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Concise report

Environmental factors associated with disease flare in juvenile and adult dermatomyositis

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Abstract

Objective. The aim was to assess environmental factors associated with disease flare in juvenile and adult dermatomyositis (DM).

Methods. An online survey of DM patients from the USA and Canada examined smoking, sun exposure, infections, medications, vaccines, stressful life events and physical activity during the 6 months before flares, or in the past 6 months in patients without flares. Differences were evaluated by χ^2 and Fisher's exact tests, and significant univariable results were examined in multivariable logistic regression. Residential locations before flare were correlated with the National Weather Service UV index.

Results. Of 210 participants (164 juvenile and 46 adult DM), 134 (63.8%) experienced a disease flare within 2 years of the survey. Subjects more often reported disease flare after sun exposure [odds ratio (OR) = 2.0, P = 0.03], although use of photoprotective measures did not differ between those with and without flare. Urinary tract infections (OR = 16.4, P = 0.005) and gastroenteritis (OR = 3.2, P = 0.04) were more frequent in the preceding 6 months in those who flared. Subjects who flared recently used NSAIDS (OR = 3.0, P = 0.0003), blood pressure medicines (OR = 3.5, P = 0.049) or medication for depression or mood changes (OR = 12.9, P = 0.015). Moving to a new house (OR = 10.3, P = 0.053) was more common in those who flared. Only sun exposure (OR = 2.2) and NSAIDs (OR = 1.9) were significant factors in multivariable analysis.

Conclusion. Certain classes of environmental agents that have been associated with the initiation of DM, including sun exposure and medications, may also play a role in disease flares.

Key words: dermatomyositis, juvenile dermatomyositis, disease flare, environmental factors

CLINICAL SCIENCE

Rheumatology key messages

- Several environmental factors were related to disease flare in subjects with DM.
- Sun exposure and NSAID use were the most significant environmental risk factors associated with flare in DM.

Introduction

DM is a rare autoimmune disease characterized by chronic skeletal muscle and skin inflammation. DM may develop in genetically predisposed individuals [1] after environmental exposures such as infections, drugs, vaccines, medical devices, physical exertion, emotional stress and ultraviolet radiation (UVR) [2–6]. The contribution of environmental

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factors to DM pathogenesis is not fully understood, but *in utero* exposure to pollutants has been implicated [7]. To date, most environmental associations with DM disease onset are based on case–control studies, registries, case series and reports [2]. The role of the environment in disease exacerbation has not been examined. We assessed environmental exposures in relationship to increased disease activity (flare) in juvenile and adult DM through an online patient questionnaire. Our aim was to screen for factors suggestive of a contribution to flare.

Methods

Subjects

An online survey was conducted for juvenile (n = 164) and adult (n = 46) DM patients from the USA and Canada who were $\geqslant 1$ year from diagnosis. Subjects were recruited through myositis clinics and patient support groups. Participants were diagnosed with DM between 1980 and 2011. Parents completed the questionnaire for paediatric patients. The Institutional Review Board at The George Washington University approved the study, and no informed consent form was required. Research was performed in accordance with the Declaration of Helsinki. Data were collected from February 2011 to February 2013. The survey included questions to confirm a diagnosis of probable or definite DM. Positive responses were ascertained for muscle weakness (95%), Gottron's papules (87%), heliotrope rash (84%) and elevation of serum muscle enzymes (83%). Fifty-five individuals (41%) reported a muscle biopsy that supported the diagnosis. The survey assessed disease activity rather than severity. It was not designed to capture features of disease burden (e.g. historical frequency of flares or function). Our questionnaire (Supplementary Data, available at *Rheumatology* Online) solicited information relating to the 6 months before flare (if the patient experienced a flare within the past 2 years) or in the past 6 months (if no flare within the past 2 years). A 2-year window was chosen to obtain adequate numbers of patients who had experienced a flare, but also to minimize recall bias. Although we inquired about the date of DM diagnosis, our aim was not to assess the relationship between disease onset and flare. Adjudication of the distinction between symptom onset and disease diagnosis was beyond the scope of this project.

Definitions

Disease flare was defined as the onset of increasing disease activity requiring therapy intensification. Specifically, subjects were told that a myositis disease flare is defined for this study as an increase in signs or symptoms related to the myositis illness in which the patient's doctor has told you that the disease is more active and this has required an increase in medicine(s) or the addition of new medicine(s). Subjects who responded affirmatively were asked if the flare involved skin rash, muscle weakness, joint swelling, fatigue, fever, swallowing difficulty, lung disease or other organ system.

The environmental exposures assessed included smoking, sun exposure, infections, medications, vaccines, stressful events and sports. The UVR index was obtained from the National Weather Service UV Index Cities Forecast Archive (ftp://ftp.cpc.ncep.noaa.gov/long/uv/cities). The UVR index data for 30 and 90 days before the date of DM flare was based upon the residential city at the time of flare (or for patients without flare, a date 2 years before the survey), as published previously [5].

Unusual sun exposure was defined as red or painful sunburn that lasted a day or more. Infection before disease flare was defined as skin infection, cold or upper respiratory infection, influenza (the flu), urinary tract infection, strep throat, pneumonia, hepatitis, nausea, vomiting and/or diarrhoea (a stomach virus or gastroenteritis), fever or a febrile illness or other infection.

Statistical analysis

GraphPad InStat version 3.06 for Windows (GraphPad Software, San Diego, CA, USA) and SAS Enterprise Guide 5.1 (SAS Institute Inc., Cary, NC, USA) were used. To compare proportions between the groups, the χ^2 and Fisher's exact tests were used. Logistic regression analysis used significant predictors identified from univariable analysis with stepwise selection ($P < 0.05$). P-values were adjusted for multiple comparisons using Holm's procedure [8]. P-values were determined as significant when the adjusted P-values were <0.05.

Results

Of the 210 participants with DM, 63.8% (103 juvenile; 31 adult) experienced a flare and 36.2% (61 juvenile, 15 adult) did not experience a flare within the past 2 years (Table 1). Respondents reported that a flare involved rashes in 70.9% and muscle weakness in 64.2% of cases. Fewer patients aged 0–5 years did not experience a flare (2.9 *vs* 19.7%), P = 0.0005; OR = 0.12 (95% CI: 0.04, 0.42). There were no differences in gender, in race distribution or in myositis medication reduction in the prior 3 months between those who did and did not flare.

Subjects who flared more often reported unusual sun exposure (44.4 *vs* 28.6%, P = 0.03; OR = 2.0, 95% CI: 1.1, 3.7; Table 2), with worsening of rash (39.6%), muscle weakness (15.0%) and fatigue (26.8%) compared with those who did not flare. Patients who flared more frequently spent time outdoors (but <30 min/day) compared with those who did not flare (22.6 *vs* 11.3%, P = 0.04; OR = 2.5, 95% CI: 1.1, 6.1). However, use of photoprotective measures did not differ between the two groups.

Subjects who flared more frequently experienced urinary tract infections (10.2 *vs* 0.0%, P = 0.005; OR = 16.4, 95% CI: 0.96, 280.2) and gastroenteritis (16.5 *vs* 5.8%, P = 0.04; OR = 3.2, 95% CI: 1.1, 0.8) within 6 months of flare compared with those who did not flare. They also more often used NSAIDs (63.4 *vs* 36.8%, P = 0.0003; OR = 3.0, 95% CI: 1.7, 5.3), blood pressure medicines (12.7 *vs* 3.9%, P = 0.049; OR = 3.5, 95% CI: 1.0, 12.5) and psychiatric medications (7.5 *vs* 0.0%, P = 0.001; OR = 12.9, 95% CI: 0.74, 223.5). Moreover, within the

TABLE 1 Demographic features of survey participants with JDM and adult DM

Demographic Feature	JDM patients			DM patients		
	Who experienced disease flare n (%) n = 103	Who did not experience disease flare n (%) n = 61	All JDM n (%) n = 164	Who experienced disease flare n (%) n = 31	Who did not experience disease flare n (%) n = 15	All DM n (%) n = 46
Age, years						
0–5	3 (2.9)	12 (19.7)*	15 (9.1)	0	0	0
6–10	38 (36.9)	23 (37.7)	61 (37.2)	0	0	0
11–15	30 (29.1)	9 (14.8)	39 (23.8)	0	0	0
16–20	16 (15.5)	9 (14.8)	25 (15.2)	0	0	0
21–30	10 (9.7)	6 (9.8)	16 (9.8)	4 (12.9)	1 (6.7)	5 (10.9)
31–40	6 (5.8)	2 (3.3)	8 (4.9)	7 (22.6)	4 (26.7)	11 (23.9)
41–50	0	0	0	9 (29.0)	5 (33.3)	14 (30.4)
51–60	0	0	0	8 (25.8)	1 (6.7)	9 (19.6)
61–70	0	0	0	2 (6.5)	4 (26.7)	6 (13.0)
71–80	0	0	0	1 (3.2)	0	1 (2.2)
Gender						
Female	69 (67.0)	40 (65.6)	109 (66.5)	30 (96.8)	13 (86.7)	43 (93.5)
Race						
Caucasian	79 (76.7)	49 (86.0)	128 (78.8)	27 (87.1)	12 (80.0)	39 (84.8)
African-American	2 (1.9)	1 (1.8)	3 (1.8)	3 (9.7)	0	3 (6.5)
Hispanic	9 (8.7)	1 (1.8)	10 (6.1)	1 (3.2)	3 (20.0)	4 (8.7)
Asian	3 (2.9)	1 (1.8)	4 (2.4)	0	0	0
Other	10 (9.7)	4 (7.1)	14 (8.5)	0	0	0
Duration to disease flare, mean (S.D.), months	13 (9.0)			10 (8.1)		
Percentage (CI) with myositis medication reduced in the past 3 months	48 (46.6)	27 (44.3)	75 (45.7)	12 (38.7)	6 (40.0)	18 (39.1)

Note that percentages may not reflect the number divided by the total number of subjects when data are missing. For the variables gender and ethnicity, $P > 0.05$. *$P = 0.0005$; odds ratio (95% CI): 0.12 (0.04, 0.42), P-values after Holm's adjustment for multiple comparisons (using family-wise error rates of 5%).

JDM group alone, patients who flared were more likely to report taking NSAIDs within the previous 6 months than those who did not flare ($P = 0.0005$; $= 3.457$; data not shown). Patients who flared were more likely to have received HPV vaccine within 6 months of the flare compared with those who did not flare (8.2 *vs* 0.0%, $P = 0.03$; OR = 10.0, 95% CI: 0.6, 175.5). Specifically, nine subjects reported flare (six JDM and three DM) with HPV vaccine (but of these, only five were under the age of 20 years). There was a trend in more frequent stressful events among those patients who flared, including moving to a new house (6.0 *vs* 0.0%, $P = 0.053$; OR = 10.3, 95% CI: 0.58, 180.8) and experiencing financial difficulties within 6 months of the flare (17.2 *vs* 7.9%, $P = 0.065$; OR = 2.4, 95% CI: 0.9, 6.2). Subjects who flared also tended to be more active physically (exercised one to five times/week; 74.7 *vs* 57.7%, $P = 0.06$; OR = 2.2, 95% CI: 1.0, 4.6). Other infections, medications, vaccines or stressors did not differ in frequency between those who did or did not flare (Table 2). From multivariable logistic regression analysis, only myositis worsening after sun exposure ($P = 0.017$; OR = 2.2, 95% CI: 1.2, 4.3) and NSAID use ($P = 0.023$; OR = 1.9, 95% CI: 1.2, 3.4) were significant risk factors for flare (overall likelihood ratio $\chi^2 = 11.35$, $P = 0.0034$).

We compared the residential UVR index for 30 and 90 days before the onset of disease flare with residential UVR exposure in patients who did not flare in the past 6 months. There was no difference in UV index between the two groups or by gender, race and age or when stratified by disease subset [4, 5] (JDM *vs* DM, or for the juvenile and adult groups combined).

Discussion

Clinical features of DM associated with disease mortality have been identified [9]. Little is known about factors associated with disease flare. This is important because flare may be associated with a poorer treatment response [10]. To this end, we sought to discover environmental factors contributing to disease exacerbation. The need to investigate this is underscored by two recent studies. Crude measures of socioeconomic status (postal codes, occupation) are associated with the incidence of biopsy-proven myositis [11]. In addition, there is an association

TABLE 2 Environmental factors associated with disease flare in patients with juvenile and adult DM

Environmental factors	DM patients who experienced disease flare, n (%)	DM patients who did not experience disease flare, n (%)	P-value	Odds ratio (95% CI)
Sun exposure				
Myositis worsening after sun exposure	59 (44.4)	20 (28.6)	0.03*	2.0 (1.1, 3.7)
Infection				
Any infection	51 (40.2)	21 (30.4)	0.22	1.5 (0.82, 2.9)
Cold or URI	37 (29.1)	22 (31.9)	0.75	0.88 (0.47, 1.7)
Gastroenteritis	21 (16.5)	4 (5.8)	0.04*	3.2 (1.1, 8.9)
Fever or febrile illness	13 (10.2)	6 (8.7)	0.81	1.2 (0.45, 3.3)
UTI	13 (10.2)	0	0.005*	NC
Skin infection	12 (9.4)	4 (5.8)	0.43	1.7 (0.52, 5.0)
Influenza	11 (8.7)	2 (2.9)	0.14	3.2 (0.71, 14.7)
Strep throat	6 (4.7)	4 (5.8)	0.74	0.81 (0.21, 2.6)
Pneumonia	1 (0.8)	4 (5.8)	0.053	0.13 (0.011, 0.81)
Hepatitis	1 (0.8)	0	1.000	NC
Medication				
NSAIDs	85 (63.4)	28 (36.8)	0.0003*	3.0 (1.7, 5.3)
Antibiotic or medicine to treat infection	45 (33.6)	18 (23.7)	0.16	1.6 (0.86, 3.1)
MTX	38 (28.4)	20 (26.3)	0.87	1.1 (0.60, 2.0)
HCQ	24 (17.9)	14 (18.4)	1.000	0.97 (0.46, 2.1)
Blood pressure medicine	17 (12.7)	3 (3.9)	0.049*	3.5 (1.0, 12.5)
Medicine for depression or mood changes	10 (7.5)	0	0.015*	NC
Acne medicine	6 (4.5)	7 (9.2)	0.23	0.46 (0.15, 1.4)
Oral contraceptive	3 (2.2)	0	0.55	NC
Cholesterol-lowering drugs				
Statins	5 (3.7)	0	0.16	NC
Niacin	2 (1.5)	0	0.54	NC
Fibrates	1 (0.7)	0	1.000	NC
AZA	3 (2.2)	0	0.55	NC
Anti-seizure medicine	0	1 (1.3)	0.36	NC
Flare following vaccine				
Any vaccine	56 (45.5)	29 (42.0)	0.74	0.86 (0.46, 1.7)
Influenza, not defined	46 (41.8)	28 (52.8)	0.24	0.64 (0.34, 1.3)
Swine flu, H1N1	34 (30.9)	16 (30.2)	1.000	1.0 (0.51, 2.1)
Hepatitis B	10 (9.1)	2 (3.8)	0.34	2.6 (0.61, 11.9)
HPV	9 (8.2)	0	0.03*	NC
Tetanus	6 (5.5)	5 (9.4)	0.34	0.55 (0.15, 1.7)
Other	5 (4.5)	2 (3.8)	1.000	1.2 (0.25, 6.3)
Stressful life events				
Change school or job	33 (24.6)	15 (20.7)	0.49	1.3 (0.67, 2.6)
Patient ill or injured	29 (21.6)	12 (15.8)	0.37	1.5 (0.70, 3.1)
Serious financial difficulties	23 (17.2)	6 (7.9)	0.065	2.4 (0.9, 5.9)
Spouse, partner, close relative or friend died	22 (16.4)	7 (9.2)	0.21	1.9 (0.78, 5.1)
Spouse, partner, close relative or friend ill or injured	20 (14.9)	8 (10.5)	0.41	1.5 (0.61, 3.4)
Move to a new house	8 (6.0)	0	0.053*	NC
Loss of job	7 (5.2)	1 (1.3)	0.26	4.1 (0.69, 47.1)
Separation or divorce	6 (4.5)	4 (5.3)	0.75	NC
Physical assault	4 (3.0)	0	0.30	NC
Convicted crime	0	0		

Note that percentages may not reflect the number divided by the total number of subjects when data are missing. Univariable analyses are reported. Odds ratios are NC when the frequency is 0% in one group. *$P \leqslant 0.05$ values after Holm's adjustment for multiple comparisons (using family-wise error rates of 5%). NC: not calculable; URI: upper respiratory tract infection; UTI: urinary tract infection.

between exposure to air pollution and disease activity in paediatric SLE [12].

Our study design emphasized a patient survey to capitalize on a web-based strategy. We hoped to capture a larger cohort of subjects not otherwise accessible to a single centre. The geographical breadth of our outreach was enhanced by the support of a non-profit foundation with a disease-specific interest. Hence, a high response from paediatric cases was captured. Our study design poses validity and reliability challenges. Two challenges include recall bias and attribution error. To address validity issues related to self-reporting, we required respondents to relate their personal experience of flare to intensification of medical management. Likewise, in order to address reliability issues related to self-reporting, we required respondents to attribute changes in the construct being measured (disease activity) to clinically accepted end-organ manifestations (rash, weakness, swallowing problem, etc.). In this manner, we addressed internal consistency and the potential for measurement error. In essence, we operationalized patient-centred disease activity reporting and did not simply rely upon a global score. Thus, we discerned a number of factors that are significantly associated with flare, including sun exposure, medications (NSAIDs, anti-hypertensives, antidepressants), certain infections (urinary tract infections, gastroenteritis) and possibly HPV vaccination. Nevertheless, these data are underpowered for performing meaningful subgroup analyses (e.g. for age-restricted medication effects). Finally, we found a non-significant trend for DM flare associated with stressful events (moving to a new house, financial stress), illuminating a possible adverse impact of psychosocial factors. Vaccines other than HPV did not show a signal. Of the predictor variables, the best minimal subset yields a model for flare that includes sun exposure and NSAIDs.

Our finding that self-reported sun exposure is associated with flare is consistent with previous research demonstrating an association between UVR and clinical and serological phenotypes [4, 5]. Although it might be challenging for subjects to quantify the duration of personal UVR exposure, we are encouraged that self-reported melanoma risk factors, which include such UVR exposure information, are reproducible [13]. Our inability to corroborate this finding with published 30- and 90-day meteorological data could reflect seasonal or geographical differences in the groups or be attributale to insufficient power. It could also reflect lack of exposure information at the individual level (personally worn UV monitors).

It is not surprising that antecedent infection may be associated with DM flare, given reports of an association with DM onset [2, 14, 15]. More surprising, however, is our finding that commonly used medications (NSAIDs, anti-hypertensives) may contribute to disease activity. Research into the photosensitizing nature of these drugs may be fruitful [16]. Whether our findings are clinically meaningful (e.g. whether they imply cause or effect) will require dedicated hypothesis testing in follow-up studies. Finally, our data highlight the need for research into surrogate measures of sun exposure.

We recognize important study limitations. Study design enriched participation rate by in-person invitation at specialty clinics and online advertising. This was at the expense of being able to capture the overall response rate. Our survey relied upon self-identified patient reporting, and the survey psychometric properties were not validated by confirmation of diagnosis and flare in medical records or in the exposures. Inherent in the nature of our study design was the possibility of recall bias. Additional error may have been introduced with the choice of time line for reporting (6-month lead-time before flare). Together, these latter issues may contribute to over-ascertainment. This tendency to inflate the significance of preconceived risk factors is called the labelling effect [17]. In future studies, such limitations should be addressed either with long-term randomized interventions or by careful population-based observational studies. Another limitation is low statistical power to assess some associations, evident by the wide confidence intervals for many of the findings. An assessment of the intensity of environmental exposure for each parameter studied was beyond the scope of this project. Likewise, an unappreciated evolution (during the 2-year time frame antecedent to data collection) of prevalent medical practice patterns could impact the validity of our findings. Therefore, the findings of this study should be considered exploratory. They neither allow for ascertainment of whether the overall effects are applicable to clinically important subgroups nor for better delineation of potential interactions between risk factors.

In conclusion, these questionnaire data in a large population of juvenile and adult DM patients suggest that a number of environmental exposures that have been related to the onset of DM may also operate ultimately to contribute to disease exacerbation.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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