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Antiphospholipid Syndrome: To Classify or Not to Classify?

Antifosfolipid Sendromu: Sınıflandırmalı mı Yoksa Sınıflandırmamalı mı?

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Abstract

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder resulting in thrombosis, microvascular disease, morbidity in pregnancy, and/or non-thrombotic manifestations. The recently introduced 2023 American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) APS classification criteria, with significantly higher specificity compared to the revised Sapporo criteria, now reflect the current thinking about APS and provide a new foundation for future APS research. The purpose of this short commentary is to discuss the appropriate circumstances under which the 2023 ACR/EULAR classification criteria could be used and to demonstrate how the new criteria can be applied to simple case scenarios.

Keywords: Antiphospholipid syndrome, Classification criteria, Antiphospholipid antibodies

Öz

Antifosfolipid sendromu (AFS) tromboz, mikrovasküler hastalık, gebelik morbiditesi ve/veya trombotik olmayan belirtilerle sonuçlanan sistemik otoimmün bir bozukluktur. 2023'te tanıtılan Amerikan Romatoloji Koleji (ACR) ve Avrupa Romatoloji Birlikleri İttifakı (EULAR) AFS sınıflandırma kriterleri, revize edilmiş Sapporo kriterlerine kıyasla önemli ölçüde daha yüksek özgüllüğe sahip olduğundan güncel AFS yorumunu yansıtmakta ve gelecekte AFS araştırmaları için yeni bir temel sağlamaktadır. Bu kısa yorumun amacı, 2023 ACR/EULAR sınıflandırma kriterlerinin kullanılabileceği uygun durumları tartışmak ve yeni kriterlerin nasıl basit vaka senaryolarına uygulanabileceğini göstermektir.

Anahtar Sözcükler: Antifosfolipid sendromu, Sınıflandırma kriterleri, Antifosfolipid antikorları

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder resulting in thrombosis, microvascular disease, morbidity in pregnancy, and/or non-thrombotic manifestations such as cardiac valve disease or thrombocytopenia [1]. The three commonly used tests to detect the antibodies responsible for APS, namely antiphospholipid antibodies (aPLs), are the anticardiolipin antibody (aCL) enzyme-linked immunosorbent assay (ELISA), anti-β_2-glycoprotein-I antibody (aβ_2GPI) ELISA, and lupus anticoagulant (LA) functional coagulation assay.

Disease classification criteria are used to capture well-defined homogeneous cohorts for research. Given the strict and standardized definitions included in classification criteria, the goal is not to identify the "entire universe" of all possible patients, but rather to capture a majority of patients who share the key features of the condition of interest [2]. Thus, classification criteria are not "diagnostic criteria" and they should not be used for diagnostic and therapeutic decisions in clinical settings.

The APS classification for research was established based on the Sapporo criteria, published in 1999 [3] and revised in 2006 [4]. Given the limitations of the Sapporo criteria [5], including a lack of strict definitions, an international multidisciplinary effort was initiated, supported by the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR), to develop new APS classification criteria. These recently introduced 2023 ACR/EULAR APS classification criteria, with significantly higher specificity (99%) compared to the revised Sapporo criteria (86%), now reflect the current thinking about APS and provide a new foundation for future APS research. The new criteria have hierarchically clustered and weighted independent clinical and laboratory domains; APS classification based on the new criteria requires a threshold to be achieved (Table 1).

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The purpose of this short commentary is to discuss the appropriate circumstances under which the 2023 ACR/EULAR classification criteria could be used and to demonstrate how the new criteria can be applied to simple case scenarios. Detailed discussion about the diagnosis and management of APS can be found elsewhere [6,7].

When to Classify and When Not to Classify?

The new 2023 ACR/EULAR APS classification criteria aim to identify homogeneous APS cohorts for research purposes; thus, both researchers and clinicians should fully understand the implications of the criteria. In fact, for both research and clinical practice settings, it will be helpful to clarify two potential misunderstandings:

"This patient does not meet APS classification criteria; thus she/he cannot participate in any research study": this is an incorrect statement because if a patient does not meet the APS classification criteria, i.e., falls below the threshold at which a significant number of experienced physicians would feel comfortable calling the case "APS" for research purposes, the case may still be uncertain, equivocal, or controversial rather than a case of "no APS." As discussed above, classification criteria do not necessarily capture patients with rare and unusual manifestations of a disease. Thus, rather than performing no research with these patients, they should be studied or analyzed separately, i.e., not combined with cases meeting the 2023 ACR/EULAR APS classification criteria. Ideally, those patients who do not fulfill the classification criteria should meet either clinical OR laboratory criteria. In fact, the results of such studies may

Table 1. Summary of 2023 ACR/EULAR antiphospholipid syndrome (APS) classification criteria (please refer to the original publication [1] or the online calculator [8] for details and definitions; patients accumulating at least three points each from the laboratory and clinical domains are classified as having APS).

Entry criteria	
At least one clinical criterion listed below (domains 1-6) plus positive antiphospholipid antibody (aPL) test (lupus anticoagulant test, or moderate-to-high titers of anticardiolipin or anti-β_2-glycoprotein-I antibodies [IgG or IgM]) within 3 years of the clinical criterion	
Clinical domains and criteria:	**Weight**
Domain 1. Macrovascular (venous thromboembolism [VTE])	
• VTE with a high VTE risk profile	1
• VTE without a high VTE risk profile	3
Domain 2. Macrovascular (arterial thrombosis [AT])	
• AT with a high cardiovascular disease (CVD) risk profile	2
• AT without a high CVD risk profile	4
Domain 3. Microvascular*	
• Suspected	2
• Established	3
Domain 4. Obstetric	
• Three or more consecutive pre-fetal (<10w) and/or early fetal (10w 0d to 15w 6d) deaths	**1**
• Fetal death (16w 0d to 33w 6d) in the absence of preeclampsia (PEC) with severe features or placental insufficiency (PI) with severe features	**1**
• PEC with severe features (<34w 0d) or PI with severe features (<34w 0d) with/without fetal death	**3**
• PEC with severe features (<34w 0d) and PI with severe features (<34w 0d) with/without fetal death	**4**
Domain 5. Cardiac valve	
Thickening	**2**
Vegetation	**4**
Domain 6. Hematology	
Thrombocytopenia (lowest 20-130x10^9/L)	**2**
Laboratory (aPL) domains and criteria:	**Weight**
Domain 7. aPL test by coagulation-based functional assay (lupus anticoagulant test [LA])	
Positive LA (single - one time)	**1**
Positive LA (persistent)	**5**
Domain 8. aPL test by solid-phase assay (anti-cardiolipin antibody [aCL] ELISA and/or anti-β_2-glycoprotein-I antibody [aβ_2GPI] ELISA [persistent])**	
Moderate-high positive (IgM) (aCL and/or aβ_2GPI)	**1**
Moderate positive (IgG) (aCL and/or aβ_2GPI)	**4**
High positive (IgG) (aCL or aβ_2GPI)	**5**
High positive (IgG) (aCL and aβ_2GPI)	**7**

***Suspected:** Livedo racemosa, livedoid vasculopathy lesions by exam, or acute/chronic aPL nephropathy by physical examination and/or laboratory, or pulmonary hemorrhage by symptoms and imaging; **Established:** Livedoid vasculopathy by pathology; acute/chronic aPL nephropathy by pathology; pulmonary hemorrhage by bronchoalveolar lavage or pathology; myocardial disease by imaging or pathology; or adrenal hemorrhage by imaging or pathology.
****Moderate** (40-79 U) and **high** (>80 U) levels of aCL/aβ_2GPI are based on ELISA.
ELISA: Enzyme-linked immunosorbent assay; ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology.

guide future updates of the 2023 ACR/EULAR APS classification criteria.

"If this patient fulfills the classification criteria, then we can confirm the diagnosis and start treatment": this is also an incorrect statement given, as discussed above, the fact that classification criteria should serve research, not clinical decision-making. Meanwhile, the diagnosis of APS is a complex equation performed by physicians, which should be based on the aPL profile, the strength of the association between aPLs and the event, and the potential other causes of the event. For instance, in an aPL-positive patient with deep vein thrombosis and multiple additional venous thromboembolism (VTE) risk factors, the diagnosis of APS can be easily questioned. Thus, the treatment recommendations may deviate from standard APS recommendations. Similarly, some aPL-positive patients, e.g., those with obstetric morbidity, may be managed as having APS even if they do not fulfill the classification criteria. Future research based on the new criteria is expected to provide better management guidance to clinicians.

How to Classify?

The 2023 ACR/EULAR APS classification criteria include entry criteria (at least one positive aPL test within 3 years of an aPL-associated clinical criterion) followed by weighted criteria clustered into six clinical (macrovascular VTE, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematological) and two laboratory (LA functional coagulation assay and aCL and/or $a\beta_2$GPI IgG/M ELISA) domains. For different aPL-related items included in these domains: a) strict definitions, based on a literature review and steering committee consensus, are also provided [1]; b) when "equally or more likely" causes exist (except the consideration of VTE and cardiovascular disease risk factors), then the item in question should not be scored; and c) the highest weighted item in each domain should be counted toward the total score. Patients accumulating at least three points each from the clinical and laboratory domains are classified as having APS. For the details of the classification criteria and item definitions, please refer to the original publication [1] or the online criteria calculator [8]. Some of the novel features of the new criteria, with the guidance of simple case scenarios to demonstrate the criteria in action, are summarized in Table 2.

Conclusion

The highly specific 2023 ACR/EULAR APS classification criteria will increase the quality of APS research and hopefully trigger further interest in developing and conducting well-designed, risk-stratified, and controlled clinical trials of aPL-positive patients. Thus, the long-term goal would be to provide clinicians with high-quality evidence-based study results and guidelines for improved management decisions and patient outcomes. In the short run, the new classification criteria should not be used for APS diagnosis and management;

Table 2. Novel features of the 2023 ACR/EULAR antiphospholipid syndrome (APS) classification criteria summarized with the guidance of the simple case scenarios (please refer to the original publication [1] or the online calculator [8] for details and definitions; patients accumulating at least three points each from the laboratory and clinical domains are classified as having APS).

Laboratory (aPL) results (item weight in parentheses)	Clinical presentation (item weight in parentheses)	Classçification met[a]?
Persistent LA positivity[b] (5)	VTE with active malignancy[c] (1)	No
	VTE with active malignancy (1) + history of thrombocytopenia[d] (2)	Yes
	Unprovoked VTE (3)	Yes
Persistent triple aPL positivity with high positive IgG aCL and IgG $a\beta_2$GPI[e] (12)	Pulmonary hemorrhage (suspected)[d, f] (2)	No
	Pulmonary hemorrhage (suspected)[d, f] (2) + cardiac valve thickening[d] (2)	Yes
	Pulmonary hemorrhage (established)[d, f] (5)	Yes
Persistent moderate positive IgG aCL and IgG $a\beta_2$GPI[e] (5)	Fetal death (28w) without placental insufficiency (PI) (severe)[d] (1)	No
	Fetal death (28w) without PI (severe)[d] (1) + livedo racemosa (2)	Yes
	Fetal death (28w)[d] with PI (severe) (3)	Yes
Persistent high positive IgM aCL and IgM $a\beta_2$GPI[e, g] (1)	Stroke without high-risk CVD profile[c] (4)	No

[a]Patients accumulating at least three points each from the laboratory and clinical domains are classified as having APS; [b]Performed according to International Society for Thrombosis and Hemostasis guidelines [9]; [c]Risk stratification of thrombotic events is required for macrovascular domains by traditional VTE and CVD risk factors; [d]Otherwise unexplained; [e]Two levels of aCL/$a\beta_2$GPI positivity are defined, moderate (40-79 U) and high (>80 U), based on enzyme-linked immunosorbent assay, not based on new automated systems; [f]Suspected pulmonary hemorrhage is based on symptoms and imaging, whereas established pulmonary hemorrhage is based on symptoms, imaging, and bronchoalveolar lavage or biopsy; [g]Isolated persistent IgM aCL/$a\beta_2$GPI positivity is not sufficient for APS classification, even when clinical criteria are met.

aCL: Anticardiolipin antibody; aPL: antiphospholipid antibody; $a\beta_2$GPI: anti-β_2-glycoprotein-I antibody; CVD: cardiovascular disease; LA: lupus anticoagulant test; VTE: venous thromboembolism; ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology.

however, they can partially serve as a guide while evaluating aPL-positive patients.

Ethics

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