European Journal of Internal Medicine 111 (2023) 1–4

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Review Article

Antiphospholipid antibodies in chronic thromboembolic pulmonary hypertension

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ARTICLE INFO

Keywords:
Chronic thromboembolic pulmonary hypertension
Antibodies
Phospholipids
Lupus inhibitor

ABSTRACT

Acquired thrombophilia and in particular the presence of antiphospholipid antibodies (aPL) may play an important role in the development of chronic thromboembolic pulmonary hypertension (CTEPH). Young patients suffering from an episode of unprovoked pulmonary embolism (PE), or PE provoked by mild risk factors, should be tested for aPL. In case of a positive result, they should be closely followed up and lifelong anticoagulant treatment should be considered. Indeed, aPL-induced thrombophilia may favor PE recurrence with the consequence of possible CTEPH development. The aPL profiles play an important role in this pathway. Patients with PE and triple positivity (lupus anticoagulant, LAC, anti-cardiolipin, aCL, and anti-β2-glycoprotein I, aβ2GPI) are at the highest risk of recurrence and deserve maximum protection by anticoagulant treatment with warfarin.

1. Definition of CTEPH

Pulmonary hypertension (PH) is a chronic progressive condition characterized by an increase of mean pulmonary artery pressure above 25 mmHg at rest. Chronic thromboembolic pulmonary hypertension (CTEPH) is classified as a separate group (group IV), resulting from an incomplete resolution of pulmonary embolism (PE) and formation of chronic obstruction in the main pulmonary arteries [1]. The accepted criteria for the diagnosis of CTEPH is the presence of pre-capillary hypertension with at least one segmental perfusion defect on lung scan and typical findings on conventional pulmonary angiography or computed tomographic angiography after at least 3 months of anticoagulation [2].

2. Incidence of CTEPH

Although associated with significant morbidity and mortality, CTEPH is still considered a relatively rare complication of PE. Poli et al. reported the incidence of CTEPH after a first episode of PE at 0.4% in their series of 239 PE patients [3]. A meta-analysis reported that the pooled incidence of CTEPH was 0.56% in 4047 patients with symptomatic PE [4]. One reason for this low incidence is that most patients who survived a PE become asymptomatic with relatively normal lung perfusion, causing a long latency from the embolic episode to the onset symptoms (mean time-interval of 18 months) [5]. However, residual pulmonary obstruction on lung perfusion scan 6 months after acute PE may predict the development of CTEPH [6]. Conducting a large single-center prospective study, our group found that the cumulative incidence of symptomatic CTEPH was 1%, 3%, and 4% at 6, 12, and 24 months after an episode of PE, despite anticoagulant therapy [7]. Symptomatic CTEPH affects about 4% patients within two years after the first episode of symptomatic PE, with no subsequent increase in incidence. In the U.S. and Europe, the crude annual incidence of CTEPH was 3–5 cases per 100,000 individuals/year, and the incidence following an episode of PE ranged from 0.1% to 9.1%[8]. Furthermore, according to the International CTEPH Registry, 74.8% of the included patients had a previous acute PE and thrombophilia was identified in 31.9% of subjects [9]. In a prospective long-term follow-up study, the cumulative incidence of CTEPH in patients with first-time diagnosed PE, was 11.2% at 3 months, 12.7% at 1 year, 13.4% at 2 years, and 14.5% at 3 years, respectively [10]. Notably, CTEPH may occur months to years after the initial thromboembolic event. Therefore, it's recommended that CTEPH be diagnosed after at least 3 months of effective anticoagulation to discriminate this condition from "subacute" PE [11].

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https://doi.org/10.1016/j.ejim.2023.01.012
Received 25 November 2022; Received in revised form 7 January 2023; Accepted 11 January 2023
Available online 13 January 2023

2.1. Comment

The setting in which PE was diagnosed (ward or Intensive Care Unit) may explain, at least in part, the differences in the incidence of CTEPH after an initial episode of PE reported in various studies. Indeed, the extent of PE is independently associated with the development of CTEPH [7].

3. Prevalence of CTEPH in APS

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by thromboembolic events and/or fetal loss in the presence of persistently positive antiphospholipid (aPL) antibodies on two or more occasions at least 12 weeks apart. APS can be idiopathic, termed primary APS, or occur in the context of other autoimmune disease, most commonly systemic lupus erythematosus (SLE), and known as secondary APS [12]. It has been estimated that the prevalence of PH in APS ranges between 1.8% and 3.5% [13,14]. In the Euro-phospholipid cohort of 1000 patients with APS, the rate of PH was 2.2% [15]. A recent study has estimated that the prevalence of CTEPH among APS was 3.8%, and 5.4% and 0.6% for primary and secondary APS, respectively [16]. The CTEPH in APS-positive patients is unique as pulmonary artery lesions are more proximal and hemodynamic profiles are less compromised [17].

4. aPL antibodies in APS

4.1. Classical aPL antibodies

Classic aPL are detected by the three tests: two immunological assays to detect anti-β2-glycoprotein I (aβ2GPI) and anti-cardiolipin (aCL) antibodies and a functional clotting assay to detect lupus anticoagulant (LAC) [12]. These tests are not the formal laboratory tools to diagnose the syndrome, but parameters to stratify the risk of developing the clinical manifestations. Classification category I includes patients with more than one positive test in any combination, while category II includes patients with a single positive test (IIa LAC, IIb aCL, IIc aβ2GPI antibodies). Positivity for all the three tests is now considered the highest risk aPL profile for thromboembolic events [18]. However, despite conflicting data, LAC is still considered the strongest predictor of thrombosis [19]. It was initially correlated with the presence of aβ2GPI [20], but recent evidence show that the main contributors to LAC activity are anti-phosphatidylserine/prothrombin (aPS/PT) antibodies [21]. Indeed, as LAC is a poorly standardized [22] and cumbersome test that becomes false-positive in plasma containing anticoagulant drugs, aPS/PT antibodies could be used as a surrogate test for LAC [23]. Isolated aβ2GPI antibodies and isolated aCL positivity [24–27] are not associated with an increased risk of thrombosis. If one refers to the different isotypes, thrombotic complications are more strongly associated with antibodies of the IgG isotype [28,29]. Elevated IgM antibodies may be related to specific risk categories. Unfortunately, the lack of distinction of thrombosis subtypes (arterial, venous, or undefined sites) and the absence of paired IgG and IgM results in many studies hampers the analysis of isotype-specific risk categories and the added value of isolated IgM positivity. It has been proposed that aβ2GPI antibodies of the IgA isotype be included in the laboratory criteria for APS, as *in vivo* results support the pathogenic role of β2GPI-dependent IgA in mediating thrombus formation [30]. However, this is not supported by available clinical data, according to which single IgA positivity is more commonly associated with non-criteria manifestations, and IgA testing has not been shown to increase the diagnostic accuracy for APS [31].

In conclusion, the different combinations of aPL antibodies (aPL profiles) are used to stratify risk [32]. Triple positivity, defined by the presence of LAC and medium/high titers of both aCL and aβ2GPI antibodies is the profile most predictive of clinical manifestations and relapse despite conventional treatment [23,33,34].

Besides, Otomo et al. attempted for the first time to score the aPL profiles to quantify thrombotic risk [35].

4.2. Additional aPL antibodies in APS

Further laboratory tests have been reported to detect aPLs: the most important 'non-classification' tests still concern the two major phospholipid-binding proteins thought to represent the true antigenic targets for aPL antibodies, namely β2GPI and prothrombin (PT) [18]. Antibodies against specific Domains (Domain 1 and Domain 4/5) are particularly useful in identifying patients at risk of thromboembolic events [27,36]. To be recognized, human PT must be coated on activated plates or exposed to immobilized phosphatidylserine (PS) by calcium ions [37]. However, heterogeneity of anti-prothrombin antibodies has been found to correlate with thrombosis [38]. The wide variability of epitope specificities and detection methods results in a disparity between available studies on the prevalence and clinical significance of aPT antibodies. The prevalence of antibodies targeting PT also depends on selection of study populations. Recently, through a systematic review, it was shown the high rate of positive aPS/PT in APS patients with an overall prevalence of 65.0%. Both IgG and IgM isotypes of aPS/PT had a comparable prevalence of 50.4% and 45.4%, respectively. When APS patients were LAC positive, the prevalence of aPS/PT positivity increased to 84.6%. Furthermore, a comparable prevalence of 83.4% was observed in triple positive APS patients [23]. In line with these findings, a multicenter study demonstrated aPS/PT positivity rate of 65.5% in 197 thrombotic APS patients, and 95% in 104 triple positive APS patients [39].

5. Role of aPL antibodies in CTEPH

In 1985, Asherson et al. first reported the presence of aPL antibodies in patients with PH [40]. Subsequently, Karmochkine et al. found a high prevalence of aPL antibodies in patients with PH, most of IgG isotype [41]. Since then, the association of aPL antibodies with PH has been investigated in many studies. A recent meta-analysis considering the weighted mean proportion and 95% confidence intervals (CIs) yields a rate of aPL antibody-positive profile of 12.06% (95% CI 8.12–16.65%) among the patients with CTEPH in the random effects model [42]. Patients with positive aPL antibodies are prone to venous thrombosis and may have a recurrent pulmonary embolism, a major risk factor for CTEPH [7]. According to the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee 2020 guideline, LA testing should be performed, together with testing for aCL, and aβ2GPI, to assess the risk profile, in patients who are likely to have APS, including younger patients (<50 years) with unprovoked venous thromboembolism (VTE)[43]. In general, patients with APS at high risk of relapse are young people with an average age of 41 years [33]. Specifically, patients with APS and associated CTEPH are significantly younger than nonAPS-CTEPH patients [17]. Among the 23 patients positive for aPL in a group of 297 patients with CTEPH, 17 patients (74%) had a high-risk triple positive aPL profile [17]. Compared with the APS-negative group, APS patients were significantly younger (30.0 $\pm$ 11.1 vs. 55.6 $\pm$ 12.9 years, $p < 0.0001$), had a more frequent history of pulmonary embolism (95.6% vs. 65.7%, $p = 0.003$), and more frequently had an associated autoimmune disease (43.5% vs. 2.9%, $p < 0.0001$). In APS-positive patients, pulmonary artery lesions were more proximal and hemodynamic profiles were less impaired. These results demonstrated that patients with APS are a unique group of CTEPH patients with well-defined clinic and hemodynamic features. Overall, it appears reasonable to test for aPL all the patients with PE and age less than 50 years and this is mandatory if they have associate autoimmune diseases [17]. Additional features that encourage testing for aPL are VTE provoked by mild risk factors (i.e. oral contraceptive therapy, prolonged car or air travel, laparoscopic surgery)[44] and VTE in uncommon sites [32,43].

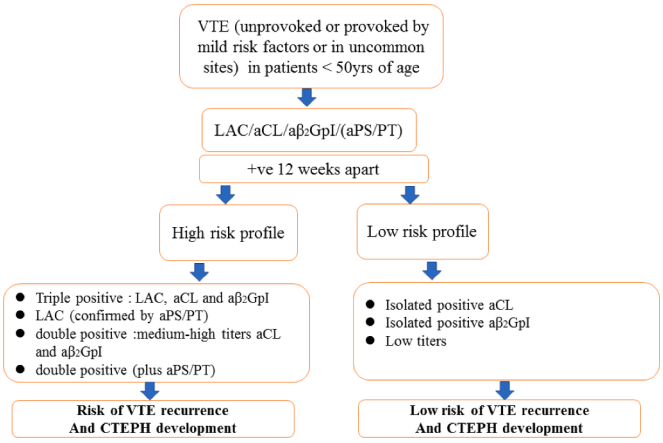

Fig. 1. Guidance to aPL testing and interpretation in patients with VTE. Testing for aPL should be preferentially reserved to patients indicated in the first box. LAC, aCL, aβ$_2$GPI aPS/PT denote Lupus Anticoagulant, anti-cardiolipin, anti-β$_2$Glycoprotein I and anti-phosphatidylserine/prothrombin antibodies, respectively. Combination of positive tests rsults in high or low risk profiles that in turn determine high or low probability of recurrent VTE and possible consequent CTEPH development.

6. Treatment of CTEPH

Despite consistent advances in medical treatment, PH is still responsible for substantial mortality, although in patients with APS, the contribution of PH to mortality is unknown [45]. The Euro-Phospholipid Project on morbidity and mortality in APS did not mention PH as a cause of death[15]. The management of CTEPH involves pulmonary thrombo-endarterectomy (PTE), a surgical procedure in which the blood vessels of the lungs are freed of clot and scar material. Patients in WHO functional classes II–IV with surgically accessible thrombi are candidate to PTE, regardless of age and aPL status [46]. There are few reports of a positive outcome of PTE in patients with APS, with aPL positivity not affecting early mortality and major complications, with the exception of neurological sequelae and thrombocytopenia [47–50]. APS patients with PAH or CTEPH are candidates to lifelong anticoagulation with Vitamin K Antagonists (VKAs) at a target INR of 2.0 to 3.0 [14]. In the US CTEPH registry, warfarin was the most commonly used anticoagulant (47%), followed by direct oral anticoagulants (DOACs) (40%) and low-molecular-weight heparins (9%) [51]. Few data exist on the efficacy and safety of DOACs in CTEPH [2,52]. In a retrospective multicenter study of 1078 patients with CTEPH undergoing PTE, the choice of anticoagulation had no effect on functional and hemodynamic outcomes, bleeding events, and survival. However, recurrent VTE was significantly higher in patients treated with DOACs than in those treated with VKAs [53]. Notably, Triple positivity (LAC, aCL, and aß2GPI antibodies) is a contraindication to the use of DOACs [54].

7. Conclusion

If present, aPL antibodies may play an important role in determining CTEPH. Indeed, aPL-induced thrombophilia may increase the recurrence of PE which in turn is the leading cause of CTEPH. Screening for aPL is essential in young patients with PE to establish a life-long treatment with oral anticoagulants. A guidance for testing and interpretation is shown in Fig. 1.

Declaration of Competing Interest

The authors declare no conflict of interest.

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