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Myositis autoantibodies, clinical features, and environmental exposures at illness onset are associated with disease course in juvenile myositis

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Abstract

Objective—To identify early factors associated with disease course in patients with juvenile idiopathic inflammatory myopathies (JIIM).

Methods—Univariable and multivariable multinomial logistic regression analyses were performed in a large JIIM registry (n=365), including demographics, early clinical features, serum muscle enzyme levels, myositis autoantibodies, environmental exposures, and immunogenetic polymorphisms.

Results—Multivariable associations with chronic or polycyclic courses compared to monocyclic included myositis-specific autoantibodies (multinomial odds ratio (M-OR) 4.2 and 2.8, respectively), myositis-associated autoantibodies (M-OR 4.8 and 3.5), and a documented infection within six months of illness onset (M-OR 2.5 and 4.7). A higher overall clinical symptom score at diagnosis was associated with chronic or monocyclic courses compared to polycyclic.

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Furthermore, a severe illness onset was associated with chronic compared to monocyclic or polycyclic courses (M-OR 2.1 and 2.6), while anti-p155/140 autoantibodies were associated with chronic or polycyclic courses compared to monocyclic (M-OR 3.9 and 2.3). Additional univariable associations of chronic compared to monocyclic course included photosensitivity, “V-sign” or “Shawl-sign” rashes, and cuticular overgrowth (OR 2.2–3.2). The mean and highest ultraviolet index in the month before diagnosis were associated with a chronic compared to polycyclic course in boys (OR 1.3 and 1.5), while residing in the Northwest was less frequently associated with a chronic course (OR 0.2).

Conclusion—Myositis autoantibodies, in particular anti-p155/140, and a number of early clinical features and environmental exposures were associated with a chronic course in patients with JIIM. These findings suggest early factors can be identified that are associated with poorer outcomes in JIIM.

Keywords

juvenile idiopathic inflammatory myopathies; myositis; juvenile dermatomyositis; p155/140 autoantibodies; disease course; environmental factors

The juvenile idiopathic inflammatory myopathies (JIIM) embody a heterogeneous group of systemic autoimmune diseases affecting muscle, skin and internal organs. Juvenile dermatomyositis (JDM) is the most common clinicopathological form of JIIM. Additional phenotypes with higher morbidity and mortality are juvenile polymyositis (JPM), without the characteristic rashes of JDM, and juvenile connective tissue myositis (JCTM), in which patients meet the criteria for JIIM and at least one other autoimmune disease (1,2). The disease courses of JIIM can be distinguished into three types: monocyclic, polycyclic, and chronic (3,4). Long-term outcome studies have indicated that patients with JDM with a chronic disease course display greater disability, weakness, and disease damage, as well as more frequent calcinosis and lipodystrophy (3,5–7). Patients with a chronic course also require long-term immunosuppressive therapy (4).

Several factors available at the time of diagnosis have been reported to be associated with a chronic disease course, including the tumor necrosis factor α (TNFα)-308A allele (8), extensive myopathic and severe arteropathic changes in affected muscle tissue (9), longer duration of untreated disease, higher baseline skin activity (10), and age at illness onset >3 years (11). However, these studies were relatively small, only included the JDM phenotype, and were often not replicated (10,12,13). Furthermore, they explored only a few potentially relevant determinants.

The current study examined the association of a number of factors with disease course in a large JIIM population, including demographics, early clinical and laboratory features, environmental exposures, and immunogenetic polymorphisms.

PATIENTS AND METHODS

Patients and study design

This study included 365 patients from the United States (U.S.) and Canada who had probable or definite JDM, JPM, and JCTM by Bohan and Peter criteria (14). The patients were enrolled in investigational review board-approved natural history studies of myositis and signed informed consent, as previously described (2). This included a national registry study at the U.S. Food and Drug Administration (FDA) from 1990–2002 (n=219), and specific myositis protocols at the National Institutes of Health (NIH) Clinical Research Center in Bethesda, MD, from 1993–2012 (n=146), including one multi-center protocol. Additional exclusion criteria for the current study were a diagnosis before 1980 (n=16) and an undefined disease course, with <2 years of follow-up after diagnosis (n=73). Of the 365 included patients, 300 were diagnosed before the year 2000. The median follow-up time after diagnosis was 4.8 years (interquartile range (IQR): 3.0 to 7.8).

Disease course was classified as monocyclic if the patient achieved remission with or without immunosuppressive treatment, without evidence of active disease within 2 years of diagnosis, based on the treating physician's assessment of muscle strength, skin rashes and other clinical features, and laboratory testing of serum muscle enzymes that indicate no signs of active disease; as polycyclic if the patient had recurrence of active disease after a definite clinical remission; and as chronic if active disease persisted for more than 2 years, despite immunosuppressive treatment (3).

Variables

Variables examined included demographics, early clinical features present prior to or at diagnosis (see Supplementary appendix), laboratory features (highest recorded serum muscle enzyme levels and the presence of myositis autoantibodies), environmental exposures at illness onset or diagnosis, and immunogenetic polymorphisms ((2,15) for detailed information). Severity of illness onset, up to the time of diagnosis, was graded on a 4-point Likert scale as determined by the enrolling physician and analysed in two categories (mild/moderate and severe/very severe disease activity). A symptom score was developed based on the presence or absence of signs or symptoms prior to or at diagnosis for each organ system (i.e. muscle, joint, cutaneous, gastrointestinal, pulmonary, cardiac, and constitutional systems), which was defined as the number of symptoms present related to that system prior to or at diagnosis, divided by the number of symptoms assessed; values ranged from 0 to 1. The overall clinical symptom score, which included 45 symptoms, was calculated by averaging scores of the seven organ systems (see Supplementary appendix).

Patient sera from the time of enrollment (median 2.1 years after diagnosis, *IQR* 3.3) were tested for myositis autoantibodies (see footnote Table 1) by validated methods, including protein and RNA immunoprecipitation (IP) using radiolabeled HeLa or K562 cell extracts and double immunodiffusion (2). For anti-p155/140, anti-MJ, and anti-MDA5 autoantibodies, serum samples were screened by IP, with confirmation testing by IP-blotting (16).

Environmental exposures included the mean and highest ultraviolet (UV) index within 30 days of illness onset and within 30 days of diagnosis, geographic zone, geoclimatic zone, and planting zone, (http://planthardiness.ars.usda.gov?PHZMWeb/), based on each patient's residential location at illness onset (17). These were assessed only in patients residing in the U.S. For the UV index, we analyzed all patients together, and then conducted separate analyses by race, as well as by gender (17). Season and month of illness onset, and documented infections within six months of illness onset were also examined (18).

Polymorphic immunogenetic loci previously investigated as potential risk and protective factors for JIIM were assessed for associations with disease course in Caucasian patients. This included alleles and genotypes of TNF-α (−308 and −238), interleukin (IL)-1α (−889 and +4845), and IL-1β (−511 and +3953) (12), MHC DRB1 and DQA1 alleles and binding motifs (19), and immunoglobulin allotypes and phenotypes (20).

Statistical methods

Analyses were performed using SPSS Statistics for Windows (Version 21.0., IBM Corporation, Armonk, NY) and were considered exploratory. Univariable analysis for continuous variables was conducted using Kruskal-Wallis to test for differences among all three disease courses, followed by examination of pairwise differences using the Wilcoxon Rank Sum test. For nominal and ordinal variables, a Chi-Square or Fisher Exact test was used. Univariable associations were considered probable ($p<0.01$) or possible ($p<0.05$). Missing data were noted when exceeding 5%.

Multivariable multinomial logistic regression with backward elimination was conducted to further identify factors that were independently associated with disease course. All variables from the univariable analysis with an overall p-value of <0.05 were included. These variables were distributed into two different analyses to avoid overlapping variables: a *General analysis* (n=296), which included umbrella variables (e.g. any myositis-specific autoantibodies) and a *Specific analysis* (n=226), which included specific variables (e.g. anti-p155/140 autoantibodies). Variables were removed from the model when the likelihood ratio p-value was ≥0.05. To decrease the number of missing values on which the multinomial odds ratios were based, analyses were redone, including only variables with a likelihood ratio p-value <0.05 in the multinomial logistic regression. Consequently, the General and Specific analysis included finally 297 and 342 patients.

Some variables had an overall p-value <0.05 in the univariable analysis, but could not be included in the multivariable analyses because of their low frequencies. These included dyspnea at rest, palpitations, and syncope. Serum aldolase was also not included in the multivariable analyses due to 15% missing values. MDA-5 autoantibodies, the immunogenetic polymorphisms and UV index were *a priori* excluded from multivariable analysis, as they were assessed in a subset of patients.

RESULTS

Univariable associations of early clinical and laboratory features with disease course

Table 1 presents results of the univariable analyses for key demographics, as well as significant associations of early clinical and laboratory features with disease course. No associations with disease course were found for age at illness onset or diagnosis, delay to diagnosis, gender, race, and clinical subgroup.

Chronic vs monocyclic course

Probable associations with a chronic compared to monocyclic course included photosensitivity (odds ratio (OR) [95% confidence interval (95%CI)] 2.9 [1.5–5.8]), cuticular overgrowth (OR 3.2 [1.4–7.5]), the presence of any myositis-specific autoantibodies (OR 2.9 [1.6–5.3], including anti-MDA5 autoantibodies) and in particular anti-p155/140 autoantibodies (OR 3.6 [1.9–7.0]), as well as any myositis-associated autoantibodies (OR 3.2 [1.3–7.9]) and in particular anti-Ro autoantibodies (OR 10.0 [1.3–76.9]). Possible associations included severe illness at onset (OR 1.7 [1.0–3.1]) and “V-sign” and/or “Shawl-sign” rashes (OR 2.2 [1.0–4.9]).

Polycyclic vs monocyclic course

Elevated aldolase level (OR 4.4 [1.4–13.9]) had a probable association with a polycyclic compared to monocyclic course. Possible associations with a polycyclic compared to monocyclic course included a lower clinical symptom score (OR 0.05 [0.0–0.8] per 0.01 unit increase in score), any myositis-specific autoantibodies (OR 2.1 [1.1–3.8], not including anti-MDA5 autoantibodies) and in particular anti-p155/140 autoantibodies (OR 2.3 [1.1–5.0]). Contractures (OR 0.4 [0.2–0.9]), weight loss (OR 0.4 [0.2–0.9]), and distal weakness (OR 0.4 [0.2–0.9]) were less frequently observed in a polycyclic compared to monocyclic course.

Chronic vs polycyclic course

Probable associations with a chronic compared to polycyclic course included severe illness onset (OR 2.7 [1.4–5.0]), “V-sign” and/or “Shawl-sign” rashes (OR 3.2 [1.3–8.0]), contractures (OR 2.6 [1.3–5.0]), and weight loss (OR 2.5 [1.3–4.7]). Patients with a chronic illness course had a higher clinical symptom score (OR 48 [4–556] per 0.01 unit increase in score). Dyspnea at rest was possibly associated with a chronic compared to polycyclic course (OR 8.5 [1.1–66.7]).

Other variables

Other clinical and laboratory features were not found to be associated with disease course, including the muscle and cutaneous system scores, as well as anti-nuclear antibodies and other serum muscle enzyme levels. Some symptoms were only observed in patients developing a chronic course, although infrequent, including gastrointestinal bleeding and ulceration, abdominal perforation, pneumothorax or pneumomediastinum (n=1 each). All six patients with anti-signal recognition particle (SRP) autoantibodies had JPM with a chronic

course, and removal of these patients did not impact the overall findings. Syncope was present in two patients developing a polycyclic course.

All variables that were significant in the univariable analyses of the JIIM group were also examined in the JDM subgroup. Significant associations with disease course in JIIM overall were also significant for patients with JDM, except for weight loss (p=0.1), palpitations (p=0.3), dyspnea at rest (p=0.2), and elevated aldolase level (p=0.1). In the JDM subgroup, antip155/140 autoantibodies were also associated with a chronic course (overall p=0.00002); chronic vs. monocyclic: OR 4.8 [2.4–9.7], p=0.000005; polycyclic vs. monocyclic: OR 2.5 [1.1–5.6], p=0.03; and chronic vs. polycyclic: OR 1.9 [1.0–3.6], p = 0.04).

Univariable associations of environmental exposures and immunogenetic polymorphisms with disease course

Table 2 presents significant univariable associations of environmental exposures and immunogenetic polymorphisms with disease course. A documented infection within six months of illness onset was probably associated with a polycyclic compared to monocyclic course (OR 3.2 [1.4–7.4]). A higher mean and highest UV index in the month before diagnosis was probably associated with a chronic compared to polycyclic course in boys (OR 1.5 [1.1–2.1] and 1.3 [1.1–1.7] per 0.01 unit increase in UV index, respectively). A higher average UV index in the month before diagnosis was possibly associated with a polycyclic compared to monocyclic course in Caucasian girls (OR 1.3 [1.1–1.6] per 0.01 unit increase in UV index). No associations with disease course and the mean or highest UV index were observed in African American patients. The season and month of illness onset also did not differ among disease courses. Patients with a chronic course were less likely to reside in the Northwest geoclimatic zone of the U.S. at illness onset, compared to those with a monocyclic or polycyclic course (ORs 0.2 [0.1–0.6]). Geographic regions and planting zones were not found to be associated with disease course. Significant variables in the overall group were also significant in the JDM subgroup, except for the mean UV index in the month before diagnosis in Caucasian girls.

There were no clear associations of disease course with HLA alleles, cytokine polymorphisms of TNF-α, IL-1α, and IL-1β, or immunoglobulin allotypes and phenotypes. The only exception was a possible association of HLA-DRB1*1501, which was present less frequently in Caucasian patients developing a chronic or polycyclic course compared to a monocyclic course (OR 0.2 [0.1–0.8] or 0.2 [0.0–0.9], respectively). The TNFα-308A allele had a similar frequency in patients with monocyclic (64%), polycyclic (59%), and chronic courses (66%).

Multivariable associations with disease course

Table 3 presents results of the multivariable analyses. In the *General analysis*, independent associations with a chronic or polycyclic compared to monocyclic course included the presence of any myositis-specific autoantibodies (multinomial OR (M-OR) [95%CI] 4.2 [2.2–7.9] or 2.8 [1.4–5.8], respectively), any myositis-associated autoantibodies (M-OR 4.8 [1.8–12.9] or 3.5 [1.1–11.1]), and a documented infection within six months of illness onset (M-OR 2.5 [1.0–5.8] or 4.7 [1.9–11.9]). In the same analysis, a higher overall clinical

symptom score was associated with a chronic compared to polycyclic course (M-OR 146 [8–2526] per 0.01 unit increase in score), and a lower score was associated with a polycyclic compared to monocyclic course (M-OR 0.02 [0.0–0.6] per 0.01 unit increase in score).

In the *Specific analysis*, the presence of anti-p155/140 autoantibodies was associated with a chronic or polycyclic compared to monocyclic course (M-OR 3.9 [2.0–7.7] or 2.3 [1.1–5.0], respectively). Severe illness at onset was associated with a chronic compared to monocyclic (M-OR 2.1 [1.2–3.8]) or polycyclic course (2.6 [1.4–4.9]).

When the multivariable analyses were done with only the JDM subgroup, the same variables were included in the model and comparable odds ratios and *p*-values were found (data not shown).

DISCUSSION

The current study examined the association of demographics, early clinical features, laboratory features (serum muscle enzyme levels and myositis autoantibodies), environmental exposures, and immunogenetic polymorphisms with disease course in a large national population of patients with JIIM. We found several factors that were associated with disease course. This study is of additional value as we investigated a relatively large group of JIIM patients, included not only patients with JDM, but also patients with JPM and JCTM, and explored new potentially relevant associations.

The presence of any myositis-specific autoantibodies, in particular, anti-p155/140 autoantibodies, and any myositis-associated autoantibodies, were associated with a chronic course, and to a smaller degree, also with a polycyclic course. The clinical utility of myositis-specific autoantibodies in predicting prognosis in both adult and juvenile onset myositis has been noted by others (1,15).

Our results suggest that early cutaneous features present prior to or at diagnosis are associated with a chronic course. This is consistent with other studies which found an association of skin disease activity at diagnosis and persisting beyond the first several months of illness with a polycyclic or chronic course (10,21). In the multivariable analyses, these cutaneous features were not of additional value as compared to anti-p150/140 autoantibodies, as they are strongly associated with anti-p155/140 autoantibodies (15).

We showed for the first time associations between early environmental exposures with disease course in patients with JIIM. A higher UV index close to diagnosis was associated with a chronic course, consistent with our finding that patients with a chronic course were less likely to have resided in the Northwest region of the U.S. at the time of illness onset, a geographic zone with a relatively low UV index (17). We did not have information on personal UV exposure in individual patients at illness onset or during the course of illness, as the UV index data is based only on residential location and ground surface measurements, without information about time spent outdoors, travel, and the use of photoprotective measures (17). The role of UV exposure on influencing disease course needs further study. This study also indicated that infections within 6 months of illness onset were associated with a polycyclic and chronic course. Infections have been previously reported to be

associated with the onset of illness in JDM (18,22,23), but the association of infections in proximity to illness onset with long-term outcomes has not been examined before.

Delay to diagnosis was associated with a chronic course in an earlier study (10), but it was not associated with disease course in our study and in others (8,21). Patients with a longer delay to diagnosis may have a milder disease phenotype with a more gradual onset, which may explain the lack of association (24). Our data confirmed earlier studies that gender (8,10,21) and ethnicity (21) were not associated with disease course. Age at illness onset was associated with disease course in one study (11), but this was not confirmed here or in other studies (8–10,13,21). The presence of the TNFα-308A allele was associated with a chronic course in an earlier study (8), but not subsequently (10) nor in our study.

Some variables were not found to be associated with disease course, but could be clinically relevant. First, several symptoms, including gastrointestinal bleeding, abdominal perforation, and pneumothorax or pneumomediastinum, as well as anti-SRP autoantibodies, were present only in patients developing a chronic disease course, but these did not reach statistical significance due to their infrequent occurrence. Other variables, including dyspnea at rest, palpitations, and syncope, reached significance in univariable analysis, but could not be included in the multivariable analysis. These features had insufficient statistical power due to their infrequent presentation, but they still could be clinically relevant. Registries of larger size are required to determine the relevance of these factors in predicting disease course. Furthermore, calcinosis, lipodystrophy and cutaneous ulcerations are not typically present at onset or diagnosis, as analysed in this study, but have been found in some cohorts to be associated with a chronic illness course or longstanding active disease in patients with JIIM (5,25).

This study has several limitations. The presence of myositis autoantibodies was determined at study enrollment, with a median of 2.1 years after diagnosis, and consequently the results could have been affected by medication or disease inactivity (26). We also did not quantify the severity of muscle and skin involvement and disease activity utilizing validated disease activity measures, such as the Childhood Myositis Assessment Scale, the Myositis Disease Activity Assessment Tool, and the Disease Activity Score, as these were not part of the data collection for this registry. In contrast, other JDM cohorts have shown strong associations between disease activity in muscle and skin early in the course of illness with disease course and long term damage in JIIM (10,27,28,29). In addition, illness severity at onset, an important factor that is associated with disease course, is difficult to operationalize and its definition may have changed throughout the study period, which covers several decades. However, we examined the clinical symptom score and specific organ system scores, as potentially more objective measures of the extent of involvement and thus, a possible surrogate for illness severity.

For this exploratory study, correction for multiple comparisons was not performed. Therefore, the univariable results were treated cautiously in describing probable and possible associations, and results from this study require confirmation. It should also be noted that the multivariable results should not be interpreted as a model that could adequately predict disease course.

Treatment regimens changed during the study period, including the introduction of various corticosteroid-sparing immunosuppressive drugs and biologic therapies (30). Unfortunately, treatment data were not available in this study and future studies should investigate whether treatment has an effect on disease course. Additional limitations of the data from this registry were previously described (2,15).

In conclusion, myositis-specific and -associated autoantibodies, specifically anti-p155/140 autoantibodies, and a number of clinical features and environmental exposures at illness onset or diagnosis were associated with a chronic disease course in patients with JIIM. These findings suggest that early factors can be identified that are associated with poorer outcomes in JIIM. Future studies are needed to confirm these associated factors and to identify their value in prognosis.

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Appendix

Members of the Childhood Myositis Heterogeneity Study Group who participated in the current study

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Table 1

Key demographics and significant univariable associations of early clinical and laboratory features with disease course in patients with juvenile idiopathic inflammatory myopathies.

Variable	Number (%) or Median (interquartile range)			Overall p-value	Odds ratio [95% confidence interval]		
	Monocyclic (n=88)	Polycyclic (n=86)	Chronic (n=191)		Chronic vs. Monocyclic	Polycyclic vs. Monocyclic	Chronic vs. Polycyclic
Demographics							
Age at diagnosis, *years*	7.5 (4.7–12.5)	6.5 (4.6–11.8)	8.1 (5.6–11.6)	0.3	NA	NA	NA
Delay to diagnosis, *months*	3.0 (1.4–7.4)	4.0 (2.0–9.0)	4.3 (2.0–11.7)	0.2	NA	NA	NA
Female gender	60 (68)	65 (76)	140 (73)	0.5	NA	NA	NA
Race				0.1	NA	NA	NA
Caucasian	62 (71)	62 (72)	116 (61)				
African American	10 (11)	9 (11)	39 (20)				
Other	16 (18)	15 (17)	36 (19)				
Clinical subgroup							
Juvenile dermatomyositis	76 (86)	69 (80)	150 (79)	0.4	NA	NA	NA
Juvenile polymyositis	6 (7)	8 (9)	14 (7)				
Juvenile connective tissue myositis*	6 (7)	9 (11)	27 (14)				
Clinical features							
Severe illness onset	23 (26)	16 (19)	73 (38)	0.003	1.7 [1.0–3.1]	NS	2.7 [1.4–5.0]
Photosensitivity‡	12 (15)	18 (24)	59 (34)	0.005	2.9 [1.5–5.8]	NS	NS
“V-sign” and/or “Shawl-sign” rashes†	9 (11)	6 (8)	38 (21)	0.008	2.2 [1.0–4.9]	NS	3.2 [1.3–8.0]
Contractures†	28 (32)	14 (17)	59 (35)	0.01	NS	0.4 [0.2–0.9]	2.6 [1.3–5.0]
Cuticular overgrowth ‡	7 (8)	14 (19)	38 (23)	0.02	3.2 [1.4–7.5]	NS	NS
Weight loss	28 (33)	14 (17)	63 (34)	0.02	NS	0.4 [0.2–0.9]	2.5 [1.3–4.7]
Palpitations	0 (0)	4 (5)	2 (1)	0.03	NS	NS	NS
Dyspnea at rest	4 (5)	1 (1)	17 (9)	0.03	NS	NS	8.5 [1.1–66.7]
Syncope	0 (0)	2 (2)	0 (0)	0.04	NA	NS	NS
Distal weakness†	37 (45)	20 (26)	69 (38)	0.05	NS	0.4 [0.2–0.9]	NS
Overall clinical symptom score [0–1]§	0.23 (0.14–0.31)	0.18 (0.12– 0.25)	0.23 (0.14–0.32)	0.01	NS	0.05 [0.0–0.8]	48 [4–556]
Laboratory features							

Variable	Number (%) or Median (interquartile range)			Overall p-value	Odds ratio [95% confidence interval]		
	Monocyclic (n=88)	Polycyclic (n=86)	Chronic (n=191)		Chronic vs. Monocyclic	Polycyclic vs. Monocyclic	Chronic vs. Polycyclic
Aldolase elevated‡	58 (79)	68 (94)	143 (87)	0.03	NS	4.4 [1.4–13.9]	NS
Any myositis-specific autoantibodies† || (not including anti-MDA5)	38 (45)	50 (63)	122 (69)	0.001	2.7 [1.6–4.7]	2.1 [1.1–3.8]	NS
Any myositis-specific autoantibodies (including anti-MDA5)‡ ||	47 (60)	53 (75)	132 (81)	0.002	2.9 [1.6–5.3]	NS	NS
Anti-p155/140 autoantibodies†	13 (15)	24 (30)	70 (40)	0.0004	3.6 [1.9–7.0]	2.3 [1.1–5.0]	NS
Any myositis-associated autoantibodies¶	6 (7)	12 (14)	35 (19)	0.03	3.2 [1.3–7.9]	NS	NS
Anti-Ro autoantibodies	1 (1)	4 (5)	19 (10)	0.01	10.0 [1.3–76.9]	NS	NS

*Connective tissue diseases that were associated with myositis included: systemic lupus erythematosus (n=11), juvenile idiopathic arthritis (n=8), systemic sclerosis (n=7), localized scleroderma (n=5), insulin-dependent diabetes (n=3), psoriasis (n=2), Sjögren's syndrome (n=2), eosinophilic fasciitis (n=2), discoid lupus (n=1), juvenile idiopathic arthritis and systemic lupus erythematosus (n=1).

†5–10% missing data;

‡10–15% missing data; otherwise: <5% missing data.

§Odds ratio: per 0.01 increase in overall clinical symptom score.

||Any myositis-specific autoantibodies included anti-p155/140 (present in n=107 patients), anti-MJ (n71), anti-MDA5 (n=56), anti-Jo1 (n=10), anti-PL-12 (n=5), anti-KS (n=1), anti-Mi-2 (n=10), and anti-SRP (n=6). Anti-PL-7, anti-OJ, anti-Zo, anti-EJ, and anti-Ha autoantibodies were also tested, but were not observed.

¶Any myositis-associated autoantibodies included anti-Ro (n=24), anti-U1-RNP (n=19), anti-U2-RNP (n=1), anti-U5-RNP (n=1), anti-PM-Scl (n=11), anti-Sm (n=4), anti-La (n=3), anti-Ku (n=2), anti-Th (n=1), anti-SUMO (n=1), and anti-TMG cap (n=1) autoantibodies. Anti-U3-RNP and anti-U4-RNP were also tested, but were not observed. The sera from 81 patients had no identified myositis-specific (including anti-MDA5 autoantibodies) or -associated autoantibodies.

NA: Not applicable; NS: not significant (i.e. $p \geq 0.05$).

Table 2

Significant univariable associations of environmental exposures and immunogenetic polymorphisms with disease course in patients with juvenile idiopathic inflammatory myopathies.

Variable	Number (%) or Median (interquartile range)			Overall p-value	Odds ratio [95% confidence interval]		
	Monocyclic (n=88)	Polycyclic (n=86)	Chronic (n=191)		Chronic vs. Monocyclic	Polycyclic vs. Monocyclic	Chronic vs. Polycyclic
Any infection within six months of illness onset[||]	9 (12)	23 (30)	34 (20)	0.02	NS	3.2 [1.4–7.4]	NS
Gastrointestinal infection within six months of illness onset[‡]	0 (0)	4 (5)	2 (1)	0.04	NS	NS	NS
Mean ultraviolet index, 30 days before diagnosis, boys[†]	3.7 (1.9–6.1)	2.5 (1.4–3.7)	4.8 (2.2–6.9)	0.01	NS	NS	1.5 [1.1–2.1]
Highest ultraviolet index, 30 days before diagnosis, boys[†]	5.4 (3.4–8.2)	3.9 (2.6–5.3)	7.4 (4.0–8.8)	0.03	NS	NS	1.3 [1.1–1.7]
Mean ultraviolet index, 30 days before diagnosis, Caucasian girls[†]	4.3 (1.2–5.6)	5.7 (4.0–6.6)	4.6 (2.2–6.1)	0.03	NS	1.3 [1.1–1.6]	NS
Northwest geoclimatic zone at illness onset[*]	16 (19)	16 (20)	10 (6)	0.0004	0.2 [0.1–0.6]	NS	0.2 [0.1–0.6]
HLA-DRB1[*]1501 (Caucasians only)[¶]	8 (22)	2 (5)	6 (7)	0.01	0.2 [0.1–0.8]	0.2 [0.0–0.9]	NS

[*] Nine geoclimatic zones were defined. Univariable analysis including all nine zones comparing the three disease courses gave an overall p-value of 0.04; sub-analyses were done for the each geoclimatic zone separately; only the Northwest geoclimatic zone was significantly associated with disease course.

[†] Odds ratio: per 0.01 unit increase in ultraviolet index.

[‡] 5–10% missing data;

[||] 10–15% missing data;

[¶] Available in 169 of 240 Caucasians.

NS: not significant (i.e. $p \geq 0.05$).

Table 3

Significant associations with disease course in patients with juvenile idiopathic inflammatory myopathies from multinomial logistic regression analyses.

	p-value Likelihood ratio test	Multinomial odds ratio [95% confidence interval]		
		Chronic vs. Monocyclic	**Polycyclic vs. Monocyclic**	**Chronic vs. Polycyclic**
Significant determinants from *General analysis*[†]		**n=73**	**n=71**	**n=153**
Any myositis-specific autoantibodies[#]	0.00002	4.2 [2.2–7.9]	2.8 [1.4–5.8]	NS
Any myositis-associated autoantibodies	0.003	4.8 [1.8–12.9]	3.5 [1.1–11.1]	NS
Any infections within six months of illness onset	0.002	2.5 [1.0–5.8]	4.7 [1.9–11.9]	NS
Overall clinical symptom score[*]	0.002	NS	0.02 [0.0–0.6]	146 [8–2526]
Significant determinants from *Specific analysis*[‡]		**n=85**	**n=80**	**n=177**
Anti-p155/140 autoantibodies	0.00008	3.9 [2.0–7.7]	2.3 [1.1–5.0]	NS
Severe illness onset	0.002	2.1 [1.2–3.8]	NS	2.6 [1.4–4.9]

[*] Odds ratio: per 0.01 increase in overall clinical symptom score.

[†] Removed from the model in General analysis in backward elimination: severe illness onset

[#] Anti-MDA5 autoantibodies were not included in the variable “any myositis-specific autoantibodies” in the multinomial logistic regression analysis, as 54 patients’s sera were not tested for this autoantibody.

[‡] Removed from the model in Specific analysis in backward elimination: photosensitivity, “V-sign” and/or “Shawl-sign” rashes, contractures, cuticular overgrowth, weight loss, distal weakness, anti-Ro autoantibodies, geoclimatic zone at illness onset, and gastrointestinal infection within six months of illness onset.

NS: not significant (i.e. $p \geq 0.05$).

Data was adjusted for the included variables ($p < 0.05$) in each model.