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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.

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*Definitions*. 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 eryhtema, 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 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.

Table 1
Characteristics and the frequency of different atopic allergies in each group.

	Cases, N (%)	Controls, N (%)	*P* Value[a]
Age (Mean ± SD)	32.2 ± 9.0	31.7 ± 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.

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