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Antiphospholipid antibodies and lipoprotein (a) as etiologic or contributory factors in patients with idiopathic cavernous transformation of portal vein

İdiopatik portal ven kavernöz transformasyonu olan hastalarda etiolojik veya yardımcı faktör olarak antikardiolipin antikorlar ve lipoprotein (a)

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Background/aims: *Antiphospholipid antibodies consisting of anticardiolipin antibodies and lupus anticoagulant are strongly associated with thrombosis in adult patients. It is also well known that there is a close relationship between antiphospholipid antibodies and lipoprotein (a) in thrombous formation. The aim of this study was to determine whether antiphospholipid antibodies and lipoprotein (a) have any effect on the formation of thrombosis in the portal vein of patients with 'idiopathic' cavernous transformation of the portal vein.* ***Methods:*** *Twenty seven patients with idiopathic cavernous transformation of the portal vein (Group 1) seen at Hacettepe University Hospital were identified and prospectively studied. All were investigated for antiphospholipid antibodies and lipoprotein (a). Anticardiolipin antibodies, lupus anticoagulant and lipoprotein (a) were measured using commercially available kits. The findings of these 27 patients were compared with those of 20 healthy control subjects (Group 2).* ***Results:*** *Anticardiolipin antibodies, especially ACA Ig G and lipoprotein (a) levels were found to be higher than of healthy controls and statistically significant differences were documented in two of these parameters, which seems to play an important role in thrombous formation in the portal vein. There was no correlation for lupus anticoagulant between the two groups.* ***Conclusions:*** *Anticardiolipin antibodies and lipoprotein (a) are strongly associated with thrombosis in the portal vein, producing a favorable medium for and acting as contributory factors in thrombous formation. It is suggested that these factors should be evaluated carefully in patients with 'idiopathic cavernous transformation of the portal vein'.*

Key words: Cavernous transformation of portal vein, antiphospholipid antibodies, Lipoprotein (a) anticardiolipin antibodies, lupus anticoagulant.

Amaç: *Antikardiolipin antikorları ve Lupus antikoagülanını bünyesinde barındıran antifosfolipid antikorlar erişkin yaştaki trombozlarla yakından ilişkilidir. Ayrıca trombüs oluşumunda antifosfolipid antikorlar ile lipoprotein (a) arasında da yakın bir ilişki vardır. Bu çalışmada "idiopatik" portal ven kavernöz transformasyonu olan vakalarda, portal vende trombüs gelişimine antifosfolipid antikorlar ve lipoprotein (a) nın etkisinin olup olmadığını araştırmayı amaçladık.* ***Yöntem:*** *Bu amaçla, Hacettepe Üniversitesi hastanesi tarafından takip edilen ve idiopatik portal ven kavernöz transformasyonu tanısı alan 27 hasta (Grup 1) çalışmaya alındı. Hastaların tümü antifosfolipid antikorlar ve lipoprotein (a) yönünden incelendi. Antikardiolipin antikorları, lupus antikoagülanı ve lipoprotein (a) ölçümleri hazır ticari kitler kullanılarak yapıldı. Hasta grubundan elde edilen bulgular, 20 kişilik sağlıklı kontrol (Grup 2) grubundan elde edilen bulgularla karşılaştırıldı.* ***Bulgular:*** *Hasta grubunda antikardiolipin antikorları, özellikle de antikardiolipin antikorları Ig G ve lipoprotein (a) düzeyleri kontrol grubuna oranla yüksek olarak ölçüldü. Bu iki parametre bakımından iki grup arasında istatistiksel olarak fark saptandı. Bu bulgu, antikardiolipin antikorları Ig G ve lipoprotein (a)'nın portal vende trombüs gelişiminde önemli rolü olabileceğini göstermektedir. Lupus antikoagülanı bakımından iki grup arasında farklılık saptanmadı.* ***Sonuç:*** *Antikardiolipin antikorları ve lipoprotein (a) portal vende trombüs gelişimi ile yakından ilişkilidir. Bunlar, gerek tromboz için uygun ortamı hazırlayarak gerekse de yardımcı faktör olarak portal vende tromboz gelişimine neden olmaktadırlar. Bu çalışmada, portal vende tromboz gelişimi ile antikardiolipin antikorları Ig G ve lipoprotein (a) düzeyleri arasında bir korelasyon olduğu ve bu faktörlerin kombinasyonlarında da tromboz insidansının arttığı saptanmıştır. Dolayısıyla bu faktörler idiopatik portal ven kavernöz transformasyonu olan hastalarda dikkatli bir şekilde araştırılmalıdır.*

Anahtar kelimeler: Portal venin kavernöz transformasyonu, antifosfolipid antikorlar, lipoprotein (a), lupus antikoagülanı.

INTRODUCTION

Portal vein thrombosis (PVT) was first described by Balfour and Steward in 1869. This condition is one of the most common causes of extrahepatic pre-sinuzoidal portal hypertension (1). Incomplete recanalization of the portal vein (PV) leads to extensive hepatic portal venous collaterals and a

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Table 1. The laboratory findings of the two groups. Group 1: patients with CTPV of unknown etiology, Group 2: controls

	ACA (Ig G)	**ACA (Ig M)**	**LA**	**Lp (a)**
Normal Range	*(0-15 GPL unit)*	*(0-15 MPL unit)*	*+ / -*	*(M:22-490, F:21-570 mg / L)*
Group 1	6 (22 %)	2 (7.4 %)	1 (3.7 %)	8 (29.6 %)
(n =27)	(16.3±2.1)*ø	(7.8±1.8)ø		(374.3±52.9)*ø
Group 2	1 (5 %)	-	-	1 (5 %)
(n = 20)	(8.4±1.0)ø	-	-	(247.3±31.1)ø

+: positive, M: male, - : negative, F: female,* $p < 0.05$
ø: mean±SEM

cavernous appearance is seen called "cavernous transformation of the portal vein" (2,3). Although many clinical conditions, including cirrhosis, hepatocellular carcinoma, myeloproliferative disorders, abdominal surgeries, the use of oral contraceptives, trauma and intraabdominal infections are associated with pathologic thrombosis in the PV, the etiologic factors remains obscure in approximately 50% of adult patients. Risk factors for thrombosis in PV are known to be more than those of other large veins in the abdomen (4). The causes of this predominancy is not clear.

Antiphospholipid antibodies (APA), which consist of antiocardiolipin antibodies (ACA) and lupus anticoagulant (LA) are strongly associated with thrombosis and seem to be the most commonly acquired causes of thrombosis in adult patients (5,6). The entity that occurs with these antibodies is called antiphospholipid thrombosis syndrome, consisting of thrombosis of both arteries and mostly veins, with recurrent fetal loss and thrombocytopenia. Although these factors cause a similar clinical presentation, it is has become clear that LA and ACA are two separate entities. The mechanism(s) of thrombus formation have not yet been found in either, although in LA it has been suggested that there might be an interaction with the vasculature, thereby altering prostaglandin release, there may be activation of platelets and changes in prostaglandin metabolism or that the antibodies may block protein C or alter phospholipid interactions with activated factor V. It has also been suggested that hyperactivity of the fibrinolytic system and increased levels of plasminogen activation inhibitor may occur. It is known that ACA's have an affinity with important phospholipids involved at many points in the hemostasis system and they are directed primarily against important phospholipids in hemostasis (7). It is also well known that there is a close relationship between APA and Lp (a) in thrombous formation and the latter, which has been previously identified as a risk factor for atherosclerosis, was recently found to promote thrombotic events by interfering with the fibrinolytic functions of plasminogen and/or plasmin (8,9). The most commonly acquired factors have not yet been determined in patients with idiopathic CTPV. This study was therefore undertaken to evaluate the incidence of APA's and LA in patients with CTPV of unknown etiology.

MATERIALS AND METHODS

A total of 27 patients (16 male, 11 female, mean age 34 ± 9.8 years.) with a diagnosis of idiopathic CTPV and who had undergone detailed evaluation for ACA, LA and Lp (a) in the previous 12 years were included in the study. ACA (Imulys ACA Biopool, Sweden), LA (Bioclot LA Biopool, Sweden) and Lp (a) (Dako, Denmark) were measured using commercially available kits.

In all subjects, CTPV had been diagnosed by physical examination, abdominal Doppler ultrasonography (US) and splenoportography (SPG). Liver biopsies were obtained in each idiopathic CTPV patient for histologic evaluation, for confirmation of the diagnosis of CTPV and to exclude any primary liver disease. After a full clinical, biochemical, radiological and routine hematological evaluation, the patients were diagnosed as having idiopathic CTPV if no recognizable etiologic factor(s) for thrombosis were found in the portal vein.

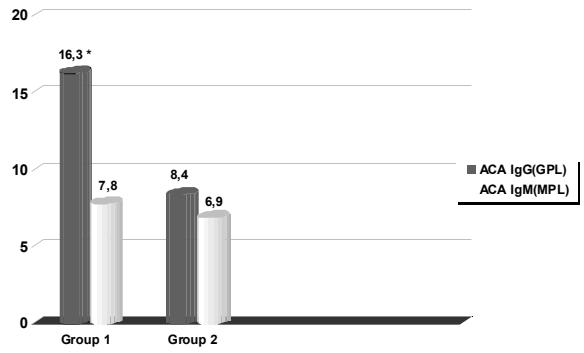

Figure 1. ACA Ig G and ACA Ig M levels of the two groups.

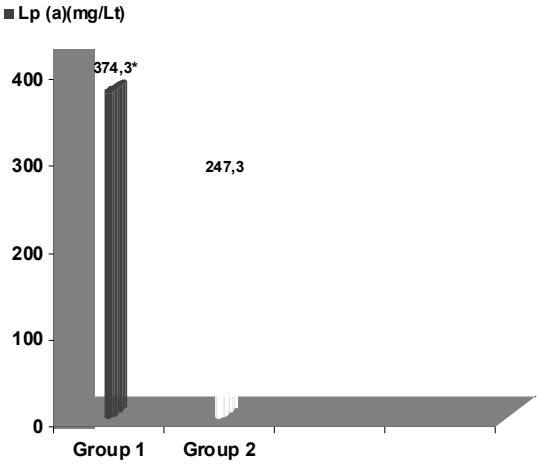

Figure 2. Lipoprotein (a) levels of the two groups

Twenty healthy controls (12 male, eight female, mean age 36 ± 7.9 years) were also included in the study for statistical comparison.

Abdominal doppler ultrasonography was performed on fasting patients and in the supine position (Toshiba SSA - 270A). Patencies of the portal vein, its tributaries and the splenic vein, were examined. Splenoportography was also carried out to confirm the diagnosis of CTPV. The procedure was carried out using a fine needle and direct splenic injection, known as the classic technique. Finally, ultrasonography-guided percutaneous liver biopsies were taken using a 14 gauge, 15 cm tru-cut needle.

The Student's t test and the Chi square test were used to compare hematological and biochemical variables for statistical analyses. A p value less than 0.05 was considered to be significant. All data are represented as mean values ± SEM.

RESULTS

In all 27 patients (Group 1) on whom color Doppler ultrasonography was performed, the portal vein was not observed and extensive portal venous collateral's, especially in the porta hepatis - were seen. It was sometimes difficult to distinguish extensive portal venous collaterals from the extrahepatic biliary tree. These group 1 patients had splenoportography performed revealing extrahepatic portal venous obstruction and multiple tortuous portal, paracholedocal and peripancreatic collaterals. Liver biopsies demonstrated no paranchimal disease in any of the subjects.

The laboratory findings of group 1 and the control group (group 2) are summarized in Table 1. Six (22%, 16.3± 2.1 GPL unit) patients had higher ACA IgG, two (7.4%) had higher ACA Igm and eight (29.6%, 37.4± 52.9 mg/Lt) had higher LpA levels than control subjects. The normal ranges of ACA Ig G and ACA Ig M were 0-15 GPL units and 0-15 MPL unit respectively. For Lp(a), normal ranges were different in males and females; in male patients a value within 22-490 mg/Lt and in female patients a value within 21-570 mg/Lt was considered normal. Only one patient (3.7 %) had LA positivity, while two of them were found to be combined with ACA and Lp (a) together. Other abnormalities were found to be isolated.

In controls, we found only one patient with higher levels of ACA Ig G (5%, 8.4±1.0 GPL units) and Lp (a) (5%, 247.3±31.1 mg/Lt). No LA positivity was detected in this group.

All 27 patients had been followed up for a median period of 3.9 ± 0.2 years and no systemic or local disease had been identified during this period. Only one patient had a previous history of recurrent deep veins thrombosis and was diagnosed with both ACA Ig G and Lp (a) abnormality.

In conclusion, it was found that ACA Ig G and Lp (a) levels were very high in group 1 and statistically important differences were documented between the two groups ($p < 0.05$).

DISCUSSION

Antiphospholipid syndrome consist of two different clinical syndromes, the first being lupus anti-

coagulant thrombosis syndrome and the other being the anticardiolipin antibody thrombosis syndrome. The clinical outcome of these two syndromes is similar but they have distinct laboratory and biochemical differences. The ACA thrombosis syndrome is much more common than LA thrombosis syndrome and although LA induces an anticoagulant effect in vivo, it is paradoxically associated with arterial and venous thrombosis (10,11). The etiology of thrombosis with LA remains obscure. Various mechanisms, such as altering prostaglandin release via interaction with the vasculature, changes in prostaglandin metabolism, blocking protein C or altering phospholipid interactions with activated factor V by the antibodies have been suggested, but there is no consensus on this issue (12). In this study only one out of 27 patients (3.7%) had LA positivity. Thus LA seems unlikely to be a causal factor in portal vein thrombosis.

In the patient group ACA Ig G and Lp (a) levels were found to be higher (13.3 ± 2.1 GPL, 374.3 ± 52.9 mg/Lt respectively) and significant differences were obtained, which is concordant with the literature.

ACA and LA are strongly associated with thrombosis and they seem to be the most common reasons of aquired blood protein defects causing thrombosis. These antibodies are a family of autoimmune and alloimmune Ig's (Ig G, Ig M, Ig A) which recognize phospholipid protein complexes in vivo laboratory test systems (5,6,13). The pathophysiologic mechanism of APA is not clear. A variety of mechanisms have been suggested to explain the role of APA in thromboembolic disease, such as alteration of platelet endothelial axis, inhibition of the heparin sulfate AT III regulatory system and abnormalities of the Pr C system (14-17). It is known that the risk of venous thrombosis increases when the level of ACA Ig G is higher than 10 GPL units. In our study, six of 27 patients (22%) had higher ACA Ig G levels than normal (normal range: 0-15 GPL units) and a significant difference was demonstrated between the two groups. We found no similar correlation with ACA Ig M (Figure 1).

There is a close association between Lp (a) levels and thrombosis (7). Lp (a) is known to be a risk factor for coronary atherosclerosis in general and in recent studies it was found to promote thrombotic events by interfering with the fibrinolitic functions of plasminogen and /or plasmin. It competes with plasminogen in binding to endothelial cells and macrophages and thus prevents assembly of the fibrinolytic system on cell surfaces (8-9). In this study, Lp (a) levels were found to be higher than normal in eight of 27 patients (29.6%) (normal ranges: males; 22-490 mg/lt, females: 21-570 mg/lt) and a significant difference was found between the two groups (Figure 2).

In conclusion, aquired thombogenic factors, in particular ACA IgG and Lp(a), were found to cause or contribute to idiopathic CTPV. It is therefore suggested that these should be carefully evaluated in CTPV patients.

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