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Height associated with different clinical expressions in primary antiphospholipid syndrome female patients

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Abstract. – OBJECTIVE: To compare clinical and laboratory data obtained from patients with primary antiphospholipid syndrome (pAPS) above and below 165 cm of height.

PATIENTS AND METHODS: A cross-sectional study with 66 (83.3% female) pAPS patients was performed. Demographic, clinical, drug use, and antiphospholipid antibodies data were evaluated. Patients were subdivided into one of two groups: pAPS ≥ 165 cm and pAPS < 165 cm and compared.

RESULTS: In this sample 19/66 (28.8%) of patients were ≥ 165 cm and 47 were < 165 cm of height. Primary APS > 165 cm exhibited a lower frequency of female sex (52.6% *vs.* 95.7%, *p*<0.0001) and abortions (0 *vs.* 34%, *p*=0.008). A significant higher frequency of antimalarial use was seen in taller patients compared to those < 165 cm (36.8% *vs.* 14.9%, *p*=0.04). Furthermore, the analysis of females showed lower mean age (32.3 ± 9.9 *vs.* 41.3 ± 10.5, *p*=0.016), higher weight (85.5 ± 25.3 *vs.* 69.7 ± 17.6 kg, *p*= 0.023), higher frequency of venous events (100% *vs.* 66.7%, *p*=0.025) and lower rate of stroke (10% *vs.* 44.4%, *p*=0.043) in taller female than in the smaller.

CONCLUSIONS: This study used a systematic design to show that different heights in individuals with pAPS are associated with different diseases' expressions. When analyzing females exclusively, the taller ones were younger, heavier with more venous events, and more minor strokes than the smaller ones.

Key Words:
Antiphospholipid syndrome, Height, Abortion, Ischemic limb, Thrombosis, Antiphospholipid antibodies.

Introduction

Antiphospholipid syndrome (APS) is an acquired autoimmune disorder characterized by vascular thrombosis and/or obstetric events with or without thrombocytopenia in the presence of moderate/high titers of antiphospholipid antibodies[1].

APS is a heterogeneous condition in terms of clinical manifestations and of autoantibodies profile. Unlike other thrombophilia, both venous and arterial vessels may be involved. Deep vein thrombosis is one of the most common clinical presentations; arterial bed involvement may manifest as stroke, coronary artery disease, and peripheral artery disease, causing limb ischemia[2,3].

We previously performed a study on limb ischemia secondary to pAPS (primary APS) and found differences in clinical expressions of the disease regarding the patients' height. In that study, those with limb ischemia were smaller than patients without this ischemic lesion [*article submitted*]. According to Park et al[4], that studied patients submitted to extracorporeal life support, short stature was the only factor independently linked to limb ischemia in that context. Furthermore, the authors divided in patients above and below 165 cm. Therefore, the small diameter of arteries in these individuals was the only given explanation[4]. Therefore, we analyzed our pAPS cohort to verify if these patients have distinct clinical expressions based on height differences based on these two facts.

Herein we studied a sample of pAPS patients to know if there are clinical, demographic, and laboratory differences in patients above and below 165 cm of height.

Patients and Methods

This study has a cross-sectional design and included sixty-six pAPS patients regularly fol-

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lowed at a private clinic. All subjects completed the Sidney criteria for primary APS[5]. Patients of both genders with ages equal to or greater than 18 years were included. The authors fulfilled the Helsinki World declaration, and all participants signed informed consent to participate.

Data, including age, gender, occupation, medical history, body height, weight, and BMI, were obtained from medical records at the diagnosis time. Stroke and vascular events were confirmed by computed tomography (CT), magnetic resonance imaging (MRI), computed tomography angiography (CTA), and/or magnetic resonance angiography (MRA). Other vascular events, arterial (including limb ischemia) or venous, were diagnosed by the clinical presentation followed by imaging confirmation by CT, MRI, CTA, MRA, Doppler sonography, ventilation/perfusion scintigraphy, and/or arteriography. Thrombocytopenia was defined as a platelet count less than 100,000/mm^3 on at least two consecutive occasions. Livedo reticularis diagnosis was based on typical *livedo reticularis* on the physical examination. In the case of clinical doubt, a skin biopsy was performed. Sneddon's syndrome was considered as the presence of livedo reticularis and stroke[6]. In addition, the presence of comorbidities such as smoking, arterial hypertension (defined by blood pressure > 140/90 mmHg), diabetes (defined as glucose above 126 mg/dL), and dyslipidemia (defined by the National Cholesterol Education Program[7]), as well as the use of medications (corticosteroid, warfarin, antimalarial, statins, acetylsalicylic acid), were also recorded. The weight measurement was performed by a single professional using a portable digital balance Welmy® and the height was measured using a mobile stadiometer Avanutri®.

Thyroid dysfunction was defined as hypothyroidism (low free T4 or high TSH levels) and hyperthyroidism (high free T4 or low TSH levels) in sera independently of thyroid symptoms.

We have chosen 165 cm based on a previous study on thrombosis in extracorporeal surgery in which compared people dividing by height and found differences[4].

Statistical Analysis

Results were expressed as mean ± standard deviation (SD). Statistical analysis was carried out using JASP 0.12.2 version Software. Student's *t*-test or Mann-Whitney's test were used to compare means, and comparisons between proportions were calculated using the chi-square or Fisher tests. *p*-values below 0.05 were considered statistically significant.

Results

Description of the Studied Sample

In the sample of 66 APS, 55/66 (83.3%) were females, and 11/66 (16.6%) were males. The main epidemiological, clinical, and treatment characteristics of this sample are in Table I.

In this sample, 19/66 (28.8%) of patients were ≥ 165 cm, and 47/66 (71.2%) were <165 cm in height.

Comparison of pAPS Patients ≥165 cm and < 165 cm

The comparison of clinical and epidemiological data between patients ≥ or < 165 cm is in Table II. On this table it is possible to observe that the group with pAPS > 165 cm exhibited a lower frequency of female sex (52.6% *vs.* 95.7%, $p<0.0001$) and abortions (0 *vs.* 34%, $p=0.008$). Taller subjects had higher weight (83.8 ± 19.3 *vs.* 69.1 ± 17.7, $p=0.0004$). The other pAPS manifestations and comorbidities did not differ significantly ($p>0.05$). A significantly higher frequency of antimalarial use (36.8% *vs.* 14.9%, $p=0.04$) was seen in taller patients than those < 165 cm.

Analyses of autoantibodies of patients in the PAPS ≥ 165 cm of height and those < 165 cm were similar regarding lupus anticoagulant (94.7% *vs.* 80.9%, $p=0.16$), IgG anticardiolipin (47.4% *vs.* 63.8%, $p=0.17$), IgM anticardiolipin (42.1% *vs.* 76.6%, $p=0.56$) and antinuclear antibodies (31.2% *vs.* 29.8%, $p=0.52$).

Comparison of Female pAPS Patients ≥165 cm and < 165 cm

The comparison of clinical and epidemiological data between female patients ≥ or < 165 cm is in Table III. This table shows that the pAPS > 165 cm exhibited a lower mean age (32.3 ± 9.9 *vs.* 41.3 ± 10.5, $p=0.016$). Regarding weight, taller subjects had higher weight (85.5 ± 25.3 *vs.* 69.7 ± 17.6 kg, $p=0.023$). Furthermore, a higher frequency of venous events (100% *vs.* 66.7%, $p=0.025$) and a lower chance of stroke (10% *vs.* 44.4%, $p=0.043$) was observed in taller patients smaller ones. No other significant differences were found between these two groups of female patients, including the antiphospholipid antibodies profile ($p>0.05$).

Table I. Description of studied sample (66) patients with primary antiphospholipid antibody syndrome).

Epidemiological aspects	
Mean age- years	39.1 ± 10.9
Mean disease duration (months)	74.1 ± 61.4
Ethnic background	Caucasians – 50/66 – 75.7% Afro-descendants – 16/66-24.2%
Tobacco exposure	Current smokers - 7/66 – 10.6% Ex-smokers – 26/66 – 39.4%
Body mass index - kg/m^2	28.1 ± 6.7
Clinical manifestations	
Arterial events	38/66 – 57.6%
Venous events	43/66 – 65.2%
Obstetrical events	21/66 – 31.8%
Deep venous thrombosis	42/66 – 63.6%
Livedo reticularis	19/66- 28.8%
Sneddon's syndrome	13/66 – 19.7%
Stroke	25/66 – 37.9%
Convulsions	7/66 – 10.6%
Myocardial infarction	4/66 – 6.1%
Angina	3/66 – 4.5%
Thrombocytopenia	7/66 – 10.6%
Pulmonary embolism	15/66 – 22.7%
Thrombotic microangiopathy	5/66 – 7.6%
Laboratory data	
Anticardiolipin IgM	37/66 – 56.1%
Anticardiolipin IgG	34/66 – 51.5%
Lupus anticoagulant	56/66 – 84.8%
Triple positive	26/66 – 39.4%
Comorbidities	
Arterial hypertension	25/66 – 37.9%
Diabetes mellitus	3/66 – 4.5%
Dyslipidemia	20/66 – 30.3%
Thyroid disorder	9/66 – 13.6%
Protein C deficiency	6/66 – 9.1%
Treatment data	
Acetylsalicylic acid	21/66 – 31.8%
Warfarin	53/66 – 80.3%
Antimalarial	11/66 – 16.7%
Statins	17/66 – 25.8%
Glucocorticoid	Current – 6/66 – 9.1% Previous – 26/66 – 39.4%

The analysis of males ≥ 165 cm and 165 cm was not performed since only two patients were below 165 cm.

Discussion

Our results have shown differences in the clinical manifestations of pAPS regarding patients' height, mainly in females. High stature was associated with minor stroke and more deep venous thrombosis in women.

Primary APS is a syndrome that affects not only both arterial and venous vessels but also large, medium, and small vessels[3,4,8]; thrombosis occurrence may suffer influence not only of the vessel subset (arterial or venous) but also of its size[4,9].

Animal studies have shown that the blood vessel diameters (arterial and venous) are proportional to the animal's size[10], and smaller arterial vessels are more prone to obstruction than larger ones[4]. Furthermore, vessels with a small diameter were an independent risk factor for restenosis

Table II. Comparison of clinical and epidemiological data of primary antiphospholipid antibody syndrome (pAPS) patients ≥ 165 cm of height and those < 165 cm.

	pAPS ≥ 165 cm n = 19	pAPS < 165 cm n = 47	*p*
Mean age (SD) (years)	35.7 ± 10.2	40.4 ± 11.1	0.12
Female sex, n (%)	10 (52.6)	45 (95.7)	< **0.0001**
The white race, n (%)	9 (47.4)	41 (87.2)	0.26
Current smoking, n (%)	2 (10.5)	5 (10.6)	0.88
Previous smoking, n(%)	10 (52.6)	16 (34)	0.33
Mean body mass index (SD) (kg/m^2)	28.9 ± 7.1	27.8 ± 6.6	0.57
Weight (kg)	83.8 ± 19.3	69.1 ± 17.7	**0.0004**
Arterial events, n (%)	9 (47.4)	29 (61.7)	0.29
Venous events, n (%)	15 (78.9)	30 (63.9)	0.31
Obstetric events, n (%)	3 (15.8)	17 (36.2)	0.07
Spontaneous abortion, n (%)	0	16 (34)	**0.008**
Stroke, n (%)	5 (26.3)	20 (42.5)	0.22
Sneddon's syndrome, n (%)	1 (5.3)	12 (25.5)	0.06
Livedo reticularis n (%)	3 (15.8)	16 (34)	0.17
Acute myocardial infarction, n (%)	1 (5.3)	3 (6.4)	0.87
Angina, n (%)	0	3 (6.4)	0.27
Deep venous thrombosis, n (%)	14 (73.7)	28 (59.6)	0.29
Pulmonary thromboembolism, n (%)	3 (15.8)	12 (25.5)	0.40
Thrombocytopenia, n (%)	3 (15.8)	4 (8.5)	0.82
Thrombotic microangiopathy n (%)	1 (5.3)	4 (8.5)	0.66
Seizures, n (%)	1 (5.3)	6 (12.8)	0.37
Arterial systemic hypertension, n (%)	6 (31.6)	19 (40.4)	0.07
Dyslipidemia, n (%)	7 (36.8)	13 (27.7)	0.98
Diabetes mellitus, n (%)	1 (5.3)	2 (4.3)	0.88
Thyroidopathy, n (%)	3 (15.8)	6 (12.8)	0.93
Current corticosteroid use, n (%)	1 (5.3)	5 (10.6)	0.48
Previous corticosteroid use, n (%)	8 (42.1)	18 (38.3)	0.86
Warfarin use, n (%)	18 (94.7)	34 (72.3)	0.06
Antimalarial use, n (%)	7 (36.8)	7 (14.9)	**0.04**
Statins use, n (%)	3 (15.8)	14 (29.8)	0.23
Acetylsalicylic acid use, n (%)	12 (63.2)	25 (53.2)	0.81

one year after aortoiliac stenting[11]. This fact may explain more strokes in individuals with a lower height than those with a higher height. Nevertheless, the vessel's diameter may not be the only player in this context, as the present results point to a different performance if a venous or arterial bed is involved.

Arterial blood vessels are subjected to a higher shear stress magnitude[12], which favors endothelial lesions such as atherosclerosis. In addition, the endovascular injury seems to be more critical for thrombus formation in arterial events than changes in hemostasis[13]. So, arterial thrombus formation may appear, especially when atherosclerotic plaques are present[14], which are usually more common in places where the hemodynamic forces are high.

Several authors have already observed that tall men and women have an increased risk of first and recurrent venous thrombosis than the reference category[15-20]. According to Flinterman et al[15], which studied 4464 individuals, body height affected venous pressure dynamics, causing more stasis in the legs, which is a given explanation for the increased risk. However, others have found that leg length is more important than total height. This fact explained the relation of height to venous thromboembolism and added the possibility of a greater venous surface area and a more significant number of venous valves to the list of explanations[20].

Low stature also seems to be related to spontaneous abortion. In fact, in a large study with 5,132 women enrolled in a Danish internet-based prospective cohort study of pregnancy planners, the authors found that obesity is a decisive risk factor for early pregnancy losses and that small stature and low waist-to-hip ratio are associated with an increased risk of spontaneous abortions[21]. Our finding of increased risk for spontaneous abortion in patients smaller than 165 cm confirms these previous data.

Table III. Comparison of clinical and epidemiological data of primary antiphospholipid antibody syndrome (pAPS) female patients ≥ 165 cm of height and those < 165 cm.

	pAPS ≥ 165 cm n = 10	pAPS < 165 cm n = 45	*p*
Mean age (SD) (years)	32.3 ± 9.9	41.3 ± 10.5	**0.016**
The white race, n (%)	6 (60)	37 (82.2)	0.13
Current smoking, n (%)	1 (10)	5 (11.1)	0.85
Previous smoking, n (%)	6 (60)	16 (35.6)	0.24
Mean body mass index (SD) (kg/m^2)	30.9 ± 10.0	27.9 ± 6.5	0.28
Weight (kg)	85.5 ± 25.3	69.7 ± 17.6	**0.023**
Arterial events, n (%)	4 (40)	28 (62.2)	0.20
Venous events, n (%)	10 (100)	30 (66.7)	**0.025**
Obstetric events, n (%)	3 (30)	18 (40)	0.68
Spontaneous abortion, n (%)	0	10 (22.2)	0.08
Stroke, n (%)	1 (10)	20 (44.4)	**0.043**
Sneddon's syndrome, n (%)	0	12 (17.5)	0.06
Livedo reticularis n (%)	3 (30)	16 (34)	0.74
Acute myocardial infarction, n (%)	0	3 (6.4)	0.41
Angina, n (%)	0	3 (6.4)	0.41
Deep venous thrombosis, n (%)	9 (90)	26 (59.6)	0.05
Pulmonary thromboembolism, n (%)	3 (30)	12 (26.7)	0.83
Thrombocytopenia, n (%)	1 (10)	4 (8.9)	0.75
Thrombotic microangiopathy n (%)	0	4 (8.9)	0.34
Seizures, n (%)	0	6 (13.3)	0.22
Arterial systemic hypertension, n (%)	2 (20)	19 (42.2)	0.06
Dyslipidemia, n (%)	3 (30)	13 (28.9)	0.93
Diabetes mellitus, n (%)	0	3 (6.4)	0.41
Thyroidopathy, n (%)	2 (20)	6 (12.8)	0.82
Current corticosteroid use, n (%)	0	4 (8.9)	0.33
Previous corticosteroid use, n (%)	3 (30)	17 (37.8)	0.66
Warfarin use, n (%)	0	33 (73.3)	0.06
Antimalarial use, n (%)	3 (30)	7 (15.6)	0.84
Statins use, n (%)	1(10)	14 (31.1)	0.17
Acetylsalicylic acid use, n (%)	4 (40)	26 (57.8)	0.26

A curious finding was the association of taller height with antimalarial use. Although we have no proper explanation for this finding, there is, in the literature, the observation that in children with malaria, antimalarial use was associated with a small positive effect on children's height[22]. Therefore, a possible explanation is that children protected from malaria by receiving antimalarial drugs tended to be taller and heavier than control children since the disease was under control[23]. However, a pathophysiological explanation for the present finding that patients ≥ 165 cm used more commonly antimalarial is unknown as all patients were adults when the pAPS diagnosis was made.

No relationship between individuals' height and antibody profile was found. It is possible that our findings are not confined to those with pAPS but related to thrombosis risk in general. Nevertheless, they do modulate the clinical findings in this syndrome. Knowing the influence of body height in thrombosis may help the clinician to understand the clinical variability found in pAPS.

This study's strengths are first, including only patients who fulfilled the international criteria for APS; second, the exclusive inclusion of primary APS patients. Regarding limitations, a cross-sectional design, a low number of participants, and unicentric observation are some. In addition, multicentric studies with multiethnic participation to confirm the present data are desirable.

Conclusions

This study used a systematic design to show that different heights in individuals with pAPS are associated with different diseases' clinical expressions. When analyzing the female APS participants exclusively, the taller ones had a more venous event and were less prone to stroke than the smaller group.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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