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Early Infectious Exposures are Not Associated with Increased Risk of Pediatric-Onset Multiple Sclerosis

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Abstract

Objective—We sought to determine if early infectious exposures such as daycare, early use of antibiotics, vaccinations and other germ exposures including pacifier use and playing on grass are associated with multiple sclerosis (MS) risk in children.

Methods—This was a case-control study of children with MS or clinically isolated syndrome (CIS) and healthy controls enrolled at sixteen clinics participating in the US Network of Pediatric MS Centers. Parents completed a comprehensive environmental questionnaire that captured early infectious exposures, habits, and illnesses in the first five years of life. A panel of at least two pediatric MS specialists confirmed diagnosis of participants. Association of early infectious variables with diagnosis was assessed via multivariable logistic regression analyses, adjusting for age, sex, race, ethnicity, US birth region, and socioeconomic status (SES).

Results—Questionnaire responses for 326 eligible cases (mean age 14.9, 63.5% girls) and 506 healthy pediatric subjects (mean age 14.4, 56.9% girls) were included in analyses. History of flu with high fever before age five (p=.01), playing outside in grass and use of special products to treat head lice or scabies (p=0.04) were associated with increased risk of MS in unadjusted analyses. In the multivariable model adjusted for age, sex, race, ethnicity, and mother's highest educational attainment, these results were not statistically significant. Notably, antibiotic use (p=.22) and regular daycare attendance before age 6 (p=.09) were not associated with odds of developing MS.

Conclusion—Early infectious factors investigated in this study were not associated with MS risk.

Keywords

Multiple sclerosis; epidemiology; childhood infection; neonatal exposure

INTRODUCTION

In genetically susceptible individuals, early life environmental exposures may contribute to the immune dysregulation that underpins the etiology of multiple sclerosis (MS). Immune system development and maturation in infancy and early childhood may be especially sensitive to encounters with environmental and infectious agents. Epidemiologic studies of autoimmune disorders such as Crohn's and celiac disease, have identified associations between disease development and previous viral infection in the first years of life.[1,2,3] Similarly, case-control studies of potential associations of perinatal exposures and the development of juvenile arthritis and systemic lupus erythematous have shown that serious infection (requiring hospitalization) may contribute to risk of pediatric and adult-onset disorders of autoimmunity.[4,5] Exposure to Epstein-Barr Virus (EBV), a widely recognized risk factor for MS and other autoimmune diseases, is thought to contribute to immune dysregulation as a result of persistent B-cell infection and resulting T-cell surveillance.[6] However, late infection and subsequent mononucleosis clinical syndrome are thought to be associated with higher risk for MS compared to very early life EBV exposure.[7,8]

Apart from strong association between EBV seropositive status and MS risk, little is known about the potential contributions of various infections to the development of pediatric MS.

Studying pediatric MS offers the unique opportunity to capture patients early in disease course and in close temporal proximity to early childhood infectious exposures. In this retrospective case-control study of one of the largest cohorts of pediatric MS, we sought to investigate potential associations between early infectious exposures and risk of MS in children.

METHODS

Subjects and Design

As described in a previous investigation of maternal exposures and risk of pediatric-onset MS,[9] participants of this case-control study included children with MS or clinically isolated syndrome with at least two silent MR demyelinating lesions and healthy pediatric subjects recruited as part of a large nationwide study of environmental risk factors in MS between November 1, 2011 and July 1, 2016. Case status was established by the treating neurologist and subsequently confirmed by adherence to published criteria for pediatric demyelinating disease as determined by a panel of at least two MS specialists. [10,11] Subjects were recruited from sixteen clinics participating in an environmental risk factor study through the US Network of Pediatric MS Centers. All participating centers obtained institutional review board approval as well as written informed consent from parents of pediatric participant as well as assent as appropriate from children. Inclusion criteria for cases mandated enrollment within four years of disease onset. Healthy controls were enrolled from primary care, urgent care, and other pediatric clinics at the same institutions from which cases were recruited. Eligibility criteria for controls required (1) absence of any autoimmune disease, apart from eczema and asthma, as well as (2) negative history of MS in either parent. Demographic data, including race and ethnicity categories consistent with National Institutes of Health guidelines, and factors related to socioeconomic status (level of education of both parents) were provided by parents of pediatric participants.

Environmental Questionnaire

A comprehensive environmental questionnaire was completed by parents and captured information regarding early infectious history, behaviors in infancy and childhood, and residential and community exposures during early life.[12] Of the 166 items listed in the survey, 95 entries pertain to childhood experiences and only questions relevant to infectious exposures in the first five years of life were included in our analyses. This questionnaire is publically available (http://www.usnpmsc.org/Documents/EnvironmentalAssessment.pdf) and was adapted by Drs. Waubant and Barcellos with reference to previous questionnaires used in MS and other autoimmune diseases including type 1 diabetes. Investigators employed the questionnaire in 30 families at the University of California, San Francisco to detect and resolve any problems with wording of questions that may have compromised understanding and accuracy of responses. Questions of interest that were deemed especially prone to recall instability by coauthors were removed.

Statistical Methods

Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC). Categorical variables were described using frequencies and percentages and continuous

variables as means or medians as appropriate. Characteristics of cases and controls were compared using chi-squared tests and Kruskal-Wallis tests for categorical and continuous variables, respectively. Descriptors included demographic data and highest education level achieved by biological mother at the time of the subject's birth. Infection-related risk factors compared between cases and controls included gastrointestinal or respiratory infections, daycare and kindergarten attendance, and antibiotic use in first five years of life, among others.

Multivariable logistic regression analyses were used to determine association of early infectious exposures with case status adjusting for age, sex, race, ethnicity, and mother's education. Demographic variables, including maternal education as a measure of socioeconomic status, are known to be associated with rates of exposure and infection. Age similarly influences the likelihood of both cumulative infectious exposures and age-dependent susceptibility to disease.

RESULTS

Questionnaire responses were available for 326 eligible cases (mean age 14.9 years, 63.5% girls) and 506 healthy pediatric subjects (mean age 14.4 years, 56.9% girls). No significant differences between cases and controls were observed by age, sex, or race, but cases were more likely to be of Hispanic descent than controls (30% vs 19%, $P<.001$). Mother's education, as an indicator of socioeconomic status, also differed between cases and controls as mothers of healthy subjects were more likely to have higher terminal degrees than their case counterparts ($P<.001$).

Differences in frequencies of infection-related environmental exposures are shown in Table 2. In these unadjusted analyses, infection with flu-like illness before age five (42.4% vs. 32.5%, $P=.01$) and history of playing outside on grass (79.7% vs. 85.2%, $P=.04$) were associated with risk of MS (Table 2). The use of special products to treat head lice or scabies (i.e. Kwell or NIX) was greater among cases than in controls (24.5% vs. 18.4%, $P=.04$). All other environmental and infectious factors investigated were not associated with increased risk of pediatric-onset MS.

In a multivariable model adjusted for age, sex, race, ethnicity, and mother's highest educational attainment, the point estimate for history of flu-like illness with high fever before age five still suggested 29% higher odds for MS, but the difference did not reach statistical significance ($P=.15$, Table 3). Associations with playing outside in the grass and use of lice or scabies treatment products similarly did not remain statistically significant following multivariable adjustments. Notable negative results include lack of association of diarrheal illnesses, antibiotic use, and daycare exposure with risk of pediatric-onset MS.

DISCUSSION

Early infectious exposures, as determined by patient history, did not appear to have influence on MS risk. Having a flu-like illness with high fever in the first five years of life was suggestive of twenty-nine percent increased odds to have MS, but was not statistically significant in multivariable models. Notably other exposures – including daycare attendance,

respiratory and gastrointestinal infections, and use of antibiotics in the first five years of life – did not appear to contribute to risk of disease development. Absence of any correlation between the studied exposures and disease risk despite what is known about EBV as an established environmental risk factor in MS, may signal the importance of herpes virus-specific contributions to disease pathogenesis as opposed to overall infectious exposures. Our findings suggest that the cumulative burden of early life infections do not appreciably contribute to the risk of developing MS.

These results, however, do not exclude the possibility that there may be particular infectious triggers of disease immediately prior to the onset of symptoms. Our questionnaire is unable to elicit or detect critical but subtle features of the reported infections (e.g. causative agent, severity, duration) to discriminate between particular infectious strains or illnesses. Capture of this data, however, is itself challenging as evidence of these infections may dissipate by the time of diagnosis and research evaluation. Previous research regarding the epidemiologic association between EBV positive sero-status and increased MS risk locates evidence of causality in particular features of this pathogen – cross-reactivity of EBV-induced antibodies or T-cells directed against EBV antigens – rather than attribute this risk elevation to infection more generally.[13]

It is important to recognize distinctions in the process of data acquisition that may have contributed to our results – namely, the questionnaire-based, family-reported responses regarding the occurrence of various infections and exposures rather than acute serological analyses. Our queries, while extensive, may not have probed all possible infectious processes or manifestations of greatest relevance to the pathophysiology of MS. Our methods differ from approaches employed in the evaluation of EBV serostatus and its role in development of MS as evidence of remote EBV infection may be confirmed serologically via detection of specific antibodies.[14] Imperfect resolution of the nature of reported illnesses may extend to the instrument's interrogation of the timing and sequence of particular infections within the first five years of life. It is reasonable to purport that such infections must occur during a precise and likely vulnerable period of immune development to induce aberrant immune activation and dysfunction and influence the likelihood of pediatric-onset disease. Alternatively, EBV exposure later in childhood or adolescence not captured in this investigation may influence onset later in adulthood. This is especially important given age-dependent variation in the manifestation of EBV infection. Primary infection with EBV in the first ten years of life is noted to be predominantly asymptomatic while infection in adolescent populations is more likely to engender infectious mononucleosis – a well-studied risk factor in adolescents and young adults in the development of MS.[15,16] Age-dependent contributions of individual infectious agents aside, this analysis explores and precludes the general role of early life infectious burden on MS development. Associations of smaller magnitude, however, cannot be excluded as our cohort – while relatively large given the rarity of pediatric MS – is not sufficiently powered to detect such small-scale effects.

Strengths of this investigation are rooted in the number of well-phenotyped pediatric patients represented in the cohort. Despite limited database records of pediatric populations in MS care and research, this study leverages the largest collection of available data in pediatric-onset MS. Childhood exposures such as regular kindergarten attendance and tonsillectomy

are less likely to be influenced by diminished recall in pediatric studies reliant on parental participation than in adult studies and are similarly less liable to differential recall between cases and controls. Some measure of differential recall among parents of ill and healthy children may nevertheless persist and data regarding broad categories of infection in the first years of life may be difficult to retrieve in recall-based studies.

Additional strengths include case recruitment shortly after MS diagnosis at a dedicated pediatric MS clinic, representation of a multitude of racial and ethnic backgrounds, and careful confirmation of case diagnosis by MS specialists. The present study did not seek out a particular infectious trigger of pediatric-onset MS, but instead captured a historical view of infections in the first few years of life. Future studies may involve serologic confirmation of specific viruses or infectious illnesses near the time of initial MS presentation in children to identify potential triggers of disease. While we cannot exclude the possibility of small magnitude associations between various early life infectious illnesses and risk of pediatric-onset MS, our data indicate that large effects of early infectious exposures are unlikely.

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Highlights

- In a unique dataset of children with MS, parents completed a detailed questionnaire of early life exposures.
- History of flu-like illness with high fever before age five and of playing outside on grass were each associated with increased risk of MS but this difference did not reach statistical significance in multivariable models.
- Overall, early infectious exposures in the first years of life do not appear to significantly alter risk of development of pediatric-onset multiple sclerosis.

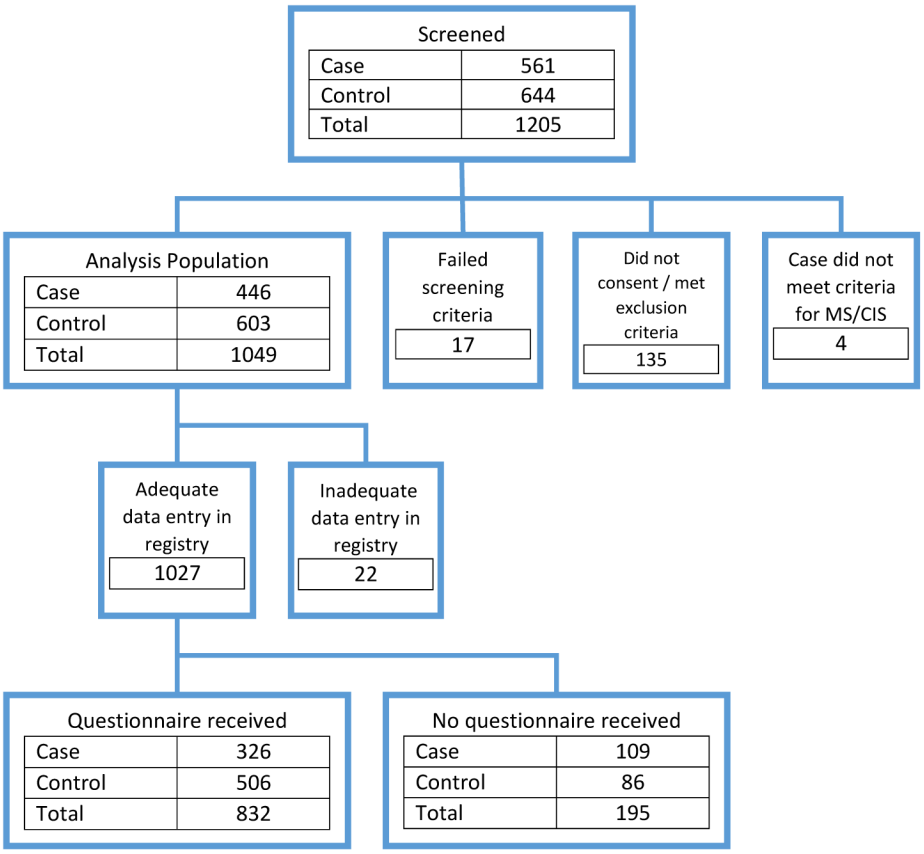

Figure 1:
Case and control inclusion and exclusion criteria

Table 1:

Baseline characteristics between cases and controls

Demographic	Controls N = 506	Cases N = 326	P-value
Age at enrollment: Mean years (SD)	14.4 (3.91)	14.9 (3.21)	0.062[1]
Sex			0.059[2]
Male	218 (43.1%)	119 (36.5%)	
Female	288 (56.9%)	207 (63.5%)	
Race			0.682[2]
White	330 (67.5%)	214 (70.4%)	
Black	83 (17.0%)	47 (15.5%)	
Asian	29 (5.9%)	13 (4.3%)	
Other	46 (9.4%)	30 (9.9%)	
Ethnicity			<.001[2]
Hispanic or Latino	97 (19.2%)	98 (30.1%)	
Not Hispanic or Latino	395 (78.2%)	216 (66.3%)	
Unknown or Not	14 (2.8%)	12 (3.7%)	
Reported			<.001[2]
Mother's Education			
None	29 (6.1%)	37 (12.1%)	
High School or Associate's	222 (46.9%)	167 (54.6%)	
Bachelor's or Graduate	222 (46.9%)	102 (33.3%)	

[*] there were 40 missing value for Race

[*] there were 53 missing values for Mother's Education

[1] Kruskal-Wallis test

[2] Chi-squared test of no association

Table 2:

Early infectious exposures

Exposure	Total	Controls	Cases	P-value[1]
Infections first two weeks of life	17	11 (2.3%)	6 (1.9%)	0.70
First year daycare smoke exposure	13	9 (1.9%)	4 (1.3%)	0.54
Severe diarrhea or vomiting in first five years of life	166	103 21.7%	63 21.4%	0.90
Ear infection in first five years of life	512	308 (65.8%)	204 (69.6%)	0.28
Flu with a high fever in first five years of life	270	150 (32.5%)	120 (42.4%)	0.01
Any other infection in the first five years of life	424	255 (54.8%)	169 (58.3%)	0.35
Suck on pacifier between years 1-5	436	257 (53.4%)	179 (56.7%)	0.37
Suck on thumb/fingers between years 1-5	201	128 (26.7%)	73 (23.2%)	0.26
Put things in mouth between years 1-5	504	308 (65.1%)	196 (62.2%)	0.41
Regularly attend daycare before age 6	662	399 (81.3%)	263 (83.2%)	0.48
Ever attend kindergarten	760	461 (96.0%)	299 (94.9%)	0.45
Smoke exposure in daycare between years 1-5	14	9 (1.9%)	5 (1.6%)	0.77
Child travel outside of the United States	362	225 (46.3%)	137 (43.9%)	0.51
Ever treated with special products (for lice etc.)	165	89 (18.4%)	76 (24.5%)	0.04
Child ever have worms	24	14 (2.8%)	10 (3.2%)	0.79
Child ever have tonsillectomy	88	47 (9.5%)	41 (12.9%)	0.12
Child ever have adenoidectomy	84	49 (9.9%)	35 (11.0%)	0.60
Child ever play outside on bare soil (not including parks/playgrounds)	230	147 (30.2%)	83 (26.7%)	0.29
Child ever play outside on grass (not including parks/playgrounds)	663	415 (85.2%)	248 (79.7%)	0.04
Child ever have antibiotics in first five years of life	516	316 (80.4%)	200 (81.6%)	0.70

[1] Chi-squared test of no association

[*] Unadjusted comparison between cases and controls

Note: the total number of responses vary for each exposure due to missing responses

Table 3:

Adjusted early infectious exposures

Exposure: Yes vs. No	Odds Ratio	95% CI	P-value
Infections first two weeks of life	0.86	0.28-2.61	0.79
First year daycare smoke exposure	0.59	0.15-2.25	0.44
Severe diarrhea or vomiting in first five years of life	0.95	0.64-1.41	0.78
Ear infection in first five years of life	1.16	0.81-1.65	0.43
Flu with a high fever in first five years of life	1.29	0.91-1.83	0.15
Any other infection in the first five years of life	1.27	0.90-1.78	0.18
Suck on pacifier between years 1-5	1.02	0.74-1.40	0.91
Suck on thumb/fingers between years 1-5	0.82	0.56-1.18	0.28
Put things in mouth between years 1-5	0.97	0.70-1.34	0.85
Regularly attend daycare before age 6	1.45	0.94-2.22	0.09
Ever attend kindergarten	0.73	0.34-1.57	0.41
Smoke exposure in daycare between years 1-5	0.89	0.29-2.76	0.84
Child travel outside of the United States	0.94	0.67-1.32	0.71
Ever treated with special products (for lice etc.)	1.17	0.79-1.73	0.44
Child ever have worms	0.87	0.32-2.36	0.78
Child ever have tonsillectomy	1.41	0.85-2.34	0.19
Child ever have adenoidectomy	1.23	0.73-2.04	0.44
Child ever play outside on bare soil (not including parks / playgrounds)	0.82	0.57-1.17	0.28
Child ever play outside on grass (not including parks / playgrounds)	0.89	0.58-1.38	0.61
Child ever have antibiotics in first five years of life	1.36	0.83-2.22	0.22

*Multivariable analysis adjusted for age, sex, race, ethnicity, and mother's highest level of education