

Multispecialty approach for improving outcomes in juvenile dermatomyositis

This article was published in the following Dove Press journal:
Journal of Multidisciplinary Healthcare

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Abstract: Juvenile dermatomyositis (JDM) is a pediatric rheumatic disease characterized by inflammation of the muscle and skin. Prognosis of JDM in children has improved in general owing to medical progress; however, pathogenesis and management of JDM in children and prognosis in refractory JDM remain challenging. For elucidation of JDM pathophysiology and establishment of appropriate treatment for JDM, pediatric rheumatologists need to adopt a multispecialty approach that involves experts in genetics, immunology, pathology, musculoskeletal medicine, dermatology, pulmonology, cardiology, hematology, gastroenterology, endocrinology, ophthalmology, psychology, radiology, pharmacology, physiotherapy, surgery, preventive medicine, and adult rheumatology. Such collaborations will potentially lead to improved outcomes in children with JDM.

Keywords: liposteroid, pathophysiology, physiotherapy, preventive medicine, psychology

Introduction

Juvenile dermatomyositis (JDM) is a multisystem disease of uncertain origin, characterized by chronic inflammation of the striated muscle and skin.¹ Although its prognosis has improved in general owing to medical progress, some issues regarding the pathogenesis and management of JDM in children, and prognosis in children with refractory JDM, remain unresolved. To date, pediatricians have performed the majority of JDM research and treatment approaches. This review summarizes the various fields of recent medicine that could collaboratively investigate JDM through a multispecialty approach. Although each field can make individual contributions to medical progress, a collaborative effort spearheaded by pediatric rheumatologists will help improve JDM medical care in future.

Genetics

JDM is associated with immune-related genes of the human leukocyte antigen (HLA) region.² The International Myositis Genetics Consortium reported the first genome-wide analysis of JDM, which confirmed the HLA region as the strongest genetic risk region for JDM.³ Three new genetic associations with myositis were identified, namely *PLCL1*, *BLK*, and *CCL21*. Complement C4A deficiency appears to be an important factor of the genetic risk and pathogenesis of JDM, particularly in patients with HLA-DR3-positive background.⁴ Gene expression profiling has revealed a prominent type I interferon (IFN) signature in JDM muscles that could be related to viral exposure.⁵

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Immunology

JDM is an autoimmune disease, with regular occurrence of autoantibodies and evidence of antigen-driven clonal B- and T-cell expansion in the inflamed muscle.² Characteristic abnormalities in JDM include excess type I IFN production in blood and muscles, leading to immune cell activation and vasculopathy. Type I IFN, produced by dendritic cells, stimulates the production of pro-inflammatory cytokines, and enhances the expression of HLA class I and II molecules.⁶ Patients with JDM having high levels of eotaxin and monocyte chemoattractant protein 1 show early signs of organ damage.⁷ The association of IFN- γ -inducible protein 10, galectin 9, or tumor necrosis factor (TNF) receptor 2 with disease activity has been confirmed in JDM.⁸ Different markers of muscle inflammation, suggested in patients with JDM, include CD59, vascular cell adhesion molecule, intercellular adhesion molecule, and Toll-like receptors 2, 3, 4 or 7.⁹ Examination of subcutaneous calcinosis called “milk of calcium” in JDM revealed abnormally high levels of interleukin (IL)-6, TNF- α , and IL-1 β .¹⁰ Remarkably elevated serum levels of IL-18, B-cell activating factor, and a proliferation-inducing ligand in patients with JDM were observed in rapidly progressive interstitial lung disease (ILD).¹¹

Autoantibodies are detected in more than 60–70% of patients with JDM.^{2,12} Moreover, patients frequently test positive for antinuclear antibodies, although no diagnostic value has yet been established. The most common myositis-specific autoantibodies (MSAs) in JDM are anti-transcription intermediary factor 1- γ (TIF1- γ) and anti-nuclear matrix protein 2 antibodies, found in 20–35% and 15–25% of patients, respectively.^{5,13} Anti-TIF1- γ antibody is associated with more serious cutaneous involvement. Anti-nuclear matrix protein 2 antibody is associated with calcinosis, gastrointestinal ulceration, severe disease course, and persistent disease activity. Anti-melanoma differentiation-associated gene 5 (MDA5) antibody is associated with ILD, skin ulceration, and arthritis. Anti-Mi-2 antibody is associated with severe muscle disease, although patients with JDM having the antibody are more susceptible to drug-free remission.¹⁴ Histological severity predicts increased risk of being treated, whereas anti-Mi-2 antibody provides a protective effect.

Pathology

Muscle biopsy is important for the diagnosis of JDM. Up regulation of HLA class I in muscle cells is one of the

earliest changes detected by light microscopy.² Histologic abnormalities in JDM shows B and T cell, macrophage, and dendritic cell infiltration, and regulatory T cells are significantly increased in JDM muscle tissue compared to control muscle tissue.¹⁵ Muscle tissues show not only immune cell infiltrates but also C5b-9 deposits.¹⁶ Impaired function of JDM vasculature includes immune complex deposition, altered expression of cell adhesion molecules that predominantly induce T helper 17 cell infiltration, and endothelial cell dysfunction.¹⁷ The early phase of myogenesis appears to be associated with endothelial cell activation. However, an altered expression of myogenic regulatory factors in perifascicular regions with capillary depletion suggests an impairment of myogenic differentiation that may contribute to perifascicular muscle fiber atrophy in JDM.¹⁸ An international consensus group proposed a scoring system for JDM muscle biopsies based on four domains: inflammatory, vascular, muscular, and connective tissue; the inflammatory and muscular domains are strongly correlated with disease activity.¹⁹ The severity of histological changes in a biopsy closely correlated with MSAs.^{2,20} Small-vessel vasculitis is considered to be related to severe extramuscular manifestations of the disease such as calcinosis, skin ulceration, and ILD.^{16,21} Activated macrophages play an important role in calcinosis in JDM.²²

Musculoskeletal medicine

Ninety-five percent of patients with JDM have symmetrical and proximal muscle weakness at the time of diagnosis.¹⁶ Chronic muscle weakness or dysfunction, owing to long-term active muscle disease, is clinically found in 34% of patients with JDM.²³ Muscle strength should be strictly tested using validated tools, such as the childhood myositis assessment scale or manual muscle test.⁹ Electromyography or nerve conduction velocity is adopted only when diagnosis is uncertain. Arthritis is another common manifestation of JDM, with a reported prevalence of 23–64%.¹⁶ It may occur early in the disease course and is usually non-erosive. Vertebral fractures develop in up to 10% of patients treated with glucocorticoid (GC) for 12 months, whereas osteopenia or osteoporosis developed in 6–35% of patients in long-term outcome studies.¹

Dermatology

Cutaneous abnormalities, mainly consisting of Gottron's papules and heliotrope rash, are apparent in approximately

75% of patients with JDM.¹⁶ Calcinosis is a recognized complication in this disease, with a reported prevalence of 10–70%.²⁴ It often occurs later in the disease course, on an average of 2.9 years after disease onset.²⁵ Skin ulceration occurs in 33% and 12% of patients, before and after their fifth birthday, respectively,²⁶ and are occasionally reported as severe complications.²⁷ Lipodystrophy occurs in 10–30% of patients, mostly after 5 years of JDM diagnosis.⁵ Most patients with JDM have nailfold capillary changes at the time of diagnosis, and represent a sensitive measure of skin, muscle, and lung disease, but not of cardiac disease activity.²⁸ Persistent capillary abnormalities and Gottron's papules at 6 months after diagnosis of JDM are associated with longer time to remission.⁹ Cutaneous scarring or atrophy, resulting from long-lasting skin disease, are reported in 53% of patients.²³

Pulmonology

ILD is identified in 8% of patients with JDM.²⁹ Although it is often asymptomatic, the assessment is important because ILD is a significant cause of morbidity and mortality.⁹ Serum Krebs von den Lungen-6 and ferritin levels are elevated in JDM patients with ILD, and these may be early markers.¹ The correlation between Krebs von den Lungen-6 and IL-18 suggests that alveolar macrophages may be associated with ILD pathogenesis.³⁰ There are ethnic differences in the relationship between anti-MDA5 autoantibody and ILD, with 9% (21/242) of patients with JDM having anti-MDA5 autoantibodies in the UK²⁰ and 41% (18/44) in Japan.³⁰ In anti-MDA5 antibody-positive patients with JDM, 19% (4/21) have ILD in UK, and 100% (18/18) in Japan. Moreover, in JDM patients with rapidly progressive ILD, no patients having anti-MDA5 antibodies were observed in the UK, whereas all patients have them in Japan. Further studies are needed to clarify these ethnic differences. Although anti-aminoacyl transfer ribonucleic acid synthetase (ARS) antibodies are rare in JDM patients, 63% of juvenile idiopathic inflammatory myopathies patients with these autoantibodies have ILD.³¹ These patients have high mortality rates owing to ILD. Spontaneous pneumothorax and pneumomediastinum rarely occur, likely owing to vasculopathy.³² All patients with JDM should undergo pulmonary function tests, including carbon monoxide diffusing capacity, at the time of diagnosis.⁹ A regular assessment of pulmonary function may be prudent in patients with anti-MDA5 and anti-ARS antibodies.³³

Cardiology

Patients with JDM have increased prevalence of electrocardiogram abnormalities and reduced heart rate variability.³⁴

Pericarditis and myocarditis have also been reported. Long-axis strain and the ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity are markers for systolic and diastolic involvement on echocardiograms.⁵ Although most patients are asymptomatic, systolic and diastolic dysfunction is detected by echocardiography in patients with high early skin disease activity.³⁵ Vasculopathy in the myocardium may resemble vasculopathy in the skin. Cardiorespiratory fitness was found to be lower in patients with JDM, both with active and inactive disease, compared with controls after a mean 20 years of disease duration.³⁶ Electrocardiogram and echocardiography are recommended for all patients with JDM.⁹

Hematology

Patients with JDM-associated macrophage activation syndrome (MAS) have occasionally been reported.³⁷ Four boys and two girls, the median age of whom was 12 years, ranging between 4 and 14, were studied. All six patients survived JDM-associated MAS after immunosuppressive therapy, although systemic juvenile idiopathic arthritis-associated MAS is a life-threatening condition; the mortality rates reach 20%.³⁸ Distinct changes in IL-6 and IL-18 levels during treatment may indicate the unique pathophysiology of JDM-driven complications. JDM has not been generally associated with the development of malignant neoplasms.³⁹

Gastroenterology

Ulceration and perforation can occur in any part of the gastrointestinal tract,¹ although these reports are old and should be replicated. Nonetheless, assessment is important because it can be a cause of mortality.

Endocrinology

Growth failure is a feature of cumulative damage in JDM and occurs in around 10% of patients.⁵ Patients with lipodystrophy have increased risk of hypertriglyceridemia, insulin resistance, and diabetes.⁴⁰ In such cases, cooperation of registered dietitians is necessary. Using GC can affect the hypothalamus-pituitary-adrenal axis in patients.

Ophthalmology

Chorioretinopathy is a rare finding in JDM.⁴¹ Although patients with JDM do not usually warrant ophthalmologic examinations, any patient with visual symptoms should have a careful dilated examination for retinopathy or GC-induced cataracts. GC treatment may lead to ocular complications, and the occurrence of ocular hypertension may be related to

GC susceptibility. Therefore, regular eye monitoring is important for the patients suffering from JDM.

Psychology

In JDM, disease activity may affect school attendance, exam performance, and disrupt friendships.⁵ On the other hand, using GC can lead to psychotic symptoms. Without adequate support, this may limit educational and career prospects, impair the ability to form social relationships, and damage self-esteem. Moreover, not only patients, but also their siblings and parents, are vulnerable to psychological distress, and could benefit from psychosocial assessments and interventions at disease onset and throughout its course.⁴² Thus, many pediatric rheumatology services have engaged dedicated psychologists and social workers for addressing this issue.

Radiology

Magnetic resonance imaging (MRI) is a sensitive and reliable method for detecting and quantifying muscle inflammation at the time of diagnosis in JDM.⁴³ In addition, it can help differentiate between active and inactive disease during follow-up. A muscle MRI facilitates objective assessments of JDM flares. MRI findings of subcutaneous fat involvement are characteristic of early-diagnosed JDM and correlates with elevated serum aldolase.⁴⁴ MRI has also been suggested to be useful in confirming diagnosis of lipodystrophy or monitoring response to treatment strategies.⁵ A whole body MRI scoring system for muscular, subcutaneous tissue, and myofascial abnormalities has revealed its immense ability to estimate the overall inflammatory burden and treatment-related changes.⁴⁵

Ultrasonography is a useful tool for myositis.⁴⁶ When MRI or muscle biopsy is unavailable, muscle ultrasonography can be an alternative to assess myositis activity.⁹

Actively exploring calcinosis by manual palpation and plain radiographs is highly recommended, whereas computed tomography (CT) has shown no additional benefits over radiographs for the detection of calcinosis in JDM.⁴⁷ On the other hand, patients with JDM should undergo high-resolution CT when restrictive pulmonary disease is present;⁹ however, the risk of radiation associated with repeated CT must be considered.⁴⁸

Therapeutics

Pharmacology

GC remains the first-line treatment for JDM, followed by GC-sparing agents. The prognosis of JDM has significantly improved over the last few decades owing to the use of

GC¹⁶. Early aggressive treatment is reported to improve the long-term outcome. Methotrexate (MTX) also remains an important therapy for JDM and is used extensively both as mono- and combination therapy.⁴⁹ Approximately 70% of patients with JDM benefit significantly from MTX therapy. Cyclosporine A (CsA), tacrolimus, or azathioprine may also be used, if MTX is not tolerated. In refractory cases, intravenous immunoglobulin⁹ can be added as a second-line treatment. Mycophenolate mofetil^{50,51} may be a second- or third-line agent before using cyclophosphamide (CPA), because of fewer side effects. CPA⁵² is emerging as a third-line agent in more severe or refractory cases.

Rituximab, abatacept, adalimumab, infliximab, or tocilizumab are treatment options for refractory JDM.^{16,53,54} However, TNF inhibitors may be contraindicated because of worsening of radiological and clinical symptoms and the activation of the type I IFN system in several cases of adult refractory idiopathic inflammatory myopathies.⁵⁵ Further prospective studies are needed to explore the potential safety and efficacy of Janus kinase inhibitors in JDM, not only for refractory cases, but also as a first-line treatment.⁵⁶ In rapidly progressive ILD, a combination therapy of methylprednisolone pulse therapy, CsA, and CPA can be administered. Liposteroid, a lipid emulsion containing dexamethasone, provides greater efficacy, and much less risk for systemic adverse effects than dexamethasone sodium phosphate.⁵⁷ Liposteroid has been effectively used for the treatment of macrophage activation syndrome in Japan, because lipid emulsions are easily taken up by phagocytosis and are retained in macrophages. Liposteroid (intravenous dexamethasone palmitate: 10 mg/m²/day as dexamethasone in two divided doses) with CsA is one of the preferred treatment options for pediatric MAS,^{37,58,59} including JDM-associated MAS.⁶⁰ The risk of posterior reversible encephalopathy syndrome is presumably lower under liposteroid therapy compared with methylprednisolone pulse therapy.⁵⁷

Physiotherapy

Exercise has been suggested to relieve chronic systemic inflammation in patients with JDM.⁶¹ It has been shown that expression of genes involved in disease activity and inflammation is decreased by exercise, and it is further reported that mitochondrial enzyme activity is increased and muscle oxygen consumption is improved.⁶² In exercise therapy for myositis, both intensive aerobic and weight training have been postulated to reduce myopathic disease activity and inflammation and improve muscle

metabolism.⁶³ A 12-week home-based exercise program was safe, and led to significant improvement in long jump distance, 30-s push-ups and sit-ups, and the child health assessment questionnaire score completed by parents.⁶⁴ Using myometry and MRI, and measuring serum creatine kinase and lactate dehydrogenase levels, exercise was not found to increase muscle inflammation.⁵

Stem cell transplantation

Autologous hematopoietic stem cell transplantation might be safe and effective in treating refractory JDM, and can provide long-term drug-free survival.⁶⁵ However, this remains to be confirmed in studies with larger populations.

Surgery

Surgical resection may be a candidate treatment for established calcinosis⁶⁶ if drug therapy fails to control the disease. Aggressive biological treatments and timely surgical interventions are important in reducing mortality rate in gastrointestinal ulceration and perforation.⁵

Preventive medicine

Sunscreen

In patients with JDM, dermatitis is photosensitive, and ultraviolet (UV) light may increase the risk of recurrence. Sunscreen protection against both UV-A and -B wavelengths, with high sun-protection factors (SPF), are necessary.¹ The protection rate from UV radiation is approximately 93%, 97%, and 99% for SPF 15, 30, and 70, respectively. Photosensitivity often necessitates use of SPF 70 or higher, although a recent international upper limit allows the display of SPF 70 as 50+. Thus, using SPF 50+ is desirable. On the other hand, a recent study in a large cohort of patients with JDM reported an association between UV radiation, calcinosis, and ethnicity; with increasing UV radiation, the probability of calcinosis markedly decreased in black subjects and steadily increased in non-black subjects.⁶⁷ Thus, the indication of sunscreen use in JDM patients might be carefully considered.

Vaccination

Although inactivated vaccines are considered safe,⁶⁸ the antibody titers after vaccination are lower in patients with JDM than in healthy children.⁶⁹ There is little knowledge about the safety of live-attenuated vaccines for patients with JDM treated with GC and immunosuppressants.

Adult rheumatology

Relationship between juvenile and adult dermatomyositis

Similarities and differences between JDM and adult dermatomyositis (ADM) have been reported.¹ For example, vasculopathy, calcinosis, and skin ulceration are more pronounced in JDM than in ADM. Conversely, there is less chance of ILD and the development of malignant neoplasms in JDM than in ADM. Moreover, patients with JDM have a better life prognosis than those with ADM. In MSAs of ADM, anti-ARS antibodies are common, and anti-TIF1- γ antibody is associated with malignant neoplasms.

Transitional care

Considering the management of transitional care, it is crucial to construct a system that provides whole-person care to every patient by coordinating between the departments of pediatric rheumatology and adult rheumatology.⁷⁰ In addition, basic and clinical studies evaluating long-term clinical course of JDM and the difference between pediatric and adult onset diseases are necessary. These efforts may contribute to the development of better treatment strategies in the future.

Summary

Juvenile dermatomyositis (JDM) is strongly associated with immune-related genes of human leukocyte antigen region. Characteristic abnormalities include excess type I interferon production in blood and muscles, leading to immune cell activation and vasculopathy. The most common myositis-specific autoantibodies in JDM are anti-transcription intermediary factor 1- γ and anti-nuclear matrix protein 2. The severity of histological changes from muscle biopsy is closely correlated with myositis-specific autoantibodies. Magnetic resonance imaging is a sensitive and reliable method for detecting and quantifying muscle inflammation; muscle strength may be tested using the childhood myositis assessment scale or manual muscle test. Nailfold capillary changes also provide a sensitive measure of disease activity. Interstitial lung disease and gastrointestinal ulceration assessment, electrocardiogram, and echocardiography are indicated for all children with JDM. Growth failure is also a key feature of cumulative damage in JDM. Regular eye monitoring is important for children suffering from JDM. Children with JDM, siblings, and parents are vulnerable to psychological distress, and could benefit from psychosocial assessments and interventions. Glucocorticoid remains the first-line

treatment in this regard, followed by methotrexate, and mycophenolate mofetil and biologic agents can treat refractory cases. Children reported with JDM-associated macrophage activation syndrome survived after immunosuppressive therapy. Exercise can relieve chronic systemic inflammation, and established calcinosis might respond to surgical resection. Sunscreen protection against ultraviolet light is generally necessary. Management of transitional care by coordinating between pediatric and adult rheumatologists is essential. Furthermore, updates on epidemiology are also important. Overall, for the elucidation of JDM pathophysiology and establishment of appropriate treatment for children with JDM, more extensive multispecialty collaborations are warranted.

Disclosure

The author reports no conflicts of interest in this work.

References

- Rider LG, Lindsley CB, Miller FW. Juvenile dermatomyositis. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, editors. *Textbook of Pediatric Rheumatology*. 7th ed. Philadelphia: Saunders Elsevier; 2016:351–383.
- Rider LG, Nistala K. The juvenile idiopathic inflammatory myopathies: pathogenesis, clinical and autoantibody phenotypes, and outcomes. *J Intern Med*. 2016;280(1):24–38. doi:10.1111/joim.12444
- Miller FW, Cooper RG, Vencovsky J, et al. Genome-wide association study of dermatomyositis reveals genetic overlap with other autoimmune disorders. *Arthritis Rheum*. 2013;65(12):3239–3247. doi:10.1002/art.38137
- Lintner KE, Patwardhan A, Rider LG, et al. Gene copy-number variations (CNVs) of complement C4 and C4A deficiency in genetic risk and pathogenesis of juvenile dermatomyositis. *Ann Rheum Dis*. 2016;75(9):1599–1606. doi:10.1136/annrheumdis-2015-207762
- Wu Q, Wedderburn LR, McCann LJ. Juvenile dermatomyositis: latest advances. *Best Pract Res Clin Rheumatol*. 2017;31(4):535–557. doi:10.1016/j.berh.2017.12.003
- Simon JP, Marie I, Jouen F, Boyer O, Martinet J. Autoimmune myopathies: where do we stand? *Front Immunol*. 2016;7:234. doi:10.3389/fimmu.2016.00234
- Sanner H, Schwartz T, Flatø B, Vistnes M, Christensen G, Sjaastad I. Increased levels of eotaxin and MCP-1 in juvenile dermatomyositis median 16.8 years after disease onset; associations with disease activity, duration and organ damage. *PLoS One*. 2014;9(3):e92171. doi:10.1371/journal.pone.0092171
- Enders FB, Delemarre EM, Kuemmerle-Deschner J, et al. Autologous stem cell transplantation leads to a change in proinflammatory plasma cytokine profile of patients with juvenile dermatomyositis correlating with disease activity. *Ann Rheum Dis*. 2015;74(1):315–317. doi:10.1136/annrheumdis-2014-206287
- Enders FB, Bader-Meunier B, Baildam E, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. *Ann Rheum Dis*. 2017;76(2):329–340. doi:10.1136/annrheumdis-2016-209287
- Miyamae T, Sano F, Ozawa R, Imagawa T, Inayama Y, Yokota S. Efficacy of thalidomide in a girl with inflammatory calcinosis, a severe complication of juvenile dermatomyositis. *Pediatr Rheumatol Online J*. 2010;8(1):6. doi:10.1186/1546-0096-8-6
- Kobayashi N, Kobayashi I, Mori M, et al. Increased serum B Cell activating factor and a proliferation-inducing ligand are associated with interstitial lung disease in patients with juvenile dermatomyositis. *J Rheumatol*. 2015;42(12):2412–2418. doi:10.3899/jrheum.140977
- Tansley SL, Simou S, Shaddick G, et al. Autoantibodies in juvenile-onset myositis: their diagnostic value and associated clinical phenotype in a large UK cohort. *J Autoimmun*. 2017;84:55–64. doi:10.1016/j.jaut.2017.06.007
- Rosina S, Varnier GC, Mazzoni M, Lanni S, Malattia C, Ravelli A. Innovative research design to meet the challenges of clinical trials for juvenile dermatomyositis. *Curr Rheumatol Rep*. 2018;20(5):29. doi:10.1007/s11926-018-0734-4
- Deakin CT, Yasin SA, Simou S, et al. Muscle biopsy findings in combination with myositis-specific autoantibodies aid prediction of outcomes in juvenile dermatomyositis. *Arthritis Rheumatol*. 2016;68(11):2806–2816. doi:10.1002/art.39753
- Vercoulen Y, Bellutti EF, Meering J, et al. Increased presence of FOXP3+ regulatory T cells in inflamed muscle of patients with active juvenile dermatomyositis compared to peripheral blood. *PLoS One*. 2014;9(8):e105353. doi:10.1371/journal.pone.0105353
- Papadopoulou C, Wedderburn LR. Treatment of juvenile dermatomyositis: an update. *Pediatr Drugs*. 2017;19(5):423–434. doi:10.1007/s40272-017-0240-6
- Papadopoulou C, McCann LJ. The vasculopathy of juvenile dermatomyositis. *Front Pediatr*. 2018;6:284. doi:10.3389/fped.2018.00284
- Baumann M, Gumpold C, Mueller-Felber W, et al. Pattern of myogenesis and vascular repair in early and advanced lesions of juvenile dermatomyositis. *Neuromuscul Disord*. 2018;28(12):973–985. doi:10.1016/j.nmd.2018.09.002
- Varsani H, Charman SC, Li CK, et al. Validation of a score tool for measurement of histological severity in juvenile dermatomyositis and association with clinical severity of disease. *Ann Rheum Dis*. 2015;74(1):204–210. doi:10.1136/annrheumdis-2013-203396
- Tansley SL, Betteridge ZE, Gunawardena H, et al. Anti-MDA5 autoantibodies in juvenile dermatomyositis identify a distinct clinical phenotype: a prospective cohort study. *Arthritis Res Ther*. 2014;16(4):R138. doi:10.1186/ar4600
- Wakiguchi H, Takei S, Imanaka H, et al. Severe gluteal skin ulcers in an infant with juvenile dermatomyositis. *Eur J Dermatol*. 2016;26(2):192–193. doi:10.1684/ejd.2015.2701
- Shimizu M, Ueno K, Ishikawa S, Kasahara Y, Yachie A. Role of activated macrophage and inflammatory cytokines in the development of calcinosis in juvenile dermatomyositis. *Rheumatology (Oxford)*. 2014;53(4):766–767. doi:10.1093/rheumatology/ket360
- Ravelli A, Trail L, Ferrari C, et al. Long-term outcome and prognostic factors of juvenile dermatomyositis: a multinational, multicenter study of 490 patients. *Arthritis Care Res (Hoboken)*. 2010;62(1):63–72. doi:10.1002/acr.20015
- Hoeltzel MF, Oberle EJ, Robinson AB, Agarwal A, Rider LG. The presentation, assessment, pathogenesis, and treatment of calcinosis in juvenile dermatomyositis. *Curr Rheumatol Rep*. 2014;16(12):467. doi:10.1007/s11926-014-0467-y
- Balin SJ, Wetter DA, Andersen LK, Davis MD. Calcinosis cutis occurring in association with autoimmune connective tissue disease: the Mayo clinic experience with 78 patients, 1996–2009. *Arch Dermatol*. 2012;148(4):455–462. doi:10.1001/archdermatol.2011.2052
- Martin N, Krol P, Smith S, et al. Comparison of children with onset of juvenile dermatomyositis symptoms before or after their fifth birthday in a UK and Ireland juvenile dermatomyositis cohort study. *Arthritis Care Res (Hoboken)*. 2012;64(11):1665–1672. doi:10.1002/acr.21753
- Wakiguchi H, Takei S, Kawano Y. Axillary skin ulcers in infants with juvenile dermatomyositis. *Pediatr Neonatol*. 2017;58(3):287–288. doi:10.1016/j.pedneo.2016.07.001

28. Barth Z, Schwartz T, Flatø B, et al. The association between nailfold capillary density and pulmonary and cardiac involvement in medium- to long-standing juvenile dermatomyositis. *Arthritis Care Res (Hoboken)*. 2019;71(4):492–497. doi:10.1002/acr.23687
29. Mathiesen PR, Buchvald F, Nielsen KG, Herlin T, Friis T, Nielsen S. Pulmonary function and autoantibodies in a long-term follow-up of juvenile dermatomyositis patients. *Rheumatology (Oxford)*. 2014;53(4):644–649. doi:10.1093/rheumatology/ket380
30. Kobayashi N, Takezaki S, Kobayashi I, et al. Clinical and laboratory features of fatal rapidly progressive interstitial lung disease associated with juvenile dermatomyositis. *Rheumatology (Oxford)*. 2015;54(5):784–791. doi:10.1093/rheumatology/keu385
31. Rider LG, Shah M, Mamyrova G, et al. The myositis autoantibody phenotypes of the juvenile idiopathic inflammatory myopathies. *Medicine (Baltimore)*. 2013;92(4):223–243. doi:10.1097/MD.0b013e31829d08f9
32. Dogra S, Suri D, Shah R, Rawat A, Singh S, Sodhi KS. Spontaneous pneumomediastinum: a rare complication of juvenile dermatomyositis. *Int J Rheum Dis*. 2012;15(5):e131–133. doi:10.1111/apl.2012.15.issue-5
33. Prestridge A, Morgan G, Ferguson L, Huang CC, Pachman LM. Pulmonary function tests in idiopathic inflammatory myopathy: association with clinical parameters in children. *Arthritis Care Res (Hoboken)*. 2013;65(9):1424–1431. doi:10.1002/acr.22014
34. Cantez S, Gross GJ, MacLusky I, Feldman BM. Cardiac findings in children with juvenile dermatomyositis at disease presentation. *Pediatr Rheumatol Online J*. 2017;15(1):54. doi:10.1186/s12969-017-0182-0
35. Schwartz T, Sanner H, Gjesdal O, Flatø B, Sjaastad I. In juvenile dermatomyositis, cardiac systolic dysfunction is present after long-term follow-up and is predicted by sustained early skin activity. *Ann Rheum Dis*. 2014;73(10):1805–1810. doi:10.1136/annrheumdis-2014-205310
36. Berntsen KS, Edvardsen E, Hansen BH, Flatø B, Sjaastad I, Sanner H. Cardiorespiratory fitness in long-term juvenile dermatomyositis: a controlled, cross-sectional study of active/inactive disease. *Rheumatology (Oxford)*. 2019;58(3):492–501. doi:10.1093/rheumatology/key342
37. Wakiguchi H, Hasegawa S, Hirano R, Kaneyasu H, Wakabayashi-Takahara M, Ohga S. Successful control of juvenile dermatomyositis-associated macrophage activation syndrome and interstitial pneumonia: distinct kinetics of interleukin-6 and -18 levels. *Pediatr Rheumatol Online J*. 2015;13:49. doi:10.1186/s12969-015-0048-2
38. Chrom AA. Macrophage activation syndrome. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, editors. *Textbook of Pediatric Rheumatology*. 7th ed. Philadelphia: Saunders Elsevier; 2016:642–649.
39. Morris P, Dare J. Juvenile dermatomyositis as a paraneoplastic phenomenon: an update. *J Pediatr Hematol Oncol*. 2010;32(3):189–191. doi:10.1097/MPH.0b013e3181bf29a2
40. Bingham A, Mamyrova G, Rother KI, et al. Predictors of acquired lipodystrophy in juvenile-onset dermatomyositis and a gradient of severity. *Medicine (Baltimore)*. 2008;87(2):70–86. doi:10.1097/MD.0b013e31816bc604
41. Choi RY, Swan RJ, Hersh A, Vitale AT. Retinal manifestations of juvenile dermatomyositis: case report of bilateral diffuse chorioretinopathy with paracentral acute middle maculopathy and review of the literature. *Ocul Immunol Inflamm*. 2018;26(6):929–933. doi:10.1080/09273948.2017.1305421
42. Kountz-Edwards S, Aoki C, Gannon C, Gomez R, Cordova M, Packman W. The family impact of caring for a child with juvenile dermatomyositis. *Chron Illness*. 2017;13(4):262–274. doi:10.1177/1742395317690034
43. Malattia C, Damasio MB, Madeo A, et al. Whole-body MRI in the assessment of disease activity in juvenile dermatomyositis. *Ann Rheum Dis*. 2014;73(6):1083–1090. doi:10.1136/annrheumdis-2014-205310
44. Sakurai N, Hino-Shishikura A, Nozawa T, et al. Clinical significance of subcutaneous fat and fascial involvement in juvenile dermatomyositis. *Mod Rheumatol*. Epub 2018 Oct 18. doi:10.1080/14397595.2018.1511026
45. Abdul-Aziz R, Yu CY, Adler B, et al. Muscle MRI at the time of questionable disease flares in juvenile dermatomyositis (JDM). *Pediatr Rheumatol Online J*. 2017;15(1):25. doi:10.1186/s12969-017-0154-4
46. Habers GE, Van Brussel M, Bhansing KJ, et al. Quantitative muscle ultrasonography in the follow-up of juvenile dermatomyositis. *Muscle Nerve*. 2015;52(4):540–546. doi:10.1002/mus.24564
47. Shahi V, Wetter DA, Howe BM, Ringler MD, Davis MD. Plain radiography is effective for the detection of calcinosis cutis occurring in association with autoimmune connective tissue disease. *Br J Dermatol*. 2014;170(5):1073–1079. doi:10.1111/bjd.2014.170.issue-5
48. Pouessel G, Deschildre A, Le Bourgeois M, et al. The lung is involved in juvenile dermatomyositis. *Pediatr Pulmonol*. 2013;48(10):1016–1025. doi:10.1002/ppul.22742
49. Ruperto N, Pistorio A, Oliveira S, et al. Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial. *Lancet*. 2016;387(10019):671–678. doi:10.1016/S0140-6736(15)01021-1
50. Dagher R, Desjonquères M, Duquesne A, et al. Mycophenolate mofetil in juvenile dermatomyositis: a case series. *Rheumatol Int*. 2012;32(3):711–716. doi:10.1007/s00296-010-1653-5
51. Rouster-Stevens KA, Morgan GA, Wang D, Pachman LM. Mycophenolate mofetil: a possible therapeutic agent for children with juvenile dermatomyositis. *Arthritis Care Res (Hoboken)*. 2010;62(10):1446–1451. doi:10.1002/acr.20269
52. Deakin CT, Campanillo-Marques R, Simou S, et al. Efficacy and safety of cyclophosphamide treatment in severe juvenile dermatomyositis shown by marginal structural modeling. *Arthritis Rheumatol*. 2018;70(5):785–793. doi:10.1002/art.40418
53. Oddis CV, Reed AM, Aggarwal R, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. *Arthritis Rheum*. 2013;65(2):314–324. doi:10.1002/art.37754
54. Orandi AB, Dharmidharka VR, Al-Hammadi N, Baszis KW. CARRA legacy registry investigators. Clinical phenotypes and biologic treatment use in juvenile dermatomyositis-associated calcinosis. *Pediatr Rheumatol Online J*. 2018;16(1):84. doi:10.1186/s12969-018-0299-9
55. Dastmalchi M, Grundtman C, Alexanderson H, et al. A high incidence of disease flares in an open pilot study of infliximab in patients with refractory inflammatory myopathies. *Ann Rheum Dis*. 2008;67(12):1670–1677. doi:10.1136/ard.2007.077974
56. Papadopoulou C, Hong Y, Omyonimi E, Brogan PA, Eleftheriou D. Janus kinase 1/2 inhibition with baricitinib in the treatment of juvenile dermatomyositis. *Brain*. 2019;142(3):e8. doi:10.1093/brain/awz005
57. Wakiguchi H, Ohga S. Clinical utility of the liposteroid therapy: potential effects on the macrophage activation. *Jpn J Clin Immunol*. 2016;39(3):190–196. doi:10.2177/jsci.39.190
58. Nakagishi Y, Shimizu M, Kasai K, Miyoshi M, Yachie A. Successful therapy of macrophage activation syndrome with dexamethasone palmitate. *Mod Rheumatol*. 2016;26(4):617–620. doi:10.3109/14397595.2014.906053
59. Shimizu M, Yokoyama T, Tokuhisa Y, et al. Distinct cytokine profile in juvenile systemic lupus erythematosus-associated macrophage activation syndrome. *Clin Immunol*. 2013;146(2):73–76. doi:10.1016/j.clim.2012.11.004
60. Wakiguchi H. Liposteroid therapy for juvenile and adult dermatomyositis: efficacy and side effects. *Ann Transl Med*. 2017;5(5):110. doi:10.21037/atm
61. Omori CH, Silva CA, Sallum AM, et al. Exercise training in juvenile dermatomyositis. *Arthritis Care Res (Hoboken)*. 2012;64(8):1186–1194. doi:10.1002/acr.21684

62. Alemo Munters L, Dastmalchi M, Katz A, et al. Improved exercise performance and increased aerobic capacity after endurance training of patients with stable polymyositis and dermatomyositis. *Arthritis Res Ther*. 2013;15(4):R83. doi:10.1186/ar4263
63. Alexanderson H. Physical exercise as a treatment for adult and juvenile myositis. *J Intern Med*. 2016;280(1):75–96. doi:10.1111/joim.12481
64. Habers GE, Bos GJ, van Royen-Kerkhof A, et al. Muscles in motion: a randomized controlled trial on the feasibility, safety and efficacy of an exercise training programme in children and adolescents with juvenile dermatomyositis. *Rheumatology (Oxford)*. 2016;55(7):1251–1262. doi:10.1093/rheumatology/kew026
65. Zhu J, Su G, Lai J, et al. Long-term follow-up of autologous hematopoietic stem cell transplantation for refractory juvenile dermatomyositis: a case-series study. *Pediatr Rheumatol Online J*. 2018;16(1):72. doi:10.1186/s12969-018-0284-3
66. Welborn MC, Gottschalk H, Bindra R. Juvenile dermatomyositis: a case of calcinosis cutis of the elbow and review of the literature. *J Pediatr Orthop*. 2015;35(5):e43–46. doi:10.1097/BPO.0000000000000358
67. Neely J, Long CS, Sturrock H, Kim S; CARRA Registry Investigators. The association of short-term UV radiation exposure and disease severity in juvenile dermatomyositis. *Arthritis Care Res (Hoboken)*. Epub 2019 Feb 4. doi:10.1002/acr.23840
68. Guissa VR, Pereira RM, Sallum AM, et al. Influenza A H1N1/2009 vaccine in juvenile dermatomyositis: reduced immunogenicity in patients under immunosuppressive therapy. *Clin Exp Rheumatol*. 2012;30(4):583–588. doi:none
69. Ogimi C, Tanaka R, Saitoh A, Oh-Ishi T. Immunogenicity of influenza vaccine in children with pediatric rheumatic diseases receiving immunosuppressive agents. *Pediatr Infect Dis J*. 2011;30(3):208–211. doi:10.1097/INF.0b013e3181f7ce44
70. Mori M. Pediatric rheumatic diseases: a review regarding the improvement of long-term prognosis and the transition to adults. *Immunol Med*. 2018;41(1):2–5. doi:10.1080/09114300.2018.1451591

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