

RESEARCH PAPER

Food allergies are associated with increased disease activity in multiple sclerosis

Rami Fakihi, Camilo Diaz-Cruz, Alicia S Chua, Cindy Gonzalez, Brian C Healy, Neda Sattarnezhad, Bonnie I Glanz, Howard L Weiner, Tanuja Chitnis

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/jnnp-2018-319301>).

Partners MS Center, Brigham and Women's Hospital (BWH), Harvard Medical School, Boston, Massachusetts, USA

Correspondence to

Dr Tanuja Chitnis, Partners Multiple Sclerosis Center, Boston, MA 02115, USA; tchitnis@rics.bwh.harvard.edu

Received 24 July 2018

Revised 29 September 2018

Accepted 3 October 2018

ABSTRACT

Objective The association between allergy and multiple sclerosis (MS) is still unclear. In our study, we assessed the association between a self-reported history of allergic conditions with MS clinical and MRI disease activity.

Methods A subset of 1349 patients enrolled in the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital (CLIMB) study completed a self-administered questionnaire on environmental, food and drug allergies. Patients were distributed among four allergy groups: (1) environmental, (2) food, (3) drug, (4) no known allergies (NKA). Clinical (number of attacks, expanded disability status scale (EDSS), MS severity score (MSSS)) and radiological variables (presence of gadolinium-enhancing lesions and lesion count), and their associations with the different allergy groups or those with NKA, were assessed.

Results The food allergy group had a 1.38 times higher rate for cumulative number of attacks compared with the NKA group ($P=0.0062$); this difference remained significant in the adjusted analysis (relapse rate ratio 1.27, $P=0.0305$). The food allergy group showed more than twice the likelihood (OR 2.53, $P=0.0096$) of having gadolinium-enhancing lesions on MRI. The environmental and drug allergy groups did not show significant differences when compared with the NKA group. The EDSS and MSSS were not affected by any type of allergy.

Conclusions MS patients with food allergy had more relapses and a higher likelihood of gadolinium-enhancing lesions compared with patients with no known allergy. Future prospective studies are needed to confirm our findings and investigate underlying biological mechanisms, which may unveil new therapeutic and preventative strategies for MS.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system (CNS) with an unknown aetiology. Both genetic and environmental factors contribute to disease risk and disease course.¹ An increasing number of lifestyle and environmental factors have been identified which trigger and exacerbate MS.² Established MS-associated risk factors are high latitude, female sex, smoking, low vitamin D levels, the Epstein-Barr virus (EBV) infection, and obesity during adolescence.² The mechanistic understanding is still in its infancy, though the influence of environmental factors identified so far can be traced to their effects on the immune system, as can the genetic predisposing factors, which strongly

supports the argument that the peripheral immune system has a primary role in driving MS.

Epidemiological studies investigating the association between a history of allergy and the risk of MS have shown conflicting results.^{3–9} A population-based case-control study conducted in Italy showed that a history of atopic allergies, especially allergic asthma, was associated with a significantly lower risk for MS.⁶ On the other hand, a prospective study of comorbid conditions in a large cohort of MS patients showed a significantly increased rate of asthma besides other Th1 and Th17 driven diseases.⁴ Another case-control study nested in the Nurse's Health Study I and II showed no association between allergy history and MS risk; however, a family history of other autoimmune diseases was associated with a higher risk, suggesting common genetic risk factors or environmental triggers.⁸ A meta-analysis of 10 observational studies concluded that there is no evidence supporting an association between allergic diseases and MS risk.⁹

Despite this controversy regarding the risk for MS among atopic patients, one relevant question remains unanswered: is MS activity less or more intense among patients with an atopic history? To our knowledge, no studies have addressed this question in an adult MS population. A case-control study from 16 centres across the USA studied the association between allergy history and relapse rate in a paediatric MS population, and reported that patients with food allergies in the first 5 years of life had a lower absolute relapse rate (ARR) compared with patients without comorbid food allergies (0.14 vs 0.48, $P=0.01$), and found no association between relapse rate and other types of allergies.¹⁰ The aim of our study was to assess the association between a self-reported history of allergic conditions with MS clinical and MRI disease activity in adults.

METHODS

Design, setting and participants

A subset of 1349 patients enrolled in the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital (CLIMB) study at the Partners MS Center¹¹ completed a one-time self-administered questionnaire on environmental, food and drug allergies between 2011–2015. All patients had a diagnosis of MS according to the 2010 McDonald criteria.¹² Demographic characteristics, estimated date of MS symptoms onset and MS treatment history were recorded. Patients had a complete neurological examination



© Author(s) (or their employer(s)) 2018. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Fakihi R, Diaz-Cruz C, Chua AS, et al. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jnnp-2018-319301

Multiple sclerosis

including a measurement of the Expanded Disability Status Scale score (EDSS) and symptoms suggestive of a new relapse were recorded along with their onset date. Patients diagnosed with clinically isolated syndrome (CIS) or with a known allergy to any disease-modifying therapy (DMT) were excluded. This study was approved by the Partners Institutional Review Board and all participants provided written informed consent.

Allergy history

Patients completed a self-reported allergy history questionnaire, which assessed the presence of drug, environmental or food allergy. Secondary questions assessed the specific allergen, and whether the allergy was confirmed by a physician. Symptoms of allergy were recorded and options included: hives, itching, nasal congestion, rashes, watery/red eyes, tingling or itching in the mouth, swelling (tongue, lips, face, throat or other parts of the body), trouble breathing, abdominal pain, diarrhoea, nausea, vomiting, dizziness or anaphylaxis. Environmental allergy was defined as any reported allergy to pollen, grass, tree, dust, mite, pets or other. Food allergy was defined as any reported allergy to eggs, dairy, wheat, soy, fish, shellfish, fruits, or nuts or other food products. A single questionnaire was completed by each subject; thus longitudinal changes in allergy were not assessed in this study.

For our analysis, subjects were stratified as either the no known allergy (NKA) group, or the 'any allergy' group. The 'any allergy' group was defined as subjects who selected 'Yes' to at least one of these fields: history of environmental allergy, food allergy, or drug allergy; and required the allergy to be confirmed by a physician. Patients in the NKA group were defined as subjects who selected 'No' to all three of these fields. Patients with unknown values to any of these fields were excluded from the NKA group. A medical chart review was performed to review any inconsistencies among the reported drug allergies. Subanalysis was conducted for each allergy subgroup, 'environmental allergy', 'food allergy' and 'drug allergy', defined as those who selected 'Yes' for the respective allergy type. Patients with unknown values were removed from the corresponding allergy group. The NKA group was used for all comparisons.

Clinical and MRI outcomes

Our primary clinical outcome was the cumulative number of attacks over the course of the entire patient's disease course. The secondary clinical outcomes were the EDSS and the Multiple Sclerosis Severity Score (MSSS) at the patient's last encounter at our clinic. The MSSS corrects EDSS for disease duration by comparing an individual's disability with the distribution of scores in patients having similar disease duration.¹³ The secondary outcomes of interest were the presence of new gadolinium (Gad)-enhancing lesions, and the new Gad-enhancing lesion count on the brain MRI corresponding to the allergy questionnaire date (± 90 days of the questionnaire's date).

Imaging acquisition

Of the 1349 subjects, 753 subjects had an MRI scan with gadolinium, performed within ± 90 days of the clinic visit when the allergy questionnaire was completed. Brain MRI scans were acquired on the 1.5 T Signa GE family scanners at the Brigham and Women's Hospital. MRI protocols included axial dual-echo conventional spin-echo images: TR=2350–3167 ms, TE1/TE2 30/80 ms, slice thickness 3 mm, with no inter-slice gaps, and pixel size 0.7812–0.9375 mm². Quantitative image analysis was performed using an automated segmentation pipeline (three

times a day +).^{14 15} The number of Gad-enhancing lesions per scan were measured by trained MRI raters and re-reviewed by a single rater for this study.^{16 17}

Statistical analysis

In our first analyses, we compared the demographic and clinical characteristics at last clinic visit in 922 any allergy patients and 427 NKA patients. Categorical variables were described by counts and percentages and continuous variables by mean and SD. Means were compared with a two-sample t-test or a Mann-Whitney U test for non-normal data while proportions were compared via a χ^2 test or Fisher's exact test for contingency tables.

In the primary analyses, we compared the cumulative number of attacks since disease onset between (1) any allergy versus NKA, (2) environmental allergy versus NKA, (3) food allergy versus NKA, and (4) drug allergy versus NKA using the negative binomial regression model, performing both a univariate and a multivariable analysis. The multivariable analysis controlled for sex, age at symptom onset, race (non-white vs white), disease category (progressive vs relapsing), and percentage of time on DMT. Disease duration was used as the offset parameter. The relapse rate ratios were subsequently calculated for each group.

Our secondary analysis focused on the EDSS, MSSS, presence of new Gad-enhancing lesions, and comparison of the total count of new Gad-enhancing lesions among the four different groups. For EDSS, we performed a univariate and multivariable proportional odds logistic regression model and then a univariate and multivariable linear regression model on the natural log of MSSS. Next, to compare the presence of new Gad-enhancing lesions among the four groups, we used a logistic regression model in both a univariate and a multivariable analysis. Finally, a negative binomial regression model compared the Gad-enhancing lesion count between the different groups. All multivariable analyses were adjusted for sex, age at symptom onset, disease category (progressive vs relapsing), percentage of time on DMT, and disease duration. Statistical analyses were performed using the SAS 9.4 software (SAS Inc, Cary, NC, USA).

RESULTS

Patients characteristics

A total of 1349 patients participated in the questionnaire and were included in the main cross-sectional analysis. Demographic and clinical characteristics of subjects stratified by NKA (n=427) versus any allergy (n=922) are provided in [table 1](#). The mean (SD) follow-up period between the questionnaire date and the last visit date was 2.0 (1.8) years for the whole cohort. The mean disease duration at last visit was the same for both groups at around 16 years, and almost 75% of the patients were in the RRMS phase. A higher percentage of males was found in the NKA group (35%) compared with the any allergy group (21%); the rest of the variables were comparable between the two groups. The mean (SD) EDSS at last visit was similar between the two groups (2.0 $\pm$ 3.0 in the NKA group and 2.0 $\pm$ 2.5 in the any allergy group); the MSSS at last visit was similar between the two groups (1.70 $\pm$ 3.91 and 1.70 $\pm$ 3.10). [Table 2](#) shows the patients' characteristics stratified by the type of allergy. The specific reported allergies are found in online supplementary tables 1–3.

Effect of allergy history and allergy type on the cumulative number of attacks

In total, 922 patients in the any allergy group, 586 patients in the environmental allergy group, 238 patients in the food allergy

Table 1 Demographic characteristics of study subjects, stratified by 'No known allergy' versus 'Any allergy'

Variables	No known allergy	Any allergy	P values
N	427	922	
Age at last visit, mean (SD), years	50.02 (12.31)	49.41 (11.79)	0.3832*
Age at first symptom, mean (SD), years	34.12 (10.48)	33.36 (10.13)	0.2047*
Male, n (%)	150 (35.13)	194 (21.04)	<0.0001†
Disease duration at last visit, mean (SD), years	15.95 (10.91)	16.09 (9.75)	0.8103*
Disease category, n (%)			
Primary progressive MS	25 (5.85)	44 (4.77)	0.0515†
Secondary progressive MS	85 (19.91)	138 (14.97)	
Relapsing-remitting MS	310 (72.60)	731 (79.28)	
Progressive relapsing MS	7 (1.64)	9 (0.98)	
Race, n (%)			
Asian	4 (0.94)	5 (0.54)	0.1474‡
Black or African American	12 (2.81)	38 (4.12)	
More than one race	5 (1.17)	24 (2.60)	
Native Hawaiian/Pacific Islander	0 (0.00)	2 (0.22)	
Unknown or not reported	10 (2.34)	13 (1.41)	
White	396 (92.74)	840 (91.11)	
Ethnicity, n (%)			
Hispanic or Latino	15 (3.51)	44 (4.77)	0.1797‡
Not Hispanic or Latino	407 (95.32)	874 (94.79)	
Unknown or not reported	5 (1.17)	4 (0.43)	
% time on DMT, mean (SD)	48.29 (30.96)	46.74 (29.38)	0.3758*
EDSS at last visit, median (IQR)	2.0 (3.0)	2.0 (2.5)	0.9748§
MSSS at last visit, median (IQR)	1.70 (3.91)	1.70 (3.10)	0.5094§

*Means were compared with a two-sample t-test.

†Proportions were compared via a χ^2 test for contingency tables.

‡Proportions were compared via a Fisher's exact test for contingency tables.

§Rank scores were compared via the Mann-Whitney U test.

DMT, disease-modifying therapy; EDSS, expanded disability status scale; MS, multiple sclerosis; MSSS, multiple sclerosis severity scale.

group, 574 in the drug allergy group and 427 in the NKA group contributed to this analysis (table 3). Univariate analysis demonstrated that the any allergy group had a 1.22 times greater rate for cumulative number of attacks compared with the NKA group ($P=0.0204$); however, in adjusted analysis, there was no significant difference between the groups ($P=0.1497$).

When stratified by allergy group, the food allergy group demonstrated a 1.38 times higher rate for cumulative number of attacks compared with the NKA group ($P=0.0062$); this difference remained significant in the adjusted analysis, where the rate was 1.27 times higher in the food allergy group ($P=0.0305$). The drug allergy and environmental allergy groups had non-significantly different attack rates compared with the NKA group in adjusted analysis.

Effect of allergy history and allergy type on clinical disability: EDSS and MSSS

In the multivariable analysis shown in table 4, although patients who reported having allergies trended towards higher EDSS scores, this effect was not statistically significant in any group except the drug allergy group (any allergy OR 1.20 (95% CI 0.98 to 1.48), $P=0.0771$; environmental allergy OR 1.21 (95% CI 0.97 to 1.52), $P=0.0920$; food allergy OR 1.16 (95% CI 0.87 to 1.55), $P=0.3135$; drug allergy OR 1.29 (95% CI 1.03 to 1.62), $P=0.0294$). When we assessed the association between MSSS and the different allergy types, no significant association was found (table 4).

Effect of allergy history and allergy type on brain MRI Gad-enhancing lesions

Five hundred and sixteen patients in the any allergy group, 327 in the environmental allergy group, 133 in the food allergy group, 330 in the drug allergy group and 237 in the NKA group contributed to this analysis (table 5). Patients who reported having any allergy were more likely to have new Gad-enhancing lesions on brain MRI compared with those with NKA (OR 1.78 (95% CI 1.02 to 3.11), $P=0.0431$) while holding the other covariates constant. The food allergy group had more than twice the likelihood (OR 2.53 (95% CI 1.25 to 5.11), $P=0.0096$) of having a Gad-enhancing lesion while adjusting for other covariates. The environmental allergy and drug allergy groups trended towards a higher likelihood of having new Gad enhancing lesions compared with the NKA group; however, that was not shown to be significant. For the Gad-enhancing lesion count ratio in the different allergy groups compared with the NKA group, there was a trend towards a higher Gad-enhancing lesion count in the allergy groups; however, no significance difference was found in any of the different allergy groupings (table 6).

DISCUSSION

Our findings suggest that MS patients with allergies have more active disease than those without allergies, and that this effect is driven by food allergies. We showed that patients with food allergy have a 1.3 times significantly higher rate for cumulative number of attacks compared with patients with no allergies, along with a 2.5 times higher likelihood of having a Gad-enhancing lesion on brain MRI. The environmental allergy and drug allergy groups did not show major differences when compared with the group with no reported allergies. The EDSS and MSSS were not affected by the history of allergy.

The question of the effect of allergy on MS disease course is an important factor which has biological and potentially therapeutic implications. A previous case-control study analysed the association between allergy history and relapse rate in a paediatric MS cohort. Their findings suggested that food allergies in the first 5 years of life had a lower ARR compared with patients without food allergies (0.14 vs 0.48, $P=0.01$), with no association found between relapse rate and other types of allergies.¹⁰ These findings contrast with our results which showed a higher attack rate in adult MS patients who reported food allergy. The differences between these two studies could be due to several factors, including different patient populations, study designs and sample sizes. The different age groups may affect the prevalence of food allergy, which is known to be more prevalent in children and decreases into adulthood (4–7% in preschool children vs 1–2% in adults).¹⁸ The disease durations for the cases in the paediatric population was 10 months, versus 16 years in our cohort. In the paediatric study, history of allergy reflected the first 5 years of life only, whereas we were interested in the history of allergy at any point in life by the time the questionnaire was administered; this could yield differences in prevalence as well as in recall bias, where parents reported allergy in their children as opposed to our adult population who reported it by itself. In addition, there was a significant difference in sample size between the two studies where we included more than 1300 MS cases versus 271 cases in the paediatric MS study. Relapse data were available from even fewer patients ($n=193$) in the paediatric study, with a subgroup of MS patients with food allergies limited by an even smaller sample size ($n=9$), compared with a sample size of 238 food allergy patients in our relapse number analysis. Furthermore, immunological mechanisms of food allergy differ between

Multiple sclerosis

Table 2 Demographic characteristics of study subjects, stratified by allergy type

Variables	Environmental allergy	Food allergy	Drug allergy
N	586	238	574
Age at last visit, mean (SD), years	49.05 (11.56)	48.52 (11.19)	50.55 (11.72)
Age at first symptom, mean (SD), years	33.39 (9.97)	33.00 (9.87)	33.56 (10.31)
Male, n (%)	130 (22.18)	37 (15.55)	89 (15.51)
Disease duration at last visit, mean (SD), years	15.66 (9.55)	15.52 (9.16)	17.06 (10.01)
Disease category, n (%)			
Primary progressive MS	23 (3.92)	11 (4.62)	31 (5.40)
Secondary progressive MS	75 (12.80)	31 (13.03)	88 (15.33)
Relapsing-remitting MS	483 (82.42)	191 (80.25)	449 (78.22)
Progressive relapsing MS	5 (0.85)	5 (2.10)	6 (1.05)
Race, n (%)			
Asian	4 (0.68)	0 (0.00)	2 (0.35)
Black or African American	24 (4.10)	15 (6.30)	26 (4.53)
More than one race	21 (3.58)	9 (3.78)	10 (1.74)
Native Hawaiian/Pacific Islander	1 (0.17)	0 (0.00)	1 (0.17)
Unknown or not reported	8 (1.37)	2 (0.84)	6 (1.05)
White	528 (90.10)	210 (88.24)	529 (92.16)
Ethnicity, n (%)			
Hispanic or Latino	30 (5.12)	13 (5.46)	24 (4.18)
Not Hispanic or Latino	554 (94.54)	224 (94.12)	548 (95.47)
Unknown or not reported	2 (0.34)	1 (0.42)	2 (0.35)
% time on DMT, mean (SD)	47.71 (29.57)	45.14 (29.45)	45.38 (29.35)
EDSS at last visit, median (IQR)	2.0 (2.5)	2.0 (2.5)	2.0 (2.5)
MSSS at last visit, median (IQR)	1.64 (3.04)	1.83 (3.19)	1.77 (2.96)

DMT, disease-modifying therapy; EDSS, expanded disability status scale; MS, multiple sclerosis; MSSS, multiple sclerosis severity scale

children and adults. In children, food allergies are IgE mediated, while in adults, eosinophilic oesophagitis and IgA-mediated and T cell-mediated mechanisms predominate.¹⁹

Immune-mediated adverse reactions to food can be divided into immediate and delayed hypersensitivity reactions.²⁰ Immediate reactions to food antigens are IgE-mediated and dependent on activation of mast cells. The delayed immune reaction to food antigens are mediated by IgG, IgA and IgM, and T cells.²⁰ Unlike the immediate effects of IgE-mediated allergy, this delayed type food allergy can take several days to appear.²⁰ Levels of IgG, IgM and IgA antibodies in the blood against different food antigens

have been used to demonstrate delayed food allergy and intolerance reactions, found that even an individual who may not have IgG, IgA and IgM antibodies against antigens prepared from raw food could show positive results when tested against antigens prepared from cooked food.²⁰ One explanation of the effect of food allergy on MS disease course could be due to this antigen modification to a 'neo antigen', that occurs from exposure to processed food.²⁰ Subjects can develop antibodies to the modified food antigen, which have been shown to be associated with high levels of antibodies against advanced glycation end products (AGEs). According to one study, antibodies against AGEs could react with self-proteins and attack the patient's tissue in an autoimmune manner, leading to degenerative and autoimmune diseases such as diabetes, autoimmunity, neurodegeneration and neuro-autoimmunity.²¹ This immune repertoire, the spectrum of antigen specificities, is important for MS and was shown to be largely driven by non-heritable influences.²²

Food allergies could lead to an increase in MS inflammatory activity in adults through a variety of mechanisms.²³ Genetic data suggest that the pathogenesis of MS shares important features with a variety of non-CNS autoimmune diseases.²⁴ Shared autoimmune mechanisms include those that decrease regulatory T cell predominance and also increase Th2 and type 2 innate lymphoid cells (ILC2), leading to a more proinflammatory environment in the gut epithelial tissue.^{23 25} In addition, dysregulation of members of the T cell immunoglobulin and mucin domain (Tim) gene family are shared in MS and food allergy.²⁶

Another possible mechanism of food allergies' effect on MS is its association with gut microbiome dysbiosis, which is the disruption of the normal microbiota balance in favour of pathogenic bacteria. A role of the gut microbiome on the risk and disease course of MS has been recently demonstrated with differences

Table 3 Association and rate ratio of cumulative number of attacks by allergy type

Variables	Estimate	Relapse rate ratio	95% CI	P values
Any allergy vs NKA				
Unadjusted	0.1966	1.217	(1.031 to 1.437)	0.0204
Adjusted*	0.1165	1.124	(0.959 to 1.317)	0.1497
Environmental allergy vs NKA				
Unadjusted	0.1892	1.208	(1.008 to 1.448)	0.0407
Adjusted*	0.1211	1.129	(0.948 to 1.345)	0.1754
Food allergy vs NKA				
Unadjusted	0.3201	1.377	(1.095 to 1.732)	0.0062
Adjusted*	0.2423	1.274	(1.023 to 1.587)	0.0305
Drug allergy vs NKA				
Unadjusted	0.1588	1.172	(0.977 to 1.407)	0.0879
Adjusted*	0.0918	1.096	(0.918 to 1.308)	0.3086

*The multivariate model adjusted for sex, age at symptom onset, race (non-white vs white), disease category (progressive vs relapsing), and percentage of time on disease-modifying therapy. Disease duration was used as the offset parameter.

NKA, no known allergy.

Table 4 Association of EDSS and MSSS by allergy type

Variables	EDSS*			MSSS†		
	OR	95% CI	P values	Estimate	95% CI	P values
Any allergy vs NKA						
Unadjusted	1.00	(0.821 to 1.225)	0.9747	−0.039	(−0.193 to 0.116)	0.6253
Adjusted	1.20	(0.980 to 1.478)	0.0771	0.058	(−0.074 to 0.191)	0.3865
Environmental allergy vs NKA						
Unadjusted	0.94	(0.756 to 1.168)	0.5730	−0.071	(−0.239 to 0.097)	0.4063
Adjusted	1.21	(0.969 to 1.517)	0.0920	0.077	(−0.069 to 0.222)	0.3008
Food allergy vs NKA						
Unadjusted	0.97	(0.733 to 1.275)	0.8114	−0.017	(−0.230 to 0.196)	0.8751
Adjusted	1.16	(0.869 to 1.547)	0.3135	0.075	(−0.105 to 0.256)	0.4137
Drug allergy vs NKA						
Unadjusted	1.10	(0.884 to 1.368)	0.3929	−0.020	(−0.189 to 0.149)	0.8143
Adjusted	1.29	(1.026 to 1.618)	0.0294	0.088	(−0.056 to 0.231)	0.2320

*The multivariate model adjusted for sex, age at symptom onset, race (non-white vs white), disease category (progressive vs relapsing), percentage of time on disease-modifying therapy (DMT), and disease duration (DD).

†The multivariate model adjusted for sex, age at symptom onset, race (non-white vs white), disease category (progressive vs relapsing), and percentage of time on DMT. DD was used as the offset parameter.

EDSS, expanded disability status scale; MSSS, multiple sclerosis severity score; NKA, no known allergy.

in several species between MS patients and controls.^{27 28} Gut microbes can additionally produce neuroactive molecules that affect the enteric nervous system and the CNS leading to the concept of 'microbiota-gut-brain axis'.²⁷ In experimental autoimmune encephalomyelitis (EAE) models, a germ-free environment has been associated with a milder disease course and protection against the disease, while introduction of microbiota in the mice's gut restored disease susceptibility.²⁹ These findings support the hypothesis that the type and distribution of gut microbiota could affect the risk and course of MS, probably in a way similar to how food allergy affects MS. Enhanced gut leakiness in food allergy could allow for bacterial antigens, lipopolysaccharide and toll-like receptor (TLR) agonists to penetrate and activate immune cells.^{30 31}

Gad-enhancing lesions are known to be markers of active disease, and their correlation with relapse rate and disability was demonstrated in multiple studies,^{32 33} as well as its predictor value for future disability.³⁴ As far as we know, this is the first study to link food allergy with higher likelihood of Gad-enhancing lesions in a multivariate analysis. Our group has previously

demonstrated an association of seasonality and Gad-enhancing lesions,³⁵ and further studies are needed to determine whether food allergies contribute to this association.

A strength of our study was our large sample size of more than 1300 patients, as well as the availability of MRI scans with Gad-enhancing lesion counts data for over 750 patients. Limitations to our study included reliance on subjects for reporting history of allergies, without blood/skin testing, or diagnosis confirmation by an allergy specialist. Additionally, our questionnaire cannot differentiate between true food allergy and other adverse reactions to food, especially since food allergy can sometimes be over diagnosed. A possible question about the temporal relationship between allergy history and disease could be raised; however, we do not claim to establish causality. The cross-sectional design revealed an interesting association between food allergy history and disease activity, accounting for several covariates, and future longitudinal studies could confirm our results and possibly establish causality. Nonetheless, relapse rates, EDSS and MSSS measures were all analysed at the patient's last visit after the questionnaire was done, so conveying a temporal

Table 5 Logistic regression models for presence of gadolinium (Gad) lesions by allergy type

	New Gad lesion n (%)	No new Gad Lesion n (%)	Unadjusted			Adjusted*		
Variable			OR	95% CI	P values	OR	95% CI	P values
Any allergy								
Known allergy	67 (13)	449 (87)	1.71	1.003 to 2.922	0.0486	1.78	1.018 to 3.114	0.0431
NKA	19 (8)	218 (92)						
Environmental allergy								
Known allergy	43(13)	284 (87)	1.74	0.984 to 3.066	0.0567	1.69	0.934 to 3.062	0.0830
NKA	19(8)	218 (92)						
Food allergy								
Known allergy	23 (25)	110 (75)	2.40	1.253 to 4.593	0.0083	2.53	1.253 to 5.112	0.0096
NKA	19 (8)	218 (92)						
Drug allergy								
Known allergy	37 (11)	293 (89)	1.45	0.811 to 2.588	0.2106	1.54	0.833 to 2.858	0.1676
NKA	19 (8)	218 (92)						

*The multivariate model adjusted for sex, age at symptom onset, disease category (progressive vs relapsing), percentage of time on disease-modifying therapy and disease duration.

NKA, no known allergy.

Table 6 Association and rate ratio of gadolinium lesions count by allergy type

Variable	Estimate	Lesion count rate ratio	95% CI	P values
Any allergy vs NKA				
Unadjusted	0.603	1.828	0.853 to 3.918	0.1210
Adjusted*	0.404	1.497	0.695 to 3.223	0.3026
Environmental allergy vs NKA				
Unadjusted	0.442	1.555	0.696 to 3.476	0.2817
Adjusted*	0.104	1.120	0.483 to 2.552	0.8064
Food allergy vs NKA				
Unadjusted	1.037	2.822	1.060 to 7.510	0.0378
Adjusted*	0.810	2.248	0.822 to 6.154	0.1147
Drug allergy vs NKA				
Unadjusted	0.493	1.637	0.668 to 4.012	0.2817
Adjusted*	0.353	1.424	0.556 to 3.642	0.4613

*The multivariate model adjusted for sex, age at symptom onset, disease category (progressive vs relapsing), and percentage of time on disease modifying therapy. Disease duration was used as the offset parameter. NKA, no known allergy.

association. It is possible that patients with food allergies had more contact with physicians, and therefore may have over-reported relapses; however, the MRI substudy, which demonstrated that Gad-enhancing lesions were increased in the food allergy group, is not subject to recall bias and therefore argues against this.

This is the first study to assess the relation between allergy and MS disease course as measured by clinical and MRI variables in an adult MS population. Our study showed that patients with food allergy had more relapses and a higher likelihood of Gad-enhancing lesions as compared with MS patients with no allergy. Future prospective studies are needed to confirm our findings and understand the underlying biological mechanism, by analysing blood biomarkers of allergy, which can lead to new therapeutic and preventative strategies for MS.^{19 36 37}

Acknowledgements The authors wish to thank the following colleagues at the Brigham and Women's Hospital: Mariann Polgar-Turcsanyi, MS and Mark Anderson, MS for their role in managing the Partners MS Center Research Database, as well as Taylor Saraceno, BA for her assistance in manuscript preparation.

Contributors Study concept and design: TC, CDC. Additional study design: RF. Data collection, validation and analysis: CDC, ASC, RF, CG, NS. Additional analysis design and data interpretation: CG, BCH. Drafting of the manuscript: RF. Critical revision of the manuscript: All authors. Study participant enrolment: BIG. Study supervision: TC, HLW. All co-authors gave their approval of the manuscript to be published.

Funding We thank Merck Serono and the National MS Society Nancy Davis Center Without Walls for their support of the CLIMB study.

Competing interests RF reports no conflicts of interests. CDC reports no conflicts of interests. ASC reports no conflict of interests. CG reports no conflicts of interests. BCH reports grants from Verily Life Sciences, grants from Novartis, grants from Merck Serono, grants from Genentech, outside the submitted work. NS reports no conflicts of interests. BIG reports grants from Merck Serono, during the conduct of the study, and grants from Verily Life Sciences, outside the submitted work. HLW reports support from NIH, NMSS, Verily Life Sciences, EMD Serono, Biogen, Teva Pharmaceuticals, Sanofi, and Novartis. Research support and consulting fees from Genentech, Inc, Tilos Therapeutics, Tiziana Life Sciences, and IM Therapeutics. Personal and consulting fees from vTv Therapeutics and MedDay Pharmaceuticals. TC reports consulting fees from Biogen Idec, Novartis, Sanofi, Bayer, and Celgene, outside the submitted work.

Patient consent Not required.

Ethics approval The Partners Institutional Review Board approved this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data used in this manuscript are available to qualified health care professionals under the guidance of the Partners Human Research Committee and Partners Data Use Agreements.

REFERENCES

- Giovannoni G, Ebers G. Multiple sclerosis: the environment and causation. *Curr Opin Neurol* 2007;20:261–8.
- Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat Rev Neurol* 2017;13:25–36.
- Solaro C, Messmer Uccelli M, Guglieri P, et al. Prevalence of atopy in multiple sclerosis patients: a case-control study. *J Neurol* 2001;248:239–40.
- Edwards LJ, Constantinescu CS. A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. *Mult Scler* 2004;10:575–81.
- Karimi P, Modarresi SZ, Sahraian MA, et al. The relation of multiple sclerosis with allergy and atopy: a case control study. *Iran J Allergy Asthma Immunol* 2013;12:182–9.
- Pedotti R, Farinotti M, Falcone C, et al. Allergy and multiple sclerosis: a population-based case-control study. *Mult Scler* 2009;15:899–906.
- Ponsonby AL, Dwyer T, van der Mei I, et al. Asthma onset prior to multiple sclerosis and the contribution of sibling exposure in early life. *Clin Exp Immunol* 2006;146:463–70.
- Alonso A, Hernán MA, Ascherio A. Allergy, family history of autoimmune diseases, and the risk of multiple sclerosis. *Acta Neurol Scand* 2008;117:15–20.
- Monteiro L, Souza-Machado A, Menezes C, et al. Association between allergies and multiple sclerosis: a systematic review and meta-analysis. *Acta Neurol Scand* 2011;123:1–7.
- Bourne T, Waltz M, Casper TC, et al. Evaluating the association of allergies with multiple sclerosis susceptibility risk and disease activity in a pediatric population. *J Neurol Sci* 2017;375:371–5.
- Gauthier SA, Glanz BI, Mandel M, et al. A model for the comprehensive investigation of a chronic autoimmune disease: the multiple sclerosis CLIMB study. *Autoimmun Rev* 2006;5:532–6.
- Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.
- Roxburgh RH, Seaman SR, Masterman T, et al. Multiple Sclerosis Severity Score: using disability and disease duration to rate disease severity. *Neurology* 2005;64:1144–51.
- Duan Y, Hildenbrand PG, Sampat MP, et al. Segmentation of subtraction images for the measurement of lesion change in multiple sclerosis. *AJNR Am J Neuroradiol* 2008;29:340–6.
- Liguori M, Meier DS, Hildenbrand P, et al. One year activity on subtraction MRI predicts subsequent 4 year activity and progression in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2011;82:1125–31.
- Oommen VV, Tauhid S, Healy BC, et al. The effect of fingolimod on conversion of acute gadolinium-enhancing lesions to chronic T1 hypointensities in multiple sclerosis. *J Neuroimaging* 2016;26:184–7.
- Regev K, Healy BC, Khalid F, et al. Association between serum MicroRNAs and magnetic resonance imaging measures of multiple sclerosis severity. *JAMA Neurol* 2017;74:275–85.
- Turnbull JL, Adams HN, Gorard DA. Review article: the diagnosis and management of food allergy and food intolerances. *Aliment Pharmacol Ther* 2015;41:3–25.
- Muraro A, Lemanske RF, Castells M, et al. Precision medicine in allergic disease—food allergy, drug allergy, and anaphylaxis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. *Allergy* 2017;72:1006–21.
- Vojdani A, IgE Dof. Detection of IgE, IgG, IgA and IgM antibodies against raw and processed food antigens. *Nutr Metab* 2009;6:22.
- Ramasamy R, Vannucci SJ, Yan SS, et al. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. *Glycobiology* 2005;15:16R–28.
- Brodin P, Jojic V, Gao T, et al. Variation in the human immune system is largely driven by non-heritable influences. *Cell* 2015;160:37–47.
- Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. *Nat Rev Immunol* 2016;16:751–65.
- Farh KK, Marson A, Zhu J, et al. Genetic and epigenetic fine mapping of causal autoimmune disease variants. *Nature* 2015;518:337–43.
- Roychoudhuri R, Hirahara K, Mousavi K, et al. BACH2 represses effector programs to stabilize T(reg)-mediated immune homeostasis. *Nature* 2013;498:506–10.
- Li Z, Ju Z, Friier M. The T-cell immunoglobulin and mucin domain (Tim) gene family in asthma, allergy, and autoimmunity. *Allergy Asthma Proc* 2013;34:21–6.
- Bhargava P, Mowry EM. Gut microbiome and multiple sclerosis. *Curr Neurol Neurosci Rep* 2014;14:492.
- Jangi S, Gandhi R, Cox LM, et al. Alterations of the human gut microbiome in multiple sclerosis. *Nat Commun* 2016;7:12015.
- Berer K, Mues M, Koutrosos M, et al. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. *Nature* 2011;479:538–41.
- Escribano BM, Medina-Fernández FJ, Aguilar-Luque M, et al. Lipopolysaccharide binding protein and oxidative stress in a multiple sclerosis model. *Neurotherapeutics* 2017;14:199–211.

- 31 Teixeira B, Bittencourt VC, Ferreira TB, *et al.* Low sensitivity to glucocorticoid inhibition of in vitro Th17-related cytokine production in multiple sclerosis patients is related to elevated plasma lipopolysaccharide levels. *Clin Immunol* 2013;148:209–18.
- 32 Fisniku LK, Brex PA, Altmann DR, *et al.* Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain* 2008;131(Pt 3):808–17.
- 33 Brex PA, Ciccarelli O, O’Riordan JI, *et al.* A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med* 2002;346:158–64.
- 34 Bermel RA, You X, Foulds P, *et al.* Predictors of long-term outcome in multiple sclerosis patients treated with interferon β . *Ann Neurol* 2013;73:95–103.
- 35 Meier DS, Balashov KE, Healy B, *et al.* Seasonal prevalence of MS disease activity. *Neurology* 2010;75:799–806.
- 36 Freeland DMH, Manohar M, Andorf S, *et al.* Oral immunotherapy for food allergy. *Semin Immunol* 2017;30:36–44.
- 37 Otani IM, Nadeau KC. Biologic therapies for immunoglobulin E-mediated food allergy and eosinophilic esophagitis. *Immunol Allergy Clin North Am* 2017;37:369–96.