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Research Article

Comparison of Primary versus Secondary Effects of Antiphospholipid Syndrome on the Development of Thrombosis

Haneen Sait[1*], Ahmed Saleh[1], Waleed Alshehri[1], Mohammed Alsheef[2]

[1]Research Center, King Fahad Medical City, Riyadh, Saudi Arabia;[2]Thrombosis Clinics, King Fahad Medical City, Riyadh, Saudi Arabia

ABSTRACT

Background: Antiphospholipid syndrome (APS) is an autoantibody-mediated acquired thrombophilia. It is characterized by the presence of antiphospholipid antibodies (APL) that increase the risk of thrombosis.

Objective: To compare primary versus secondary effect of APS on the development of thrombosis and its outcomes.

Design: Retrospective cohort

Setting: Thrombosis clinics at KFMC

Materials and methods: A retrospective chart review from medical and electronic records for all patients who were confirmed to have APS and attended thrombosis clinic from 2009 to 2019 at King Fahad Medical City in Riyadh Saudi Arabia. A total of 100 patients fulfilled our inclusion criteria.Variables collected include thrombotic risk factors and outcomes.

Results: A total of 100 patients were included in the final analysis. Primary APS was present in (67%) and secondary APS was present in (33%). Recurrent of DVT was associated with a 4.8-fold increase the risk of thrombosis in patients with triple positive (p=0.01). DVT progressed to PE was associated with a 3.06-fold increase risk for recurrent thrombosis in general (p=0.03). Unprovoked thrombosis was seen in most of the cases accounting for 89% showing no statistically significant differences between both groups. In pregnancy complications no major difference was observed when comparing both groups.

Conclusion: Based on our retrospective analysis of aPL database shows that thrombosis is greater in primary APS than in APS associated with SLE. However, patients with triple positive demonstrate risk factor of recurrent of DVT. Moreover, DVT progressed to PE was associated with an increased risk of thrombotic in general.

Keywords: Antiphospholipid syndrome; Lupus anticoagulant; Phospholipids; Systemic lupus erythematosus; Thrombosis

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by arterial and venous thrombosis and it is major cause of strokes in people under the age of 50 [1,2]. Pregnancy morbidity associated with the presence of persistent antiphospholipid antibodies (aPL) [3,4]. It's consisted of a family of heterogeneous immunoglobulins targeted phospholipid-binding plasma proteins [5]. It is likely that mechanisms other than simple vascular thrombosis contribute to various APS manifestation [6]. APS is divided into two types primary APS without an underlying disease, and secondary APS that is associated with another autoimmune syndrome, most commonly Systemic Lupus Erythematosus (SLE) [7]. The most severe type is catastrophic APS (CAPS) which is a very rare form of APS affecting 1% of cases. CAPS exhibit thrombotic microangiopathy in multiple organ thrombotic events occurs simultaneously or over a short period of time at multiple sites leading to organ failure and a high mortality [8]. Primary APS can occur in 36.2% and secondary APS occurring in 53.1% and the remaining 10.7% APS associated with other diseases [9]. APS is more common in female with a female to male ratio is 3.5:1 for primary and 7:1 for secondary [8]. APS is a rare disease with estimated incidence in the general population of 2.1 (1.4-2.8) per 100 000, and the prevalence of 50 (42-58) per 100 000 [10]. These antibodies are essential for the diagnosis and likely

Correspondence to: Haneen Sait, Cellular and Molecular Research Center, Yasuj University of Medical Sciences, Yasuj, Iran; E-mail: s.afrouz92@gmail.com

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to play a pathogenic role in various disease manifestations [11]. Thrombotic events in APS are rarely accompanied by histological evidence of vessel wall inflammation, yet many APS patients have underlying systemic autoimmune disease [12]. Anti-PL antibodies increase the risk of thrombosis through different mechanisms that go beyond a simple dysregulation of coagulation pathways [13]. Patients with APS are more at risk of recurrent thrombosis [14]. APL can be diagnosed with three tests, lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-β2-Glycoprotein I antibodies (aβ2GPI). Individuals may be positive for one, two or three of these tests [15-17]. Patients with APS and triple positivity for aPL are at high risk of developing future thromboembolic events [18]. The cumulative incidence of recurrent thrombosis in these patients was 44.2% after 10 years of follow-up period by Pengo V, et al. [18]. The aim of this study was to compare primary versus secondary effects of APS on the development of thrombosis and its outcomes.

MATERIAL AND METHODS

This is a retrospective chart review from medical and electronic records for all patients who were confirmed to have APS and attended thrombosis clinic from 2009 to 2019 at King Fahad Medical City in Riyadh Saudi Arabia.This study was approved by IRB with log number: 20-263. A total of 100 patients fulfilled our inclusion criteria. Patients were divided into primary APS (n=67) and secondary (n=33). Demographic data for both groups was depicted in Table 1. We included patient's age >18 years with positive tests for lupus anticoagulant, anticardiolipin antibodies, β2-glycoprotein at least 12 weeks apart and a history of thrombosis (venous, arterial, or both). Additionally, we included patients manifested with pregnancy complications; recurrent fetal loss, preterm delivery and pregnancy induced hypertension. Recurrent fetal loss was considered when two or more unexplained deaths of a morphologically normal fetus early <10 weeks or late ≥ 10 weeks by ultrasound.

Table 1: Baseline comparisons for characteristics of primary APS versus secondary APS.

Characteristic	Primary APS N= 67 (%)	Secondary APS N= 33 (%)	p value
Age	39.8 ± 10.4	41.2 ± 9.4	0.5
Age at diagnosis	31.6 ± 9.7	30.9 ± 9.3	0.7
Gender			
Male	17 (25.4)	5 (15.2)	0.2
Female	50 (74.6)	28 (84.8)	0.2
Wight (kg)	81.0 ± 18.6	77.2 ± 18.9	0.3
Hight (cm)	1.6 ± 0.9	1.6 ± 0.1	0.9
BMI	30.6 ± 7.1	30.3 ± 7.3	0.8
Family history	5 (7.5)	1 (3.0)	0.3
Hypertension	10 (15.0)	7 (21.2)	0.4
Diabetes mellitus	7 (10.4)	3 (9.0)	0.8
Thyroid disease	15 (22.3)	6 (18.1)	0.6
Renal disease	6 (9.0)	10 (30.3)	0.006
Cardiac disease	4 (6.0)	5 (15.2)	0.1

Abbrevations: APS: Antiphospholipid Syndrome; BMI: Body Mass Index

Laboratory APS diagnosis

Methods and results for laboratory diagnosis of APL tests were performed according to the biological classification criteria, diagnosis includes: LA was determined by the modified dilute Russell's Viper Venom time test (dRVVT) and activated partial thromboplastin time (aPTT) according to the recommended criteria from the International Society on Thrombosis and Haemostasis (ISTH), aCL were determined by enzyme linked immu-nosorbent assay (ELISA) (Inova Diagnostics, Inc., San Diego, CA, US), and were considered positive when antibodies, exceeded 20 U/mL IgG phospholipid (GPL) and/or 20 IgM phospholipid (MPL) unitsf >20 U/mL, aβ2GPI were considered positive if >20 U/mL, which performed by enzyme linked immu-nosorbent assay according to the manufacturer's instruc-tions using QUANTA Lite kits from Inova (Table 2).

Table 2: APS patients with positive antibodies tests of study population (n=100).

Antibodies	Primary APS N= 67	Secondary APS N= 33	Missing data	p value
LA	19 (28.3)	9 (27.2)	7 (7.0)	0.8
aCL	0.8	0.8	0.8	0.8
IgM	21 (31.3)	3 (9.0)	9 (9.0)	0.03
IgG	34 (51.4)	17 (51.5)	7 (7.0)	0.4
aβ2GPI	0.8	0.8	0.8	0.8
IgM	13 (19.4)	8 (24.2)	5 (5.0)	0.3
IgG	26 (39.0)	17 (51.5)	5 (5.0)	0.08
Triple Ab positive	16 (24.9)	10 (30.3)	4 (4.0)	0.2

Thrombotic events

Intracerebral thrombosis was assessed by Computed Tomographic scanning (CT), magnetic resonance imaging (MRI) or angiography, pulmonary embolism was diagnosed by ventilation-perfusion lung scan or pulmonary angiography, deep vein thrombosis (DVT) was diagnosed using compression ultrasonography or venography.

Statistical analyses

Mean values and standard deviations were calculated for the continuous variables. The quantitative variables were compared using the Student t test for grouped data, and the qualitative variables by means of the Chi-square test to assess the association between primary APS and secondary APS with development of thrombosis. Univariate comparisons with a p-value<0.1 were included in multivariate analyses in which statistical significance threshold was accepted as p<0.05. Logistic regression analysis was used to study simultaneous effect of selected variables with the odds ratios (OR) and the confidence intervals for each variable being adjusted (SPSS version 25) software was used for statistical analyses.

RESULTS AND DISCUSSION

A total of 100 patients were included in the final analysis. Primary APS was present in (67%) and secondary APS was present in (33%). Baseline comparison for characteristics of primary APS versus secondary APS (Table 1). We found female: male ratio in secondary was 5.6:1 and in primary 2.9:1. Antiphospholipid antibodies laboratory results showed that only aCL; IgM was significantly higher in primary versus secondary (Table 2). The most common thrombotic manifestation of antiphospholipid syndrome in general was DVT affecting left lower limb however, it was much more common in primary APS p=0.003. Other Sites and clinical manifestation of venous and arterial thrombosis where similar in both groups (Table 3). Regarding recurrence of thrombotic events, 37 patients of the study population experienced another event, and it was observed that the most common sites of recurrence were PE and DVT collectively in both groups with no significant difference in other sites (Table 4). In the univariate analyses with

triple positive as dependent variable recurrent of VTE, PE and peripheral arteries were excluded, only recurrent of DVT was significant in the multivariate analyses with OD=4.8, CI 95% (1.5-15.4), p=0.01. The results of univariate analyses of recurrent thrombosis were not associated with the baseline characteristics of APS and all sites of thrombotic event. DVT progressed to PE remained as an independent risk factor for recurrent thrombosis in general were entered logistic regression model, OD=3.06, CI 95% (1.08-8.85), p=0.03. Unprovoked thrombosis was seen in most of the cases accounting for 89% showing no statistically significant differences between both groups with regards to provoking factors (Table 5). In terms of pregnancy complications, no major difference was observed when comparing both groups, but early pregnancy loss <10 weeks was the most common complication in all study population with p-value=0.009 when compared to late pregnancy loss ≥ 10 weeks (Table 6).

Table 3: Sites of thromboembolic events of study population (n=100).

Sites of thrombosis	Primary APS N=67	Secondary APS N=33	p value
Venous sites	4 (6.0)	4 (6.0)	4 (6.0)
Cerebral vein thrombosis	6 (9.0)	4 (12.1)	0.6
Inferior vena cava thrombosis	4 (6.0)	3 (9.1)	0.5
Jugular vein thrombosis	1 (1.5)	2 (6.0)	0.2
Upper extremity or limb DVT	0 (0.0)	1 (3.0)	0.1
Subclavian thrombosis	2 (2.9)	0 (0.0)	0.3
Renal vein thrombosis	2 (2.9)	2 (6.0)	0.4
Splanchnic vein thrombosis	2 (2.9)	1 (3.0)	0.9
Gonadal vein thrombosis	1 (1.5)	0 (0.0)	0.4
DVT Bilateral lower limb	5 (7.5)	5 (15.2)	0.2
DVT Right lower limb	6 (9.0)	4 (12.1)	0.6
DVT Left lower limb	35 (52.2)	7 (21.2)	0.003
DVT progressed to PE	13 (19.4)	5 (15.2)	0.6
Arterial sites	4 (6.0)	4 (6.0)	4 (6.0)
Arterial thrombosis cerebral	9 (13.4)	4 (12.1)	0.8
Arterial thrombosis coronary	1 (1.5)	1 (3.0)	0.6
Peripheral arteries	1 (1.5)	0 (0.0)	0.4
Pulmonary embolism without DVT	5 (7.5)	2 (6.0)	0.7

Table 4: Recurrence thrombosis of study population (n=100).

Variables	Primary APS N=67	Secondary APS N=33	p value
Recurrence of VTE	13 (19.4)	5 (15.2)	0.6
Recurrence of DVT alone	11 (16.4)	3 (9.0)	0.3
Recurrence of PE alone	2 (2.9)	2 (6.0)	0.4
Recurrence of Peripheral arteries	1 (1.5)	0 (0.0)	0.4
Total	27 (40.2)	10 (30.3)	0.3

Table 5: Precipitating factors of study population (n=100).

Precipitating factors	Primary APS N=67	Secondary APS N=33	p value
Precipitated with surgery	2 (2.9)	1 (3.0)	0.9
Precipitated with OCP	3 (4.5)	0 (0.0)	0.2
Precipitated with pregnancy	5 (7.5)	0 (0.0)	0.4
Total	10 (15.0)	1 (3.0)	0.07

Table 6: Obstetric complications of study population (n=100).

Complication	Primary APS N=67	Secondary APS N=33	p value
Early pregnancy loss (<10 weeks)	13 (19.4)	5 (15.2)	0.6
Late pregnancy loss (³10 weeks)	5 (7.5)	1 (3.0)	0.3
Preeclampsia/ eclampsia	1 (1.5)	1 (3.0)	0.6
Live birth with prematurity	1 (1.5)	0 (0.0)	0.4
Total	20 (29.9)	7 (21.2)	0.4
Total population n=100	Early pregnancy loss (<10 weeks)	Late pregnancy loss (³10 weeks	p value
	18 (18.0)	6 (6.0)	0.009

APS is an autoimmune disorder that can affect multiple systems in the presence of antiphospholipid antibodies. It can present in two forms primary or secondary to other diseases, both of which are characterized by the development of thrombotic events [19]. Due to its possible different clinical manifestations and outcomes, it is especially important to study the difference between primary versus secondary APS. Data concerning APS in the Kingdom of Saudi Arabia are scarce and either case reports [20]. To the best of our knowledge, this is the first study conducted in the kingdom of Saudi Arabia which addressed the main difference in terms of clinical manifestations and outcomes of patients with different types of APS.

In the present study, primary APS was higher than secondary APS accounting for 67% of patient population which is slightly a higher percentage than previously reported studies [21,22]. One possible reason can explain this higher number of primary APS is the short follow up of this study as some of patients with primary APS might develop secondary autoimmune disease in their lifetime as reported by Freire PV et al. [23]. The commonest clinical manifestation in patients with primary and secondary APS collectively was venous thrombosis which correlates well with Hwang et al. [24]. Interestingly, left lower limb DVT was the most frequent site affecting more than one third of the study population especially primary APS. Left lower limb DVT predominance was described previously [25]. In the literature but was never related to antiphospholipid syndrome. Although variable between studies, the recurrence of thrombosis in our study was (37%) for 10 years follow-up period which is considered high when compared to previous studies reporting 12-30% with no difference in rate of recurrence between the groups [18-26]. Triple antiphospholipid antibody positivity was a main risk of recurrence of DVT with p-value=0.01 which was consistent with previous reported results [27]. The high recurrence rate highlights the importance of aggressive and long-term treatment of APS to prevent further thrombosis especially in triple positive patients.

In our study we found that, 40 APS patients with persistent aPL disappearance had thrombosis recurrence 30 (44.8) of them were primary APS versus 10 (30.3) secondary APS. Additionally, a small proportion of patients presented other non-recurrence APS manifestations.

In the univariate analyses with triple positive as dependent variable recurrent of VTE, PE and peripheral arteries were excluded, only recurrent of DVT was significant in the multivariate analyses with

OD=4.8, CI 95% (1.5-15.4), p=0.01.Univariate analysis of recurrent thrombosis in our retrospective data showed that there is no significant deferent with age, gender, family history, hypertension, diabetes millets, thyroid disease, cardiac disease, cerebral vein thrombosis, arterial thrombosis cerebral, arterial thrombosis coronary, peripheral arteries, inferior vena cava thrombosis, jugular vein thrombosis, upper extremity or limb deep vein thrombosis (DVT), subclavian thrombosis, pulmonary embolism without DVT, renal vein thrombosis, pregnancy complication, splanchnic vein thrombosis, gonadal vein thrombosis, DVT bilateral lower limp, DVT right lower limp and DVT left lower limp. Only DVT progressed to PE remained as an independent risk for recurrent thrombosis in a logistic regression model. In the multivariate analysis DVT progressed to PE was independent associates of recurrent thrombosis, OD=0.3, CI 95% (0.1-0.9), p=0.03.

CONCLUSION

In conclusion, based on our retrospective analysis of aPL database, 67% primary APS versus 33% secondary APS. The frequency of thrombosis is greater in primary APS than in APS associated with SLE. However, patients with triple positive demonstrate risk factor of recurrent of DVT. Moreover, DVT progressed to PE was associated with an increased risk of thrombotic in general.

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