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Full Length Article

Recurrent thrombosis in antiphospholipid syndrome may be associated with cardiovascular risk factors and inflammatory response

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ABSTRACT

Introduction: Antiphospholipid syndrome (APS) is a pro-thrombotic autoimmune disease that affects different vascular beds, with potential risk for recurrence. Systemic lupus erythematosus (SLE), specific autoantibodies profile and atherogenic disorders have been described as risk factors for the occurrence of first thrombosis in patients with antiphospholipid antibodies (aPL). However, factors associated with recurrent thrombosis have not yet been completely elucidated in APS. The aim of this study was to evaluate the association of recurrent thrombosis with markers of inflammation, autoimmunity and the presence of atherogenic disorders in APS patients.
Materials and methods: We performed a retrospective evaluation of a cohort of APS patients in order to determine if markers of inflammation, autoimmunity and cardiovascular risk were associated with recurrence of thrombosis.
Results: One hundred fifteen patients with APS were included, 60% had primary APS. History of recurrent thrombosis was positive in 38.3% of patients, and 40% of them were on oral anticoagulants at the time of recurrence. Independent risk factors associated with recurrent thrombosis were arterial hypertension (OR = 3.7, 95% CI = 1.6–8.5, P = 0.002) and monocytosis above 500 u/mm^3 (OR = 2.4, 95% CI = 1.2–5.3, P = 0.02). These factors were particularly relevant in cases of venous index event.
Conclusion: The results suggest that arterial hypertension and monocyte counts may be independent factors for thrombosis recurrence in APS. Given the morbidity of recurrent cases, the results may support the evaluation of therapeutic measures to a rigid control of blood pressures and modulation of inflammatory response in APS, as additional prophylaxis against the recurrence of vascular events.

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1. Introduction

Antiphospholipid syndrome (APS) is a pro-thrombotic autoimmune condition that affects different vascular beds with potential risk for thrombosis recurrence [1]. The described incidence of recurrent thrombosis ranges from 5 to 16% [2–4]. The discontinuation of antithrombotic treatment is the leading cause of recurrences [5–8]. However, in more than 5% of cases, antithrombotic treatment may not be enough to prevent recurrent thrombosis [5,9]; and significant morbidity and mortality have been detected [2,10]. In addition to antitrombotic treatment, further factors may therefore play a role on thrombosis recurrence in APS.

Antiphospholipid antibodies (aPL) may activate endothelial cells, monocytes and platelets inducing both procoagulant and inflammatory states that enhance the individual risk for thrombosis [11]. Indeed, the profile of aPL antibodies and the diagnosis of systemic lupus erythematosus (SLE) are markers of APS severity [4,6,12,13]. However, the presence of autoantibodies and inflammation may not be enough to trigger thrombosis, and additional mechanisms may be necessary [11]. Clinical studies have demonstrated that the risk for thrombosis in patients with positive aPL is increased in the presence of additional cardiovascular risk factors [14], such as hypertension [12,15], dyslipidemia [12,15] and smoking [16]. Whether these atherogenic disorders could also play a role on thrombosis recurrence in patients with APS has not, however, been well established yet.

Therefore, we hypothesized that the described risk factors for first thrombosis could possibly contribute for thrombosis recurrence in

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APS. In this context, the aim of this study was to evaluate the association of recurrent thrombosis with biological markers of inflammation, autoimmunity and the presence of atherogenic disorders in APS patients.

2. Material and methods

2.1. Study design and patients selection

This is a retrospective cohort study on the risk of thrombosis recurrence in APS patients. The study cohort included patients who had a clinical diagnosis of APS and were treated at the Hematology and Hemostasis Center at the University of Campinas, Brazil. The cohort had been followed-up since APS was diagnosed. Patients were evaluated every month for oral anticoagulation control, clinical features were recorded every 6 months and routine laboratory tests of peripheral blood smear, blood glucose, lipids disorders, renal function and autoimmune disease were performed at least once a year. In order to prevent thrombosis recurrence, after the diagnosis of thrombotic APS was confirmed, patients received prolonged anticoagulant treatment; patients with arterial thrombosis also received antiplatelets.

Sydney classification criteria were used for APS diagnosis [17]. APS was diagnosed in patients with persistent positive aPL antibody plus a history of thrombosis or APS-associated pregnancy complications. Persistent positive aPL were defined as persistent positive lupus anticoagulant (LA); persistent positive IgG or IgM anticardiolipin (aCL) at moderate to high titles (>40 GPL or MPL) or persistent positive (>the 99th percentile) IgG/IgM anti-beta2 glycoprotein 1 (aβ2GP1), at two distinct times, at least 12 weeks apart. Two tests were performed for LA identification: partial thromboplastin activated time and dilute Russell's viper venom time; LA was considered positive if at least one of the two tests was positive. In house ELISA assays were performed for the detection of aCL and aβ2GP1, as previously described [18]. All aPL assays were performed in the Laboratory of Hemostasis at the Hematology and Hemotherapy Center at the University of Campinas, Brazil. The laboratory participates in UK National External Quality Assessment Scheme for Blood Coagulation (UKNEQAS), an international external quality assessment (EQA) program.

Thrombotic events were characterized as venous or arterial, according to the vascular bed where thrombosis occurred. Venous thrombosis events were further divided into venous thromboembolism and thrombosis of unusual sites. Arterial thrombosis events were divided into stroke and non- stroke ischemic events, such as myocardial infarction, peripheral arterial thrombosis or ischemia of small extremities. Thrombotic events were confirmed by image exams, such as ultrasound (US), computerized tomography (CT), magnetic resonance (MR), ventilation/perfusion lung scan, or biopsies, according to the site of thrombosis.

In cases of clinical suspicions of recurrent venous thrombosis, a new US was performed and the results were compared with those of the last available examination. Recurrent venous thrombosis was diagnosed in the case that a previously fully compressible segment (contralateral or ipsilateral) was no longer compressible or in the case that an increase of the residual thrombus during compression was detected. In cases of suspicion of a new arterial thrombosis, symptoms of ischemia and new images exams (CT or MR) were performed to confirm the diagnosis. Diagnosis of myocardial infarction depended on the alterations of electrocardiogram and cardiac enzymes.

Patients were enrolled for the study between November 2013 and December 2014. The inclusion criteria comprised diagnosis of APS and history of at least one thrombotic episode. Patients who did not fulfill the diagnostic criteria for APS and patients without previous thrombosis were excluded. The diagnosis of SLE was performed according to established criteria [19,20].

One hundred and twenty one patients diagnosed with APS were attended at the outpatient unit of the Hematology and Hemostasis Center at the University of Campinas during the enrollment period. Excluded patients had APS with only obstetric complications (2), positive aPL without APS (2) and lack of laboratory criteria for the APS diagnosis (2). One hundred fifteen patients were included in the study.

The study was conducted in compliance with the Helsinki Declaration. The local Ethical Committee on Human Research approved this study and written informed consent was obtained from patients or their attending relatives.

2.2. Patients' clinical evaluation

Following the enrollment for the study, patients' clinical features were retrospectively collected from medical charts and interviews. The comorbidities related to the risk of cardiovascular disease evaluated were: obesity, hypertension, dyslipidemia, diabetes and chronic renal disease. Obesity was defined as body mass index above 30 kg/m^2; arterial hypertension was defined as persistent systolic blood pressure above 130 mm Hg, persistent diastolic blood pressure above 90 mm Hg, or use of antihypertensive drugs. Dyslipidemia was defined as high levels of low density cholesterol (LDL ≥ 160 mg/dL or 4.1 mmol/L), high levels of triglycerides (TG ≥ 150 mg/dL or 1.7 mmol/L), or low levels of high density cholesterol (HDL < 40 mg/dL or 1.0 mmol/L for men or HDL < 50 mg/dL or 1.3 mmol/L for women), or use of statins. Diabetes and chronic renal disease were diagnosed according to established criteria [21,22]. To evaluate whether the anticoagulation control was adequate, time within therapeutic range (TTR) of all patients was calculated according to previous studies [23].

Data regarding laboratory testing, such as cholesterol and triglycerides, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody by fluorescence (ANA), anti-DNA antibody (aDNA), complement components C3 and C4, creatinine, urea and proteinuria, were collected retrospectively and recorded in structured study form. Laboratory exams were performed in the Laboratory of Clinical Pathology of the Clinical Hospital at the University of Campinas. Blood counts were performed using ADVIA® Hematology System (Siemen Healthcare Diagnostics Inc., USA) and confirmed manually, biochemistry exams were performed using COBAS® Modular Analyzer (Roche Diagnostics, Switzerland), serum high sensitive CRP, C3 and C4 levels were measured with a nephelometric method, with a BNProSpec Analyzer (Siemen Healthcare Diagnostics Inc., USA), ANA was evaluated using indirect immunofluorescence on HEp-2 cells (Kallestad™, Biorad, USA), aDNA was evaluated using indirect immunofluorescence (Virgo®, Hemagen, USA). ESR was performed by pipetting anticoagulated whole blood in a narrow vertical tube and then waiting for 1 h for the erythrocytes to settle down, the height of supernatant clear plasma was measured in millimeters (mm).

Current clinical data were collected from structured questionnaires by the study personnel during outpatients visits and historical clinical data were obtained from electronic or paper medical charts. Image exams confirming the thrombotic episode and laboratory exams were also obtained from medical charts. All patients' clinical and laboratory data were reviewed by two hematologists.

As the purpose of the study was to evaluate factors associated with thrombosis recurrence, for patients with multiple thrombosis we considered the clinical data and laboratory tests recorded during the year of the last recurrence. Also, TTR was calculated using INR values from at least 3 months before the recurrence. For patients with single thrombosis, we considered clinical and laboratory data at inclusion and TTR from the total follow-up period.

2.3. Statistical analysis

Categorical data are expressed as absolute number and percentage (%), continuous data are expressed as median and interquartile (IQ). Categorical variables were compared using Chi-square or Fisher exact test. To compare continuous variables between two groups Mann–Whitney rank test was performed. Logistic regression and ROC curve were performed to identify risk factors for thrombosis recurrence and

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