Activated Protein C Resistance and Its Correlation with Thrombophlebitis in Behçet's Disease

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Received: March 31, 2010
Accepted: May 13, 2011

SUMMARY Patients with Behçet's disease (BD) have been recognized to be at an increased risk of thrombosis and thrombotic complications have been reported in 12%-40% of patients. The precise pathogenetic mechanisms underlying the thrombotic tendency of BD are not known. In recent researches, it is reported that procoagulant mutations might play a role in thrombotic process in BD patients. We aimed to evaluate the frequency of activated protein C resistance (APCR) in our BD patients and to investigate the association between thrombophlebitis and APCR. The study included 116 patients with BD who fulfilled the International Study Group criteria and 70 healthy individuals as a control group. APCR levels were measured by the clotting method. APCR levels were 129.63±39.70 and 152.26±22.62 in BD patients and control group, respectively ($P<0.01$). APCR was found in 47.4% and 8.6% of BD patients and control group, respectively ($P<0.01$). There was no statistically significant difference regarding APCR levels between patients with thrombophlebitis and without thrombophlebitis (46.4% *vs*. 48.3%). We found the frequency of APCR to be increased in BD patients with or without thrombophlebitis. The lack of association between thrombophlebitis and APCR in our series of BD patients suggests that some factors like endothelial abnormalities other than thrombophilia play a major role in the pathogenesis of thrombosis in BD.

KEY WORDS: activated protein C resistance, Behçet's disease, thrombophlebitis, thrombophilia, factor V Leiden mutation, thrombosis

INTRODUCTION

Behçet's disease (BD) is a multisystemic, chronic and vasculitic disease characterized by recurrent oral and genital ulcerations. Genetic, immune and environmental factors as well as viral and bacterial infections, vascular endothelial pathologies and coagulation abnormalities have been implicated in the pathogenesis of the disease (1,2). The risk of thrombosis is known to be increased and 12%-40% of BD patients have been reported to have thrombotic complications (3-6). Venous or arterial thrombosis occurs in 7%-38% of patients. Venous thrombosis is more common than arterial thrombosis, with relative frequency of 90% and 10%, respectively (7).

Thrombosis has been associated with coagulation abnormalities such as protein C, protein S and antithrombin deficiency, and existence of antiphos-

pholipid antibodies beyond endothelial dysfunction caused by vascular inflammation (2,4,8).

Activated protein C (APC) shows anticoagulant activity by inactivating factor V, which is included in homeostasis cascade. Under *in vitro* testing circumstances, APC resistance (APCR) defines a decreased anticoagulant response in plasma. APCR is caused by a point mutation on factor V gene, referred to as factor V Leiden mutation. This mutation results in inefficient inactivation of factor V by APC, which leads to thrombosis (9,10). This increased risk of thrombosis in BD is regarded as a prethrombotic process (11).

In this study, we aimed to determine whether APCR is associated with thrombosis in BD patients with or without thrombophlebitis.

PATIENTS AND METHODS

The study included 116 patients with BD treated at our Behçet's Disease Polyclinic who fulfilled the International Study Group criteria and 70 healthy individuals without recurrent oral aphthae, systemic drug use, pregnancy and history of thrombosis as a control group. Exclusion criteria were existence of systemic disease, pregnancy, and heparin or anticoagulant use. Patient charts of BD patients were evaluated retrospectively. Blood APCR was measured in control subjects and study patients on a STA-R Stago device with APCR kit (Diagnostica Stago, Asnieres, France; Cat. No: 00721) by the clotting method. Values under 120 were considered positive and those over 120 negative. Statistical evaluation was performed with NCSS 2007 PASS 2008 Statistical Software; definitive tests, Student's t-test, χ^2-test and Fisher's exact test were used on interpretation of results. The level of significance was set at $P<0.05$.

RESULTS

Ninety (77.6%) of 116 BD patients were male and 26 (22.4%) were female, mean age 36.76. Control group consisted of 29 (41.4%) male and 41 (58.6%) female subjects, mean age 40.55. Thrombophlebitis was present in 56 (48.3%) patients (deep vein thrombosis in 11 (9.5%) of them), oral aphthae in all 116 (100%) patients, genital ulceration in 100 (86.2%), papulopustular lesions in 72 (62.1%), erythema nodosum in 80 (69%), ocular involvement in 36 (31%), arthritis and/or arthralgia in 60 (51.7%) and neurologic involvement in 4 (3.4%) patients. Forty-three (37.1%) patients had a positive pathergy test. There was no difference between BD patients with and without thrombophlebitis regarding genital ulceration, papulopustular lesions, pathergy positivity, ocular, articular and neurologic involvement ($P>0.05$), while erythema nodosum was found to be more prevalent in patients with thrombophlebitis ($P<0.01$) (Table 1).

Table 1. Activated protein C resistance (APCR) levels in Behçet's disease (BD) patients and control group

	BD	Control	PΣ
	Mean ± SD	Mean ± SD	
APC levels	129.6±39.70	152.26±22.62	0.001*
	n (%)	n (%)	PΨ
APCR (+)	55 (47.4%)	6 (8.6%)	0.001**
APCR (-)	61 (52.6%)	64 (91.4%)	

Σ = Student's t-test; Ψ = χ^2-test; *$P<0.05$; **$P<0.01$

The mean values of APCR was 129.63±39.70 in patients and 152.26±22.62 in controls; this between-group difference was statistically significant ($P<0.001$). APCR values under 120 were regarded as 'APCR positive' and over 120 were regarded as 'APCR negative'. Therefore, 55 (47.4%) BD patients and 6 (8.6%) control subjects were found to be APCR positive, which was statistically significant ($P<0.001$). APCR was found in 26 (46.4%) patients with thrombophlebitis, 29 (48.3%) patients without thrombophlebitis and 6 (8.6%) control subjects, which was statistically significant ($P<0.001$). Patients with and without thrombophlebitis did not differ according to APCR ($P>0.05$) (Table 2). There was no statistically significant difference between APC levels and presence of genital ulceration, papulopustular lesions, erythema nodosum, pathergy positivity, ocular, articular and neurologic involvement ($P>0.05$).

Table 2. Activated protein C resistance (APCR) levels in patients with and without thrombophlebitis

	APCR (+)	APCR (-)	PΨ
Thrombophlebitis (+)	26 (46.4%)	30 (53.6%)	0.837
Thrombophlebitis (-)	29 (48.3%)	31 (51.7%)	
Controls	6 (8.6%)	64 (91.4%)	0.001

Ψ = χ^2-test

DISCUSSION

Behçet's disease is a vasculitic disease with a chronic and multisystemic course that may involve all kinds of vessels (1). Vascular involvement is an important cause of mortality and morbidity and accounts for 25% of deaths due to BD (3). A main factor caus-

ing hypercoagulation are inherited thrombophilias, of which APCR is the most prevalent (9). APCR prevalence in healthy population is 5%-13%, whereas half of the patients with idiopathic thrombosis may have APCR (12). Factor V Leiden (FVL) mutation accounts for more than 90% of APCR in the general population (13). However, the role of APCR in the pathogenesis of thrombophlebitis development in BD is unknown. Factor V Leiden mutation in BD has been evaluated and heterozygous mutation was found in 37.5% (12/32) of patients with a history of deep vein thrombosis, 9.4% (3/32) of patients without any thrombotic event and 10.3% (11/107) of healthy individuals. The authors conclude that FVL mutation might play a major role in the development of venous thrombosis in BD (14). Other studies found FVL mutation in 37%, 42% and 60% of BD patients with thrombosis, postulating that the mutation is a risk factor for the development of thrombosis in BD (15-17).

Studies evaluating the association between APCR and thrombosis in BD ended up in conflicted results. Mader *et al*. report that patients with BD do not have APCR based on the results of their study including 25 BD patients of which 8 had thrombosis (18). Guermazi *et al*. found APCR in 9.2% (6/65) of BD patients, 10.6% (8/75) of normal subjects and 30% (21/70) of patients with isolated thrombosis. Only one of the BD patients with a history of thrombosis had APCR. The authors conclude that APCR does not explain the risk of thrombosis in BD patients (19). Koşar *et al*. report that 29.3% (17/58) and 5% (16/320) had APCR and the prevalence of thrombosis was 35% (6/17) and 7.3% (3/41) in patients with and without APCR, respectively. Both findings were statistically significant and the authors suggest that APCR plays a role in thrombotic predilection in BD (20). Zarrinanbour *et al*. found 34.3% (11/32) of BD patients to have APCR, while none of the controls had APCR; the prevalence of APCR was 44.4% among 18 BD patients with thrombosis and 22.2% among 14 BD patients without thrombosis. The authors conclude that besides other factors APCR might predispose patients to venous thrombosis in BD and it could be useful to check for its presence to determine the necessity of prophylactic anticoagulation (12).

Similar to the results reported by Koşar *et al*. (20) and Zarrinanbour *et al*. (12), we found an increased prevalence of APCR in BD patients compared to controls. However, APCR levels did not differ between BD patients with and without thrombosis (12,20). APCR has been reported to be associated with retinal vascular occlusion in some studies (21-23). We did not find any statistically significant difference between APC levels and presence of genital ulceration, papulopustular lesions, erythema nodosum, pathergy positivity, ocular, articular and neurologic involvement.

CONCLUSION

We found the APCR frequency to be increased in BD patients with and without thrombophlebitis. The lack of association between thrombophlebitis and APCR in our series of BD patients suggests that some factors like endothelial abnormalities other than thrombophilia play a major role in the pathogenesis of thrombosis in BD. The role of APCR in the pathogenesis of BD, if APCR is a primary phenomenon or is acquired, needs to be elucidated in additional studies, which will investigate both APCR and FVL mutations in BD patients.

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