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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 ($p = 0.01$), 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.

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Notably, antibiotic use ($p = 0.22$) and regular daycare attendance before age 6 ($p = 0.09$) were not associated with odds of developing MS.

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

1. 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 (Bouziat et al., 2017; Porter et al., 2008; Gradel et al., 2009). Similarly, case-control studies of potential associations of perinatal exposures and the development of juvenile arthritis and systemic lupus erythematosus have shown that serious infection (requiring hospitalization) may contribute to risk of pediatric and adult-onset disorders of autoimmunity (Shenoi et al., 2016; Edwards et al., 2006). 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 (Ascherio and Much, 2000). 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 (Cohen, 2000; Ascherio and Munger, 2007).

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.

2. Methods

2.1. Subjects and design

As described in a previous investigation of maternal exposures and risk of pediatric-onset MS (Graves et al., 2017), 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 (Krupp et al., 2013; Belman et al., 2016). 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.

2.2. 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 (Frederiksen et al., 2013). 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.usnpsc.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.

2.3. 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.

3. 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%, $P < 0.001$). 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 ($P < 0.001$) (Table 1).

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%, $P = 0.01$) and history of playing outside on grass (79.7% vs. 85.2%, $P = 0.04$) 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%, $P = 0.04$). 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

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