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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.

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INTRODUCTION

Multiple sclerosis (MS) is a progressive T-cell autoimmune disease with chronic inflammation and demyeliniation of the central nervous system (CNS).[1] Prevalence of MS varies from 5.3 to 12.8 cases per 100000 people in different locations of Iran.[2,3]

MS is considered as the leading cause of neurologic disability in young adults.[4] The exact etiology remains unclear,[5] but it is likely that diverse immunological factors, genetic susceptibility and environmental factors contribute to MS pathology.[6-8] MS has been linked to a reduced risk of IgE-mediated allergy.[9]

Allergy and MS are thought to be T helper cell type2 (Th2) and T helper cell type 1 (Th1) mediated diseases, respectively.[10,11] The prevalence of allergic disorders is different in various locations of Iran with a range from 10% to 27.5%.[12-14] 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.[15] 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.[16]

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.[17,18]

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.[7,19-23] Because MS and other disorders of immune system can portion some common risk factors,[24] allergy can play a major role in clinical disease activity in patients with MS.[25] Thus, several studies have demonstrated the relationship between MS and allergy that gave discordant findings.[26] While some studies have shown higher allergy prevalence among MS patients,[27-29] others have demonstrated similar[14,30-34] or reduced[31,35-37] 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[38] 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.

Furthermore, in MS group, the following clinical characteristics were collected: clinical course of the disease (RR: relapsing-remitting; PP: primary progressive; SP: secondary progressive), initial symptoms (visual, motor and sensory disturbances), and Expanded Disability Status Scale (EDSS).

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 elatior, Artemisia vulgaris, Plantago lanceolata, Chenopodium album, Salsola kali), Grass Mix (Cynodon dactylon, Lolium perenne, Phleum 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 strobus, Eucalyptus spp., Acacia longifolia, Melaleuca leucadendron), Dermatophagoides farinae,

Dermatophagoides Pteronyssinus and Epidermal and animal proteins mix (cat dander, horse dander, caw dander, dog dander).

Patients with positive history of allergy and positive IgE ImmunoCAP test were diagnosed as allergic patients[39,40] 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) (Table2).

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%) GrassMix, 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.

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

Clinical information	MS Group (n=40)	Control group (n=40)	*p*-value
Gender: female/male	33/7	33/7	
Mean age (S.D)	30.55 ± 9.5	31.17 ± 9.8	
Mean disease duration in months (S.D)	5 ± 1.5		
Initial symptom			
Long tract sensory	17 (44.7)		
Visual disturbance	14(36.8)		
Long tract motor	7 (18.4)		
Childhood infections [n,(%)]	29 (72.5)	33(82.5)	0.108
Chicken Pox	25 (62.5)	30(75)	0.228
Mumps	14 (35)	11(27.5)	0.469
Measles	4 (10)	8(20)	0.210
Hepatitis A	4 (10)	5(12.5)	0.723
Rubella	2 (5)	4(10)	0.396
Hepatitis B	0	0	
Familial history of MS [n,(%)]			0.077
No	37 (92.5)	40(100)	
Yes	3 (7.5)	0	
History of Vaccination [n,(%)]			0.108
No	6 (15)	12 (30)	
Yes	34 (85)	28 (70)	
History of High Hygiene [n,(%)]			0.230
No	27 (71.1)	33 (82.5)	
Yes	11 (28.9)	7 (17.5)	

Table 2. Allergy in MS patients and controls.

Allergy	MS Group	Control Group	*p*-value
Any Allergy	20 (50)	20 (50)	1.00
Manifested as:			
Rhinitis	15 (37.5%)	8 (20)	0.137
Conjunctivitis	6 (15)	4 (10)	0.532
Eczema, Urticaria	3 (7.5)	7 (17.5)	0.193
Asthma	1(2.5)	1 (2.5)	1.00
Positive specific IgE	20 (50)	19 (47.5)	0.821
Weeds Mix	15 (38.5)	17 (44.7)	0.647
Grass Mix	5 (12.5)	8 (20)	0.377
Trees Mix(1)	2 (5)	4 (10)	0.675
Trees Mix (2)	2 (5)	4 (10)	0.430
Dermatophagoides Farinae	3 (7.7)	3 (7.7)	1.00
Dermatophagoides pteronyssinus	6 (15.4)	3 (7.7)	0.481
Epidermal and animal proteins mix	1(5)	2 (10)	0.701
Family history of Allergy	13 (32.5)	20 (50)	0.108
Serum total IgE (mean±SD)	104.69±37.09	118.41 ± 59.32	0.340

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).

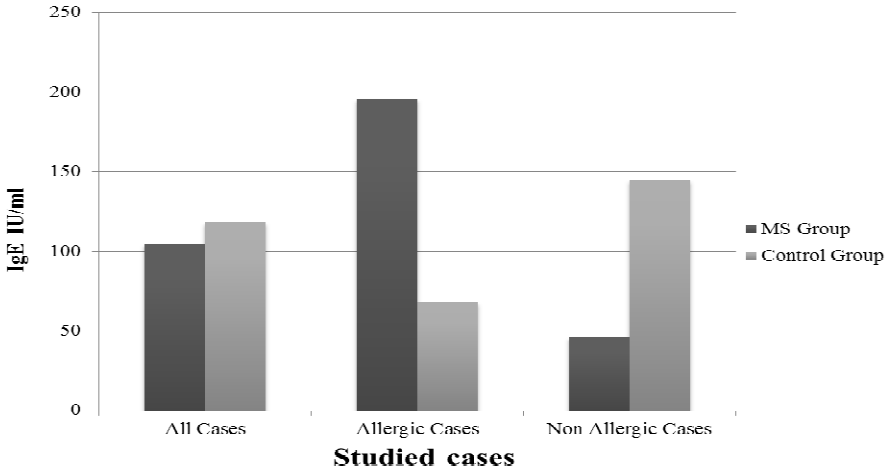

Figure 1. Total serum IgE comparison in the patients and control group.

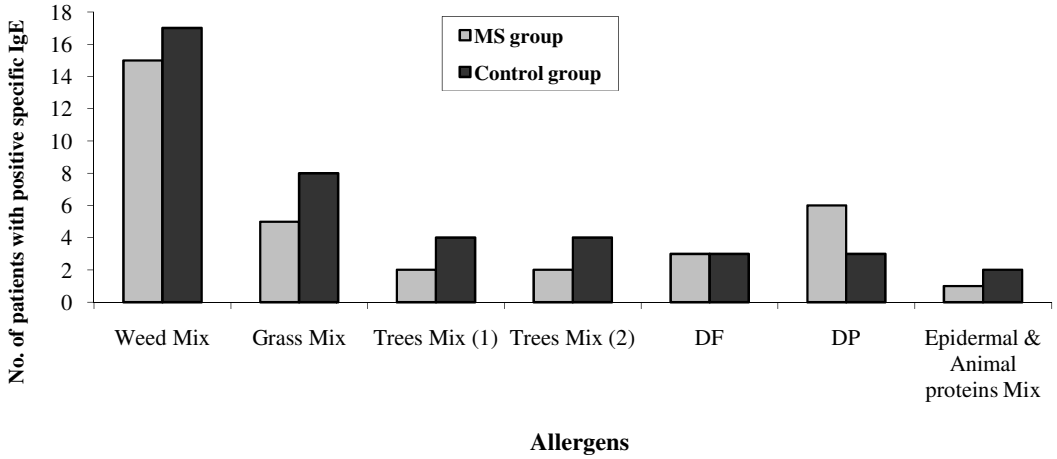

Figure 2. Comparison of positive serum specific IgE in the patients and controls.

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.[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.[26-34]

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

In another study by Oro *et al.,*[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 *et al*,[36] Pedotti *et al.*[32] Tremlett *et al.*[42] and Neukirch *et al.,*[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.[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.[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 et al study.[44]

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[27-29] or reduced[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,[45] but the studies showed conflicting results, while some studies showed that childhood infections may have a protective effect on MS[46-48] and the others demonstrated that infections may irritate immune system and play a role in MS in genetically predisposed individuals.[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

1. Jackson SJ, Lee JE, Nikodemova M, Fabry Z, Duncan ID. Quantification of myelin and axon pathology during relapsing progressive experimental autoimmune encephalomyelitis in the Biozzi ABH mouse. J Neuropathol Exp Neurol 2009; 68(6):616-25.
2. Ghandehari K, Riasi HR, Nourian A, Boroumand AR. Prevalence of multiple sclerosis in north east of Iran. Mult Scler 2010; 16(12):1525-6.
3. Etemadifar M, Maghzi AH. Sharp increase in the incidence and prevalence of multiple sclerosis in Isfahan, Iran. Mul Scler 2011; 17(8):1022-7.
4. Kim SE. Daclizumab treatment for multiple sclerosis. Pharmacotherapy 2009; 29(2):227-35.

5. Friese MA, Fugger L. Pathogenic CD8+ T cells in multiple sclerosis. Ann Neurol 2009; 66(2):132-41.
6. Ingram G, Hakobyan S, Robertson N, Morgan BP. Complement in multiple sclerosis: its role in disease and potential as a biomarker. Clin Exp Immunol 2009; 155(2):128-39.
7. McFarland HF, Martin R. Multiple sclerosis: a complicated picture of autoimmunity. Nat Immunol 2007; 8(9):913-9.
8. Giovannoni G, Ebers G. Multiple sclerosis: the environment and causation. Curr Opin Neurol 2007; 20(3):261.
9. Evans J, Rogers C, Wiles CM, Luscombe DK, Tremlett HL. General practitioners' prescribing data for multiple sclerosis patients indicates a link with asthma. Br J Gen Pract 2000; 50(453):323.
10. Navikas V, Link H. Review: cytokines and the pathogenesis of multiple sclerosis. J Neurosci Res 1996; 45(4):322-33.
11. Singh VK, Mehrotra S, Agarwal SS. The paradigm of Th1 and Th2 cytokines: its relevance to autoimmunity and allergy. Immunol Research 1999; 20(3):147-61.
12. Miri S, Farid R, Akbari H, Amin R. Prevalence of allergic rhinitis and nasal smear eosinophilia in 11-to 15 yr-old children in Shiraz. Pediat Allergy Immunol 2006; 17(7):519-23.
13. Bazzazi H, Gharagozlou M, Kassaiee M, Parsikia A, Zahmatkesh H. The prevalence of asthma and allergic disorders among school children in Gorgan. J Res Med Scienc 2007; 12(1):28-33.
14. Varasteh AR, Fereidouni M, Shakeri MT, Vahedi F, Abolhasani A, Afsharian MS, et al. Prevalence of allergic disorders among the population in the city of Mashhad, Northeast Iran. J Public Health 2009; 17(2):107-12.
15. Kay A. Allergy and allergic diseases. Second of two parts. N Eng J Med 2001; 344(2):109.
16. Kidd P. Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease. Altern Med Rev 2003; 8(3):223-46.
17. Klemens C, Rasp G, Jund F, Hilgert E, Devens C, Pfrogner E, et al. Mediators and cytokines in allergic and viral-triggered rhinitis. Allergy Asthma Pro 2007; 28(4):434-41.
18. Tesmer LA, Lundy SK, Sarkar S, Fox DA. Th17 cells in human disease. Immunol Rev 2008; 223(1):87-113.
19. Iwakura Y, Nakae S, Saijo S, Ishigame H. The roles of IL-17A in inflammatory immune responses and host defense against pathogens. Immunol Rev 2008; 226(1):57-79.
20. Komiyama Y, Nakae S, Matsuki T, Nambu A, Ishigame H, Kakuta S, et al. IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis. J Immunol 2006; 177(1):566-73.
21. Kasper LH, Shoemaker J. Multiple sclerosis immunology: The healthy immun system vs the MS immun system. Neurology 2010; 74(1 Supplement 1):S2-8.
22. Pedotti R, DeVoss JJ, Steinman L, Galli SJ. Involvement of both allergic'and autoimmune'mechanisms in EAE, MS and other autoimmune diseases. Trends Immunol 2003; 24(9):479-84.
23. Costantino CM, Baecher-Allan C, Hafler DA. Multiple sclerosis and regulatory T cells. J clin Immunol 2008; 28(6):697-706.
24. Alonso A, Hernan M, Ascherio A. Allergy, family history of autoimmune diseases, and the risk of multiple sclerosis. Acta Neurol Scand 2008; 117(1): 15-20.
25. Sospedra M, Martin R. Immunology of multiple sclerosis. Annu Rev Immunol 2005; 23:683-747.
26. Rudwaleit M, Andermann B, Alten R, Sörensen H, Listing J, Zink A, et al. Atopic disorders in ankylosing spondylitis and rheumatoid arthritis. Ann Rheum Dis 2002; 61(11):968-74.
27. Airaghi L, Tedeschi A. Results of the US Third National Health and Nutrition Examination Survey support the hygiene hypothesis. J Allergy Clin Immunol 2004; 113(1):179-80.
28. Ponsonby AL, Dwyer T, Van Der Mei I, Kemp A, Blizzard L, Taylor B, et al. Asthma onset prior to multiple sclerosis and the contribution of sibling exposure in early life. Clin Exp Immunol 2006;146(3): 463-70.
29. Edwards L, Constantinescu C. A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. Multiple sclerosis 2004; 10(5):575-81.
30. Solaro C, Messmer UM, Guglieri P, Murialdo A, Sormani MP, Battaglia MA, et al. Prevalence of atopy in multiple sclerosis patients: a case-control study. J Neurol 2001; 248(3):239-40.
31. Neukirch F, Lyon-Caen O, Clanet M, Bousquet J, Feingold J, Druet P. Asthma, nasal allergies, and multiple sclerosis. J Allergy Clin Immunol 1997; 99(2):270-1.
32. Pedotti R, Farinotti M, Falcone C, Borgonovo L, Confalonieri P, Campanella A, et al. Allergy and multiple sclerosis: a population-based case-control study. Multiple sclerosis 2009; 15(8):899-906.

33. Alonso A, Jick SS, Hernán MA. Allergy, histamine 1 receptor blockers, and the risk of multiple sclerosis. Neurology 2006; 66(4):572-5.
34. Monteiro L, Souza-Machado A, Menezes C, Melo A. Association between allergies and multiple sclerosis: a systematic review and meta-analysis. Acta Neurol Scand 2011; 123(1):1-7.
35. Tang L, Benjaponpitak S, DeKruyff RH, Umetsu DT. Reduced prevalence of allergic disease in patients with multiple sclerosis is associated with enhanced IL-12 production. J Allergy Clin Immunology 1998; 102(3):428-35.
36. Bergamaschi R, Villani S, Crabbio M, Ponzio M, Romani A, Verri A, et al. Inverse relationship between multiple sclerosis and allergic respiratory diseases. Neurol Sci 2009; 30(2):115-8.
37. Ramagopalan SV, Dyment DA, Guimond C, Orton SM, Yee IM, Ebers GC, et al. Childhood cow's milk allergy and the risk of multiple sclerosis: A population based study. J Neurol Sci 2010; 291(1):86-8.
38. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001; 50(1):121-7.
39. Durham SR, Church MK. Principles of allergy diagnosis. In: Holgate ST, Church MK, Lichtenstein LM, eds. Allergy, 2nd London: Mosby, 2001:3–16.
40. Bush RK. Approach to patients with symptoms of food allergy. Am J Med 2008; 121(5): 376-8.
41. Sly PD, Boner AL, Björksten B, Bush A, Custovic A, Eigenmann PA, et al. Early identification of atopy in the prediction of persistent asthma in children. Lancet 2008; 372(9643):1100-6.
42. Tremlett H, Evans J, Wiles CM, Luscombe DK. Asthma and multiple sclerosis: an inverse association in a case-control general practice population. Qjm 2002; 95(11):753-6.
43. Oro AS, Guarino TJ, Driver R, Steinman L, Umetsu DT. Regulation of disease susceptibility: decreased prevalence of IgE-mediated allergic disease in patients with multiple sclerosis. J Allergy Clin Immunol 1996; 97(6):1402-8.
44. Kira J, Kawano Y, Yamasaki K. Multiple sclerosis with mite antigen-specific IgE. J Neurol Sci 1998; 157(2):138-42.
45. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002; 347(12):911-20.
46. Waubant E, Mowry EM, Krupp L, Chitnis T, Yeh EA, Kuntz N, et al. Common viruses associated with lower pediatric multiple sclerosis risk. Neurology 2011; 76(23):1989-95.
47. Canradi S, Malzahn U, Schroter F, Paul F, Quill S, Spruth E, et al. Environmental factors in early childhood are associated with multiple sclerosis: a case-control study. BMC Neurol 2011; 11:123.
48. Leibowitz U, Antonovsky A, Medalie J, Smith HA, Halpern L, Alter M. Epidemiological study of multiple sclerosis in Israel. II. Multiple sclerosis and level of sanitation. J Neurol Neurosurg Psychiatry 1966; 29(1):60-8.
49. Levin LI, Munger KL, Rubertone MV, Peck CA, Lennette ET, Spiegelman D, et al. Multiple sclerosis and Epstein-Barr virus. JAMA 2003; 289(12):1533-6.
50. Ponsonby AL, van der Mei I, Dwyer T, Blizzard L, Taylor B, Kemp A, et al. Exposure to infant siblings during early life and risk of multiple sclerosis. JAMA 2005; 293(4):463-9.