Comparing and contrasting clinical and serological features of juvenile and adult-onset myositis: implications for pathogenesis and outcomes

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Purpose of review
To explore the different characteristics of the serological phenotypes identified in juvenile and adult myositis, consider how differences between the two groups might be explained and discuss how this enhances our understanding of disease pathogenesis.

Recent findings
Current research has focussed on two main areas: first, defining the autoantibody associated disease phenotype in greater detail, particularly with regard to cutaneous disease and within specified populations such as juvenile-onset disease and different ethnic groups, and second, we have gained new insights into disease pathogenesis through studies analysing genetic associations and autoantigen expression.

Summary
Although there are many clinically important differences between adult and juvenile-onset myositis, recent work has highlighted many of the similarities at least within autoantibody-defined subgroups. Viewing age at disease onset as a continuum with its own influence on disease phenotype strengthens the ability of autoantibodies to define homogenous disease groups, and may be important in understanding the relationship between autoantibodies and disease pathogenesis.

Keywords
carrierbody, juvenile, muscle disease, myositis

INTRODUCTION
The idiopathic inflammatory myopathies (IIM) are a group of rare diseases that affect not only muscle and skin but many other organ systems. IIM have a bimodal incidence with a first peak in childhood and a second peak in adults [1]. The distinction between juvenile and adult myositis is defined by age at disease onset with an arbitrary cut-off typically at 16 years of age (or in the United States and Canada, 18 years). In juvenile disease dermatomyositis is by far the most common subtype of the IIM, with polymyositis seen in less than 5\% cases; in adults however, the inverse is true and polymyositis is typically more common [1]. The two groups share the hallmark disease features of muscle inflammation, weakness and, in the case of dermatomyositis the pathognomic rash. Although at first glance the juvenile and adult forms of myositis may appear similar, it is important to note that even within the dermatomyositis subgroup there are several differences in disease presentation, complications and outcomes, which suggest children are not simply suffering from an identical disease to adults occurring at an earlier age. Children with dermatomyositis are more likely to develop calcinosis, ulceration and vasculopathy and yet despite this have a better overall prognosis with improved survival compared with adults who are more likely to develop life-limiting complications such as malignancy or interstitial lung disease (Table 1) [1,2,3,4–19].

Myositis is a heterogeneous disease and the clinical course ranges from relatively mild disease...
responsive to immunosuppressive therapy to severe disease associated with significant morbidity and mortality despite aggressive treatment. The concept of myositis has evolved from the previously described subgroups of polymyositis, dermatomyositis and IBM, which do not adequately explain all of the variation in this complex disease and the boundaries between these traditional subgroups are becoming less distinct as our understanding grows. Myositis-specific autoantibodies (MSA) can be identified in a significant proportion of patients (approximately 65% children and 80% adults). These MSA have been established as a useful means in which to subdivide patients into more homogenous groups with more clearly defined risks of clinically important complications. As standard testing for MSAs in both adult and juvenile-onset disease becomes more widely available, these autoantibodies are increasingly being used to predict disease course and guide investigations.

In this review, we discuss recent advances in understanding of the serological phenotypes identified in juvenile and adult-onset disease, consider how differences between the two groups might be explained and discuss how this enhances our understanding of disease pathogenesis. Sporadic inclusion body myositis, a clinically distinct subgroup of patients with slowly progressive muscle weakness and atrophy leading to severe disability, is seen exclusively in adult patients and is not discussed.

**CLINICAL FEATURES OF AUTOANTIBODY SUBGROUPS**

Clinical features of autoantibody subgroups are summarised in Fig. 1.

**Anti-NXP2**

Anti-NXP2, also known as anti-Mj or p140, is a common autoantibody in juvenile myositis cohorts and is identified in 20–25% [3,5,20]. This MSA has

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...Variation in patient selection and follow-up between studies influences reported mortality. Most common causes of death are cancer, lung disease, cardiac disease, and infections [19].
been associated with calcinosis, a greater degree of muscle weakness, increased risk of hospitalisation, worse functional status and more severe disease \cite{3,5,20}. Anti-NXP2 is less common in adult-onset groups, although reported frequencies vary widely with the population studied (1.6–17\%) \cite{12,13,21}. Similar associations with calcinosis have also been reported in adults \cite{12,18}. Given that calcinosis is also associated with a younger age at disease onset in a strikingly linear fashion \cite{3}, this and the increased frequency of anti-NXP2 autoantibodies in juvenile populations may begin to explain the high frequency of calcinosis observed in this group. Interestingly, a study \cite{18} of adult patients identified an association between calcinosis and fingertip ulcers and, given the known association of digital ulceration and calcinosis in systemic sclerosis, the authors postulate a role for vascular injury in the development in calcinosis. This is in keeping with a greater degree of both vasculopathy and calcinosis in juvenile disease. Calcinosis is a major cause of morbidity in JDM occurring in up to 33\% patients versus 10–20\% adults \cite{3,5,18}. Although the identification of anti-NXP2 may help to identify those at highest risk of calcinosis, there is not yet any robust evidence to recommend a differential treatment approach. Anti-NXP2 has been associated with an increased risk of malignancy in adult patients \cite{13,21} and as such its identification, particularly in older patients may justify a more extensive ‘malignancy screen’.

**Anti-TIF1γ**

It is interesting that another major juvenile dermatomyositis autoantibody anti-TIF1γ, identifiable in 23–32\% of children with dermatomyositis, is also strongly associated with malignancy in adult-onset disease \cite{2,5,14,21–23}. Despite the well established links between these autoantibodies and malignancy in adult patients, to date there is no evidence for an increased cancer risk in children. In contrast, even within the adult population there is evidence that a substantial proportion of patients do not have malignancy and that younger adults and females are at a lower risk \cite{14,24**}. This highlights that patients with myositis should be considered as a continuum according to age rather than as two distinct subgroups defined by an arbitrary cut-off.

In juvenile-onset disease, anti-TIF1γ has been associated with more severe widespread skin disease and has also been linked to the development of lipodystrophy \cite{2,24**,25}. Fiorentino et al. have recently established that adult patients with
anti-TIF1γ also are more likely to suffer from more severe skin disease. Although there were no cutaneous features suggestive of malignancy, they describe ‘red and white’ lesions characteristic of this autoantibody and also noted the rash of patients with anti-TIF1γ was more likely to be in a photo-exposed pattern [24**]. The authors draw the link between the photo-exposed pattern of rash in this patient group and the previous observation by Shah et al. [26] that juvenile patients with a higher historical UV exposure in the month prior to diagnosis are at higher risk of having anti-TIF1γ antibodies. Although the mechanism for this has not been established, Shah et al. speculate that sunlight may upregulate interferon type 1 cytokines which secondarily upregulate the TRIM proteins (including the TIF1γ autoantigen), leading to an autoantibody response.

**Anti-MDAS**

Anti-MDA5 can be identified in both adult and juvenile dermatomyositis populations and the prevalence varies widely depending on the population studied (7–36%) [11,24**,27–30]. In adult patients, anti-MDAS has been associated with ILD, clinically amyopathic myositis and limited muscle involvement, a distinct cutaneous phenotype with ulceration and palmar papules in addition to arthri-
tis [11,29]. These features are also seen in patients with juvenile-onset disease [4,6]. The prognosis of patients with anti-MDA5 is highly variable and depends on the population studied. In East Asian populations, anti-MDAS is strongly associated with rapidly progressive ILD [29] and a high mortality in both adults and children despite aggressive treatment [6,31,32]. Rapidly progressive ILD is a major cause of death in juvenile dermatomyositis in Japan [32]. Kobayashi et al. recently described the clinical and laboratory features associated with rapidly progressive ILD in juvenile DM. They describe 10 cases with an age at disease onset between 1 and 13 years. Seven patients died, despite intensive treatment. All patients had anti-MDAS compared with 10 out of 14 cases with chronic ILD and none of 22 patients without ILD. In contrast, in United States and European cohorts rapidly progressive ILD appears less common and patients often respond well to standard therapies and can achieve remission [4,30].

Clinically amyopathic myositis, presenting with the hallmark dermatomyositis skin rash in the absence of clinical evidence of muscle involvement on examination or muscle enzyme analysis for more than 6 months, is a well described disease phenotype. Amyopathic myositis is recognised in juvenile-onset disease but it is reported to be rare with patients more often having mild or progressive muscle disease, at least within European and U.S. case series [33]. Although the association between anti-MDAS autoantibodies and clinically amyopathic myositis has been known for some time, we have recently demonstrated for the first time histological differences on muscle biopsy between juvenile patients with and without anti-MDAS [4]. These suggest that in addition to clinical phenotype autoantibodies also reflect variations in muscle disorder. Both adults and children with anti-MDAS, therefore, have a distinct phenotype with pronounced skin and lung disease but minimal muscle involvement.

In a recent study Narang et al. [34**] have provided further understanding into the relationship between clinical features of those with anti-MDAS. According to this study, in multivariate analysis, anti-MDAS patients are at higher risk of ILD if they also have ulceration, and anti-MDAS patients without ulceration are less likely to develop ILD. Although the numbers are small, this study [34**] offers some insight into potential pathogenic mechanisms in this subgroup of patients, as an underlying vasculopathy may explain the link between cutaneous ulceration and ILD.

It seems that for anti-MDAS positive patients, the differences between populations are far more striking than those between adults and juveniles. We note with interest that Chen et al. [27] have recently identified differences in both the prevalence and the clinical associations of anti-MDAS between Chinese and Japanese patient groups. These populations have previously been considered to be similar, and although this study did not examine genetic differences, this observation further strengthens the assumption that genetic and/or environmental factors can have a significant influence on disease phenotype.

**Anti-Mi2**

In both adults and children, anti-Mi2 autoantibodies are associated with ‘classic’ dermatomyositis with proximal muscle weakness and pathognomonic rashes. Despite significant muscle and skin disease at presentation, this group often respond well to standard therapies. In the UK Juvenile Dermatomyositis Biomarker and Cohort Study, children with anti-Mi2 have higher biopsy scores indicative of more severe histopathological disease but are more likely to be in remission and off medication at 2 years postdiagnosis [35] (manuscript in preparation).

**Antisynthetase antibodies**

Antisynthetase autoantibodies are the most common autoantibody in adult myositis cohorts with
Anti-Jo-1 being identified in 20–30% of patients and one of the seven other antisynthetase autoantibodies in 10–20% of patients [10]. They are more common in those classified as polymyositis. Antisyntetase autoantibodies are much rarer in juvenile-onset disease (<5%) and are more likely to be found in older children [5]. The antisynthetase syndrome in both adult and juvenile-onset disease is characterised by myositis, nonerosive polyarthritis, Raynaud’s phenomenon, fever, ‘mechanics hands’ and interstitial lung disease. Although in juvenile-onset myositis ILD is considered rare, at least in European and U.S. series, in those with antisynthetase autoantibodies this has been reported to occur in more than 60% of patients [5]. In adult patients with antisynthetase autoantibodies this rises to 90% [36**]. In this group prognosis is predominantly affected by lung involvement and certainly in juvenile-onset disease these antibodies confer an increased mortality [5]. Adults with non-Jo-1 antisynthetase autoantibodies have worse survival than those with anti-Jo-1 and this may relate to a delay in diagnosis and their propensity to present with non-myositis connective tissue disease symptoms and pulmonary manifestations [36**].

Anti-SRP

Anti-SRP autoantibodies have been identified in patients with necrotising autoimmune myopathy, a recently recognised subgroup of IIM characterised by marked myofibre necrosis, with minimal or no inflammatory infiltrate on muscle biopsy. These patients typically present with severe proximal weakness and a very high creatinine kinase level. Anti-SRP autoantibodies have rarely been identified in juvenile-onset disease but where described the clinical phenotype is similar to adults [5]. An association with cardiac involvement and dysphagia has been described in adult patients but data are conflicting and larger studies are needed to evaluate this further. Cardiac involvement in juvenile-onset disease has also been suggested but again larger studies are needed [5]. Aggressive immunosuppressive treatment is generally recommended as this group of patients are often refractory to standard myositis treatment regimens.

Anti-HMGCR

Anti-HMGCR autoantibodies have also been associated with necrotising autoimmune myopathy and statin use, although it is noteworthy that 40–70% of adult patients have no history of statin exposure [37**,38]. Anti-HMGCR autoantibodies have also been identified in juvenile necrotising autoimmune myopathy cases who similarly to adults in the cohort presented with both rapidly progressive and more insidious muscle weakness. Extra-muscular involvement is uncommon [37**]. Anti-HMGCR has not been identified in patients with statin intolerance associated with myalgias or mild elevations of creatinine kinase and appears to be specific for those with a necrotising autoimmune mediated myopathy [38].

Anti-SAe

Anti-SAe is an uncommon autoantibody in both adult and juvenile cohorts (~5% adult and <1% juvenile) [39–41] (and personal data). Patients present with cutaneous disease then subsequently develop muscle involvement. Some studies describe an association with dysphagia [39].

AUTOANTIBODIES AND DISEASE PATHOGENESIS

The presence of autoantibodies provides strong evidence for the role of autoimmunity in the pathogenesis of IIM. In predominantly Caucasian populations, the HLA 8.1 ancestral haplotype (HLA-B*08/DRB1*03/DQA1*05/DQB1*02) has been linked to increased risk of many autoimmune diseases, including adult and juvenile dermatomyositis [42]. It is well established that the HLA system (also known as MHC) confers susceptibility to a variety of autoimmune diseases. A recent genome wide association analysis demonstrated that the MHC is the major genetic region associated with dermatomyositis and other non-MHC genetic features associated with dermatomyositis were also shared with other autoimmune diseases [43]. The relationship between autoantibodies and genetic predisposition to myositis through HLA haplotype has provided an insight into potential mechanisms of disease pathogenesis. For example, the association between the HLA 8.1 ancestral haplotype and dermatomyositis has been shown to be stronger in certain autoantibody subgroups, and specific HLA alleles have also been shown to be associated with anti-Jo-1, anti-PmScl, anti-Mi2, anti-SRP, anti-TIF1γ and anti-SAe [39,44–46]. Furthermore, amino acid sequences that are predicted to be important in peptide binding have also been identified as risk and protective factors for different myositis phenotypes [44]. The affinity of different antigenic peptides for MHC might explain why risk genes for one phenotype are protective for another and thus the mutual exclusivity of most myositis autoantigens.

3-Hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) is upregulated by statins in regenerating muscle. The association of anti-HMGCR
autoantibodies with statin use, which exert their mechanism of action by inhibiting HMGCR provides evidence of the role of environmental factors acting as a trigger for myositis development. In a seminal study Casciola-Rosen et al. demonstrated upregulation of myositis autoantigens (anti-Mi2, anti-Jo-1, anti-U1 and anti-Ku) in regenerating muscle cells in myositis muscle, with very low levels of expression in control muscle. They postulated that upregulation of myositis autoantigens as part of tumourgenesis or muscle injury might be sufficient to induce immunogenicity [47]. Recently the same group have similarly shown marked upregulation of TIF1γ during muscle regeneration in humans and in a mouse model of muscle injury and repair [48**]. Given that patients typically express only one autoantibody and yet increased expression of multiple dermatomyositis autoantigens were seen (anti-TIF1γ, Jo-1 and Mi2) the authors now suggest that factors in addition to increased expression are needed to explain the immunogenicity of myositis antigens, including genetic susceptibility and/or posttranslational modifications of the target antigen [48**].

CONCLUSION

Like other autoimmune diseases, current evidence suggests that myositis develops in response to an environmental trigger in a genetically predisposed individual. In addition, it appears that individuals may be genetically predisposed to develop one serologically defined subgroup of myositis rather than another. The prevalence of the different autoantibodies varies with age at disease onset and is possibly influenced by disease trigger or other age-dependant factors. The clinical phenotype within autoantibody subgroups is remarkably similar for both adult and juvenile forms of the disease with the notable exception of certain key disease features including calcinosis and malignancy, both of which are independently influenced by age at disease onset. The influence of age as a continuum on disease phenotype is important to recognise as the phenotype associated with autoantibody subgroup and in particular the risk of these important complications can vary not just between but within adult and juvenile populations. Whether autoantibodies are truly pathogenic or epiphenomena acting as a biomarker for a particular pathogenic process remains unknown but what is currently clear is their ability to define homogenous disease groups that cross the arbitrary divide between adult and juvenile subsets.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: • of special interest
  • of outstanding interest

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24. Fiorentino DF, Kuo K, Chung L, et al. Distinctive cutaneous and systemic features associated with anti-transcriptional intermediary factor-1γ antibodies in adults with dermatomyositis. J Am Acad Dermatol 2015; 72:448–455. This study examines the distinctive cutaneous features of adult patients with anti-TIF1γ. No features suggestive of malignancy were identified but cutaneous features unique to patients with anti-TIF1γ are described.