

Autoimmune diseases prior to the diagnosis of multiple sclerosis: a population-based case-control study

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Abstract

The objective of this study was to determine whether patients with multiple sclerosis (MS) are more likely to have other autoimmune disorders particularly prior to the diagnosis of MS. We conducted a population-based case-control study of patients enrolled in the Northern California Kaiser Permanente Medical Care Program. Electronic clinical records through 2005 were used to ascertain incident and prevalent MS cases and identify the presence and timing of 44 other diagnoses. Controls were matched 5:1 for gender, age, and Kaiser membership characteristics. We identified 5296 MS cases (including 924 diagnosed between 2001 and 2004) and 26,478 matched controls. Prior to MS diagnosis, cases were more likely than controls to have uveitis (OR = 3.2, 95% CI 1.7–5.7), inflammatory bowel disease (IBD, OR = 1.7; 95% CI 1.2–2.5), and Bell's palsy (OR = 3.2; 95% CI 1.2–8.3). Cases were also more likely to develop Guillain-Barré syndrome (GBS, OR = 5.0; 95% CI 1.6–15.4) and bullous pemphigoid (OR = 6.7; 95% CI 1.5–29.9). Cases were not more likely than controls to have or to develop rheumatoid arthritis, lupus or thyroiditis. MS may share environmental triggers, genetic susceptibilities and/or alterations in immune homeostasis with IBD and uveitis, but not with other autoimmune disorders.

Keywords

multiple sclerosis, disease modifying therapies, immunology, epidemiology

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory condition of the central nervous system that predominantly affects women during their childbearing years. Well-described risk factors for MS include residing in northern latitudes, cigarette smoking, vitamin D insufficiency, Epstein-Barr virus (EBV) infection^{1,2} and carrying alleles of the MHC class II HLA-DR locus and interleukin (IL)-7 receptor.^{3,4} These risk factors are shared with other autoimmune diseases yet it is unclear whether MS patients are at higher risk of developing comorbid autoimmune conditions.

If other autoimmune disorders do co-occur with MS at a greater than chance frequency, this would point to either shared genetic susceptibilities and/or environmental triggers, or an alteration of immune homeostasis caused by one disease (or its treatment) which results in increased or decreased susceptibility to another.

Previous studies of the prevalence of comorbid autoimmune conditions (AICs) in MS cohorts report

conflicting results. However, most studies were limited either by small sample sizes, inadequate or absent control groups, unconfirmed diagnoses or selection bias. In addition, most studies did not attempt to ascertain which condition was diagnosed first.

In this study, we identified a large, population-based cohort of MS cases and appropriately matched controls to determine whether the prevalence of other autoimmune diseases is increased in patients with MS, particularly before the diagnosis of MS.

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Methods

Study population

The Kaiser Permanente Northern California (KPNC) medical care program is a large, health maintenance organization that serves over 3 million members at any given time, including approximately 30% of the population in the San Francisco Bay Area and Sacramento Valley, USA. Ethnicity, age and gender distribution of KPNC members is similar to the general population in the same area with the exception of under-representation of the extremely poor and wealthy⁵. KPNC's computerized records are described in detail elsewhere.⁶ Briefly, computerized hospitalization records were introduced between 1971 and 1988, and computerized outpatient records were introduced in 1994. By 1996, all facilities were using electronic clinical records (ECRs), which include diagnostic and procedure codes, as well as pharmacy, laboratory and radiology records. The study was approved by the Institutional Review Boards at Kaiser Foundation Research Institute and Stanford University.

Identification of cases and controls

Cases and controls were identified by searching Kaiser's computerized membership, medical, pharmacy, laboratory and radiology records through December 2005. An algorithm to identify the full spectrum of both incident and prevalent MS cases was developed (benign to bedridden) based on number of MS diagnostic codes entered by neurologists and primary care physicians; use of the MS-specific medications, beta-interferons and/or glatiramer acetate, and for incident cases, evidence that appropriate MS diagnostic tests were conducted (brain magnetic resonance imaging (MRI) and/or lumbar puncture) and duration and continuity of KPNC membership. Using this algorithm, we identified 5611 potentially eligible cases. For records with scant membership or diagnostic data or otherwise equivocal data (e.g. two or more MS codes entered by primary care physicians only) the complete ECRs were reviewed by a neurologist (ALG) to adjudicate MS cases using a diagnostic classification scheme similar to Visscher et al.⁷ Of the 840 (15%) records reviewed, 315 potentially eligible cases were excluded, typically because the ECRs contained insufficient information to establish a diagnosis of MS or represented a misuse of the MS diagnostic code (e.g. patients with diseases that rhyme with MS; 45% and 36% of records excluded, respectively). Thus, we identified a total of 5296 MS cases. The ECRs from a 5% random sample of the total MS cases were reviewed and showed 99% accuracy for case selection.

Among the total MS cases, 1310 were classified as potentially incident cases, because the first MS code occurred between 1 January 2001 and 31 December 2004, following an appropriate diagnostic evaluation (brain MRI with or without lumbar puncture or evoked potentials). For cases that had only one MS code, two or more MS codes but none by a neurologist, no history of MS procedures or initial diagnosis within the first year of KPNC membership, full ECRs were reviewed ($n=646$). In total, 924 incident cases were identified. A review of the complete ECRs of a 10% random sample of these records showed >99% accuracy for distinguishing incident from prevalent cases.

Five electronic KPNC controls were then matched to each incident and prevalent case based on gender, birth year (± 2 years), KPNC facility, and duration and timing of KPNC membership.

Identification of other conditions

A priori, we developed a list of 44 other autoimmune and allergic conditions by searching publicly available databases (Table A1 in the Appendix). ECRs were searched through 2005 for individuals with at least two codes of the condition entered by an appropriate medical specialist at any time during KPNC membership. For asthma, subjects with codes for chronic obstructive pulmonary disease were excluded. Complete ECRs were reviewed for cases and controls with conditions that could be confused with MS (central nervous system (CNS) vasculitis, Bell's palsy and Guillain-Barré syndrome (GBS)), and cases in which statistically significant associations were based on a small number of affected individuals (myasthenia gravis, bullous pemphigoid, giant cell arteritis and juvenile rheumatoid arthritis). ECRs for ulcerative colitis and Crohn's disease were reviewed and combined into one category (inflammatory bowel disease).

To determine the relative timing of other conditions and MS, the incident cases (2001–2004) were analyzed separately. A condition was considered to precede the diagnosis of MS if the first code for the other condition preceded first MS code. For this analysis, the first MS code was defined as either MS, optic neuritis, transverse myelitis or central nervous system demyelinating disease, whichever came first.

Statistical analyses

Adjusted and unadjusted odds ratios and 95% confidence intervals (95% CI) were calculated separately using unconditional logistic regression for the total and incident population. Analyses were adjusted for gender, age and membership months through 2005 and stratified by gender and MS-specific medication

use (interferon-beta and glatiramer acetate). All analyses were conducted using SAS software v9.1 (Cary, NC, USA).

Results

Patient characteristics

From the KPNC electronic database through 2005 we identified 5296 patients with MS and 26,478 controls that had received care within KPNC between 1994 and 2004. Of the MS cases, 56% never received MS-specific treatments and 924 (17%) were incident cases diagnosed between 2001 and 2004. The two subgroups of cases and the controls were similar in age at the end of 2005, duration of KPNC membership and gender distribution (Table 1).

Risk of autoimmune disease in patients with MS

Table 2 shows the risk of autoimmune diseases in the entire MS population compared to controls diagnosed at any time in their disease course (Table 2 and Table A2). Overall, MS patients were significantly more likely than controls to have uveitis, inflammatory bowel disease (IBD), Bell's palsy, GBS and bullous pemphigoid. They also had a statistically non-significant increase in the risk of giant cell arteritis and Sjögren's syndrome. Unadjusted odds ratios were similar to adjusted estimates (data not shown).

We found similar results when restricting the analyses to MS patients who had never received MS-specific treatments (Table A3). The risks of uveitis (adjusted OR = 1.7; 95% CI = 1.2–2.6, $p = 0.006$), IBD (adjusted OR = 1.9; 95% CI = 1.2–2.9, $p = 0.005$), bullous pemphigoid (adjusted OR = 6.6; 95% CI = 1.5–29.6, $p = 0.01$), Bell's palsy (adjusted OR = 4.7; 95% CI = 2.1–10.3, $p < 0.001$) and GBS (adjusted OR = 3.8; 95% CI = 0.9–17.1, $p = 0.08$) were increased in cases compared with their matched controls.

Relative timing of diagnoses

Patients in the incident MS subgroup were significantly more likely than controls to have been diagnosed with uveitis, IBD and Bell's palsy *before* being diagnosed with MS, optic neuritis, transverse myelitis or central nervous system or demyelinating disease (Table 3 and Table A4).

Furthermore, review of the complete electronic clinical records to assess the relative timing of diagnoses among the total MS population revealed that GBS occurred prior to the onset of MS in four of six patients (66%). Bell's palsy was diagnosed both before and after the onset of MS and bullous pemphigoid and giant cell arteritis were always diagnosed after the onset of MS.

In contrast, the risk of other diseases characterized by excess Th1/Th17 cytokine production (e.g. rheumatoid arthritis, psoriasis) were not elevated, nor was there evidence that MS patients were protected from developing asthma, eczema or lupus erythematosus (Tables 2 and 3).

Discussion

We found that people with multiple sclerosis are more likely than age- and gender-matched controls to have been diagnosed with inflammatory bowel disease, uveitis, and Bell's palsy prior to being diagnosed with multiple sclerosis. In addition, MS patients appear more likely to develop IBD, uveitis, Bell's palsy, GBS and bullous pemphigoid during their disease course. The associations we found were strong (odds ratios ranging from 1.7 to 6.9) yet the overall number of people afflicted with these autoimmune diseases was rare among controls as well as MS patients.

In contrast, we found that people with MS were not more or less likely to have been diagnosed with rheumatoid arthritis, autoimmune thyroiditis, lupus, psoriasis, type I diabetes, asthma, or eczema when compared with controls.

Table 1. Demographic characteristics of the total KPNC MS population and two MS subgroups compared with their controls

	Total MS population		Incident MS		Untreated MS	
	MS cases	Controls	MS cases	Controls	MS cases	Controls
Sample size	5296	26,478	928	4620	2974	14,869
Female %	75	75	75	75	74	74
Age ^a in years, mean (SD)	54.5 (13.7)	54.5 (13.7)	45 (11.6)	45 (11.6)	59.6 (13.5)	59.5 (13.5)
KPNC membership duration in years, mean (SD)	16.2 (8.0)	16.4 (7.7)	15.6 (8.3)	15.8 (8.3)	16.2 (7.7)	16.5 (7.9)

Abbreviations: KPNC, Kaiser Permanente Northern California; SD, standard deviation.

^aAt the end of 2005.

Table 2. Frequency and adjusted odds ratios of other autoimmune and allergic conditions in the total KPNC MS population and controls

	MS cases (n = 5296) n (%)	Controls (n = 26,478) n (%)	Adjusted OR ^a (95% CI)	p-value
<i>Diseases characterized by excess IFNγ- and TNF-producing T cells</i>				
Psoriasis	70 (1.3)	319 (1.2)	1.1 (0.8–1.4)	–
Diabetes mellitus type I	45 (0.85)	240 (0.9)	0.9 (0.7–1.3)	–
Rheumatoid arthritis	44 (0.83)	228 (0.86)	1.0 (0.7–1.3)	–
Uveitis	71 (1.3)	160 (0.6)	2.2 (1.7–2.9)	<0.001
Inflammatory bowel disease	42 (0.8)	120 (0.45)	1.7 (1.2–2.5)	0.002
Hashimoto's thyroiditis	9 (0.17)	47 (0.18)	1.0 (0.5–1.9)	–
Membranous glomerulonephritis	1 (0.02)	9 (0.03)	0.6 (0.1–4.4)	–
<i>Diseases characterized by excess IL-10- and IL-4-producing T cells</i>				
Asthma (without COPD)	146 (2.8)	800 (3.0)	0.9 (0.8–1.1)	–
Atopic dermatitis/eczema	174 (3.3)	845 (3.2)	1.0 (0.9–1.2)	–
Grave's disease	13 (0.25)	92 (0.35)	0.7 (0.4–1.3)	–
Systemic lupus erythematosus	20 (0.4)	75 (0.3)	1.3 (0.8–2.2)	–
<i>EBV-related illnesses</i>				
Bell's palsy	21 (0.4)	36 (0.14)	2.9 (1.7–5.0)	<0.001
Guillain-Barré syndrome	6 (0.1)	6 (0.02)	5.0 (1.6–15.4)	0.006
<i>Unclassified autoimmune diseases</i>				
Polymyalgia rheumatica	8 (0.15)	64 (0.24)	0.6 (0.3–1.3)	0.20
Vitiligo	5 (0.09)	29 (0.11)	0.9 (0.3–2.3)	–
Raynaud's phenomenon	8 (0.15)	28 (0.11)	1.4 (0.6–3.0)	–
Rheumatic heart disease	3 (0.06)	28 (0.11)	0.5 (0.2–1.8)	–
Undiff connective tissue disease	4 (0.08)	21 (0.08)	0.9 (0.3–2.8)	–
Idiopathic thrombocytopenia purpura	6 (0.11)	20 (0.08)	1.5 (0.6–3.7)	–
Sjögren's syndrome	8 (0.15)	20 (0.08)	2.0 (0.9–4.5)	0.10
Systemic sclerosis	3 (0.06)	15 (0.06)	1.0 (0.3–3.4)	–
Giant cell arteritis	5 (0.09)	15 (0.06)	1.7 (0.6–4.6)	–
Myasthenia gravis	6 (0.11)	12 (0.05)	2.5 (0.9–6.6)	0.07
Pernicious anemia	3 (0.06)	7 (0.03)	2.1 (0.6–8.3)	–
Autoimmune hepatitis	3 (0.06)	6 (0.02)	2.5 (0.6–9.9)	0.20
Primary biliary cirrhosis	1 (0.02)	5 (0.02)	1.0 (0.1–8.4)	–
Autoimmune hemolytic anemia	1 (0.02)	4 (0.02)	1.3 (0.1–11.2)	–
Wegener's granulomatosis	1 (0.02)	4 (0.02)	1.2 (0.1–11.0)	–
Bullous pemphigoid	4 (0.08)	3 (0.01)	6.7 (1.5–29.9)	0.01
Juvenile rheumatoid arthritis	2 (0.04)	3 (0.01)	3.4 (0.6–20.1)	0.18
Hypersensitivity angitis	2 (0.04)	2 (0.01)	4.9 (0.7–35.1)	0.11

Odds ratios adjusted for, age, gender and KPNC membership duration. P-values > 0.20 are not reported.

Abbreviations: COPD, chronic obstructive pulmonary disease; EBV, Epstein-Barr virus; OR, odds ratio; KPNC, Kaiser Permanente Northern California; Undiff, undifferentiated.

Our findings indicate that MS may share environmental triggers, genetic susceptibilities and/or alterations in immune homeostasis with IBD and uveitis but not with other autoimmune disorders. This suggests that future studies focusing on unique factors shared between IBD and MS and uveitis and MS may improve our understanding of MS susceptibility. While our data do not exclude the possibility that an individual may be born

with an inherited susceptibility to develop an autoimmune disease, they do suggest having MS does not lead to an increased risk of most other autoimmune diseases.

Previous studies of comorbid AICs in MS cohorts have reported conflicting results. However, most of these studies were limited either by small sample sizes, inadequate^{8–16} or absent control groups,^{17–22} unconfirmed diagnoses^{13,23} or selection bias.^{8,9,13,17–20}

Table 3. AICs diagnosed prior to ms: frequency and adjusted odds ratios among the incident KPNC MS cases and controls

	MS cases (n = 924) n (%)	Controls (n = 4620) n (%)	Adjusted OR ^a (95% CI)	p-value
Psoriasis	11 (1.2)	31 (0.7)	1.8 (0.9–3.6)	0.10
Diabetes mellitus type I	4 (0.4)	24 (0.5)	0.8 (0.3–2.4)	–
Rheumatoid arthritis	2 (0.2)	21 (0.4)	0.5 (0.1–2.0)	–
Uveitis	18 (1.9)	29 (0.6)	3.2 (1.7–5.7)	<0.001
Inflammatory bowel disease	7 (0.8)	13 (0.3)	2.7 (1.1–6.8)	0.03
Hashimoto's thyroiditis	1 (0.1)	1 (0.02)	5.0 (0.3–80.2)	–
Asthma (without COPD)	50 (5.3)	273 (5.8)	0.9 (0.7–1.2)	–
Atopic dermatitis/eczema	23 (2.4)	105 (2.2)	1.1 (0.7–1.7)	–
Grave's disease	2 (0.2)	15 (0.3)	0.7 (0.2–2.9)	–
Systemic lupus erythematosus	4 (0.4)	15 (0.3)	1.3 (0.4–4.0)	–
Bell's palsy	7 (0.7)	11 (0.2)	3.2 (1.2–8.3)	0.02
Guillain-Barré syndrome	0	1 (0.02)	–	–

^aOdds ratios were adjusted for, age, gender and KPNC membership duration.

p-values > 0.20 are not reported.

Abbreviations: COPD, chronic obstructive pulmonary disease; KPNC, Kaiser Permanente Northern California; OR, odds ratio.

Because AICs are rare, studies with small sample sizes^{8–13,16–21,23–26} are likely to be underpowered to detect even large relative differences between groups. In addition, comparing the frequency of diseases in the general population^{14,17,22,25,26} or spousal controls¹⁵ with MS cohorts is likely to lead to erroneous conclusions because MS predominantly affects women in their forties and fifties. In contrast, estimates of disease frequency in the general population are typically drawn from equal numbers of older men and women. Similarly, the spouses of MS patients are more likely to be older and male than the cases. Thus, studies that compare the prevalence of AICs in MS cohort with general population estimates^{14,16,17,21,22,25,26} or spousal controls are likely to erroneously identify an excess of other AICs with a female preponderance (e.g. SLE and autoimmune thyroiditis) and more likely to miss associations with AICs that increase with age (e.g. bullous pemphigoid).

Not surprisingly, the results of previous reports are conflicting, with some showing an increased risk of or no association with autoimmune thyroiditis,^{8,10,12,15,17,21,26,27} diabetes mellitus type I^{9,10,14,15,17–19,22,27} allergies^{13,24} and inflammatory bowel disease (IBD)^{8,9,11,15–17,20,23,27}; and others showing an increased^{17,25} or decreased²³ risk of asthma.

The only other large, population-based study²⁷ that examined the co-occurrence of MS and other autoimmune conditions found results similar to ours. Specifically, this Danish study showed that MS patients had a significantly increased risk of developing UC and pemphigoid (uveitis was not measured) compared to national sex- and age-specific incidence rates (relative

risk (RR) = 2.0, 95%CI = 1.4–2.8 and RR = 15.4, 95%CI = 8.7–27.1, respectively).²⁷ However, this study²⁷ excluded MS patients who had any autoimmune diseases diagnosed prior to MS, and thus incompletely addressed the question of AIC clustering. In addition, this study was not able to examine the possibility that other diseases might pre-dispose to MS by altering immune homeostasis.

Our findings that the risk of IBD or uveitis is elevated even prior to the diagnosis of MS suggests that these diseases may be altering the immune system in such a way that pre-disposes to MS. Alternatively, IBD and MS and uveitis and MS might be caused by the same agents (e.g. gut-derived antigens or non-myeelin uveal antigens) in at least in a subgroup of patients, with clinical manifestations and/or diagnosis of MS lagging behind those of IBD or uveitis. Uveitis is a well-described, albeit rare, ocular manifestation of MS and our findings suggest that uveitis could be the first manifestation of MS. Thus, our findings suggest that assessment of uveitis patients should consider MS in the differential diagnosis and include a neurological evaluation.

EBV infection, particularly later in life, and serological evidence of EBV reactivation are strong risk factors for MS². Interestingly, reactivation of EBV and other herpes-family viruses has been linked to Bell's palsy and GBS – both of which were associated with MS both before and after diagnosis in our study. It is possible that the physicians of some of our patients confused Bell's palsy and GBS with typical neurological manifestations of MS (e.g. facial weakness and sensory/motor changes due to central rather than peripheral nervous

system involvement). However, we think this is unlikely, as the majority of these diagnoses were made by neurologists, and peripheral nervous system involvement in MS, while previously reported, is rare.

We, like other investigators,^{15,17,27} found that MS patients have the same risk of comorbid asthma and eczema as people of similar age and gender. These findings do not support the hypothesis that people with a disease like MS that is characterized immunologically by Th1/Th17 cytokine production will be protected from diseases that are characterized by excess T-helper type 2 (Th2) cytokines, and suggest a more complicated relationship between Th1/Th17 and Th2 cells in humans.

Because we relied on electronic clinical records collected as part of routine medical care, possible limitations of our study include the potential for inaccurate or missed diagnoses among cases and controls and the potential that patients with MS may be diagnosed more often with other illnesses because they have more contacts with the health care system. In the first instance, because the physicians were not aware of the hypothesis of our study, we think it is unlikely that diagnostic accuracy was different in patients with MS and the controls. The second possible limitation should affect only diagnoses made after the diagnosis of MS and were therefore unlikely to affect our estimates of associations with IBD or uveitis as these illnesses were more likely to have been diagnosed before MS.

Another potential limitation of this study is that we could not match the control group based on race/ethnicity because it is not routinely collected as part of the ECRs. While we indirectly addressed this issue by selecting controls from the same Kaiser facility and by matching a relatively large number of controls to each case, it is still possible that disorders that are strongly associated with Asian American or Hispanic race (16% and 12% of the general KPNC population, respectively) may be over-represented among the controls and thereby obscure an association with MS.

It should be noted that because we only examined whether having *ever received* treatment for MS with biological agents might effect the risk of being diagnosed with another AIC, we cannot rule out the possibility that total cumulative dose, duration of use or recency of use could result in an increased (or decreased) risk of the diseases we examined. Rather our subgroup analysis of only the untreated patients was conducted to confirm that the associations that we found were truly related to having MS and not solely attributable to treatment.

Finally, it should also be noted that the total MS population we identified includes patients that were KPNC members with MS as early as the 1980s and did not require that the subjects still be KPNC

members in 2005. Thus the total MS population does not represent a true prevalence estimate. In addition, because treatment of MS with biological agents did not become a widespread practice until the late 1990s, the inclusion of these older cases also explains the apparent low rate of treatment observed in the total MS population.

Strengths of our study include the large, population-based sample of cases and controls. Our study addressed important limitations of previous studies by comparing the rates of other conditions among MS patients to appropriately matched controls (matched on age, gender, KPNC facility and the duration and year of Kaiser membership). Other strengths include the inclusive MS case definition, the comprehensive list of autoimmune conditions examined and the careful identification of incident MS cases. To our knowledge, this is the first study of MS and associated conditions to examine the relative timing of diagnoses.

In summary, our study results suggest that MS may share etiological factors with IBD and uveitis but not with other autoimmune diseases. Our data add to a growing body of high-quality studies showing that people with MS are in general, not at increased risk of having other autoimmune diseases.

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