

Inverse relationship between multiple sclerosis and allergic respiratory diseases

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Abstract Th1 up-regulation seems to favour autoimmunity, while Th2 up-regulation seems to favour humoral immunity. Accordingly, subjects affected by atopic diseases (such as allergic respiratory diseases, ARDs) should be less prone to autoimmune diseases (such as multiple sclerosis, MS), and vice versa. The recent identification of Th17 cells, which seem to favour the development of both autoimmunity and allergy, led to the revision of the classic Th1/Th2 paradigm. We studied 200 MS patients and 200 controls to analyze the relationships between ARDs and MS. MS patients had less probability to suffer from ARDs (OR = 0.30, $p < 0.001$) and allergic rhinitis (OR = 0.25, $p < 0.001$), after adjusting for environmental factors. MS tended to be less severe when associated to ARDs. Our findings add some elements for the comprehension of immune mechanisms involved in MS pathogenesis and suggest to analyze other MS cohorts, in order to evaluate if MS patients affected by allergic diseases show particular clinical findings.

Keywords Allergic diseases · Epidemiology · Rhinitis · Asthma · Multiple sclerosis · Th1/Th2 balance

Introduction

Previous studies gave conflicting findings on the relationships between allergic and autoimmune diseases. Rudwaleit et al. [1] found asthma and allergies less frequent in patients with rheumatoid arthritis (RA) than in controls (13.1 vs. 20.7%), while Provenzano et al. [2] found a rather high prevalence of atopic respiratory diseases (ARDs) in RA patients.

Concerning allergies and multiple sclerosis (MS), past researches produced discordant results, reporting direct [3], inverse [4, 5] or absent [6, 7] associations between the two pathologies.

To obtain further epidemiological information, we carried out a case-control study to analyze the relationship between symptoms suggestive for ARDs and MS.

Materials and methods

Study population

A case-control study was conducted in the area of the province of Pavia in Northern-Western Italy that covers 2,965 km² and has 493,753 inhabitants according to the 2001 census.

Cases of MS diagnosed according to the McDonald criteria [8] and resident in the province of Pavia were enrolled from the patients admitted consecutively for check-ups at the Multiple Sclerosis Centre of the Neurological Institute Mondino of Pavia, that is the only Neurological Centre in the area.

Controls were randomly selected from the general population resident in the same administrative area in the province of Pavia in Northern-Western Italy.

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The cases and controls were unmatched and no relative was comprised in the control group.

The research received prior approval by the Ethical Committee of the Neurological Institute ‘C. Mondino’ of Pavia. Informed consent was obtained from each participating subject.

The MS patients and controls answered a questionnaire administered by a trained physician. The questionnaire had already been used in the multicenter study ECRH II [9] (<http://www.ecrhs.org/Quests/mainquest.pdf>). The questionnaire investigated asthma-like symptoms, asthma, nasal allergies, and correlated factors such as smoking habits, occupational exposure, environmental household exposure (i.e. pets, gas cooking), and use of therapies for asthma. The classification of the people in affected or unaffected by ARDs was made ‘at posterior’ by an epidemiologist (M.P.) based on the answering to the questionnaire. Epidemiologist was not aware of the interviewed person status (healthy or MS affected). ARD was determined as the presence of asthmatic status or allergic rhinitis. In particular, the asthmatic status was defined as the presence of an attack of asthma in the last 12 months and/or current use of asthma medication [10]. Allergic rhinitis was determined using the positive answer to the question investigating nasal allergies, including ‘hay fever’ [11].

The following clinical characteristics were collected for the MS cases: age at clinical onset of MS; disease duration; clinical course of the disease (relapsing–remitting, RR; secondary progressive, SP; primary progressive, PP); neurological impairment, quantified according to Kurtzke’s Expanded Disability Status Scale (EDSS) [12]; disease severity quantified according to the Multiple Sclerosis Severity Score (MSSS) [13]; previous or current use of immune therapies (IT).

Statistical analysis

Considering a prevalence of ARD in general population living in Northern Italy equal to 24% (European Community Respiratory Health, ECRHS, unpublished data), an $\alpha = 0.05$, a power of 80%, the sample size was estimated in at least 194 subjects for each group.

The association between ARDs and MS was estimated using an unconditional logistic regression model controlling for potential confounding: gender, age, smoking habits, home pet keeping, sleeping with other children before the age of 5 years, hospitalisation for respiratory diseases before the age of 2 years. MS patients were stratified into two groups: suffering from ‘MS alone’ or from ‘MS plus ARD’. The differences in the clinical features (i.e. age, age at onset, the disease’s duration, EDSS and MSSS scores) among ‘MS alone’ and ‘MS plus ARD’ were evaluated applying unpaired *t* test or Mann–Whitney non-parametric test. The χ^2 test was used for categorical clinical features.

Results

Two hundred MS cases and 200 controls were included; no one refused to attend the study.

The MS cases had a higher proportion of females (70 vs. 46%, $\chi^2 = 24.52$, $p < 0.001$) and a younger age (39.3 ± 10.4 vs. 43.5 ± 7.4 , $t = 4.65$; $p < 0.001$) than the controls. No difference in smoking habits between the two groups was found ($\chi^2 = 1.99$, $p = 0.37$): smoker cases were 25.8% and smoker controls were 29.5%.

A lower percentage of MS cases compared to controls had ARDs (11.5 vs. 23.5%) and allergic rhinitis (9.5 vs. 23.5%). Similarly, the proportion of asthmatic subjects was lower among MS cases (2%) than in controls (3.5%).

The MS patients were significantly less likely than the controls to have ARDs (OR = 0.33, $p < 0.001$) and to suffer from allergic rhinitis (OR = 0.27, $p < 0.001$) (Table 1). An inverse trend for asthma too was observed, but it was not statistically significant due to the poor number of observations. When the analysis was adjusted for other factors (home pet presence, sleeping with other children before 5 years of age, hospitalisation for respiratory diseases before 2 years of age) in addition to gender, age, and smoking habits, the trend towards a lower risk of asthma in MS subjects was more noticeable (Table 1).

The mean age at the onset of asthma was significantly higher in MS cases than in controls (34.5 ± 7.7 vs.

Table 1 Adjusted associations (odds ratio, OR, and 95% confidence interval, CI) of MS with asthmatic status, allergic rhinitis and at least one ARD

	MS Cases (<i>n</i> = 200)	Controls (<i>n</i> = 200)	OR ^a	95% CI	<i>p</i> value	OR ^b	95% CI	<i>p</i> value
At least one ARD	23	47	0.33	0.18–0.59	<0.001	0.30	0.16–0.57	<0.001
Asthma	4	7	0.41	0.11–1.47	0.169	0.29	0.08–1.11	0.07
Allergic rhinitis	19	47	0.27	0.14–0.50	<0.001	0.25	0.13–0.48	<0.001

^a Adjusted for gender, age and smoking habits

^b Adjusted for gender, age, smoking habits, home pet presence, sleeping with other children before 5 years of age, hospitalisation for respiratory diseases before 2 years of age

18.3 ± 10.1 years, Mann–Whitney test = 2.08, $p = 0.037$). Further, no asthmatic MS patient had early-asthma, defined as an onset of the disease before age 12 years of age [14], while 29.6% of the asthmatic controls did.

When we compared the environmental factors, we found no significant difference between the MS patients and controls concerning cats in their home (27.6 vs. 27%) and dogs kept in their home (16.5 vs. 19.5%). The MS cases slept less frequently than controls in a bedroom with other children before 5 years old (52.5 vs. 61.5%, $\chi^2 = 8.05$, $p = 0.045$). No MS subject was hospitalised before the age of two for lung diseases, and only 1% of the controls were ($\chi^2 = 2.00$, $p = 0.157$).

No relevant difference was found for the age at MS onset, the disease duration, the clinical course of the disease, or the use of IT, comparing ‘MS plus ARD’ patients with ‘MS alone’ (Table 2). Note that in the ‘MS plus ARD’ subgroup, IT treatment invariably started after the onset of the allergy. ‘MS plus ARD’ patients, compared to ‘MS alone’ patients, showed lower EDSS (1.5 vs. 2.5) and MSSS (2.33 vs. 3.34) mean values, but the differences were not statistically significant.

Discussion

The influence of T-helper1/T-helper2 balance (Th1/Th2) on immune regulation is still unclear. Th1 and Th2 subpopulations drive different immune responses, the ‘cellular immunity’ and the ‘humoral immunity’, to produce different patterns of cytokines. Consequently, over-activation of either pattern could favour the appearance of different types of disease [15]. In particular, Th1 up-regulation could favour autoimmune diseases, while Th2 up-regulation could favour atopic allergies. Accordingly, Th2-mediated diseases, such as asthma and allergic rhinitis, might

‘protect’ against Th1-mediated autoimmune diseases, such as RA and MS. However, this hypothesis is probably an oversimplification, since human cytokine activities rarely fall into exclusive pro-Th1 or pro-Th2 patterns [15]. The relatively polarized Th1 or Th2 response depends on both individual genetic background and environmental factors, which could act directly on regulatory T-cell populations, and hence favour the development of both autoimmunity and allergy. In addition, allergy-associated mechanisms and mediators may contribute to the pathogenesis or progression of autoimmune diseases [16]. More recently, the identification of novel Th subsets, namely Th17 cells [17], led to the revision of the classic Th1/Th2 paradigm [18].

Th17 are characterized by production of IL-17, and may have evolved for host protection against microbes. IL-17 has not only an important role in host defence, but also mediates effects on stromal cells, resulting in recruitment of neutrophils, thus creating a link between innate and adaptive immunity [19]. Th17 cells seem to be crucial for the development of both autoimmune diseases, such as MS, [19] and allergic diseases, such as asthma [20] and rhinitis [21]. Accordingly, subjects affected by autoimmune diseases should also be prone to allergic diseases.

Our case–control study indicated an inverse relationship between ARDs and MS, while past researches produced discordant results, reporting direct [3], inverse [4, 5] or absent [6, 7] relationships between MS and atopic disorders. These discrepancies could be partially attributable to the lack in the previous studies of one of the factors that characterized our study: case–control design, use of a directly administered and validated questionnaire to ascertain allergies, and control for possible confounding factors.

Our results did not seem to be affected by possible bias, such as smoking habits or the effect of ITs. As a matter of fact, MS patients did not show a different propensity to

Table 2 Clinical features of patients with ‘MS alone’ or with ‘MS plus ARD’

Clinical features	MS alone ($n = 177$)	MS plus ARD ($n = 23$)	Total ($n = 200$)	Tests and p values
Gender, F/M	122/55	18/5	140/60	$\chi^2 = 0.84$, $p = 0.358$
Age (years)	39.7 ± 10.7 [18.8–66.6]	36.2 ± 7.6 [19.4–48.2]	39.3 ± 10.4 [18.8–66.6]	$t = 1.97$, $p = 0.05$
Clinical course RR/SP/PP	135/35/7	20/2/1	155/37/8	$\chi^2 = 1.66$, $p = 0.436$
Age at MS onset (years)	29 ± 9 [12–57]	26.9 ± 7.7 [17–46]	28.7 ± 8.9 [12–57]	$t = 1.05$, $p = 0.297$
Disease duration (years)	10.7 ± 8.5 [1–53]	9.3 ± 6.0 [1–19]	10.6 ± 8.2 [1–53]	Mann–Whitney = 0.36, $p = 0.716$
EDSS	2.5 (1.5–4.0)	1.5 (1.5–2.5)	2.5 (1.5–4.0)	Mann–Whitney = 1.84, $p = 0.07$
MSSS	3.34 (1.71–5.87)	2.33 (1.28–4.55)	3.34 (1.68–5.87)	Mann–Whitney = 1.47, $p = 0.14$
No. of patients treated with IT	100	16	116	$\chi^2 = 1.43$, $p = 0.232$

For age, age at MS onset and disease duration, the mean values and standard deviations (mean ± SD), and ranges (in square brackets) are given. For EDSS and MSSS, median values, the 25th and 75th percentile ranges (in brackets) are given

RR relapsing–remitting, SP secondary progressive, PP primary progressive, EDSS expanded disability status scale, MSSS multiple sclerosis severity score, IT immune therapies

smoke, compared to the general population. We did not observe any significant difference in the use of IT in patients suffering from MS alone compared with patients suffering from MS plus ARD; in addition, allergies started before the use of ITs in all the cases. This is in accordance with Tremlett's findings [5], which confirmed the inverse relationship between MS and asthma, even after excluding patients treated with ITs. Our findings suggest that the presence of allergies could play a protective role towards autoimmunity. Added to the observation that Th2 cells may be responsible for re-myelination through the stimulation of repair-enhancing antibody producing B-cells [22], these findings remind us of the protective effect attributed to the Th1 to Th2 shift induced by pregnancy [23] and by glatiramer acetate therapy [24]. Hence, a 'Th2-atopic environment' could not only influence the occurrence of MS, but also its severity. In fact, the subjects with ARDs seem to have a lower risk of MS and, when they are affected by MS, to have a less severe neurological impairment, as suggested by the lower values of EDSS and MSSS scores.

The inverse relationship that we found seems to be opposite with the recent data sustaining the role of Th17 in favouring both MS and ARDs [19]. However, ARDs such as asthma can be divided into two subtypes, a 'non-atopic non-Th2 type' (whose pathogenesis is more related to Th17) and an 'atopic Th2 type' (whose pathogenesis is more related to Th2) [18]. Under these considerations, a protective role on MS could be effective only in the case of Th2 type ARDs.

In conclusion, our findings give us some suggestions about the relationships between allergies and MS, and indicate a need for further analyses of other MS cohorts, in order to verify if MS patients affected by allergic diseases show particular clinical findings (i.e. a later onset of ARD, a more benign course of MS) correlated to different immune patterns. The join analysis of epidemiological data and immunological findings could inspire future research about MS treatments.

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