Environmental factors preceding illness onset differ in phenotypes of the juvenile idiopathic inflammatory myopathies

Lisa G. Rider, Lan Wu, Gulnara Mamyrova, Ira N. Targoff, and Frederick W. Miller on behalf of the Childhood Myositis Heterogeneity Collaborative Study Group*

Abstract

Objective. To assess whether certain environmental factors temporally associated with the onset of juvenile idiopathic inflammatory myopathies (JIIMs) differ between phenotypes.

Methods. Physicians completed questionnaires regarding documented infections, medications, immunizations and an open-ended question about other noted exposures within 6 months before illness onset for 285 patients with probable or definite JIIM. Medical records were reviewed for 81% of the patients. Phenotypes were defined by standard clinical and laboratory measures.

Results. Sixty per cent of JIIM patients had a reported exposure within 6 months before illness onset. Most patients (62%) had one recorded exposure, 26% had two and 12% had three to five exposures. Patients older than the median age at diagnosis, those with a longer delay to diagnosis and those with anti-signal recognition particle autoantibodies had a higher frequency of documented exposures (odds ratios [ORs] 95% CI 3.4, 31). Infections were the most common exposure and represented 44% of the total number of reported exposures. Non-infectious exposures included medications (18%), immunizations (11%), stressful life events (11%) and unusual sun exposure (7%). Exposures varied by age at diagnosis, race, disease course and the presence of certain myositis autoantibodies.

Conclusion. The JIIMs may be related to multiple exposures and these appear to vary among phenotypes.

Key words: Juvenile myositis, Environmental factor, Phenotype, Myositis autoantibody, Infection, Medication.

Introduction

The juvenile idiopathic inflammatory myopathies (JIIMs) are a heterogeneous group of acquired systemic autoimmune diseases characterized by symmetric proximal weakness, the presence of characteristic rashes and other systemic features. While the aetiology of these disorders remains unknown, many lines of evidence suggest that they result from the interaction of multiple genetic risk factors and environmental exposures [1].

The JIIMs, like other autoimmune disorders, appear to be comprised of a number of clinical and serological phenotypes, each of which defines more homogeneous subsets of patients in terms of demographic features, the presence of certain myositis-associated autoantibodies, immunogenetics and outcomes [2, 3]. For example, patients with anti-PL155 autoantibodies form a phenotype characterized by the frequent presence of cutaneous involvement and characteristic photosensitive rashes of JDM and the HLA-DQA1*0301 allele, whereas patients with anti-synthetase autoantibodies frequently have moderate to severe weakness, arthritis, RP, mechanic's

1Environmental Autoimmunity Group, National Institute of Environmental Health Sciences, National Institutes of Health, DHHS, Bethesda, MD, *Veteran’s Affairs Medical Center and Oklahoma Medical Research Foundation, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.

Present address: Gulnara Mamyrova, Department of Medicine, Division of Rheumatology, George Washington University School of Medicine, Washington, DC, USA.

*See Appendix 1 for the members of the Childhood Myositis Heterogeneity Collaborative Study Group.

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hands, fevers, interstitial lung disease and HLA DRB1*0301 [3–5]. Clinical features of illness also appear to differ by age, gender, race and even disease course phenotypes [6–8]. Such homogeneous phenotypes might share unique combinations of environmental and genetic risk factors that result in a discrete disorder [9].

Several genetic risk factors for the JIIM have been defined, including MHC Class II alleles [10, 11], cytokine polymorphisms [12, 13], the protein tyrosine phosphatase gene N22 [14] and Gm and KM allotypes [15].

Environmental risk factors in JIIMs are not as well understood, and most efforts have focused on the potential role of infections in their aetiologies. Studies of cohorts of patients with JDM indicate that respiratory and gastrointestinal infections may be temporally associated with the onset of JIM [16, 17]. Prior studies of other autoimmune diseases suggest differences in environmental risk factors in different phenotypes [9], but the relationship between environmental risk factors and phenotypes has not been examined in the JIIMs [16, 17].

We, therefore, undertook this study to examine whether environmental factors that are temporally associated with the clinical onset of JIIM differ in selected phenotypes, focusing on a large, well-characterized population with data on both infectious and non-infectious exposures.

Patients and methods

Patients

Four hundred and twenty-three patients with probable or definite JDM or juvenile PM (JPM) [18] were enrolled into the NIH Clinical Center or Food and Drug Administration’s investigational review board-approved natural history protocols from September 1994 until July 2008; subjects’ written consent/assent was obtained according to the Declaration of Helsinki. The study was approved by the NIDDK/NAMS Institutional Review Board. Enrolled patients provided a blood sample for autoantibody testing and the treating physician completed a questionnaire that included clinical, demographic and laboratory data. For 285 of these patients, questions about factors temporally associated with illness onset were also completed, which is the basis of the present study. Informed consent/parent assent was consistent with the Declaration of Helsinki. Phenotypes were defined by age of illness onset, clinical features, disease course, race or autoantibodies. Disease course was classified as monocyclic if the patient achieved remission without evidence of active disease, based on clinical examination and laboratory testing, within 2 years of diagnosis; as polycyclic if the patient had recurrence of active disease after a definite remission; as chronic continuous if disease activity persisted for >2 years; and as undefined if follow-up was <2 years from the time of diagnosis [8]. Clinical, demographic and autoantibody characteristics of the study population are described in Table 1. Only the autoantibody phenotypes defined as anti-aminoacyl-tRNA synthetase, anti-signal recognition particle (anti-SRP), anti-MI2, anti-p155, anti-MJ, anti-U1 RNP and autoantibody negative were included in the analyses of environmental factors.

The physician questionnaire contained three questions about environmental exposures that had been previously suggested to be possibly associated with the onset of JDM [16, 17, 19, 20]. These included whether the patient had any documented infections, received any immunizations or took any medications (including vitamins, minerals, herbal preparations and dietary supplements) within 6 months before illness onset. The questionnaire also included an additional open-ended question about other environmental exposures within 6 months before illness onset relating to other possible triggers of disease and to specify these and when they occurred. Stressful life events were categorized as major vs minor and as

Table 1 Selected phenotypes of patients with JIIMs (n = 285) included in the environmental-onset study

| Phenotypes                  | n (%) |
|-----------------------------|-------|
| **Clinical subgroup**       |       |
| JDM                         | 263 (92) |
| Juvenile polymyositis       | 22 (8) |
| Myositis autoantibody       |       |
| Anti-p155                   | 44 (24) |
| Anti-MJ                     | 23 (13) |
| Anti-tRNA synthetases       | 10 (5) |
| Anti-U1 RNP                 | 10 (5) |
| Anti-MI2                    | 8 (4)  |
| Anti-SRP                    | 5 (3)  |
| Other myositis autoantibodies | 32 (17) |
| None detected               | 52 (29) |
| **Gender**                  |       |
| Female                      | 212 (74) |
| Male                        | 73 (26) |
| **Race**                    |       |
| White                       | 199 (70) |
| Black                       | 39 (14) |
| Hispanic                    | 22 (8)  |
| Other                       | 10 (4)  |
| Mixed                       | 15 (5)  |
| **Disease course**          |       |
| Monocyclic                  | 47 (17) |
| Polycyclic                  | 64 (22) |
| Chronic continuous          | 117 (41) |
| Undefined                   | 57 (20) |
| **Age at diagnosis, years** |       |
| Median                      | 7.5    |
| Interquartile range         | 5.1–12.2 |
| **Delay to diagnosis, months** |     |
| Median                      | 4      |
| Interquartile range         | 2.4–8.4 |

One hundred and twenty-one patients were tested by IP immunoblotting. Other myositis autoantibodies, which were not examined in the environmental exposure analysis, included: anti-Ro (n = 15), anti-PM/Scl (n = 5), anti-Sm (n = 3), anti-La (n = 2), anti-U5 RNP (n = 1), anti-U3 RNP (n = 1), anti-Ku (n = 1) and anti-Th (n = 1). Some patients have more than one myositis autoantibody. One hundred and one patients were not tested for myositis autoantibodies.
network, family, academic or unknown type, based on the Adolescent Perceived Event Scale of Compas et al. [21] (personal communication: B. Compas, Vanderbilt University). Illness onset was defined as the month and year when the first symptom related to myositis developed. A paediatric rheumatologist (L.G.R. or G.M.) reviewed available medical records for 81% of the patients in order to confirm the reported exposures, as well as the diagnostic and clinical material contained in the questionnaire.

Patient sera were tested for myositis autoantibodies by validated methods [22, 23]. For anti-p155/140 and anti-MJ autoantibodies, serum samples were screened by immunoprecipitation (IP), and this was confirmed by IP blotting [5, 24]. Sera were considered positive if they blotted the antigen in immunoprecipitates prepared using reference serum (direct) or if reference serum blotted the antigen in immunoprecipitates prepared using patient serum (reverse). Since some IP-positive sera do not react by immunoblotting, reverse IP blotting was used for most sera [5].

Case-only analyses were conducted to describe the frequency of exposures overall and in relation to patient phenotype. Statistical analysis was performed using Sigma Stat Version 3.1 (Systat Software, Inc., Chicago, IL, USA), including \( \chi^2 \) and Fisher’s exact tests to determine differences in the proportion of patients with different environmental exposures. Odds ratios (ORs) and 95% CIs were calculated using GraphPad InStat version 3.06 (GraphPad Software, San Diego, CA, USA). P-values were adjusted for multiple testing using Holm’s procedure [25], using SAS System for Windows, version 9.1.3 and SAS Enterprise Guide Version 4.1 (SAS Institute, Cary, NC, USA).

Results

Frequency of documented exposures

Sixty per cent of JIIM patients had one or more reported exposures within 6 months before illness onset (Table 2). The total number of reported exposures was more frequent in white patients than in other racial groups (\( P = 0.008; \) OR 2.1; 95% CI 1.2, 3.5; Table 2). Although most patients (62%) had only one reported exposure, 26% had two exposures, and 12% had three to five recorded exposures in the 6 months before illness onset (Table 2). Of the 64 patients with more than one exposure, 50% had a combination of infection and medication, and 27% had a combination of infection and immunization. The combination of infection and immunization was more frequent in patients from non-white racial groups (\( P < 0.0001; \) OR 22.0; 95% CI 5.9, 81.7).

Patients who were >7.5 years of age at diagnosis (the median age at diagnosis) more often had three to five reported exposures compared with younger patients (\( P = 0.027; \) OR 3.7; 95% CI 1.3, 10.6; Table 2), and patients with anti-SRP autoantibody more often had three to five exposures compared with patients without a myositis autoantibody (\( P = 0.027; \) OR = 31.0; 95% CI 1.9, 507). Patients with a longer delay to diagnosis (>4 months, the median delay) were more likely to have three to five exposures than patients with a shorter delay (\( P = 0.034; \) OR 3.4; 95% CI 1.2, 9.8). There were no other significant differences in the frequency or number of noted exposures between clinical phenotypes (JDM vs juvenile PM [JPM]), nor by gender, disease course, delay to diagnosis or between other autoantibody phenotypes (data not shown).

Types of exposures

Infections were the most common type of exposure identified within 6 months before diagnosis, consisting of 45% of the total number of reported exposures, followed by medications (18%) and immunizations (11%) (Table 2). Patients <7.5 years of age at onset, those with ≤4 months delay to diagnosis, those with a polycyclic illness course and those who were myositis autoantibody negative were more likely to have an infection in the 6 months before diagnosis than older patients, those with greater delay to diagnosis, those with a monocyclic or chronic continuous illness course or those who had anti-p155 or anti-SRP autoantibodies (ORs 1.8–4.3, Table 2 and data not shown). There were no other differences between documented types of exposure between clinical or other autoantibody phenotypes, nor by gender, disease course, race or delay to diagnosis.

From the open-ended exposure question, stressful life events constituted 11% of the reported exposures. Patients >7.5 years of age reportedly experienced a stressful life event more frequently in the 6 months before diagnosis than younger patients (\( P = 0.003; \) OR 3.5; 95% CI 1.5, 7.9). Unusual sun exposures comprised 7% of the total exposures in the 6 months before diagnosis and occurred exclusively in patients with JDM, not JPM. Unusual sun exposures included those resulting in sunburn, as well as receiving more sun than usual or travel to a more sunny location. An unusual chemical exposure was recorded 3% of the time and included application of pesticides inside or around the home, painting the home, use of formaldehyde to clean the child’s bed and application of a hair perming chemical. Seven (2%) reported exposures involving unusual animal contact within 6 months of illness onset, including a dog or cat scratch, exotic bird bite or multiple flea or mosquito bites. Four (2%) exposures involved weight-training exercise or physical trauma, and two (0.6%) exposures involved dietary supplement usage before illness onset, including creatine monokinase and Echinacea. These less-frequent exposures were present exclusively in patients with JDM, except that weight-training exercise was also noted in one JPM patient. Weight training, physical trauma and dietary supplements were seen exclusively in patients >7.5 years of age at diagnosis and in patients with a greater delay to diagnosis.

Infectious exposures

White patients and patients who did not have an identified myositis autoantibody were more likely to have a documented infection within 6 months before illness onset than those from other racial groups or those with the anti-p155 autoantibody (\( P = 0.0008; \) OR 2.7; 95% CI 1.5, 4.8 and...
| Environmental exposure | JIIM (n = 285), n (%) | Age at diagnosis | Race | Disease course | Myositis autoantibody |
|-------------------------|------------------------|-----------------|------|----------------|----------------------|
|                         | ≤ 7.5 years (n = 150), n (%) | > 7.5 years (n = 135), n (%) | White (n = 199), n (%) | Other (n = 86), n (%) | Monocyclic (n = 47), n (%) | Polycyclic (n = 64), n (%) | Chronic Continuous (n = 117), n (%) | Anti-p155 (n = 44), n (%) | Autoantibody negative (n = 52), n (%) |
| None                    | 114 (40)               | 62 (41)          | 69 (35)          | 15 (32)          | 4 (6)                 | 2 (7)               | 5 (5)                 | 19 (46)               | 5 (10)                 |
| No. of patients exposed | 171 (60)               | 88 (59)          | 83 (62)          | 130 (65)         | 41 (48)               | 32 (68)             | 33 (52)               | 24 (54)               | 33 (64)               |
| No. of exposures per patient | 1                      | 107 (62)         | 54 (61)          | 79 (61)          | 22 (68)               | 2 (7)               | 1 (3)                 | 2 (8)                 | 2 (6)                 |
|                          | 2                      | 44 (26)          | 29 (33)          | 35 (27)          | 8 (25)                | 2 (7)               | 1 (3)                 | 2 (8)                 | 2 (6)                 |
|                          | 3–5                    | 20 (12)          | 5 (6)            | 16 (12)          | 2 (7)                | 1 (3)               | 1 (3)                 | 2 (8)                 | 2 (6)                 |
| Total no. of exposures   | 336                    | 158              | 178              | 267 (69)         | 57 (58)               | 143                 | 45 (75)               |
| Exposure type            |                        |                  |                  |                  |                      |                     |                      |                      |                      |
| Infection               | 152 (45)               | 87 (55)          | 65 (36)          | 126 (47)         | 20 (35)               | 34 (59)             | 60 (42)               | 10 (22)               | 33 (44)               |
| Medication              | 62 (18)                | 27 (17)          | 35 (20)          | 48 (18)          | 11 (19)               | 13 (22)             | 26 (18)               | 8 (11)                | 6 (8)                 |
| Immunization            | 37 (11)                | 16 (10)          | 21 (12)          | 29 (11)          | 10 (18)               | 4 (7)               | 14 (10)               | 5 (11)                | 6 (8)                 |
| Other                   | 85 (25)                | 28 (18)          | 57 (32)          | 64 (24)          | 16 (28)               | 7 (12)              | 43 (30)               | 15 (33)               | 28 (37)               |

Bold values represent P < 0.05 after Holm’s adjustment for multiple comparisons (using family-wise error rates of 5%). Environmental exposure type represents total number of patients (%) with a given exposure calculated as a percentage of the total number of exposures. Note that some patients may have more than one exposure type. Patients with >1 exposure of a given type are counted only once. *P = 0.008; OR 2.1; 95% CI 1.2, 3.5. †P = 0.04; OR 2.2; 95% CI 1.1, 4.6. ‡P = 0.027; OR 3.7; 95% CI 1.3, 10.6. §P = 0.027; OR 3.1; 95% CI 1.9, 5.0. ¶P = 0.001; OR 2.1; 95% CI 1.4, 3.3. **Polycyclic vs monocyclic: P = 0.047; OR 2.0; 95% CI 1.1, 3.6. ***Polycyclic vs chronic continuous: P = 0.027; OR 2.1; 95% CI 1.2, 3.4. yyP = 0.005; OR 4.2; 95% CI 1.6, 10.9. yyP = 0.004; OR 2.2; 95% CI 1.3, 3.7. **P = 0.026; OR 3.1; 95% CI 1.3, 7.5.
Environmental factors before onset of juvenile myositis

The majority (68%) of patients with an infectious exposure had one documented infection, but 28% had two and 4% had three to five infections documented within 6 months of illness onset. Patients >7.5 years of age were more likely than younger patients to have two infections ($P = 0.038$; OR 2.7; 95% CI 1.1, 6.3; Table 3).

Respiratory infections were the most common type of infection reported, followed by mucocutaneous and gastrointestinal infections (Table 3). Pharyngitis was the most frequent specific infection and was more prevalent in patients >7.5 years of age than in younger patients ($P = 0.017$; OR 2.7; 95% CI 1.2, 6.0; Table 3). A flu or febrile illness and otitis media were each seen in 13% of patients, and an upper respiratory infection in 10% of patients within 6 months before illness onset. There were no other differences noted in the infection site or type of infection among clinical or autoantibody phenotypes, nor by gender, race, disease course or delay to diagnosis.

Drug exposures

Patients ≤7.5 years of age were more likely to have one drug exposure ($P = 0.004$; OR 15.4; 95% CI 1.8, 135), whereas those >7.5 years of age were more likely to have two drug exposures ($P = 0.008$; OR 18.9; 95% CI 1.0, 358) in the 6 months before illness onset (Table 4). Of interest, >25% of the medication usage documented included drugs that were potentially photosensitizing or myopathic [26–31]. There were no other differences noted in medication usage between clinical or autoantibody phenotypes, nor were there any differences by gender, race, disease course or delay to diagnosis.

Immunizations

There was no difference in the proportion of patients who received an immunization in the 6 months before illness onset or in the number of immunizations received, between clinical or autoantibody phenotypes, nor by age, gender, race, disease course or delay to diagnosis. Patients with a polycyclic illness course were more likely than patients with a monocyclic illness course to have received an immunization or to have received a measles–mumps–rubella (MMR) vaccine in the 6 months before illness onset (21 vs 6%; $P = 0.023$; OR 4.1; 95% CI 1.2, 13.9 and 50 vs 6%; $P = 0.035$; OR 17.0; 95% CI 1.3, 223, respectively). Given the time period under study, it was not surprising that patients >7.5 years of age at diagnosis were more likely to have received a hepatitis B vaccine than younger patients (47 vs 12%; $P = 0.002$; OR 6.2; 95% CI 2.0, 19.7), whereas patients ≤7.5 years of age were more likely to have received a diphtheria–pertussis–tetanus vaccine (22 vs 6%; $P = 0.033$; OR 8.2; 95% CI 0.98, 69.8).

Stressful life events

Nine per cent (n = 26) of patients had at least one stressful life event in the 6 months before illness onset, with 72% of these being major stressors and the remainder being

Table 3 Reported infections in selected JIIM phenotypes within 6 months of illness onset

| Infection characteristic | JIIM (n = 285), n (%) | Age at diagnosis | Race | Myositis autoantibody |
|--------------------------|----------------------|-----------------|------|----------------------|
|                          | ≤ 7.5 years (n = 150), n (%) | > 7.5 years (n = 135), n (%) | White (n = 199), n (%) | Other (n = 86), n (%) | Anti-p155 (n = 44), n (%) | Autoantibody negative (n = 52), n (%) |
| No infection             |                      |                 |      |                      |                  |                              |
|                          | 175 (61)             | 85 (57)         | 90 (67) | 109 (55)             | 66 (77)          | 36 (82)                        |
|                          | 7.5 years of age at diagnosis | | | | | |
|                          | 110 (39)             | 65 (43)         | 45 (33) | 90 (45)              | 20 (23)          | 8 (18)                          |
|                          | 7.5 years of age at diagnosis | | | | | |
|                          | 75 (68)              | 49 (75)         | 26 (58) | 60 (67)              | 15 (75)          | 6 (75)                          |
|                          | 2                    | 13 (20)         | 18 (40)§ | 27 (30)              | 4 (20)           | 25 (62)                         |
|                          | 3–5                  | 4 (4)           | 3 (5)   | 1 (2)                | 3 (3)            | 0 (0)                           |
| Total no. of infections  | 152                  | 87              | 65      | 126                  | 26               | 10                              |
| Infection site*          |                      |                 | | | | |
| Respiratory              | 101 (66)             | 54 (62)         | 47 (72) | 84 (66)              | 17 (65)          | 5 (50)                          |
| Mucocutaneous            | 17 (11)              | 10 (12)         | 7 (11)  | 14 (11)              | 3 (12)           | 2 (20)                          |
| Gastrointestinal         | 7 (5)                | 7 (8)           | 0 (0.0) | 7 (6)                | 0 (0.0)          | 0 (0.0)                         |
| Unclassified             | 27 (18)              | 16 (18)         | 11 (17) | 21 (17)              | 6 (23)           | 3 (30)                          |
| Most common infections#  |                      |                 | | | | |
| Pharyngitis              | 34 (22)              | 13 (15)#        | 21 (32)# | 32 (25)              | 2 (8)            | 2 (20)                          |
| Flu or febrile illness   | 19 (13)              | 12 (14)         | 7 (11)  | 16 (13)              | 3 (11)           | 2 (20)                          |
| Otitis media             | 19 (13)              | 15 (17)         | 4 (6)   | 16 (13)              | 3 (11)           | 1 (10)                          |
| Upper respiratory infection | 16 (10)            | 10 (11)         | 6 (9)   | 11 (9)               | 5 (19)           | 0 (0.0)                          |
| Other                    | 64 (42)              | 37 (43)         | 27 (42) | 51 (40)              | 13 (51)          | 5 (50)                          |

Conventions as per Table 2. Bold values represent $P < 0.05$ after Holm’s adjustment for multiple comparisons (using family-wise error rates of 5%). $^1P = 0.0008$; OR 2.7; 95% CI 1.5, 4.8. $^2P = 0.007$; OR 3.9; 95% CI 1.5, 9.9. $^3P = 0.038$; OR 2.7; 95% CI 1.1, 6.3. $^4P = 0.017$; OR 2.7; 95% CI 1.2, 6.0.
minor stressors. The majority of these patients (65%) had one stressor, but 31% had two recorded stressors and 4% had three stressors. The categorization of stressors included network (50%), family (25%), academic (19%) and unknown types (6%). Patients >7.5 years of age had a stressful life event more frequently than younger children \( P = 0.003 \); OR 3.5; 95% CI 1.5, 7.9. There were no differences in the proportion of patients with a reported stressor or in the number or type of stressor in 6 months before illness onset between clinical or autoantibody phenotype, nor by gender, race, disease course or delay to diagnosis.

**Discussion**

The availability of a large, well-characterized population enabled us to examine the relationship between environmental exposures before illness onset and phenotypes in JIIM. We confirmed a number of exposures that had also been seen in prior studies of JDM, particularly the temporal association of respiratory infections preceding illness onset [16, 17]. We identified for the first time that a number of other non-infectious exposures occurred within 6 months of the first signs of illness, including medications, many of which are potentially myopathic or photosensitizing, immunizations, stressful life events and sun exposure. The main novel findings of this study were differences in some exposures by age at diagnosis, delay to diagnosis, race, disease course and autoantibody phenotypes. For example, children younger than the median age at the time of diagnosis had a higher frequency of documented infections, whereas older children had a higher frequency of stressful life events in the months before illness onset. Patients without a myositis autoantibody had a higher frequency of infections in the 6 months before illness onset than was seen in patients with anti-p155 or anti-SRP autoantibodies, whereas patients with anti-SRP autoantibodies had a greater number of documented exposures than patients without a myositis autoantibody. These findings suggest that environmental exposures may differ by phenotype, and that they could be useful in understanding pathogeneses [1].

We found that an infectious illness, particularly a respiratory infection, frequently occurs within several months before juvenile myositis onset, supporting the findings of other studies of exposures temporally associated with the onset of JDM. In one study, a prospective registry of patients within 6 months of illness onset in which data were based on a parent environmental interview and medical record review, respiratory infections were identified within 3 months of illness onset in 57% of patients [16]. The other, a retrospective cohort with review of medical records by infectious disease specialists, identified infections within 3 months before
the first symptoms of JDM in 33–50% of patients, and respiratory infections accounted for 80% of the infections [17]. The lack of control comparator groups in all of these studies, however, does not enable one to conclude that these exposures differ from a healthy population, nor that they are associated with the onset of illness. While infections, particularly upper respiratory infections, are reported frequently in school age children [32], a prospective matched cohort of new-onset JDM patients reported a higher frequency of antecedent illness in the JDM patients compared with friend controls from the same geographical region [19].

We identified for the first time that a number of other non-infectious exposures also occurred within 6 months of the first signs of illness, including medications, many of which are potentially myopathic or photosensitizing, immunizations, stressful life events and sun exposure. Pachman et al. [16] noted medication use in >60% of patients, including medications for symptoms of early illness or antibiotics to treat associated infections. A listing of medications taken by patients in the present study and in others includes similar medications (Table 4), and we noted that many of the medications could be potentially myopathic or phototoxic [26, 27, 29, 30]. Drug-induced myositis has been well described with a number of different medications, including d-penicillamine, lipid-lowering agents, L-tryptophan and IFN-\(\alpha\) [33, 34]. Myopathic or phototoxic drugs, however, could lead to the first symptoms of myositis. Other environmental factors reported here, including ultraviolet light exposure, emotional stress and heavy weight lifting, have been reported as possible risk factors for adult DM or PM in case-controlled studies [35–38].

Almost 40% of the patients in this study had two or more reported exposures within 6 months before illness onset, rather than a single documented exposure. This is consistent with the concept that, just as systemic autoimmune diseases are polygenic [39], they might also be polyenvironmental, meaning that patients may have more than one exposure before developing the disease. These exposures may also be dependent on gene–gene, environment–environment and gene–environment interactions. In diseases such as cancer, multiple infectious and non-infectious environmental factors have been associated with specific malignancies, and these environmental exposures have been shown to affect the development of disease in different ways, including altering mutagenesis, promotion and direct carcinogenesis [40]. Synergistic interactions between some of these environmental factors, including viral and non-infectious exposures, have also been seen in certain malignancies [41, 42]. It is possible, though, that there was a confounding between exposures, such as an infectious illness and the use of antibiotics, as noted by Pachman et al. [16]. Our data suggest that further investigation of the interaction between environmental exposures may be useful.

It is important to emphasize that the temporal association of environmental exposures with illness onset does not imply causality. For example, certain exposures, such as trauma or weight training, could have occurred after the onset of illness as a consequence of the first unrecognized symptoms of disease, such as fatigue or muscle weakness. Rather, exposures with temporal relationships to disease onset, as were seen in this hypothesis-generating study, constitute a first step for determining which factors may trigger the onset of illness and warrant further investigation. Additional support for a relationship between these exposures and disease pathogenesis could be provided by dechallenge data, which did not exist in this cohort-based study, from laboratory investigations and from case-controlled epidemiological studies [43]. A case–control study by Pachman et al. [19] did not find any significant differences in pesticide use, psychological stress or exposure to animals in 80 JDM patients within 6 months of illness onset compared with 63 age-matched geographically similar healthy controls with similar school or daycare experiences, nor was parvovirus found to be an aetiological factor in recent-onset JDM patients compared with age-, gender- and race-matched controls [44]. However, both of those studies may not have been adequately powered to detect differences between the cases and controls. Also, the extent of matching of controls may have obscured differences with JDM patients. For example, in the parvovirus study [44], the controls were age, race and gender matched to patients, but they were not geographically matched, whereas in the study of Pachman et al. [19], the healthy controls, frequently age-matched classmates and neighbours, may have been geographically overmatched, but they were not gender or race matched. An appropriately powered prospective case-controlled study is needed to confirm the observations from this and other previous reports.

There are a number of potential limitations in this study. A primary limitation is the absence of a control group. Thus, the frequencies of exposures observed in juvenile myositis patients overall may not differ from healthy control populations and these exposures may not be associated with the onset of illness. In addition, there could be under- or over-reporting of potential exposures, including a selection bias in the patients who had the environmental component of the questionnaire completed. We also found more exposures, including infectious illnesses, in white patients compared with patients in other racial groups. This could potentially be the result of differences in access to health care, resulting in better documentation of such exposures. The somewhat arbitrary period of 6 months before the onset of illness for identification of environmental factors might not be relevant to the initiation of myositis for all exposures. Certain exposures could require a longer period to induce their effects, as has been reported in malignancies, silicosis and other disorders, while for other exposures a shorter time frame might be more relevant [37, 38]. Also, exposures other than infections, drugs and vaccines were reported in an open-ended manner, and patients were not required to be directly interviewed to obtain information about environmental exposures. We attempted to
overcome these possible biases by conducting a formal review of most of the medical records of the study subjects. However, the medical records might also have selection bias by reporting only some of the significant environmental exposures. Certain exposures, such as exposures in the home and use of certain chemicals, are likely not captured uniformly in the medical record by the treating physician. Nonetheless, the fact that our data on infections before illness onset are similar to those of other large cohorts suggests that the quality of the data and reporting are reliable [16, 17]. Finally, while some of the ORs in our study are large, the CIs may be wide and estimates could be inflated due to relatively small numbers of patients in some groups.

In summary, we have identified a number of environmental exposures, including infectious and non-infectious agents that occurred within 6 months before illness onset, varied by phenotype and may be important in the pathogenesis of JIIM. These findings suggest that a search for a single environmental factor that causes or triggers a single disease as currently defined, such as JIIM, may be unproductive, as patients could have several environmental exposures and these could vary with the disease phenotype that develops. These exposures require confirmation in case-controlled studies to identify whether they are associated with illness onset and whether they play any role in aetiology, yet they suggest focused areas of further research to better understand the environmental factors associated with the onset of JIIM phenotypes and their possible interrelationships with genetic risk factors.

Rheumatology key messages
- Environmental exposures before the onset of juvenile myositis include infections, medications, vaccinations, sun exposure and stressful life events.
- Exposures vary by disease phenotype, defined by age of illness onset, race and autoantibody status.

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References

1. Cooper GS, Miller FW, Germolec DR. Occupational exposures and autoimmune diseases. Int Immunopharmacol 2002;2:303–13.
2. Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. Lancet 2008;371:2201–12.
3. Rider LG. The heterogeneity of juvenile myositis. Autoimmun Rev 2007;6:241–7.
4. Gunawardena H, Wedderburn LR, North J et al. Clinical associations of autoantibodies to a p155/140 kDa doublet protein in juvenile dermatomyositis. Rheumatology 2008;47:324–8.
5. Targoff IN, Mamyrova G, Trieu EP et al. A novel autoantibody to a 155-kd protein is associated with dermatomyositis. Arthritis Rheum 2006;54:3682–9.
6. Pachman LM, Abbott K, Sinacore JM et al. Duration of illness is an important variable for untreated children with juvenile dermatomyositis. J Pediatr 2006;148:247–53.
7. Christen-Zaech S, Seshadri R, Sundberg J, Paller AS, Pachman LM. Persistent association of nailfold capillaroscopy changes and skin involvement over thirty-six months with duration of untreated disease in patients with juvenile dermatomyositis. Arthritis Rheum 2008;58:571–6.
8. Huber AM, Lang B, LeBlanc CM et al. Medium- and long-term functional outcomes in a multicenter cohort of children with juvenile dermatomyositis. Arthritis Rheum 2000;43:541–9.
9. Gourley M, Miller FW. Mechanisms of disease: environmental factors in the pathogenesis of rheumatic disease. Nat Clin Pract Rheumatol 2007;3:172–80.
10. Mamyrova G, O’Hanlon TP, Monroe JB et al. Immunogenetic risk and protective factors for juvenile dermatomyositis in Caucasians. Arthritis Rheum 2006;54:3979–87.
11. O’Hanlon TP, Rider LG, Mamyrova G et al. HLA polymorphisms in African Americans with idiopathic inflammatory myopathy: allelic profiles distinguish patients with different clinical phenotypes and myositis autoantibodies. Arthritis Rheum 2006;54:3670–81.
12. Pachman LM, Liotta-Davis MR, Hong DK et al. TNFalpha-308A allele in juvenile dermatomyositis: association with increased production of tumor necrosis factor alpha, disease duration, and pathologic calcifications. Arthritis Rheum 2000;43:2368–77.
13. Mamyrova G, O’Hanlon TP, Sillers L et al. Cytokine gene polymorphisms as risk and severity factors for juvenile dermatomyositis. Arthritis Rheum 2008;58:3941–50.
14. Chinoy H, Platt H, Lamb JA et al. The protein tyrosine phosphatase N22 gene is associated with juvenile and adult idiopathic inflammatory myopathy independent of the HLA 8.1 haplotype in British Caucasian patients. Arthritis Rheum 2008;58:3247–54.
15. O’Hanlon TP, Rider LG, Schiffenbauer A et al. Immunoglobulin gene polymorphisms are susceptibility factors in clinical and autoantibody subgroups of the idiopathic inflammatory myopathies. Arthritis Rheum 2008;58:3239–46.
16 Pachman LM, Lipton R, Ramsey-Goldman R et al. History of infection before the onset of juvenile dermatomyositis: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Research Registry. Arthritis Rheum 2005;53:166–72.
17 Manlhiot C, Liang L, Tran D, Bitnun A, Tyrrell PN, Feldman BM. Assessment of an infectious disease history preceding juvenile dermatomyositis symptom onset. Rheumatology 2008;47:526–9.
18 Bohan A, Peter JB. Polymyositis and dermatomyositis. Parts 1 and 2. N Engl J Med 1975;292:344–7, 3403–7.
19 Pachman LM, Hayford JR, Hochberg MC et al. New-onset juvenile dermatomyositis: comparisons with a healthy cohort and children with juvenile rheumatoid arthritis. Arthritis Rheum 1997;40:1526–33.
20 Christensen ML, Pachman LM, Schneiderman R, Patel DC, Friedman JM. Prevalence of Coxsackie B virus antibodies in patients with juvenile dermatomyositis. Arthritis Rheum 1986;29:1365–70.
21 Compas BE, Davis GE, Forsythe CJ, Wagner BM. Assessment of major and daily stressful events during adolescence: the Adolescent Perceived Events Scale. J Consult Clin Psychol 1987;55:534–41.
22 Arnett FC, Targoff IN, Mimori T, Goldstein R, Warner NB, Reveille JD. Interrelationship of major histocompatibility complex class II alleles and autoantibodies in four ethnic groups with various forms of myositis. Arthritis Rheum 1996;39:1507–18.
23 Targoff IN. Autoantibodies to aminocarboxyl-transfer RNA synthetases for isoleucine and glycine. Two additional synthetases are antigenic in myositis. J Immunol 1990;144:1737–43.
24 Targoff IN, Trieu EP, Miller FW. Reaction of anti-OJ autoantibodies with components of the multi-enzyme complex of aminocarboxyl-tRNA synthetase in addition to isoleucyl-tRNA synthetase. J Clin Invest 1993;91:2556–64.
25 Holm S. A simple sequentially rejective multiple test procedure. Scand J Statist 1978;6:69–70.
26 Gould JW, Mercurio MG, Elmet CA. Cutaneous photosensitizing diseases induced by exogenous agents. J Am Acad Dermatol 1995;33:551–73.
27 Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. Drug Saf 2002;25:345–72.
28 Walsh RJ, Amato AA. Toxic myopathies. Neurol Clin 2005;23:397–428.
29 Guis S, Mattei JP, Liote F. Drug-induced and toxic myopathies. Best Pract Res Clin Rheumatol 2003;17:877–907.
30 Wald JI. The effects of toxins on muscle. Neurol Clin 2000;18:695–718.
31 Love LA, Miller FW. Noninfectious environmental agents associated with myopathies. Curr Opin Rheumatol 1995;3:712–8.
32 Lambert SB, Allen KM, Druce JD et al. Community epidemiology of human metapneumovirus, human coronavirus NL63, and other respiratory viruses in healthy preschool-aged children using parent-collected specimens. Pediatrics 2007;120:e929–37.
33 Seidler AM, Gottlieb AB. Dermatomyositis induced by drug therapy: a review of case reports. J Am Acad Dermatol 2008;59:872–80.
34 Dourmishev LA, Dourmishev AL. Activity of certain drugs in inducing of inflammatory myopathies with cutaneous manifestations. Expert Opin Drug Saf 2008;7:421–33.
35 Lyon MG, Bloch DA, Hollak B, Fries JF. Predisposing factors in polymyositis-dermatomyositis: results of a nationwide survey. J Rheumatol 1989;16:1218–24.
36 Okada S, Weatherhead E, Targoff IN, Wesley R, Miller FW. Global surface ultraviolet radiation intensity may modulate the clinical and immunologic expression of autoimmune muscle disease. Arthritis Rheum 2003;48:2285–93.
37 Miller FW. Inflammatory myopathies: polymyositis, dermatomyositis, and related conditions. In: Koopman W, Moreland L, eds. Arthritis and allied conditions: a textbook of rheumatology. Philadelphia: Lippincott Williams & Wilkins, 2005:1593–620.
38 Miller FW. Noninfectious environmental agents and autoimmunity. In: Rose NR, Mackay IR, eds. The autoimmune diseases. Boston: Elsevier, 2006:297–308.
39 Coenen MJ, Gregersen PK. Rheumatoid arthritis: a view of the current genetic landscape. Genes Immun 2009;10:101–11.
40 Belpomme D, Irigaray P, Hardell L et al. The multitude and diversity of environmental carcinogens. Environ Res 2007;105:414–29.
41 Seli S. Mouse models to study the interaction of risk factors for human liver cancer. Cancer Res 2003;63:7553–62.
42 Chen CJ, Yu MW, Liaw YF. Epidemiological characteristics and risk factors of hepatocellular carcinoma. J Gastroenterol Hepatol 1997;12:S294–308.
43 Miller FW, Hess EV, Clauw DJ et al. Approaches for identifying and defining environmentally associated rheumatic disorders. Arthritis Rheum 2000;43:243–9.
44 Mamyrova G, Rider LG, Haagenson L, Wong S, Brown KE. Parvovirus B19 and onset of juvenile dermatomyositis. JAMA 2005;294:2170–1.

Appendix 1

Members of the Childhood Myositis Heterogeneity Collaborative Study Group, who referred patients to this study: Leslie S. Abramson, Barbara S. Adams, Daniel A. Albert, Bita Arabshahi, Eugene R. Arthur, Balu H. Athreya, Alan N. Baer, Imelda M. Balboni, Catherine A. Bingham, William P. Blocker, Gary Ruy Carrasco, Victoria W. Cartwright, Gail D. Cawkwell, Elizabeth J. Chalom, Darryl Crisp, Randy O. Cron, Marietta M. DeGuzman, Barbara S. Edelheit, John F. Eggert, Andrew H. Eichenfield, Janet Ellsworth, Terri H. Finkel, Christos A. Gabriel, Vernon F. Garwood, Stephen W. George, Harry L. Gewanter, Ellen A. Goldmuntz, Donald P. Goldsmith, Alexia C. Gospodinoff, Thomas A. Griffin, Brandt P. Groh, Melissa Hawkins-Holt, C. E. Hendricks, Michael Henrickson, J. Roger Hollister, Lisa F. Imundo, Jerry C. Jacobs (posthumous), Courtney R. Johnson, Olcay Y. Jones, Lawrence K. Jung, Thomas V. Kantor, Ilidy M. Katona, Yukiko Kimura, Daniel J. Kingsbury,
