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Lipoprotein (a) in Behçet's disease as an indicator of disease activity and in thrombotic complications

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PURPOSE. *To evaluate the utility of plasma concentrations of lipoprotein (a) (Lp(a)) as an indicator of disease activity in Behçet's disease and to investigate its role in thrombotic complications of this disease.*

METHODS. *30 patients (19 male, 11 female) with Behçet's disease (8 active, 22 inactive) were enrolled in the study group and 30 healthy individuals (16 male, 14 female) in the control group. Seven of the inactive Behçet's disease patients had a history of thrombotic complications. The disease activity was evaluated by clinical manifestations (oral aphthous lesions, genital ulcerations, uveitis and vasculitis) and laboratory investigations (leucocyte count, lipoprotein (a), C-reactive protein (CRP), complement 3 (C3) and complement 4 (C4) concentrations).*

RESULTS. *Plasma Lp(a) and other acute phase reactant concentrations were significantly higher in the study group than in the controls ($p < 0.01$). These concentrations were also higher during the active period of the disease than during the inactive phase ($p < 0.01$). Lp(a) concentrations were significantly correlated with concentrations of other acute phase reactants. There was no difference between the groups with and without thrombotic complications for any of these measurements.*

CONCLUSIONS. *Plasma levels of Lp(a) might be an indicator of disease activity in Behcet's disease. There is no correlation between Lp(a) levels and thrombotic sequela in inactive Behçet's disease. However, further studies are needed on the thrombogenic role of Lp(a) during the active phase of thrombophlebitis, and in larger series. (Eur J Ophthalmol 2001; 11: 62-5)*

KEY WORDS. *Behcet's disease, Lipoprotein(a), Acute phase reactants, Thrombosis*

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INTRODUCTION

Behçet's disease is a multisystemic disease characterized by mucocutaneous, ocular, articular and neurological involvement. The histopathological mechanism is vasculitis, characterized by perivascular and intramural lymphonuclear cell infiltration. This leads to fibrinoid necrosis with vascular obliteration. Venous thrombosis is seen in 7-37% of the patients (1, 2). Decreased fibrinolytic activity is thought to result in venous thrombosis in Behçet's disease but the exact mechanism is not known. Defective fibrinolytic activity, in turn, is thought to result from the low levels of tissue plasminogen activator (tPA), and increased plasminogen activator inhibitor-1 (PAI-1), and the competitive inhibition between lipoprotein(a) – Lp(a) – and plasminogen.

As acute phase reactants, PAI-1 and Lp(a) levels increase in many nonspecific disorders. Thus, the thrombotic events and abnormal fibrinolysis might be relat-

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ed to the disease activity (3, 4). Lp(a) is an atherosclerogenic and thrombogenic plasma protein (4). It behaves like an acute phase reactant (5). We investigated the role of Lp(a) in Behçet's disease as an indicator of disease activity and in thrombotic complications.

METHODS

The study included 30 Behçet's disease patients (19 male, 11 female) in the study group and 30 healthy individuals (16 male, 14 female) in the control group, admitted to the Department of Ophthalmology, Uvea and Behçet's Disease Section, at Ankara Numune Hospital. All patients gave informed consent. The diagnosis of Behçet's disease was established according to the International Study Group criteria (5). The mean age was 34.8 years (range 21-50) in the study group and 32.3 years (20-50) in the control group. The study group was divided into two subgroups according to the disease activity: eight with active disease and 22 with inactive disease. Disease activity was evaluated by clinical manifestations such as oral aphthous lesions, genital ulcerations, uveitis and vasculitis, and laboratory investigations such as leucocyte count, Lp(a), CRP, C3 and C4 levels (5). In the inactive disease group, seven patients had a history of thrombotic complications.

The leucocyte count was taken with an Abbott CELL-DYNE 1700 blood count analyzer. The reference range was 4100-10900/µl. Serum specimens were used for CRP analysis, done with a Behring nefelometer analyzer. The upper normal limit of CRP was 0.5 mg/dl. C3 and C4 were also analysed with the Behring analyzer, nefelometrically in the serum samples. Commercial C3 and C4 nefelometric kits (S.A. Socolab N.V.) were used. The reference ranges were 75-140 mg/dl for C3 and 10-34 mg/dl for C4. For Lp(a), serum specimens were analyzed by a lipoprotein(a) calibrator (LPA cal), using the Beckman Immunohistochemistry Systems Lipoprotein (a) reagent commercial kit. The reference range was 0-300 mg/L.

Statistical analysis was done with the Mann-Whitney U test and Wilcoxon Signed Ranks Sum test.

RESULTS

Mean levels of Lp(a), WBC, CRP, C3 and C4 in Behçet's disease (active and inactive) group and in the

TABLE I - MEAN LEVELS OF LP(a) AND OTHER ACUTE PHASE REACTANTS IN THE CONTROL GROUP, AND IN ACTIVE AND INACTIVE BEHÇET'S DISEASE

	Control n=30	**Behçet's (active) n=22**	**Behçet's (inactive) n=8**
Lp(a) (mg/l)	206.0 ± 1121.3	746.7 ± 319.7	302.4 ± 76.4
WBC (cells/µl)	7403.3 ± 1944.3	12725.0 ± 1897.1	9209.0 ± 2004.9
CRP (mg/dl)	0.5 ± 0.6	6.67 ± 2.2	1.09 ± 1.2
C3 (mg/dl)	132.3 ± 21.0	178.2 ± 37.1	143.1 ± 26.4
C4 (mg/dl)	21.7 ± 5.0	38.4 ± 5.7	28.7 ± 5.9

TABLE II - LP(a) AND OTHER ACUTE PHASE REACTANT LEVELS IN PATIENTS IN INACTIVE BEHÇET'S DISEASE

	Inactive Behçet's disease Thrombosis(+)	**Inactive Behçet's disease Thrombosis (-)**
Lp(a) (mg/L)	342.3 ± 92.6	283.8 ± 62.6
WBC (cells/µl)	8757 ± 1853.7	9420.0 ± 2099.4
CRP (mg/dl)	1.5 ± 2.1	0.98 ± 0.5
C3 (mg/dl)	138.8 ± 29.8	145.2 ± 25.6
C4 (mg/dl)	28.0 ± 6.0	29.0 ± 6.1

control group are shown in Table I. All these parameters were higher in the Behçet's disease groups than in the controls ($p<0.01$). They were also higher in the active disease than in the inactive disease ($p<0.01$). Lp(a) levels were highly correlated with other phase reactants such as CRP, C3, C4 and WBC.

The mean levels of Lp(a) and other acute phase reactants in inactive Behçet's disease with and without thrombotic complications are shown in Table II. In the inactive Behçet's disease group, there was no difference in Lp(a) levels in patients with and without thrombotic complications (Mann Whitney U Test, Wilcoxon Signed Ranks Test; $p>0.05$).

DISCUSSION

Behçet's disease is a systemic vasculitis, complicated with venous thrombosis in 7-37% of cases (1). The pathogenesis of the thrombotic complications is not clear. Decreased fibrinolytic activity might be involved and abnormal fibrinolysis and a thrombotic tendency might be related with the disease activity. The reduced secretion of t-PA from the damaged and vasculitic endothelium, and the high concentrations of PAI-1, an acute phase reactant, lead to defective fibrinolysis (3).

Lp(a) might also have a role in the pathogenesis of the thrombotic complications in Behçet's disease (7). Lp(a) is an atherosclerogenic and thrombogenic plasma protein. Like low-density lipoprotein (LDL), it has a lipid nucleus and an apoprotein B-100 subunit but, unlike any other lipoproteins, it also includes an apoprotein(a) subunit bound with disulfide bonds (7-9).

Apo(a) of Lp(a) is structurally similar to plasminogen which is the precursor of plasmin. Plasmin breaks down fibrin – the main component of blood clots – proteolytically. Plasminogen can bind to all body cells including endothelial cells and macrophages through its central elements called kringles (4). This binding can be inhibited by Lp(a) by its kringle-like structures. Lp(a) competes with plasminogen for these binding sites in a dose-dependent manner. As a result, Lp(a) suppresses fibrinolysis at high concentrations. Lp(a) also inhibits PAI-1 binding to the surface of tPA (8). Therefore, Lp(a) inhibits the inhibition of t-PA by PAI-1. What is the combined effect of Lp(a) on fibrinolysis, then? Örem et al found higher Lp(a) levels in Behçet's disease patients with thrombotic complications (n=6) than in controls. They suggested that high Lp(a) levels were a risk factor for thrombotic complications and patients should be followed up for this complication (7). In our study, there was no significant difference in Lp(a) and other acute phase reactant levels in patients with and without thrombotic complications in the inactive Behçet's disease group ($p>0.05$).

Above 300 mg/L, Lp(a) levels are considered to double the risk of atherosclerosis, and this is the situation in 35% of Behçet's disease patients (10). In our series, Lp(a) levels were above 300 mg/L in 53% of the patients. In Behçet's disease, thrombotic events are more common than atherosclerosis, underlining the thrombogenic property of Lp(a). We did not assess the risk of atherosclerosis due to Lp(a).

Besides in atherosclerosis, Lp(a), like other acute phase reactants, increases in cirrhosis, nephrotic syndrome, and some systemic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and Behçet's disease (8, 11-14). Lp(a) levels rise during the acute phase of Behçet's disease and fall during remissions (8). The rise during the active phase might be either due to excessive synthesis or to reduced breakdown. Also, active episodes might affect Lp(a) levels through compartmental (extra/intravascular) redistribution of Lp(a). However, these mechanisms await clarification (15).

In conclusion, Lp(a) acts as an acute phase reactant and is therefore an indicator of disease activity in Behçet's disease. Our active disease group had no active thrombophlebitis but in the inactive Behçet's disease group, seven cases had sequelae of thrombophlebitis. We did not find any correlation between Lp(a) levels and thrombotic sequela in this inactive Behçet's disease group. Further studies investigating Lp(a) levels in patients with active thrombotic complications and in larger series should cast useful light on the role of Lp(a) in thrombogenesis in Behçet's disease.

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