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Original article

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

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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.

CLINICAL SCIENCE

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-p155 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

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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 JIIM [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/NIAMS 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.

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[a]	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. [a]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.

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

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 χ^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

Table 2 Environmental exposures documented in selected JIIM phenotypes within 6 months of disease onset

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)	52 (38)	69 (35)	45 (52)	15 (32)	31 (48)	49 (42)	20 (46)	19 (36)
No. of patients exposed	171 (60)	88 (59)	83 (62)	**130 (65)**[†]	**41 (48)**[†]	32 (68)	33 (52)	68 (58)	24 (54)	33 (64)
No. of exposures per patient										
1	107 (62)	54 (61)	53 (64)	79 (61)	28 (68)	22 (68)	22 (67)	41 (60)	14 (58)	23 (70)
2	44 (26)	29 (33)	15 (18)[‡]	35 (27)[‡]	9 (22)	8 (25)	10 (30)	15 (22)	8 (34)	8 (24)
3–5	20 (12)	5 (6)[§]	15 (18)[§]	16 (12)	4 (10)	2 (7)	1 (3)	12 (18)	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)	26 (38)	20 (35)**	34 (59)**	60 (42)**	10 (22)[††]	33 (44)[††]
Medication	62 (18)	27 (17)	35 (20)	48 (18)	14 (20)	11 (19)	13 (22)	26 (18)	**15 (33)**[‡‡]	8 (11)[‡‡]
Immunization	37 (11)	16 (10)	21 (12)	29 (11)	8 (12)	10 (18)	4 (7)	14 (10)	5 (11)	6 (8)
Other	85 (25)	**28 (18)**[§§]	**57 (32)**[§§]	64 (24)	21 (30)	16 (28)	7 (12)[¶¶]	43 (30)[¶¶]	15 (33)	28 (37)

Bold values represent $P \leqslant 0.05$ 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 31.0; 95% CI 1.9, 507. [#]$P = 0.001$; OR 2.1 95% CI 1.4, 3.3. **Polycyclic *vs* monocyclic: $P = 0.019$; OR = 2.6; 95% CI 1.2, 5.6; Polycyclic *vs* chronic continuous: $P = 0.047$; OR = 2.0; 95% CI 1.1, 3.6. [††]$P = 0.027$; OR 2.8; 95% CI 1.2, 6.4. [‡‡]$P = 0.005$; OR 4.2; 95% CI 1.6, 10.9. [§§]$P = 0.004$; OR 2.2; 95% CI 1.3, 3.7. [¶¶]$P = 0.026$; OR 3.1; 95% CI 1.3, 7.5.

$P = 0.007$; OR 3.9; 95% CI 1.5, 9.9, respectively; Table 3). 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* (%)
None	175 (61)	85 (57)	90 (67)	109 (55)	66 (77)	36 (82)	28 (54)
No. of patients infected	110 (39)	65 (43)	45 (33)	**90 (45)**[†]	**20 (23)**[†]	**8 (18)**[‡]	**24 (46)**[‡]
No. of infections							
1	75 (68)	49 (75)	26 (58)	60 (67)	15 (75)	6 (75)	17 (71)
2	31 (28)	13 (20)[§]	18 (40)[§]	27 (30)	4 (20)	2 (25)	6 (25)
3–5	4 (4)	3 (5)	1 (2)	3 (3)	1 (5)	0 (0)	1 (4)
Total no. of infections	152	87	65	126	26	10	33
Infection site[¶]							
Respiratory	101 (66)	54 (62)	47 (72)	84 (66)	17 (65)	5 (50)	22 (67)
Mucocutaneous	17 (11)	10 (12)	7 (11)	14 (11)	3 (12)	2 (20)	4 (12)
Gastrointestinal	7 (5)	7 (8)	0 (0.0)	7 (6)	0 (0.0)	0 (0.0)	0 (0.0)
Unclassified	27 (18)	16 (18)	11 (17)	21 (17)	6 (23)	3 (30)	7 (21)
Most common infections[¶]							
Pharyngitis	34 (22)	13 (15)[#]	21 (32)[#]	32 (25)	2 (8)	2 (20)	7 (21)
Flu or febrile illness	19 (13)	12 (14)	7 (11)	16 (13)	3 (11)	2 (20)	6 (18)
Otitis media	19 (13)	15 (17)	4 (6)	16 (13)	3 (11)	1 (10)	3 (9)
Upper respiratory infection	16 (10)	10 (11)	6 (9)	11 (9)	5 (19)	0 (0.0)	3 (9)
Other	64 (42)	37 (43)	27 (42)	51 (40)	13 (51)	5 (50)	14 (43)

Conventions as per Table 2. Bold values represent $P \leqslant 0.05$ after Holm's adjustment for multiple comparisons (using family-wise error rates of 5%). [†]$P = 0.0008$; OR 2.7; 95% CI 1.5, 4.8. [‡]$P = 0.007$; OR 3.9; 95% CI 1.5, 9.9. [§]$P = 0.038$; OR 2.7; 95% CI 1.1, 6.3. [¶]Based on total number of infections, because some patients had >1 documented infection. $P = 0.017$; OR 2.7; 95% CI 1.2, 6.0.

Table 4 Reported drug therapies in children with JIIM within 6 months of illness onset

Drug exposure	JIIM ($n = 285$), *n* (%)	Age at diagnosis	
		⩽7.5 years ($n = 150$), *n* (%)	>7.5 years ($n = 135$), *n* (%)
None	237 (83)	125 (83)	112 (83)
No. of patients exposed	48 (17)	25 (17)	23 (17)
No. of drug exposures			
1	38 (79)	**24 (96)***	**14 (61)***
2	6 (13)	**0 (0)†**	**6 (26)†**
3	4 (8)	1 (4)	3 (13)
Total	62	27	35
Type of drug[a]			
Potentially myopathic only	3 (5)	0 (0)	3 (9)
Potentially photosensitizing only	3 (5)	0 (0)	3 (9)
Potentially myopathic and photosensitizing	11 (18)	5 (19)	6 (17)
Not myopathic or photosensitizing	31 (50.0)	13 (48)	18 (51)
Unknown type	14 (22)	9 (33)	5 (14)

Conventions as per Table 2. Bold values represent $P \leqslant 0.05$ after Holm's adjustment for multiple comparisons (using family-wise error rates of 5%). [a]Based on total number of drug exposures, because some patients had >1 documented drug exposure. Potentially myopathic drugs included penicillin ($n = 2$) and ranitidine ($n = 1$) [28–31]. Potentially photosensitizing drugs included loratadine ($n = 1$), diphenhydramine ($n = 1$) and sertaline ($n = 1$) [26, 27]. Drugs classified as potentially both myopathic and photosensitizing included ibuprofen ($n = 5$), trimethroprim/sulphamethoxazole ($n = 3$), isoniazid ($n = 2$) and erythromycin–sulfisoxazole ($n = 1$). Drugs not known to be either myopathic or photosensitizing included amoxicillin ($n = 4$), cefaclor ($n = 3$), pseudoephedrine ($n = 2$), cetirizine ($n = 1$), albuterol inhaler ($n = 1$), flecainide ($n = 1$), bromopheniramine maleate ($n = 1$), nedocromil ($n = 1$), oxybutynin ($n = 1$), permethrin ($n = 1$), pyrethrine ($n = 1$), cantharidine ($n = 1$), cefadroxil ($n = 1$), acetaminophen ($n = 1$), streptomycin ($n = 1$), erythromycin ($n = 1$) and nystatin ($n = 1$). Drugs whose classification is unknown included unknown antibiotic ($n = 10$), birth control ($n = 3$) and anaesthetic ($n = 1$). *$P = 0.004$; OR 15.4; 95% CI 1.8, 135. †$P = 0.008$; OR 18.9; 95% CI 1.0, 358.

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-α [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 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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Appendix 1

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