Lipoprotein(a) in primary antiphospholipid syndrome

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ABSTRACT

Objective: To evaluate levels of lipoprotein(a) in patients with primary antiphospholipid syndrome (PAPS) and its possible associations with clinical and laboratory features. **Methods:** Transversal study with 46 (93.5% female) PAPS patients (Sapporo criteria). Demographic, clinical, drugs use, and antiphospholipid antibodies data were evaluated, as well as measurements of lipoprotein(a) serum fasting levels. **Results:** Elevated levels of lipoprotein(a) (> 30 mg/dL) were observed in 43.5% of PAPS patients, with a mean of 42 ± 43.5 mg/dL. A comparison between patients with lipoprotein(a) higher than 30 mg/dL and those with ≤ 30 mg/dL did not show any differences regarding demographics (age, gender, white race, weight, height, body mass index), diseases features (arterial, venous or obstetric events, thrombocytopenia), cardiovascular manifestations (acute myocardial infarct, angina, stroke), comorbidities, life style (physical activity, smoking), drugs use (corticosteroids, statins, chloroquine), as well as the frequency of positivity of antiphospholipid antibodies. **Conclusion:** PAPS patients had a high frequency of increased levels of lipoprotein(a), however there was no association of this abnormality with the clinical and laboratorial features herein studied.

Keywords: lipoprotein(a), Lp(a), antiphospholipid syndrome, antiphospholipid antibodies.

INTRODUCTION

Antiphospholipid syndrome (APS) is one acquired autoimmune thrombophilia characterized by the presence of vascular thrombosis and/or obstetric events, accompanied or not by thrombocytopenia in the effectiveness of moderate and persistent levels of antiphospholipid antibodies.[1]

Recently, this syndrome has been associated to the presence of early atherosclerosis in coronary events.[2] The traditional risk factors for cerebrovascular disease have been demonstrated in APS; however the role of other nontraditional risk factors is less studied. Lipoprotein(a) [Lp(a)], one genetically determined circulating lipid particle, has been associated to atherosclerosis, acute myocardial infarction and thrombosis when it is in elevated levels.[3] Few studies have evaluated the role of this lipoprotein in patients with APS and in most of them also included patients with systemic lupus erythematosus.[5-7]

Due to the fact that patients with APS suffer an increased risk of atherosclerotic disease and thrombosis and the studies in primary APS being scarce, the objective of the present study was to investigate the levels of lipoprotein(a) in a population of primary APS and evaluate its possible association with clinical and laboratorial findings of the disease.

PATIENTS AND METHODS

In this study, 46 patients, of both genders, above 18 years old, with diagnosis of primary APS according to the Sapporo criteria, were included.[8] They were followed-up in the APS Clinic of the Rheumatology Service of the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HC-FMUSP).

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In the evaluation appointment for this work, demographic data were collected, the medical records were reviewed (characterizing primary APS and previous events of venous and/or gestational arterial thrombosis, presence of thrombocytopenia, duration of disease), presence of cardiovascular and cerebrovascular events (angina, acute myocardial infarction and stroke), evaluation of the presence of comorbidities, medicines being used and the collection of venous blood sample.

The exclusion criteria were the conditions that elevate lipoprotein(a) levels, such as chronic renal insufficiency, nefrotic syndrome, systemic lupus erythematosus, pulmonary hypertension and obliterative thromboangiitis.

Dosage of lipoprotein (a): One venous blood sample was collected after 12 hours fasting for measurement of lipoprotein(a). Lp(a) was measured by immunoturbidimetry, with a commercial kit (DiaSorin, Sallugia, Italy). The calibration of the apparatus was performed with calibrators supplied by the kit. Altered values were those higher than 30 mg/dL.

Statistical analysis: The results were presented in means and standard deviations. The statistical analysis was performed using GraphPad InStat 2.00. A Student's t-test was used for means comparison and Fisher's exact test for the frequencies. The results were considered as having a significant value when $P < 0.05$.

RESULTS

The mean age of all 46 patients with APS was 38.9 ± 11.5 years – 93.5% of the female gender and 78.6% of white color. The mean duration of the disease was 68.1 ± 56.4 months. Regarding vascular events, 68.9% had arterial thrombosis, 39.1% venous thrombosis, 26% obstetric events, and 21.7% presented thrombocytopenia.

The levels of lipoprotein(a) had a mean of 42 ± 43.5 mg/dL, with median of 27.5 mg/dL, ranging from 6.9 to 187 mg/dL. Considering those patients with Lp(a) above 30 mg/dL, 20 (43.5%) patients were in this group.

Comparing the group with levels of Lp(a) higher than 30 mg/dL and those equal or below this value, significant differences were not observed in relation to age (41 ± 11 *versus* 37 ± 12 year, P = 0.18), white color frequency (100 *versus* 88.5%, P = 0.25), weight (73.8 ± 20.5 *versus* 74.6 ± 21.7 kg, P = 0.90), height (158.5 ± 7.41 *versus* 160.4 ± 6.4 cm, P = 0.38), body mass index (29.2 ± 7.32 *versus* 28.9 ± 7.85 kg/m^2, P = 0.89), as well as regarding the time of the disease (64.4 ± 52.2 *versus* 71 ± 60.3 months, P = 0.70) (Table 1).

In relation to the clinical manifestations of the disease, the patients with elevated Lp(a) did not differ significantly from those with normal levels regarding the frequencies of: venous, arterial or obstetric events, thrombocytopenia, stroke, Sneddon's syndrome, limb ischemia, acute myocardial infarction, angina, deep venous thrombosis, pulmonary thromboembolism, systemic arterial hypertension and osteonecrosis (P = NS – non-significant). Lifestyle also did not differ in both groups in relation to the physical activity frequency, preceding and current smoking (P = NS) (Table 2).

Both groups of patients were similar regarding the use of the following medications: corticoids (preceding and current use), cloroquin, warfarin, statins and acid acetylsalicylic (P = NS) (Table 3).

The frequencies of antiphospholipid antibodies in both groups were comparable in relation to the mean of anticardiolipin IgG (33.9 ± 45.8 *versus* 38.9 ± 49.4 GPL, P = 0.53) and anticardiolipin IgM (25.7 ± 38.5 *versus* 31.7 ± 41.1 MPL, P = 0.64). By analyzing the frequency of positivity of lupus anticoagulant, anticardiolipin IgG, anticardiolipin IgM, presence of at least one of these last antibodies (IgG or IgM) and the presence of at least anticardiolipin IgG or IgM or lupus anticoagulant, there was not a significant difference between the groups (P = NS) as well (Table 4).

DISCUSSION

The present study demonstrated an elevated frequency of the levels of lipoprotein(a) in patients with primary antiphospholipid syndrome.

Table 1
Comparison between the demographic, anthropometric and duration of disease data in patients with primary antiphospholipid syndrome (PAPS) with higher Lp(a) and those equal or lower than 30 mg/dL

Data	PAPS Lp(a) > 30 mg/dL N = 20	PAPS Lp(a) ≤ 30 mg/dL N = 26	P
Age (years)	41 ± 11	37 ± 12	0.18
Female gender, n(%)	20 (100)	23 (88.5)	0.25
White color, n(%)	15	21	0.73
Weight (kg)	73.8 ± 20.5	74.6 ± 21.7	0.90
Height (cm)	158.5 ± 7.41	160.4 ± 6.4	0.38
Body mass index (kg/cm^2)	29.2 ± 7.32	28.9 ± 7.85	0.89
Duration of the disease (months)	64.4 ± 52.2	71 ± 60.3	0.70

The data are presented in means ± standard deviations or percentage. Applied tests: Fisher's exact test and Student's t-test, when appropriate.

Table 2
Comparison between the clinical data, cardiovascular events, comorbidities and lifestyle in patients with primary antiphospholipid syndrome (PAPS) with higher Lp(a) and those lower or equal to 30 mg/dL

Data	PAPS Lp(a) > 30 mg/dL N = 20	PAPS Lp(a) ≤ 30 mg/dL N = 26	P
Arterial event, n(%)	12 (60)	16 (61.5)	1.00
Venous event, n(%)	6 (30)	12 (46.2)	0.36
Obstetric event, n(%)	7 (35)	5 (19.2)	0.31
Stroke, n(%)	7 (35)	12 (46.2)	0.55
Sneddon's syndrome, n(%)	3 (15)	4 (15.4)	1.00
Limb ischemia, n(%)	4 (20)	4 (15.4)	0.71
Acute myocardial infarction, n(%)	3 (15)	0	0.18
Angina, n(%)	1 (5)	1 (19.2)	1.00
Deep venous thrombosis, n(%)	11 (55)	20 (76.9)	0.20
Pulmonary thromboembolism, n(%)	5 (25)	10 (38.5)	0.36
Thrombocytopenia, n(%)	4 (20)	6 (23)	1.00
Systemic arterial hypertension, n(%)	9 (45)	11 (42.3)	1.00
Osteonecrosis, n(%)	0	2 (7.7)	0.49
Physical activity, n(%)	9 (45)	5 (19.2)	0.11
Current smoking, n(%)	2 (10)	2 (7.7)	1.00
Preceding smoking, n(%)	9 (45)	11 (42.3)	1.00

Applied test: Fisher's exact test.

Table 3
Comparison between the frequencies of medications in patients with primary antiphospholipid syndrome (PAPS) with higher Lp(a) and those equal or lower than 30 mg/dL

Data	PAPS Lp(a) > 30 mg/dL N = 20	PAPS Lp(a) ≤ 30 mg/dL N = 26	P
Current use of corticoid, n(%)	0	3 (11.5)	0.25
Previous use of corticoid, n(%)	7 (35)	10 (38.5)	0.16
Use of warfarin, n(%)	16 (80)	20 (76.9)	1.00
Use of cloroquin, n(%)	2 (10)	7 (26.9)	0.26
Use of statin, n(%)	8 (40)	7 (26.9)	0.53
Current use of acid acetylsalicylic, n(%)	8 (40)	5 (19.2)	0.19

Applied test: Fisher's exact test.

Table 4
Comparison between the frequencies of antinuclear factor and antiphospholipid antibodies in patients with primary antiphospholipid syndrome (PAPS) with higher Lp(a) and those lower or equal to 30 mg/dL

Data	PAPS Lp(a) > 30 mg/dL N = 20	PAPS Lp(a) ≤ 30 mg/dL N = 26	P
Lupus anticoagulant, n(%)	14 (70)	23 (88.5)	0.15
ACL IgG, GPL	33.9 ± 45.8	38.9 ± 49.4	0.73
ACL IgM, MPL	25.7 ± 38.5	31.7 ± 41.1	0.64
Positivity of aCL IgG, n(%)	11 (55)	17 (65.4)	0.55
Positivity of ACL IgM, n(%)	10 (50)	16 (61.5)	0.55
Positivity of ACL IgG or IgM	14 (70)	17 (65.4)	1.00
Positivity of ACL, IgG or IgM or lupus anticoagulant, n(%)	18 (90)	25 (96.2)	0.57

The data are presented in means ± standard deviations or percentage.
ACL = anticardiolipin antibody. Applied test: Fisher's exact test.

Lipoprotein(a) is a lipid particle rich in cholesterol, very similar to LDL-cholesterol, whose difference is the presence of an additional apolipoprotein [apo(a)] connected to apolipoprotein B-100.[9] Apo(a) presents a very elevated homology with the plasminogen molecule and has the capacity of competing with it and inhibiting fibrinolysis.[10] Lp(a) is synthesized in the liver and seems to have a biological function in tissue repair. About 90% of its plasmatic levels are determined by the genetic variability of the apo(a) locus.

Caucasians in 70% of the cases have their serum values < 30 mg/dL and the black people about three times more than the white.[11] As this study had three quarters of its population of Caucasoids, the cut value of 30 mg/dL was used.

Diverse conditions can elevate the levels of Lp(a), such as nephrotic syndrome, chronic renal insufficiency, systemic lupus erythematosus, hypotireoidism and obliterative thromboangiitis;[12] therefore, such conditions were totally excluded from the present work to assure the clinical relevance of the results. The use of statins did not demonstrate any difference between the groups here studied, as it is well-known in the literature that these drugs do not have significant effect over the levels of Lp(a).[12]

Interestingly, about 40% of the studied population in the present study presented elevated levels of Lp(a), which suggests that this lipoprotein should deserve attention in the patients with primary APS.

Nevertheless, the elevated levels of Lp(a) were not associated to cardiovascular and cerebrovascular events. Diverse studies, such as the Québec Cardiovascular Study, have demonstrated that lipoprotein(a) isolatedLy really does not seem to be a risk factor to atherosclerotic cardiac disease.[13] Similarly, there is controversy in the literature about whether Lp(a) determines risk of stroke.[14]

About 80% of the patients with APS present recurring venous or arterial thrombosis, and strokes are the more common arterial manifestations. The presence of anticardiolipin or lupus anticoagulant cannot discriminate the diverse clinical manifestations of the patients with APS, hence there is need for other possible markers, as well as for the identification of one risk population for future. In the population studied, none of the parameters evaluated, whether they were clinical, demographic, laboratorial, and of medications and antiphospholipid antibodies, was associated to the presence of increased levels of this lipoprotein. One previous study of Lp(a) in patients with primary APS revealed increased levels of apoprotein(a), but not Lp(a) as a predictive cerebrovascular risk factor in this population.[15] Atsumi *et al*. found an association with reduced fibrinolysis and elevated levels of lipoprotein(a) in patients with APS; however there were patients with associated SLE.[6] At last, also in an APS population but not exclusively primary, the study of Yamazaki *et al*. demonstrated more elevated serum levels of Lp(a) in patients with arterial events than in those with venous events.[16]

This study showed that many patients with primary antiphospholipid syndrome present elevated serum levels of lipoprotein(a). Nevertheless, this finding was not associated with clinical and laboratorial manifestations of the disease, as well as with the presence of cerebrovascular and cardiovascular morbidities of the population here studied.

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