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Review

The clinical phenotype associated with myositis-specific and associated autoantibodies: A meta-analysis revisiting the so-called antisynthetase syndrome

Jean-Christophe Lega [a,b,*], Nicole Fabien [c], Quitterie Reynaud [a], Isabelle Durieu [a], Stéphane Durupt [a], Marine Dutertre [a], Jean-François Cordier [d], Vincent Cottin [d]

[a] Department of Internal and Vascular Medicine, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Claude Bernard University Lyon 1, University of Lyon, France
[b] UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, CNRS, Claude Bernard University Lyon 1, University of Lyon, France
[c] Department of Immunology, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Claude Bernard University Lyon 1, University of Lyon, France
[d] National Reference Centre for Rare Pulmonary Diseases, Department of Respiratory Medicine, Louis Pradel Hospital, Hospices Civils de Lyon, UMR 754, Claude Bernard University Lyon 1, University of Lyon, France

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ABSTRACT

Objective: To describe the clinical spectrum associated with aminoacyl-transfer RNA synthetase (ARS) autoantibodies in patients with idiopathic inflammatory myositis defined according to Peter and Bohan's criteria.
Methods: Cohort studies were selected from MEDLINE and Embase up to August 2013. Two investigators independently extracted data on study design, patient characteristics, and clinical features (interstitial lung disease [ILD], fever, mechanic's hands [MH], Raynaud's phenomenon [RPh], arthralgia, sclerodactyly, cancer and dermatomyositis-specific rash) according to the presence of myositis-specific (anti-aminoacyl-transfer RNA synthetase [ARS], anti-signal recognition particle [anti-SRP] and anti-Mi2) and myositis-associated (anti-PM/Scl, anti-U1-RNP and anti-Ku) autoantibodies.
Results: 27 studies (3487 patients) were included in the meta-analysis. Arthralgia (75%, CI 67–81) and ILD (69%, CI 63–74) were the most prevalent clinical signs associated with anti-ARS autoantibodies. Anti-Mi2 and anti-SRP autoantibodies were associated with few extramuscular signs. ARS autoantibodies were identified in 13% of patients with cancer-associated myositis (5–25). Patients with non-anti-Jo1 ARS had greater odds of presenting fever (RR 0.63, CI 0.52–0.90) and ILD (RR 0.87, CI 0.81–0.93) compared to those with anti-Jo1 autoantibodies. The frequencies of myositis (RR 1.60, CI 1.38–1.85), arthralgia (RR 1.52, CI 1.32–1.76) and MH (RR 1.47, CI 1.11–1.94) were almost 50% higher in patients with anti-Jo1 compared to non-anti-Jo1 ARS autoantibodies. Patients with anti-PM/Scl differed from those with anti-ARS autoantibodies by a greater prevalence of RPh (RR 0.70, CI 0.53–0.94) and sclerodactyly (RR 0.47, CI 0.25–0.89). ILD was less frequent in patients with anti-U1-RNP autoantibodies (RR 3.35, CI 1.07–10.43). No difference was observed between anti-ARS and myositis-associated autoantibodies for other outcomes.
Conclusions: The presence of anti-ARS autoantibodies delimits a heterogeneous subset of patients with a high prevalence of myositis, MH, arthralgia in anti-Jo1 patients, and RPh and fever in non-anti-Jo1 patients. The clinical signs of populations positive for anti-PM/Scl and anti-ARS autoantibodies largely overlap, especially with regard to ILD, challenging the clinical delimitation of the antisynthetase syndrome.

Contents

Abbreviations: ARS, anti-aminoacyl-tRNA synthetase autoantibodies; ASS, antisynthetase syndrome; CAM, cancer-associated myositis; CTD, connective tissue disease; DM, dermatomyositis; IBM, inclusion body myositis; IIM, idiopathic inflammatory myopathy; ILD, interstitial lung disease; MAA, myositis-associated antibodies; MH, mechanic's hands; MSA, myositis-specific antibodies; OM, overlap myositis; PM, polymyositis; RPh, Raynaud's phenomenon; SL, systemic lupus; SRP, signal recognition particle; SSc, systemic sclerosis.

* Corresponding author at: Département de Médecine Interne et Vasculaire, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, 69495 Pierre-Bénite, France. Tel.: +33 4 78 86 19 79; fax: +33 4 78 86 32 64.

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1. Introduction

Idiopathic inflammatory myopathies (IIMs) comprise a group of acquired, heterogeneous, systemic diseases characterized by muscle involvement, elevated serum levels of muscle enzymes, electromyographic abnormalities, and inflammatory infiltrates in muscle biopsies [1–3]. According to their characteristic histopathologic features, IIMs can be classified as polymyositis (PM), dermatomyositis (DM), or inclusion body myositis (IBM) [1,2]. IIMs are associated with numerous autoantibodies, present in around 50% of patients with PM or DM and directed towards defined nuclear and cytoplasmic antigens. Some of these autoantibodies, namely anti-SS-A, U1-RNP, and PM/Scl, are frequently detected in patients with other connective diseases associated with myositis, especially systemic sclerosis, and are referred to as myositis-associated autoantibodies (MAAs) or systemic sclerosis (SSc)-associated autoantibodies [4]. Other autoantibodies, recognizing a subset of aminoacyl-transfer RNA synthetases (ARS), SRP components, and nuclear helicase-ATPase Mi-2, are considered specific to IIMs (myositis-specific antibodies, MSAs) [2,3]. Anti-ARS autoantibodies include anti-Jo1 (anti-histidyl), the most common, as well as anti-PL7 (anti-analyl), anti-PL12 (anti-threonyl), anti-OJ (anti-isoleucyl), anti-EJ (anti-glycyl), anti-KS (anti-asparaginyl), anti-SC (anti-lysyl), anti-JS (anti-glutaminyl), anti-Ha (or anti-YRS, anti-threonyl), anti-tryptophanyl, and anti-Zo (anti-phenylalanyl) autoantibodies [2,3]. Several studies have shown an increased risk of interstitial lung disease (ILD) in patients with myositis who are positive for anti-ARS autoantibodies, compared to seronegative controls, an association often referred to as the so-called antisynthetase syndrome (ASS), encompassing arthritis, mechanic's hand [MH], fever, Raynaud's phenomenon [RPh], myositis and ILD [2,5].

Several authors, including our group, have questioned the clinical delimitation and singularity of ASS. The definition of ASS was in fact based on a single, uncontrolled, historical series [5]. Comparisons with the clinical spectrum associated with other MSA or MAA are lacking or limited by a small sample size [6–8]. Moreover, the homogeneity of ASS is debated, several reports suggesting variable occurrences of particular symptoms according to the subtype of anti-ARS autoantibodies [9,10]. Lastly, the clinical features described as being associated with anti-ARS autoantibodies largely overlap those of anti-PM/Scl-positive patients [11,12]. The aim of this study is to provide an evidence-based description of the clinical characteristics of patients positive for anti-ARS and to compare these characteristics to those associated with other MSA and with MAA.

2. Methods

The methods used were in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group [13].

2.1. Literature search

We searched Embase and MEDLINE for original articles published in any language up to August 2013. Search criteria combined free text search and exploded MESH/EMTREE terms. The search equation for PubMed was: ("Polymyositis" [Mesh] OR "Dermatomyositis" [Mesh]) AND ("Autoantibodies" [Mesh] OR "Antisynthetase syndrome" [Supplementary Concept] OR [RNA, Transfer, Amino Acyl]) and for Embase it was: ('polymyositis'/exp/mj OR 'dermatomyositis'/exp/mj) AND ('autoantibody'/exp OR 'antisynthetase syndrome'/exp). Additional articles were identified from the reference lists of relevant papers obtained through the electronic search.

2.2. Study selection

Observational studies were eligible if they reported data on series of patients positive for anti-ARS autoantibodies and presenting connective tissue disease (IIM, SSc, systemic lupus [SL], rheumatoid arthritis, undifferentiated or mixed connective tissue disease [CTD]) or ILD and if a 2 × 2 table could be constructed based on the presence of other MSA (anti-Mi2 or anti-SRP) autoantibodies or MSA/SSc-associated autoantibodies (anti-PM/Scl, anti-U1-RNP or anti-Ku autoantibodies) [4] and related clinical features, namely ILD, fever, RPh, MH, arthralgia, sclerodactyly, cancer, and DM-specific rash, encompassing manicure sign, heliotrope rash and Gottron's papules. Patients were classified as presenting PM, DM, overlap myositis (OM), cancer-associated myositis (CAM), or IBM according to Peter and Bohan's criteria [14]. A minimum of 5 patients aged over 18 years was required for inclusion of the study. Series reporting separately data on anti-ARS autoantibodies and on other autoantibodies, published by the same authors within an interval of 5 years, were considered in the meta-analysis [15,16]. Series including exclusively patients with ILD with an IIM prevalence of <80% were excluded to avoid selection bias.

Two reviewers (JCL, VC) independently applied these criteria to the titles and abstracts of all articles identified. If there was any possibility that it might be relevant, the paper was retrieved and independently assessed by the same reviewers for a final decision on its inclusion in the meta-analysis. Any disagreement was resolved by consensus.

2.3. Meta-analysis

Pooled prevalences of autoantibodies and associated clinical features, with the corresponding 95% confidence intervals (95% CI), were computed by weighted averages in which the weight of each study was defined by its sample size. Cochran's Q and I^2 tests were used to analyse heterogeneity [17]. In the absence of heterogeneity, the pooled relative risks (RRs) of individual clinical features were weighted by the inverse of their variance and combined according to a fixed-effects model [18]. In the event of heterogeneity, considered present at

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