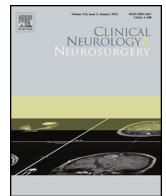




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Respiratory tract rather than cutaneous atopic allergy inversely associate with multiple sclerosis: A case–control study

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ABSTRACT

Background: It has been previously shown that genetic or environmental factors, which promote susceptibility to allergic conditions, prevent the development of Th1-mediated inflammatory disease of multiple sclerosis (MS). To investigate the prediction value of lifetime atopic allergy in development of the future MS, a case–control study was designed.

Methods: Cases and controls were interviewed between December 2007 and April 2008 and they were asked if they had symptoms or diagnosis of allergies (including respiratory tract allergy, RTA; coetaneous allergy, CA; food/drug allergy, FDA) before MS diagnosis.

Results: Of 390 participants (195 controls and 195 cases), 125 healthy controls (64.1%) and 105 cases (53.8%) reported history of at least one type of atopic allergy ($P=0.04$). A positive history of RTA (OR 0.43; 95% CI 0.28–0.66) or FDA (OR 0.24; 95% CI 0.13–0.43) was inversely associated with the risk of MS. No statistically significant association was found between the history of CA and MS.

Conclusions: There is a significant inverse association between RTA and MS that is compatible with a Th1/Th2 imbalance. History of RTA can be considered as a clinically useful risk reducing factor of MS.

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1. Introduction

Multiple sclerosis (MS) is a disorder of the central nervous system, manifesting as acute focal inflammatory demyelination and axonal loss with limited remyelination, culminating in the chronic multifocal sclerotic plaques. Myelin-reactive T cells from patients with multiple sclerosis produce cytokines which is more consistent with a Th1-mediated response, whereas, myelin-reactive T cells from healthy persons are more likely to produce cytokines that characterize a Th2-mediated response [1]. On the other hand, switching B cells to IgE production and accumulation of eosinophils are under the control of Th2 lymphocytes. These cells also produce cytokines, which contribute to airway hyper responsiveness in asthma [2]. The hypothesis that MS may be associated with a reduced risk of Th2-associated diseases has been investigated in a number of clinical studies, so far. However, the results are extremely controversial [3–6]. To clarify the capability of the lifetime involvement with different types of prevalent atopic allergies in predicting the development of MS, a case–control study was designed and carried out.

2. Material and methods

Participants. Cases were defined as multiple sclerosis patients according to the revised McDonald's criteria [7] and were recruited consecutively in MS Research Center/Clinic, Sina University Hospital, Tehran, Iran. Healthy control subjects from non-relative companion or neighbors of patients with MS, residing in the same region, were enrolled. This was to achieve similar socioeconomic and environmental status. Controls were individually matched to cases with respect to the gender, age (± 2 years) and where possible, place of birth. The controls either had no family history or history of any symptoms that might suggest undiagnosed MS.

The response rate was 96.1% (200 out of 208) and 85.4% (200 out of 234), among the MS patients and controls who were asked for participation, respectively. Informed consent was formally obtained from all participants at the beginning of each interview.

Assessments. Face to face interviews were conducted on cases and controls between December 2007 and April 2008 by one research assistant with MD qualification in a random manner without knowledge of their status, at the MS research center, Sina Hospital, Tehran. The interviewer was instructed by an allergist with regards to conducting the interview and recording of assessment. The questionnaire covered questions about demographics, family history, sign and symptoms of different allergies (allergic asthma, allergic rhinitis, eczema, and acute urticaria-angioedema) and allergy to different allergens. Questions on asthma, allergic

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rhinitis, and eczema were derived from European Community Respiratory Health Survey (ECRHS) [8]. Before the start of the study, the questionnaire was verified with a group of patients to assess the clarity and completeness of the content, under the supervision of the main investigator.

Clinical history of MS cases including age at the onset of MS, disease duration, previous or current medication, clinical course of MS and Expanded Disability Status Scale score (EDSS) were determined in an interview by a neurologist who was not involved in allergy questionnaire processing. In this case the greatest level of discretion was maintained. Asthma was considered to be present if a subject reported a physician diagnosed asthma which leads to the prescription of anti-asthmatic medication including inhalers, aerosols or tablets. Patients with asthmatic attacks triggered by anxiety, cold or dry air, strenuous exercise, smoke and chest infection were considered as intrinsic asthma (i.e. non atopic) and were excluded. In order to confirm allergic rhinitis, the subjects were asked if they ever had seasonal or perennial occurrences of nasal symptoms including pruritus, congestion, rhinorrhea, or paroxysm of sneezing, which may be associated with eye erythema, itching, irritation, or tearing.

Atopic dermatitis (Eczema) was verified if the participant had experienced pruritic, exudative, lichenified eruption on face, neck, upper trunk, wrists, hands, or in the antecubital or popliteal folds with a tendency to recur. Acute urticaria was recorded if less than 24–36 hours-lasting large, irregularly shaped, pruritic, erythematous wheals were present in past medical history. Angioedema was diagnosed with a history of deep, subcutaneous swelling involving periorbital, circumoral, and facial regions.

Allergens were categorized into two groups of food or drug and non specific (including dust, animal dander, and etc. which were rarely mentioned by patients).

To determine whether there is any association between the history of atopic allergies and disabling phases of MS, primary progressive (PPMS) and secondary progressive MS (SPMS) were classified as progressive MS and were compared with less disabling form of relapsing remitting MS (RRMS).

Besides, atopic allergies were classified into two major groups of respiratory tract allergy (RTA) including allergic rhinitis and asthma; cutaneous allergy (CA) including urticaria, angioedema, and eczema. The project received ethical approval from the Human Research Ethics Committee of the Tehran University of Medical Sciences.

Statistical analysis. The data were entered in the SPSS 13.0 statistical package (SPSS Inc., Chicago, IL, USA). Using the χ^2 test, possible associations were analyzed between categorical variables and dichotomous variable of MS incidence. To apply parametric tests, normality of distributions was evaluated using the one-sample Kolmogorov–Smirnov test. Independent sample *t*-test (Mann–Whitney if appropriate) was used to determine if there were any differences of continuous variables' means between two groups of case and control. Binary logistic regression analysis was performed to assess the association between history of allergic diseases and multiple sclerosis after adjusting for age, sex, residential area, and family history. Mean values were reported as ± 1 standard error (SD) and 95% confidence interval (CI). Two-sided probability values less than 0.05 were considered to be significant.

3. Results

At the final evaluation of the questionnaires, of the four hundred interviewed subjects, ten participants were excluded due to insufficient or vague responses to the allergy questions while 390 (195 cases versus 195 controls) were considered eligible to be

Table 1

Characteristics and the frequency of different atopic allergies in each group.

	Cases, N (%)	Controls, N (%)	P Value ^a
Age (Mean $\pm$ SD)	32.2 $\pm$ 9.0	31.7 $\pm$ 8.1	0.62
Females	152 (77.9%)	159 (81.5%)	0.40
Positive FH of allergy	78 (40.0%)	86 (44.1%)	0.41
Conditions:			
Asthma	1 (0.5%)	9 (4.6%)	0.02
Allergic rhinitis	49 (25.1%)	84 (43.1%)	<0.001
Urticaria/Angioedema	44 (22.6%)	49 (25.1%)	0.55
Eczema	55 (28.2%)	54 (27.7%)	0.91
Allergy to:			
Food or drug	16 (8.2%)	53 (27.2%)	<0.001
Non specific agent	94 (48.2%)	79 (40.5%)	0.13

^a The P value to compare mean were computed using an Independent T test. χ^2 test was considered for dichotomous data.

analyzed of which 313 [80.3%] were female. The mean age of them was 31.9 ± 8.5 years, that is, from 16 to 62 years.

One hundred and thirty three MS patients were under maintenance therapy (102 interferon beta-1a and 31 interferon beta-1b) at the time of the study. A median duration of MS diagnosis was 36 months. Overall, 125 healthy controls (64.1%) and 105 cases (53.8%) reported at least one type of atopic allergy in their past medical history that indicated a significant inverse association between history of allergy and MS ($P=0.04$). Table 1 shows the characteristics and the frequency of different atopic allergies in each group. Compared with those who had history of CA (79 MS cases [40.5%] versus 85 controls [43.6%]; $P=0.54$), participants who reported RTA (49 MS cases [25.1%] versus 85 controls [43.6%]; $P<0.001$) seemed to have lower risk of the development of MS.

EDSS was associated with neither preceding history of allergy ($P=0.18$) nor CA ($P=0.73$). However; at the time of the study, the patients with a positive history of RTA before MS onset had a lower EDSS (2.5 ± 1.5) than those with no previous RTA (2.9 ± 1.5 ; $P=0.05$). More RRMS patients had past medical history of allergy than the patients of progressive phases (93 [57.4%] versus 11 [36.7%]; $P=0.04$).

Binary logistic regression analysis revealed that a positive history of RTA (OR 0.43, 95% CI 0.28–0.66; $P<0.001$) or FDA (OR 0.24, 95% CI; 0.13–0.43; $P<0.001$) was inversely associated with the risk of MS; a history of both RTA and FDA increased the inverse association (Table 2). Risk for MS was unrelated to the presence of both RTA and Eczema. (PV = 0.22)

4. Discussion

Our findings support the hypothesis that having a history of atopic allergy reduces the risk of both development of multiple sclerosis and progressive MS. In particular, respiratory tract allergies including allergic rhinitis and asthma decreased the lifetime risk of MS as well as allergy to food/drug. However, the magnitude of this risk reduction was modest (OR, 0.43, 0.24, respectively). The risk was significantly lower in participants who had history of both RTA and food/drug allergy. In contrast, family history of cutaneous atopic allergies (acute urticaria, angioedema, and eczema), and allergy to allergens other than food/drug seemed not to be related with the risk of MS.

Our result is consistent with the findings from previous studies in which patients with MS were found to have a lower prevalence of allergic diseases [4–6,9,10], however there are still controversies concerning this issue [3,11]. In a recent report, a population based case control study on 423 cases and 643 population controls, pedotti et al. [4] showed that a history of atopic allergies (asthma and rhino conjunctivitis) was associated with a decreased risk for MS. In another study by Bergamaschi et al. [6], it was found that MS

Table 2

Odds ratios with 95% confidence intervals for multiple sclerosis according to past medical history of respiratory allergy, eczema and allergy to food or drug.

	Case, N (%)	Control, N (%)	OR (95% CI) ^a	PV
Neither RTA nor FDA	135 (69.2%)	88 (45.1%)	Reference	
RTA or FDA	60 (30.8%)	107 (54.9%)	0.36 (0.23–0.57)	<0.001
RTA only	49 (25.1%)	85 (43.6%)	0.44 (0.28–0.70)	<0.001
FDA only	16 (8.2%)	53 (27.2%)	0.23 (0.12–0.43)	<0.001
RTA plus FDA	5 (2.6%)	31 (15.9%)	0.14 (0.05–0.37)	<0.001
RTA plus eczema	21 (10.8%)	30 (15.4%)	0.68 (0.37–1.29)	0.22

Abbreviations: RTA, respiratory tract allergy; FDA: food drug allergy; OR, odds ratio.

^a Adjusted for age, sex, residential area and family history.

patients were less likely to suffer from ARDs and allergic rhinitis, adjusting for environmental factors.

On the other hand, a study by Alonso et al. [12] revealed no association between history of allergic conditions and the risk of MS. Moreover, a meta analysis by Monteiro et al. [3] assessing 10 epidemiological studies, did not find convincing evidence for the association between allergic disease, asthma, allergic rhinitis, eczema and MS. In their analysis, although they found a trend toward an inverse association between allergy and MS, it was not statistically significant. However, the methodological heterogeneity among the included studies and interethnic differences among the corresponding subjects are the two factors that limit the reliability of their results. Besides, the diagnosis of atopic allergies in most of these studies was only relied on the patient reports which raise the possibility of misclassification [3].

To the best of our knowledge, releasing the allergic mediators in the upper or lower respiratory tract and superficial, mid, and deeper layers of the skin, may lead to allergic rhinitis, allergic asthma, dermatitis, urticaria, and angioedema, respectively.

How allergic conditions might protect against the development of MS has not been fully explained yet. Recent investigations have taken steps to elucidate the underlying pathophysiological pathways. In this context, some studies indicate that the development of immune responses against stimulatory environmental factors (allergens or infectious agents) inhibits responses to auto-antigens [13–15].

On the other hand, a recent experimental study shows that myelin-specific autoimmune cells transit the lungs before establishing disease in the CNS [13]. Using a Lewis rat model of experimental autoimmune encephalomyelitis (EAE), Odoardi et al. [13] demonstrated that T cells fundamentally gain the capacity to migrate and enter the CNS after local stimulation when they pass through airways and bronchus lymph tissues. Interestingly, lung serves as a niche where both activated and memory T cells reprogram their gene expression profile and could be readily activated to become pathogenic. These findings suggest that respiratory allergy might directly elicit the pathogenic response in these T cells.

Another possible mechanism is through T helper 1 (Th 1) to T helper 2 (Th 2) immune deviation [16]. Cytokines are critical components of the immune inflammatory process and are implicated in oligodendrocyte cell death, axonal degeneration and neuronal dysfunction, which are key features in MS pathology and the substrate of irreversible deficits [17,18]. Immediate hypersensitivity reactions are mediated by IgE. Th cells, which are CD4+, have been divided into 2 broad classes based on the cytokines they produce: Th1 and Th2. Through producing interferon gamma and some other cytokines, Th1 is believed to be responsible for the development of delayed hypersensitivity reaction. Th2 cells, on the other hand, produce IL-4 and IL-13, which promote the production of antigen-specific IgE and consequently immediate hypersensitivity reactions. Besides, interferon gamma produced by Th1 cells seems to diminish the production of Th2 cells [16]. Patients who are atopic are thought to have a higher Th2-to-Th1 cell ratio whereas

organ-specific autoimmune diseases such as MS might be dominated by Th1 activity [16,19].

RTA divided into non-atopic and atopic subtypes. The inverse association between MS and allergies were conceivable only in the case of atopic RTA which pathogenesis is related to Th2 cells [6]. Here, by employing a validate questionnaire through a direct interview, we minimize the misclassification errors in identifying the atopic subjects.

Present study proposes that either genetic or environmental factors that promote susceptibility to RTA and allergy to food/drug, prevent the development of Th1-mediated inflammatory disease of MS. This could be explained either by antigenic competition, or by redirection of the immune response toward aTh2 cells [15].

The fact that the prevalence of RTA greatly diminishes in patients with MS has been previously shown in several studies [4–6]. However, the discrepancy between RTA and CA has never been explored in much detail as was done in this study by including cases with eczema, urticaria and angioedema. A reduced prevalence of CA was found in MS population which does not reach statistical significance. This finding is consistent with Tremlett et al. report [5]. Why CA is not associated with MS is still unclear. However, there is some evidence showing that in acute atopic dermatitis, the increase in the number of activated Th1 cells and an augmented production of interferon gamma result in inflammatory skin changes. [20,21]. Similar to atopic dermatitis, it may seem unlikely that urticaria/angioedema are entirely rooted in elevated activity of just one type of Th cells, as was once thought.

Additionally, the sensitivity to food/drug allergens was examined and similar inverse association was observed with MS. These inverse associations are compatible with a Th1/Th2 imbalance. Except for food and drug, other allergens, which were mostly unidentified to the participants, seemed not to be related to MS. The reason for this phenomenon is not clear to the authors. However, it is possible that unknown allergens stimulate different allergic flow in different scale that share less patho-physiological pathway with MS.

The capability of atopic allergy in prediction of progressive and more disabling forms of MS was another interesting finding of this study that should be confirmed by further research.

The prevalence of allergic rhinitis in the Middle East region has a greater diversity compared to western population [22,23]. There is limited data assessing the prevalence of allergic diseases in Iran, particularly in adults. The prevalence of asthma, allergic rhinitis, and eczema was estimated up to 7%, 35.5%, and 19%, respectively [24]. Exposure to traffic related air pollutants is known to be associated with the increased risk of allergies [25]. This could explain the fairly higher prevalence of allergic diseases in this study, which was over represented by participants that are residing in Tehran, a city with severe air pollution in Iran.

We did not specify the type of allergy with respect to the family history and that is possibly why there was no association between family history and MS incidence. On the other hand, recall bias and misinformation could affect the data collection.

Furthermore, prediction and prevention of the subsequent MS, especially in patients with clinically isolated syndrome (CIS), is considered to be one of the most important interests of neurological research [26]. Researchers and clinicians are seeking for some practical indicators to estimate the risk of MS and its severity, and to define the best time to initiate the therapy. Therefore, the significance of allergy as an indicator of Th1/Th2 imbalance in prediction of the future RRMS in CIS patients might be a remarkable topic for further research. Although laboratory tests were not performed to confirm the different patterns of allergies in MS patients, a shift from Th1 cytokine dominance toward Th2 may provide new drug-targeting routes for MS. While this needs to be confirmed in a larger observational study, our findings show that past medical history of RTA and allergy to food/drugs can be considered as a clinically useful risk reducing factors of MS and play an important role in clinical decision making.

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