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Allergy and multiple sclerosis: a population-based case-control study

R Pedotti¹, M Farinotti², C Falcone², L Borgonovo³, P Confalonieri¹, A Campanella¹,
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Background Epidemiological studies on the association between allergic disorders, T-helper type 2 (Th2) mediated, and multiple sclerosis (MS), a T-helper type 1 (Th1)/Th17-mediated disease, provided conflicting results.

Objective The aim of this study was to further examine the association between allergic disorders and MS.

Methods The association between MS and previous medical history of any type of allergy has been investigated in a population-based case-control study conducted in Northern Italy, based on telephone interviews to 423 cases and 643 population controls (refusal rates 3.7% and 9.4%, respectively). Controls were a random sample of the general population.

Results A history of atopic allergies seems to confer protection against MS (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.38–0.89; $P = 0.012$). In particular, the prevalence of allergic asthma was 4.9% in people with MS and 12% in control subjects (OR = 0.38; 95% CI 0.22–0.66, $P < 0.01$). No association was found between MS and nonatopic allergies.

Conclusions Our findings are confirmatory of the putative protective effect of Th2-mediated disorders on Th1 immune responses associated with MS. A unifying theory on the mechanisms by which previous history of atopic allergies may modify the risk of MS is still lacking. *Multiple Sclerosis* 2009; 15: 899–906. <http://msj.sagepub.com>

Key words: allergy; atopy; case-control study; immunology; multiple sclerosis; risk factors

Introduction

The hygiene hypothesis, formulated to explain increasing frequency of allergic diseases in developed countries, proposes that exposure to infections early in life confers later protection against allergic disorders [1]. More specifically it was thought that improved hygiene reduces the frequency of infections that tend to elicit the production of T-helper type 1 (Th1) cells, skewing the immune system toward the production of T-helper type 2 (Th2) cells, and hence the secretion of cytokines associated with allergy. Allergic diseases are now increasing in developing countries as socio-economic and sanitation conditions improve, lending

support to this idea [2]. However, developed countries are characterized not only by increasing allergic disorders but also by marked increases in the frequency of autoimmune diseases, such as insulin-dependent diabetes, rheumatoid arthritis, and multiple sclerosis (MS) [3], all considered to be partly mediated by Th1 immunity, with involvement of the cytokine interleukin-17 (IL-17) and the Th17 pathway [4]. Furthermore, epidemiological studies suggest that allergic and autoimmune diseases can occur in the same individuals [3,5–7], and are not mutually exclusive as the Th1/Th2 paradigm suggests [8]. This epidemiological evidence, together with findings in animal models of autoimmunity (reviewed in [9,10]), have prompted a

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modified hygiene hypothesis, which suggests that immune-regulatory mechanisms activated by interaction with the microbial environment early in childhood, or even *in utero*, might maintain a balance between Th1- and Th2-driven effector responses ("the immunoregulatory twist of the hygiene hypothesis" [10]). The result would be that early exposure to a wide range of antigens provides protection against both allergic and autoimmune diseases [3,9,10].

MS is an autoimmune disease in which Th1 cells, activated against central nervous system white matter, orchestrate an immune attack leading to inflammation, myelin destruction, and often degeneration of the underlying axon. MS etiology remains uncertain, although both genetic and environmental factors seem to be involved [11]. The fact that MS may be related to childhood exposure to environmental factors (including greater hygiene in childhood) is consistent with numerous data: it is more prevalent in developed countries; people who migrate from high-risk to low-risk areas after adolescence tend to take their MS risk with them, whereas those moving from high-risk to low-risk areas before adolescence acquire a lower risk; there is an inverse geographic correlation between MS prevalence and virus seropositivity rates below age six and also parasite seropositivity; people with MS develop common childhood viral infections, including Epstein-Barr virus, later than normal; and, finally, an association of MS with birth order and sibship size (considered proxies of infectious load in early childhood) has been proposed (reviewed in [11]).

With regard to the hypothesis of a relation between MS and allergic conditions, epidemiological investigations have produced conflicting results [12–20]. However, when animals with experimental autoimmune encephalomyelitis (EAE) – a Th1- and Th17-mediated model of human MS – are reexposed to myelin autoantigens, they develop anaphylactic shock [21], the most severe manifestation of an allergic reaction. Thus in the animal model of MS, allergic and autoimmune responses can coexist. It has also been suggested that mechanisms and mediators associated with allergic responses play a role in EAE and MS (reviewed in [22]). For example, mast cell-deficient ($\text{Kit}^W/\text{Kit}^{W-v}$) mice have less severe EAE than wild-type mice [23]; blockade of histamine receptor 1 – a major mediator of allergic reactions – reduces EAE severity [24]; and use of histamine 1 receptor blockers was associated with a significant reduction in MS incidence in a prospective study [19]. Thus, the determination of the association between allergies and MS might improve our understanding of the pathophysiology of this disease, and hopefully to help finding new therapeutic strategies for this disease.

To further test the hypothesis of an association between MS and allergies, we conducted a

population-based case-control study in the Lombardy Region, Northern Italy, by means of telephone interviews.

Methods

Cases and controls

Cases were identified from the population-based Regional Health Service Register, which archives reports of all Lombardy residents qualified to an exemption from medical expenses for a diagnosis of MS (ICD-9: code 340) at public and private hospitals, and at outpatient clinics. The reports of all patients with MS registered for the first time between January 1st and December 31st, 2003 were examined to verify that they had been diagnosed according to standardized criteria [25]. MS diagnosis was confirmed in 541 reports. Diagnosis, age at diagnosis, and therapies were investigated directly from the individuals during the interview.

Aiming to select two controls for each patient with MS, we identified 1082 controls randomly sampled from Lombardy residents born in Italy and archived in the Regional Health Service database. All residents of the Lombardy region are listed in this regularly updated database. These controls were individually matched to cases by date of birth (± 3 months), sex, and area of residence defined as the Local Health Unit. The study was approved by the Ethics Committee of the Neurological Institute C. Besta.

Questionnaire

The questionnaire was based on the Italian version of the European Community Respiratory Health Survey [26,27], modified with the assistance of two allergologists (EP and LB) to create a phone script during which the questionnaire was administered. The questionnaire investigated the entire medical history for allergy: the occurrence of symptoms typical of allergic asthma, rhinitis (including hay fever), and conjunctivitis due to inhalant allergens; atopic dermatitis and atopic eczema; contact dermatitis; food allergy; drug allergy; and allergy to insect sting or bite. Further questions enquired about first and most recent occurrence of an allergic condition, whether it was diagnosed by a physician, and what if any treatment was taken. The questions on allergies were cognitively verified with a group of patients, physicians, and nurses, attending both the Neurological Institute C. Besta and the Allergy Clinic of Ca' Granda Hospital, for clarity, completeness, and relevance of the content. The questionnaire was pilot-tested by phone interviews with 50

patients who had been registered in the Regional Register before January 2003 and 50 controls (these patients and controls were not included in this study) to ensure that interviewed subjects interpreted the questions correctly and that the algorithms to assess the different types of allergy were working properly [28]. The length of the interview was recorded and the quality of the information collected was rated as poor, fair, good, or excellent by the interviewer.

Compiled questionnaires were assessed for completeness by a neurologist (RP) and an allergologist (LB), blinded to interviewee status (case or control). The completed responses were analyzed to identify respondents: 1) who reported a history of one or more allergies diagnosed by a physician and based on a positive history (comprising symptoms, exposure to allergens, age at first and most recent episode, and whether treatment including avoidance of allergen was undertaken), and for asthma and rhinoconjunctivitis also on positivity of skin prick tests and/or IgE levels (self-reported physician-diagnosed allergies); 2) who reported a history of one or more allergies but had never consulted a doctor (self-reported allergies); and 3) who reported no allergies (no allergies).

According to the criteria of the European Academy of Allergology and Clinical Immunology [29], we considered those individuals with IgE-mediated asthma, rhinitis, conjunctivitis, atopic eczema/dermatitis syndrome, or food allergy (this last one only when accompanied by respiratory allergies), which are typical symptoms developed by a person of the "atopic constitution" as atopic. We considered those individuals with contact dermatitis, reaction to insect bites or stings, reaction to medications, or food allergy without respiratory allergies as non-atopic. Although food allergy can be an atopic manifestation, we considered it as nonatopic when not accompanied by respiratory allergies as it is difficult to be distinguished in questionnaire responses from other immunologically mediated food hypersensitivities (e.g., celiac disease), or intolerance due to enzyme deficiency (e.g., lactase deficiency).

Interviews

Cases and controls were contacted by letter explaining the study and soliciting participation in a telephone interview. The letter also stated that consent would be sought by the interviewer, and if not given, the interview would not proceed. General practitioners were also contacted and urged to contact their patients (potential cases and controls) to encourage participation. To minimize selection bias, 10 attempts were made to contact a person (mornings, afternoons, evenings, and weekends),

before exclusion for nonresponse. Interviews were conducted from September 2005 through August 2006. Three persons blinded to interviewee status and unaware of the study hypothesis conducted the interviews, employing a standard approach to administer the questionnaire. The interviewers had been trained by one of the authors (MF) and also referred to a specially prepared manual. The training program and manual are available on request.

To maintain blindness each interviewer was assigned the same proportion of cases to controls; furthermore personnel involved in identification of cases and controls or aware of subject identity were not involved in questionnaire processing. Author MF listened in periodically to interviews to ensure they were being conducted correctly.

Statistical analyses

Assuming a prevalence of allergy in the Italian population of 40% and odds ratios (ORs) for allergy in MS patients of either 2.0 or 0.5, 108 cases and 216 controls, or 124 cases and 248 controls were needed, respectively, with 80% power and 5% significance.

ORs with 95% confidence interval (CI) were calculated as approximations to relative risks. Initial conditional logistic regression examined the association between allergy and MS risk. Subsequently, unconditional logistic regression with adjustment for matching variables (age as continuous variable, sex, and area of residence) was carried out on matched cases and controls (as in the conditional analysis) [30]. The results of the conditional and unconditional analyses were of similar magnitude and in the same direction, so the final analysis was an unconditional logistic regression on the complete dataset to maximize statistical power. The results of the conditional analysis are available upon request. To avoid potential confounding effects due to the use of chronic immune-modulating therapy that might be taken by some MS patients very early after the diagnosis, only allergies that manifested before the age of diagnosis of MS or corresponding age for controls matched to that case, were included in the analysis. Since atopic and nonatopic allergies are considered to be associated with different immunological mechanisms, we estimated ORs for atopic allergies, nonatopic allergies, and both. The analyses were performed with the SAS statistical package (SAS Institute, Inc., Cary, NC, version 9.1 for Windows) and all tests were two-sided.

Results

The Figure shows the study flow chart. Overall 3.7% of cases and 9.4% of controls refused to participate,

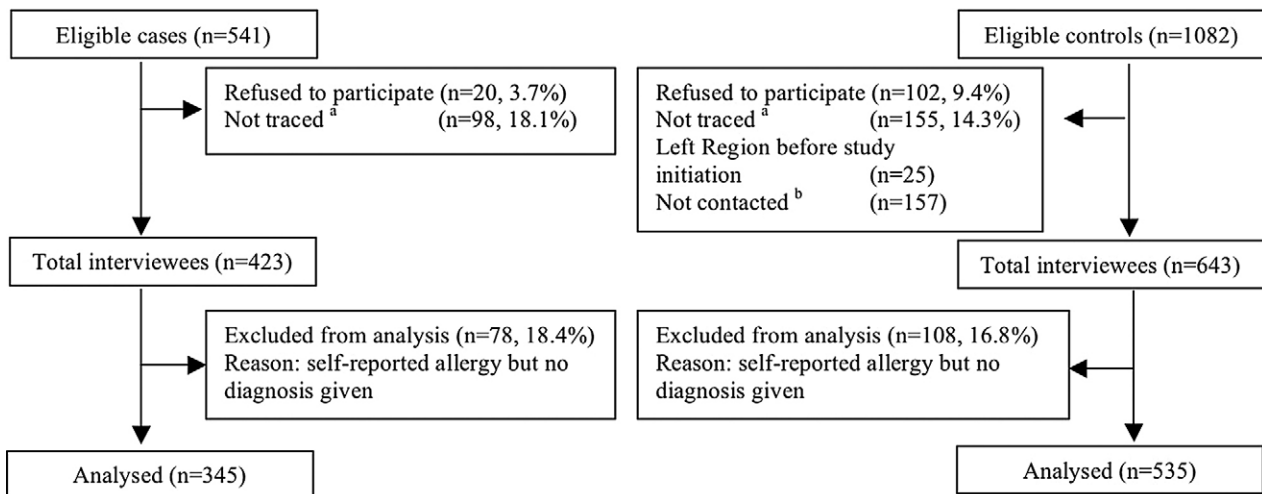


Figure 1 Study flowchart. ^aPersons were considered not traced after at least 10 telephone attempts to contact them. ^bControls were not contacted because their matched cases refused to participate or was not traced.

and 18.1% of cases and 14.3% of controls were not traced. A total of 232 cases were matched to two controls and 155 cases to one control; 36 cases had no controls, and 24 controls had no cases.

Median interview length was 8 min (range 3–34 min) and did not differ between cases and controls; 92% of interviews were rated as good or excellent. A complete response interview was obtained from 423 people with MS, 297 (70.2%) women and 126 men, and from 643 controls, 458 (71.2%) women and 185 men. Median case age was 33 years (range 18–52 years), compared to 32 years (range 18–52 years) for controls. The prevalence of allergies in controls was comparable with those reported in the Italian population (Table 1).

To minimize errors in the classification of the allergic status of the subjects, only individuals reporting one or more physician-diagnosed allergies and those reporting no allergy were included in the analysis, whereas those reporting allergies that were not physician-diagnosed (self-reported allergies) were excluded.

We analyzed 345 cases and 535 controls. A history of one or more physician-diagnosed allergies was reported by fewer cases (121/345, 35.1%) than controls (216/535; 40.4%) (Table 2). Compared with persons reporting no allergy history, persons with a history of allergy had a lower, although non-significant, risk for MS (OR = 0.79; 95% CI 0.59–1.05; $P = 0.107$). Stratification by allergy subtypes (Table 2) revealed that atopic allergy was associated with a significantly decreased risk for MS (OR = 0.58; 95% CI 0.38–0.89; $P = 0.012$). In particular, the prevalence of allergic asthma was 4.9% in people with MS and 12% in control subjects (OR = 0.38; 95% CI 0.22–0.66; $P < 0.01$). The risk was also decreased in persons with atopic allergies

together with nonatopic allergies (OR = 0.48; 95% CI 0.24–0.96; $P = 0.036$). Risk for MS was unrelated to the presence of nonatopic allergies. Adjustment for education (up to 16 years and beyond 16 years) as a proxy of socioeconomic status did not affect the results (data not shown).

Discussion

We present here the results of a population-based case-control study in which the most common allergic diseases have been investigated by a phone-administered questionnaire. Our study shows that there is no significant association between MS and all types of allergy considered together. However, the presence of one or more atopic allergies is significantly associated with a decreased risk for MS.

Allergic diseases are associated with hypersensitivity reactions initiated by specific immunological mechanisms. Under the “umbrella term” of allergic diseases, antibody-mediated or cell-mediated allergies can be found. Atopy is a “personal and/or familial tendency to become sensitized and produce IgE antibodies in response to ordinary exposure to allergens” [29]. Asthma, rhinoconjunctivitis, and atopic dermatitis are typical allergic disorders that can develop in a person with atopy. From the immunological perspective, atopic allergies and IgE are associated with a set of cytokines such as IL-4, IL-5, and IL-13 (Th2 cytokines), which induce antibody isotype switching toward IgE and eosinophilia [36]. The results of our study suggest that only individuals of the atopic constitution, that is, with Th2-associated atopic allergies, and not individuals with any kind of allergy (which could be associated

Table 1 Frequencies of allergies in controls ($n = 643$), with median age at onset, in relation to allergy prevalences in the Italian population

	Controls	Median age at onset in years (range)	Published Italian prevalence rates ^a
Asthma			
Physician-diagnosed	63/643 (9.8%)	16 (0–50)	2.5–13% [31]
Self-reported	16/643 (2.5%)	15.5 (0–45)	
Rhinitis			
Physician-diagnosed	87/640 (13.6%)	18 (1–51)	7–18% [31]
Self-reported	46/640 (7.2%)	20 (0–48)	
Conjunctivitis			
Physician-diagnosed	37/641 (5.8%)	18 (5–51)	7–18% [31]
Self-reported	60/641 (9.4%)	18 (3–52)	
Contact dermatitis			
Physician-diagnosed	49/642 (7.6%)	23 (0–48)	6% [32]
Self-reported	62/642 (9.7%)	18 (4–40)	
Atopic dermatitis			
Physician-diagnosed	27/642 (4.2%)	21 (0–50)	2.5–9% [31]
Self-reported	7/642 (1.1%)	20 (6–45)	
Food allergy			
Physician-diagnosed	35/641 (5.5%)	23 (0–51)	8% [33]
Self-reported	32/641 (5.0%)	20 (0–40)	
Drug hypersensitivity			
Physician-diagnosed	51/641 (8.0%)	19 (0–47)	2–8% [34]
Self-reported	18/641 (2.8%)	17 (0–37)	
Insect sting/bite allergy			
Physician-diagnosed	25/642 (3.9%)	28 (0–48)	3% [35]
Self-reported	11/642 (1.7%)	29.5 (5–40)	

^aReported prevalence may be physician-diagnosed or self-reported physician-diagnosed allergies.

either with Th1 or with both Th1 and Th2 responses) [29] have a reduced risk for MS, classically considered a Th1/Th17-associated disease.

Our data are uninformative on the mechanisms of reduced MS risk in people who develop atopic allergies. Possible mechanisms include an inhibitory effect of Th2 responses on Th1 responses associated with MS. It is also possible that genetic susceptibility or exposure to environmental factors could render an individual more prone to develop atopic allergies than autoimmune MS. The recent finding that parasite infection, which induces a strong antiparasite Th2 response and increased activity of regulatory T cells, reduces the clinical severity of relapsing-remitting MS [9,37] suggests an inhibitory effect of

Th2 responses on MS, although other mechanisms are not excluded. It must be noted that in mice with EAE that develop anaphylaxis upon reexposure to self myelin antigens, autoantigen-specific IgE have never been detected [21,24,38,39]. A similar conclusion is indicated also by the finding that anaphylactic shock developed in nonobese diabetic mice (model of diabetes mellitus) following immunization and reexposure to glutamic acid decarboxylase or insulin peptide, appears not to be mediated exclusively by IgE (reviewed in [22]). These observations suggest that alternative IgE-independent pathways of anaphylaxis might be involved in the development of anaphylaxis in these animal models [39]. It is worth mentioning here that several

Table 2 Physician-diagnosed allergies in population controls and people with multiple sclerosis (MS). Odds ratios (OR) were adjusted for sex, age as continuous variable, and health area of residence

	MS cases	Controls	OR (95% CI)	P-value
	($n = 345$) ^a	($n = 535$) ^b		
No allergy	224 (64.9%)	319 (59.6%)	1	
One or more allergies	121 (35.1%)	216 (40.4%)	0.79 (0.59–1.05)	0.107
	($n = 342$) ^c	($n = 529$) ^d		
Atopic allergy	36 (10.5%)	88 (16.6%)	0.58 (0.38–0.89)	0.012
Nonatopic allergy	70 (20.5%)	87 (16.5%)	1.13 (0.79–1.63)	0.503
Atopic plus nonatopic allergy	12 (3.5%)	35 (6.6%)	0.48 (0.24–0.96)	0.036

Missing data for: ^a2 MS cases; ^bfor 5 controls; ^cfor 3 MS cases; ^dfor 6 controls. In bold statistically significant results.

epidemiological data suggest that atopy is associated with a reduced risk for cancer [40], and polymorphisms for the IL-4 gene might be related to the risk of developing pancreatic cancer [41]. Thus, atopy might confer protection also against nonimmune-mediated diseases, with mechanisms that still need to be clarified.

Our findings are consistent with the observation made by Oro, *et al.* [13] of a reduced prevalence of IgE-mediated allergic diseases in MS patients compared to controls with noninflammatory neuroconvulsive disorders. Our data are also in line with the lower frequencies of nasal allergies and asthma reported in previous case-control studies on people with MS [14,15]. Two other studies [17,18] found that people with MS were significantly more likely to have asthma than non-MS controls. The first one was an ecological study conducted on a hospital MS case series, whose prevalence of allergies was compared with that derived from different population surveys [17]. The second study was a well conducted population-based case-control study in which the frequency of asthma was found exceptionally high (17%), likely because a distinction between allergic and nonallergic asthma was not done [18]. Two other studies [19,20] found no relation between allergic asthma and MS. In the first study, based on the General Practice Research Database in the United Kingdom, information on the history of allergies was limited to the 3 years before the onset of MS [19]. In the second study, a self-administered questionnaire mailed to female nurses was used [20]. It must be noted that in these previous studies, assessment of exposure, when reported, was not clearly defined, and that some of these studies investigated lifetime history of allergy, and not only allergies that manifested before the age of diagnosis of MS.

Strengths of our study are its large sample size, population design, low-refusal rate, and good-quality interviews obtained by trained interviewers. However, several methodological limitations need to be kept in mind. First, selection bias could have arisen in the process of recruiting cases and controls for study participation. This possibility was minimized, however, through identification of cases from the population-based Regional Health Service Register and the use of randomly selected controls from corresponding geographic areas in the same Region. Moreover, participation rates for cases and controls were high. Selection bias could also have been introduced by individuals who did not participate. Although it is unlikely that this bias occurred for individuals who were not traced (18.1% of cases and 14.3% of controls), it is possible that selection occurred for controls who refused to be interviewed (3.7% of cases and 9.4% of controls) if they were less likely to have allergies. This could have resulted

in overestimation of the prevalence of allergy in controls. This is also unlikely, however, as the frequency of allergies in our control population was similar to the Italian prevalence reported by others [31–35]. The exclusion of subjects reporting allergies that were not physician-diagnosed might have produced an underestimation of the prevalence of allergies in our population. Indeed sufferers from the most common allergies, such as allergic rhinitis, may not attend a physician and instead self-medicate [42]. However, this is also unlikely given the similarity of the frequency of allergies in our control population to the Italian one reported earlier (Table 1) [31–35].

Second, differential misclassification of cases and controls on allergic status may have influenced our findings for several reasons. Recall bias could have resulted from an increased likelihood of cases, under close medical surveillance, to remember having an allergy compared with controls. However, underreporting of allergies by controls would tend to produce a positive association between allergies and MS, and therefore cannot explain the results of our study. Underestimation of allergies prior to MS in cases might also have occurred, as patients might focus on their MS and disregard mild asthma or allergies. However, although we cannot formally rule out this possibility, the lack of any significant associations between a general history of allergy and MS, and the observation of a specific association between atopy (and asthma in particular) and MS, suggest that this is unlikely. Bias resulting from systematic interviewing differences between cases and controls is also unlikely as interviewers were blinded to interviewee status and unaware of the study hypothesis. A temporal bias, that is, MS or treatments for MS affected the risk of developing atopic allergies, is unlikely as in our study median age at allergy onset was 17 years (range 0–42 years) and that at MS diagnosis was 34 years (range 15–52 years). Furthermore, in subjects with MS and allergies, the time between allergy onset and MS diagnosis was >8 years in 75% of the cases and >3 years in 90% of cases. It must be noted here that, given our choice of considering in this study only allergies that manifested before the age at diagnosis of MS or corresponding age for controls (see Methods), bias theoretically resulting from the use of treatments for allergy or asthma, that might prevent or delay the onset of MS [19], cannot be excluded.

In conclusion, our study shows that a history of atopic allergies, such as asthma and rhinoconjunctivitis, developing in younger age is associated with a decreased risk for MS. The mechanisms by which previous medical history of atopy may modify the risk of MS remain an open field for investigation.

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Disclosure

The authors report no conflicts of interest.

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