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ANTIPHOSPHOLIPID ANTIBODY (aPL) PRESENCE IN COVID-19 PATIENTS

COVID-19 HASTALARINDA ANTİFOSFOLİPİD ANTİKOR (AFA) VARLIĞI

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ABSTRACT

Objective: In our study, we aimed to show whether there is a relationship between antiphospholipid antibody (aPL) positivity and complications of COVID-19.

Material and Methods: Eighty-three patients who were diagnosed with COVID-19 infection and hospitalized in the intensive care unit (ICU) of Bakirkoy Dr. Sadi Konuk Research and Training Hospital were included in our study as the case group and 79 healthy volunteers as the control group. Only patients with a positive Polymerase Chain Reaction (PCR) test were included in the case group. Serum antiphospholipid antibodies (aPL IgM/G), C-Reactive Protein (CRP), ferritin, procalcitonin (PCT), plasma D-Dimer levels, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) were analyzed by routine laboratory methods.

Results: Both groups were found statistically similar in terms of gender (χ^2 test, p=0.236). The mean age of the case group and control group was 60.54±16.86 and 51.47±14.64 years, respectively. When aPL positivity was evaluated between the case and control groups, a statistically remarkable difference was found between the groups (p=0.046). The case group showed an aPL positivity of 7.5% and the control group 1%. The correlation between D-Dimer, PT, INR, aPTT levels, and aPL IgM/G positivity in the case group was significant.

Conclusion: Our results revealed that aPL positivity in patients with COVID-19 infection relate to the severity of the disease, in-

ÖZET

Amaç: Çalışmamızda antifosfolipid antikor (AFA) pozitifliği ile COVID-19 komplikasyonları arasında bir ilişki olup olmadığını göstermeyi amaçladık.

Gereç ve Yöntem: Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi yoğun bakım servisinde yatan COVID-19 enfeksiyonu tanısı almış 83 hasta olgu grubu olarak, 79 sağlıklı gönüllü de kontrol grubu olarak çalışmamıza dahil edildi. Olgu grubuna sadece Polimeraz Zincir Reaksiyon (PZR) test sonucu pozitif olan hastalar alındı. Serum antifosfolipid antikorları (AFA IgM/G), C-Reaktif Protein (CRP), ferritin, prokalsitonin (PCT) ve plazma D-Dimer seviyeleri, protrombin zamanı (PT) ve uluslararası normalleştirilmiş oran (INR), aktive parsiyel tromboplastin zamanı (aPTT), rutin laboratuvar yöntemleriyle analiz edildi.

Bulgular: Her iki grup cinsiyet açısından istatistiksel olarak benzer bulundu (χ^2 testi, p=0,236). Olgu grubu ve kontrol grubunun yaş ortalaması sırasıyla 60,54±16,86 ve 51,47±14,64 yıl idi. Olgu ve kontrol grupları arasında AFA pozitifliği değerlendirildiğinde, gruplar arasında istatistiksel olarak anlamlı fark bulundu (p=0,046). Olgu grubu %7,5 ve kontrol grubu %1 AFA pozitifliği gösterdi. Olgu grubunun D-Dimer, PT, INR, aPTT seviyeleri ile AFA IgM/G pozitifliği arasındaki korelasyon anlamlı bulundu.

Sonuç: Sonuçlarımız, COVID-19 enfeksiyonu olan hastalarda AFA pozitifliğinin yaş ve cinsiyetten bağımsız olarak hastalığın şiddeti ile ilişkili olduğunu ortaya koydu. Bu çalışmanın sonucunu

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dependent from age and gender. To confirm the result of this study further studies with participation of larger patient groups from national and international hospitals are required.

Keywords: COVID-19, thromboembolism, antiphospholipid antibody

doğrulamak için ulusal ve uluslararası hastanelerden daha geniş hasta gruplarının katılımıyla daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, tromboemboli, antifosfolipid antikor

INTRODUCTION

Corona viruses are enveloped and single-stranded RNA viruses that can infect humans and animals. Rapidly spreading, the disease following such an infection was named COVID-19 in February 2020 by the World Health Organization, which means 2019 coronavirus disease (1). Most of the patients suffer from high fever, mild cough, headache, shortness of breath, myalgia, and arthralgia. Some patients need breathing support from a ventilator. Other symptoms of this disease are diarrhea and a loss of taste or smell (2). Several studies have indicated the association of blood clots with COVID-19 as patients who are treated for COVID-19 in hospital have shown such clots (for example, deep vein thrombosis, pulmonary embolism) more frequently than expected. Micro-thrombosis has also been found in COVID-19 patients (3).

Antiphospholipid antibody are specific for negatively charged phospholipids, such as phosphatidylserine, phosphatidylinositol, phosphatidic acid, and neutral phosphoethanolamine (4). Recent studies show that asymptomatic individuals who are positive for one or multiple types of aPL have increased thrombotic risk (5, 6).

A great variety of bacterial and virus infections are accompanied by a transient increase in aPL. Although an increase in aPL-Ig M antibody is mostly observed, high aPL-IgG antibody can also be observed in these infections (7).

Our aim in this study is to show an increased aPL positivity in COVID-19 patients, and our result contributes to the explanation of the elevated risk for thromboembolism and related complications such as pulmonary embolism, deep vein thrombosis, acute mycordial ischemia in this disease.

MATERIAL AND METHODS

Patient selection

Eighty-three patients who were diagnosed with COVID-19 and hospitalized in the intensive care unit (ICU) of Bakirkoy Dr. Sadi Konuk Research and Training Hospital were selected in our study as a case group. These patients were diagnosed with a severe COVID-19 infection, according to their clinical and radiological presentation and positive RT-PCR results. All the patients received anticoagulant therapy with prophylactic or therapeutic enoxaparine. None of them used any other anticoagulant drug before intensive care unit (ICU) admission. As a control group, we enrolled 79 healthy volunteers. Participants with a history of infections in the last six months, renal dysfunction, cancer, autoimmune diseases, and patients using medication with chlorpromazine, procainamide, or diphenylhydantoin were excluded from this study. This study was approved by the ethics committee of Health Science University, Bakirkoy Dr. Sadi Konuk Research and Training Hospital (Date: 18.05.2020, No: 202-11-25).

Blood sampling and measurement of the laboaratory tests

The case groups' serum and plasma samples were taken immediately after their admission to the hospital. After clotting, the samples were centrifuged at 3000 rpm for 10 minutes and analyzed for routine biochemistry tests. All tests were performed at the clinical laboratories of Bakirkoy Dr. Sadi Konuk Research and Training Hospital. Aliquoted samples were stored immediately at -20°C for antiphospholipid antibody measurement. Hemolyzed samples were excluded from the study. The quantitative sandwich enzyme immunoassay was developed for the measurement of serum aPL levels by use of a commercially available ELISA kit (AESKULISA Phospholipid Screen-GM Reference No 3224, AESKU DIAGNOSTIC GmbH&Co Germany). The inter-assay and intra-assay variabilities were 3.4% and 4.76%, respectively. From the optic density (OD) of each sample, the corresponding antibody concentrations were expressed in U/ml. According to the kit instruction, aPL Ig M/G levels <12 U/ml, between 12-18U/ml, and >18U/mL are accepted as a normal reference range, equivocal range, and positive results, respectively.

Statistical analysis

Statistical analyses were done by using the SPSS version 21 software (SPSS, Inc., Chicago, USA). The normality measurements of continuous variables were done by using the Kolmogorov-Smirnov test, and it was observed that normality was achieved. Statistical associations between groups and categorical independent variables were done by the Chi square test (χ^2) and continuous variables analysis was done with independent sample t test. Since there is an age difference between case and control groups, multivariate ANCOVA analysis was carried out while evaluating aPL positivity by taking age and gender as a covariate. The Pearson correlation analysis was used on continuous variables in the case group, and the difference in aPL Ig M and aPL IgG was demonstrated by this analysis.

RESULTS

In our study the case and control groups were found statistically similar in terms of gender (χ^2 test, p=0.236) (Table 1). Patients with aPL results within the equivocal range (12-18 U/mL) were excluded from case-control positivity comparison (n=3) and from control group (n=1). A values with the stars (*) next to them indicate this correlation. Statistical significance level (alpha) was accepted as 0.05. According to this analysis, the correlation with aPL Ig G positivity and coagulation tests (D-Dimer, PT, INR, and aPTT) is significant. The statistical significance level (alpha) was accepted as 0.05 (Table 4).

Table 1: Gender distribution between case and control groups

			Gender		Total
			Female	Male	
Case-control	Case	Count	46	37	83
		% Within case-control	55.4%	44.6%	100.0%
	Control	Count	51	28	79
		% Within case-control	64.6%	35.4%	100.0%
Total		Count	97	65	162
		% Within case-control	59.9%	40.1%	100.0%

χ^2 test, p=0.236

Table 2: Case-control groups positivity comparison aPL-Ig M/G

Crosstab

			aPL		Total
			Negative	Positive	
Case-control	Case	Count	74	6	80
		% Within case-control	92.5%	7.5%	100.0%
	Control	Count	77	1	78
		% Within case-control	98.7%	1.3%	100.0%
Total		Count	151	7	158
		% Within case-control	95.6%	4.4%	100.0%

p=0.046

significant statistical difference in aPL positivity between the groups was found (p=0.046). There are more positive cases (7.5%) than in the control group (1%) (Table 2). Both groups' relation with aPL positivity is also shown in Figure 1 and 2, i.e., for both aPL IgM and aPL IgG. The mean age of the case group and control group was 60.54±16.86 and 51.47±14.64, respectively. Due to the age difference between the groups, we took age and gender as a covariate, and a multivariate ANCOVA analysis was carried out for evaluating aPL positivity. The aPL positivity was found independent from age and gender (Table 3). Serum CRP, ferritin, PCT and plasma D-dimer, PT, INR, and aPTT levels were analyzed by routine laboratory methods in the case group, and aPL IgM/G positivity was evaluated for correlations. A Pearson correlation analysis was used to determine the correlation of aPL IgM and aPL IgG antibodies with laboratory variables in the case group. The

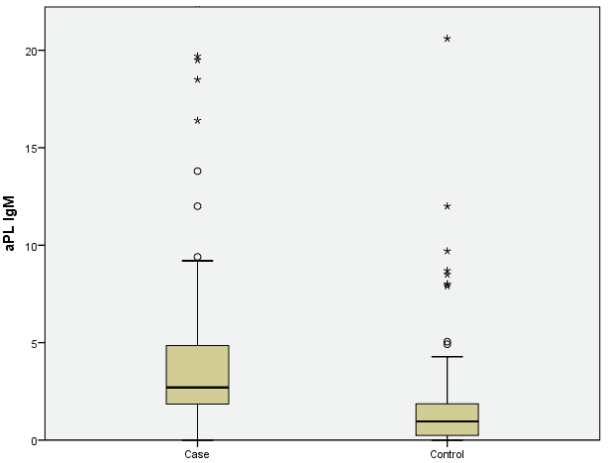

Figure 1: Statistical significance in case group (patient with COVID-19) aPL IgM positivity

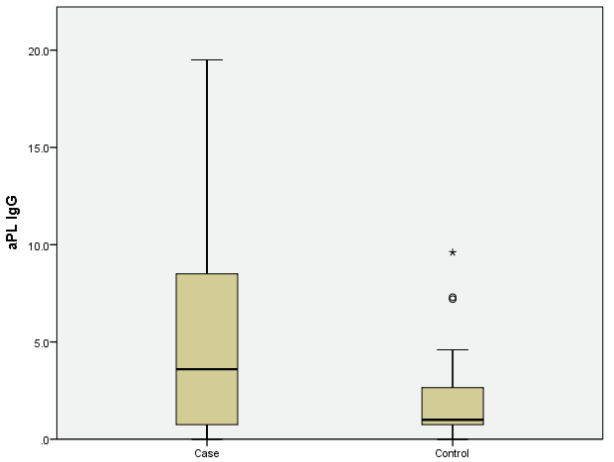

Figure 2: Statistical significance in case group (patient with COVID-19) aPL IgG positivity

to microthrombus formation, there is a tendency towards clotting disorder in these patients. However, there is not enough data on bleeding and thrombosis yet. It was observed that the D-Dimer levels of intensive care patients were significantly higher than those who were not in intensive care. Prothrombin time and D-Dimer levels stand out as markers associated with the severity of the disease (8). In our study we found increased positivity in the case group compared to the control group (7.5%) (Table 2). We show in Table 4 the case groups' abnormal coagulation tests (such as D-dimer, PT, INR, aPTT) and aPL positivity were found to be associated. Abnormal anticoagulation tests in COVID-19 patients may relate to increased risk for venous thromboembolism (6).

Our aim in this study is to show an increased aPL positivity in COVID-19 patients, and our result contributes to the explanation of the elevated risk for thromboembolism in this infection.

Table 3: Comparison of aPL positivity of the groups in terms of age and gender

Tests of between-subjects effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected model	aPL Ig M	556.421[a]	3	185.474	5.675	0.001
	aPL IgG	964.817[b]	3	321.606	7.481	0.000
Intercept	aPL Ig M	232.771	1	232.771	7.122	0.008
	aPL IgG	192.864	1	192.864	4.487	0.036
Age	aPL Ig M	123.770	1	123.770	3.787	0.053
	aPL IgG	1.369	1	1.369	0.032	0.859
Gender	aPL Ig M	20.384	1	20.384	0.624	0.431
	aPL IgG	38.419	1	38.419	0.894	0.346
Case-control	aPL Ig M	477.646	1	477.646	14.614	0.000
	aPL IgG	858.670	1	858.670	19.975	0.000
Error	aPL Ig M	5164.039	158	32.684		
	aPL IgG	6791.948	158	42.987		
Total	aPL Ig M	7866.823	162			
	aPL IgG	10652.370	162			
Corrected total	aPL Ig M	5720.460	161			
	aPL IgG	7756.765	161			

[a]: R Squared=0.097 (Adjusted R Squared=0.080), [b]: R Squared = 0.124 (Adjusted R Squared=0.108)
Multivariate ANCOVA analysis. aPL IgM: antiphospholipid immunoglobulin M antibody, aPL IgG: antiphospholipid immunoglobulin G antibody

DISCUSSION

COVID-19 is a pandemic disease and threatens the whole world. Its pathophysiology is under continuous efforts to be understood. Patients with COVID-19 suffer from mild or severe respiratory failure and multiorgan failure. Due

COVID-19 patients with pulmonary thrombosis or embolism develop acute respiratory distress (ARDS) due to decreased pulmonary oxygen (9). Recent studies show

Table 4: Correlation of aPL IgM and aPL IgG positivity with laboratory variables in case group

Correlations	aPL IgM			aPL IgG		
	Pearson correlation	Sig. (2-tailed)	n	Pearson correlation	Sig. (2-tailed)	n
Age	-0.122	0.270	83	0.043	0.698	83
CRP	-0.204	0.064	83	-0.029	0.798	83
Procalcitonin	-0.091	0.415	83	-0.101	0.363	83
Ferritin	0.139	0.211	83	-0.027	0.805	83
D-Dimer	0.071	0.526	83	0.227*	0.039	83
Thrombocytes	-0.164	0.139	83	-0.204	0.065	83
NLR	-0.110	0.324	83	0.125	0.261	83
PT	0.082	0.462	83	0.414**	0.000	83
INR	0.155	0.161	83	0.413**	0.000	83
aPTT	0.114	0.304	83	0.264*	0.016	83

Pearson correlation analysis. The values with the stars (*) next to it indicate correlation.
The values with the stars (**) next to it indicate strong correlation. Statistical significance level (alpha) was accepted as 0.05.
aPL IgM: antiphospholipid immunoglobulin M antibody, aPL IgG: antiphospholipid immunoglobulin G antibody, CRP: C-reactive protein, NLR: Neutrophils Lymphocytes ratio, PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time

that severe cases of the disease have a higher thromboembolic risk. This condition also worsens the prognosis (9). According to current post-mortem studies, COVID-19 shows inflammation causing vascular wall thickening, vascular lumen stenosis, and microthrombus formation, resulting in organ failures (10). Thrombosis can occur in both the arterial and venous systems in any tissue and organ. Various studies show that the prevalence of aPL in a young, healthy population to be between 1-5%. It is reported that the prevalence of aPL increases with age and especially in elderly patients with a chronic disease (4). Although aPL positivity increases with age, we have shown in our study that it increases regardless of age and gender (Table 3). We found increased positivity in the case group compared to the control group (7.5%). There are several prospective and retrospective studies showing the relationship between aPL and deep vein thrombosis, myocardial infarction, and stroke (5,6). However, the role of the aPL in the pathogenesis of thrombosis is not fully understood. In vitro studies try to explain the aPL-thrombosis relationship, which can be summarized as follows:

1) aPL activation of endothelial cell: aPL increases the release of pro-adhesive and pro-inflammatory substances from the endothelium, induces tissue factor release and apoptosis, increases endothelin release, and increases the procoagulant effect of annexin V.
2) Interaction with the natural anticoagulant system: aPL uses proteins C and S as cofactors, causes acquired APC resistance, disrupts annexin V framework, inhibits antithrombin.
3) Activation of platelets and induce aggregation.
4) Interaction of aPL with eicosanoid metabolism: The production of prostacyclin from the endothelium is decreased, thromboxane A2 production from thrombocytes is increased; In this way, the thromboxane / prostacyclin ratio has been shown to increase significantly (11,12).

There are publications indicating that aPL impairs fibrinolytic mechanisms. Some environmental factors, infections, and the use of chlorpromazine, procainamide, and diphenylhydantoin affect antibody positivity (13, 14). Some researchers have been suggesting that aPL-positive people should take prophylaxis in risky situations such as operations, puerperal period, intensive care, etc., but there is no controlled study on this subject. aPL positivity may be temporary, and the patient may recover without need for anticoagulant treatment. Permanent aPL positivity may cause antiphospholipid syndrome (14,15). Transient aPLs may occur when using procainamide, chlorpromazine, and diphenylhydantoin. Permanent aPL positivity may happen with chronic infections, such as HCV and HIV infections (14-16).

There is no clear understanding yet of the blood clot formation in COVID-19 patients. Increased cytokines levels cause systemic inflammation, and as a result, clot formation and multiple organ failure may occur (6, 17). We believe that the duration of this disease that has antibody positivity should be followed for at least 6 months or a year. So far, the direct association of aPL positivity in this disease remains a topic for further investigation because the stud-

ies show opposing results. Supporting the association, the study conducted by Virginie Siguret et al. explains the increase of clots and connected aPL positivity (18).

Studies that do not support the direct relation show, for example, that aPL positivity may be observed in acute phase of the disease, but without clear understanding of the relationship, and that the aPL might not be involved in the pathogenesis of venous thromboembolism in patients suffering from pneumonia (19, 20).

CONCLUSION

Clinical laboratory tests play a crucial role in the diagnosis, prognosis, and follow-up treatment of COVID-19 patients. Conducting studies with wider national and international participation will result in a better understanding of the disease and in the decision-making process concerning treatment. We believe that our study sheds light on previous studies and indicates a necessity to further examine the role of aPL positivity.

Ethics Committee Approval: This study was approved by the ethics committee of Health Science University, Bakirkoy Dr. Sadi Konuk Research and Training Hospital (Date: 18.05.2020, No: 202-11-25).

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