The Relation of Multiple Sclerosis with Allergy and Atopy: A Case Control Study

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ABSTRACT

Multiple Sclerosis (MS) and Allergy are believed to up regulate T helper cell type 1 (Th1) and T helper cell type 2 (Th2) responses, respectively. It has been shown that disequilibrium in the ratio of Th1/Th2 activities may increase frequency of one disease and decrease the frequency of the other. The aim of this study was to investigate the relation of MS with allergy and atopy in new diagnosed MS patients.

This case-control study was conducted on 40 new diagnosed MS patients and the same number of normal controls. All of the patients were diagnosed (according to McDonald criteria) at most 2 years prior to the study. Demographic data and clinical characteristics of both groups were recorded in a questionnaire. The total IgE and allergen specific IgE in the serum were measured in all the cases.

Forty MS patients (female/male: 4.71) with mean age of 30.55±9.5 years and 40 healthy controls entered in this study. History of allergy was observed in 20(50%) of MS patients (including 15 (37.5%) rhinitis, 6 (15%) conjunctivitis, 3 (7.5%) urticaria and eczema, 1 (2.5%) asthma), and 20 (50%) of the controls (including 8 (20%) rhinitis, 4 (10%) conjunctivitis, 7 (17.5%) urticaria and eczema, 1 (2.5%) asthma). The differences between the two groups were not statistically significant. Neither the serum total IgE, nor the frequency of specific IgE against Weed mix, Grass Mix, Tree mix1, Tree mix 2, Dermatophagoides Farinae, Dermatophagoides pteronyssinus and Epidermal and animal proteins mix differed statistically between the two groups. There was also no significant relationship between MS clinical manifestations and allergy prevalence and also between MS and atopy.

The results of this study as some other similar studies showed the same prevalence of allergy in MS patients and controls and also demonstrated no relation between MS and atopy.

Keywords: Allergy; Atopy; Multiple Sclerosis; Immunoglobulin E.
INTRODUCTION

Multiple sclerosis (MS) is a progressive T-cell autoimmune disease with chronic inflammation and demyelination of the central nervous system (CNS). Prevalence of MS varies from 5.3 to 12.8 cases per 100000 people in different locations of Iran. MS is considered as the leading cause of neurologic disability in young adults. The exact etiology remains unclear, but it is likely that diverse immunological factors, genetic susceptibility and environmental factors contribute to MS pathology. MS has been linked to a reduced risk of IgE-mediated allergy.

Allergy and MS are thought to be T helper cell type2 (Th2) and T helper cell type 1 (Th1) mediated diseases, respectively. The prevalence of allergic disorders is different in various locations of Iran with a range from 10% to 27.5%. The pathogenesis of allergic diseases is based on the production of allergen-specific immunoglobulin E (IgE). Th2 cells facilitate production of allergen-specific IgE and Th1 cells decrease production of IgE. Therefore, it has been shown that Th2 mediated disease by producing interleukine (IL)-4, IL-5, IL-6, IL-10 and IL-13 cytokines may protect against Th1 mediated disease.

On the other hand it has been demonstrated that the mediators associated with Th2 mediated diseases play a role in progression of some Th1 mediated diseases.

Furthermore, it has been shown that IL-17 which is produced by a variety of cell types such as Th0, Th1, Th2, neutrophils, eosinophils, etc., depending on the state of the disease, has been increased in allergic and autoimmune diseases and may contribute to progression of allergic and autoimmune diseases. Because MS and other disorders of immune system can portion some common risk factors, allergy can play a major role in clinical disease activity in patients with MS. Thus, several studies have demonstrated the relationship between MS and allergy that gave discordant findings. While some studies have shown higher allergy prevalence among MS patients, others have demonstrated similar or reduced allergic diseases among patients with MS.

As reported results have been inconsistent, efforts to understand this relationship persist. Therefore, this study was conducted to clarify the relation of MS with allergy and atopy in new diagnosed MS patients.

MATERIALS AND METHODS

Forty new diagnosed MS patients, referring to department of Neurology of Sina hospital were enrolled in this case-control study. Control group was chosen from healthy blood donor volunteers, matched by age, sex and region of living. The sample size was estimated in at least 40 subjects for each group according to a confidence of 90% and a power of 80%.

All of the patients were diagnosed at most 2 years prior to the study, according to McDonald criteria by two expert neurologist clinicians. Only patients who had not received corticosteroids or immunomodulatory therapy, that might cause reduced prevalence of allergy, were included. Patients with other neurologic diseases or infections were excluded.

Allergy history was collected by face to face interview including personal history of allergy, clinical manifestations of allergy (conjunctivitis, rhinitis, urticaria and eczema, and asthma) and family history of allergy in both groups. Moreover, history of vaccination, history of childhood infections (Chicken Pox, Mumps, Measles, Rubella, Hepatitis A and B), familial history of MS, and history of hygienic behaviors in childhood were collected in the two groups.

From each individual of both case and control groups, 5 ml venous blood was collected and centrifuged at 2500 rpm for 10 minutes. Serum samples were stored at -20 °C until the tests were performed. Serum total IgE and specific IgE were measured by Immuno CAP system purchased from Phadia AB Co, Uppsala, Sweden. Serum specific IgE was determined for the following antigens: Weeds Mix (Ambrosia eliator, Artemisia vulgaris, Plantago lanceolata, Chenopodium album, Salsola kali), Grass Mix (Cynodon dactylon, Lolium perenne, Pileum pratense, Poa pratensis, Sorghum halepense, Paspalum notatum), Trees Mix1 (Acer negundo, Quercus alba, Ulmus americana, Populus deltoides, Carya pecan), Trees Mix2 (Olea europaea, Salix caprea, Pinus strobos, Eucalyptus spp., Acacia longifolia, Melaleuca leucadendron), Dermatophagoides farinae,
Dermatophagoides Pteronyssinus and Epidermal and animal proteins mix (cat dander, horse dander, cow dander, dog dander).

Patients with positive history of allergy and positive IgE ImmunoCAP test were diagnosed as allergic patients\(^9,40\) while the others were considered as non-allergic patients.

Patients considered as atopic with one or more of the following criteria: positive history of allergy and/or positive family history of allergy and/or increased levels of serum total IgE.\(^41\)

Statistical analysis was done by SPSS 16.00 software using chi-square tests, t-test, Mann-Whitney test. \(P\)-value less than 0.05 was considered statistically significant.

This project was received prior approval by the Ethical Committee of the Immunology, Asthma & Allergy Research Institute, Tehran University of Medical Sciences. Moreover, informed consent was obtained from each participant.

**RESULTS**

Forty new diagnosed MS patients and the same number of healthy controls were included in this study.

In MS group, 33 (82.5%) were female and 7 (17.5%) were male. The mean age of the patients was 30.55 ± 9.5 years (range of 17–57 years). Mean disease duration since the diagnosis was 5 ± 1.5 months (range of 1–24 months), and mean EDSS was 1.7 ± 1.3 (range of 0–6).

Most of them (89%) had EDSS less than 3. Initial presenting symptoms were sensory in 17 (44.7%) followed by visual in 14 (36.8%), and motor disturbances in 7 (18.4%) patients. All of the patients were classified as relapsing-remitting (RR) MS. Only 3 of the patients had positive family history of MS. Moreover, none of the patients were active or passive smokers.

In control group, 33 (82.5%) were female and 7 (17.5%) were male. The mean age of the people in this group was 31.17 ± 9.8 years (range of 18–57 years). No one had family history of MS. None of them were active or passive smoker.

History of childhood infections, vaccination and too hygienic behavior in MS group were 72.5%, 85% and 28.9% while in control group were 82.5%, 70% and 17.5%, respectively and the differences between the two groups were not significant (\(p =0.108, p =0.108\) and \(p=0.230\) respectively).

The clinical features of the patients and controls are summarized in Table 1.

History of allergy was observed in 20 (50%) of MS patients (Including 15 (37.5%) rhinitis, 6 (15%) conjunctivitis, 3 (7.5%) urticaria and eczema and 1 (2.5%) asthma) and 20 (50%) of the controls (Including 8 (20%) rhinitis, 4 (10%) conjunctivitis, 7 (17.5%) urticaria and eczema and 1 (2.5%) asthma) and the differences were not statistically significant between the two groups (\(p =1.00\)). Moreover, the positive family history of allergic diseases was identified in 13 (32.5%) of the patients and 20 (50%) of the controls (\(p=0.108\)). Atopy was observed in 25 (62.5%) of the MS patients and 27 (69.2%) of the controls (\(p=0.637\)) (Table 2).

Confirmed history of drug allergy was observed in 4 (10%) of the patients. Two of them were sensitive to cotrimoxazole, which caused dyspnea, vomiting and diarrhea. The two remaining were sensitive to Penicillin. Symptoms of the patients disappeared after drug withdrawal with no hospital admission. There was no history of drug allergy in control group.

Mean serum levels of total IgE in patients and control group was 104.69 ± 37.09 KU/L (range of 2.02-1031.00 KU/L) and 118.41 ± 59.32 KU/L (range of 0.00-2178 KU/L), respectively. There was no significant difference among the two groups (\(p=0.340\)).

Total IgE in allergic and non-allergic MS patients was 195.44±88.88, 45.98±8.99, respectively and in control group was 67.9±23.2, 144.68±89.57. In both groups, allergy was present in 13 and 27 persons were non-allergic.

There was nearly significant differences in total IgE in allergic MS patients 195.44±88.88 and allergic controls 67.9±23.2 (\(p=0.052\)) and in non allergic individual in both groups. (MS 45.98±8.99 and control 144.68±89.57) (\(p=0.053\)) (Figure 1)

Specific IgE was detected in 20 (50%) of the patients; 15 (37.5%) against Weeds Mix, 5 (12.5%) against Grass Mix, 2 (5%) against Trees Mix (1), 2 (5%) against Trees Mix (2), 3 (7.5%) against Dermatophagoides Farinae, 6 (15%) against Dermatophagoides Pteronyssinus and 1 (2.5%) against Epidermal and animal proteins Mix. ImmunoCAP test with other allergens was negative.

In control group, specific IgE was found in 19 (47.5%) of them, 17 (42.5%) against Weeds Mix, 8 (20%) Grass Mix, 4 (10%) Trees Mix (1), 4 (10%) Trees Mix (2), 3 (7.5%) Dermatophagoides Farinae, 3 (7.5%) Dermatophagoides Pteronyssinus and 2 (5%) Epidermal and animal proteins Mix.
The Relation of Multiple Sclerosis with Allergy and Atopy

Table 1. Demographic and clinical summary of the MS patients and controls.

<table>
<thead>
<tr>
<th>Clinical information</th>
<th>MS Group (n=40)</th>
<th>Control Group (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: female/male</td>
<td>33/7</td>
<td>33/7</td>
<td></td>
</tr>
<tr>
<td>Mean age (S.D)</td>
<td>30.55 ± 9.5</td>
<td>31.17 ± 9.8</td>
<td></td>
</tr>
<tr>
<td>Mean disease duration in months (S.D)</td>
<td>5 ± 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial symptom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long tract sensory</td>
<td>17 (44.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>14 (36.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long tract motor</td>
<td>7 (18.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Childhood infections [n,( %)]</td>
<td>29 (72.5)</td>
<td>33(82.5)</td>
<td>0.108</td>
</tr>
<tr>
<td>Chicken Pox</td>
<td>25 (62.5)</td>
<td>30(75)</td>
<td>0.228</td>
</tr>
<tr>
<td>Mumps</td>
<td>14 (35)</td>
<td>11(27.5)</td>
<td>0.469</td>
</tr>
<tr>
<td>Measles</td>
<td>4 (10)</td>
<td>8(20)</td>
<td>0.210</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>4 (10)</td>
<td>5(12.5)</td>
<td>0.723</td>
</tr>
<tr>
<td>Rubella</td>
<td>2 (5)</td>
<td>4(10)</td>
<td>0.396</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Familial history of MS [n,( %)]</td>
<td>37 (92.5)</td>
<td>40(100)</td>
<td>0.077</td>
</tr>
<tr>
<td>History of Vaccination [n,( %)]</td>
<td>3 (7.5)</td>
<td>0</td>
<td>0.108</td>
</tr>
<tr>
<td>History of High Hygiene [n,( %)]</td>
<td>27 (71.1)</td>
<td>33 (82.5)</td>
<td>0.230</td>
</tr>
</tbody>
</table>

Table 2. Allergy in MS patients and controls.

<table>
<thead>
<tr>
<th>Allergy</th>
<th>MS Group</th>
<th>Control Group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Allergy</td>
<td>20 (50)</td>
<td>20 (50)</td>
<td>1.00</td>
</tr>
<tr>
<td>Manifested as:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>15 (37.5%)</td>
<td>8 (20)</td>
<td>0.137</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>6 (15)</td>
<td>4 (10)</td>
<td>0.532</td>
</tr>
<tr>
<td>Eczema, Urticaria</td>
<td>3 (7.5)</td>
<td>7 (17.5)</td>
<td>0.193</td>
</tr>
<tr>
<td>Asthma</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Positive specific IgE</td>
<td>20 (50)</td>
<td>19 (47.5)</td>
<td>0.821</td>
</tr>
<tr>
<td>Weeds Mix</td>
<td>15 (38.5)</td>
<td>17 (44.7)</td>
<td>0.647</td>
</tr>
<tr>
<td>Grass Mix</td>
<td>5 (12.5)</td>
<td>8 (20)</td>
<td>0.377</td>
</tr>
<tr>
<td>Trees Mix(1)</td>
<td>2 (5)</td>
<td>4 (10)</td>
<td>0.675</td>
</tr>
<tr>
<td>Trees Mix (2)</td>
<td>2 (5)</td>
<td>4 (10)</td>
<td>0.430</td>
</tr>
<tr>
<td>Dermatophagoides Farinae</td>
<td>3 (7.7)</td>
<td>3 (7.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Dermatophagoides pteronyssinus</td>
<td>6 (15.4)</td>
<td>3 (7.7)</td>
<td>0.481</td>
</tr>
<tr>
<td>Epidermal and animal proteins mix</td>
<td>1(5)</td>
<td>2 (10)</td>
<td>0.701</td>
</tr>
<tr>
<td>Family history of Allergy</td>
<td>13 (32.5)</td>
<td>20 (50)</td>
<td>0.108</td>
</tr>
<tr>
<td>Serum total IgE (mean±SD)</td>
<td>104.69±37.09</td>
<td>118.41 ± 59.32</td>
<td>0.340</td>
</tr>
</tbody>
</table>
There was no significant differences in specific IgE among the two groups (p=0.821) (Figure 2).

According to the history of allergy and positive specific IgE test, 13 (32.5%) of MS patients and 13 (32.5%) of the controls were allergic (p=1.00). There was no significant differences in allergy between the two groups.

No relationship was found between MS initial symptoms and allergy (p=0.776). Furthermore, allergy to different allergens or specific allergic manifestations was not associated with MS clinical manifestations (p=0.265). There was no relation between increased EDSS and allergy in MS group (p=0.392). Mean age of the patients was not different noticeably in allergic and non allergic MS patients (p=0.863). In addition, there was no relationship between familial history of MS and allergy (p=0.108).

![Figure 1. Total serum IgE comparison in the patients and control group.](image1.png)

![Figure 2. Comparison of positive serum specific IgE in the patients and controls.](image2.png)
DISCUSSION

The influence of Th1 mediated diseases on Th2 mediated diseases is still unclear, while some studies have shown that disequilibrium in the ratio of Th1/Th2 may increase the frequency of one disease and decrease the frequency of another.\textsuperscript{37,42}

Interestingly, in clinical studies the relation between allergy and MS has been under question for years. Previous studies gave conflicting findings and this relation differed among the studies.\textsuperscript{26-34}

The present study showed no relationship between allergy and MS. This was in accordance with two meta-analyses by Monteiro \textit{et al.}\textsuperscript{34} and Alonso \textit{et al.}\textsuperscript{24} that demonstrated no statistically significant relationship between other Th2-associated diseases and MS, and contrary to the study by Edward \textit{et al.}\textsuperscript{29} in 2004.

In another study by Oro \textit{et al.},\textsuperscript{43} a reverse relationship between allergy and MS has been shown. These researchers reported the patients with MS had significantly lower number of positive allergen-specific IgE test results, fewer allergic symptoms, and lower composite allergy indices than control group. In other studies by Bergamaschi \textit{et al.},\textsuperscript{36} Pedotti \textit{et al.},\textsuperscript{32} Tremlett \textit{et al.},\textsuperscript{42} and Neukirch \textit{et al.},\textsuperscript{31} an inverse relationship between multiple sclerosis and allergic diseases existed, but our results did not support this association.

However, most of these studies had basic methodological limitations such as having no control group, assessing allergy by history and no lab tests, self-reported information by study participants, recall bias and having no formal validation study.\textsuperscript{24,32} Moreover, some of these studies were based on MS patients who came to hospital clinics or general practice, and presenting MS cases might not represent all cases arising from the source population.\textsuperscript{28,32}

In the present study, prevalence of allergy was investigated by careful history and positive specific IgE against seven common allergens (with at least one positive test). Although our study did not have most of the limitations mentioned above but small sample size, recall bias and limited number of allergens tested were our limitations.

History and lab tests demonstrated that 13 (32.5\%) of the MS patients and 13 (32.5\%) of the controls were allergic. Atopy was seen in 25 (62.5\%) of patients and 27 (67.5\%) of the controls that showed no relationship between MS and atopy.

In our study, the difference in serum total IgE between MS patients and controls was ignorable that was in agreement with Kira \textit{et al.}\textsuperscript{34}

Asthma was observed in only 1 of the patients. This result is supported by other studies that showed no relation between MS and asthma but in contrast to others that demonstrated higher\textsuperscript{27-29} or reduced\textsuperscript{24,31,33,35,36} asthma prevalence. Moreover, positive specific IgE against Weeds Mix, GrassMix, Trees Mix (1), Trees Mix (2), Dermatophagoides Farinae, Dermatophagoides Pteronyssinus and Epidermal and animal proteins mix were not statistically different between the two groups.

Although improved hygiene, vaccination and childhood infections affect MS,\textsuperscript{45} but the studies showed conflicting results, while some studies showed that childhood infections may have a protective effect on MS\textsuperscript{46-48} and the others demonstrated that infections may irritate immune system and play a role in MS in genetically predisposed individuals.\textsuperscript{49,50} However, our study did not show any significant difference in childhood infections, vaccination and improved hygiene in the two groups.

In conclusion, these findings suggest no relationship between MS and allergy, and also between MS and atopy. Further studies are required to confirm or refute these findings.

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REFERENCES

The Relation of Multiple Sclerosis with Allergy and Atopy