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Long-term Outcomes in Juvenile Myositis Patients

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Abstract

Objective—Juvenile idiopathic inflammatory myopathies (JIIM) are rare, chronic autoimmune muscle diseases of childhood, with the potential for significant morbidity. Data on long-term outcomes is limited. In this study we investigate correlations between clinical and demographic features with long-term outcomes in a referral population of adult patients with JIIM.

Methods—Forty-nine adults with JIIM were assessed at two referral centers between 1994 and 2016. Features of active disease and damage at a cross-sectional assessment were obtained. Regression modeling was used to examine factors associated with long-term outcomes, defined by the presence of calcinosis or a higher adjusted Myositis Damage Index (MDI) score. A multivariable model of MDI was constructed using factors that were statistically significant in bivariate models.

Results—At a median of 11.5 [IQR 4.5-18.9] years following diagnosis, median American College of Rheumatology (ACR) functional class was 2 [1.5-3.0], Health Assessment Questionnaire (HAQ) score was 0.4 out of 3.0 [0.0-1.0], and manual muscle testing (MMT) score was 229 out of 260 [212.6-256.8]. Median MDI score was 6.0 [3.5-8.9], with the most commonly

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damaged organ systems being cutaneous and musculoskeletal. Factors associated with an elevated MDI score were the presence of erythroderma and other cutaneous manifestations, disease duration, and ACR functional class. Calcinosis was present in 55% of patients. The strongest predictors of calcinosis were disease duration, periungual capillary changes, and younger age at diagnosis.

Conclusion—In a tertiary referral population, long-term functional outcomes of JIIM are generally favorable, with HAQ scores indicative of mild disability. Although most patients had mild disease activity and virtually all had significant disease damage, severe or systemic damage was rare. Certain clinical features are associated with long-term damage and calcinosis.

Keywords

juvenile dermatomyositis; calcinosis; damage; outcome; treatment

Introduction

The juvenile idiopathic inflammatory myopathies (JIIM) are a rare, heterogeneous group of autoimmune diseases characterized by chronic muscle weakness and inflammation, presenting in childhood. They include juvenile dermatomyositis (JDM) with characteristic and frequent photosensitive rashes, juvenile polymyositis (JPM) with primary muscle inflammation and no characteristic rashes, and juvenile connective tissue myositis (JCTM), where patients also meet criteria for another connective tissue disease (1). JDM is the most common phenotype among the JIIM, but remains a rare disease, with an annual incidence of two to four cases per million children in the United States. JDM is a small-vessel vasculopathy, and though the skeletal muscle is the most frequently affected target organ, it is a systemic disease that also involves other organs such as the skin, gastrointestinal tract, and pulmonary parenchyma(2). The course and severity of the disease is highly variable, but disease course can be generally divided into three types: monocyclic, polycyclic, and chronic continuous (3).

Corticosteroids have been the first-line treatment of JDM for the last three decades, but with the emergence of methotrexate, other disease modifying anti-rheumatic drugs (DMARDs) and biologic therapies, the treatment options for JDM have greatly expanded within the last ten years (4). Data from North American, European and Latin American cohorts have shown that long-term outcomes of the disease are now generally favorable in terms of low mortality, but with a significant amount of disease damage (5–8). Although greater than 60% of patients had some evidence of organ damage, the most commonly affected organ is the skin, and only a small percentage of patients have serious functional disability (6, 7). Studies from Europe document that patients diagnosed after 1990 have less end-organ damage (9, 10). Once patients reach adulthood, although their health-related quality of life is reduced, their overall quality of life in other domains is comparable to matched controls, particularly in marital status, educational attainment, and occupation (11). However, preliminary data from the United Kingdom found that patients above age 18 were twice as likely to be unemployed as their peers, and that nearly half of those who attended college reported educational difficulties related to their myositis. (12)

Recent data on long-term outcomes of JDM patients within the United States (U.S.) has been limited. Additionally, there has been no data in the U.S. on outcomes of JIIM when patients reach adult age. The purpose of our study was to better characterize the long-term outcomes of these diseases, particularly in patients of adult age, in a diverse referral population, as well as to explore factors early in the disease course that may provide predictive value for these patients' long-term outcomes.

Methods

Patients and data collection

Patients with probable or definite JIIM (13, 14) were referred to either the National Institutes of Health (NIH) or the George Washington University (GWU) Myositis Center between 1994 and 2016. Patients were enrolled in study protocol approved by the NIH and GWU institutional review boards and signed informed consent. Subjects included in the present study were of adult age (age > 18 years) at time of the last cross-sectional evaluation. A total of 51 patients were evaluated for inclusion in the study. Two patients were excluded due to >50% missing data related to MDI items collected at the cross-sectional visit, and the remaining 49 patients were included in the analysis.

Each patient had a single cross-sectional visit with a pediatric and/or adult rheumatologist, which consisted of a review of medical records to complete a questionnaire of signs/symptoms and disease outcomes (15), a complete history and physical exam, laboratory data including creatine kinase levels, prior radiological imaging and pulmonary function tests (PFTs), and standardized disease activity and damage assessments, including patient and physician global activity and global damage visual analog scales (VAS), the Health Assessment Questionnaire (HAQ), manual muscle testing of 26 individual muscle groups (MMT26 score), and the Myositis Damage Index (MDI). The total extent-of-damage MDI score was gender-adjusted as described. (7, 16). A clinical symptom score was developed by determining the presence or absence of specific signs/symptoms ever present and at the cross-sectional evaluation from each of six major organ systems (3). All patients with interstitial lung disease had confirmation by chest CT imaging and restrictive lung disease on PFTs. Serum from 40 patients was tested for 13 myositis specific autoantibodies (MSAs) and 19 myositis associated autoantibodies (MAAs) by standard immunoprecipitation(17) and immunoprecipitation-immunoblotting methods(18) at a median disease duration of 5.9 years, at first study evaluation. Serum was unavailable for testing in the remaining patients.

Statistical analysis

All analysis was done using SAS 9.3 (SAS Institute, Cary, NC). Clinical, demographic and laboratory data were analyzed and descriptive statistics computed for each predictor variable: frequencies for categorical variables, means and standard deviations for continuous normally distributed variables, and medians and interquartile ranges (IQR) for other interval and continuous variables.

The two outcome variables, total extent-of-damage MDI score and presence of calcinosis at most recent assessment, were chosen as proxies for overall disease damage, particularly due

to the high prevalence of calcinosis in this group of patients. We started with 102 potential predictor variables (Supplemental Table 1). Eight variables were eliminated due missing data in ≥ 50% of patients (5 variables), lack of variation (2 variables), and redundant information (1 variable). We also eliminated documentation of past calcinosis as a predictor for the calcinosis outcome, as all patients with prior documentation of calcinosis still had calcinosis at study assessment. This left 94 variables for the bivariate analysis of adjusted MDI score and 93 variables for the bivariate analysis of calcinosis. To assess bivariate associations with adjusted MDI score, we used point-biserial correlation tests for dichotomous predictors, analysis of variance (ANOVA) for other categorical predictors, and Spearman's rank correlation tests for ordinal and continuous predictors. For bivariate analysis of the presence of calcinosis outcome, we used Pearson's chi-squared tests or Fisher's exact tests for categorical predictors, and logistic regression for ordinal and continuous predictors. We used multiple regression modeling to predict total MDI score. Predictor variables that were statistically associated with the outcome at an alpha = 0.15 in bivariate analysis were included in the initial model. We then used backward selection to produce a final model that minimized the Schwarz Bayesian information criterion statistic. We attempted to perform multiple logistic regression for the calcinosis outcome, but none of the models converged.

Results

Demographic and Clinical Features, Disease Assessment and Therapeutic History.

Of the 49 JIIM patients included, 76% had a diagnosis of JDM. Median age at time of cross-sectional evaluation was 24 years (interquartile range 19-29, range 18-51), with a median disease duration of 11.5 years. Of the 41 patients for whom autoantibodies were obtained, two-thirds had a detectable myositis-specific and 30% had a detectable myositis-associated autoantibody, with the most frequent being anti-pl55/140 (TIF-1), present in 27.5%, anti-MJ (NXP2) in 22.5% and anti-Ro60 in 20% of sera tested. Disease course was chronic continuous in 63% of patients, with 30% having a polycyclic course and only 6% with a monocyclic course. Other features of the population are presented in Table 1.

Patients tended to have poor global function in the past. The median worst recorded American College of Rheumatology (ACR) functional class was 4 out of 5, though function had significantly improved by the cross-sectional evaluation visit, with a median ACR functional class of 2. Patients at last evaluation had mild disease activity and moderate disease damage (median physician global activity and global VAS damage 1.7 and 3.0, respectively), mild functional disability by the HAQ (median score 0.4), and moderate weakness by MMT with a median MMT26 score of 229 out of 260 (Table 1).

All patients received oral corticosteroids during their disease course, and the majority (86%) received methotrexate previously. Only 57% were still receiving oral corticosteroids and 39% were receiving methotrexate at the cross-sectional evaluation visit. Sixty percent of patients required intravenous (IV) corticosteroids, and 60% had at least one course of IV immune globulin (IVIG), though fewer than 40% were receiving these at cross-sectional evaluation. Only 31% of patients had received biologic therapies, rituximab being most frequent in 26% of patients, and only 9% were currently using biologic therapy.

In terms of signs and symptoms of illness, the most common organ systems involved were muscle (100% of patients) and cutaneous (96%). Within these systems, the most common disease manifestations were proximal weakness (98%), fatigue (90%), Gottron's papules (88%), and periungual capillary changes (84%), as expected. Notably, the prevalence of calcinosis was 55% in this population. At the cross-sectional evaluation, 90% of patients still had muscular manifestations, and 90% still had cutaneous manifestations. However, the frequency of proximal weakness had decreased to 70%. All patients that had previously developed calcinosis still had some calcinosis present at the cross-sectional evaluation. Most organ system scores decreased at cross-sectional evaluation, except there was no change in the cutaneous and cardiopulmonary systems. Table 2 describes all documented clinical manifestations in the patient population.

Myositis Damage Index

Using the MDI, 95% of patients had detectable damage on last evaluation by the Extent of Damage score, and the median extent of damage score was 6.0 out of 38, with an interquartile range from 3.5 to 8.9. Damage was most frequent in the cutaneous and muscle systems, with skeletal and endocrine damage also being frequent, and these systems also had the highest extent of damage system scores. Notable damage items included joint contractures present in 63% of patients, muscle atrophy in 49%, cutaneous scarring or atrophy in 60%, and lipodystrophy in 33% of patients. Additionally, 32% of female patients reported irregular menses. This was significantly correlated with use of prednisone at the cross-sectional visit ($p = 0.027$), but not with use of cyclophosphamide ($p = 0.6$). One patient developed papillary thyroid carcinoma (Table 3). Other damage items were less frequently endorsed, and their associated extent of damage system scores were in a mild range.

Predictors of damage and calcinosis

Twenty predictor variables correlated significantly ($p < 0.05$) with the adjusted extent of damage MDI score (Supplementary Table 1). The most strongly associated was the presence of erythroderma, which had a point-biserial correlation coefficient (r_{pb}) of 0.42. Other variables with a significant relationship with MDI score included shawl sign ($r_{pb} = 0.35$), falling episodes ($r_{pb} = 0.34$) and the use of a wheelchair at any point during the disease course ($r_{pb} = 0.31$).

Thirty-three variables were associated with adjusted MDI score at $p < 0.15$ and were thus potential candidates for inclusion in the multivariable model. Eighteen of these were excluded due to missing data (2), collinearity with other variables (2), or their inclusion in the MDI itself (14), leaving 15 variables for inclusion in the initial model (Table 4). Backwards selection further reduced the model to five predictors, all of which remained significantly associated with the MDI score after adjustment for the other variables in the model. The presence of erythroderma was associated with an increase of almost 4 points in the MDI score ($b = 3.94$, $p = 0.01$). Each additional year of JIIM disease duration was associated with a MDI score increase of 0.08 points ($p = 0.04$). For each additional point in the worst ACR functional score, the MDI score increased by 1.31 ($p = 0.001$). Other positive

indicators were past presence of shawl sign (b = 2.71, p = 0.006) and heliotrope rash (b = 2.06, p = 0.05).

Calcinosis was found in 27 of the 49 patients (55.1%) at last assessment. A history of Gottron's papules was strongly associated with the outcome, with 62.8% having calcinosis compared with 0.0% for patients with no history of Gottron's papules (p = 0.005) (Table 5). The odds of having calcinosis was nearly 9 times higher for patients who had ever had periungual capillary changes compared to patients without them (OR = 8.65; 95% CI = 1.63 – 46.08). For each additional year of disease duration, the odds of calcinosis increased by 12% (OR = 1.12; 95% CI = 1.03 – 1.21). For each additional year of age at diagnosis, the odds of calcinosis decreased by 19% (OR = 0.81; 95% CI = 0.70 – 0.95). The likelihood of calcinosis was also greater for people with ever documented falling episodes (OR = 5.89; 95% CI = 1.38 – 25.23), lipodystrophy (OR=5.07; 95% CI = 1.21 – 21.28), or contractures (OR = 3.98; 95% CI = 1.02 – 15.51). Convergence was not obtained for a multivariable model of predictors of calcinosis.

Discussion

This is the largest study of long-term outcomes for JIIM patients in the U.S. who are now of adult age, and examines in some detail predictors of damage and calcinosis. Our patient population was generally more severely affected than prior studies, most likely due to the nature of our highly selected referral population seen in specialty clinics and research studies, but also possibly related to the long disease duration since diagnosis at the cross-sectional evaluation. Approximately 70% of patients had on average moderate muscle weakness at the cross-sectional evaluation, which is greater than the 10-40% frequency and more mild degree of weakness of other JIIM populations (6, 8, 10, 19). Despite these findings of moderate weakness, JIIM patients tended to have favorable functional outcomes in adulthood, with severe disability being uncommon and a median HAQ score of 0.4, representing relatively low disability, which is similar to less severely affected cohorts in Canada, Norway and Denmark (8, 9, 19).

Overall damage in our study was also more extensive than the European and Canadian cohorts, with median MDI extent of damage score of 6.3 compared to a median range of 1-3 in other long-term outcomes studies (8, 9). Individual system scores in the MDI tended to be higher in our study as well, particularly median muscle, skeletal, and skin extent of damage scores (6). Severe clinically evident end-organ damage was uncommon, with only three patients developing vision loss, one patient with anti-Jol autoantibodies having pulmonary fibrosis, and no patients developing gastrointestinal infarction, pulmonary hypertension, or cardiac arrhythmias. One patient developed papillary thyroid carcinoma, although their JDM was not paraneoplastic, since the patient developed cancer many years after their JDM diagnosis.

From this more severely affected population, we were able to identify multiple clinical factors associated with long-term damage, including several novel factors not previously identified. The clearest association was between disease duration and MDI score, increasing almost linearly for each year of disease since diagnosis. This suggests that the organ damage

from JIIM may be ongoing throughout the disease course. Interestingly, the presence of "classical" skin findings of JDM, such as heliotrope rash, or cutaneous features associated with the pl55/140 (TIF-1) autoantibodies (15, 18, 23) such as shawl sign or erythroderma, were strongly associated with damage later in life. This may relate to the strong association with the clinical subgroup of JDM having higher damage scores, or the association of anti-pl55/140 (TIF-1) autoantibodies with a chronic illness course (3), though our study did not detect such an association of these clinical or myositis autoantibody groups directly with the MDI. Preliminary data from the UK also suggests that anti-MDA5 may be associated with worse disease outcomes; however, our study did not detect this association (24).

A prevalence of calcinosis in 55% of JIIM patients in our long-term outcome study was higher than the European and Canadian cohorts, which reported a prevalence of 15-25% (6, 19). A comparable rate of calcinosis to ours was reported in data from Brazil (22), which was similarly a single referral center study. Our data confirm prior associations of calcinosis with increased disease duration (6), younger age at diagnosis (29), and lipodystrophy (30). The association of calcinosis with Gottron's papules and periungual capillary changes may simply be a corollary of the diagnosis of JDM, which itself is associated with calcinosis, although persistent skin disease and nailfold capillaropathy have also been associated with a longer illness course, which may be associated with calcinosis (25–28). Some clinical manifestations we found to be associated with calcinosis, including falls, contractures, and constipation, have not been previously reported. Because of the limited sample size and our desire to identify possibly important predictors, the statistical analysis did not adjust for multiple testing, which would have further reduced statistical power. Therefore, replication in other samples will be needed to confirm those associations. We were also unable to obtain convergence for a multivariable model of calcinosis, likely due to an insufficient sample size.

Fifty-six percent of patients were still requiring prednisone at the cross-sectional visit, which suggests that active disease was still ongoing for these patients. Many patients also required medications other than prednisone to manage their disease. IVIG in particular was used much more frequently than in prior studies, with nearly 40% of our patients requiring IVIG at the last evaluation, compared to 20% in a large European outcome study (20). Unfortunately, adverse effects of corticosteroids were not uncommon, with about 12% of patients developing diabetes mellitus, 8% osteoporosis, 8% hypertension, and 4% avascular necrosis, as noted in the damage index evaluation, and growth was significantly impaired, with a median final height at the 30th percentile. None of these findings were significantly different from prior studies (6, 7). We were unable to identify any medication that was associated with long-term damage, so we are unable to state whether early risk stratification could affect treatment decision making. This finding correlates with prior European studies, which showed no difference in long-term end organ damage and use of specific medications (6, 9).

This was a highly selected referral population and likely the long-term outcomes at cross-sectional evaluation in the young adult years are not representative of the US JIIM population more generally. In particular, patients who have died or those who attained remission and were not seeking specialty care, were not part of this study, and this could

have altered the findings. In fact, we observed a low frequency of patients with a monocyclic disease course (3, 8, 20, 22). Further studies are needed to assess quality-of-life measures, educational attainment, and employment in this patient population. Our patient population was relatively young with a median age of 24 years, so we are unable to extrapolate their longer-term risks, such as cardiovascular disease, which was previously shown to be elevated in an older cohort (31).

In summary, we were able to evaluate long-term outcomes of a reasonably large U.S. cohort of primarily young adults with JIIM, which revealed significant long-term disease damage, especially persistent muscle weakness, calcinosis and other skin damage, but without severe, clinically-appreciable damage to other organ systems or significant functional limitations. This referral cohort, enriched in more severe disease, was valuable in identifying predictors of long-term damage and calcinosis, namely the classical skin findings of JDM, anti-p155/140 (TIF-1)-associated cutaneous findings, and several novel clinical manifestations, . These findings, if confirmed by additional data, could suggest a method for early risk stratification in JIIM patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Demographics and clinical features of 49 adult patients with juvenile idiopathic inflammatory myopathies

Clinical Diagnosis, %		
Juvenile dermatomyositis	75.5	
Juvenile polymyositis	10.2	
Juvenile connective tissue myositis (JCTM)	14.3	
Age, years, median [IQR]	24.0	[19.0-28.6]
Race, %		
Caucasian	59.2	
African American	11.1	
Hispanic	17.7	
Other[a]	12.0	
Female sex, %	81.6	
Age at diagnosis, years, median [IQR]	11.0	[8.5-15.7]
Disease duration at cross-sectional evaluation, years, median [IQR]	11.5	[4.5-18.9]
Delay to diagnosis, months, median [IQR]	6.0	[2.3-13.7]
Any myositis specific autoantibodies[b], %	67.5	
Anti-p155/p140 (TIF-1)	27.5	
Anti-MJ (NXP2)	22.5	
Anti-Jo1	7.5	
Anti-MDA5	5.0	
Anti-SRP	5.0	
Any myositis associated autoantibodies[b], %	40.0	
Anti-Ro60	20.0	
Anti-Ro52	17.1	
Anti-U1-RNP	12.5	
Other[c]	7.5	
Severity at onset Likert scale (0-4), median [IQR]	1.0	[1.0-2.0]
Disease Course, %		
Chronic continuous	63.3	
Polycyclic	30.6	
Monocyclic	6.1	
Height percentile at cross-sectional evaluation	30.7	[10.0-60.1]
Current physician global activity score 10 cm VAS, median [IQR]	1.6	[1.0-3.7]
Current physician global damage score 10 cm VAS, median [IQR]	3.0	[2.0-4.4]
Current HAQ score, median [IQR]	0.4	[0.0-1.0]
Current MMT26 score, 0-260[d], median [IQR]	229.0	[212.6-256.8]
ACR functional class, worst ever (1-4), median [IQR]	4.0	[3.0-4.0]
ACR functional class at cross-sectional evaluation (1-4), median [IQR]	2.0	[1.5-3.0]
Maximal number of medications ever used, median [IQR]	5.0	[3.0-8.0]
Prednisone ever used, %	100	

Methotrexate ever used, %	86.0	
IV methylprednisolone ever used, %	60.5	
IVIG ever used,%	60.5	
DMARDs ever used[e], %	59.1	
Biologic therapy ever used[f], %	31.8	
Cyclophosphamide ever used, %	17.5	
Number of medications at cross-sectional evaluation, median [IQR]	3.0	[1.0-4.0]
Prednisone at cross-sectional evaluation, %	56.5	
Methotrexate at cross-sectional evaluation, %	39.1	
IVIG at cross-sectional evaluation, %	38.6	
DMARDs at cross-sectional evaluation, %	32.6	
IV methylprednisolone at cross-sectional evaluation, %	15.6	
Biologic therapy at cross-sectional evaluation, %	9.1	
Cyclophosphamide at cross-sectional evaluation, %	2.3	

[a] Race was self-reported. “Other” includes Indian (n = 1), Yemeni (n = 1), Korean (n = 1), and Not Reported (n = 4).

[b] All autoantibodies were tested in 40 patients, except Anti-Ro52, which was tested in 35 patients.

[c] Other MAAs included anti-PM/Scl (2.5%), anti-La (2.5%), and anti-Smith (2.5%). 10%> of patients had multiple MAAs. The MSA anti-Mi-2 was not present in this cohort.

[d] MMT26 scores were available in 47 patients

[e] DMARDS included azathioprine (n = 14), cyclosporine (n = 12), mycophenolate mofetil (n = 13), and tacrolimus (n = 2).

[f] Biologics included abatacept (n= 2), adalimumab (n = 1), anakinra (n = 1), etanercept (n = 3), infliximab (n = 2), and rituximab (n = 11).

Abbreviations: ACR: American College of Rheumatology; DMARDs: Disease-Modifying Anti-Rheumatic Drugs; HAQ: Health Assessment Questionnaire; IQR: interquartile range; IV: intravenous; IVIG: intravenous immunoglobulin; JCTM: Juvenile connective tissue myositis; MMT26: Manual Muscle Testing-26; VAS: visual analog scale

Table 2:

Past and current disease manifestations of the 49 adult patients with juvenile idiopathic inflammatory myopathies.

	Ever present, N (%)	Maximal system Score[a], median [IQR]	Present within one month of evaluation, N (%)	System score at evaluation[a], median [IQR]
Any Muscular Features	49 (100)	4.0 [3.0-5.0]	44 (89.8)	3.0 [1.0-5.0]
Proximal weakness	48 (98.0)		34 (70.8)	
Distal weakness	35 (74.5)		20 (42.5)	
Atrophy	31 (64.6)		25 (52.1)	
Myalgia	31 (64.6)		19 (40.4)	
Falling episodes[b]	22 (59.5)		0 (0)	
Asymmetric weakness	16 (32.6)		16 (32.6)	
Any Cutaneous Features	47 (95.9)	8.0 [4.0-9.0]	44 (89.8)	6.0 [3.0-10.0]
Gottron's papules	43 (87.8)		31 (48.9)	
Periungual capillary changes	29 (84.4)		18 (63)	
Heliotrope rash	37 (78.7)		23 (7.9)	
Other erythema	37 (75.5)		25 (52.1)	
Malar rash	30 (61.2)		16 (34.0)	
Calcinosis	27 (56.3)		27 (55.1)	
Photosensitivity	26 (55.3)		19 (39.6)	
V-sign rash	24 (49.0)		16 (33.3)	
Cuticular overgrowth	22 (45.8)		16 (34.0)	
Mucous membrane lesions	18 (37.5)		13 (29.5)	
Lipodystrophy	14 (29.2)		16 (33.3)	
Raynaud phenomenon	13 (26.5)		7 (14.6)	
Shawl sign rash	11 (22.5)		10 (20.8)	
Cutaneous ulceration	7 (14.3)		5 (10.4)	
Mechanic hands	5 (10.4)		4 (8.3)	
Erythroderma	4 (8.2)		2 (4.2)	
Any Skeletal Features	44 (89.8)	2.0 [1.0-3.0]	33 (67.3)	1.0 [0.0-2.0]
Contractures	36 (75.0)		28 (58.3)	
Arthralgia	30 (62.5)		12 (26.1)	
Arthritis	26 (54.2)		13 (27.1)	
Any Constitutional Features	46 (93.9)	1.0 [1.0-2.0]	33 (67.3)	1.0 [0.0-1.0]
Fatigue	44 (89.8)		31 (66)	
Fever	16 (33.3)		2 (4.2)	
Adenopathy	13 (28.9)		5 (10.6)	
Any Gastrointestinal Features	30 (61.2)	1.0 [0.0-2.0]	20 (40.8)	0.0 [0.0-1.0]
Dysphagia	19 (38.8)		7 (14.6)	
Reflux	15 (31.3)		7 (14.6)	
Abdominal pain	12 (24.5)		6 (12.5)	

	Ever present, N (%)	Maximal system Score[a], median [IQR]	Present within one month of evaluation, N (%)	System score at evaluation[a], median [IQR]
Constipation	8 (16.3)		1 (2.1)	
Gastrointestinal ulceration	3 (6.1)		0 (0)	
Any Pulmonary Features	18 (36.7)	0.0 [0.0-1.0]	9 (17.8)	0.0 [0.0-0.0]
Abnormal PFTs[b]	14 (35.9)		7 (18.4)	
Dyspnea on exertion	14 (29.8)		4 (10.3)	
Dyspnea at rest	2 (4.2)		1 (2.4)	
Interstitial lung disease	2 (4.1)		2 (4.6)	
Total Features	49 (100)	16.0 [12.0-20.0]	48 (98.0)	13.0 [8.0-16.0]

[a]Clinical symptom score for each organ system was developed by determining the presence or absence of specific signs/symptoms ever present and within one month of cross-sectional evaluation from each of six major organ systems (3). System score at diagnosis was not available.

[b]All variables were evaluated in 45-49 patients, except for Abnormal PFTs, which was evaluated in 39 patients, and Falling episodes, which was evaluated in 37 patients.

Abbreviations: IQR: interquartile range; PFTs: pulmonary function tests

Table 3:

Myositis Damage Index scores of the 49 adult patients with juvenile idiopathic inflammatory myopathies at cross-sectional evaluation.

	Patients Affected N (%)	Extent of Damage Score Median [IQR]
Cutaneous Damage (0-5)[a]	39 (79.6)	2.0 [1.0-3.0]
Cutaneous scarring or atrophy	28 (59.6)	
Calcinosis	27 (55.1)	
Lipodystrophy	16 (33.3)	
Alopecia	8 (16.3)	
Poikiloderma	6 (12.5)	
Muscle Damage (0-3)	28 (77.6)	2.0 [1.0-3.0]
Weakness	35 (71.4)	
Muscle Dysfunction	31 (64.7)	
Muscle Atrophy	24 (49.0)	
Skeletal Damage (0-4)	32 (65.3)	1.0 [0.0-2.0]
Joint Contracture	31 (63.3)	
Deforming Arthropathy	8 (16.7)	
Osteoporosis with fracture	4 (8.2)	
Avascular Necrosis	2 (4.1)	
Endocrine Damage (0-6)[b]	15 (30.6)	0.0 [0.0-1.0]
Irregular Menses	10 (32.3)	
Hirsutism	7 (14.9)	
Diabetes	6 (12.2)	
Amenorrhea	4 (12.1)	
Infertility	1 (3.2)	
Pulmonary Damage (0-4)	9 (18.4)	0.0 [0.0-0.0]
Impaired lung function	7 (14.6)	
Dysphonia	4 (8.2)	
Pulmonary Fibrosis	1 (2.1)	
Ocular Damage (0-2)	7 (14.3)	0.0 [0.0-0.0]
Cataract	4 (8.3)	
Vision Loss	3 (6.1)	
Gastrointestinal Damage (0-3)	6 (12.2)	0.0 [0.0-0.0]
Dysmotility	5 (10.2)	
Dysphagia	3 (6.1)	
Infection (0-2)	5 (10.4)	0.0 [0.0-0.0]
Chronic Infection	5 (10.4)	
Multiple Infections	4 (8.3)	
Cardiovascular Damage (0-4)	4 (8.2)	0.0 [0.0-0.0]
Hypertension	4 (8.2)	
Peripheral Vascular Damage (0-4)	4 (8.2)	0.0 [0.0-0.0]
Tissue or pulp loss	4 (8.2)	

	Patients Affected N (%)	Extent of Damage Score Median [IQR]
Digit or limb loss	1 (2.0)	
Malignancy (0-1)[c]	1 (2.0)	0.0 [0.0-0.0]
Total Damage (0-38)	47 (95.9)	6.0 [3.5-8.9]

[a]Items with a frequency of zero included gastrointestinal infarction, ventricular dysfunction, angina, myocardial infarction, pulmonary hypertension, thrombosis, claudication, and sexual dysfunction and are not shown in the table. Numbers and percentages associated with organ system headers represent any damage in a particular system. Values in parentheses represent the potential score range for each system.

[b]Irregular menses, amenorrhea, and infertility were evaluated in 31-33 patients (female patients only). All other variables were evaluated in 47-49 patients.

[c]One patient had papillary carcinoma of the thyroid

Abbreviations: IQR: Interquartile range

Table 4:

Top factors associated with the Myositis Damage Index score at cross-sectional evaluation in 49 adult patients with juvenile idiopathic inflammatory myopathies.

	Bivariate Analysis		Multivariable Regression		
Predictors of MDI Score	**Corr. Coef.[a]**	**P value**	**Est[b]**	**SE**	**P value[c]**
Erythroderma (ever)	0.42	**0.003**	3.94	1.50	**0.01**
Shawl sign (ever)	0.35	**0.01**	2.71	0.94	**0.006**
Wheelchair (ever)	0.31	**0.03**			
Disease duration (per year)	0.31	**0.03**	0.08	0.04	**0.04**
Age at diagnosis (per year)	−0.30	**0.04**			
Falling episodes (ever)[d]	0.34	**0.04**			
Gottron's papules (ever)	0.29	**0.04**			
Clinical subgroup (JDM, JPM, JCTM)	NA	**0.04**			
Worst ACR functional class (per level)	0.28	**0.05**	1.31	0.37	**0.001**
Azathioprine use (ever)	0.28	**0.05**			
Disease course	NA	**0.05**			
Ulceration (ever)	0.25	0.09			
Malar rash (ever)	0.23	0.11			
Antinuclear antibodies'[d]	0.26	0.12			
Cuticular overgrowth (ever)	0.22	0.13			
Heliotrope rash (ever)	0.22	0.13	2.06	1.01	**0.05**
Number of DMARDs used	0.21	0.14			

[a]Point-biserial correlation coefficient for dichotomous variables; Spearman correlation coefficient for ordinal or continuous variables; correlation coefficient not applicable for 3-level categorical variables (p-value based on analysis of variance test).

[b]Estimated slope (b)

[c]P-values are not adjusted for model selection and therefore may overstate the significance of the associations.

[d]For falling episodes, N = 37; for antinuclear antibodies, N = 38. Due to missing data, these variables were not included in the multivariable model.

Blank cells represent variables that were removed during backward selection of the multivariable model.

Abbreviations: ACR: American College of Rheumatology; DMARDs: Disease-Modifying Anti-Rheumatic Drugs; JCTM: juvenile connective tissue overlap myositis; JDM: juvenile dermatomyositis; JPM: juvenile polymyositis; NA: not applicable; MDI: Myositis Damage Index; SE: standard error

Table 5:

Top factors associated with the presence of calcinosis using bivariate analysis at cross-sectional evaluation in 49 adult patients with juvenile idiopathic inflammatory myopathies

Predictors of Calcinosis	Odds Ratio (95% CI)	P value
Gottron's papules (ever)	[a]	**0.005**
Disease duration (per year)	1.12 (1.03-1.21)	**0.006**
Constipation (ever)	[b]	**0.006**
Periungual capillary changes (ever)	8.65 (1.63-46.08)	**0.007**
Age at diagnosis (per year)	0.81 (0.70-0.95)	**0.008**
Falling episodes (ever)[c]	5.89 (1.38-25.23)	**0.01**
Clinical subgroup (JDM, JPM, JCTM)	[c]	**0.01**
Lipodystrophy (ever)	5.07 (1.21-21.28)	**0.02**
Contractures (ever)	3.98 (1.02-15.51)	**0.04**

[a]Odds ratio could not be calculated: 62.8% of patients with history of Gottron's papules and 0.0% of those without Gottron's papules had calcinosis at last assessment.

[b]Odds ratio could not be calculated: 100.0%> of patients with history of constipation and 46.3%> of those without constipation had calcinosis at last assessment.

[c]Odds ratio could not be calculated: 57.1%> of JCTM patients, 62.2% of JDM patients, and 0.0%> of JPM patients had calcinosis at last assessment.

Abbreviations: CI: confidence interval; JCTM: juvenile connective tissue overlap myositis; JDM: juvenile dermatomyositis; JPM: juvenile polymyositis