Allergy, histamine 1 receptor blockers, and the risk of multiple sclerosis

Alvaro Alonso, MD, PhD; Susan S. Jick, DSc; and Miguel A. Hernán, MD, DrPH

Abstract—*Background:* It is unclear whether allergic diseases are associated with multiple sclerosis (MS), but histamine 1 receptor blockers, used in the treatment of allergic conditions, decreased the severity of experimental autoimmune encephalomyelitis (an animal model of MS). *Objective:* To assess the association of allergy history and use of histamine 1 receptor blockers with the risk of MS. *Methods:* Using a case–control study nested in the United Kingdom–based General Practice Research Database cohort, the authors identified 163 incident cases of MS with at least 3 years of follow-up before their first symptoms (index date). Up to 10 controls matched to the cases by age, sex, general practice, and time in the cohort were selected. Previous history of allergic disease and use of histamine 1 receptor blockers in the 3 years before the index date were assessed through computerized medical records. *Results:* History of any allergic condition in the 3 years before the index date was not associated with MS risk (adjusted odds ratio [OR] 1.2, 95% CI 0.8 to 1.8). However, use of sedating histamine 1 receptor blockers was associated with decreased MS risk (adjusted OR 0.2, 95% CI 0.1 to 0.8). *Conclusion:* These results do not support a strong link between allergic conditions and multiple sclerosis (MS) risk but suggest a possible beneficial effect of antihistamines on the onset of MS.

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Histamine 1 receptor blockers (H1RBs) decrease the severity of experimental autoimmune (formerly allergic) encephalomyelitis (EAE), an animal model of multiple sclerosis (MS).[1-3] Because these drugs are commonly used for the treatment of allergic conditions, it is conceivable that allergy and MS may share some risk factors. This hypothesis is indirectly supported by recent increases in the incidence of both allergic disorders and MS, and with the association of both conditions in individuals.[4,5]

The identification of a link between allergy or H1RB use and MS could improve our understanding of MS physiopathology and help to develop new therapies. However, no studies have evaluated the relation between H1RB use and the development of MS in humans, and epidemiologic studies on the association between MS and allergic conditions[6-20] provide conflicting results that are difficult to interpret because of design limitations.

We assessed whether allergic conditions and H1RB use were associated with MS risk in a prospectively followed population using the General Practice Research Database (GPRD).

Methods. *Study population.* The GPRD contains prospective health information on more than 3 million Britons who are enrolled with selected general practitioners (GPs).[21] These physicians have been trained to record their patients' medical and demographic information in a standard manner and have agreed to supply it anonymously for research purposes. In addition, practices used in this study agree to collaborate in specific projects by providing photocopies of their patients' paper medical records after personal identifiers have been removed. Drug prescriptions were computer generated by the physicians and automatically recorded in the database using a coded drug dictionary based on that of the United Kingdom Prescription Pricing Authority. Medical diagnoses were entered using a classification compatible with the International Classification of Diseases (ICD). The GPRD data has been found to be of satisfactory quality for epidemiologic research.[22,23]

Case ascertainment. The assessment of incident cases of MS in the GPRD has been described previously.[24] Briefly, we identified individuals with a new diagnosis of MS (ICD-9 code 340.0) recorded in the GPRD between January 1, 1993, and December 31, 2000. We then requested photocopies of all their MS-related medical records available in the GP's office, including laboratory results, specialist referrals, and hospital discharges. Two study physicians reviewed independently the paper medical records and classified participants into MS, possible MS, or no MS diagnosis according to standardized criteria.[25,26] This review confirmed 438 (61.4%) of the 713 individuals identified as potential cases. Reasons to exclude the other 275 participants were 1) they were prevalent cases of MS (83, diagnosed before January 1, 1993), 2) they had a diagnosis of possible MS (59), 3) their medical records could not be obtained because of transfer into another general practice (71) or death of the patient (10), or 4) they did not have MS (52). Ninety-eight percent of the cases were diagnosed by a neurologist, and 87% of the diagnoses were supported by MRI.

From the 438 cases, 282 had their first symptoms after their first computer-recorded medical information. To ensure at least 3 years of exposure information, our primary analysis included only the 163 cases with at least 3 years of information in the GPRD before the date of first symptoms.

Study design. We conducted a case–control study nested in the GPRD. Cases were defined as patients with a confirmed diagnosis of MS between January 1, 1993, and December 31, 2000, and with at

From the Department of Epidemiology, Harvard School of Public Health, Boston, MA (A.A., M.A.H.), and Boston Collaborative Drug Surveillance Program, Boston University, Lexington, MA (S.S.J.).

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Address correspondence and reprint requests to Dr. Alvaro Alonso, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115; e-mail: aalogut@alumni.unav.es

Table 1 *Multiple sclerosis risk by type of allergic conditions in the 3 years before index date*

	Cases, n (%)	Controls, n (%)	OR (95% CI)*	OR (95% CI)†
No allergy condition	118 (72.4)	1132 (74.3)	1 (ref.)	1 (ref.)
Allergic rhinitis/hay fever	8 (4.9)	68 (4.5)	1.1 (0.5–2.3)	1.3 (0.6–2.7)
Urticaria/angioedema	5 (3.1)	38 (2.5)	1.2 (0.5–3.2)	1.5 (0.6–4.1)
Asthma	8 (4.9)	84 (5.5)	0.9 (0.4–2.0)	0.9 (0.4–2.0)
Eczema/atopic dermatitis	14 (8.6)	128 (8.4)	1.1 (0.6–1.9)	1.1 (0.6–2.1)
Other allergy	3 (1.8)	9 (0.6)	3.4 (0.9–12.8)	2.5 (0.6–11.3)
More than one diagnosis	7 (4.3)	64 (4.2)	1.0 (0.5–2.3)	1.2 (0.5–2.8)

* Adjusted for matching factors (age, sex, practice, time in the cohort).
† Further adjusted for previous use of histamine 1 receptor blockers (H1RBs) and smoking.

OR = odds ratio.

least 3 years of continuous recording in the GPRD before first symptoms. Up to 10 controls per case were selected, matched by age (±1 year), sex, practice, and date of joining the practice (±1 year). Controls had to be alive, be free of an MS diagnosis, be present in the database at the date of first symptoms of their corresponding case (the index date), and have at least 3 years of continuous recording in the database before the index date. The characteristics of the 163 cases and 1,523 controls have been previously described.[24]

Table 2 *Association of histamine 1 receptor blocker use with multiple sclerosis risk*

	Cases, n (%)	Controls, n (%)	OR (95% CI)*	OR (95% CI)†
Use of H1RBs				
No	141 (86.5)	1,259 (82.7)	1 (ref.)	1 (ref.)
Yes	22 (13.5)	264 (17.3)	0.7 (0.5–1.2)	0.6 (0.3–1.1)
Cumulative duration of use of H1RBs				
0	141 (86.5)	1,259 (82.7)	1 (ref.)	1 (ref.)
>0 to ≤1 mo	12 (7.4)	159 (10.4)	0.7 (0.4–1.2)	0.5 (0.3–1.2)
>1 to ≤2 mo	1 (0.6)	38 (2.5)	0.2 (0.03–1.8)	0.2 (0.03–1.7)
>2 mo	9 (5.5)	67 (4.4)	1.2 (0.6–2.4)	0.9 (0.4–2.0)
Time since last H1RB use				
No use	141 (86.5)	1,349 (88.6)	1 (ref.)	1 (ref.)
>1 y	15 (9.2)	147 (9.7)	0.9 (0.5–1.6)	0.8 (0.4–1.5)
≤1 y	7 (4.3)	117 (7.7)	0.5 (0.2–1.1)	0.4 (0.2–1.0)
Use of nonsedating H1RBs				
No	143 (87.7)	1,317 (86.5)	1 (ref.)	1 (ref.)
Yes	20 (12.3)	206 (13.5)	0.9 (0.5–1.4)	0.8 (0.4–1.6)
Cumulative duration of use of nonsedating H1RBs				
0	143 (87.7)	1,317 (86.5)	1 (ref.)	1 (ref.)
>0 to ≤1 mo	11 (6.8)	117 (7.7)	0.8 (0.4–1.6)	0.8 (0.4–1.7)
>1 to ≤2 mo	1 (0.6)	37 (2.4)	0.2 (0.03–1.8)	0.3 (0.03–2.2)
>2 mo	8 (4.9)	52 (3.4)	1.4 (0.6–3.0)	1.2 (0.5–3.0)
Time since last nonsedating H1RB use				
No use	143 (87.7)	1,317 (86.5)	1 (ref.)	1 (ref.)
>1 y ago	14 (8.6)	110 (7.2)	1.2 (0.7–2.2)	1.0 (0.5–2.1)
≤1 y ago	6 (3.7)	96 (6.3)	0.6 (0.3–1.4)	0.6 (0.2–1.5)
Use of sedating H1RBs				
No	161 (98.8)	1,438 (94.4)	1 (ref.)	1 (ref.)
Yes	2 (1.2)	85 (5.6)	0.2 (0.1–0.9)	0.2 (0.1–0.8)

* Adjusted for matching factors (age, sex, practice, time in the cohort).
† Further adjusted for history of allergic diseases, smoking and, for risk associated with histamine 1 receptor blocker (H1RB) types, use of sedating or nonsedating H1RBs.

OR = odds ratio.

Exposure assessment. Diagnoses of allergic diseases and H1RB prescriptions were obtained from the computerized medical records. We identified history of allergic rhinitis/hay fever, asthma, urticaria/angioedema, eczema/atopic dermatitis, and other allergic conditions before the index date. For each H1RB prescription received in the 3 years before the index date, we obtained the type of drug (sedating or nonsedating), the timing of use, and its duration. When duration was missing (24.7% of total H1RB prescriptions), we assigned the median duration (30 days). Analyses restricted to prescriptions with known duration yielded similar results (data not shown).

Statistical analysis. We used conditional logistic regression to compute odds ratios (ORs) and their 95% CIs adjusted for the matching factors. Under our design, the OR is a consistent estimator of the incidence rate ratio of MS in exposed vs unexposed subjects. Statements about statistical significance refer to the conventional (and arbitrary) 0.05 cutoff.

Results. A diagnosis of allergic disease in the 3 years before the index date was not associated with the incidence of MS (OR 1.1, 95% CI 0.8 to 1.6). Adjustment for smoking status and previous H1RB use had little effect on the estimate (OR 1.2, 95% CI 0.8 to 1.8). Specific allergic conditions were not clearly associated with the risk of MS (table 1). Results were similar when we considered allergy diagnosis 2 or 5 years before the index date. MS risk was not significantly different in individuals with both asthma and other allergic disease compared with those without an allergic disease (OR 1.6, 95% CI 0.6 to 4.5).

Use of H1RBs in the 3 years before the index date was nonsignificantly associated with a reduced MS risk. The association was stronger for the use of sedating H1RBs, but these results are based on a small number of exposed subjects (table 2). No clear trend between cumulative use of H1RBs or nonsedating H1RBs and MS risk was evident, but MS risk was lower among those with recent H1RB use (within the year before the index date).

Discussion. In our prospective study, we found that use of any H1RB was associated with a nonsignificant 40% reduction in the incidence of MS, and that use of sedating H1RBs was associated with a significant 80% reduction. The association between history of allergic conditions and MS was weak. These findings are unlikely to be affected by recall bias (because the data were collected before first symptoms of MS) or bias in the selection of the controls (because we nested our case–control study in a well-defined cohort).

The weak association between history of allergy and MS risk may partly result from nondifferential misclassification. Even though the consultation rates for asthma and hay fever and treatment rates for asthma in the GPRD are similar to those in the general population,[27] it is not possible to determine the lifetime history of allergy in these data.

Another obvious limitation of our study is the low number of cases exposed to sedating H1RBs, the type of H1RBs that can easily cross the blood–brain barrier and thus have a pharmacologic effect on the CNS. However, a low number of exposed cases would be expected if sedating H1RBs actually had a strong protective effect. The expected number of exposed cases under the assumption of no association between sedating H1RBs and MS risk is nine, instead of the observed two.

Table 3 *Association of history of allergic disease with the risk of multiple sclerosis: Review of the literature*

Publication year (ref.)	Location	Cases/controls	Exposure assessment	Adjustment	OR (95% CI)
1952 (6)	London, UK	250/250	Questionnaire	Not specified	1.8 (1.2–2.8)
1965 (7)	Israel	241/964	Questionnaire	Not specified	Allergy before age 15 y: 3.2 (1.8–5.7); allergy after age 15 y: NS
1967 (8)	Norway	100/100	Questionnaire	Not specified	2.6 (1.4–5.0)
1968 (9)	Minnesota, US	36/72	Questionnaire	Not specified	NS
1969 (10)	Western Poland	300/300	Questionnaire	Not specified	0.6 (0.4–0.8)
1973 (11)	Finland	229/219	Questionnaire	Not specified	NS
1976 (12)	Minnesota, US	36/40	Review of medical records	Not specified	0.9 (0.3–3.1)
1980 (13)	Orkney and Shetland Islands, Scotland	77/154	Questionnaire	Not specified	1.3 (0.7–2.3)
1981 (14)	Alberta, Canada	100/100	Questionnaire	Not specified	1.0 (0.5–1.7)
1990 (15)	Paris, France	230/230	Questionnaire	Age and sex	NS
1994 (16)	Ferrara, Italy	104/150	Questionnaire	Not specified	2.4 (1.0–5.6)
1996 (17)	Moscow, Russia	155/155	Questionnaire	Not specified	1.1 (0.7–1.8)
1997 (18)	Paris, France	302/3,152	Questionnaire	Not specified	0.6 (0.5–0.8)
2001 (19)	Genoa, Italy	312/312	Questionnaire	Age, sex, area of residence	1.1 (0.7–1.7)
2002 (20)	Wales, UK	320/320	Computerized medical records	Not specified	0.4 (0.3–0.7)

OR = odds ratio; NS = nonsignificant differences and not enough information to compute odds ratios.

Although not conclusive, our findings for sedating H1RBs and MS are consistent with those of animal experiments that showed a beneficial effect of sedating H1RBs on the risk of EAE.[1-3] In contrast with the classic view that the immunologic pathways involved in allergic diseases (increased secretion of interleukin-4, -5, and -10 by T-helper 2 cells) and autoimmune disorders (increased secretion of interleukin-2, interferon-γ by T-helper 1 cells) are separate, recent evidence suggests that these two disorders share some pathophysiologic mechanisms, such as the presence of activated mast cells and overexpression of the histamine 1 receptor gene.[28]

Several case–control studies have evaluated the association between allergic conditions and MS. Their main characteristics and results are summarized in table 3. All of these studies used prevalent cases and assessed exposure retrospectively. Most did not adjust for age, sex, or other potential confounding variables. The pooled OR (95% CI) for MS and allergy was 1.1 (0.8 to 1.7), and the *p* value for heterogeneity was less than 0.001, but the diversity of the methods (e.g., exposure definition, case and control selection procedures) of these studies makes it difficult to interpret the summary measure and to compare it with our estimate. Two additional studies found lower levels of immunoglobulin E, a marker of allergic disease, in MS patients than in patients with other neurologic disorders.[12,29] However, both reports were based on prevalent MS cases and thus could not prove the directionality of the association.

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