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Autoantibodies in juvenile-onset myositis: Their diagnostic value and associated clinical phenotype in a large UK cohort

Sarah L. Tansley [a, b, *], Stefania Simou [c], Gavin Shaddick [d], Zoe E. Betteridge [b], Beverley Almeida [c, e], Harsha Gunawardena [f], Wendy Thomson [g], Michael W. Beresford [h, i, j], Angela Midgley [h, j], Francesco Muntoni [k], Lucy R. Wedderburn [c, e, l, 1], Neil J. McHugh [a, b, 1], on behalf of the JDRG

[a] Royal National Hospital for Rheumatic Diseases, Royal United Hospitals Bath NHS Foundation Trust, Upper Borough Walls, Bath, BA1 1RL, UK
[b] Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath, BA2 7AY, UK
[c] Inflammation and Rheumatology Section, UCL Institute of Child Health and Arthritis Research UK Centre for Adolescent Rheumatology at UCL, UCLH and GOSH, London, UK
[d] Department of Mathematics, University of Bath, Claverton Down, Bath, BA2 7AY, UK
[e] Department of Rheumatology, Great Ormond Street Children's Hospital, London, UK
[f] Clinical and Academic Rheumatology, North Bristol NHS Trust, Southmead Hospital, Bristol, BS10 5NB, UK
[g] Arthritis Research UK Centre Genetics and Genomics, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester and NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester NHS Foundation Trust, UK
[h] Institute of Translational Medicine, University of Liverpool, Liverpool, UK
[i] Department of Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK
[j] Arthritis Research UK Experimental Arthritis Treatment Centre for Children, Liverpool, UK
[k] Developmental Neuroscience Programme, UCL Great Ormond Street Institute of Child Health, MRC Centre for Neuromuscular Diseases, UCL, London, UK
[l] Arthritis Research UK Centre for Adolescent Rheumatology at UCL, UCLH and GOSH, London, UK

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ABSTRACT

Objectives: Juvenile myositis is a rare and heterogeneous disease. Diagnosis is often difficult but early treatment is important in reducing the risk of associated morbidity and poor outcomes. Myositis specific autoantibodies have been described in both juvenile and adult patients with myositis and can be helpful in dividing patients into clinically homogenous groups. We aimed to explore the utility of myositis specific autoantibodies as diagnostic and prognostic biomarkers in patients with juvenile-onset disease.
Methods: Using radio-labelled immunoprecipitation and previously validated ELISAs we examined the presence of myositis specific autoantibodies in 380 patients with juvenile-onset myositis in addition to, 318 patients with juvenile idiopathic arthritis, 21 patients with juvenile-onset SLE, 27 patients with muscular dystrophies, and 48 healthy children.
Results: An autoantibody was identified in 60% of juvenile-onset myositis patients. Myositis specific autoantibodies (49% patients) were exclusively found in patients with myositis and with the exception of one case were mutually exclusive and not found in conjunction with another autoantibody. Autoantibody subtypes were associated with age at disease onset, key clinical disease features and treatment received.
Conclusions: In juvenile patients the identification of a myositis specific autoantibody is highly suggestive of myositis. Autoantibodies can be identified in the majority of affected children and provide useful prognostic information. There is evidence of a differential treatment approach and patients with anti-TIF1γ autoantibodies are significantly more likely to receive aggressive treatment with IV cyclophosphamide and/or biologic drugs, clear trends are also visible in other autoantibody subgroups.

1. Introduction

Juvenile-onset myositis refers to a group of rare childhood autoimmune diseases that typically present with proximal muscle

* Corresponding author. Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath, BA1 1RL, UK.
E-mail address: s.tansley@nhs.net (S.L. Tansley).
[1] Joint senior authors.

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Abbreviations

JDCBS	Juvenile Dermatomyositis Cohort and Biomarker Study
CAPS	Childhood Arthritis Prospective Cohort Study
CMAS	Childhood Myositis Assessment Score
PGA	Physician Global Assessment visual analogue score
Anti-TIF1γ	anti-transcription intermediary factor gamma autoantibody
Anti-NXP2	anti-nuclear matrix protein 2 autoantibody
Anti-MDA5	anti-melanoma differentiation associated protein 5 autoantibody
Anti-SRP	anti-signal recognition peptide autoantibody
Anti-HMGCR	anti-3-hydroxy-3-methyl-glutaryl-coenzyme A reductase autoantibody
Anti-SAE	anti-small ubiquitin-like modifier activating enzyme autoantibody
Anti-PmScl	anti-Polymyositis Scleroderma autoantibody
Anti-U1RNP	anti-U1 Ribonucleoprotein autoantibody
MSA	Myositis specific autoantibody
MAA	Myositis associated autoantibody

weakness and elevated muscle enzymes; more than 90% of affected children have associated skin disease and are thus classified as Juvenile Dermatomyositis (JDM) [1]. Juvenile myositis is clinically highly heterogeneous with muscle weakness ranging from profound and requiring hospitalisation, to clinically amyopathic dermatomyositis with normal muscle strength. Extra-muscular disease including skin and internal organ involvement contributes significantly to disease morbidity. Patient sub-stratification is desirable to inform prognosis and guide further investigation and treatment. Traditionally subgroups based on clinical and histopathological criteria include polymyositis, dermatomyositis and overlap syndromes but this classification fails to explain all of the variation in what is a complex disease and the boundaries between traditional subgroups are becoming increasingly indistinct. Autoantibodies identifiable in patients with myositis are often described as either myositis specific (MSA) or myositis associated (MAA). MSA are believed to occur exclusively in patients with an idiopathic inflammatory myopathy while MAA may also occur in patients with other connective tissue diseases or an overlap disorder. Collectively autoantibodies have been identified in 60–70% of patients with juvenile myositis and can divide patients into clinically homogenous subgroups [2–6]. There is growing evidence for the utility of autoantibodies as biomarkers to predict disease features and outcome in juvenile myositis [2–8].

Despite well described pathognomonic features, the diagnosis of juvenile myositis can be challenging; a recent study from North America reported a median delay in diagnosis of 4–6 months [9]. The differential diagnosis of muscular weakness in children is wide and additional features such as arthralgia or Raynaud's phenomenon may lead to consideration of other more common childhood rheumatological diseases such as juvenile idiopathic arthritis (JIA) or juvenile-onset systemic lupus erythematosus (JSLE). The possibility of overlap disorders compounds this problem. Furthermore, the muscular dystrophies and other genetic muscle diseases are important to exclude. It is crucial that diagnostic difficulties can be overcome as early diagnosis and initiation of aggressive treatment has been shown to reduce morbidity and improve patient outcome [9–12]. Myositis specific autoantibodies are believed to occur exclusively in patients with myositis and have not been found in patients with genetic muscle disease in the absence of a coexistent inflammatory myopathy [13]. As standard testing for myositis specific autoantibodies becomes more widely available, there is growing interest in their use in diagnosis and predicting prognosis. In this study we analyse the prevalence and clinical associations of MSA/MAA in a large cohort of UK children with juvenile myositis compared to healthy children and those suffering from diseases with overlapping clinical features, JIA and JSLE.

2. Materials and methods

2.1. Patients with juvenile myositis

Patient serum samples and clinical data were available for 380 children enrolled in the UK Juvenile Dermatomyositis Cohort and Biomarker Study (JDCBS). The JDCBS is a large cohort of UK patients with myositis, the majority with JDM [1]. Patients are recruited from paediatric rheumatology departments across the UK, and data are collected prospectively on standardised proformas. Patients aged ≤16 years are included based on a diagnosis of definite or probable JDM or polymyositis by Bohan and Peter criteria [14]; as well as JDM or polymyositis with overlap connective tissue disease features. The JDCBS was established in 2001 and many patients have more than 15 years of follow-up data available. The median length of time from symptom onset to time of analysis of patients included in this study was 9.31 years.

We investigated the presence or absence of key disease features occurring at any point over the follow-up period including calcinosis, dysphagia, cutaneous ulceration, lipoatrophy and arthritis. The lowest ever recorded childhood myositis assessment score (CMAS) was used as a measure of the maximum recorded muscle weakness: CMAS is a systematic and validated measure of muscle strength in children with juvenile myositis. The score ranges between 0 and 52, with lower scores corresponding to a greater degree of clinical weakness [15]. We used the highest ever recorded physician global assessment visual analogue score (PGA) as a proxy measure for maximal disease activity/severity. PGA graded 0–10, is used as an overall measure of disease activity, a higher score reflecting more active disease.

In the UK first line treatment for juvenile-onset myositis is typically methotrexate with cortico-steroids, a regime recently been shown in an international randomised trial, to be optimal compared to steroids alone [16]. Strict guidelines exist for the administration of biologic drugs and these are reserved for the most unwell patients, who have failed to respond to first-line medications. We determined whether patients had at any point received treatment with any biologic drug and/or intravenous cyclophosphamide.

2.2. Patients with JIA

Patient serum samples were obtained for 318 children enrolled in the Childhood Arthritis Prospective Study (CAPS), a prospective longitudinal inception cohort study of children with new onset inflammatory arthritis [17]. Patients are recruited from 7 tertiary referral centres across the UK. Children aged ≤16 years with newly diagnosed inflammatory arthritis in one or more joints, which had persisted for at least 2 weeks, are invited to participate. Exclusion criteria include septic arthritis, haemarthrosis, arthritis caused by malignancy or trauma and connective tissue disease.

2.3. Patients with JSLE

Patient serum samples were obtained for 21 children enrolled in the UK Juvenile Systemic Lupus Erythematosus (JSLE) Cohort Study

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