

Assessment of Anticardiolipin antibodies, Circulating Lupus anticoagulant, Protein C, Protein S, Antithrombin III & Activated Protein C Resistance and Their Relation to Thromboembolic and Other Clinical Manifestations in Behcet's Disease

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Abstract

Background: Venous and arterial thrombosis occurs in patients with Behcet's disease and is associated with significant morbidity and mortality. Studies on a possible association between the occurrence of thrombosis and thrombophilia in patients with this disease have been controversial. The objective of this study was to assess the frequency and clinical relevance of anticardiolipin antibodies (aCL) & other thrombophilic factors and their relationship to thromboembolic & clinical manifestations in Behcet's disease (BD).

Materials and methods: IgG, IgM and IgA anticardiolipin antibodies (aCL) isotypes, presence of circulating lupus anticoagulant(LAC), protein C, protein S, antithrombin III & activated protein C resistance were investigated in 25 patients with BD and 25 patients with various rheumatic diseases not known to be associated with venous or arterial thromboembolic phenomena served as controls. Twelve of the patients with BD (48%) had either deep vein thrombosis (8 patients), arterial thromboembolic phenomena (4 patients), or both (2 patients).

Results: The IgA aCL elevated in 14 (56%) patients with BD compared with one (4%) patient in the control group ($P < 0.01$). IgG aCL levels were elevated in 13 (52%) patients with Behcet's disease (BD) compared with one (4%) patient in the control group ($P < 0.01$). Also patients with BD do not have decreased protein S, or antithrombin III activity, activated protein C resistance, circulating lupus anticoagulant (LAC), or elevated IgM aCL. No significant differences were found between any variable in both groups. No association between elevated IgMaCL levels and venous or arterial thrombosis and no statistical correlation was found between any factor and clinical manifestations of the disease.

Conclusion: A significant number of patients have elevated levels of IgA & IgG aCL but they are not associated with venous or arterial thrombosis. These results do not suggest a primary role for aCL in BD and do not support the role of coagulation abnormalities in the pathogenesis of thromboembolic complications of Behcet's disease but suggest vascular inflammation as the main pathogenetic event in the vascular lesions in Behcet's disease.

KEY WORDS: Procoagulant factors, Anticardiolipin antibodies, Thromboembolic manifestations, Behcet's disease.

Introduction

Behcet's disease (BD) is a chronic multisystem inflammatory disorder that can involve the skin, eyes, central nervous system, arteries, veins, lungs, and gastrointestinal tract. The common manifestations are recurrent oral and genital ulcers and ocular inflammation. Venous or arterial

thrombosis occurs in 7–38% of patients (Sakane *et al.*, 1999). Venous thrombosis is more common than arterial thrombosis, with relative frequencies of 90% and 10%, respectively. Deep or superficial venous thrombosis in the lower extremities is the common sites of thrombosis (Gul *et al.*,

1996; Kuzu *et al.*, 1994). Vasculitis underlies the thrombotic tendency in Behcet's disease, but it is not clear why some patients present with thrombosis and others do not. Decreased levels of tissue plasminogen activator and thrombomodulin, and increased levels of plasminogen activator inhibitor-1, von Willebrand factor, thrombin-antithrombin complex, prothrombin fragment 1+2, and lipoprotein (a) (Lp (a)) have all been described in patients with Behcet's disease and related to the thrombotic tendency (Leiba *et al.*, 2001; Ozatli *et al.*, 2002). The possible role of acquired and inherited thrombophilias has also been evaluated. However, there are conflicting data in patients with and without thrombosis over the prevalence of factor V Leiden, methylenetetrahydrofolate reductase (MTHFR) C677T homozygosity, homocysteine level, prothrombin G20210A polymorphism, and levels of factor VIIa, factor VIII, and factor XII (Kiraz *et al.*, 2002). A recently described thrombophilic index-decreased plasma glucosylceramide concentration-has not been examined yet in patients with Behcet's disease (Deguchi *et al.*, 2001).

The cause and pathogenesis of BD are unclear, but various immunological abnormalities associated with both humoral and cellular immune systems have been reported (Direskeneli *et al.*, 1999). Anticardiolipin antibodies (aCL) are antibodies against the phosphodiester group of negatively charged phospholipids. Recurrent thrombosis, fetal loss and thrombocytopenia have been reported to be associated with the presence of aCL, especially in autoimmune diseases such as systemic lupus erythematosus (SLE) (Harris *et al.*, 1986). BD is also characterized by recurrent vascular thrombosis and vasculitis. Although some previous studies suggest an increased frequency of aCL in BD, the low numbers of patients in most of these studies, especially patients with thrombotic complications, make it difficult to draw definite conclusions (Pereira *et al.*, 1989 ; Kang *et al.*, 1998 & Ozdemir *et al.*, 1997; Mader *et al.*, 1999). Ethnic and geographical differences in BD related to the clinical manifestations, such as

gastrointestinal involvement, positive pathergy reaction and HLA-B51, are well known (Yurdakul *et al.*, 1996 ; Yazc *et al.*, 1984), and aCL levels might be influenced by these factors. Therefore, this study aimed to assess the frequency and clinical relevance of IgG, IgM and IgA anticardiolipin antibodies (aCL) isotypes, presence of circulating lupus anticoagulant (LAC), protein C, protein S, antithrombin III & activated protein C resistance and their relationship to thromboembolic & clinical manifestations in Behcet's disease (BD).

Materials and methods

Patients

Patients with Behcet's disease (BD) ($n=25$; 12 females, 13 males; mean age 36.8 ± 5.7 yr) and patients with various rheumatic diseases ($n=25$; 17 females, 8 male; mean age 39.0 ± 4.2 yr) attending the rheumatology outpatient clinical at the El-Hussein University Hospital. All Behcet's disease patients fulfilled the Criteria for diagnosis of BD. Twelve of the patients with BD (48%) had either deep vein thrombosis, confirmed by Doppler ultrasound, (8 patients), arterial thromboembolic phenomena (4 patients), or both (2 patients). Three patients had pulmonary embolism (supported by lung scan ventilation/perfusion mismatched) and one patient had cerebral vascular accident.

In the control group there were 25 patients with various rheumatic diseases not known to be associated with venous or arterial thromboembolic phenomena (10 with osteoarthritis, 9 with rheumatoid arthritis, 3 with psoriatic arthritis and 3 with fibromyalgia). Careful history and clinical examination were done to all patients.

Biochemical analysis

Venous blood samples (10 ml) were collected after an overnight fasting in tubes containing EDTA and were immediately centrifuged at 1500 rpm for 15 min at 4°C. Plasma samples were protected from light & frozen at - 80°C and stored until analysis. Plasma IgG, IgM and IgA anticardiolipin antibodies (aCL) were determined accor-

ding to the method of Gharavi *et al* . (1987) using the standard ELISA method (Reaads, westminister). Circulating lupus anticoagulant (LAC) test was performed by measurement of the activated partial thromboplastin time (APTT) without and with mixing of normal plasma pool, dilute Russell's viper venom time (Bioclot LA), and Koalin clotting time (Gradipore Ltd). A positive test was defined by abnormal results by at least 2 techniques and confirmed by platelet neutralizing procedures. Protein S activity was measured by an automated functional clotting, protein S assay based on prolongation time (IL Spa). Protein C activity and antithrombin III activity were measured by chromogenic assay (IL Spa). Activated protein C resistance test is a modified activated partial thromboplastin time (APTT) in which the anticoagulant response to standerized addition of activated protein C is measured by clotting time of APTT (Chromogenix) the ratio of the tests with and without addition of activated protein C is calculated and a low ratio (<25) is suggestion of activated protein C resistance.

Statistical analysis

Statistical analysis was performed using fisher's exact test to detect correlation of variable studies between patients and controls and to detect correlation between variables and clinical manifestations.

Results

According to (Table 1), the clinical manifestations of 25 patients with Behcet's disease involved mouth ulcers in 23 patients (92%), genital ulcers in 21 patients (84%), eye lesions in 16 patients (64%), skin lesions in 14 patients (56%), positive pathergy test in 10 patients (40%), arthritis in 15 patients (60%), deep vein thrombosis in 8 patients (32%), other thromboembolic phenomena in 4 patients (16%) and neurological manifestations in 3 patients (12%).

According to (Table 2) and (Fig. 1&2), the results showed statistically higher prevalence of IgA aCL isotype in 14 patients (56%)& IgG aCL isotype in 13 patients with Bechcet's disease (52%) then prevalence of IgA , IgG aCL in only one patient from control group (4%) with $P<0.01$. However, no correlation was found between elevated level of aCL and thromboembolic complications or other clinical manifestation of the disease. Other procoagulant factors such as IgM aCL isotype, LAC, protein C activity and antithrombin III activity showed no significant elevation of their levels, no difference between levels in both patients with Behcet's disease and control group and no correlation between any one of them and clinical disease manifestations. Among 5 patients with low activated protein C resistance ratio, one patient had elevated level of IgG aCL.

Table (1): Clinical characteristics in patients with Behcet's disease.

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Clinical manifestations	Number of patients (%)
Mouth ulcers	23 (92%)
Genital ulcers	21 (84%)
Eye involvement:	16 (64%)
-Anterior uveitis	10 (40%)
-Posterior uveitis	3 (12%)
-Retinal vasculitis	3 (12%)
Skin involvement:	14 (56%)
-Erythema nodosum	8 (32%)
-Pseudofolliculitis	4 (16%)
-Papulopustulatic lesions	2 (8%)
Positive pathergy test	10 (40%)
Arthritis	15 (60%)
Vascular lesion:	12 (48%)
-Deep vein thrombosis	8 (32%)
-Pulmonary embolism	3 (12%)
-Cerebral vascular accident	1 (4%)
Neurological manifestations	3 (12%)

Table (2): Thrombophilic factors in patients with Behcet's disease and controls.

Thrombophilic factors	BD	Controls
-Elevated IgA aCL	14 (56%)	1 (4%)
-Elevated IgG aCL	13 (52%)	1 (4%)
- Elevated IgM aCL	3 (12%)	1 (4%)
- Positive lupus anticoagulant(LAC)	1 (4%)	0 (0%)
-low Protein C activity	0 (0%)	0 (0%)
-low Protein S activity	1 (4%)	0 (0%)
-low antithrombin III activity	1 (4%)	1 (4%)
-low activated protein C resistance	5 (20%)	1 (4%)

Fig. (1): IgG, IgM and IgA anticardiolipin antibodies in patients with Behcet's disease and controls.

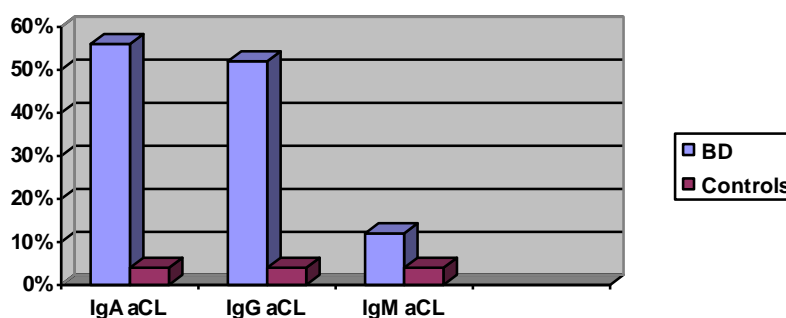
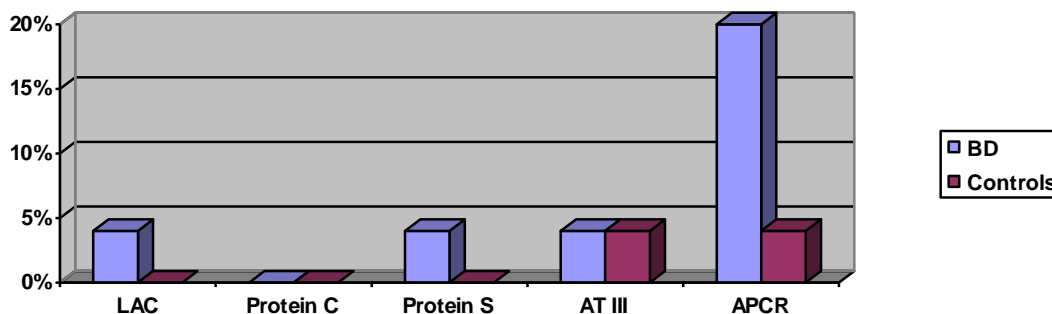


Fig. (2): Thrombophilic factors in patients with Behcet's disease and controls.



Discussion

Behcet's disease (BD) is a chronic, inflammatory vasculitis characterized by mucocutaneous, ocular, vascular, arthritic and neurological involvement (Yazc *et al.*, 1999). Pulmonary aneurysms represent the major complication of pulmonary Behcet's disease and have a poor prognosis, being associated with massive haemoptysis. In situ pulmonary artery thrombus can lead to pulmonary infarction. Superior vena cava thrombosis progresses slowly, allowing the development of a prominent collateral circulation. Vascular inflammation can spread to the mediastinum, the pleura and the lungs with diffuse pulmonary haemorrhages, bronchiolitis and organising pneumonia (Hamzaoui and Hamzaoui, 2005). Venous thrombosis affects one in 1000 individuals per year causing significant morbidity and mortality (Rosendaal, 1997). Vascular lesions can involve both arterial and venous systems which are often the major cause complicating the disease course of Behcet's disease. Vascular lesions can be the presenting sign of Behcet's disease preceding classical symptoms (Sarica-Kucukoglu *et al.*, 2006). Our results showed that the prevalence of vascular involvement in BD was 48%. The venous lesions represented 32% and were mainly venous occlusions, the arterial lesions represented 16% and were either arterial aneurysms and/ or arterial occlusions.

The pathogenesis of arterial and venous thrombosis in Behcet's disease is not completely understood. It is generally

accepted that vasculitis, a hallmark of Behcet's disease, partially explains the initiation of thrombosis in small as well as large blood vessels (Sarica-Kucukoglu, 1997). Vasculitic lesions are characterized by perivascular lymphocyte and mononuclear cell infiltration, endothelial edema, degeneration of the elastic lamina interna, fibrinoid necrosis, and deposition of immune complexes within the vascular wall. The inflammation usually affects all layers of the vessel wall with very adherent thrombi in the lumen. For this reason, although large segments of the vessel wall are affected, pulmonary emboli are quite rare in BD. Pulmonary disease consists mainly of pulmonary artery thrombi, infarcts, aneurysms, and arteriobronchial fistula. Endothelial cell injury due to vasculitis seems to be a key event in the prethrombotic state of BD (Leiba *et al.*, 2001). Vascular endothelial growth factor (VEGF) is a stimulant of angiogenesis secondary to ischemia while monocyte chemoattractant protein 1 (MCP-1) is induced by shear stresses leading to vascular collateral development. MCP-1 has been also shown to contribute to the recanalization of venous thrombi. Tumour necrosis factor-alpha (TNF-alpha) is known to play a major role in the pathogenesis of BD. Furthermore, up-regulation of secreted MCP-1 and VEGF was observed following stimulation with TNF-alpha. Increased levels of VEGF and MCP-1 detected in BD thrombosis suggest the possible role of those angiogenic cytokines in the

pathogenesis. Although not specific for BD, detection of VEGF or MCP-1 levels seems to serve as an assay for differentiation of BD patients with acute thrombosis from chronic (Bozoglu *et al.*, 2005).

In the literature, the frequency of aCL in BD ranges between 0 and 50%. Hull *et al* (1984) first reported 19% positivity for aCL and found an association between increased IgM and IgG aCL levels and retinal vasculitis. A similar relationship with uveitis was later suggested in other studies. Pereira *et al.* (1989) observed IgG aCL positivity in three of 10 patients (30%) with ocular disease and a lower frequency in patients taking corticosteroids (27.3 vs 55.6%). Musabak *et al.* (2005) also found that anticardiolipin antibody -IgG and IgM levels were higher in patients with active BD than healthy controls but not higher than patients with inactive BD. Zouboulis *et al.* (1993) reported high IgM aCL titres in patients with cutaneous vasculitis and erythema nodosum. Apart from these studies, no correlation was observed with any specific manifestation of BD and aCL antibodies, especially with thrombotic events, as might be expected. In Tokay *et al.* (2001) study, which includes the largest number of patients reported, they found that the frequency of IgG and IgM aCL to be 2.4% in BD, 50% in SLE and 5.6% in healthy controls. While the frequencies in the SLE and control groups were similar to those in other studies, they did not find increased IgM and IgG aCL in BD. They were also unable to show any significant association between aCL and vascular or ocular involvement, disease duration, pathergy positivity, a high erythrocyte sedimentation rate or immunosuppressive treatment. In the current study the IgA aCL elevated in 14 (56%) in patients with BD compared with one (4%) patient in the control group ($P<0.01$). IgG aCL levels were elevated in 13 (52%) in patients with Behcet's disease compared with one (4%) patient in the control group ($P<0.01$). Also patients with BD do not have decreased protein S, or antithrombin III activity, activated protein C resistance, circulating lupus anticoagulant (LAC), or elevated IgM aCL. No significant differences were found

between any variable in both groups. No association between elevated IgM aCL levels and venous or arterial thrombosis and no statistical correlation was found between any factor and clinical manifestations of the disease. These results are in agreement with most previous reports, especially study of Mader *et al.* (1999) who suggest an increased frequency of IgG aCL in BD and Tokay *et al*(2001) who found a slight increase of IgA aCL in BD patients and also no correlation was found between serum IgA levels and IgA aCL. In our study the prevalence of elevated anticardiolipin antibodies (aCL) was elevated in about 50% of BD patients with vascular thrombosis. The aCL neither correlate with clinical manifestations of BD, nor correlate with other coagulation abnormalities. Thrombophilia does not seem to play a major role in the tendency to thrombosis in Behcet's disease. However, dyslipidaemia, predominantly hypertriglyceridaemia, might be a risk factor (Leiba *et al.*, 2004).

In our patients, although statistical significance was not achieved, 5 patients had an abnormal activated protein C resistance test. It seems that aCL might interfere with the activation of protein C, reducing the circulating levels of activated protein C and increasing risk of thrombosis. Activated protein C inhibits the procoagulant function of activated factor V (FVa), through proteolytic cleavages at Arg306, Arg506 and Arg679. The cleavage at Arg506 is kinetically favored, but protected by factor Xa (FXa). Protein S has been suggested to annihilate the inhibitory effect of FXa, a proposal that has been challenged. Protein S counteracted the inhibition by FXa of the Arg506 cleavage, whereas protein S and FXa yielded additive stimulatory effect of the cleavage at Arg306. This suggests that FXa and protein S interact with distinct sites on FVa, which is consistent with the observed lack of inhibitory effect on FXa binding to FVa by protein S. The apparent annihilation of the FXa protection of the Arg506 cleavage by protein S is due to enhanced rate of Arg506 cleavage of FVa not bound to FXa resulting in depletion of free FVa and dissociation of

FXa-FVa complexes (Norstrom *et al.*, 2006).

Conclusion

A significant number of patients have elevated levels of IgA& IgG aCL but they are not associated with venous or arterial thrombosis. These results do not suggest a primary role for aCL in BD and do not support the role of coagulation abnormalities in the pathogenesis of thromboembolic complications of Behcet's disease, but suggest vascular inflammation as the main pathogenetic event in the vascular lesions in Behcet's disease.

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تقييم دور الأجسام المضادة للكارديوليبيين و عوامل التجلط في إحداث تخثرات و جلطات الدم في الأوعية الدموية المصاحبة لمرض بهست

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يهدف هذا البحث ألي قياس مستوي و تقييم دور عوامل التجلط في أحداث تخثرات و جلطات الدم في الأوعية الدموية المصاحبة لمرض بهست و علاقة هذه العوامل بالأعراض الإكلينيكية للمرض.

وقد اجري هذا البحث علي عدد 25 مريض يعانون من مرض بهست منهم 8 مرضي يعانون من جلطة بأوردة الساق و 4 مرضي يعانون من تخثرات و جلطات بشرايين الرئة و المخ. كما شمل البحث 25 مريضا بامراض روماتيزمية مختلفة لا يعانون من إصابات بالأوعية الدموية و ذلك كحالات ضابطة.

وقد تم اخذ التاريخ المرضي و عمل فحص إكلينيكي شامل للمرضي المصابين بمرض بهست. كما تم عمل الفحوصات الآتية لكل من مرضي مرض بهست و الحالات الضابطة و تشمل : قياس مستوي الأجسام المضادة لمادة الكارديوليبيين و الأجسام المضادة للتجلط في مرض الذئبة الحمراء و نشاط بروتين س و نشاط بروتين اس و نشاط مضاد التجلط رقم 3 وكذلك اختبار مقاومة نشاط بروتين س.

وقد وجد ان مستوي الأجسام المضادة للكارديوليبيين مرتفع في اكثر من نصف حالات مرض بهست و في حالة واحدة من الحالات الضابطة ولكن هذا الارتفاع لا يرتبط بنشاط المرض الإكلينيكي او مضاعفات الأوعية الدموية للمرض. اما عوامل التجلط الأخرى فلم يظهر اي نشاط لهذه العوامل سواء في مرض بهست او الحالات الضابطة. و يستخلص من هذا البحث ان عوامل التجلط ليس لها دور اساسي في أحداث جلطات و تخثرات الأوعية الدموية المصاحبة لمرض بهست و ان كان لها دور ثانوي مصاحب لالتهابات الأوعية الدموية.