THESES (Ph.D.)

ANTIPHOSPHOLIPID ANTIBODIES IN CLINICAL MANIFESTATIONS OF ATHEROTHROMBOSIS

Katalin Veres, M.D.

3rd Department of Medicine, Institute for Internal Medicine,
Medical and Health Science Center, University of Debrecen

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INTRODUCTION

Antiphospholipid syndrome (APS) is mediated by a heterogeneous group of antibodies [lupus anticoagulant (LA) and antibodies to cardiolipin (aCL)]. The interaction of antiphospholipid antibodies and surface membranes (platelets, monocytes, endothelial cells) has an effect on the clotting cascade and it generates a thrombotic status. Antiphosholipid antibodies bind to complexes of phospholipids and plasma proteins, such as β2-glycoprotein I (βGPI), prothrombin and annexin V. Expression of β2GPI is detectable on endothelial and throphoblast cells, which tissues are affected in clinical manifestations of APS. Binding of antiphospholipid antibodies to endothelial cells results in developing a procoagulant and proinflammatoric fenotype with expression of adhesion molecules, production of prostaglandins and proinflammatoric cytokines and chemokines (IL-1, IL-6, IL-8, MCP-1). Antibodies to phospholipids influence expression of tissue factor, metabolism of eicosanoids, activation of protein C/S, binding of annexin V, synthesis of pre-pro-endothelin and also apoptosis. These factors result hypercoagulation and proinflammatoric state. β2GPI as autoantigen plays role in immuno-inflammatoric processes of atherosclerotic plaques and has a pathological role in atherosclerosis.

Other autoantigen in the atherosclerotic plaque is oxidized low density lipoprotein (oxLDL). It has become clear recently that there is a connection between mechanisms mediated by β2GPI and oxLDL. Namely, oxLDL supports conformational changes of β2GPI and helps binding of antiphospholipid antibodies. β2GPI influences the intake of oxLDL by macrophages. The complex of oxLDL and β2GPI is located next to immunoreactive lymphocytes in atherosclerotic plaques. Mechanisms mediated by IgG type antibodies to autoantigen complex of oxLDL/β2GPI show strong correlation with arterial thromboses. Internalisation of oxLDL/β2GPI complex via phagocytosis in macrophages is mediated by IgG type aβ2GPI antibodies.

Elevated C-reactive protein level is an independent cardiovascular risk factor (CRP). CRP in not only a biomarker but plays role as active mediator in the pathogenesis of atherosclerosis and also has a prognostic value.

APS is an autoimmune disease characterized by arterial and venous thromboses at various anatomic sites in the presence of antibodies to phospholipids. APS is the most frequent acquaired thrombophilia and frequent cause of obstetric complications. In primary antiphospholipid syndrome, there is no detectable underlying disease, while secondary antiphospholipid syndrome is usually associated with other clinical syndromes including systemic autoimmune diseases, infections, or malignancies.

Bick and Baker recommended a helpful classification of thrombotic events in 1999. This classification differentiates 6 types of thromboses by localisation. The diagnosis of APS is based on clinical and laboratory criteria by Wilson and coworkers, which was published in 1999.

Catastrophic Antiphospholipid Syndrome (CAPS) is a life-threatening variant of APS, which involves 3 or more organs in the same time or in a few weeks. Small vessel thromboses are detectable with histopathologic methods, medium-to-large blood vessel thromboses are rare. Like CAPS, different fatal events such as massive pulmonary embolia, myocardial infarction, stroke, critical limb ischemia, TTP/HUS, DIC, ARDS and HELLP syndrome can occur in APS.

AIMS

Our first aim was to perform a retrospective study on primary antiphospholipid syndrome patients whose diagnosis was made between 1986-1999. Then we started prospective clinical studies to investigated the prevalence of antiphospholipid antibodies in clinical manifestatios of atherothrombosis such as acute coronary syndrome, stable coronary artery disease and peripheral artery diseases. I had a chance to participate in the treatment of patients suffering from life-threatening forms of APS. I present a case of a young pregnant woman with the association of APS and HELLP syndrome causing severe clinical state.

1. Antiphospholipid antibodies were detected in 1519 patients between 1986-1999 at the 3rd Department of Medicine, Institute for Internal Medicine, Medical and Health Science Center, University of Debrecen. We determined the rate of antiphospholipid syndrome and the rate of primary and secundary APS in our former work. Our aim was to perform a retrospective study of 138 primary antiphospholipid syndrome patients using computer database, in which we examined developement of systemic autoimmune diseases. We classified primary APS patients by thrombotic events at the time of the diagnosis. We raised the question whether the type of antiphospholipid antibodies detected at the time of the diagnosis of APS has an influence on transition of primary APS to the secondary type. We determined the recurrence of thrombotic events and the localization of thromboses according to the type of antithrombotic therapy.

2. We started prospective study to determine the prevalence of lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein I antibodies in acute coronary syndrome. 111 acute coronary syndrome patients treated in Intensive Care Unit of 3rd Department of Internal Medicine was involved in the study. We investigeted cardiovascular risk factors based on patients' medical history, clinical and laboratory results (dyslipidemia, hypercholesterolemia, obesity, smoking, hypertension, diabetes mellitus) and previous cardial, cerebral and thrombotic events. We deteremined the prevalence and type of antiphospholipid antibodies, and their correlation with traditional cardiovascular risk factors, as well as the outcome of the cardiac event.

3. Given the connection between β2-glycoprotein I and oxidized LDL and pathologic mechanisms against these autoantigens, we also investigated the prevalence of antibodies to oxLDL in acute coronary syndrome and stable coronary artery disease. C-reactive protein levels was also measured, and correlation

between anti-ovLDL and CRP was examined.

4. We determined the prevalence of lupus anticoagulant, antibodies against cardiolipin and β2-glycoprotein I in 139 patients with peripheral arterial disease of the lower extremity. Besides conventional cardiovascular risk factors (smoking, hypercholesterolemia, hypertriglyceridemia, elevated LDL-cholesterol, hypertension, diabetes mellitus) we estimated cardial and cerebrovascular manifestations of atherothrombosis in these patients looking for correlation between the presence of antiphospholipid antibodies and clinical symptoms. We tried to answer to the question that the presence of antiphospholipid antibodies was independent vascular risk factor or not.

5. I report the case of a 26-year old pregnant woman with primary antiphospholipid syndrome associated with HELLP syndrome who was treated in our Intensive Care Unit. There were symptoms and signs related to antiphospholipid syndrome in the patient's history (spontaneous abortion, fals positive VDRL-reaction), and HELLP syndrome developed during her second pregnancy. She developed two other symptoms of APS during preeclampsia: deep venous thrombosis of left lower extremity and ischemic nervus opticus laesion. Histologic examination of placenta detected placentar infarctions showing pathologic role of antiphospholipid antibodies. Laboratory findings included antibodies to cardiolipin and β2-glycoprotein I. I present accurate medical history of the patient, the results of examinations, and the details of a combinated treatment protocol leading full recovery.

PATIENTS AND METHODS

Criteria of antiphospholipid syndrome

Clinical criteria

1. Vascular thrombosis

One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or doppler studies or histopathology, with the expection of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity

A. One or more unexplained deaths of a morphologically normal fetus a tor beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct exanimation of the fetus, or

B. One or more premature births of a morphologically normal neonate a tor before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency, or

C. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. Anticardiolipin antibody of IgG and/or IgM isotype in blood, present in medium or high titer, on 2 or more occasions, at least 6 weeks apart, measured by a standardized enzyme-linked immunosorbent assay for β2-glycoprotein I-dependent anticardiolipin antibodies.

2. Lupus anticoagulant present in plasma, on 2 or more occasions, at least 6 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis.

Detection of antibodies to phospholipids including antibodies to β2-glycoprotein I was done with ELISA technique in Regional Immunologic Laboratory.

Classification of thrombotic manifestations

Thrombotic manifestations were classified by recommendation of Bick and Baker (superficial thrombophlebitis was classified as type I). We investigated only fetal losses (type V), other pregnancy morbidity was not considered.

I. type:	Deep venous thrombosis with or without pulmonary embolus
II. type:	Coronary artery thrombosis
	Peripheral artery thrombosis
	Aortic thrombosis
	Carotid artery thrombosis
III. type:	Retinal artery thrombosis
	Retinal vein thrombosis
	Cerebrovascular thrombosis
	Transient ischemic attacks
IV. type:	Mixtures of types I, II, III
V. type:	Placental vascular thrombosis
	Fetal wastage common in first trimester
	Fetal wastage can occur in 2nd and 3rd trimester
	Maternal thrombocytopenia
VI. type:	Antiphospholipid antibodies
	No apparent clinical manifestations

1. Follow-up studies in primary antiphospholipid syndrome

IgG, IgM and IgG/IgM type antiphospholipid antibodies were detected in 1519 patients between 1986-1999 in 3rd Department of Medicine, Institute for Internal Medicine, Medical and Health Science Center, University of Debrecen. Two hundred and eighteen patients were identified with primary antiphospholipid syndrome based on international criteria. We had the opportunity to do a retrospective study of 138 of them using computer database. We examined the developement of polysystemic autoimmune diseases, the occurrence of new symptoms of APS, and whether primary APS developed into secondary APS in the study period. We determined the number of recurrent thrombotic events and the location of thromboses according to the actual antithrombotic therapy.

Thrombosis must be confirmed by imaging or doppler studies or histopathology. Cerebral thrombotic events were diagnosed by positive CT or MRI results. In case of myocardial infarction or instable angina coronary thrombosis was accepted. Concerning pregnancy morbidity we had information about recurrent fetal losses, accurate investigation of pregnancy morbidity was not among our aims.

Data were analyzed with chi^2 and Fisher's exact test.

2. Prospective studies in acute coronary syndrome

Prospective study to determine the prevalence of lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein I antibodies in acute coronary syndrome. 111 acute coronary syndrome patients treated in Intensive Care Unit of 3rd Department of Internal Medicine were involved in the study (66 men and 45 women, age: 31-85). The patients' diagnoses were: 38 unstable angina, 26 acute myocardial infarction without ST-segment elevation and 47 acute myocardial infarction with ST-segment elevation.

Myocardial necrosis was confirmed by positive CK-MB or troponin T (Cardiac Reader) test. Blood samples were taken before therapy.

We surveyed cardiovascular risk factors based on patients' medical history, clinical and laboratory results (dyslipidemia, hypercholesterolemia, obesity, smoking, hypertension, diabetes mellitus) and previous cardial, cerebral and thrombotic events.

Measurement of anticardiolipin antibodies type IgG and IgM was done using ELISA technique by international recommendation (reference range: < 22 GPLU/ml and < 16 MPLU/ml, respectively). Detection of antibodies to β2GPI (IgG, IgA and IgM type) was also done by ELISA method, as published previously (referential range: IgG: < 14,6 SGU/ml, IgA: < 43 U/ml, IgM: < 34 U/ml). Tests were performed in the Clinical Immunopathology Laboratory of the 3rd Department of Medicine.

Detection of lupus anticoagulant based on international criteria was made in Institute of Clinical Biochemistry and Molecular Pathology.

We compared these data with data from 40 patients with stable coronary artery disease. Stable coronary artery patients' mean age was 65,6 years (31-85 years), gender: 26 men and 14 women. The diagnosis of stable coronary artery disease was defined according to: myocardial infarction in medical history (28 patients), positive coronarography (4 patients) and positive stress test (8 patients).

50 healthy blood donors served as controls. There were no cardial or cerebral thrombotic events, thromboses in their medical history.

Qualitative analysis was made with Fisher's exact test, quantitative analysis was done with Mann-Whitney U test. Correlation between antibody levels was analysed with Spearman's non-parametric test. Correlation was significant in case of $p < 0,05$.

3. Antibodies to oxidized LDL and C-reactive protein in acute coronary syndrome and stable coronary artery disease

33 patients suffering from acute coronary syndrome were involved in this study. Mean age of patients: 74,46 years (52-87 years), gender: 17 men and 16 women. The patients' diagnoses were: 7

unstable angina, 8 myocardial infarction without ST-segment elevation and 18 myocardial infarction with ST-segment elevation.

Results were correlated with data obtained from 62 patients with stable coronary artery disease. Mean age of this group: 66,88 years (31-84 years), gender: 43 men and 19 women. The diagnosis of stable coronary artery disease was defined: myocardial infarction in medical history (27 patients), positive coronarography (3 patients) and positive stress test (32 patients).

Control group was the same 50 healthy blood donors mentioned previously.

Detection of antibodies and measurement of CRP was done in the Clinical Immunopathology Laboratory of the 3rd Department of Medicine. Antibodies to oxLDL and β2GPI were measured with ELISA, while CRP detection was done with turbidimetry.

We used Statistica for Windows (Version 6) program. In case of normal distribution T-test and Pearson correlation, in case of unnormal distrubution Mann-Withney test and Spearman correlation were used. If correlation was significant regression coefficient (R) was marked.

4. Antiphospholipid antibodies in peripheral artery disease

We determined the prevalence of antiphospholipid antibodies in 139 patients with peripheral artery disease of the lower extremity treated in 3rd Department of Medicine, Institute for Internal Medicine or in Out-patient Clinic of Angiology. Confirmation with antiphospholipid antibodies was investigated by the criteria of Wilson and coworkers.

Besides conventional cardiovascular risk factors, lupus anticoagulant, anticardiolipin antibodies and antibodies against β2-glycoprotein I were studied. We tried to find a connection between antiphospholipid antibodies and clinical implications of atherothrombosis – coronary artery disease and cerebrovascular thrombotic episods.

50 healthy blood donors served as control group.

Confirmation of peripheral artery disease was done by color duplex ultrasonography and/or angiography.

The diagnosis of coronary artery disease was defined based on myocardial infarction, unstable angina or stable angina in medical history, positive coronarography and positive stress test.

Previous cerebrovascular atherothrombosis was diagnosed in case of positive carotis ultrasound and/or positive angiography and/or positive CT or MRI or former TIA and ischemic stroke.

The following traditional risk factors were studied: smoking, hypercholesterolemia (cholesterol > 5,2 mmol/l), hypertriglyceridemia (triglycerid > 1,7 mmol/l), elevated LDL-cholesterol (LDL-chol. > 3,4 mmol/l), hypertension, diabetes mellitus.

Data were analyzed with chi^2 and Fisher's exact test.

5. HELLP syndrome and primary antiphospholipid syndrome - case report

I report the case of a 26-year old pregnant woman with primary antiphospholipid syndrome associated with preeclampsia and HELLP syndrome, who was treated in our Intensive Care Unit during her second pregnancy. There are only a few publications about this association in international computer database. To our best knowledge this is the first Hungarian report.

NEW RESULTS

1. We had the opportunity to review the case of 138 primary APS patients. The diagnosis remained primary antiphospholipid syndrome after a mean 5,18 years of follow-up in 63.8 % of them (88 patients). In 25 patients (18.1%) primary antiphospholipid syndrome associated with various features of other connective tissue diseases. The clinical picture was non-differentiated pre-phase of systemic autoimmune diseases (Non Differentiated Collagenosis). However, in 25 patients (18.1%), definitive systemic autoimmune disease developed during the mean of 9.75 years of the follow-up. Our findings support the idea that we can expect the development of secondary APS in patients with arterial or cerebrovascular thrombosis as the first thrombotic event, moreover in those with IgG type antibodies to cardiolipin at the beginning. Recurrent thrombotic events were registered in 26.8 % of the patients (37 events).

2. We investigated the presence of antiphospholipid antibodies and lupus anticoagulant in 111 acute coronary syndrome patients treated at our Intensive Care Unit. No lupus anticoagulant was present in the patients. 6 patients (5.4 %) had antibodies to cardiolipin and 16 patients (14.4 %) had antibodies to β2-glycoprotein I (any isotype). Among them three of them had both antibodies. The frequency of antibodies to β2-glycoprotein I was significantly higher (14.4 %) in patients with acute coronary syndrome than in healthy individuals (2.0 %) ($p < 0,02$). The presence of this thrombogenic factor emphasizes the importance of secondary antithrombotic prevention in acute coronary syndrome, because previous ischaemic stroke was significantly more frequent in these patients' medical history, futhermore the risk of venous thromboembolism is higher in these patients.

3. Detection of antibodies to oxidized LDL and β2-glycoprotein I and C-reactive protein in the serum of patients suffering from acute coronary syndrome and patients with stable coronary artery led to the following clonclusions: the level of antibodies to β2-glycoprotein I was higher in the acute coronary syndrome group compared to the stable coronary arterial disease. The levels of antibodies to oxidized LDL were significantly higher in both groups of patients, and there was no significant difference between the two groups. In contrast, C-reactive protein level in patients with acute coronary syndrome was significantly higher than in those with stable coronary artery disease. Our findings support the idea that the presence of antibodies to oxidized LDL correlates with coronary artery disease, while C-reactive protein and anti-β2-glycoprotein I antibodies are related to the acute clinical manifestations of atherothrombosis. The presence of antibodies to β2GPI correlates with higher mortality rate.

4. Besides the conventional cardiovascular risk factors, we determined the prevalence of antiphospholipid antibodies in 139 patients with peripheral artery disease of the lower extremity. One patient was positive for lupus anticoagulant, while 30 patients had anticardiolipin antibodies and antibodies against β2-glycoprotein I could be detected in 41 cases. Occurence of previous cerebrovascular ischemic disease could be detected significantly more frequently when antibodies against cardiolipin and β2-glycoprotein I were present. Interestingly, anti-β2-glycoprotein I antibodies could be detected significantly more often in smokers and patients with hypertension, so the presence of this antibody can not be defined as an independent risk factor. In contrast, antibodies to cardiolipin were not more frequent in smokers and patient with hypertension, so the presence of anticardiolipin antibodies can be defined as an independent risk factor in the presence of cerebrovascular ischemic disease in this group. Our data suggest that the presence of antiphospholipid antibodies in patients with peripheral artery disease is of great importance, in order to choose the effective antithrombotic therapy, because these patients have high risk to develop venous thrombosis.

5. I report the case of a pregnant woman with antiphospholipid syndrome associated with HELLP syndrome (*H*emolysis, *E*levated *L*iver enzymes and *L*ow *P*latelet count) during her second pregnancy. She was treated in our Intensive Care Unit and we used the treatment protocol for Catastrophic Antiphospholipid Syndrome. She responded to the therapy well and eventually recovered completely. To our knowledge, this is the first Hungarian report about this rare and unique association and its successful treatment.

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