Comparison of pre- and post-natal environmental exposures in United States *versus* Brazilian patients with juvenile dermatomyositis

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Abstract

Objective

The objective of this study is to assess the differences in environmental exposures of juvenile dermatomyositis (JDM) patients in Brazil versus United States (U.S.).

Methods

JDM patients from 4 centres [3 U.S. (n=66), 1 Brazil (n=36)] were enrolled. Exposures during pregnancy were assessed by questionnaire, including occupational exposures, sources of inhalable pollution near the mother's home and work, and exposure to tobacco/alcohol.

Results

JDM mean age onset was 7.12 (SD±4.02) years for U.S. patients and 5.30 (SD±2.52) for Brazilians (p=0.004). During pregnancy, American mothers more frequently worked outside home than Brazilians (65.2% vs. 41.2%; p=0.032). Americans more often worked in offices (51.2% vs. 14.3%; p=0.027) and Brazilians, as teachers (28.6% vs. 4.8%; p=0.029). Americans commuted to work more frequently by subway (68.3% vs. 7.1%; p=<0.01), Brazilians, by bus (64.3% vs. 14.6%; p=0.001). Brazilians were more frequently exposed to dust (42.9% vs. 9.5%; p=0.01) and tobacco (50% vs. 23.1%; p=0.01). Places where Brazilians worked (35.7% vs. 9.1%; p=0.03) and lived (50% vs. 10.6%; p=<0.01) during pregnancy were closer to factories and quarries, as well as where the child was born (32.3% vs. 8.6%; p=0.007). After birth, Brazilian patients were more frequently exposed to tobacco, both through their fathers' smoking (26.5% vs. 6.2%; p=0.009) and other household residents (36.4% vs. 9.2%; p=0.002).

Conclusion

Earlier onset of symptoms, possibly related to early life environmental exposures, was observed in Brazilian patients. Their mothers lived and worked closer to factories and quarries, commuted to work by bus and were more exposed to dust and tobacco.

Key words

juvenile dermatomyositis, environmental exposure, occupational exposure, pregnancy, second hand smoking

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Introduction

Juvenile dermatomyositis (JDM) is a rare chronic systemic autoimmune disease and characterised by symmetric proximal muscle weakness and pathognomonic rash (1). The pathogenesis is not completely understood, but a relevant aspect of the pathophysiology of JDM is the expression of the major histocompatibility complex (MHC) and complement activation with deposition of the membrane attack complex (C5b-9) in endomysial capillaries, with associated perivascular inflammation, capillary depletion, muscle ischemia, necrosis, and muscle fibre atrophy (2, 3). It is likely that immune-mediated vascular reactions arise from exogenous exposures that trigger the disease in genetically susceptible individuals. These environmental exposures may include maternal smoking, drugs, infections, ultraviolet radiation (UVR) and pollutant gases (4). Air pollution is one of the environmental factors involved in systemic inflammation and autoimmunity and consists of a heterogeneous mixture of gases and particles that include carbon monoxide (CO), nitrates, sulfur dioxide (SO_2), ozone (O_3), lead, toxic products of tobacco smoke, and particulate matter (PM). Oxidative stress and inflammation induced by inhaled pollutants can result in acute and chronic respiratory disorders, as well as contribute to a state of systemic inflammation and autoimmunity (5). Previous studies have identified environmental triggers for JDM and other rheumatological diseases (6-8). The question arises regarding the characteristics, differences, or similarities of the triggering factors in different locations around the globe (9). We conducted a study to evaluate and compare predetermined early life environmental and pregnancy related factors that may be risk factors for JDM across Brazil and the United States of America (USA).

Methods

This is a cross-sectional study that included JDM patients at four centres: Children and Adolescent Institute, University of São Paulo, Brazil and three U.S. centres (National Institutes of Health Clinical Center, Bethesda, MD, Seattle Children's Hospital, Seattle, WA; and University of California San Francisco, San Francisco, CA). JDM diagnosis was based on meeting probable or definite classification criteria according to Bohan and Peter's criteria (1). Parents completed a questionnaire (7, 8) to assess demographic data and environmental exposures during pregnancy, as well as following pregnancy prior to disease diagnosis. The questionnaire inquired regarding into prenatal, in utero and postnatal exposures around parental occupational exposures to demolition, chalk, construction and/or quarry dust, paints, varnish, gasoline vapor, and/or battery fluids. It also inquired about stationary sources of inhalable pollution near the mother's home and work; maternal use of tobacco and alcohol, second-hand smoking (partner/father/husband or another person residing in the same household); maternal occupational exposure to one of the inhalable agents: demolition/construction/quarry dust or school chalk dust and volatile components (paints, varnishes, battery fluids, and fuel residues); and distance in meters between the residence and sources of inhalable pollutants present in the environment, including gas stations, factories, and quarries. Other variables included were gestational age (term, preterm, post-term) and patient birth weight (≤2.5 kg, ≥2.5 kg).

For statistical analysis across U.S. (all 3 U.S. centres) and Brazilian groups, continuous variables are presented as mean ± standard deviation (SD) or medians with interquartile range. Categorical variables are presented in absolute and relative values. Data was compared using Student's t-test or Mann-Whitney test for continuous variables, and Fisher's exact test for categorical variables. Statistical significance levels were set at 5% ($p<0.05$). Logistic regression was performed to identify potential risk factors to early symptom onset (≤7 years). A p-value<0.05 was considered statistically significant.

An additional socioeconomic analysis was assessed between 27 Brazilian JDM patients and 124 Brazilian health

Table I. Comparison of environmental pregnancy-related and early life exposures in United States (U.S.) and Brazilian patients with juvenile dermatomyositis (JDM).

	Patients		
	U.S. (N=66) n (%)	**Brazil (N=36)** n (%)	*p*-value
Mean age at symptoms onset	7.3 (SD ± 4.02)	5.3 (SD ± 2.52)	
Female	35 (59.3)	19 (54.3)	0.670
Age of diagnosis > 7 years old	31 (47)	6 (16.2)	0.004
Exposure			
Mother's occupation during pregnancy	43 (65.2)	14 (41.2)	0.032
• Office work	22 (51.2)	2 (14.3)	0.027
• Teacher	2 (4.8)	4 (28.6)	0.029
• Gas station attendant	1 (2.3)	2 (14.3)	0.146
• Saleswoman/ retail	8 (18.6)	1 (7.1)	0.427
• Kitchen/ restaurant	1 (2.4)	2 (14.3)	0.151
• Seamstress	1 (2.4)	1 (7.1)	0.434
• Healthcare	6 (14)	1 (7.1)	0.669
Maternal occupational exposures during pregnancy			
• Dust	4 (9.5)	6 (42.9)	0.01
• Varnish or paint	3 (7.1)	2 (14.3)	0.590
• Metals	3 (7.1)	0 (0.0)	0.565
• Batteries	7 (16.7)	0 (0.0)	0.174
• Fluorescent Lamp	6 (15.8)	0 (0.0)	0.163
Transport and commute to work			
• Subway commute to work	28 (68.3)	1 (7.1)	<0.001
• Bus commute to work	6 (14.6)	9 (64.3)	0.001
• Distance between work and factory/ quarry (<500 m)	4 (9.1)	5 (35.7)	0.03
Residential exposure during pregnancy			
• Distance between work and gas station (<500 m)	25 (49)	9 (6.3)	0.375
• Distance between residence and factory/ quarry (<500 m)	7 (10.6)	15 (50)	<0.001
• Distance between residence and gas station (<500 m)	20 (30.8)	13 (43.3)	0.254
Maternal habits during pregnancy			
• Passive smoke exposure	15 (23.1)	17 (50)	0.012
• Active smoking	7 (10.6)	5 (14.7)	0.536
• Passive smoke exposure	15 (23.1)	17 (50)	0.012
• Alcohol consumption	2 (3)	0 (0.0)	1.0
Birth factors			
• Prematurity	7 (11.9)	5 (19.2)	0.5
• Birth weight <2.5kg	10 (16.1)	2 (7.7)	0.497
• Birth weight >2.5 kg	30 (48.4)	10 (52.5)	0.798
Post-birth residential distances prior to JDM diagnosis			
• Distance between residence and factory/ quarry (<500 m)	5 (8.6)	10 (32.3)	0.007
• Distance between residence and gas station (<500 m)	17 (29.8)	12 (38.7)	0.478

SD: standard deviation.

children from the same geographic region and matched by age and sex distribution was included.

Results

A total of 36 patients were enrolled at the Brazilian centre and 66 at the three U.S. sites. The mean age at JDM symptom onset was significantly lower in Brazilian patients compared to U.S. patients (5.30±2.52 *vs*. 7.12±4.02 years; *p*=0.004). However, the mean time from symptom onset to diagnosis was shorter among U.S. patients (7.2±0.98 *vs*. 8.0±0.70 months), a difference with no statistical significance (*p*=0.68). Both groups had female sex predominance (59.3% U.S. and 54.3% Brazil). Table I details the comparison of environmental exposures between the Brazilian and US cohorts for JDM during gestation and early life.

Environmental factors studied in JDM patients during pregnancy

Occupational exposure during pregnancy of JDM patients. U.S. mothers worked outside their homes more frequently than Brazilian mothers (65.2% *vs*. 41.2%; *p*=0.032). U.S. mothers worked more often in offices compared to Brazilian mothers (51.2% *vs*. 14.3%; *p*=0.027). Brazilian mothers were more frequently employed as school teachers compared to U.S. mothers (28.6% *vs*. 4.8%; *p*=0.029). Brazilian mothers were more frequently exposed to dust (42.9% *vs*. 9.5%; *p*=0.01) in their work environment than U.S. mothers. No differences were found regarding employment in other areas, such as gas stations (*p*=0.146), retail and commerce (*p*=0.427), kitchens and restaurants (*p*=0.151), sewing (*p*=0.434), and healthcare (*p*=0.669). No differences were found regarding exposure to paints and varnishes (*p*=0.590), metals (*p*=0.565), batteries (*p*=0.174), and fluorescent lamps (p=0.163).

Transportation and commute to work during pregnancy

U.S. mothers used the subway to commute to work more frequently than Brazilian mothers (68.3% *vs*. 7.1%; *p*=0.01), while Brazilian mothers used buses more often (64.3% *vs*. 14.6%; *p*=0.001). The locations where Brazilian mothers worked during pregnancy were closer to factories and quarries (35.7% *vs*. 9.1%; *p*=0.03). No differences were found regarding the distance of the mothers' workplaces from gas stations (*p*=0.375).

Environmental factors studied in JDM patients during pregnancy and after birth

Residential exposure during pregnancy and after birth. The locations where Brazilian mothers lived during pregnancy were more often closer to factories and quarries (50% *vs*. 10.6%; *p*<0.0001). No differences were found regarding the distance of the residences

of Brazilian and U.S. mothers from gas stations (p=0.254).
The locations where Brazilian JDM patients lived (32.3% *vs*. 8.6%; p=0.007) were closer to factories and quarries. No differences were found regarding the distance of Brazilian and U.S. residences from gas stations (p=0.478).

Tobacco and alcohol exposure during pregnancy and after birth. Brazilian mothers were more exposed to second-hand smoke (50% *vs*. 23.1%; p=0.012) compared to U.S. mothers. There was no difference in active tobacco exposure (p=0.536) or alcohol exposure (p=1.0).
Brazilian JDM patients were more frequently exposed to passive second-hand smoke, both from paternal smoking (26.5% *vs*. 6.2%; p=0.009) and from other household members (36.4% *vs*. 9.2%; p=0.002). There was no difference in mothers' exposure to second-hand smoke.

Birth weight and prematurity
There were no differences in birth weight, whether large birth weight (p=0.798) or low birthweight (p=0.497), between Brazilian and U.S. patients. There was no difference in the frequency of prematurity (p=0.5) between Brazilian and U.S. patients.

Factors associated with early age at symptom onset
29/35 children from Brazil (83%) were significantly more likely to present symptom onset at or before 7 years of age compared with those 35/66 (53%) from the United States (p=0.004).
In univariate logistic regression analysis, Brazilian origin was associated with a higher likelihood of symptom onset ≤7 years (odds ratio [OR] 4.28, 95% confidence interval [CI] 1.57–11.67; p=0.004). Use of subway transportation was inversely associated with symptom onset ≤7 years (OR 0.22, 95% CI 0.07–0.75; p=0.015). No significant associations were observed between early symptom onset and sex, maternal occupation, maternal smoking, prematurity, low birth weight, or most prenatal and early-life environmental exposures.
In multivariable analysis including country of origin and transportation mode, none of the variables remained independently associated with early symptom onset.

Socioeconomic analyses
Brazilian socioeconomic analyses included 27 patients with JDM and 124 healthy children. Patients with JDM were more frequently represented in lower socioeconomic strata compared with controls, with significant differences observed for socioeconomic class A (2/26 (8%) *vs*. 34/124 (27%); p=0.032), class C (13/27 (48%) *vs*. 26/124 (21%), p=0.007), and combined class AB (11/27 (41%) *vs*. 95/124 (77%), p<0.001).
Median household income was also significantly lower among patients compared with healthy children (USD 10,700 (IQR: 30,818) *vs*. USD 28,918 (IQR: 38,129) p=0.017).

Discussion

This study noted a significant difference in age at JDM onset for Brazilian *versus* U.S. patients and identified several differences in early-life environmental and pregnancy-related exposures. Environmental influences in autoimmune diseases, specifically myositis, have been previously identified. Exposure to UV light, vitamin D deficiency, living in urban areas, exposure to air pollutants, tobacco, silica dust and chemical agents, medications, infections and vaccines proximal to diagnosis have been identified as environmental risk factors for adult and juvenile myositis (10-13). In addition, birth distributions appear to exhibit more pronounced seasonality in juvenile compared to adult inflammatory myopathies (14). Interestingly, Brazilian JDM patients had symptom onset an average of two years earlier compared to U.S. patients. Brazilian mothers were primarily teachers and lived and worked closer to factories and quarries, often using buses for transportation. In contrast, U.S. mothers typically worked in offices and used the subway. Brazilian mothers had greater exposure to dust and second-hand smoking from household members. These exposures to silica and other dusts, diesel fuel, and tobacco smoke prenatally and in early life are potentially involved in the onset of JDM in Brazil, where we previously found that maternal occupational exposure to school chalk dust and gasoline vapours was significantly higher in patients with JDM compared to healthy volunteers (7). Smoking mothers and exposure to second-hand smoke at home during pregnancy were also significantly more frequent in the case of patients with JDM. In multivariate analysis, maternal smoking, occupational exposure, and exposure to CO in the third trimester of pregnancy remained significant risk factors. These findings reinforce the role of inhaled pollutants and tobacco smoke during foetal development in JDM pathogenesis (7).
In a complementary study, responses from 35 patients with JDM and 124 healthy volunteers were evaluated to assess whether environmental factors could be associated with disease course or refractoriness to treatment. No associations were observed with prematurity at birth, maternal occupational exposure to pollutants during pregnancy, or exposure of the child until the fifth year of life with disease activity or refractoriness to treatment. Fifteen patients with JDM had a monocyclic course, 19 had a polycyclic or chronic course, and 18 were refractory to treatment. Maternal occupational exposure remained a trigger for JDM, along with exposure to O_3 in the fifth year of life (8).
The role of environmental factors as potential triggers for inflammatory myopathies, as well as their association with disease activity, disease course, and serologic subgroups, has been widely investigated (4, 10, 11). Evidence includes environmental pollutants, infectious agents, ultraviolet radiation, and potential effects on oral and faecal microbiota (9, 12-15). Prenatal exposures may also influence micro chimerism through maternal-foetal cell trafficking. Differences between Brazilian and American populations have not been previously explored in this context.
Given that Brazilian mothers showed higher rates of public transport use

and industrial exposure than those in the United States, a socioeconomic assessment was conducted to further investigate the Brazilian context. The socioeconomic analyses including healthy children in Brazil demonstrated that patients with JDM were more frequently represented in lower socioeconomic strata and had significantly lower household income compared with controls, suggesting that part of the observed exposure patterns may reflect broader socioeconomic and environmental conditions rather than disease-specific risk enrichment.

Differences in sample size between the United States (n=66) and Brazil (n=36), as well as variations in recruitment strategies and access to healthcare services, may have influenced the observed differences in age at symptom onset. Juvenile dermatomyositis is a rare disease, and disparities in sample size likely reflect differences in disease incidence and case ascertainment across countries. Population-based registry studies in the United States report incidence rates of approximately 3 cases per million children per year (16), whereas Brazilian data suggest lower incidence estimates (17, 18). Both cohorts were recruited from tertiary referral centres using comparable diagnostic criteria; however, differences in healthcare access and referral pathways may affect symptom recognition and timing of diagnosis. In addition, the smaller Brazilian sample size may reduce statistical power, and therefore the findings should be interpreted cautiously and considered exploratory.

Although the observed differences in exposure patterns may partially reflect underlying socio-demographic and geographic characteristics, it is important to emphasize that all participating centres are tertiary referral paediatric rheumatology centres that receive patients from broad and diverse regions nationwide, rather than from a single local area.

This study has some limitations as it was not designed to evaluate disease susceptibility. In addition, in view of the cross-sectional, questionnaire-based design, the assessment of prenatal and early-life exposures relied on retrospective reporting and may be subject to recall bias, particularly for exposures occurring many years before diagnosis.

Overall, the findings of this study point to the importance of environmental factors as potential contributors to autoimmune diseases. Differences in environmental exposures between Brazilian and American mothers may influence the age at JDM onset and potentially contribute to heterogeneous disease phenotypes. Further prospective studies incorporating healthy control groups and more detailed geographic and socioeconomic stratification are warranted.

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