 ± 41	0.90
Protein C [clot] in IU/dL	124 ± 28	143 ± 46	0.48
Protein S [func] in IU/dL	103 ± 19	100 ± 30	0.60
Antithrombin in IU/dL	111 ± 12	107 ± 12	0.45
Plasminogen in IU/dL	118 ± 14	113 ± 16	0.40
Alpha 2-antiplasmin in IU/dL	118 ± 12	119 ± 16	0.90
APCR ratio*	>2.1	>2.1	-
TPA in ng/mL	8 ± 5	7 ± 3	0.98
PAI-1 in ng/mL	26 ± 14	33 ± 22	0.70
vWF Ag in IU/dL	99 ± 14	102 ± 38	0.76
vWF:RiCoF in IU/dL	106 ± 19	99 ± 50	0.22
vWF:CBA in IU/dL	105 ± 27	99 ± 50	0.36

T+ = patients with thrombosis; T- = patients without thrombosis; [Ch] = chromogenic; [func] = functional; APCR = activated protein C resistance; TPA = tissue plasminogen activator; PAI-1 = plasminogen activator inhibitor; vWF Ag = von Willebrand factor antigen; RiCoF = ristocetin co-factor activity; CBA = collagen binding activity.

**If activated protein C ratio was <2.1 then factor V Leiden was considered positive.*

As an endothelial cell product, which mediates platelet aggregation and adhesion to the injured endothelium, vWF helps in platelet plug formation. The other important function of vWF is that it enhances the coagulation system by stabilising as well as protecting factor VIII from its proteolytic inactivation.[23,24] In BD, elevated levels of vWF have been recorded, as is the case in several other atherosclerotic diseases. In fact,

some studies have suggested that high plasma levels of vWF in subjects with cerebrovascular disease (CVD) can predict the subsequent occurrence of major clinical events such as death and myocardial infarction.[24] Furthermore, levels of vWF are elevated in other comorbid conditions which predispose individuals to atherosclerosis, such as hypertension and diabetes. The precise mechanism for the increase in vWF in CVD remains uncertain and there is debate as to whether the high levels of vWF seen in CVD disorders are the cause or consequence of the disease process.[24] High levels may merely reflect the extent of vascular damage or may reflect platelet activation which is a consistent companion of endothelial damage. In most studies in the literature, as was found in the patients of the current study, raised vWF levels in cases of BD was an almost constant finding. This could be the consequence of a chronic perturbation and stimulation of the vascular endothelium.

The current study is in agreement with many other studies in that the results showed no deficiencies in the natural anticoagulants levels of AT, protein S or protein C. On the contrary, the levels of both AT and protein S were elevated. Sengül *et al.*[12] and Probst *et al.*[16] found elevated levels similar to those in the current study. These authors explained this elevation as a result of a compensatory mechanism against the increased procoagulant activity. However, these differences could be multifactorial and may result from the different disease activity statuses in different series and/or may reflect a response to the endothelial damage. Thus, a combination of vasculitis, endothelial-leucocyte interaction with altered function, alterations in procoagulant and anticoagulant levels and altered cytokines will result in the variability of the disease activity and severity.

No significant differences in the plasma homocystine levels between BD patients and controls were found in this study, although two patients had significantly elevated plasma levels. However, there is increasing evidence to suggest that the vascular effects of elevated plasma homocysteine are mediated through an action on the endothelium by lipid peroxidation, altered vascular tone and a hypercoaguable prorombotic state leading to atherothrombogenesis.[25]

Conclusion

Although this study is limited by the small number of patients and its retrospective design, the findings show that underlying thrombophilia is unlikely to play a significant role in the pathogenesis of thrombosis in BD patients. Like many other studies, no distinct abnormalities were found either in the coagulants, anticoagulants or in the fibrinolytic system. Endothelial dysfunction as a consequence of the vasculitic process seems to be the most probable initial event. This has implications for the management of vascular BD as anti-inflammatory and immunosuppressive therapy, rather than prolonged anticoagulation treatment, seems to be the most appropriate therapeutic approach to treatment. In fact, the latest European League Against Rheumatism guidelines for the management of BD state that "There are no controlled data on, or evidence of benefit from, uncontrolled experience with anticoagulants, anti-platelet or fibrinolytic agents in the management of deep vein thrombosis, or for the use of anticoagulation for the arterial lesions of BD".[26] The recommendation is to use immunosuppressive agents to manage the vascular aspect of BD.

A prospective study in a sufficiently large number of patients would be able to test this management strategy by randomising patient treatment with anti-inflammatory/immunosuppressive *versus* anticoagulation therapy. This would require a multicentre, multinational approach. It is the authors' endeavour to initiate a multicentre registry so that the above strategy can be implemented.

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