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Thrombotic Events in Patients with Antiphospholipid Syndrome: A Single Center Study

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Abstract

Background: There is limited literature regarding risk factors for development of thrombosis and long-term thrombotic outcomes in Armenian APS patients. The aim of the study is to identify patients with APS with thrombotic complications and to evaluate the epidemiological statistics of thrombosis and thrombophilia and their complications in Armenia. **Methods:** We analyzed medical records of Patients with APS from January 2018 to December 2021 treated at the Armenian Thrombosis and Hemostasis Center was enrolled. **Results:** Both acquired and hereditary thrombophilia increase the risk of thrombosis. Thrombophilia was present in 61.5% of 123 patients. It was found that 38 pregnant women with thrombosis had a family history of VTE, myocardial infarction or stroke in the next of kin under 50 years of age. The prevalence of this history was 31.4% (11 patients) compared to 68.6% (27 patients), who did not have 41.6% of postpartum thrombotic events up to two months postpartum. **Conclusion:** Thrombosis in pregnancy is a redoubtable complication requiring an excellent cooperation between the obstetrician and hematologist. Clear detection of thrombosis in APS patients in all types allows to accurately predicting the method and duration of anticoagulant treatment and to prevent thrombotic complications.

Keywords

Thrombotic Complications, Thrombophilia, Antiphospholipid Syndrome

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune thrombophilic condition, clinically manifested by vascular thrombosis and complications of pregnancy, in the form of spontaneous miscarriages, and, less frequently, maternal thrombosis. Many other clinical manifestations are possible [1] [2] [3].

APS is stimulated by circulating antiphospholipid antibodies, which are not only disease markers but also key factors in the pathophysiology of APS. Thrombotic events in APS may be associated with various conspirators, including activated endothelial cells, platelets, neutrophil extracellular traps, the complement system, and disorders of the coagulation and fibrinolytic systems. The most characteristic clinical manifestation of APS is thrombosis as arterial foot, and venous bed. The most common site of thrombosis is the deep veins of the lower limbs [4].

APS is characterized by damage to varying degrees almost all systems of the human body. The nervous system suffers more than others. Each the third stroke in patients under 50 years of age is associated van with the presence of aPL in the blood. In addition, it is noted gradual development of cognitive impairment in more than 40% of patients with elevated aPL titer [5]. To other signs of damage to the central nervous systems include migraine, chorea, epilepsy, impaired visual impairment as a result of retinal vascular thrombosis, psychoses, etc.

A very formidable group of complications of the presence of aPL in the blood is the pathology of pregnancy and childbirth: recurring miscarriages, stillbirth, preterm birth, preeclampsia, eclampsia and etc. In addition, this includes premature detachment of a normally located placenta, fetoplacental insufficiency. Due to the physiological hypercoagulation during pregnancy, the risk of venous thrombosis increases by 5 - 6 times; it is a consequence of an increase in the concentration of procoagulant factors (I, II, VIII, IX, X), as well as fibrinolytic and natural anticoagulant blood activity (antithrombin III, proteins S and C) [6] [7]. This group of complications is due to microcirculation and thrombosis of the fetoplacental vessels, including at the earliest stages pregnancy [8] [9].

Among other clinical manifestations of APS thrombocytopenia, hemolytic anemia, damage to the heart valves (often affected mitral and aortic valves), infarction myocardium, intracardiac thrombosis, reticular asphyxia, microangiopathy of renal vessels, trans sititory ischemic attacks, amaurosis fugax (perewalking blindness), a false positive test for syphilis, etc. It should be taken into account that the presence of aPL is not always leads to the development of clinical symptoms, which due to varying degrees of circulatory activity lyating antibodies. Thus, the diagnosis of APS is established is infused only with a combination of the held thrombosis or other clinical manifestation and the presence of aPL in the blood [10].

However, the presence of only aPL in the absence of typical clinical complications does not indicate the diagnosis of APS; there are long-term asymptomatic APL-positive patients. When diagnosed in patients with an underlying autoimmune disease (usually systemic lupus erythematosys), APS is referred to as secondary APS; in healthy people, this is called primary APS. Catastrophic APL is a severe extreme degree of multiple organ thrombosis in a short period of time. The clinical spectrum of APS has been expanded [11] [12] due to important advances in the study of its pathogenesis and clinical treatment over the past few years.

In recent years, researchers from different countries have paid great attention to the association of thrombophilia with APS and pregnancy complications. Thrombophilia has now been shown to be responsible for a large number of serious pregnancy complications such as venous thrombosis, pulmonary embolism, fetal loss, miscarriage, fetal death, and preeclampsia. Hereditary thrombophilia abnormalities (factor V Leiden mutation, prothrombin 20210A gene mutation, antithrombin III, protein C, and protein S deficiencies), as well as acquired disorders, anticardiolipin syndrome, and lupus inhibitor, are responsible for a large proportion of preterm births termination of pregnancy and many of the above complications. Inherited defects associated with thrombosis include the G1691A mutation in the factor V gene, the G20210A mutation in the prothrombin gene, the C677T mutation, and the A1298C mutation in the methylenetetrahydrofolate reductase (MTHFR) gene, antithrombin C protein, protein III, C deficiency [13] [14]. Although pregnancy is a normal physiological condition, it still predisposes to thrombosis, hypercoagulability (thrombophilia), which is determined by changes in the body due to a certain hormonal constellation.

In this study, we aimed to present the structure and management of thrombotic events in patients with APS of various origins in Armenia for the period from 2018-2021 according to the data of the Center for Thrombosis and Hemostasis at the Hematology Center after Prof. R. Yeolyan.

2. Materials and Methods

2.1. Patients

Patients with APS identified using ICD-10 coding system from the medical records from January 2018 to December 2021 at the Armenian Thrombosis and Hemostasis Center were enrolled. Armenian Thrombosis and Hemostasis Center is the only medical unit/center in Armenia that provides the diagnosis and treatment of patients with a wide range of hemostasis disorders and is a leader of translational research and clinical trials in the country.

APS was diagnosed on the basis of the criteria proposed in 2006 in Sydney [15]. The study group consisted of 123 patients with APS and different types of thrombotic events: in which 52 patients with cardiovascular complications and thrombosis, 38 women with obstetric pathologies and 33 patients only with APS.

This study was approved by the Research Ethics Committee of Armenian Hematology center aft. Prof. R. Yeolyan. Due to the retrospective design of this

study based on a review of medical records, the requirement for written informed consent for mostly patients was waived. Checking the inclusion and exclusion criteria and signing the informed consent to participate in the study were carried out at the first visit to the patient. The patient's records/information were anonymized and de-identified prior to analysis.

Inclusion criteria for the study were: cardiovascular history; varicose veins; pregnant; thrombotic episodes; maternal/placental complications associated with pregnancy; acquired thrombophilia (e.g. APS), hormone-dependent cancer therapy.

Exclusion criteria for the study were: age under 18 years; epilepsy; mental illness; autoimmune pathology.

2.2. Data Collection

We retrospectively reviewed the medical records system and collected the following data with a case report form, including demographic characteristics, clinical symptoms and signs, lumbar puncture results, neurologic imaging, laboratory examinations, treatment, and prognosis.

Symptom onset was categorized as acute (<48 hour from symptom onset to admission), subacute (48 hour to 1 month from symptom onset to admission), or chronic (more than 1 month from symptom onset to admission) [8].

2.3. Statistical Analysis

All statistical analyses were performed using STATA software/SE11. Continuous quantitative variables of non-normal distribution were presented as median (interquartile range, IQR) and analyzed with a Mann-Whitney U test. Categorical variables were reported as counts and percentages and analyzed by Chi-square test or Fisher's exact test, depending on the sample size. A 2-sided P value < 0.05 was considered to be statistically significant.

3. Results

Patient characteristics and clinical manifestation: During investigation period, a total of 123 cases with mean age 28 ± 7 years were identified. All met APS classification criteria by age 18 or alder. The minimum age was 22 years and the maximum 43 years. Most patients were between 30 - 35 years old (**Table 1**).

Within this cohort, there were 38 pregnant women showed a family history of VTE, myocardial infarction or stroke in the first-degree relatives, younger than 50 years. The prevalence of this history was 31.4% (11 patients) compared to 68.6% (27 patients) who did not (**Table 2**).

Regarding the family history of thrombosis, the most important risk factor for VTE in pregnancy was thrombophilia. Thrombophilia was present in 61.5% of the 123 patients. Both acquired or inherited thrombophilia increase the risk.

The association between the occurrence of thrombosis and mutations was assessed in the study group: FV Leiden, 20210 prothrombin genes, MTHFR gene mutations (**Figure 1**).

Table 1. Distribution of patients according to the age group.

Age group	N	%
Under 29 years old	33	27
30 - 35 years old	61	50
Over 36 years old	29	23
Total	123	100

Table 2. Family history.

	N	Prevalence (%)
No history	27	68.6
History	11	31.4
Total	38	100

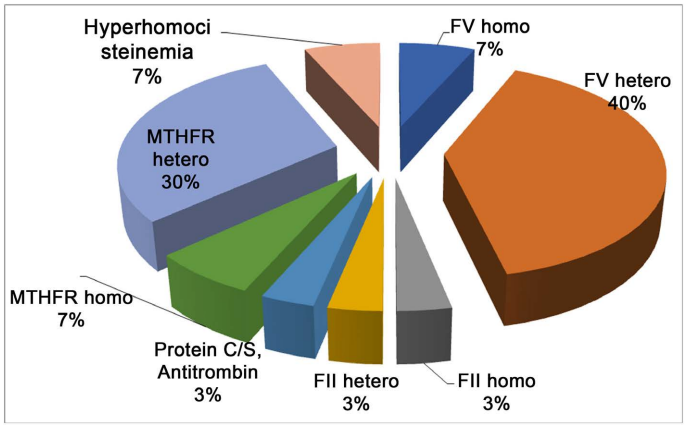

Figure 1. Thrombophilia's (61.5%) and structure.

There was a positive association between thrombosis and factor V Leiden. The association was not statistically significant but showed a trend (Table 3).

The association with the presence of FII G20210A mutation in the prothrombin gene was negative (Table 4). Unfortunately, the number of cases with this mutation in the study was too small to obtain meaningful data. In literature, the risk was 2.4 in homozygous and heterozygous, 0.5 higher than the normal population, according to ACOG.

Similar to literature, there was no positive association with MTHFR C677T mutations (Table 5).

The statistical analysis showed that of all the variables studied, only factor V Leiden and the presence of family history of thrombosis have the Odds Ratio greater than 1, so this means that these patients are at risk of thrombosis.

Results: arterial thrombosis cases: N = 19, 36%. Structure (Figures 2-4).

56% cases had a deep venous thromboembolism of lower limbs, 23% cases had pulmonary embolism, cases had cerebral venous sinuses thrombosis and three cases had cerebral ischemic stroke. Of these, 8.3% occurred in the first trimester

Table 3. Association with factor V Leiden.

	Present		
Factor V Leiden	N	%	P
Negative	65	53	0.059
Heterozygote	49	40	
Homozygote	9	7	
Total	123	100	

Table 4. Association with factor II G20210A.

	Present		
Factor II G20210A	N	%	P
Negative	119	97	0.288
Heterozygote	4	3	
Total	123	100	

Table 5. Association with MTHFR C667T.

	Present		
MTHFR C667T	N	%	P
Negative	77	63	0.416
Heterozygote	37	30	
Homozygote	9	7	
Total	123	100	

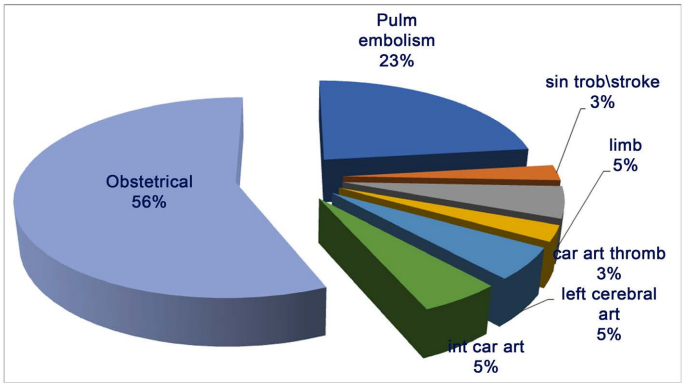

Figure 2. Results: venous thrombosis cases: N = 18, 34.6%. Structure.

of pregnancy (two cases of distal DVT), 16.6% occurred in the second trimester of pregnancy (three cases of DVT distal and one case of longitudinal cerebral sinus thrombosis), 33.3% occurred in the third trimester of pregnancy (three proximal DVT cases, three pulmonary embolisms, one ischemic stroke of the middle cerebral artery, one thrombosis of transverse cerebral sinus). 41.6% of the thrombotic events occurred postpartum, up to two months of puerperium

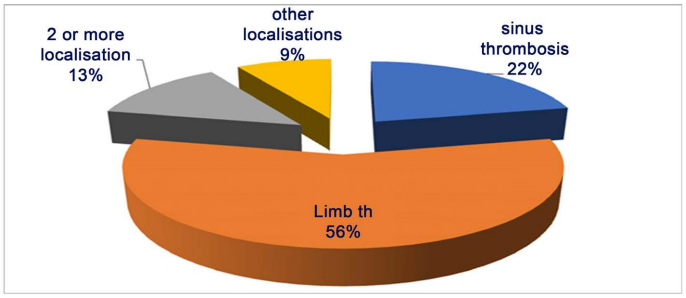

Figure 3. Supposed triggers/provokers.

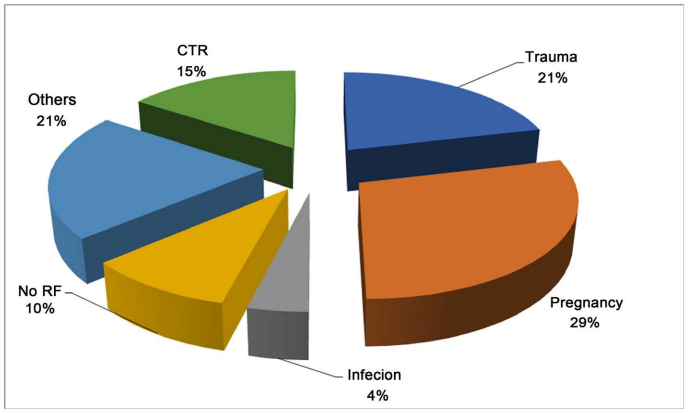

Figure 4. Distribution of patients into groups causing thrombosis.

(five cases of DVT, two pulmonary embolisms, one transient ischemic attack of the anterior cerebral artery, one longitudinal sinus thrombosis and one ischemic attack of the middle cerebral artery).

4. Conclusion

The risk of thrombosis in patients with factor V Leiden is 2.66 times higher than that of the patients negative for this mutation (OR 2.66 95% CI 0.96 - 7.37 P = 0.059). We did not find any statistical association with mutations in the MTHFR gene. Pregnant women with a family history of thrombosis present a 2.18-fold higher risk of thrombosis (OR 2.18 95% CI 0.9 - 5.26 P = 0.085). Occurrence of thrombotic events is identified in the last trimester of pregnancy, but especially postpartum. Thrombosis in pregnancy is a redoubtable complication requiring an excellent cooperation between the obstetrician and anesthesiologist.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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