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Advances in Juvenile Dermatomyositis: Myositis Specific Antibodies Aid in Understanding Disease Heterogeneity

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Although juvenile dermatomyositis (JDM) is the most common pediatric inflammatory myopathy, it is a rare disease, which has impeded our recognition of the extent of the variation in both JDM symptoms and pathophysiology. Convincing new evidence has recently emerged documenting that myositis specific antibodies (MSA) are uniquely effective in identifying specific subsets of inflammatory myopathies in children. This review will focus on the impact that these MSAs have made on our understanding of both the clinical and laboratory features of JDM and will summarize some of our options for therapy.

The common laboratory and diagnostic features of JDM have been previously described (1, 2). In brief, JDM is a systemic autoimmune vasculopathy, with a mean age of onset of 6.7 years (boys), and 7.3 years (girls); the female: male ratio is 2.3:1 (3). At diagnosis, both boys and girls with JDM are shorter and lighter than their age and sex matched controls (4). One defining clinical manifestation of JDM is symmetrical proximal muscle weakness. The second major symptom, the characteristic rash, occurs over the joints and extremities, and the shawl region of the chest (Figure 1). This rash also localizes to the area around the eyes, as well as the lids themselves, and the malar area, including the bridge of the nose. Younger children may be edematous and have scalp involvement, resulting in alopecia. In untreated

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JDM, elevated serum levels of muscle derived enzymes (aldolase, CPK, AST, ALT, LDH) are time dependent; they tend to normalize by 4.5 months after diagnosis (4). MRI identifies the patchy muscle inflammation and can help direct the physician to biopsy an inflammatory site. The typical JDM muscle biopsy displays perifasicular atrophy, muscle fiber size variation, increased expression of major histocompatibility complex (MHC) Class 1, infiltration of primarily mononuclear cells (5), extensive muscle capillary drop out and damaged mitochondria (6). This evidence aids diagnosis and the choice of immunosuppressive therapy (5).

Juvenile dermatomyositis etiology: genetics and environment

A working hypothesis is that JDM is a type-1 interferon-driven inflammatory process, triggered by one or more environmental stimuli, such as infection, exposure to smoking or ultraviolet rays (UVB), targeting a genetically susceptible child. Families of the JDM child may have a history of autoimmune disease, most often systemic lupus erythematosus (SLE) (7), but it is rare to have more than one case of inflammatory myopathy in a family. Disease susceptibility is attributed to the human leukocyte antigen (HLA) locus on chromosome 6 (8), similar to other autoimmune diseases, which was determined by testing both pediatric and adult dermatomyositis (DM) patients of European ancestry using genome wide association (GWAS) methodology (9). Further testing of Caucasians with a range of inflammatory myopathies defined additional loci; PTPN22 was associated with genome-wide significance for polymyositis (PM), but not DM or JDM (10). In Japanese myositis patients, HLA – DRB1*08:03 confers risk (11), which differs from the Han Chinese myositis patients, who are more likely to carry the HLA-DQA1*01:04, and HLADRB1*07 alleles (12). Each of these risk genes displays unique differences in the peptide-binding pocket, modifying their ability to attract and bind antigenic peptides which subsequently stimulate an immune response (13). As in SLE, some JDM children have decreased gene copy number for C4 *(A>B)*, resulting in low production of C4 (14), which may also be diminished by complement consumption. The increase incidence of JDM in girls appears to be associated with a synergy between osteopontin and the TNF-α locus (15).

A range of potential facilitating factors are under active consideration: seasonality of birth; sun/UVB exposure; prenatal smoke/pollution exposure; urban vs rural dwelling; life stressor; immunizations and medications. Of these conditions, seasonality of birth has been reported (16), which may be confounded by ante-partum exposure of the fetus to cigarette smoke and traffic pollution (17, 18). Antecedent infection may precipitate the autoimmune process (19–24), as well as a flare of disease symptoms (20), and is implicated in both JDM (19–21) and DM (22). Detection of the specific antigen (infectious agent?) in untreated biopsies has not yet been achieved. Global warming (23) may have obscured the reported seasonality of onset (spring and fall in the Midwestern USA) (21). In the 3 months prior to the first symptom of JDM, respiratory and/or gastrointestinal infection predominate (24), whereas in the 6 months preceding a JDM flare, gastroenteritis ($P = .04$) and urinary tract infections (p=0.005) are more frequent (20). Sun exposure (OR=3.5; p=0.049) preceded a flare, despite photoprotective agents (20). Vaccinations may also trigger the myopathic process (25).

Pathophysiology of juvenile dermatomyositis

The duration, or length of time of the disease process, influences both the child's symptoms and laboratory data at diagnosis (4). The duration of disease also impacts immunologic data, ranging from gene expression in the muscle biopsy of untreated children (26) to the display of specific apoptotic pathways in their muscle (27). The child's age at disease onset is also associated with specific gene activation (28). The inflammatory infiltrate in the affected JDM muscle is predominantly composed of mononuclear cells—both lymphoid and phagocytic; lymphoid aggregates are associated with severe disease (29). Along with CD3+CD4+ T cells, there is an increase in FOXP3+regulatory T cells (30) as well as mature plasmacytoid dendritic cells, which secrete type 1 interferons. Recently recognized, myogenic precursor cells (MPCs) in JDM muscle also synthesize type 1 interferons (32). The MPCs also modulate the loss of microvasculature in muscle characteristic of JDM (6). Mast cells predominate in JDM skin biopsies, even in uninvolved areas, compared with inflamed muscle from the same child (32). In JDM, there may also be a role for natural killer (NK) cells in inflicting damage (33). The absolute count of $CD3^{-}CD16^{-}56^{-}$ NK cells appears to be a useful biomarker for some forms of inflammatory myopathy, such as orbital myositis (34). The levels of proinflammatory cytokines reflect immune activation. Biomarkers, such as serum tumor necrosis factor receptor type 2 or Galactin 9 (35), and/or the17-related cytokines (36) may be useful to guide the child's therapy. Deposition of the terminal membrane attack complex, C5b-9, on the muscle microvasculature is associated with perifasicular atrophy in both adults and children with DM (37). The precise *sequence* of these immune events is not yet known, and appears to vary with the myositis specific antibodies (MSAs). RNA sequencing of peripheral blood mononuclear cells from untreated JDM showed a specific pattern of gene activation with $p155/140^{+}$ MSA, differing from peripheral blood mononuclear cells from MJ^{+} children (38).

Autoantibodies identify JDM subsets as well as myositis overlap syndromes

There are 2 major groups of autoantibodies: 1) myositis specific antibodies (MSAs), which define *subsets of JDM children*, and 2) myositis associated antibodies (MAAs), which identify children with additional symptoms of *other connective tissue diseases*. The major advance is the identification of specific MSAs, which characterize individual sub-groups of JDM children who each have specific phenotypes (Figure 2, A–C) and prognoses (39) (Table). It is generally agreed that protein immunoprecipitation is the most sensitive and consistent method to identify these antibodies (39, 40) but line–blot assays (41) or highly standardized ELISA assays may be used as well (39). These MSAs are present in 54% of children with juvenile myositis (JM) in the United States (US) (42) and about 51% in the United Kingdom (UK) (39). The most common MSA is directed against transcriptional intermediary factor 1 gamma (TIF-1-γ)/p155/140, and is associated with severe cutaneous disease, a chronic disease course and lipodystrophy, which can range from focal to generalized (43) (Figure 2, A). The second most frequent MSA is called anti-MJ in the US, but is labelled the anti-nuclear matrix protein-2 (NXP-2) in the UK and Europe, and is highly associated with the development of calcinosis at any age (Figure 2, B). The severity of the calcinosis is worse in the younger child, age 4 years or less (44). Of note, 25% of children with JDM in the US, both boys and girls, are below age 4 years at disease onset (24). Children with anti-MJ are more likely to have a chronic disease course with more

severe muscle disease, GI bleeding, ulcers and dysphagia, with worse disease outcome and impaired functional status (42, 44). The next, less common MSA, anti-MDA-5, is directed against the melanoma differentiation associated gene 5 (also known as CADM-140), (Figure 2, C, Table). Anti-MDA-5 is associated with rapidly progressive interstitial lung disease (ILD) and a high mortality rate, complicated by arthritis and ulceration (45) in the Japanese population. This antibody is present in 54% of Japanese children with JDM; higher titers are associated with elevated levels of interleukin (IL)-18, IL-6, and ferritin and very severe ILD (46), unlike children with JDM with MDA-5 (7–8%) in the US, who rarely develop ILD. The most benign MSA is anti-Mi-2, present in 3–5% of patients with JDM in the US (42), 4% in the UK (39), and its target is a nucleosome remodeling deacetylase complex (NuRD). Children with Mi-2+ demonstrate "classic" JDM symptoms, and respond well to standard therapies with an excellent prognosis. In contrast to adults with DM or PM, <5% of children have antibody to the t-RNA-synthetase antigens (39) (Table 1). The antigenic targets are listed in Table 1, and, as in adults, anti-Jo-1 is the most reported. The anti t-RNA-synthetase syndrome is characterized by myositis, interstitial lung disease, fever, mechanic's hands, Raynaud's phenomena and arthritis; it occurs in older children who have an increased risk of mortality. A relatively new group is composed of two severe *necrotizing* autoimmune myopathies: anti-signal recognition particle (SRP) (47) and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) (48, 49). Both of these necrotizing myopathies respond poorly to our current modes of therapy. SRP antibodies are more frequent in African American children who have frequent cardiac involvement and are often wheel chair bound (47, 48). Both types of myopathies have very high levels of muscle derived enzymes and display muscle cell necrosis on biopsy with scant inflammatory infiltrate. Children with HMGCR antibody may not have the typical dermatomyositis skin involvement (49), while adults often have a history of exposure to statins (50–51). Finally, the teenager that develops myositis may have an "overlap" syndrome with MAA antibodies to PmScl (3–5%) or U-RNP (5–15%) (Table 1). Other antigens in the MAA group include polymyositis/scleroderma (PM/Scl), or antibodies to U-RNP antigens which define the "overlap syndromes". To complicate matters, a child with any of the MSAs may also have a MAA, for example anti-Ro-52 (6%), associated with ILD (52). Reversal of ILD with aggressive medical therapy was reported in a child positive for anti-PL-12 (53).

The source of the antigens that elicit these antibodies is under investigation. Anti-Mi-2 is directed against antigens emerging on the regenerating myofibers in the areas of muscle perifasicular atrophy (54); other myopathic antigens are expressed by regenerating muscle fibers (55). Of note, inclusion body myositis occurs in people ≥50 years of age, not children (56).

Diagnostic and clinical characteristics of children with JDM

The common clinical findings and differential diagnosis are well established (1, 2). Figure 2 highlights the typical symptoms expressed by JDM children with anti-p155/140 (1A), anti-MJ (1B), or anti-MDA-1 (1C) antibodies. The classic features of JDM, symmetrical, proximal muscle weakness, and the typical heliotrope rash (Figure 1, A) vary *with and within* each MSA group. Lesser skin involvement may occur: a child positive for MDA-5 displayed only a small area of persistent erythema on the cheek (Figure 1, B), and another

child positive for p155/140^{+} had only erythema of the pinna the ear (Figure 1, C). The shawl sign involves the skin of the upper chest, and can display both acute and chronic inflammation (Figure 1, D). Erythema tends to occur *where the skin bends*, as over the joints of the hands (Figure 1, E), knees, and elbows. Classic Gottron papules can appear on the hands, elbows and elsewhere, become atrophic and scarred, and not infrequently, calcify. Calcifications can become exuberant, as seen in the buttocks of a 2 year old child (Figure 1, F). Microvasculopathy can be identified as either frank telangiectasia (Figure 1, G), and/or dilated capillaries at the eyelid margin (Figure 1, H). Symmetrical proximal muscle involvement, MRI image, Figure 2, I, is typical of JDM, differing from overlap syndromes, which are often unilateral. Quantitation of the number of the child's nailfold end row capillary loops reflects disease improvement or flare—Figure 2, J shows normal end row capillary loops; Figures 1, K and 1, L depict moderate and severe capillary dropout and deformation, respectively.

Soft tissue calcifications, a major contributor to morbidity and mortality, vary in frequency from 17% (57) to 44% (58), and are more severe in children of African descent (59). These dystrophic calcifications are associated with chronic cutaneous inflammation (60) as well as lipoatrophy, either focal or generalized (43). The calcifications vary in shape and location, are composed of osteopontin, osteonectin and bone sialoprotein (60) and contain small integrin-binding ligand N-linked glycoprotein (SIBLING) proteins (61); hydroxyapatite was the only mineral detected (60). The calcifications often occur at pressure points, but may be deep in the connective tissue. Response to therapy can be measured by a decrease in the calcification volume over time by use of low dose, single slice CT; the radiation dose is equivalent to a chest x-ray (62).

Childhood and adult onset dermatomyositis have differing features

Differences in epidemiology

The inflammatory myopathies are 10 times more common in adults: *incidence* = 20 cases/million people/year vs 2.3 cases/million people/year for children in the US. JDM is the most common of the inflammatory myopathies in children, 75%, compared with 14–28% of adults with DM. In the UK, the *prevalence* of dermatomyositis is 30/100,000 for adults compared with 6/100,000 children (63). In the US, the prevalence of adult inflammatory myopathy ranges from 17–32/100,000; it has not been published for children (64). Adult DM-PM with anti-p155/140 (anti-TIF-1-γ) antibody frequently (17.5%) develop cancer. In contrast, *children* with JDM, even those **with** anti-p155/140, do not develop malignancy, although sporadic lymphomas have been reported (65). Patients with JDM have more calcinosis; adult patients with DM develop more lung disease (66).

Differences in pathophysiology

There are clues to the differing pathophysiology in children and adults. Assays of miRNA expression in muscle of untreated children with JDM show a marked downregulation of miRNA-10a (67), not reported for adult DM muscle (some of whom were treated) (68). RNA-10a, a master regulator of proinflammatory cytokines via the NFkB pathway, also controls vascular system components (69). Studies of endothelial cells from adults with DM

or PM showed a decrease in PM only, not in DM (70). Similarly, the number of endothelial precursor cells were normal in children with JDM (71), providing evidence that *production* of the endothelial cells is not the problem in JDM. It is accepted that the endothelial cells are damaged in both the inflamed muscle (6, 72) as well as the capillary end row loops in the fingernails (73, 74). What *is* open to speculation is the identity of the agent, hypoxia, targeted viral infection, or the circulating and tissue based pro-inflammatory cytokines, such as TNF-α or type-1 interferons (75). Although reports of cytokine data often combined results from adults and children with DM (76, 77), when untreated patients with DM and JDM were *compared*, a marked increase in IRF-4, retinoic related orphan receptor γ, IL-6, IL-17F, IL-23A, IL-21, GATA3 and IL1β were increased in JDM blood at baseline and Stat3 and BCL6 were increased in adult DM blood. JDM muscle had higher levels of GATA3, IL-13 and STAT5B than adult DM muscle (36), suggesting significant differences in disease pathways between DM children and adults.

Compelling new data shows that 49% of children with juvenile myositis in the UK are positive for one or more MSA, specifically determined by radio-labelled immunoprecipitation and previously validated ELISA's. Furthermore, these MSA were *exclusively limited to children with inflammatory myositis,* not other forms of pediatric rheumatic disease (juvenile idiopathic arthritis, juvenile onset SLE or those with muscular dystrophies) and healthy controls (39). Importantly, these assays can confirm the diagnosis of a specific type of inflammatory myopathy. Treatment of **juvenile dermatomyositis**

Corticosteroids

The advent of corticosteroids has improved the outcome for JDM children, although the dose/route of corticosteroid administration appears to be highly variable (78). Prior to their usage, 1/3 of the JDM had calcinosis, 1/3 died, and 1/3 survived (79). As more information became available about the range of JDM symptoms, consensus derived, comparative research proposals for treatment were developed by pediatric rheumatologists who were members of the Childhood Arthritis & Rheumatology Research Alliance (CARRA) (80–83). Standardized criteria for evaluating improvement in response to therapy was also created (84). Our center usually starts with high dose intravenous methyl prednisolone (30 mg/kg, one gram maximum dose), daily for three or more consecutive daily doses once the diagnosis of JDM is confirmed. This is followed by oral corticosteroids, as presented in a recent Paediatric Rheumatology International Trials Organization (PRINTO) study (85). However, the absorption of oral prednisone is greatly impaired in JM patients with nailfold capillary loss (86), and it takes 2–3 months after recognized JDM onset to develop this nailfold drop out (87), but the intravenous route of high dose corticosteroid therapy reduces the incidence of calcinosis (57, 88). Unfortunately, adverse reactions to corticosteroids are a major cause of morbidity in JDM patients (57) and a slow corticosteroid taper should be initiated after disease stabilization. Reliable and documentable biomarkers are sorely needed to guide this process.

Methotrexate (MTX)

A folic acid analogue that inhibits nucleic acid synthesis, MTX is a first line agent for treatment of moderate to severe JDM patients (80). A recent randomized trial of 139

children with JDM compared 3 treatment plans in 22 countries: after an induction period consisting of three daily doses of IV methylprednisolone at 30 mg/kg, the children were given for 2 years either oral prednisone alone, prednisone + MTX, or prednisone + cyclosporine A (CyA). The study concluded that combined prednisone + either MTX or CyA performed better than prednisone alone; more adverse reactions occurred with a 4–5 mg/kg dose of CyA, which was then discontinued (85). Because 30% of patients with JDM do not respond to MTX, research now focuses on identifying biomarkers that both reflect a significant clinical response (89) and critical polymorphisms in the multiple genes controlling MTX transport and glutamination pathways (90). The dosage of MTX is $15mg/M^2$ every week (max=25 mg/week) with 1mg/day of folic acid, except on the day when MTX is given. The most common adverse reaction is nausea and vomiting; less usual complaints include mouth sores, bone marrow suppression, elevated liver enzyme and mild lung dysfunction. Pregnancy is a contraindication—drug contact induces fetal malformations. If serology tests for hepatitis B and C is positive, another drug should be used.

Cyclosporine A (CyA)

Another corticosteroid sparing agent, CyA has a higher frequency of clinically significant side effect than MTX. It is often given to those JDM who are corticosteroid resistant or have a persistent rash (83). An inhibitor of T cell activation, the pro-drug of CyA becomes activated after complexing with cyclophillin. This intracytoplasmic protein complex then inhibits calcineurin, a phosphatase that mediates the pharmacologic effects. Lipophilic in nature, a raised serum lipid level increases clearance of the drug, which should be given before mealtime every 12 hours; CyA trough levels should also be obtained *before* eating (91). In most children with JDM, CyA at the dose of 3 mg/kg, can maintain an 11th hour target trough level of 80–110 ng/ml.

Intravenous immunoglobulin (IVIG)

A range of mechanisms are proposed for the action of IVIG, including cytokine and autoantibody neutralization and saturation of the Fc receptor, blocking receptor activation (92). Monthly administration of IVIG (1–2 grams/kg) is recommended for children with JDM who continue to have rash as a persistent complaint (83). A retrospective study of 78 JDM concluded that IVIG controlled JDM disease activity, particularly in corticosteroid dependent cases (93). Testing for immunoglobulin A (IgA) deficiency should be obtained prior to the administration of intravenous immunoglobulin. Reactions to IVIG, flushing, flu like symptoms, such as headache and fatigue, commonly occur about 24 hours after the infusion and may last as long as 3 days. Using IVIG products that are low in IgA content may decrease these side effects (94). For steroid resistant patients with DM, the use of IVIG + corticosteroids was cost saving (95). Replacement IgG may be required, after rituximab treatment (see below) if the child develops a significantly low level of IgG (96). Hyaluronidase-facilitated immunoglobulin allows higher doses of immunoglobulin to be given subcutaneously (97).

Hydroxychloroquine (HCQ)

This drug targets NADPH oxidase and strongly reduces or completely prevents the induction of endosomal NOX by TNFα, IL-1β and aPL in human monocytes and MonoMac1 as well as blocking TLR7/9 on plasmacytoid dendritic cells, reducing the type 1 interferon signature (98). It also has an anti-thrombotic effect and is associated with a significant reduction in total cholesterol, triglycerides and low-density lipoprotein (LDL) levels (98). Patients with JDM given HCQ had an improvement in their rash within 3 months (99). HCQ was included in all three consensus clinical treatment plans by CARRA for the treatment of skin prominent disease (82). Recommendations from The American Academy of Ophthalmology regarding screening for HCQ retinopathy were changed in 2016 from “annual” to 5 years after starting the drug, when a standard complete examination should be performed (100). The dosage is 5 mg/kg/day; adverse reactions include abdominal pain ± nausea. Very rare adverse effects include cardiomyopathy, cardiac arrhythmia, elevated liver function tests, bone marrow suppression and myopathy.

Mycophenolate mofetil (MMF)

MMF is a reversible, selective, and non-competitive inhibitor of inosine monophosphate, a critical enzyme in the *de novo* purine synthesis pathway required for lymphocyte proliferation (101). There are no guidelines to identify who will benefit from MMF (102). MMF given to 50 children with JDM was both corticosteroid sparing and decreased muscle and skin inflammation without leukopenia or an increased number of infections (103). Adult DM with ILD responded well to MMF (104). Associated with congenital malformations, MMF should be discontinued 7 weeks before a planned pregnancy. Diarrhea, bone marrow suppression and reactivation of hepatitis B and C can occur; screening for hepatitis is recommended. MMF is given every 12 hours at 20mg/kg (maximum of 1,000 mg/24 hours).

Biologic Agents: rituximab, TNF inhibitors, abatacept

The biologic agents are a promising mode of intervention; the targets are specific components of the inflammatory cascade (105, 106), but the specific pathways/mechanisms have yet to be defined for each MSA/MAA combination.

Rituximab—Rituximab, a monoclonal antibody directed against CD20, depletes B cells via several mechanisms, including complement fixation, antibody-dependent cellular cytotoxicity and signaling for apoptosis (105). The initial reports (107, 108) were followed by a large multi-center randomized clinical trial to evaluate the effectiveness of rituximab in both adult and pediatric patients with refractory myositis (109–111). Reanalysis of the data suggested that specific MSAs, anti-Jo-1 and anti-Mi-2, or youth (JDM vs DM) predicted a better response to rituximab. The visual analog scale for muscle and inflammatory cytokine levels improved after 16 weeks of therapy (111). Rituximab is the most commonly used biologic in the treatment of JDM (106). Serum immunoglobulin G (IgG) levels should be monitored; 30–50% of children may develop hypogammaglobinemia in the first year of therapy (112, 113). The child’s B cell response to rituximab can be evaluated by sequential CD19+ absolute counts (flow cytometry).

TNF-inhibitors—Etanercept appeared to be ineffective in JDM (114), but other TNF-antibody inhibitors fared better (115). Of note, TNF inhibitors used to treat other autoimmune diseases may rarely precipitate the development of an inflammatory myopathy (116).

Abatacept—This fusion protein between immunoglobulin and CTLA-4, when used in conjunction with thiosulfate was successful in diminishing the calcific lesions (117).

Autologous stem cell transplant

Symptoms of DM and PM are well known “distinctive features” of chronic graft vs host disease as well as autologous bone marrow transplantation (BMT) (118–122). CD3/CD19 depleted autologous BMT successfully treated 2 patients with JDM after immunoablative conditioning with fludarabine, cyclophosphamide and anti-thymocyte globulin (118). A child with refractory PM responded to immune ablation with Campath -1H (anti-CD52) antibody alone, thus avoiding the expense and trauma of BMT (122).

Vitamin D

Low vitamin D serum levels occur in both the general population (123) and in patients with JDM (124). Essential therapy for immune system maintenance, vitamin D modulates monocyte maturation to immature dendritic cells and other antigen presenting cells as well as B and T cells (125), via 1α-hydroxylase (CYP27B1) (123). Because the sun is the major source of UVB, which promotes the formation of vitamin D, and JDM children are asked to avoid UVB exposure, supplementation with exogenous vitamin D is usually required. The recommended blood level for vitamin D is 30 IU or above, but others suggest 60 IU (123). Vitamin D supplementation is usually about 1–2,000 IU/day; more may be needed to raise the blood level to the desired range.

Physical therapy (PT)

Implementation of PT has reversed from advising bed rest for months at a time, to initiating graded resistance early in the course of illness (126). Truncal muscles are weakened in JM, impairing ventilatory capacity (52). Muscle weakness contributes to low bone mass, aerobic deconditioning and exercise intolerance, but can respond to a home-based regimen (127), decreasing travel demands on the family.

Outcomes

Although the outcome of JDM has improved—the mortality rate is now 1–2% in the US—it is elevated elsewhere, approximately 8% (58). Weakness and reduced endurance was identified in 32–45% of subjects 16.8 years after the diagnosis in childhood of JDM; MRI confirmed muscle damage in 52% (128), predicted by skin inflammation 6 months after diagnosis (129). Cardiovascular disease is present in adults who had JDM in childhood (130), and may be extensive (131). Unlike SLE, levels of SLE anticoagulant are normal in girls with DM (132). Chinese women with myositis have increased rates of miscarriage (133) and studies of fertility in women who had JDM in childhood showed evidence of compromise (134).

Hope for the Future

In summary, the documentation that MSAs identify specific disease patterns of JDM will lead to discovery of MSA specific disease mechanisms and individualized therapy (135). With increased awareness, aided by The Myositis Association and the Cure JM Foundation® (136), children with JDM will obtain medical therapy shortly after symptom onset, promoting a more successful outcome. We hope that the emotional burden now sustained by both the JDM children and their families (137) will respond to more effective interventions.

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ABBREVIATIONS

JDM	Juvenile Dermatomyositis
JM	Juvenile Myositis
MSA	Myositis Specific Antibodies
MHC	Major Histocompatibility Complex
SLE	Systemic Lupus Erythematosus
NuRD	Nucleosome Remodeling Deacetylase Complex
DM	Dermatomyositis
PM	Polymyositis
SRP	Signal Recognition Particle
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
MAA	Myositis Associated Antibody
NK	Natural Killer
CARRA	Childhood Arthritis & Rheumatology Research Alliance
MMF	Mycophenolate mofetil
IVIG	Intravenous Immunoglobulin Therapy
IgA	Immunoglobulin A
CyA	Cyclosporine A
IIM	Idiopathic Inflammatory Myopathies
IgG	Immunoglobulin G

ILD	Interstitial Lung Disease
US	United States
UK	United Kingdom
MTX	Methotrexate

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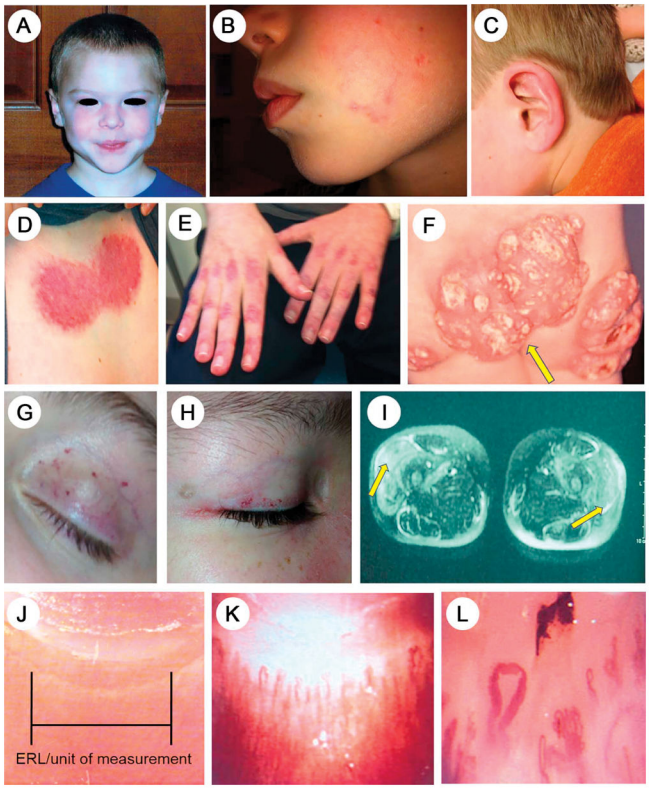

Figure 1. Clinical features, common and uncommon, of children with juvenile dermatomyositis

A. Heliotrope rash on the face, characteristic of active JDM

B. A very small patch of persistent erythema on cheek in a child as the only rash of JDM positive for MDA-5

C. Erythema of the pinna of the ear in a child as the only sign indicating a flare of JDM positive for p155/140

D. Inflammation in the shawl area on the upper anterior chest indicating both acute and chronic changes

E. Linear erythema over the metacarpal-phalangeal (MCP) as well as the proximal (PIP) and distal intercarpal phalangeal (DIP) joints of the hands. Dilated nailfold end row capillary loops are visible.

F. Microvasculopathy dilated capillaries on the upper eyelid and eyelid margin in active JDM

G. Healing telangiectasia of the eyelid of a child with JDM

H. Dilated capillaries close to the edge of the eyelid, resolving; healed medial canthus infarct

I. Closely spaced normal nailfold capillary end row loops, showing unit of measure

J. Moderate nailfold capillary dropout with vessel tortuosity

K. Severe nailfold capillary dropout, with dilated loops and fewer end row loops/mm

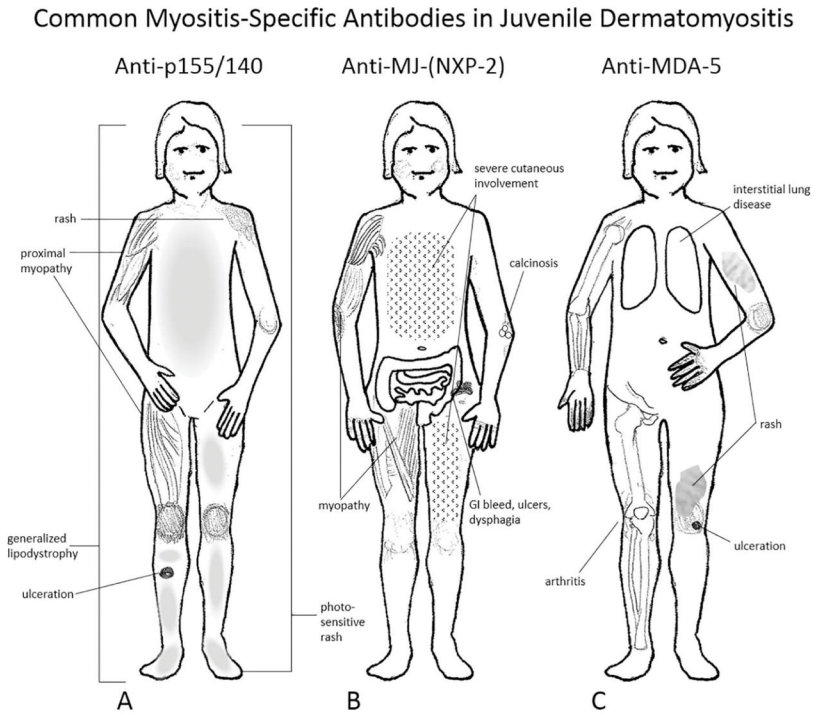

Figure 2. Phenotypes associated with the 3 most common myositis specific antibodies (MSAs) in children with myositis: anti-p155/140 (A), anti-MJ (B) and anti-MDA-5 (C)

A) Anti-p155/140, present in 18–30% of idiopathic juvenile inflammatory myopathies display an extensive photosensitive rash which ulcerates, a chronic disease course and generalized lipodystrophy. B) 15–23% of children positive for anti-MJ (NXP2 in the UK) may have disease onset at a younger age, have dysphonia, muscle cramps, atrophy and contractures, with increased weakness, and they are more likely to develop calcifications and gastrointestinal symptoms; their rash often spares the truncal area. C) Anti-MDA-5 is increased in the Japanese population (33%) vs the UK (6%) and is associated with inflammatory lung disease, oral and cutaneous ulcers, arthritis and a milder form of muscle involvement. Adapted with permission from Rider et al (42).

Table

Clinical Associations: Myositis-Specific Autoantibodies (MSA) and Myositis-Associated Antibodies (MAA) in juvenile-onset myositis. Adapted with permission from Tansley (145).

Autoantibody	Target autoantigen	Prevalence in patients with juvenile-onset myositis	Clinical associations
Common myositis-specific autoantibodies are found in 45–55% of patients with juvenile-onset myositis			
Anti-Mi2	Nucleosome remodeling deacetyalse complex (NuRD)	3–4% [42, 39]	'Classic' dermatomyositis. Responds well to standard therapies. Favorable prognosis [5, 138]
Anti-TIF1g (p155/140, TRIM33)	Transcriptional intermediary factor 1 gamma (TIF1-γ)	18–35% [39, 42]	Severe cutaneous disease. Rashes in photo-exposed pattern. Chronic disease course. Lipodystrophy [48, 140, 141, 142, 43]
Anti-NXP2 (p140, MJ)	Nuclear matrix protein 2 (NXP2)	15–22% [39, 42]	Calcinosis. More severe muscle disease. Gastrointestinal bleeding, ulcers and dysphagia. Worse disease outcome and functional status [138, 48, 44]
Anti-MDA5 (CADM-140)	Melanoma differentiation-associated gene 5 (MDA5)	6% [39]	More common in east Asia where associated with clinically amyopathic myositis, rapidly progressive interstitial lung disease and a high mortality. In Caucasian populations associated with mild muscle disease, interstitial lung disease, arthritis and ulceration [149, 45, 46]
Rare but clinically important myositis-specific autoantibodies are found in 5–8% of patients with juvenile-onset myositis Antisynthetases (Jo-1, PL12, PL7, OJ, EJ, KS, Zo and Ha)			
Antisynthetases			Antisynthetase syndrome: myositis, interstitial lung disease, fever, mechanics hands, Raynaud's phenomenon and arthritis; occurs in older children. Increased mortality [48]
- Jo-1	- Histidyl	2–3% [39, 42]	
- PL12	- Alanyl	2–3% [39, 42]	
- PL7	- Theronyl	2–3% [39, 42]	
- OJ	- Isoleucyl	2–3% [39, 42]	
- EJ	- Glycyl	2–3% [39, 42]	
- KS	- Asparaginyl	2–3% [39, 42]	
- Zo	- Phenylalanyl	2–3% [39, 42]	
- Ha	- Tyrosyl	2–3% [39, 42]	
Anti-SRP	Signal recognition particle (SRP)	2% [39, 42]	Necrotizing autoimmune myositis. Severe weakness. Cardiac involvement. Occurs in older children. May be refractory to standard treatment [48]
Anti-HMGCR	HMGCR	1% [39]	Necrotizing autoimmune myositis [143, 144]
Anti-SAE	Small ubiquitin-like modifier activating enzyme (SAE)	1% [39]	Initially amyopathic disease with muscle involvement occurring later
Myositis-associated autoantibodies are found in 16–20% of patients with juvenile-onset myositis. Some may occur in conjunction with a myositis-specific autoantibody			

Autoantibody	Target autoantigen	Prevalence in patients with juvenile-onset myositis	Clinical associations
Anti-PmScl	Exsome associated PM- Scl-75; PM-Scl-100; C1D [146]	5% [39]	Overlap syndromes [48]
Anti-U1RNP	U1RNP [147]	2% [42]	Overlap syndromes [48]
Anti-Ro52	Ro52 [148]	5% [42]	Overlap syndromes. May be found in conjunction with other MSA, particularly antisynthetases [48]

Common MSAs are present in 45–55% of the United States pediatric population with juvenile onset myositis. Rare MSAs are present in 5–8%. Myositis-Associated Autoantibodies (MAA) are found in 16–20% of juvenile-onset myositis, with or without an accompanying MSA. Adapted with permission from Tansley (145).