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 (MSAs) 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 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 JDM, elevated serum levels of muscle derived enzymes (aldolase, creatinine phosphokinse [CPK], aspartate aminotransferase [AST], alanine transaminase [ALT], lactate dehydrogenase [LDH]) are time dependent; they tend to normalize by 4.5 months after diagnosis.[4] Magnetic resonance imaging (MRI) identifies the patchy muscle inflammation and can help direct the physician to biopsy an inflammatory site. The typical JDM muscle biopsy displays perifascicular atrophy, muscle fiber size variation, increased expression of major histocompatibility complex class 1, infiltration of primarily mononuclear cells,[5] extensive muscle capillary drop out, and damaged mitochondria. This evidence aids diagnosis and the choice of immunosuppressive therapy.[5]

BMT	Bone marrow transplantation
CyA	Cyclosporine A
HCQ	Hydroxychloroquine
HLA	Human leukocyte antigen
IL	Interleukin
IVIG	Intravenous immunoglobulin therapy
JDM	Juvenile dermatomyositis
JM	Juvenile myositis
MAA	Myositis-associated antibody
MRI	Magnetic resonance imaging
MSA	Myositis-specific antibody
MTX	Methotrexate
TNF	Tumor necrosis factor
UVB	Ultraviolet ray

JDM Etiology: Genetics and Environment

A working hypothesis is that JDM is an interferon (both Type 1 and Type 2) driven inflammatory response,[6] triggered by 1 or more environmental stimuli, such as infection, exposure to smoking, or ultraviolet rays (UVB), targeting a genetically susceptible child. Families of a child with JDM may have a history of autoimmune disease, most often systemic lupus erythematosus,[7] but it is rare to have more than 1 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 patients with dermatomyositis of European ancestry using genome wide association methodology.[9] Further testing of Caucasians with a range of inflammatory myopathies defined additional loci; PTPN22 was associated with genome-wide significance for polymyositis, but not dermatomyositis or JDM.[10] In Japanese patients with myositis, HLA—DRB1*08:03 confers risk,[11] which differs from the Han Chinese patients with myositis, 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 that subsequently stimulate an immune response.[13] As in systemic lupus erythematosus, some children with JDM 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 tumor necrosis factor (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; and immunizations and medications. Of these conditions, seasonality of birth has been reported,[16] which may be confounded

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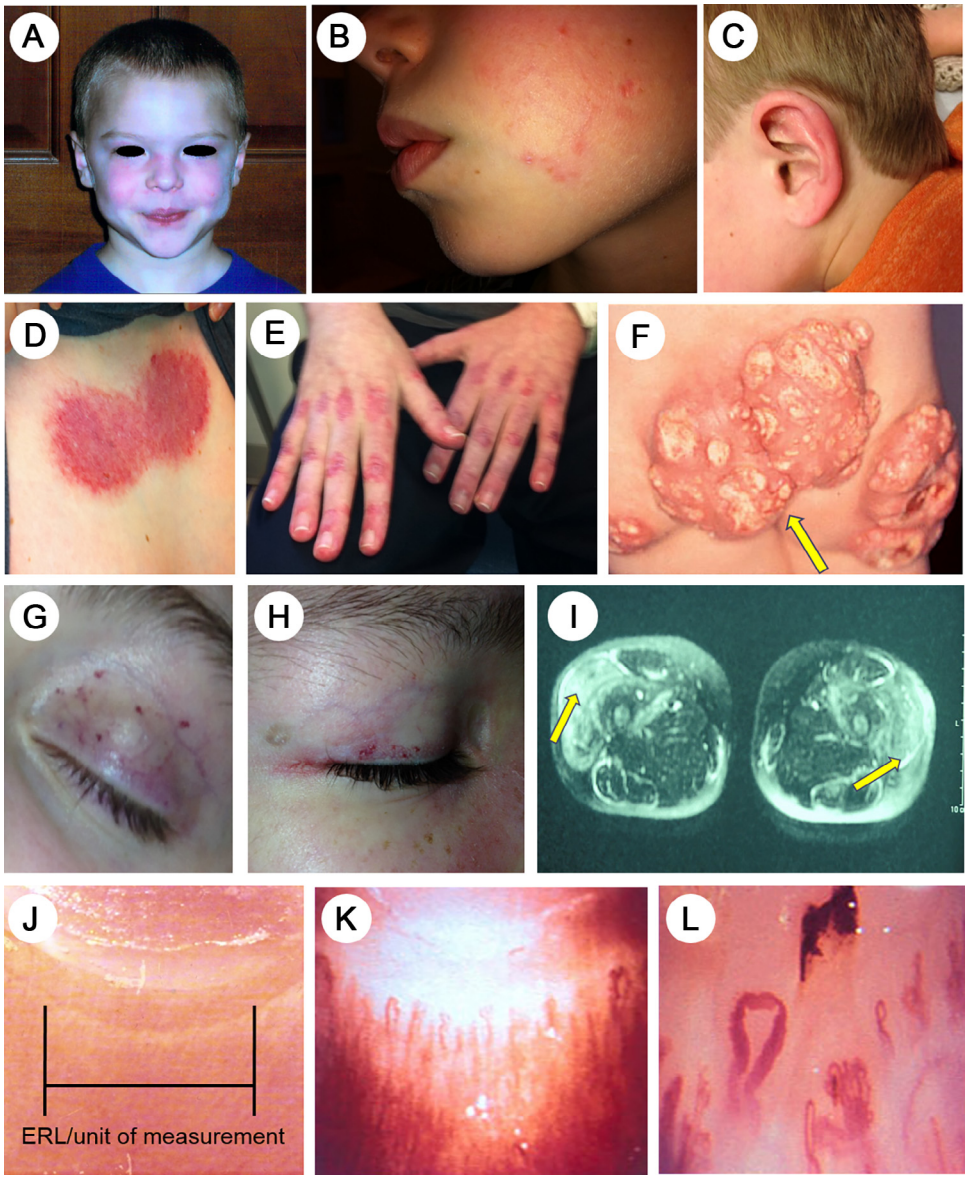

Figure 1. Clinical Features, common and uncommon, of children with juvenile dermatomyositis (JDM). **A,** Heliotrope rash characteristic of active JDM. **B,** A very small patch of persistent erythema on cheek is the only rash of a JDM child positive for MDA-5. **C,** Erythema of the pinna of the ear in a child as the only sign indicating a flare of JDM in a child positive for p155/140. **D,** Inflammation in the shawl sign on the upper anterior chest, indicating both acute and chronic changes. **E,** Erythema over the metacarpal phalangeal as well as the proximal and distal intercarpal phalangeal joints of the hands. Dilated nailfold end row capillary loops are visible. **F,** Exuberant calcifications over the buttocks (*arrow*) in a 2 year old with JDM. **G,** 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,** T-2 weighted image of proximal leg muscles showing symmetrical inflammatory effects (*arrows*). **J,** Closely spaced **normal** nailfold capillary end row loops (ERL), showing unit of measure. **K,** Moderate nailfold capillary dropout with vessel tortuosity in JDM. **L,** Severe nailfold capillary dropout, with dilated loops and intravascular clotting, fewer end row loops/mm in **severe** JDM.

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 JDM[19-21] and dermatomyositis.[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 US).[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 ($P = .005$) are more frequent.[20] Sun exposure (OR = 3.5; $P = .049$) preceded a flare, despite photoprotective agents.[20] Vaccinations may also trigger the myopathic process.[25]