Thrombotic risk in antiphospholipidic syndrome: From hypothesis to current evidence (Review)

CLAUDIA MIHAELA GAVRIȘ*, LAURENȚIU DĂNUȚ NEDELCU* and ALINA MIHAELA PASCU*

Faculty of Medicine, 'Transilvania University' of Brașov, 500036 Brasov, Romania

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Abstract. Thirty-five years after it was first described, antiphospholipid syndrome (APS) is unanimously recognized as a systemic autoimmune disease, a major acquired thrombophilia, which can affect any arterial or venous vascular territory, explaining the great diversity of clinical manifestations. The current classification criteria updated in the International Consensus Statement for Definite Antiphospholipid Syndrome from Sydney cannot explain alone the unpredictable evolution with thrombotic events of the patients diagnosed with APS. Although the link to genetics and epigenetics has not been clearly defined as in other autoimmune diseases, it is clear that a proper stratification of thrombotic risk in the era of personalized medicine must include classic biological markers (antiphospholipid antibodies, aPL), along with the already recognized phenotypes, non-conventional serological markers, and additional genetic risk factors for thrombosis. Moreover, with advancing age, a patient with APS develops other thrombotic risk factors which include: hypertension and dyslipidemia among others. According to the classification criteria, a patient is considered to have a low, moderate or high thrombotic risk. In clinical practice, patients with the same risk score may have completely different evolutions in terms of the recurrence of thrombosis. Concerning this approach, it appears that new non-conventional serological markers, phenotype-assessment and genetic determinants have an increasing importance and should be reconsidered in a proper thrombotic risk evaluation in patients with APS, compared to the initial concept of APS as first defined.

Correspondence to: Professor Laurențiu Dănuț Nedelcu, Faculty of Medicine, 'Transilvania University' of Brașov, 29 Eroilor Street, 500036 Brasov, Romania
E-mail: laurnedelcu@yahoo.com

*Contributed equally

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1. Introduction

Thirty five years after it was first described, antiphospholipid syndrome (APS) is unanimously recognized as a systemic autoimmune disease, a major acquired thrombophilia, which can affect any arterial or venous vascular territory, explaining the great diversity of clinical manifestations (1,2). Patients with APS are at a high risk for developing thrombotic arterial, venous and obstetric complications (recurrent pregnancy loss). The diagnostic criteria include the presence of any of the clinical criterion mentioned above plus at least one laboratory criterion out of three possible antiphospholipid antibodies (aPLs): i) IgG and IgM anticardiolipin (aCL) at a titer >40 IU/ml; ii) lupus anticoagulant (LA); iii) anti-$\beta_2$glycoprotein-1 antibodies (aβ_2GPI). Medium/high titer of aCL/aβ_2GPI has been defined as >99th percentile. Low-titer aCL/aβ_2GPI positivity (>95th to <99th percentile) is considered positive for obstetric but not for thrombotic APS (1,2).

Thrombotic risk assessment in patients with APS is essential for establishing an appropriate treatment for the primary and secondary prophylaxis of arterial or venous and obstetrical thrombotic events which define the clinical picture. In the assessment of the thrombotic risk, the role of classical serological markers is limited. Galli *et al* (3) proposed three major modifications: implementing strict guidelines for the performance of LA assays, excluding aCL assays from the criteria, despite the fact they are currently used and, restricting the measurement of aβ_2GPI antibodies to IgG. Efforts to standardize antiphospholipid antibody assays have been reported (3-8).

There is currently no predictive factor for the evolution of thrombotic complications in APS. There are studies that have evaluated the role of a high titer of aPL/LA, and, respectively, the association of several laboratory criteria, with controversial results. Patients with a high aPL titer and the presence of all

three biological markers do not always evolve with recurrent thrombosis (more than 2) and vice versa (9-14).

For a proper antibody profile of these patients, all of the three tests should be performed at the same time, and should be positive on at least two different testing occasions at least 12 weeks apart. Triple-positive patients (aCL, LA and aβ_2GPI IgG and IgM) are at high risk for thrombosis and APS-related pregnancy morbidity (1,15).

A few studies have evaluated the β_2GPI domain I antibodies (aDI), a subgroup of aβ_2GPI IgG, as an independent risk factor for thrombosis, and have revealed that aD1 had no added value to the current aPL diagnostic panel (16,17).

Therefore, the overall thrombotic risk of a patient with APS may be influenced by other prothrombotic factors, representing sort of a second hit to trigger a new thrombotic event.

2. Non-conventional/emerging antiphospholipid syndrome serologic markers

APS is an autoimmune disease that may have a predictable course, similar to other autoimmune diseases. Upon appearance of the first diagnostic marker, the diagnosis of seropositive APS is established. Yet, but there are also forms of seronegative APS. In this circumstance, an emerging second generation of diagnostic biological markers has been described: IgG and IgM directed against phosphatidylserine (PS), prothrombin (PT), phosphatidylserine/prothrombin (PS/PT) complex, and against phosphatidic acid (PA), phosphatidyl-ethanolamine (PE), phosphatidyl-glycerol (PG), phosphatidyl-inositol (PI), Annexin V (A5), and Annexin II (A2). To date, there are studies that have evaluated the frequency of their association in patients with seronegative APS (15-20). Which of these non-conventional, emerging biological markers has a predictive role for the evolution of recurrent thrombosis in APS warrants further investigation. Whether the positivity for multiple non-conventional markers should be considered as alternative predictors of a severe APS evolution has to be substantiated by further research.

In another autoimmune disease, rheumatoid arthritis, the second generation of biological markers has proven to have a much better predictive role for the evolution of erosive forms of arthritis than the first generation of markers, represented by the rheumatoid factor (18-20).

Antibodies against the PS/PT complex are not included in the APS laboratory criteria but their positivity has been recently proposed as a part of the global APS score (GAPSS), and has been shown to be a strong prognostic factor for both arterial and venous thrombosis (21-23).

3. Phenotype assessment of antiphospholipid syndrome

As in other autoimmune diseases, several disease phenotypes have been described in APS. Sciascia *et al* conducted a significant study by performing cluster analysis on a large cohort of patients with APS and identified 5 distinct clusters: Clusters 1, 2, 3 and 5 corresponded to well-known entities, such as primary thrombotic APS (PAPS), APS associated with systemic lupus erythematosus (SLE), secondary APS (SAPS), obstetric APS, and cluster 4. Cluster 4 included aPL patients (aPL carriers) with the highest prevalence of cytopenia (mainly thrombocytopenia) when compared to cluster 1 and cluster 2. Thrombotic risk appeared to correlate with the disease phenotype (24).

4. Genetics of antiphospholipid syndrome

Among the associated prothrombotic factors in patients with APS, genetic thrombophilia is not yet sufficiently evaluated in routine clinical practice. Patients already enrolled for long-term/life-long anticoagulant treatment are currently not always fully evaluated for a possible association with thrombophilia (25-28).

Interactions between acquired and genetic risk factors become increasingly related to a higher thrombotic risk. Many studies have determined the prevalence of common gene polymorphisms in patients with aPL. Some of these polymorphisms affect proteins directly related to aPLs (β_2GPI gene polymorphisms), others affect normal hemostasis components (tissue factor pathway inhibitor, thrombomodulin THMD mutations, polymorphism in the factor XIII gene, polymorphisms in platelet Fc gamma-receptor IIA), and others are related to immune or inflammatory pathways (endothelial protein C receptor, P-selectin glycoprotein ligand-1 gene, CD40 ligand gene) (29-32).

Patients with PAPS may be associated with a clinically underestimated genetic thrombophilia that may be responsible for triggering thrombotic events (25).

Thrombotic risk assessment scores in patients with APS do not include genetic or acquired thrombophilia, and concerning unconventional serological markers, only the antibody anti-phosphatidylserine/prothrombin complex (aPS/PT) IgG and IgM I is considered (22). These antibodies have been shown to be more useful in thrombotic risk assessment than anti-PT and, respectively, anti-PS antibodies alone, and may coexist in the same patient (33-35).

The heterogeneity of thrombotic manifestations in patients with APS suggests a possible intervention of other additional risk factors which may contribute to their prothrombotic profile. Among this, several studies have described the coexistence of numerous genetic risk factors for thrombosis: Leiden factor V, antithrombin deficiency, methylentetrahydrofolate-reductase (MTHFR), homocysteine, protein C or protein S deficiency, acquired activated-protein C resistance (19,30,36,37).

5. Conclusions and perspectives

For a systemic autoimmune disease clinically defined by thrombotic complications, as APS is to date considered, in clinical practice it is essential to stratify the global thrombotic risk. Considering the multitude of (major or minor) genetic or acquired factors that interfere with this risk, each patient represents a distinct entity. In the evolution towards personalized medicine, genome-wide linkage analysis and larger cohort case-control association studies, as well as multicenter international collaborators such as the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) (19) must address crucial questions such as:

Do non-conventional, emerging biological markers (that are not commonly evaluated in patients with seropositive APS) somehow play a predictive role in the evolution of recurrent thrombosis? Is the course of recurrent thrombosis in patients

with a reduced titer and/or the presence of a single laboratory diagnostic criterion (aCL, LA or aβ_2GPI) significantly determined by the association of thrombophilia?

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Authors' contributions

CMG and AMP performed the literature search for relevant publications on the topic. CMG, LDN and AMP participated in drafting the manuscript and provided critical insight. All the authors verified and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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