# Anticardiolipin Antibody in Patients with Behçet's Disease with and without Vascular Thrombosis

Akbar Rajaee[1*], Mohammad Ali Nazarinia[1], Seyed Modjtaba Hakim[1], Mitra Amini[1], Maryam Ayatollahi[2], Abbas Ghaderi[2,3,]

[1]Division of Rheumatology, Department of Internal Medicine, [2]Department of Immunology, [3]Shiraz Institute for Cancer Research, Shiraz University of Medical Sciences, Shiraz, Iran.

## ABSTRACT

**Objective:** The clinical value of IgG anticardiolipin antibody in patients with Behçet's disease with or without vascular thrombosis was evaluated. **Methods:** IgG isotype of anticardiolipin (aCL) antibody was assessed in 40 Behçet's disease (BD) patients with venous or arterial thrombosis, 40 BD patients without venous or arterial thrombosis and 80 healthy subjects as controls. The levels of IgG aCL were determined by an indirect ELISA method. Color Doppler Sonography, Magnetic Resonance Imaging and conventional angiography were the procedures used for other clinical evaluations. **Results:** Out of 40 patients with vascular thrombosis, 20(50%) were positive for low to moderate level of IgG aCL. In patients without thrombosis 22(55%) were positive for low to moderate level of IgG aCL while in none (0%) of the healthy subjects the IgG aCL was positive, neither low nor moderate. The number of patients with headache but having a normal cerebral magnetic resonance imaging (MRI), was higher in anticardiolipin positive patients without vascular thrombosis as compared to those with vascular thrombosis, (P = 0.001). Arthritis was noticed in both patents groups. 15% of aCL positive patients without thrombosis had arthritis as compared to none in aCL negative patients without thrombosis (P = 0.02). **Conclusion:** The results of this study indicate that although the frequency of IgG aCL was found to be higher in Iranian patients with BD in comparison with the previous reports, except in arthritis the observed elevated IgG aCL does not correlate with clinical disease manifestations, or vascular thrombotic complications.

**Key words: Anticardiolipin Antibody, Behçet's Disease, Vascular Thrombosis**

*Corresponding author: Dr. Akbar Rajaee, Department of Rheumatology, Medical School, Shiraz University of Medical Sciences, e-mail: rajaeea@sums.ac.ir

## INTRODUCTION

Behçet's disease (BD) is a chronic inflammatory vasculitis, characterized by mucocutaneous, ocular, vascular, arthritic, and neurological involvement (1,2,3). The cause and pathogenesis is unclear, but various immunological abnormalities associated with both humoral and cellular immune systems have been reported (4). Recurrent thrombosis, fetal loss and thrombocytopenia have been reported to be associated with the presence of aCL, especially in autoimmune disease such as systemic lupus erythematosus (SLE) (5).

Behçet's disease (BD) is also characterized by recurrent vascular thrombosis and vasculitis. Although some previous studies suggest an increased frequency of aCL in BD, the low number of patients in the most of these studies, especially patients with thrombotic complications, make it difficult to draw definite conclusions (6,7). The reported prevalence of aCL in BD has varied widely and the association of aCL with clinical and serological features of BD has not yet been determined (8). In this study, we investigated prevalence of IgG aCL in BD patients with and without vascular thrombosis and determined whether it may contribute to thrombotic complications.

## MATERIALS AND METHODS

Serum samples were obtained from 80 patients with BD, 40 with vascular thrombosis, 40 without vascular thrombosis and 80 healthy subjects served as controls. The BD patients with vascular thrombosis (29 males, 11 females; aged 17-50 yrs, mean = 36.12 ± 7.83 yrs) and the BD patients without vascular thrombosis (16 male, 24 females; aged 13-52 yrs, mean = 30.65 ± 7.91 yrs a) all fulfilled the criteria of the International Study Group for Behçet's disease (9) and did not have concurrent infection or other medical problems. The age of onset ranged from 16-47 years (mean = 30.51 ± 7.95 yrs) with duration of 1-25 years (mean = 5.73 ± 5.18 yrs) in BD patients with vascular thrombosis and 12-43 years (mean = 26.95 ± 6.92 yrs) with duration of 1-11 years (mean 4.6 ± 3.29 yrs) in BD patients without vascular thrombosis. To determine vascular involvement, Color Doppler Sonography was performed in 32 patients and skin biopsy in 11 patients. All patients had slit-lamp examination of their eyes, and the diagnosis of retinal vascular disease was made by intravenous fluorescein angiography. One patient had an angiographically proven coronary artery aneurysm. Magnetic resonance imaging with contrast was done for detection of CNS lesions in 4 patients. Pathergy test was done in both groups of patients with and without vascular thrombosis. Clinical characteristics of 40 BD patients with venous or arterial thrombosis and those with out thrombosis are shown in tables 1 and 2, respectively.

All BD patients and healthy control subjects were tested for aCL level of the IgG isotype by using an indirect ELISA method.

The GPL from 10-20 was regarded as low positive and 20-80 as moderate positive and bellow 10 was considered as negative. Statistical analysis was carried out using fisher's exact test for analysis of correlation of IgG aCL and either thrombosis or various clinical manifestations.

**Table 1. Clinical characteristics of 40 patients with BD and vascular thrombosis**

| | n | % |
|---|---|---|
| ***Recurrent oral aphthosus*** | 40 | 100 |
| ***Recurrent genital aphthosus*** | 25 | 62.5 |
| ***Eye Involvement*** | 13 | 32.5 |
| Anterior uveitis | 5 | 12.5 |
| Panuveitis | 6 | 15 |
| Bilateral retinal vein occlusion | 1 | 2.5 |
| Retinal vasculitis | 1 | 2.5 |
| ***Skin involvement*** | 35 | 85 |
| Erythema nodosum + pseudofolliculitis | 21 | 52.5 |
| Acneform lesion | 7 | 17.5 |
| Acneform lesion + pseudofolliculitis | 5 | 12.5 |
| ***Arthritis (wrist, elbow, knee, ankle)*** | 8 | 20 |
| ***Arthralgias*** | 21 | 52.5 |
| ***Thrombosis*** | | |
| Calf DVT | 24 | 60 |
| Superficial vein thrombosis | 3 | 7.5 |
| Superficial + DVT | 6 | 15 |
| Superficial, SVC and calf DVT | 1 | 2.5 |
| Bilateral retinal vein thrombosis | 1 | 2.5 |
| DVT + coronary artery aneurysm | 1 | 2.5 |
| Left axillary, left jugular, left Subclavian VT | 1 | 2.5 |
| Cerebral thrombosis | 3 | 7.5 |
| ***CNS*** | | |
| TIA | 2 | 5 |
| Convulsion | 2 | 5 |
| Headache | 10 | 25 |

DVT = Deep Vein Thrombosis, SVC = Superior Vena Cava, TIA = Transient Ischemic Attack

## RESULTS

Elevated levels of IgG aCL were detected in 20(50%) BD patients with vascular thrombosis and 22(55%) in BD patients without vascular thrombosis. IgG aCL was not detected in healthy control subjects. In 18 out of 40 BD patients with vascular thrombosis, the level of IgG aCL was within the low positive range and in 2 cases was within the moderate positive range. In 18 out of 40 BD patients without vascular thrombosis, the level of IgG aCL was within the low positive range and in 4 cases was within the

**Table 2. Clinical characteristics of 40 BD patients without vascular thrombosis.**

| | n | % |
|---|---|---|
| ***Recurrent oral aphthosus*** | 40 | 100 |
| ***Recurrent genital aphthosus*** | 30 | 75 |
| ***Eye involvement*** | 12 | 30 |
| Anterior uveitis | 5 | 12.5 |
| Panuveitis | 7 | 17.5 |
| ***Skin involvement*** | 36 | 90 |
| Erythema nodosum+pseudofolliculitis | 16 | 40 |
| Acneform lesion | 7 | 17.5 |
| Acneform lesion +pseudofolliculitis | 13 | 32.5 |
| ***Arthritis (knee)*** | 6 | 15 |
| ***Arthralgias*** | 20 | 50 |
| ***CNS*** | | |
| Convulsion | 1 | 2.5 |
| Headache | 21 | 52.5 |

moderate positive range. However, in both groups of patients with or without vascular thrombosis no correlation was found between levels of IgG aCL and thrombotic complications or other clinical manifestations of the disease (table 3). Twenty eight out of 40 patients with vascular thrombosis and 30 out of 40 patients without vascular thrombosis were positive for pathergy test. Arthritis was reported in BD patients with or without thrombosis. 15% of aCL positive patients without thrombosis presented with arthritis in comparison with no cases of arthritis in aCL negative BD patients without thrombosis (P = 0.02).

## DISCUSSION

The prevalence of vascular involvement in BD is estimated 10 to 28% worldwide. Eighty-eight percent is due to venous lesions and 12% to arterial lesions (6,7). The venous lesions were mainly venous occlusions, while the arterial lesions were either arterial aneurysms and/or arterial occlusion (7,10). The pathogenesis of thrombus formation in BD is poorly understood. It was assumed that mechanisms other than arterial and/or venous inflammation might be involved (7,11). In some reports the prevalence of elevated aCL is not only increased in patients with BD, but has also been considered as a predictor of more severe disease (12). The association of aCL with vascular thrombosis and neurological manifestations of BD back to the finding that nearly half of the patients had elevated aCL levels. Hull et al. detected aCL in 13 out of 70 (19%) patients with BD with a significant relation between presence of aCL, and

**Table 3. Correlation of IgG anticardiolipin antibody with the clinical features of BD patients with and without vascular thrombosis.**

| Clinical features | Behçet's disease with thrombosis (n=40) | | | Behçet's disease without thrombosis (n=40) | | |
|---|---|---|---|---|---|---|
| | IgG aCL negative (n=20) | IgG aCL positive (n=20) | P value | IgG aCL negative (n=18) | IgG aCL positive (n=22) | P value |
| ***Oral aphthosus*** | 20 | 20 | | 18 | 22 | |
| ***Genital aphthosus*** | 13 | 7 | 0.058 | 13 | 17 | 0.73 |
| ***Eye involvement*** | 9 | 9 | | 6 | 6 | 0.67 |
| Anterior uveitis | 3 | 2 | 1 | 2 | 3 | 1 |
| Panuveitis | 5 | 6 | 0.72 | 4 | 3 | 0.67 |
| Bilateral retinal vein occlusion | 0 | 1 | 1 | 0 | 0 | |
| Retinal vasculitis | 1 | 0 | 1 | 0 | 0 | |
| ***Skin involvement*** | 16 | 17 | 1 | 16 | 20 | 1 |
| Erythema nodosum + pseudofolliculitis | 10 | 11 | 0.75 | 8 | 8 | |
| Acneform lesion | 5 | 2 | 0.40 | 2 | 5 | 0.42 |
| Acneform lesion + pseudofolliculitis | 1 | 4 | 0.34 | 6 | 7 | 0.91 |
| ***Arthralgias*** | 12 | 9 | 0.34 | 9 | 11 | 1 |
| ***Arthritis*** | 4 | 4 | | 0 | 6 | 0.02 |
| ***Thrombosis*** | | | | | | |
| Calf DVT | 11 | 13 | 0.51 | 0 | 0 | |
| Superficial VT | 2 | 1 | 1 | 0 | 0 | |
| Superficial + DVT | 4 | 2 | 0.66 | 0 | 0 | |
| Superficial + SVC +calf VT | 0 | 1 | 1 | 0 | 0 | |
| Bilateral retinal VT | 0 | 1 | 1 | 0 | 0 | |
| DVT+ coronary artary aneurysm | 0 | 1 | 1 | 0 | 0 | |
| Lt axillary + Lt jugular + Lt subclavian VT | 1 | 0 | 1 | 0 | 0 | |
| Cerebral thrombosis | 2 | 1 | 1 | 0 | 0 | |
| ***CNS*** | | | | | | |
| TIA | 1 | 2 | 1 | 0 | 0 | |
| Convulsion | 0 | 2 | 0.47 | 0 | 1 | 1 |
| Headache | 7 | 3 | 0.14 | 14 | 7 | 0.001 |

DVT = Deep Vein Thrombosis, SVC = Superior Vena Cava, Lt = left, TIA = Transient Ischemic Attack

retinal vasculitis (6). Pereira et al. observed IgG aCL in 3 out of 10 patients (30%) with BD and with ocular disease (12). It has been reported that 28.6% of Korean BD patients have aCL mainly IgG class (14).

Alper et al. also found elevated aCL levels in 11(22%) of 50 patients with BD. Ocular lesions have been detected in 15(30%) of the patients group, among which 5 had IgG aCL positive (15). When 6 studies from Turkey were analyzed separately, the frequency was only 9.5% (16). It is clearly indicated that the emergence of anticardiolipin antibody in BD has been investigated with conflicting results. In our study the frequency of IgG aCL in patients with vascular thrombosis was 50% and for patients without vascular thrombosis was 55% but mostly with low to moderate range. The findings in our patients nearly are in accordance with the results of studies by Zouboulis et al. (47%) (17), Bergman et al. (50%) (18) AL-Dalaan et al. (45%) (13) and Mader et al. (40%) (7), while are in the contrary to the results of other investigators in which the level of aCL is reported to be from 0% to 22% (15,19-22). The reason for disparity between these studies remains unclear. In our study we found a higher number of BD patients with headache in the group of patients without vascular thrombosis compared to patients with vascular thrombosis ($P<0.001$).

Arthritis was presented in aCL positive BD patients without vascular thrombosis compared to BD patients with negative aCL and without vascular thrombosis (table 3). This differences was found to be significant ($P<0.02$). Our results in patients with high incidence of thrombotic problem also suggest that IgG anticardiolipin antibody do not have a pathogenetic role in the vascular complications of BD and do not support the hypothesis that IgG aCL is a marker for thrombotic complications events, as might be expected. The presence of IgG aCL did not show any relation with either clinical activity or clinical manifestations except arthritis (table 3).

To understand the possible pathological role play by aCL in patients without vascular thrombosis, a long term follow-up of this group is recommended.

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