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Review

Antiphospholipid antibodies can identify lupus patients at risk of pulmonary hypertension: A systematic review and meta-analysis☆

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ABSTRACT

Background: Pulmonary hypertension (PH) is a life-threatening condition that may affect outcomes in patients with systemic lupus erythematosus (SLE). The role of antiphospholipid antibodies (aPL) on the risk of PH is controversial. Therefore our objective was to estimate the risk of PH (WHO groups 1–5) including associated pulmonary arterial hypertension (APAH, WHO group 1 only) related to aPL in patients with SLE.
Methods: Systematic review and meta-analysis were performed: MEDLINE, EMBASE, Cochrane Library, congress abstracts, and reference lists of eligible studies were searched through 2015. Studies were selected if they included SLE patients with descriptions of the exposure to aPL and the outcomes (PH including APAH). Two reviewers extracted study characteristics and outcome data from published reports. Estimates were pooled using random effects models and sensitivity analyses. PROSPERO registration number: CRD42015016872.
Results: Of 984 identified abstracts, 31 primary studies (five cohorts, 13 case-control, 13 cross-sectional) met inclusion criteria, including 4480 SLE patients. Prevalence of PH in aPL-positive vs. aPL-negative SLE patients was 12.3% vs. 7.3%, respectively. The overall pooled odds ratio (OR) for PH was 2.28 (95% CI, 1.65 to 3.15) (I^2 = 39%). The risk of APAH was also significantly increased (OR = 2.62 [95% CI, 1.11–6.15]). The risk of PH was the highest for lupus anticoagulant (OR = 1.96 [95% CI, 1.31–2.92]) and IgG anticardiolipin antibodies (OR = 2.64 [95% CI, 1.30–5.36]) while other antibodies were not significantly associated with PH.
Conclusions: Among SLE patients, aPL can identify patients at risk for PH and APAH. These findings warrant implementation of effective screening and early treatment strategies.

Contents

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1. Introduction

Antiphospholipid antibodies (aPL) are risk factors for thrombosis and recurrent fetal loss [1]. Antiphospholipid syndrome (APS) is defined by venous, arterial or small vessels thromboses and obstetrical morbidity associated with persistent aPL detected on two or more occasions at least 12 weeks apart [2]. APS may exist in its primary form but is commonly associated with systemic lupus erythematosus (SLE) [2].

Pulmonary hypertension (PH) is a hemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure ≥ 25 mm Hg at rest as assessed by right heart catheterization [3]. Pulmonary arterial hypertension (PAH or WHO group 1 PH) is a clinical condition characterized by pre-capillary PH and pulmonary vascular resistance > 3 Wood units, in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases. In the subgroup of associated PAH conditions (APAH), the leading cause is connective tissue disease (e.g. systemic sclerosis or SLE).

Pulmonary hypertension is present in both SLE and APS patients. Conversely, aPL are present in PAH patients [4]. In APS, the high frequency of pulmonary embolism (PE) confers an increased risk of chronic thromboembolic PH supporting aPL testing in patients with this condition [3]. In SLE, PH and APAH can occur and have been studied with a special interest on aPL positivity. However, it is unclear whether aPL can increase the risk of PH in SLE patients with or without history of PE: while some studies identified a strong association between aPL-positivity and PH [5,6], this finding has not been confirmed by all the studies [7,8].

1.1. Aims

Thus, based on the current controversy, our aim was to investigate a possible association between aPL and different forms of PH (i.e. WHO groups 1–5 PH including APAH) in patients with SLE using a systematic review and meta-analysis of the literature.

2. Materials and methods

2.1. Meta-analysis protocol

Our study protocol was registered on PROSPERO (CRD42015016872). We followed the PRISMA guidelines during all stages of design, implementation, and reporting (See Supplemental Material For PRISMA Checklist).

2.2. Search strategy

We systematically searched MEDLINE, EMBASE from 1986 to May 1st, 2015. Search terms included *antiphospholipid*, *lupus*, *pulmonary hypertension* as well as MeSH terms: *Antibodies*, *Antiphospholipid*; *Antiphospholipid Syndrome*; *Lupus Coagulation Inhibitor*; *Antibodies*, *Anticardiolipin*; *beta 2-Glycoprotein I*; *Lupus Erythematosus*, *Systemic*; *Hypertension*, *Pulmonary*. The search was done without restrictions with regard to study design, language or publication date. We also searched the Cochrane Library for any recent systematic review on the subject, and the ClinicalTrials.gov database for completed or ongoing but unpublished studies. We reviewed congress abstracts (American College of Rheumatology, EUropean League Against Rheumatism) and reference lists of eligible studies.

2.3. Eligibility

Selection criteria were determined before data collection. To assess the effect estimate for a potential association between aPL (exposure) and PH (outcome) in SLE patients (study population), we selected the studies that fulfil the following inclusion criteria: study that included