Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood

Brian M Feldman, Lisa G Rider, Ann M Reed, Lauren M Pachman

Juvenile dermatomyositis, the most common inflammatory myopathy of childhood, is a rare systemic autoimmune vasculopathy that is characterised by weakness in proximal muscles and pathognomonic skin rashes. The length of time before the initiation of treatment affects presenting symptoms, laboratory measures, and pathophysiology. It also affects disease outcomes, including the development of pathological calcifications, which are associated with increased morbidity. Both genetic and environmental risk factors seem to have a role in the cause of juvenile dermatomyositis; HLA B8–DRB1*0301 ancestral haplotype is a strong immunogenetic risk factor, and antecedent infections and birth seasonality suggest that environmental stimuli might increase risk. Activation of dendritic cells with upregulation of genes induced by type-I interferon (α) in muscle and peripheral blood seems to be central to disease pathogenesis. Treatment often includes combinations of corticosteroids, methotrexate, and other immunosuppressive agents. Disease outcome, if treatment is initiated early, is generally good. Randomised controlled trials are needed to define the most effective treatments.

Introduction

Juvenile dermatomyositis is a rare, often chronic, autoimmune disease with onset during childhood. It is a systemic vasculopathy characterised by symmetrical proximal muscle weakness, raised serum concentrations of muscle enzymes, and pathognomonic skin rashes that include the heliotrope rash over the eyelids and Gottron’s papules over the extensor joint surfaces (figure 1). This disease is classified as one of the idiopathic inflammatory myopathies (table 1); the adult forms are more common. In this Seminar, we will focus on juvenile dermatomyositis, but refer to other idiopathic inflammatory myopathies with juvenile onset where relevant. We review some important advances in the understanding of the causes, epidemiology, pathophysiology, clinical features, and treatment of idiopathic inflammatory myopathies in childhood.

Causes and epidemiology

The incidence of juvenile dermatomyositis in the USA is 3·2 per million children per year,1 which is similar to that in the UK.7 The average age at onset is 7 years, but 25% of patients are younger than 4 years at onset.2 In the USA, the ratio of girls to boys is 2·3 to 1,7 compared with 5 to 1 in the UK.7 Rash is the first symptom to be recognised in half the children and weakness is the first symptom in a quarter.2,7

Childhood idiopathic inflammatory myopathies, like other autoimmune diseases, could result from environmental triggers in the setting of an underlying genetic susceptibility. Specific HLA alleles, such as B8,7 DRB1*0301,11 DQA1*0501,7 and DQA1*0301,12 are more common in juvenile dermatomyositis. Cytokine polymorphisms, including a tumour necrosis factor (TNFα)–308A promoter polymorphism,13 and intronic polymorphisms of the interleukin-1 receptor antagonist,14 are also risk factors in white patients. Geographical or seasonal clustering with the onset of disease suggests an environmental trigger for juvenile dermatomyositis—eg, an increased temporal incidence was identified in the midwestern states of the USA.15 However, this clustering was not confirmed in a national study a decade later.7

Subgroups of patients with juvenile dermatomyositis, including Hispanic patients, those with the HLA-DRB1*0301 risk-factor allele,12 and those with a specific autoantibody (anti-p155), have seasonal birth distributions which differ from patients without these features. This birth seasonality in these subgroups suggests a potential role for perinatal exposures or exposures in early life to onset of illness.16

Additional evidence suggests the presence of an infectious trigger. In two studies, most children with juvenile dermatomyositis had antecedent illnesses, which were mostly upper respiratory and gastrointestinal, in the 3 months before onset of symptoms.7,17 A history of contact with sick animals was frequently seen.7 Consequently, several microbes have been implicated, especially group A β haemolytic streptococci (GABHS), in a case–control study.18 Such patients have an increased cellular response to GABHS antigens that might result from molecular mimicry between GABHS and myosin heavy chain.19 Several other agents have also been inconsistently associated with disease onset, including cossackievirus B,20 toxoplasma,17 enterovirus,17 and parvovirus.21 In case–control studies, however, antibody titres or detection of virus by PCR-based methods in blood or muscle did not differ between patients and matched controls.22,23

Search strategy and selection criteria

We searched five databases: Medline (1950 to April week 4, 2007); Embase (1980 to week 18, 2007); Cinahl (1982 to May week 1, 2007); Evidence-Based Medicine Reviews (including the Cochrane Library); and Allied and Complementary Medicine (1985 to April, 2007). Any article on myositis in children was eligible for inclusion, with no restrictions on language or year of publication. The main search terms were “dermatomyositis”, “myositis”, “polymyositis”, “orbital myositis”, “overlap myositis”, “focal myositis”, “eosinophilic myositis”, “granulomatous myositis”, “inclusion body myositis”, “cancer-associated myositis”, “interferon 1 and rheumatic diseases”, and “interferon 1 and systemic lupus erythematosus”. We identified 2757 unique publications, many of which were related mainly to adult disease.
Figure 1: Clinical images of typical juvenile dermatomyositis
(A) Heliotrope discoloration of the eyelids, and malar or facial erythema and (B) scaly, red rash on the knuckles with Gottron’s papules.

Although evidence allows speculation about the role of environmental agents as triggers of juvenile dermatomyositis, no specific agents (shared antigens) have been consistently identified. Presumably other genetic risk factors remain undiscovered in these probably polygenic disorders, and various gene–environment interactions might be important in the pathogenesis of different phenotypes. Identification of these risk factors and an enhanced understanding of the interaction between the host’s genetic susceptibility and environmental exposures might lead to new and improved treatments.

### Pathological changes and pathophysiology

We have focused on new ideas about disease pathogenesis (figure 2) in juvenile dermatomyositis, and idiopathic inflammatory myopathies in general, rather than provide a complete review. Juvenile dermatomyositis is a vasculopathic condition. Typical histological changes in the muscle include swelling of the capillary endothelium with obliteration of the lumen, perifascicular atrophy, perivascular inflammation, muscle degeneration and regeneration, and the presence of tubuloreticular inclusions (which are visible by electron microscopy). An international consensus working group has developed a scoring system for juvenile dermatomyositis muscle biopsies. The score examines four domains: (1) endomyosial, perivascular, and perimysial inflammation; (2) vascular changes; (3) changes to muscle fibre including MHC class I overexpression, atrophy of perifascicular and other muscle fibres, degeneration or regeneration, and presence of neonatal myosin; and (4) endomyosial and perimysial fibrosis. A similar score shows that more diffuse early changes seen on biopsy samples could predict a chronic course for the disease.

The vasculopathy of juvenile dermatomyositis affects skeletal muscle, skin, the gastrointestinal tract, and other tissues such as lungs, kidneys, eyes, and heart. Both humoral and cellular immunity contribute to the pathogenesis. Evidence suggests that innate immunity...

### Table 1: Clinical classification of juvenile idiopathic inflammatory myopathies

<table>
<thead>
<tr>
<th>Myositis Type</th>
<th>Important Features</th>
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<tbody>
<tr>
<td>Dermatomyositis</td>
<td>Characteristic skin rashes of Gottron’s papules on extensor surfaces and heliotrope discoloration over eyelids; it might have many systemic manifestations in addition to proximal weakness and accounts for 85% of juvenile IIM.</td>
</tr>
<tr>
<td>Myositis associated with another autoimmune disease (overlap myositis)</td>
<td>Overlap with scleroderma most common in children, but any autoimmune disease might be associated with myositis. Seen in 3–10% of juvenile IIM.</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Characteristic skin rashes are absent and might have severe weakness. Seen in 2–8% of juvenile IIM.</td>
</tr>
<tr>
<td>Amyopathic dermatomyositis</td>
<td>Typical juvenile dermatomyositis skin rashes without muscle involvement for at least 2 years. Rare in children. Rather, mild muscle inflammation is often present but missed. Calcinosis or arthritis might be seen.</td>
</tr>
<tr>
<td>Focal myositis</td>
<td>Most often presents as an enlarging mass within the affected muscle, which is usually painful or tender to palpation. The most common sites of involvement are the thighs and calves, followed by the neck. Few case reports in children.</td>
</tr>
<tr>
<td>Orbital myositis</td>
<td>A form of focal myositis involving the extraocular muscles. Presents with orbital pain worsened by eye movement. Diplopia, proptosis, conjunctival injection, periorbital oedema, and globe retraction with narrowing of the palpebral fissure are commonly associated symptoms. Reported in more than 30 children.</td>
</tr>
<tr>
<td>Inclusion-body myositis</td>
<td>Characterised by slowly progressive proximal and distal weakness, low serum creatine kinase, and rimmed vacuoles on trichrome stain of muscle biopsy. Few case reports in children.</td>
</tr>
<tr>
<td>Cancer-associated myositis</td>
<td>Myositis develops within 2 years of cancer diagnosis. Solid organ tumours, lymphoma, and leukaemia reported. Only a few case reports in children, mainly with atypical cases of juvenile dermatomyositis. Routine screening for malignancy is neither needed nor cost effective in the assessment of childhood myositis.</td>
</tr>
<tr>
<td>Granulomatous myositis</td>
<td>Granulomas prominent in muscle biopsy, often with distal weakness. Mainly idiopathic or related to sarcoidosis in paediatric cases. Few cases reported in children.</td>
</tr>
<tr>
<td>Macrofasciitis</td>
<td>Myositis of the deltoids or quadriceps, which is predominantly macrofascic. Childhood cases might also present with hypotonia, developmental delay, and inability to thrive. Intramuscular injection of aluminium-containing vaccines might be the cause. Increasing number of childhood patients reported over the past decade.</td>
</tr>
<tr>
<td>Eosinophilic myositis</td>
<td>Prominent eosinophil infiltrates on muscle biopsy associated with peripheral eosinophilia. Eosinophilic polymyositis generally needs treatment with corticosteroids. Some reports in children, however, some cases identified as muscular dystrophy, with calpain-3 mutations.</td>
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IIM=idiopathic inflammatory myopathies. Modified from references 1 and 2.
also plays an important part. In the diseased muscle, perivascular and perifascicular lymphocytes (B cells and myocytes increase expression of MHC class I and II molecules. Complement is deposited in the vessels in the muscle and affected skin.

The importance of type-1 interferons in juvenile dermatomyositis and other idiopathic inflammatory myopathies is becoming evident. Genes regulated by type-1 interferon mediate immunoregulation; they upregulate MHC class I (many cytokines, including interferon γ, can upregulate MHC class I); activate cytotoxic effects of natural killer cells; promote activated T-cell survival; and support dendritic cell maturation. Gene expression profiles of affected skeletal muscle from untreated patients have shown that almost half the most differentially expressed genes were associated with immune responses, and most of these genes were inducible by type-1 interferons. The global pattern of gene expression in peripheral blood cells of patients with juvenile dermatomyositis shows a subset of type-1 interferon-inducible genes that parallels the pattern of systemic lupus erythematosus but is, however, unique to juvenile dermatomyositis. The magnitude of the gene expression of the chemokine interferon-inducible protein 10 (IP-10 or CXCL10) and monocyte chemoattractant protein (MCP-1 or CCL2, MCP-2 or CCL8) correlates with disease activity. Because the expression in peripheral blood mononuclear cells for mRNA of one such type-1 interferon-inducible antiviral molecule—myxovirus resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle resistance protein (MxA)—is associated with muscle activity, it might serve as a biomarker for myositis.

The mechanism by which type-1 interferons contribute to pathogenesis has not yet been elucidated. These interferons might promote inappropriate expression of MHC class I molecules in affected myofibres. Myofibres usually express very few MHC class I molecules; their upregulation is seen in myofibres from patients with all forms of idiopathic inflammatory myopathies. Overexpression of MHC class I might directly injure myofibres, and ultimately result in disease via stress to the endoplasmic reticulum. Thus, type-1 interferons could contribute to disease by inducing and sustaining inappropriate expression of MHC class I in myofibres. Another aspect of type-1 interferon action that might contribute to pathogenesis is induction of pro-inflammatory cytokines and chemokines, including interleukin 15, monokine inducible by interferon γ (MIG/CXCL9), and interferon γ-inducible T cell a chemoattractant (I-TAC/CXCL11) that might play a part in angiostasis and in recruiting lymphocytes to sites of inflammation in the
Peripheral blood,29 muscle,40 and skin.41 This process changes over time; an increased duration of chronic inflammation is associated with increased perivascular Fas-positive cells and affects the type of cells undergoing apoptosis.38

Additional key interactions in affected tissues include leucocyte and endothelial cells through specific adhesion receptors. In inflamed muscles, intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1) are upregulated on endothelial cells; these cells are surrounded by leucocytes that express lymphocyte function associated antigen 1 (LFA-1) and very late activation antigen 4 (VLA-4). This upregulation suggests that adhesion molecules are important for the development of inflammatory infiltrates in the muscle.39 It has been difficult to establish which events initiate these processes and which perpetuate them. Myocyte damage probably causes upregulation of antigens known to be present in muscle. MHC expression on the endothelium is probably an early change, but the temporal order of the pathogenic events in idiopathic inflammatory myopathies has not been well investigated.

Maternal microchimerism might be important in childhood myositis. The presence of chimeric cells of maternal origin is most often benign; however, these cells might cause graft-versus-host disease or autoimmunity.42–44 Microchimerism has been reported in more than 70% of T lymphocytes in peripheral blood cells and in 80–100% of muscle-tissue samples from patients with juvenile dermatomyositis.45–48 Chimeric T cells might be autoreactive, as shown by the production of interferon γ and by chimeric T cells in response to host cells of juvenile dermatomyositis.49

Our understanding of the immunopathogenesis of juvenile dermatomyositis has improved, but we still need to elucidate the events that initiate the cascade, and the role of dendritic cells and the interferon-α response in initiating and sustaining the disease.50 Further understanding of pathogenesis will also help us to better comprehend the associated clinical features, and help to inform treatment.

### Diagnostic criteria
Juvenile dermatomyositis is usually considered in the differential diagnosis either when erythematous rashes arise on the face or extremities or when acquired symmetrical muscle weakness is present. Many conditions might present similarly and should be considered in the differential diagnosis (table 2).43,44 The diagnosis of juvenile dermatomyositis is mainly made through a constellation of clinical and laboratory tests, as applied in the 1975 criteria by Bohan and Peter.45,46 Only two-thirds of affected children will have high creatine kinase enzyme activity in sera, so other myositis-associated enzymes, including aldolase, transaminases, and lactate dehydrogenase, should be tested and followed up.8 The criteria for diagnosis are symmetrical proximal muscle weakness, the presence of at least one of the characteristic rashes (figure 1), increased activity of muscle enzymes in serum, myopathic electromyography, and characteristic pathological changes on muscle biopsy. Patients with characteristic rashes and two other criteria are considered to have probable juvenile dermatomyositis, and those with rash and three other criteria have definite juvenile dermatomyositis.46

### Table 2: Differential diagnosis of childhood idiopathic inflammatory myopathies

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Weakness alone</td>
</tr>
<tr>
<td>Muscular dystrophies</td>
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<tr>
<td>Metabolic myopathies</td>
</tr>
<tr>
<td>Endocrine myopathies</td>
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<tr>
<td>Drug-induced myopathy</td>
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<tr>
<td>Neuromuscular transmission disorders</td>
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<tr>
<td>Motor neuron disorder</td>
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<tr>
<td>Weakness with or without rash</td>
</tr>
<tr>
<td>Viral</td>
</tr>
<tr>
<td>Bacterial and parasitic organisms</td>
</tr>
<tr>
<td>Other rheumatic conditions</td>
</tr>
<tr>
<td>Other inflammatory conditions</td>
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<tr>
<td>Rash without weakness</td>
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</tbody>
</table>

In many of these conditions, diagnosis is facilitated by muscle biopsy; muscle biopsy should be strongly considered in the absence of rashes of typical juvenile dermatomyositis.
suggesting that criteria might need to be revised; many patients with a diagnosis of juvenile dermatomyositis could only be called probable by the 1975 criteria.47

Although a biopsy sample and electromyography give specific information about the inflammatory response, they are invasive procedures. Because of their invasive nature, alternative tests are frequently sought to aid in diagnosis. In clinical practice, MRI (figure 3B) seems to be a very sensitive method to assess muscle oedema (inflammation). In a prevalence sample (all stages of the disease) of 102 patients who had childhood myositis, 78 (76%) had an abnormal MRI.48 The sensitivity and specificity at diagnosis are not yet well defined, and MRI can localise muscle oedema, but cannot ascertain its cause, since some dystrophies might also show muscle inflammation. However, many rheumatologists use MRI to establish a diagnosis of idiopathic inflammatory myopathies; the paediatric rheumatologists who were surveyed rated MRI as one of the most important diagnostic methods to be added to the revised criteria.47

Nailfold capillaroscopy49,50 (figure 3C) is highly sensitive for diagnosis of juvenile dermatomyositis. It is helpful for differentiating dermatomyositis from muscular dystrophies and other myopathies, but might not always distinguish it from other connective-tissue diseases, such as scleroderma, overlap myositis, or mixed connective-tissue disease.6 Children with this disease have reduced capillary density that shows disease activity, especially skin disease activity.49,51 Capillaroscopy is easily done at the bedside with a magnifying light, such as an otoscope, and water-soluble gel or with a DermLite™ (3Gen, LLC, San Juan Capistrano, CA, USA).52 Criteria sets for diagnosis of childhood idiopathic inflammatory myopathies need to be developed; they should be both non-invasive and cost-effective, and have the capacity to identify the substantial heterogeneity in the disease. Hence, an international, multidisciplinary effort is underway to develop new diagnostic and classification criteria. Criteria based on constellations of genetic, environmental, and pathogenic findings are needed.

Clinical features
In addition to proximal, usually progressive, muscle weakness and characteristic skin rashes (Gottron’s papules or the heliotrope eyelid rash), the presenting features of juvenile dermatomyositis are protean (figures 3 and 4,53–56, panel). Nonetheless, some characteristic features deserve further discussion. Dystrophic calcification (figure 3D) occurs in up to 30% of patients.56,57 The sites most frequently affected are pressure points: elbows, knees, digits, and buttocks. Calcinosis most often begins 1–3 years after onset of illness, but might begin at illness onset or as long as 20 years later.58 Four subtypes have been described: (1) cutaneous or subcutaneous plaques or nodules; (2) deposits that extend to muscle; (3) calcinosis along fascial planes that might lead to contractures; and (4) widespread calcium exoskeleton.59 Calcinosis can result in skin ulceration; functional disability from joint contractures;57 pain because of nerve entrapment; or local inflammation with local erythema, tenderness, and drainage that should be distinguished from cellulitis.60

Factors leading to calcinosis have been clarified. Increased local production of TNFα is associated with calcinosis in juvenile dermatomyositis and is associated with the TNFα-308 polymorphism; therefore, intensity of the inflammation might contribute to the development of calcinosis.13 The calcific lesions seem to contain hydroxyapatite, but the deposition is heterogeneous, without formal bone structure.61 Calcinosis is associated with delayed diagnosis and long duration of untreated disease, a chronic disease course, and inadequate corticosteroid therapy.62–64 Spontaneous regression, either through reabsorption or extrusion, might happen. Progression is more probable when active myositis is persistent and inadequately treated.65
Cutaneous ulcerations are pathologically the result of complement deposition with occlusive endarteropathy of dermal vessels (figure 3E). They affect fewer than 10% of patients with juvenile dermatomyositis, but might predict a severe course of illness with persistent weakness, widespread calcinosis, and poor response to therapy, possibly related to decreased gastrointestinal absorption. Vasculopathy of the intestines infrequently manifests as ulceration, haemorrhage, pneumatosis intestinalis, or perforation. Abdominal pain that is persistent, progressive, or severe should be carefully assessed clinically and radiologically, and stool should be tested for occult blood. Children not at imminent risk of perforation could undergo barium examination or contrast-enhanced CT, which might show dilatation or thickening of the bowel wall, intraluminal air, and evidence of bowel necrosis. These symptoms and signs might arise early in the disease as a result of a non-inflammatory endarteropathy or late because of chronic vasculopathy. Aggressive management with surgery and immunosuppression might have improved the outcome for this potentially life-threatening complication, since many old reports noted a high death rate. Vasculopathy sometimes causes other acute and potentially life-threatening manifestations, such as widespread oedema or anasarca, and spontaneous pneumothorax or pneumomediastinum, which are often associated with cutaneous ulceration.

10–40% of patients with juvenile dermatomyositis have acquired lipodystrophy (figure 3F), which might be generalised, partial, or local. Insulin resistance with acanthosis nigricans, diabetes, and dyslipidaemia accompanies the fat loss in many of these patients. Other sequelae include hyperpigmentation, hepatomegaly, hypertension, and menstrual irregularity.

Heterogeneity of childhood idiopathic inflammatory myopathies

Childhood idiopathic inflammatory myopathies can be divided into more homogeneous clinicopathological or serological subsets with distinctive epidemiology, and clinical, pathological, or prognostic features (tables 1 and 3). Juvenile dermatomyositis is the most common subset, representing up to 85% of childhood idiopathic inflammatory myopathies. The two other major subsets of idiopathic inflammatory myopathies are juvenile polymyositis, in which the characteristic rashes are absent, and overlap myositis—ie, polymyositis or juvenile dermatomyositis patients who also meet the criteria for another autoimmune disease. The incidence of polymyositis is much lower than that of juvenile dermatomyositis, and overlap myositis is much lower than that of juvenile dermatomyositis, and the prevalence of polymyositis is 2–8% of childhood idiopathic inflammatory myopathies. Weakness in patients with juvenile polymyositis is often both proximal and distal, and muscle atrophy is frequent. Such patients have similar degrees of dysphagia, arthritis, and contractures, as do patients with juvenile dermatomyositis.

Overlap myositis, which has a prevalence of 3–10% of childhood idiopathic inflammatory myopathies, arises when juvenile dermatomyositis or polymyositis is associated with another autoimmune disease, such as systemic lupus erythematosus, scleroderma, juvenile idiopathic arthritis, inflammatory bowel disease, type 1 diabetes mellitus, or coeliac disease. The most common form of overlap myositis in childhood is juvenile dermatomyositis with features of scleroderma. Children with overlap myositis might have milder myositis, with lower creatine kinase activity, which might be more responsive to treatment than juvenile dermatomyositis.

Amyopathic dermatomyositis—ie, typical dermatomyositis skin rash without muscle involvement for at least 2 years—is uncommon. More often, patients have mild muscle disease or progressive muscle disease that is missed on early assessment. Patients can develop calcinosis or arthritis, and the photosensitive rashes might be longstanding and benefit from systemic therapy.
Inclusion body myositis and cancer-associated myositis are seen almost exclusively in adults. Malignancies, including lymphoma, solid-organ tumours, and leukaemia, are sometimes reported in association with juvenile dermatomyositis with atypical features,\(^7\) but are so infrequent that an assessment for an occult malignancy is not routinely done in children who have myositis.

Macrophagic myofasciitis, a rare but distinct clinicopathological entity, reported mostly in French adults, is increasingly reported in young children.\(^7\) These children have shoulder or thigh weakness with high creatine kinase concentration, and frequently have myalgia, fatigue, arthralgia, and a high sedimentation rate. Biopsy of the muscle shows a predominantly macrophagic infiltrate, sometimes containing aluminium inclusions. Children might also present with hypotonia, developmental delay, and failure to thrive.\(^7\) Intramuscular injection of aluminium-containing vaccines might be the cause.\(^7\) Eosinophilic myositis and infantile polymyositis are caused by mutations in calpain-3 and merosin genes, respectively, and have been reclassified as muscular dystrophies.\(^8,9\)

Defined autoantibodies (in which the target antigen is known) have been identified in up to 70% of adult patients and 40% of children with idiopathic inflammatory myopathies (table 3). Autoantibodies noted frequently not only in idiopathic inflammatory myopathies but also in other conditions are called myositis-associated autoantibodies (MAA); those unique to idiopathic inflammatory myopathies are called myositis-specific autoantibodies (MSA). Tests for MSA or MAA with immunoprecipitation and immunodiffusion are reliable, but only available in a few laboratories. Authors of reports that show non-specificity of these antibodies have used less specific ELISA or immunoblot assays.\(^6\) MSA and MAA are associated with specific clinical features, immunogenetics, response to therapy, and prognosis (table 3). These associations have been more extensively examined in adults;\(^13\) few children with MSA have been studied, but seem to have similar associations.\(^2\)

A new MAA, anti-p155, has been identified in 30% of patients with juvenile dermatomyositis and 20% of adult dermatomyositis patients, and in most patients studied with cancer-associated dermatomyositis.\(^84,86\) Adults with this autoantibody, often a heterodimer (p155 and p140), have typical dermatomyositis features with prominent rashes.\(^84,86\) Anti-p155 might become an important diagnostic test when clinical assays become available. Because reliable tests are not widely available, MSA and MAA should probably only be tested in patients whose clinical features suggest a syndrome associated with a particular autoantibody, in unusual patients in whom the diagnosis is unclear, in severe cases, or in those who are unresponsive to usual treatments. Early diagnosis and intervention are an essential initial step, but modern molecular research methods, that use well characterised patient registries, will be instrumental in establishing long-term prognosis and the most effective treatments for the emerging clinically distinct subsets of idiopathic inflammatory myopathies.

**Clinical course**

Typically, children with myositis are followed up by serial examination of muscle strength, function, rash, other organs, and serum concentrations of muscle enzymes. However, tests for muscle enzymes are not very sensitive (more than 20% of patients have a normal creatine kinase concentration at diagnosis) and frequently become normal with corticosteroid treatment even in active disease. Two international collaborative study groups have standardised and validated measures of disease activity and disease damage. Core sets of measures for clinical studies have been proposed.\(^92,93\) These measures have been combined to develop criteria to show response to treatment.\(^92,93\) The Myositis Damage Index is a reliable assessment of disease damage.\(^92,93\) Standardised training is important for reliable application of these assessment measures.

MRI (especially short tau inversion recovery or fat-suppressed T2 images; figure 3B) seems to be a valid indicator of disease activity and is useful when the myositis activity is difficult to establish.\(^92,93\) MRI might also show oedema in the myofascia, subcutaneous tissue, and skin.\(^93\) T1-weighted images are useful to detect muscle atrophy.
and fatty infiltration in the presence of damage. For the assessment of disease complications, additional imaging techniques might be useful—eg, high-resolution CT for pulmonary complications and video-fluoroscopic swallowing studies for dysphagia or dysphonia.

The role and measurement properties of immunological and endothelial activation markers that might also be helpful in the assessment of disease activity (especially in the refractory patient), including peripheral blood mononuclear cell subsets, neopterin, von Willebrand factor VIII-related antigen, adhesion molecules, and interferon and cytokine signatures, need to be further defined. In the future, muscle pathology might be useful to assess disease outcomes in clinical trials and perhaps in practice.

### Treatment

Treatment for childhood idiopathic inflammatory myopathies have not been assessed in randomised controlled trials. Our best understanding of treatment comes from observational studies and clinical experience. Since the 1970s, standard treatment for juvenile dermatomyositis has been high-dose daily oral corticosteroids (eg, up to 2 mg/kg per day of prednisone, often in divided doses), which is continued until clinical and laboratory improvement are evident and then slowly reduced over at least a 2-year period. Much of the rationale for this approach was based on improvement in the frequency of calcinosis with early initiation of high-dose corticosteroid therapy. With this treatment, however, most patients have side-effects from corticosteroids. As a result, many patients are now treated by alternative routes or with adjunctive immunosuppressive medications in an attempt to spare high doses of daily oral corticosteroids or shorten their duration.

Some children with myositis absorb oral corticosteroids poorly, perhaps as a result of gastrointestinal vasculopathy, which is the rationale for early treatment with high-dose (pulse) intravenous methylprednisolone (usually 30 mg/kg per day, to a maximum of 1 g daily). Some physicians treat with repeated pulses of high-dose intravenous methylprednisolone combined with low-dose daily oral corticosteroid (0.5 mg/kg per day). This approach might be cost effective and lead to early remission.

Methotrexate is an important ancillary treatment for juvenile dermatomyositis. Early studies suggested that methotrexate improves strength and reduces other signs of disease activity in non-responsive (steroid-resistant) patients with acceptable side-effects and a steroid-sparing effect. Reports support aggressive treatment, including early introduction of methotrexate, to reduce calcinosis and other sequelae. Children given methotrexate (about 15 mg/m² per week orally or subcutaneously) at disease onset had half the cumulative corticosteroid dose, less weight gain, and improved height velocity, but achieved the same disease control as the comparison group who were treated only with corticosteroids. Methotrexate is now widely used by paediatric rheumatologists at the start of treatment as a steroid-sparing agent.

Ciclosporin has also been used in many centres as a steroid-sparing agent. Efficacy is supported by findings from several small case series but no comparative studies have been done. Ciclosporin frequently leads to hypertension and hirsutism in patients with juvenile dermatomyositis. The Paediatric Rheumatology International Trials Organisation has begun a multisite randomised trial to compare initial treatment with corticosteroids with treatment with corticosteroids and methotrexate, or corticosteroids and ciclosporin.

Intravenous immunoglobulin was noted to be efficacious in a controlled trial for adult dermatomyositis. Several case series have suggested efficacy of intravenous immunoglobulin for treatment of juvenile dermatomyositis. It is now widely used as an adjunctive treatment for steroid-resistant or steroid-dependent disease, especially resistant skin rash.

Other treatments, including hydroxychloroquine, systemic tacrolimus, azathioprine, mycophenolate mofetil, and cyclophosphamide for severe disease have shown some benefit in case series of refractory disease. Biological agents, widely used in other rheumatic diseases, are being developed for the treatment of childhood myositis. The use of anti-TNF agents (eg, etanercept or infliximab) in children has only been reported in meeting abstracts; however, reports of effectiveness in adult myositis are mixed. Anti-B-cell therapy (rituximab) has shown more promise for adult dermatomyositis and might be associated with remission in juvenile dermatomyositis. A randomised trial of rituximab for both adults and children with myositis is now underway.

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**Table 3: Myositis-specific and myositis-associated autoantibodies in myositis**

<table>
<thead>
<tr>
<th>Myositis-specific autoantibodies</th>
<th>Anti-signal recognition particle</th>
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<tbody>
<tr>
<td>Anti-Mi-2</td>
<td>Typical dermatomyositis features, with mild-to-moderate disease, usually responsive to therapy. Present in up to 5% of juvenile myositis patients</td>
</tr>
<tr>
<td>Anti-U-RNP</td>
<td>Seen in myositis overlap syndromes</td>
</tr>
<tr>
<td>Anti-Jo1</td>
<td>Present in up to 5% of juvenile myositis patients</td>
</tr>
</tbody>
</table>

**Myositis-associated autoantibodies**

- **Anti-Ro**: Seen in myositis overlap syndromes
- **Anti-U-RNP**: Seen in myositis overlap syndromes
- **Anti-Ku**: Associated with scleroderma–myositis overlap syndrome, with frequent Raynaud's disease, arthralgia, and reflux

Modified from references 1 and 2.
Treatments for childhood myositis have resulted in improved outcomes; mortality has been reduced to less than 2%. In the absence of controlled trials, children with typical, moderately severe myositis should be treated as rapidly as possible, initially with corticosteroids in high doses (enterally or parenterally for more severe presentations) and with a steroid-sparing agent, such as methotrexate. Patients with refractory or severe disease might benefit from intravenous immunoglobulin. Other treatments should be considered on an individual basis.

Adjunctive therapies are very important in the treatment and outcome of juvenile dermatomyositis. Routine use of photoprotective agents is suggested to minimise rashes and other skin disease, and topical agents (corticosteroids or tacrolimus) are often used to treat localised skin disease. Exercise for rehabilitation is increasingly recognised as important for improvement of muscle strength and capacity for aerobic exercise. Physiotherapy might prevent contractures and improve function, and seems safe in active disease. Calcium and vitamin D supplements are often given to improve overall bone density.

Although outcomes have improved with more aggressive immunosuppressive therapies, we should establish clinical and pharmacogenetic guidelines for selecting the best treatment for individual patients. Furthermore, we should better define the effectiveness and adverse events of current treatments and biological agents, and the effect of adjunctive therapies, including exercise. We should establish a treatment culture in which (as is the case with childhood cancer) all patients are offered research protocols to guide their treatment.

The prognosis of juvenile dermatomyositis, in terms of physical function and social participation, is now generally excellent. However, many patients continue to have chronic illness and suffer sequelae of the disease. Before the availability of corticosteroids, this disease had a dire course: a third of affected children died; a third had a progressive cripplng course, with disabling contractures, calcinosis, and weakness; and many had chronically active disease, which continued into adulthood. The clinical course has been described as monocyclic (permanent remission within 2–3 years), polycyclic (periods of remission followed by relapse), and chronic continuous. Delayed or inadequate corticosteroid treatment seems to be one of the most important predictors of poor outcome and a chronic illness course, including a decrease in bone density and chronic skin disease.

Clinical and functional outcomes have been reported to be much improved; this might be because of earlier recognition, and more aggressive treatment with immunosuppressive medication and higher doses of corticosteroids. In an inception cohort of 65 patients with juvenile dermatomyositis, who were followed up at four Canadian centres for an average of about 7 years, most showed normal physical function. Educational and vocational achievements were excellent, and growth was mostly normal. Despite this, a third developed calcinosis, and more than a third had chronically active disease, mainly rash, at follow-up. Survival has also been reported to be high in European patients, but chronic disease, calcinosis, and polycyclic relapses remain a problem. Early recognition and treatment are very important for improvement of the prognosis of children with myositis. Education of primary-care physicians to recognise the idiopathic inflammatory myopathies, so that patients can be diagnosed and treated earlier, and improvement of access to specialised care remain substantial challenges. Recognition of the importance of continued inflammation, and genetic and immunological prognostic features might be useful for selection of the most effective intervention.

In the past 10 years, important progress has been made in the understanding and the management of childhood idiopathic inflammatory myopathy. Early recognition and aggressive immunosuppressive treatment have improved prognosis. We have an improved, but as yet incomplete, understanding of the pathogenesis and cause, including the genetic and environmental risk factors, for disease initiation and progression. We should work to decrease the frequency of calcinosis and other complications. If we can better define the clinically important phenotypes, we should be able to individualise treatment to further improve outcomes.

Conflict of interest statement
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Seminar


