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Running Title: UVR and Disease Severity in JDM

Title: The Association of Short-term Ultraviolet Radiation Exposure and Disease Severity in Juvenile Dermatomyositis

Subtitle: Results from the Childhood Arthritis & Rheumatology Research Alliance Legacy Registry

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ABSTRACT

Objective: Ultraviolet radiation (UVR) is considered to be an important environmental factor in the clinical course of children with JDM. We aimed to evaluate the association between UVR and severe disease outcomes in JDM.

Methods: This is a cross-sectional study of JDM subjects enrolled in the U.S. multi-center Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry from 2010-15. Mean UV index (mUVI) in the calendar month prior to symptom onset in each subject's zip code was calculated from daily satellite solar noon measurements. Multivariable logistic regression was used to model the relationship between mUVI and calcinosis as well as other outcomes of severe disease. Covariates included sex, race, age, time to diagnosis, disease duration, and latitude.

Results: In a multivariable model, there was no association between mUVI and calcinosis. Black race was associated with a 3-fold greater odds of calcinosis. However, there was a significant statistical interaction

between race and UVI. Accounting for this interaction, the odds of calcinosis markedly decreased in black subjects and steadily increased in non-black subjects over a range of increasing mUVI. Higher mUVI was associated with decreased odds of using biologics or non-methotrexate DMARDs and skin ulceration.

Conclusions: We describe a novel association between UVR, calcinosis, and race in a large cohort of patients with JDM. This study furthers our knowledge of the role of UVR in the clinical course of JDM and highlights the complex interplay between genes and environment in the clinical phenotypes and development of calcinosis in children with JDM.

Significance and Innovations:

- This study explores the association between the environmental factor, UV radiation, and disease severity outcomes in a large registry of patients with JDM by integrating clinical and demographic data from the CARRA registry with historical NASA satellite measurements.
- Mean UVI exposure in the month prior to disease onset was associated with development of calcinosis, however, the directionality of this relationship was dependent on race.
- Mean UVI exposure was not associated with other features representative of severe disease including: skin ulceration, CHAQ>1, use of biologics or non-methotrexate DMARDs, use of IVIG, or persistent skin disease, muscle weakness, or steroid use beyond two years of disease duration.
- These results further our knowledge of the role of UVR in the clinical course of JDM and highlight the need for clinicians and researchers to be aware of the complex interplay of genes and environment in the clinical phenotypes of children with JDM.

Juvenile dermatomyositis (JDM) is the most common subtype of the juvenile idiopathic inflammatory myopathies (IIM), a group of heterogenous autoimmune disorders characterized by muscle inflammation. JDM is distinguished from other juvenile IIMs by distinctive, photo-distributed skin rashes, and UV radiation (UVR) has been postulated to play a role in disease pathogenesis[1–4]. Photosensitivity is reported in nearly half of patients with juvenile myositis[5], and exacerbations of skin disease following sun exposure have been described. Once DM is established, UVR appears to be a strong trigger: laboratory testing of non-irradiated skin of adults with dermatomyositis (DM) determined increased sensitivity to UV-B radiation compared to healthy controls, many of whom also reported photosensitivity and disease exacerbation following sun exposure[6], and questionnaire data from DM and JM patients suggested that UV exposure is an important environmental exposure correlated with disease flares[7].

Prior research investigating the link between UVR and IIMs suggests that UVR may modulate myositis phenotypes and auto-antibody profiles. A global study showed that the proportion of individuals with DM relative to polymyositis (PM) rose incrementally with increasing UVR across diverse geographical regions worldwide, and these differences could not be explained by variation in population-specific genetic structure[1]. In a study of 298 patients with juvenile myositis, those with JDM who had higher UVR exposure in the month prior to symptom onset were more likely to have anti-p155/140 antibodies[4], which have been associated with a chronic disease course[2,5]. In addition, they were less likely to have anti-MJ antibodies, which have been associated with a monocyclic disease course[5]. Among this cohort, the strongest association between UVR and anti-p155/140 antibodies was observed in white males, indicating there may be differential effects of UVR based on gender and race.

Collectively, these findings suggest that UVR may modulate clinical phenotypes. However, it is unclear if initial UVR exposure has systemic effects on the immune system that result in a more severe disease course. The development of severe disease features, such as calcinosis or skin ulcerations, and need for stronger immune suppressive agents can cause significant morbidity in JDM. Calcinosis, in particular, may cause infection, pain, limited joint mobility, and physical disfigurement. Risk factors for severe disease and calcinosis are not well understood but have been associated with delay in diagnosis, longer disease duration, race, and myositis specific autoantibodies (MSA)[5,8].

In this study, we investigated the association between mUVI in the month prior to symptom onset and disease severity in a large cohort of patients with JDM from the Childhood Arthritis & Rheumatology Research Alliance (CARRA) Legacy Registry. We used calcinosis and other measures collected in the registry, including skin ulceration, CHAQ >1, and second-line medication use as proxies for severe disease. We hypothesized higher UVR exposure would be associated with more severe disease outcomes. An enhanced understanding of the role of UVR in JDM can help clinicians to develop interventions to attenuate this exposure and improve long-term outcomes in JDM.

Patients and Methods

Patients: This is a cross-sectional study of patients meeting definite or probable diagnostic criteria for JDM by the modified Bohan and Peter criteria enrolled in the CARRA Legacy Registry. This is a U.S. multi-center registry, which enrolled subjects with a variety of childhood rheumatic diseases between 2010 and 2015. A subset of patients with JDM enrolled in this registry has been previously described[9]. Subjects were in various stages of disease at time of enrollment. Those with incomplete data for the variables “date of symptom onset” and “zip code”

were excluded. Data was abstracted from the enrollment visit or at the subsequent visit when enrollment visit data was missing.

Methods: Mean UVI was determined based on subject U.S. zip code in the calendar month prior to symptom onset. This time frame was selected in order to evaluate the effect of short-term UVR in accordance with methods used by Shah et al[4] and the seasonal variation of UVR. UVI is an internationally-standardized unit on a linear scale, ranging from 0 to the mid-teens, which quantifies the amount of skin damaging erythema when the sun is highest in the sky (i.e., solar noon). A higher number indicates a shorter amount of time to skin erythema, which is also influenced by skin color and tendency to burn. The amount of UVR reaching the earth's surface is affected by total column ozone, elevation, surface reflectivity, cloud transmissivity, and tropospheric aerosol loading (pollutants or dust), all of which are accounted for in the UVI calculation.

Mean UVI in the calendar month prior to symptom onset was obtained from the National Aeronautics and Space Administration (NASA) Total Ozone Mapping Spectrometer (TOMS) and Ozone Monitoring Instrument (OMI), satellite instruments that record daily solar noon estimates of erythema dose rate across the U.S. Calcinosis, a hallmark morbidity in JDM that reflects severe disease and damage, was used as the primary outcome. Secondary outcomes included: history of skin ulceration, CHAQ (Childhood Health Assessment Questionnaire) disability index >1, treatment with biologics or non-methotrexate DMARDs, and treatment with IVIG. In the subset of patients with disease duration >2 years, we assessed additional outcomes, including persistent weakness, persistent skin rash (malar, Gottron's, heliotrope, or V/Shawl sign), and persistent steroid use.

Statistical Analysis: Subjects were stratified by UVI quartiles and comparisons were made using chi-squared tests for categorical variables

and Kruskal-Wallis tests for continuous variables, which were non-normal. Characteristics were also evaluated stratified by race. Based on our understanding of the relationship between UVR and disease severity outcomes, we included the following covariates in our model: sex, race, age at disease onset, time to diagnosis, and disease duration. We evaluated for interactions between sex and UVI and between race and UVI based on results of prior literature[3,4]. We dichotomized race as "black" and "non-black" based on prior work related to race and calcinosis as well as differential risk for damage from UVR due to skin pigmentation.

Multivariable logistic regression was used to evaluate the association between mUVI and each disease outcome. We evaluated for linearity in the predictors mUVI and latitude by including these terms as polynomial terms and evaluating if the polynomial terms enhanced fit. We evaluated interactions between mUVI and sex, and mUVI and race for each model. We included the interaction terms in the model if they were statistically significant. To test for spatial autocorrelation, Moran's I test was run on the residuals from the model.

Results

Patient Characteristics: 522 subjects were included. Median age at disease onset was 5 years (IQR 3, 9), 71.8% of subjects were female, and 11% were black. Among non-black subjects, 89% identified as white, and the remaining 11% identified as either Asian, American Indian or Alaskan Native, Native-Hawaiian or Pacific Islander or multi-racial/other. Median time to diagnosis was 3.1 months (IQR 1.6, 7.2) and median disease duration was 1.9 years (IQR 0.5, 4.4). Eleven percent developed calcinosis, 5.6% skin ulcerations, 15.5% had CHAQ>1, 24.9% used biologics or non-methotrexate DMARDs, and 34.1% used IVIG. There were 247 patients with disease duration >2 years, of whom 26% had persistent rash, 14% persistent weakness and 25% persistent steroid use. Mean UVI was 4.9 (SD±2.6). Stratified by UVI quartiles, clinical and

demographic characteristics were similar except for a higher proportion of individuals with skin ulceration (p=0.03) and history of treatment with biologics or DMARDs (p=0.02) in lower quartiles of UVI. Patient characteristics stratified by race were similar except for a greater prevalence of calcinosis among black subjects, 24.5%, compared to 9.2% of non-black subjects (p=0.002).

Mean UVI as a predictor of calcinosis: In a multivariable logistic regression model, there was no significant association between mUVI and calcinosis (adjusted p=0.64, Table 1). Black race was associated with a 3-fold greater odds of calcinosis. However, there was significant statistical interaction between race and UVI. Accounting for this interaction, the odds of calcinosis markedly decreased in black subjects and steadily increased in non-black subjects over the range of increasing mUVI. This interaction is visualized in Figure 1 for a female at mean values of all other covariates in the model. There was no interaction between UVI and sex, therefore this term was not included in the model. Moran's I test revealed no significant residual spatial autocorrelation (p=0.36). Additional risk factors for calcinosis included: male sex, older age at disease onset, longer disease duration, and delay in diagnosis (Table 1).

Secondary Outcomes: In a univariable model, mUVI was associated with decreased odds of developing skin ulceration and treatment with biologics or non-methotrexate DMARDs (see Table 2). After adjustment for covariates, this relationship remained significant for the outcome of treatment with biologics or non-methotrexate DMARDs and trended toward significance for the outcome of skin ulceration. In the multivariable models, there was also a trend toward increased odds of having a CHAQ disability index>1, but this did not meet statistical significance.

Discussion

In this study of 522 subjects with JDM enrolled in the CARRA Legacy Registry, we describe the association between short-term UVR exposure in the month prior to disease onset and several outcomes representative of severe disease. We found a novel association between mUVI and calcinosis dependent on race. Consistent with prior studies, which identified black race as a risk factor for calcinosis in JDM[8], and we found that black subjects living in areas with lower UVI, had a 3-fold greater odds of calcinosis compared to non-black subjects. However, when accounting for interaction between race and mUVI, we were surprised to find a striking negative correlation between calcinosis and mUVI in black subjects suggesting a protective effect of higher UVR exposure on calcinosis risk in this subgroup. Non-black subjects had increased risk of calcinosis beyond those of black subjects at higher levels of mUVI suggesting a correlation between higher UVR exposure and development of calcinosis in lighter skinned subjects. These findings help to confirm the need for a personalized, differential approach to treatment and monitoring recommendations in patients with JDM.

We would like to emphasize that these findings are correlative and future research is needed to better understand the causative influence of UVR in myositis. However, our results are in accordance with prior studies in JDM and DM in the U.S. that have shown associations between UVR and clinical phenotypes to be significant only in Caucasian individuals[3,4]. Skin color is a key factor in determining "time to burn" and thus, may also determine the susceptibility of an individual to the effects of UVR on immune responses. The field of photoimmunology has shown that in addition to local immune responses, UVR also causes systemic immunomodulatory effects, which have been theorized to play a role in human autoimmune diseases[10]. In addition, there is growing evidence that vitamin D levels are associated with disease activity in autoimmune diseases, including JDM[11].

Genetic factors may also play a role in predisposing individuals with JDM to UVR sensitivity as well as calcinosis. The TNFα-308A polymorphism is a risk factor for JDM[12] and DM[13] in the Caucasian population. Stimulation of skin keratinocytes and fibroblasts with UV-B causes increased transcription of the cytokine, TNFα. This cytokine triggers cell apoptosis and release of intracellular auto-antigens, which may contribute to disease pathogenesis. Children with JDM who have the TNFα-308A polymorphism have increased risk of developing calcinosis[13,14]. Consequently, it is conceivable that non-black subjects in our study, the majority of which are Caucasians, are enriched for this genetic risk factor which may make them more susceptible to both the effects of UVR on immune responses, possibly via increased TNFα production, and the development of calcinosis.

We did not find additional evidence to support our hypothesis when evaluating additional outcomes representative of severe disease. In fact, we found decreased odds of treatment with biologics and non-methotrexate DMARDs and skin ulceration with increasing mUVI. There are several possible explanations for these unexpected results. One possibility is that children who are photosensitive and living in regions with higher UVR are more conscious of the need for sun protection and modify this risk factor. Another possibility is that genetic factors and/or myositis auto-antibodies moderate the effect of UVR on disease phenotypes. Mamyrova et al., showed that while TNFα 308A is a genetic risk factor for calcinosis, it is not a risk factor for skin or gastrointestinal ulcerations[14]. Likewise, prior research shows that anti-MJ antibodies are associated with calcinosis[5] and anti-p155/140 antibodies are associated with skin ulcerations in the JDM population[15]. While UVR is an important environmental factor in the course of JDM, it is possible genetic and serologic profiles are more influential in determining disease severity.

Prior studies investigating the role of UVR in IIM's include a more heterogeneous group of patients with various types of IIM's. Our study is

strengthened by focusing on a large cohort of patients with JDM from the CARRA registry, who reside in diverse geographical regions across the U.S. The CARRA registry highlights the versatility of large patient registries in research and demonstrates how patient registries can be integrated with other publicly available datasets to answer important questions. Furthermore, we utilized individual zip codes for calculation of mUVI, which we believe provides a more relevant and resolute estimate of UVR exposure.

There are limitations to this study to consider. Individual exposure data, such as the duration and time of day spent outdoors and use of sun protective measures (e.g., sunscreen use, hats) represent unmeasured confounders. Furthermore, behaviors modify the risk associated with UVR exposure, and there may be regional differences in awareness and use of these interventions. Historically, individual behavior and exposure data have not been practical to collect, and questionnaires are subject to recall bias. Emerging technologies may allow for in-depth studies regarding UVR and disease on the individual level in the future. In addition, we used the UVI to estimate UVR exposure, which is heavily weighted in UV-B. Unfortunately, it is not possible to separate UV-A and UV-B exposures in historical UVR recordings. Future studies, which are able to distinguish these exposures, are needed.

We were also limited in the outcomes we could assess and realize the outcomes in our study may not definitively identify subjects with severe disease. Overall, patients in the CARRA Registry trended toward milder disease with a low prevalence of severe features[9] and since screening methods are not standardized, we may not have captured the true incidence of calcinosis. In addition, the median disease duration in this cohort was 1.9 years, which may not have been long enough to identify all patients at risk for developing calcinosis.

In summary, we describe a novel association between UVR and the development of calcinosis dependent upon race in a large cohort of

patients with JDM. This study furthers our knowledge of the role of UVR in the clinical course of JDM and highlights the need for clinicians and researchers to be aware of the complex interplay of genes and environment in the clinical phenotypes of children with JDM. As we continue to study this complex autoimmune disease, it is imperative that we consider the combination of multiple data types, including the exposome, demographics, genomics, serologic patterns, and clinical phenotypes, in order to personalize our treatment approach and improve outcomes for each child affected by JDM.

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Table 1: Multivariable logistic regression model of mean UVI as a predictor of Calcinosis

Predictor	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Mean UVI	0.94	0.84-1.05	0.25	1.03	0.90 - 1.18	0.64
Black race	3.22	1.54-6.41	0.001*	3.36	1.22 - 8.10	0.01*
Mean UVI*Black race	0.69	0.48-0.95	0.03*	0.67	0.45 - 0.94	0.03*
Age at disease onset (per yr)	1.01	0.94-1.09	0.71	1.10	1.01 - 1.20	0.03*
Female sex	0.62	0.34-1.14	0.11	0.48	0.25 - 0.95	0.03*
Diagnosis interval (per mo)	1.03	1.01-1.05	0.005*	1.04	1.02 - 1.06	<0.001*
Disease duration (per yr)	1.23	1.13-1.33	<0.001*	1.30	1.18 - 1.44	<0.001*

**indicates p-value <0.05; model adjusted for sex, age at disease onset, time to diagnosis, disease duration, race*

Table 2: Mean UVI as a predictor of secondary outcomes of disease severity

Outcome	Unadjusted OR	95% CI	p-value	Adjusted OR	95% CI	p-value
All patients (N=522)						
Skin ulceration	0.85	0.72-0.99	**0.04***	0.86	0.72-1.00	0.05
CHAQ>1	1.07	0.98-1.18	0.14	1.08	0.98-1.19	0.08
Biologics or non-MTX DMARDs	0.88	0.82-0.96	**0.003***	0.87	0.80-0.95	**0.003***
IVIG	1.02	0.95-1.09	0.64	1.00	0.93-1.08	0.91
Disease duration >2 years (N=247)						
Persistent weakness	0.96	0.83-1.12	0.61	0.97	0.83-1.13	0.65
Persistent rash	0.95	0.86-1.06	0.39	0.97	0.87-1.08	0.61
Persistent steroid use	0.91	0.80-1.02	0.11	0.92	0.81-1.04	0.20

**indicates p-value <0.05; model adjusted for sex, age at disease onset, disease duration, and race*

Fig 1: Log odds of Calcinosis by Race