Síndrome antifosfolipídica
Antiphospholipid syndrome

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Resumo

A síndrome antifosfolipídica (SAF) carateriza-se pelo desenvolvimento de tromboses venosas e/ou arteriais, muitas vezes múltiplas, e pela morbidade gestacional (por perdas fetais recorrentes), na presença de anticorpos antifosfolipídicos. As estimativas indicam que a incidência da SAF é de cerca de 5 novos casos por 100 000 pessoas por ano e a prevalência é de cerca de 40-50 casos por 100 000 pessoas. Os aPL são positivos em aproximadamente 13% dos pacientes com acidente vascular cerebral, 11% com enfarte do miocárdio, 9,5% dos pacientes com trombose venosa profunda e 6% dos pacientes com morbidade gestacional.

Atualmente, há consenso no tratamento de pacientes com SAF com trombose com anticoagulação oral de longa duração e para evitar manifestações obstétricas com o uso de aspirina e heparina. Esta revisão resume os principais conhecimentos sobre os aspectos clínicos e terapêuticos desta síndrome.

Palavras-chave: Acidente Vascular Cerebral; Anticorpos Anticardiolipina; Anticorpos Antifosfolipídeos; Síndrome Antifosfolipídica

Abstract

The antiphospholipid syndrome (APS) is defined by the development of venous and/or arterial thromboses, often multiple, and pregnancy morbidity (mainly, recurrent fetal losses), in the presence of antiphospholipid antibodies (aPL). Some estimates indicate that the incidence of the APS is around 5 new cases per 100 000 persons per year and the prevalence around 40-50 cases per 100 000 persons. The aPL are positive in approximately 13% of patients with stroke, 11% with myocardial infarction, 9.5% of patients with deep vein thrombosis and 6% of patients with pregnancy morbidity.

Currently, there is consensus in treating APS patients with thrombosis with long-term oral anticoagulation and to prevent obstetric manifestations with the use of aspirin and heparin. This review summarizes the main knowledge on the clinical and therapeutic aspects of this syndrome.

Keywords: *Antibodies, Anticardiolipin; Antibodies, Antiphospholipid; Antiphospholipid Syndrome; Stroke*

Introduction

The antiphospholipid syndrome (APS) is characterized by the development of venous and/or arterial thromboses, often multiple, and pregnancy morbidity (mainly, recurrent fetal losses), in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-$\beta_2$glycoprotein-I (β_2GPI) antibodies.[1-4]

The APS can be found in patients having neither clinical nor laboratory evidence of another definable condition (primary APS) or it may be associated with other diseases, mainly systemic lupus erythematosus (SLE), but occasionally with other autoimmune conditions,[1] infections,[2] drugs,[1] and malignancies.[3] A minority of APS patients can develop a devastating variant termed catastrophic APS.[5]

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Epidemiology

The aPL can appear in different scenarios, such as asymptomatic aPL carrier patients, thrombotic APS with recurrent venous and/or arterial thrombosis, obstetric APS affecting otherwise healthy women with recurrent pregnancy loss, patients with non-APS classification criteria manifestations (i.e, thrombocytopenia, hemolytic anemia or *livedo reticularis*) or with catastrophic APS.[5]

Prevalence of the aPL in the general population ranges between 1% - 5%. However, only a minout together all the published case reports as well as the new diagnosed cases from all over the world, an international registry of patients with catastrophic APS ("CAPS Registry") was crerity of these individuals develop the APS. Some estimates indicate that the incidence of the APS is around 5 new cases per 100 000 persons per year and the prevalence around 40-50 cases per 100 000 persons.[6] Specifically, aPL are positive in approximately 13% of patients with stroke, 11% with myocardial infarction (MI), 9.5% of patients with deep vein thrombosis (DVT) and 6% of patients with pregnancy morbidity.[7]

The prevalence of the catastrophic APS is scarce (less than 1% of all cases of APS).[5,8,9] In order to pated in 2000 by

Table 1: Most common manifestations in the APS, according to the "Euro-Phospholipid Project".[12]

Manifestations	%
Peripheral thrombosis	
Deep vein thrombosis	38.9
Superficial thrombophlebitis in legs	11.7
Arterial thrombosis in legs	4.3
Venous thrombosis in arms	3.4
Arterial thrombosis in arms	2.7
Subclavian vein thrombosis	1.8
Jugular vein thrombosis	0.9
Neurologic manifestations	
Migraine	20.2
Stroke	19.8
Transient ischemic attack	11.1
Epilepsy	7.0
Multiinfarct dementia	2.5
Chorea	1.3
Acute encephalopathy	1.1
Pulmonary manifestations	
Pulmonary embolism	14.1
Pulmonary hypertension	2.2
Pulmonary microthrombosis	1.5
Cardiac manifestations	
Valve thickening/dysfunction	11.6
Myocardial infarction	5.5
Angina	2.7
Myocardiopathy	2.9
Vegetations	2.7
Coronary by-pass rethrombosis	1.1
Intraabdominal manifestations	
Renal manifestations (glomerular thrombosis, renal infarction, renal artery thrombosis, renal vein thrombosis)	2.7
Gastrointestinal manifestations (esophageal or mesenteric ischemia)	1.5
Splenic infaction	1.1
Cutaneous manifestations	
Livedo reticularis	24.1
Ulcers	5.5
Pseudovasculitic lesions	3.9
Digital gangrene	3.3
Cutaneous necrosis	2.1
Osteo-articular manifestations	
Arthralgia	38.7
Arthritis	27.1
Avascular necrosis of bone	2.4
Ophthalmologic manifestations	
Amaurosis fugax	5.4
Retinal artery thrombosis	1.5
ENT manifestations	
Nasal septum perforation	0.8
Hematological manifestations	
Thrombocytopenia (<100,000/μL)	29.6
Hemolytic anemia	9.7
Obstetric manifestations (pregnant female=590)	
Pre-eclampsia	9.5
Eclampsia	4.4
Abruptio placentae	2.0
Fetal manifestations (pregnancies=1,580)	
Early fetal losses (<10 weeks)	35.4
Late fetal losses (≥ 10 weeks)	16.9
Live births	47.7
Prematures	10.6

the European Forum on Antiphospholipid Antibodies. Currently, it documents the entire clinical, laboratory and therapeutic data of more than 500 patients.[5]

Pathogenesis

Autoantibodies associated with APS are directed against a number of proteins of the plasma or expressed on, or bound to, the surface of vascular endothelial cells or platelets. The involvement of aPL in clinically important normal procoagulant

Table 2: Revised classification criteria for the APS.[18]

Clinical criteria
1. Vascular thrombosis[1] One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall
2. Pregnancy morbidity (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, *or* (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (a) eclampsia or severe preeclampsia defined according to standard definitions, or (b) recognised features of placental insufficiency[2], *or* (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.
Laboratory criteria[3]
1. Anticardiolipin antibody of IgG and/or IgMisotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile, or >mean + 3SD of 40 healthy controls), on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay.
2. Lupus anticoagulant present in plasma, on 2 or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies).
3. Anti-β_2 glycoprotein-I antibody of IgG and/or IgMisotype in serum or plasma, present on 2 or more occasions, at least 12 weeks apart, measured by a standardized enzyme-linked immunosorbent assay, according to recommended procedures. o Definite APS is present if at least one of the clinical criteria and one[3] of the laboratory criteria are met, with the first measurement of the laboratory test performed at least 12 weeks from the clinical manifestation.[4]
[1]Coexisting inherited or acquired factors for thrombosis are **not** reason for excluding patients from APS trials. However, two subgroups of APS patients should be recognized, according to: (a) the **presence**, and (b) the **absence** of additional risk factors for thrombosis. Indicative (but not exhaustive) such cases include: age (>55 in men, and >65 in women), and the presence of any of the established risk factors for cardiovascular disease (hypertension, diabetes *mellitus*, elevated LDL or low HDL cholesterol, cigarette smoking, family history of premature cardiovascular disease, body mass index ≥ 30 kg/m^2, microalbuminuria, estimated GFR <60 mL/min), inherited thrombophilias, oral contraceptives, nephrotic syndrome, malignancy, immobilization, surgery. Thus, patients who fulfill criteria should be stratified according to contributing causes of thrombosis. [2]Generally accepted features of placental insufficiency include: (1) abnormal or non-reassuring fetal surveillance test(s), e.g., a non-reactive non-*stress* test, suggestive of fetal hypoxemia, (2) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g., absent end-diastolic flow in the umbilical artery, (3) oligohydramnios, e.g., an amniotic fluid index of 5 cm or less, or (4) a post natal birth weight less than the 10th percentile for the gestational age. [3]Investigators are strongly advised to classify APS patients in studies into one of the following categories: I: More than one Laboratory criteria present (any combination) IIa: Anti-cardiolipin antibody present alone IIb: Lupus anticoagulant present alone IIc: Anti-β_2 glycoprotein-I antibody present alone [4]Classification of APS should be avoided if less than 12 weeks or more than 5 years separate the positive aPL test and the clinical manifestation.

and anticoagulant reactions and on certain cells altering the expression and secretion of various molecules are the basis for possible mechanisms by which aPL may develop thrombotic events in patients with APS. In depth reviews of these mechanisms can be found elsewhere.[10,11]

Clinical Manifestations

The clinical picture of the APS is characterized by venous and arterial thromboses, pregnancy morbidity (mainly, fetal losses) and moderate thrombocytopenia. Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations. Any combination of vascular occlusive events may occur in the same individual and the time interval between them also varies considerably from weeks to months or even years.[12-14] The prevalence of the main manifestations in a cohort of 1000 patients with APS ("Euro-Phospholipid Project") are collected in Table 1.[12]

Several attempts have been made in order to identify the individual risk of thrombosis in aPL positive patients.[15,16] A study of pregnant women with APS reported that patients with triple aPL positivity (ie, positivity for LA, aCL, and anti-β_2GPI) and/or previous thromboembolism had an increased likelihood of poor neonatal outcomes than patients with double or single aPL positivity and no thrombosis history.[15] More recently, a global APS score (GAPSS) was developed in a cohort of 211 SLE from a single centre after the combination of several independent risk factors for both thrombosis and pregnancy loss. The final score includes 6 factors with different weights: IgG/IgM aCL (5 points), IgG/IgM anti-β_2GPI antibodies (4 points), LA (4 points), IgG/IgM anti-phosphatidylserine–prothrombin complex antibodies (3

Table 3: Preliminary criteria for the classification of catastrophic APS.[20]

Clinical criteria
1. Evidence of involvement of three or more organs, systems and/or tissues*
2. Development of manifestations simultaneously or in less than a week.
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue**.
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)***

* Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (>180/100 mmHg) and/or proteinuria (>500 mg/24 h).

** For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

*** If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.

Definite catastrophic APS: All 4 criteria

Probable catastrophic APS:
- All 4 criteria, except for only two organs, systems and/or tissues involvement.
- All 4 criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS.
- 1, 2 and 4
- 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation.

Table 4: Our treatment strategies of patients with definite antiphospholipid syndrome.

Clinical manifestation	Treatment
Thrombosis	OAC
- Venous thrombosis	INR 2.0-3.0
- Arterial thrombosis	INR 3.0-4.0 or LDA plus OAC INR 2.0-3.0
Obstetric morbidity	LDA[1] plus LMWH
- First pregnancy or with previous normal pregnancies	Close fetal and maternal control without specific treatment or LDA
- Early miscarriages without previous thrombosis	LDA
- Fetal loss or preeclampsia or HELLP syndrome	LDA plus prophylactic doses of LMWH
- APS patients with previous thrombosis	LDA plus full therapeutic doses of LMWH
- All women	Prophylactic doses of LMWH for 6 weeks during the postpartum

[1]Start aspirin before conception in all cases

Abbreviations: APS: antiphospholipid syndrome; HELLP: hemolysis, elevated liver enzymes, low count platelets; INR: international randomized ratio; LDA: low dose aspirin; LMWH: low-molecular-weight hepari

points), hyperlipidemia (3 points) and arterial hypertension (1 point). A GAPSS cut-off value higher than 10 points appears to have the best prognostic yield.[16]

Classification Criteria

A preliminary classification set of criteria was established after an expert workshop held in Sapporo, Japan, in 1999.[17] These classification criteria were updated in another workshop was held in Sydney, Australia, in 2006 in which the experts proposed the inclusion of anti-β_2GPI antibodies. Although no new clinical criteria were added, some particular features were remarked on, such as associated APS features, including cardiac valve involvement, *livedo reticularis*, thrombocytopenia, APS nephropathy, and non-thrombotic central nervous system manifestations (i.e. cognitive dysfunction)[18] (Table 2).

This revised APS classification criteria[19] provide a more uniform basis for selecting patients for APS research by emphasising risk stratification. They strongly recommend investigating coexisting inherited and acquired thrombosis risk factors in patients with APS, especially in those who are included in clinical trials. An assessment of these 2006 revised APS classification criteria has shown that only 59% of the patients meeting the 1999 APS Sapporo classification criteria met the revised criteria.[19]

The preliminary classification criteria for catastrophic APS were formulated at a workshop in Taormina, Italy, in 2002, during the 10th International Congress on aPL (Table 3).[20] A validation study showed that they have a sensitivity of 90.3%, a specificity of 99.4%, a positive predictive value of 99.4% and a negative predictive value of 91.1%.[21] A recent evidence-based set of guidelines for the diagnosis and management of catastrophic APS has formulated the recommendation that these classification criteria can be also used as diagnostic criteria.[22]

Treatment

Treatment of thrombosis in APS patients is based on long-term oral anticoagulation and treatment of obstetric manifestations on the use of aspirin and heparin.[23] These recommendations are based on randomized controlled trials and observational studies

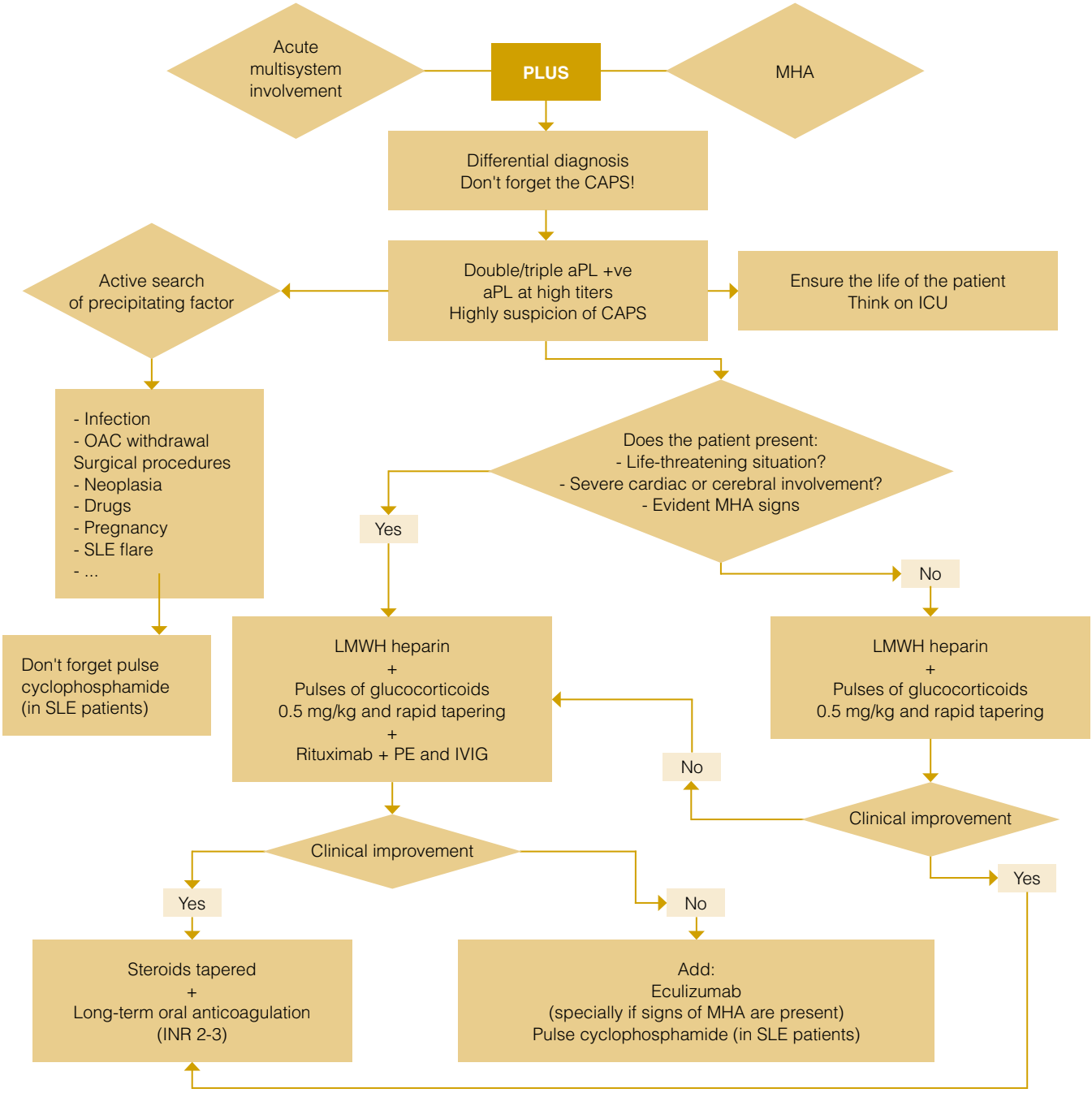

Figure 1: Algorithm for the management of catastrophic antiphospholipid syndrome.

(Table 4). In detail, patients with definite APS with first venous thrombosis have to be treated with prolonged oral anticoagulation at a target international normalized ratio (INR) of 2.0-3.0. Anticoagulation at INR of 3.0-4.0, isolated antiaggregation, anticoagulation at INR 2.0-3.0 or anticoagulation at INR 2.0-3.0 plus antiaggregation have been proposed for definite APS patients with arterial thrombosis. Regarding obstetric APS, although combined therapy with low-dose aspirin and low-molecular-weight heparin is the mainstay of treatment in women with obstetric APS, the strength of evidence of its efficacy is under discussion.[24]

Otherwise, in the field of APS there are grey areas where the evidence is scarce and where the management of certain patients is difficult. Some examples are patients with "seronegative" APS, those who do not display formal (clinical or laboratory) classification criteria for APS, those with refractory APS despite optimal treatment (recurrent thrombotic events despite optimal anticoagulation or recurrent fetal losses despite the combination of aspirin and low molecular weight heparin), and the treatment of clinical manifestations not included in the classification criteria such as hematologic manifestations (thrombocytopenia and haemolytic anemia), neurologic manifestations (chorea, myelitis or multiple sclerosis-like lesions), nephropathy and heart valve disease associated with antiphospholipid antibodies. In these cases, the recommendations are based on the common sense since the published evidence is scarce or it does not exist.[23]

In cases of catastrophic APS, an aggressive treatment is required (Fig. 1). Therefore, early diagnosis is very important to start adequate therapy and decrease the high mortality rate of these patients. Once the diagnosis is made or suspected, searching and treating the precipitating factor, mainly infection, is the first step of treatment. The specific therapy of catastrophic APS is the combination of anticoagulation with heparin, and corticosteroids as first line of treatment. Additionally adding intravenous immunoglobulins and/or plasma exchange have to be considered in life-threatening cases. In patients with associated SLE, intravenous cyclophosphamide has demonstrated be beneficial. In refractory cases, rituximab or eculizumab should be added.[22,25]

Outcome and Organ Damage

Given that APS affect predominantly young patients, assessment of organ damage is crucial but evidence in that field is limited. A retrospective analysis was published that focused in morbidity, mortality, and organ damage in 135 APS patients (89 primary APS and 46 with secondary APS).[26] Patients were clustered according to the initial event: arterial thrombosis, DVT or pregnancy morbidity. One-fourth of the patients progressed to organ damage in a mean time of 10 years from disease onset. The highest morbidity was attributed to neurologic damage, which was more common among patients with arterial thrombosis as an initial manifestation.

During the follow-up study period of the "Euro-Phospholipid Project", a 10-year survival rate of 91% was reported.[14] During this follow-up period, 93 (9.3%) patients died. The main causes of death were thrombosis (36.5%) and infections (26.9%).

Patients with APS still develop significant morbidity and mortality despite current treatment (mainly oral anticoagulants and/or antiaggregant agents); therefore, it is imperative to increase the effort in determining optimal prognostic markers and therapeutic measures to prevent these important complications of the APS. ■

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