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Publication Date

2017-04-15

DOI

10.1016/j.jns.2017.02.041

Peer reviewed

HHS Public Access

Author manuscript

J Neurol Sci. Author manuscript; available in PMC 2018 April 15.

Published in final edited form as:

J Neurol Sci. 2017 April 15; 375: 371–375. doi:10.1016/j.jns.2017.02.041.

Evaluating the association of allergies with multiple sclerosis susceptibility risk and disease activity in a pediatric population

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Abstract

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Background—Multiple sclerosis (MS) and allergies are both considered to be related to imbalanced Th1 and Th2 immune responses. Previous studies evaluating the relationship between MS and allergies provide conflicting results.

Objective—To assess allergies and asthma as risk factors for MS and as predictors of MS relapses in a pediatric cohort.

Methods—The environment and genetic risk factors for pediatric MS study is a national case-control project with 16 participating US sites. An environmental questionnaire is used that includes history of allergies in the first five years of life. Case-control data are entered in the pediatric MS Network database and cases at 12 of the 16 sites enter relapse data prospectively. Annualized relapse rate was calculated for patients with follow-up and adjusted for age at disease onset, gender, race, ethnicity, and use of disease-modifying therapy (DMT).

Results—We included 271 cases (mean age at disease onset of 15.7 years and 62% female) and 418 controls. Relapse data were available for 193 cases. There was no difference in prevalence of allergies or asthma between cases and controls. Patients with food allergies had fewer relapses compared to patients without food allergies (.14 vs .48, p = .01).

Conclusions—While allergies and asthma are not associated with pediatric MS, cases with food allergies have fewer relapses compared to those without food allergies.

Keywords

multiple sclerosis; pediatric; allergies

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disorder of the central nervous system (CNS), characterized by demyelination and axonal damage. MS is often diagnosed in young adults, and is increasingly recognized in children with an estimated 3–5% of the MS population having a pediatric onset.[1–6]

The autoimmune etiology of MS is thought to involve myelin-specific CD4+ T cells that are activated in the periphery by an unknown trigger and migrate to the CNS, where they release pro-inflammatory cytokines that contribute to demyelination and axonal loss. CD4+ T helper (Th) cells can be classified into Th1, Th2, or Th17 subsets based on the cytokines they secrete. Th1 cells release pro-inflammatory cytokines such as interferon (IFN)-gamma and tumor necrosis factor alpha (TNF-a), which have been associated with MS exacerbation and disease progression.[7–8]. Th2 cells secrete cytokines that may protect against Th1 immune responses, but also contribute to allergic disorders through the activation of eosinophils, mast cells, and B-cell production of allergen-specific immunoglobin E (IgE).[9]

Previous studies in adults have suggested that MS may be inversely related to Th2 immune responses such as seen in those with allergies and asthma.[11–13] A history of atopic allergies has been associated with a decreased risk of MS, which supports the hypothesis that Th2 immune responses may have a protective effect against MS.[12–13] In addition, Th2 cell responses may have a protective effect against MS relapses through both rebalancing the dysregulated immune response in MS and modulating tissue repair pathways.[14]

Furthermore, MS may have a less severe course when patients have comorbid allergic respiratory disease.[13] Despite these findings, the relationship between MS and allergies remains uncertain, as additional studies have reported conflicting results in part due to methodologic differences.[15–17]

Pediatric MS provides a unique opportunity to examine the environmental and genetic factors that may contribute to the risk of developing the disease as individual with an earlier disease onset may have higher burden of exposures and disease onset occurs shortly after putative environmental exposures. The relationship between MS and atopic disorders has not been examined in pediatric MS patients, and the Th1/Th2 related comorbidities in this population are unknown. Identifying the relationship between atopic disorders and MS in the pediatric population may contribute to our understanding of the Th1/Th2 paradigm. Our goal was to analyze allergies and asthma as risk factors for development of MS and as predictors of MS relapses in a pediatric cohort.

2. Materials and Methods

2.1 Study design and subject characteristics

A case-control study was conducted through the US Network of Pediatric MS Centers and affiliates with retrospective collection of environmental exposures at the time of enrollment (1R01NS071463, PI Waubant). Informed consent was obtained from all participants, and this study was approved by institutional review boards at all 16 participating centers.

Cases included children with clinically isolated syndromes (CIS) or relapsing-remitting MS with diagnosis before 18 years of age and disease duration of less than four years. Cases were confirmed by a review committee. Healthy pediatric subjects were recruited at primary care and other pediatric clinics at the same institutions from which cases were enrolled. Inclusion criteria for healthy subjects were: 1) absence of any autoimmune disease, 2) no history of treatment with immunosuppressive therapy and 3) not be a child of a parent with MS. Parents of subjects reported demographic data including race and ethnicity according to National Institutes of Health (NIH) guidelines, age, and socioeconomic factors including level of education of both parents.[20–21]

Parents or legal guardians of study participants completed a standardized environmental questionnaire and answered questions regarding the presence of allergies in the first five years of life to food, environmental factors, and antibiotics. Participants reported allergic reactions in the first five years of life, including skin reactions, rhinitis, gastrointestinal reactions and anaphylactic shock, and indicated if the child carried an epinephrine autoinjector (EpiPen) for allergic reactions. Participants reported if the child had direct physical contact with animals and if animals sleep in the house. Presence of asthma was assessed at study enrollment for control subjects, and at enrollment and follow-up visits for cases. Relapse rate (RR) was calculated for pediatric MS patients with verified follow-up information, which required that patients had a first event, history of event logs marked as up-to-date at their most recent visit, and a first visit within four years of the first event.

2.2 Definitions

All allergies were defined by parent's report for the first five years of life. Environmental allergy was defined as any reported allergy to pollen, grass, mold, or dust. Food allergy included reported allergies to eggs, dairy, wheat, or nuts. Allergic reactions were classified as skin reactions (including rashes and eczema), nose or eye reactions (including a stuffy nose or swollen eyes), gastrointestinal reactions (including diarrhea and vomiting), and anaphylactic shock. Carrying an EpiPen was defined as whether or not the child has ever carried an epinephrine autoinjector for severe allergic reactions. A history of asthma was collected from parent's report. Animal contact was defined if the child had any direct physical contact with animals at any point in time. Animals sleeping in the home were defined as whether or not the animals ever lived or slept in the home on a regular basis. Disease-modifying treatment (DMT) use was categorized into 4 groups: 1) subjects on no DMT; 2) subjects receiving interferon beta, glatiramer acetate, or teriflunomide; 3) subjects receiving dimethyl fumarate or fingolimod, 4) subjects on natalizumab, rituximab or alemtuzumab. Subjects who switched treatment during the follow-up period were categorized using the DMT with the longest follow-up time.

2.3 Statistical analysis

Demographic characteristics including age at onset/enrollment, gender, race, and ethnicity of cases and controls were compared with the Kruskal-Wallis test and Chi-squared test as appropriate. Questionnaire responses relevant to prior history of allergies between cases and controls were compared with the Chi-squared test. Multivariable logistic regression models were also used and results were adjusted for age, gender, race, and ethnicity, with odds ratio (OR) and 95% confidence interval (CI) reported. Annualized relapse rate (ARR) was modeled as the number of events over the total follow-up time period in years. ARR was adjusted for gender, age at disease onset, race, ethnicity, and DMT in a negative binomial regression model. Likelihood ratio tests were used to assess significance of differences in relapse rate. Analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1 Subject characteristics

A total of 689 subjects participated to the analysis and had completed the environmental questionnaire (271 cases, 418 controls). Baseline characteristics, including gender, race, ethnicity, and age at onset/enrollment are presented in Table 1. There were more females among the cases (62%) compared to controls (54%), and the average age at disease onset for the cases was higher than the average age of enrollment of the controls (15.7 vs 14.6 years). A higher proportion of cases were Hispanic or Latino (29%) compared to controls (16%). Mean disease duration at time of enrollment for cases was 10.1 (± 9.9) months.

3.2 Allergies and Asthma as Risk Factors for MS

In unadjusted analyses, pediatric MS patients reported fewer environmental (12.8% vs 20.4%) and food allergies (5.2% vs 9.4%) in the first five years of life compared to control

subjects (Table 2). When results were adjusted for age, gender, race, and ethnicity, there was no difference in prevalence of allergies, allergic reactions, asthma, or contact with animals between the groups (Table 3). Among the cases there was no significant difference in age at onset (p=.41), gender (p=.30), race (p=.06) or ethnicity (p=.54) between cases with and without allergies in the first five years of life.

3.3 Allergies and Asthma as Predictors of MS Relapses

Follow-up relapse data after enrollment was available from 193 cases. The demographic characteristics of these cases were similar to patients who were not included in the relapse data cohort. Mean follow-up duration was 2.2 (±1.3) years. ARR for MS patients with clinical follow-up are presented in Table 4 according to presence or not of allergies. Patients reporting food allergies in the first five years of life had a lower ARR compared to patients without comorbid food allergies (.14 vs .48, p= .01). No association between relapse rate and other types of allergies, allergic reactions, asthma, or physical contact with animals was identified.

4. Discussion

The relationship between Th1 and Th2 mediated disorders remains unclear, with some studies suggesting that atopic conditions, such as allergies and asthma, may be protective against the development of MS and other autoimmune disorders.[11–13] When adjusted for differences in baseline characteristics, our results indicate no relationship between allergic disorders and pediatric MS risk, and are consistent with other reports in adult MS.[15–17]

As it has been established that Th1 and Th2 mediated disorders are not mutually exclusive and may coexist in the same individual[19], we also examined the effect of comorbid allergic disorders on MS activity. We report a lower relapse rate in pediatric MS patients who also had food allergies in the first five years of life. No other MS study has evaluated this association. The prevalence of allergic disease has increased over the past 50 years, with an estimated 10% of preschool children suffering from food allergies.[22–23] It has been hypothesized that Th2 immunity developed to provide protection against worms and parasites; however, the majority of allergens are not helminths or their products.[14,24] The toxin hypothesis of allergy offers a different perspective, and postulates that allergic responses involve excessive immune reactivity in some individuals, as a cost of protection against noxious damage.[25–26] Although food allergies have not yet been well characterized in MS patients, some of their underlying mechanisms may pertain to gut microbiota with some dysbiosis increasing the likelihood of food allergies. In fact, we recently reported that gut microbiota composition in pediatric MS may be associated with relapse risk.[27]

We also examined risk of MS in patients with extensive physical contact with animals. It has previously been reported that contact with cats may be protective against risk of MS,[28–29] while others have found no association between household pets and MS.[30] In this study, we find no difference in MS risk between subjects with animal contact and those without animal exposure.

A strength of our study is the size and diversity of our cohort, which includes patients from 16 centers across the United States. Multivariable analyses were performed to adjust for factors associated with risk of MS, including age, gender, race, and ethnicity. Relapse rate was appropriately adjusted for gender and DMT.

Limitations to the present study include reliance on subjects for reporting history of allergies, without allergy testing or physician confirmation of the diagnosis. Additionally, our questionnaire was not able to differentiate between food allergy and food intolerance.[31] Collection of asthma data may be imbalanced, as cases were asked about asthma at follow-up visits while controls were only assessed for asthma at the initial encounter. Relapse data was available from fewer patients (n=193), and our subgroup of MS patients with food allergies was limited by a smaller sample size (n=9).

In conclusion, while we observed no relationship between allergies and risk of MS in a pediatric cohort, pediatric MS patients with food allergies were found to have fewer relapses compared to those without comorbid food allergies. This is the first study to examine the relationship between atopic conditions and risk of MS in a pediatric cohort. Future prospective studies are needed to confirm or refute our findings and understand their underlying pathophysiology.

Acknowledgments

We thank our patients and their families for contributing to this study, as well as our study coordinators for enrolling participants. This work was supported by the National Multiple Sclerosis Society (NMSS) and the National Institute of Neurological Disorders and Stroke (NINDS) through the following grants: HC0165 and 1R01NS071463.

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Table 1

Demographic characteristics of cases and controls

	Total	Control	Case	p-value
Total	689	418	271	
Age at onset/enrollment	–	14.6	15.7	0.01[1]
Median (IQR)		(11.9, 17.2)	(13.5, 17.3)	
Gender				0.04[2]
Male	288	188 (46%)	100 (38%)	
Female	389	224 (54%)	165 (62%)	
Race				0.38[2]
White	453	280 (71%)	173 (70%)	
Black	112	71 (18%)	41 (17%)	
Asian	28	19 (5%)	9 (4%)	
Other	51	26 (7%)	25 (10%)	
Ethnicity				< 0.01[2]
Hispanic or Latino	146	68 (16%)	78 (29%)	
Not Hispanic or Latino	510	332 (79%)	178 (66%)	
Unknown or Not Reported	33	18 (4%)	15 (6%)	

[1] Kruskall-Wallis test

[2] Chi-squared test of no association

Abbreviations: IQR (interquartile range)

Table 2

Unadjusted allergy and asthma history

	Total	Control	Case	p-value[1]
Have allergies in first 5 years of life	206 (32.0%)	132 (33.6%)	74 (29.5%)	0.28
Antibiotics allergy	27 (4.2%)	13 (3.3%)	14 (5.6%)	0.16
Environmental allergy	112 (17.4%)	80 (20.4%)	32 (12.8%)	0.01
Food allergy	50 (7.8%)	37 (9.4%)	13 (5.2%)	0.05
Have allergic reactions in first 5 years of life	181 (28.9%)	114 (29.7%)	67 (27.7%)	0.59
Skin reaction/rash/eczema	127 (20.3%)	84 (21.9%)	43 (17.8%)	0.21
Stuffy or runny nose/swollen or puffy eyes	76 (12.1%)	53 (13.8%)	23 (9.5%)	0.11
GI reactions/diarrhea/vomiting	24 (3.8%)	17 (4.4%)	7 (2.9%)	0.33
Anaphylactic shock	3 (0.5%)	3 (0.8%)	0 (0.0%)	0.17
Carry an Epi-Pen[2]	22 (3.6%)	16 (4.3%)	6 (2.5%)	0.26
Direct physical contact with animals	566 (84.9%)	343 (84.7%)	223 (85.1%)	0.88
Animal live/sleep in house	448 (81.3%)	264 (80.5%)	184 (82.5%)	0.55
Ever had Asthma[3]	104 (15.6%)	64 (16.2%)	40 (14.8%)	0.62

[1] Chi-squared test of no association

[2] Only asked of those for the first five years of life

[3] Cases were asked over time if they had asthma but controls were only asked once at enrollment and had 22 missing responses

Table 3

Adjusted allergy and asthma results

	Odds Ratio	95% CI	p-value
Allergies in first five years of life: Yes vs No	0.96	0.66, 1.39	0.82
Antibiotic allergy: Yes vs No	2.05	0.91, 4.60	0.08
Environmental allergy: Yes vs No	0.65	0.40, 1.06	0.08
Food allergy: Yes vs No	0.61	0.31, 1.22	0.16
Allergic reaction in first five years of life: Yes vs No	1.01	0.69, 1.49	0.95
Skin reaction/rash/eczema: Yes vs No	0.81	0.53, 1.26	0.36
Stuffy or runny nose/swollen or puffy eyes: Yes vs No	0.72	0.41, 1.28	0.27
GI reactions/diarrhea/vomiting: Yes vs No	0.70	0.27, 1.83	0.46
Carry an Epi-pen: Yes vs No	0.87	0.33, 2.34	0.79
Direct physical contact with animals: Yes vs No	1.03	0.63, 1.69	0.91
Animal live/sleep in house: Yes vs No	1.24	0.74, 2.06	0.42
Asthma: Yes vs No	1.04	0.66, 1.66	0.86

*Adjusted for Age, Gender, Race, Ethnicity

Table 4

Annualized Relapse rates adjusted for age at onset, gender, race, ethnicity, and DMT

	Response	N Patients	Relapse Rate	Standard Error	p-value
Allergies in first five years of life	Yes	51	0.36	0.16	0.12
	No	127	0.49	0.20	
Antibiotic allergy	Yes	8	0.66	0.34	0.31
	No	170	0.45	0.18	
Environmental allergy	Yes	20	0.32	0.16	0.15
	No	158	0.48	0.19	
Food allergy	Yes	9	0.14	0.09	0.01
	No	169	0.48	0.19	
Allergic reaction in first five years of life	Yes	44	0.42	0.20	0.93
	No	129	0.42	0.19	
Skin reaction/rash/eczema	Yes	28	0.36	0.18	0.42
	No	145	0.44	0.20	
Stuffy or runny nose/swollen or puffy eyes	Yes	13	0.21	0.13	0.06
	No	160	0.44	0.20	
GI reactions/diarrhea/vomiting	Yes	7	0.25	0.17	0.28
	No	166	0.44	0.20	
Carry an Epi-pen	Yes	4	0.50	0.35	0.79
	No	165	0.43	0.20	
Direct physical contact with animals	Yes	159	0.36	0.15	0.45
	No	28	0.43	0.17	
Animal live/sleep in house	Yes	133	0.41	0.20	0.74
	No	28	0.45	0.21	
Asthma	Yes	32	0.38	0.17	0.85
	No	161	0.40	0.15	