Abstract and Introduction

Abstract

Purpose of Review: Juvenile dermatomyositis is the most common of the idiopathic inflammatory myopathies in children. It is considered an autoimmune disease of relatively unknown etiology, although environmental exposures and infectious agents are thought to play a role in disease pathogenesis. More recently, data has become available regarding the molecular genetics of children affected with juvenile dermatomyositis and the impact these genes have on disease expression and clinical course. Additionally, features of the immune response, including specific pathways of the humoral and cellular immune systems, have been further described. This article summarizes the most recent advances in understanding the etiopathogenesis of juvenile dermatomyositis.

Recent Findings: This article focuses on advances made in understanding the role that complement, soluble adhesion molecules, thrombospondin-1 levels, and genetics play in the evolution of juvenile dermatomyositis. It also describes microarray technology and gene expression profiling as means of identifying those genes overexpressed in affected children and thus likely involved in disease pathogenesis; microarray technology may also be used to distinguish dermatomyositis from the other inflammatory myopathies, as well as from other myopathies.

Summary: In better understanding the pathogenetic mechanisms whereby disease evolves and the means by which genetic profiles influence susceptibility to and expression of disease, immunotherapies to better treat juvenile dermatomyositis may become available in the future.

Introduction

Juvenile dermatomyositis (JDM) is the most common of the idiopathic inflammatory myopathies in children, accounting for 85% of the pediatric inflammatory myopathy group. It is an occlusive small-vessel vasculopathy, involving arterioles and capillaries. Its most obvious effects are seen in skeletal muscle and in the skin, although other organ systems can be involved,
including the gastrointestinal tract, heart, and lungs. It is classically characterized by symmetric, frequently progressive, proximal muscle weakness, and inflammatory cutaneous lesions, including but not limited to, erythematous scaly lesions over the metacarpophalangeal and/or interphalangeal joints (Gottron papules), a violaceous hue over the eyelids (heliotrope), with or without periorbital edema, malar erythema, periungual telangiectasia, and erythematous scaly rashes over the neck, upper back, and extensor surfaces of the extremities. Among children with JDM, 3 to 5% have the amyopathic subtype with no clinical evidence of muscle weakness, but with the pathognomonic cutaneous manifestations of the disease.\textsuperscript{[1*,2*]} It has been estimated that approximately 34 to 40% of affected children have an acute course that resolves within a 2-year period and remains in remission indefinitely; these children have a monocyclic disease course.\textsuperscript{[3*]} The remaining 60-66% have chronic disease, requiring immunosuppressive therapy for more than two years and having either disease that remains continuously active or that is characterized by remissions and exacerbations (polycyclic course). Over the past 40 years, the percentage of children with JDM who have a monocyclic course has not changed significantly with the advent of corticosteroid and other immunosuppressive therapies (master's thesis, July 1, 2003); Bitnum \textit{et al.} reported that prior to the steroid era, one third of affected children completely recovered, one third died, and the remaining third had significant disability.\textsuperscript{[4]} Yet since the 1960s, those with chronic disease have had significantly less morbidity, and the mortality rate has dropped from approximately 33% to < 5% today.\textsuperscript{[1*]}

### Demographic Data

JDM affects children at an incidence of 2 to 3 per million children per year.\textsuperscript{[5*]} Recently, its incidence in the United States has been documented at a rate of 3.1 per million children per year by a NIH-sponsored registry of new-onset JDM, using capture-recapture methodology.\textsuperscript{[6]} In the United Kingdom and in Ireland, its incidence has been estimated at 1.9 per million children per year.\textsuperscript{[1*]} In a recent study, one region of the United Kingdom determined to be ethnically diverse, the West Midlands, was evaluated for the incidence and ethnic distribution of JDM, among other rheumatic diseases, including Henoch-Schonlein purpura and Kawasaki disease. The incidence of JDM among children of the West Midlands was reported as high as 4 per million children per year.\textsuperscript{[7*]}

The gender ratio varies somewhat among children with JDM throughout the world. In the United States, girls are affected twice as often as boys, while in the United Kingdom and in Ireland, the female: male ratio is reported as being 5:1.\textsuperscript{[1*]} Data from the West Midlands study noted a female: male ratio of 1.75:1.\textsuperscript{[7*]} In a recent outcome study done in India, 12 of the 19 patients (63%) with JDM followed at a tertiary care hospital in Lucknow were boys (female: male ratio of 1:1.7).\textsuperscript{[8]} In Japan, boys were marginally affected more frequently than girls (female: male ratio 1:1.3), although in China, data similar to that reported for the United Kingdom have been reported.\textsuperscript{[1*]}

Mean age at disease onset also varies worldwide. In the United States, the mean age at disease onset is 6.9 years.\textsuperscript{[6]} In the Lucknow study, the median age at diagnosis was 12 years, with a range of 2.5 to 16 years and a median duration of disease prior to diagnosis of 12 months.\textsuperscript{[8]} Among the children studied in the West Midlands, JDM showed a bimodal age distribution, with the highest annual incidence rates in children under the age of 5 years and in children of 12 to 13 years, with a mean age of onset of 7.1 years. This bimodal incidence distribution around 2 to
6 years of age and during the teenage years is consistent with incidence patterns reported previously [7*]; Pachman et al. reported that 18% of patients are diagnosed at 4 years of age or younger. [9]

Ethnicity of the affected child may vary by geographic location. In the United States, 71% of affected children are Caucasian, 12% Hispanic, and 9% African-American. [1*] In the West Midlands study, similar results were reported, with most affected children being white (79%). [7*]

Pathogenesis

JDM is thought to be autoimmune in origin; however, its pathogenesis remains unknown. While the exact triggers of the immune response in children with JDM have not been identified, recent studies have endeavored, with some success, to uncover the targets of such abnormal immune responses. This section seeks to provide an update on the most recent developments in the elucidation of the etiopathogenesis of this idiopathic inflammatory myopathy in children.

Environmental Factors

The role of the environment on the evolution of JDM, whether in regard to climate or geographic location, has not been fully identified and may vary by year and location. A recent report showed that the relative prevalence of JDM increased significantly from northern Europe (latitude 64°) to southern Europe (latitude 38°). [10] Similarly, a preliminary analysis of the JDM new-onset registry data identified geographic clusters in the United States of newly diagnosed children. [11] An earlier review of data on the onset of disease in 286 newly diagnosed JDM patients did not show seasonal predilection, [12] while epidemiological data encompassing the period from 1989 to 1992 in the United States revealed an increased frequency of disease onset in the spring and summer months among all geographic regions of the country. [13] Sun exposure, specifically, exposure to UVB light, which may induce cellular production of TNFα, [14] possibly precipitates JDM in some children because they have the TNFα-308A allele. [1*] Other noninfectious agents and exposures currently suspect in the pathogenesis of JDM are vaccines (hepatitis B, mumps-measles-rubella vaccine, typhoid, and cholera) and drugs such as D-penicillamine, and growth hormone. [1*]

Infectious Agents

In addition to climate, there may be regional differences in the occurrence of JDM due to differences in exposures to infectious agents. Some epidemiological studies have documented an antecedent illness in the 3-month period before the onset of symptoms of JDM and suggest that disease pathophysiology is indeed antigen-driven and that onset may be the result of molecular mimicry. [15] Abnormal responses to microbial antigens that share homology with self antigen targets may lead, either directly or indirectly, to the development of disease. [16**] Infectious organisms that have been implicated in the pathogenesis of JDM include viruses, particularly influenza, parainfluenza, hepatitis B, the RNA picornaviruses ( ie, coxsackie B), [1*] and, most recently, parvovirus, [17,18] as well as parasites, such as Toxoplasma gondii, [19,20] Bacterial pathogens linked with the onset of JDM include Borrelia burgdorferi and Group A β-hemolytic streptococci. [21] Additionally Streptococcus pyogenes has been associated with
recurrences or exacerbations of JDM.\[22\]

Recent research has shown that self epitopes in the human skeletal myosin heavy chain are homologous to specific amino acid sequences in the M5 protein of Streptococcus pyogenes; recognition of these self epitopes in skeletal muscle then triggers activation of disease-specific cytotoxic T cells that results in chronic autoimmune damage \[16**,23\] The homologous sequences between human skeletal myosin and the streptococcal M5 protein are different from those between the M5 protein and human cardiac myosin, which becomes relevant in the pathogenesis of acute rheumatic fever.\[16**\] In the study performed by Massa et al., the investigators identified amino acid sequences that shared homology between skeletal myosin and the Streptococcus pyogenes M5 protein and that were the targets of cytotoxic T-cell responses, with the following results: (1) there was elevated cytotoxicity to the Myo (aa114-122) peptide and to its streptococcal homolog M5 (aa367-375) in the eight patients with active JDM compared with the ten healthy control subjects (cell lines from the controls showed negligible cytotoxic responses); (2) the eight children with active JDM had significantly greater cytotoxic responses to the Myo (aa114-122) and M5 (aa367-375) peptides than did the eight JDM patients with disease remission; and (3) the cytotoxic responses to the Myo (aa114-122) peptide were significantly greater in patients not receiving steroids than in those receiving them. These results showed that that the cytotoxic response to the M5 (aa367-375) and Myo (aa114-122) peptide pair is associated with clinically active disease and the absence of steroid therapy.\[16**\] Additionally, the increase in cytotoxic T-cell response was significant only for the peptide pair Myo (aa114-122)/M5 (aa367-375), but not for other streptococcal or autologous peptides tested.

Massa et al. also found that cytotoxic activity to the Myo (aa114-122) and M5 (aa367-375) homologous peptides was significantly lower in six children with juvenile idiopathic arthritis than in those with active JDM. These data show that T-cell reactivity to the Myo (aa114-122) and M5 (aa367-375) homologous peptides is not due to a nonspecific increase in cytotoxic responses secondary to inflammation. Additionally, T cells from the three disease control patients with post-streptococcal disease (active post-streptococcal glomerulonephritis, post-streptococcal reactive arthritis, and acute rheumatic fever) did not show increased cytotoxicity to the Myo (aa114-122) peptide, demonstrating that increased cytotoxicity to the Myo (aa114-122) peptide is not a generalized consequence of streptococcal infections.

Other common pathogens share sequence homologies with the Myo (aa114-122) peptide of human skeletal myosin, including Borrelia burgdorferi, Mycoplasma hominis, Haemophilus influenzae, Helicobacter pylori, Escherichia coli, and Bacillus subtilis (HSP70).\[16**\]

Taken together, these reports suggest that the etiology and pathogenesis of JDM are antigen-driven, with a role for molecular mimicry.

The Role of Complement

Earlier studies established a primary role of complement-induced vessel injury in JDM, with evidence of activation of the complement cascade resulting in capillary damage, mediated by the membrane attack complex (C5b-9).\[24\] One of the earliest histologic abnormalities is the detection of the membrane attack complex (MAC) deposited in small arterioles and capillaries of affected muscle,\[24,25\] and its presence has been correlated with the duration of clinical disease.\[26\] Deposition of the MAC in small vessels is partially regulated by CD59, a protective regulatory membrane protein expressed in numerous cells and tissues throughout the body,
including endothelium from several sources, skin, skeletal muscle, lung, and myocardium. CD59 regulates MAC activity by binding to C8 and C9 molecules already incorporated into the MAC, blocking further C9 recruitment and polymerization, thereby preventing full assemblage of MAC.[27] The sarcolemma of normal skeletal muscle fibers has been shown to stain strongly by immunohistochemistry for CD59, using a monoclonal antibody to CD59. [28]

In a recent study by Goncalves et al.,[29**] the presence of CD59 and deposition of MAC in skeletal muscle derived from patients with untreated JDM was assessed in comparison with patients with muscular dystrophy and normal children biopsied for other diagnostic purposes. The investigators found: (1) immunohistochemical staining for CD59 was weak and irregularly distributed on the muscle fibers of all JDM patients, while strong, uniformly distributed immunoreactivity to CD59 was detected on the sarcolemma and in the intramuscular endothelium of all muscle samples from normal children and from those affected with muscular dystrophy; (2) immunostaining for MAC was present in the majority (67%) of vessels of the JDM patients, with intense staining present in 2/3 of those positive for MAC; no intense staining for MAC was found in vessels from normal children or from those with muscular dystrophy; and (3) an inverse relation existed between MAC deposition and the presence of CD59 in the vessels of the JDM muscle biopsies and in all normal and muscular dystrophy samples.

It has been shown that neutralization of CD59 renders cells susceptible to complement killing. [30] Thus, Goncalves et al. hypothesize that decreased CD59 expression in the muscle fibers and vessels of children with JDM may be associated with the onset and perpetuation of inflammation and muscle cell damage due to excessive activation of complement, mediated by deposition of the MAC. One theory for the mechanism of CD59 depletion is cleavage of the CD59 glycolipid anchor by phospholipases activated in the inflammatory process, rendering the endothelial cells susceptible to MAC activity. Deposition of MAC in the small vessels then leads to muscle ischemia and renders muscle cells incapable of maintaining synthesis of normal amounts of CD59, constituting another means for decreased protection against MAC activity. [29**]

**Soluble Adhesion Molecules**

The role of soluble adhesion molecules in the inflammatory process has been studied in the adult rheumatic disease population. Specifically, serum levels of intercellular adhesion molecule 1 (ICAM-1), ICAM-3, vascular cell adhesion molecule 1 (VCAM-1), L-selectin, and E-selectin, which are critical to leukocyte adhesion to and migration across the endothelium to sites of inflammation, have been measured and correlated with various rheumatic disease states.[31] Few similar studies of soluble adhesion molecule levels in pediatric rheumatic diseases have been done, although results of a pilot study measuring levels of these five soluble adhesion molecules in children with juvenile rheumatoid arthritis were reported in 1999.[32] Recently, measurement of serum levels of ICAM-1, ICAM-3, VCAM-1, L-selectin, and E-selectin in children with a variety of pediatric rheumatic diseases, including four with JDM, two with mixed connective tissue disease, eight with systemic lupus erythematosus, and four with various forms of vasculitis, was undertaken.[33*] Levels were compared among patients with the various diagnoses and between patients with active versus inactive disease, with the following results: (1) ICAM-1 and L-selectin levels were significantly elevated in JDM, as they were in all other diseases studied, compared with levels in normal patients; (2) VCAM-1 was significantly elevated in JDM patients (and mixed connective tissue disease patients) when compared with normal controls; and (3) ICAM-1 was significantly higher in patients with active disease compared with inactive disease across all diagnoses, suggesting that ICAM-1 may be a useful
marker for monitoring disease activity. Additionally, in active JDM, ICAM-1-positive lymphocytes are adherent to endothelial cells in the lumen of blood vessels in muscle. Upregulation of ICAM-1 on lymphocytes, coupled with vascular smooth muscle cell proliferation, may perpetuate the small vessel occlusion that occurs in JDM.\[34^\]

### Genetic Data

As more is learned about the genes involved in the pathogenesis of JDM, it becomes more apparent that the genetic background of affected children plays a role in their susceptibility to developing JDM and also in their clinical course.

#### The HLA-DQA1*0501 Allele

Among those genes identified, the class II major histocompatibility complex allele HLA-DQA1*0501 has emerged as a risk factor for all of the major clinical forms of sporadic and familial idiopathic inflammatory myopathy in both white adults and children in the United States and Europe.\[35\] HLA-DQA1*0501 has also been found to be an important predisposing factor for JDM in children of African-American and Hispanic ethnicity.\[36\] Yet the association of DQA1*0501 with dermatomyositis has not been confirmed in all ethnic backgrounds; in Korean patients with idiopathic inflammatory myopathy, no HLA allele has been found as a risk factor, suggesting that the genetic risk factors for the inflammatory myopathies in children and adults are multifactorial and may be due to regional factors.\[1^\] Additionally, the presence of the DQA1*0501 allele has not been associated with a chronic disease course,\[37\] defined as requiring immunosuppressive therapy for 36 months or longer to bring disease activity under control.

#### The TNF α-308A Allele

The TNFα-308A allele is identified by a G to A amino acid substitution at the Ncol restriction site, located in the class III region of the major histocompatibility complex on the short arm of chromosome 6, a region that is involved with the regulation of TNFα transcription.\[11\] The G-A substitution has been noted to occur at a higher frequency in white children with untreated JDM compared with age-matched controls.\[37\] Associated with increased production of TNFα by peripheral blood mononuclear cells as well as by muscle fibers themselves from children with JDM,\[37,38\] the TNFα-308A allele has been associated with a chronic disease course. It also has been associated with capillary occlusion and vascular compromise in the untreated muscle.\[39\] More recently, the TNFα-308A allele has been associated with increased plasma thrombospondin-1 (TSP-1) levels in children with JDM. Lutz et al. reported that most children with JDM who were positive for the TNFα-308A allele produced significantly more TSP-1, a potent anti-angiogenic mediator, than their TNFα-308G counterparts and normal controls.\[34^\] TSP-1 plays an important role in vascular smooth muscle cell proliferation, which leads to intimal hyperplasia and luminal narrowing, thus contributing to vaso-occlusion.\[40\] The authors conclude that the increased circulating levels of TSP-1 in children with the TNFα-308A allele may be linked to the augmented vascular occlusion seen in JDM patients with this genetic marker.

Additionally, the TNFα-308A allele has been associated with a disease course more resistant to immunosuppressive therapy and which may be complicated by a higher frequency of pathologic
It has also been associated with partial lipodystrophy, insulin-resistant diabetes, and hyperlipidemia in children with chronic symptoms of JDM.

**Gene Expression Profiling**

DNA microarray technology makes use of molecular genetics on a massive scale, providing a quantitative list of relative levels of gene expression in specific tissues, as reflected by the degree of mRNA abundance. This method for mRNA expression profiling was pioneered in the early 1990s and it has increasingly provided insight into gene function, disease classification, and disease pathophysiology by identifying as relevant to disease pathogenesis previously reported cytokines, major histocompatibility complex class I and II molecules, and soluble adhesion molecules.

Recently, Greenberg et al. used microarray technology to measure the expression of approximately 10,000 genes in muscle specimens obtained from patients in the three major muscle disease categories (muscular dystrophy, congenital myopathy, and inflammatory myopathy, including inclusion body myositis, polymyositis, and dermatomyositis). Using this approach, almost all of the patients with inflammatory myopathy were correctly classified, with each subtype of inflammatory myopathy having a distinct gene expression profile; these gene expression differences were useful in distinguishing patients with inclusion body myositis and polymyositis from patients with dermatomyositis. Using a tenfold ratio as the cutoff for gene overexpression and a minimum average expression level of 500 copies, several immunoglobulin genes were consistently overexpressed in inclusion body myositis and polymyositis relative to dermatomyositis, while a group of interferon-inducible genes exhibited the reverse pattern, being overexpressed in dermatomyositis relative to inclusion body myositis and polymyositis. The investigators noted that increased expression of interferon-inducible genes in dermatomyositis is an important distinction separating this inflammatory myopathy from inclusion body myositis and polymyositis. Additionally, the molecular profiles of muscle from patients with inflammatory myopathy were found to be distinct from normal muscle and those affected by muscular dystrophy or congenital myopathy.

Other recent work, by Tezak et al., compared gene expression profile data from children with untreated JDM, positive for the DQA1*0501 allele, with data from children with Duchenne muscular dystrophy and healthy pediatric controls. Profound dysregulation was found in muscle biopsies from the children with JDM, most of the dysregulated genes being interferon-inducible genes. In particular, increased expression of interferon (IFN) αβ-inducible genes 6 through 16, myxovirus resistance protein p78, latent cytosolic transcription factor, proteasome element LMP2, and antigen transporter TAP1 was observed. This pattern of gene expression is consistent with an IFN-αβ transcription cascade seen in an in vitro viral resistance model and supports the hypothesis that the pathogenesis of JDM is a response to an infectious agent, particularly since transcription of IFN-inducible genes is a hallmark of the host defense mechanism against infection. The similarity to a viral resistance model was more pronounced when children with JDM who were positive for the DQA1*0501 allele were compared with those who were negative for this allele.

From this profiling data, the investigators then hypothesize a model of disease pathogenesis that involves a repetitive cycle of muscle injury in which both IFN-αβ and IFN-γ cascades lead to muscle ischemia and increased production of TNF-α and nitric oxide, which, in turn, interact with the immune response cascades in the endothelium and with infiltrating T and natural killer cells,
thus exacerbating the IFN-induced processes. The IFN-induced response cascades, which inhibit mitosis and protein synthesis cascades, thereby inhibit regeneration of necrotic muscle fibers. TNF-α is an important mediator of the inflammatory response and may be one of the critical interpathway communicating proteins that, in conjunction with the effects of the IFN-induced cascades, induce muscle cell injury. The association of disease chronicity of JDM with the TNF-α-308A gene, with increased production of TNF-α, supports this model of disease pathogenesis.[44**]

Microarray technology is still relatively immature and limited by available knowledge of gene function and sequence information. Yet as it becomes more refined, it may be used to determine whether clinically relevant variables (i.e., steroid responsiveness, degree of weakness) are linked to differences in gene expression profiles. Additionally, cytokines, adhesion molecules, and chemotactic proteins, once identified in the pathophysiology of this disease, may become potential targets for directed immunotherapies in the future. [42]

Conclusions

Over the past 10 to 15 years, much has been learned about the cellular and humoral immune-mediated mechanisms involved in the pathogenesis of JDM. More recently, the role of complement, specifically the membrane attack complex, in immune-mediated vascular injury has been further elucidated. Additionally, susceptibility to developing JDM has been linked with the class II major histocompatibility complex HLA-DQA1*0501 allele, and disease course and various complications have been associated with polymorphisms at the TNFα-308 locus. In this way, the genetic background of children with JDM is integrally entwined with the type of inflammatory response elicited. Use of DNA microarray technology to identify gene expression profiles in JDM, relative to other myopathies and other inflammatory conditions in children, such as juvenile idiopathic arthritis, has allowed further understanding of how environmental exposures, specifically infection, in the genetically susceptible child can lead to antigen-driven autoimmune cytotoxic responses that result in the evolution of disease. Microarray technology will continue to become a powerful molecular tool to identify genes and inflammatory mediators central to the pathogenesis of this disease. Once elucidated, these genes may then become the targets of directed immunotherapies in the future.

References

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

   * This recent review on juvenile dermatomyositis gives a comprehensive overview of current knowledge regarding the genetics and pathophysiology that affect disease expression of JDM. It focuses on aspects of cellular and humoral immunity as well as immunogenetics of this most common of the idiopathic inflammatory myopathies in children.

   * This retrospective case review of amyopathic dermatomyositis describes a group of 37
patients, of which seven were under the age of 18 years, and supports this diagnosis as a distinct clinical entity from dermatomyositis, which does not progress to myopathy and has a favorable prognosis.

   * An easy-to-read general overview of JDM in regard to epidemiology, pathology, clinical manifestations, diagnosis, clinical course, and treatment.


   * A recent review of clinical features, clinical outcomes and prognosis.


   * This study evaluated the incidence and ethnic distribution of several primary vasculitides and conditions complicated by vasculitis, such as systemic lupus erythematosus and JDM, in children of the West Midlands, a region of the United Kingdom described as having a diverse ethnic mix.


   ** This study is important, as the investigators found evidence that the pathogenesis of JDM is antigen-driven, with molecular mimicry playing a role in disease pathogenesis. Homology was found to exist between a peptide sequence native to human skeletal myosin and one extracted from a common bacterial pathogen to which children are frequently exposed, Streptococcus pyogenes. Results of this study reportedly represent the first identification of a self epitope in JDM with potential for antigen-specific immune therapy.


18. Chevrel G, Calvet A, Belin V, et al.: Dermatomyositis associated with the presence of


** Results of this study demonstrated decreased CD59 expression on the sarcolemma and vessels in muscle of JDM patients and increased MAC deposition in the blood vessels of JDM patients, relative to patients with muscular dystrophy and children with normal muscle biopsies. These findings support the role of complement and complement-mediated vascular injury in the pathogenesis of this disease.


* This study represents a cross-sectional pilot study of several soluble adhesion molecules in some of the pediatric rheumatic diseases. While it is a relatively small cohort with no pediatric controls used, its results suggest that these molecules may become candidates for use as markers of disease activity and response to therapy.


* This study suggests yet another link between the evolution of chronic disease that is more difficult to control and the TNFalpha-308A allele in children with JDM, with increased
TSP-1 levels perhaps participating in the neovascularization of the vascular bed in this disease.


** While not specifically focusing on children with JDM, this article is important in laying the groundwork for differentiating the genetic profiles of the inflammatory myopathies from other myopathies (dystrophic and congenital myopathies) and from normal muscle. Additionally, the use of microarray technology to differentiate among the genetic profiles of the major idiopathic inflammatory myopathies was fruitful in determining relative overexpression of certain genes in dermatomyositis, a finding similar among children and adults with this disease, suggesting that while not entirely the same disease in these age groups, there is overlap in disease pathogenesis in children and adults with DM.


** This is an exceptionally important study that pulls together the results of various bodies of research into the pathogenesis of JDM to hypothesize a model of antigen-driven induction of autoimmune disease based on the dynamic interactions of at least three pathologic cascades in the muscle and vascular bed in the genetically susceptible child (HLA-DQA1*0501+), with TNF-α possibly mediating between cascades and resulting in deleterious cross-talk between cascades. This novel model of pathogenesis seems to corroborate the role of TNF-α polymorphisms and differential production of this inflammatory mediator in determining disease expression in susceptible children.


* This review article discusses some of the insights into disease pathogenesis that have resulted from use of microarray technology and gene expression profiling in JDM patients.

47. Pachman LM, Tezak Z, Bakay M, et al.: Differential gene expression profiles in DQA1*0501(+) untreated JDM muscle are associated with increased IFN response
compared with DQA1*0501 negative JDM. Arthritis Rheum 2001, 44:S399.

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Abbreviation Notes

ICAM, intercellular adhesion molecule; IFN, interferon; JDM, juvenile dermatomyositis; MAC, membrane attack complex

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