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Clinical study

The Occurrence of Autoimmune Diseases in Patients with Multiple Sclerosis and Their Families

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Abstract

The aims of this study were to determine whether the occurrence of autoimmune diseases is increased in patients with multiple sclerosis (MS) and their families and whether this is influenced by the type of MS. We conducted a case–control study using a questionnaire design to determine whether the prevalence of 11 autoimmune diseases is increased in patients with MS and their first-degree relatives compared to a random population control group and their first-degree relatives. We found that the total combined prevalence of the 11autoimmune diseases was higher in the MS patients than in the controls, with an odds ratio of 1.7 (95% confidence interval 0.9–3.2; P= 0.10) increasing to 1.9 (1.0–3.5; P= 0.05) after adjusting for age. For persons aged under 60 years, the odds ratio was 2.3 (1.1–4.6). We also found that there was a significant increase in the total combined prevalence of the autoimmune diseases in the first-degree relatives of MS patients compared to the first-degree relatives of the control group (P= 0.003, odds ratio 2.2, confidence interval 1.3–3.7). Patients with primary progressive MS did not differ from patients with relapsing–remitting or secondary progressive MS in the personal or familial occurrence of autoimmune disease. In conclusion, although there were sources of possible bias, this study suggests that individuals with MS have a genetic predisposition to autoimmunity in general.

Keywords: multiple sclerosis; autoimmune disease; autoimmunity; case–control study; genetics; family; primary progressive

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Introduction

There is increasing evidence that multiple sclerosis (MS) is an autoimmune disease.[1,2] Bias and colleagues have proposed that autoimmunity is inherited as an autosomal dominant trait with secondary genes, including major histocompatibility complex genes, determining the specific type of autoimmune disease.[3] Numerous case reports

have documented that MS can occur concurrently with other autoimmune disease including autoimmune thyroid disease,[4] autoimmune gastritis, [4] Addison's disease, [4] rheumatoid arthritis, [4] pemphigus vulgaris,[4]scleroderma,[5,6] primary biliary cirrhosis,[7–9] systemic lupus erythematosus[10] and ankylosing spondylitis.[11,12] A few studies have examined the prevalence of autoimmune diseases in patients with MS. Inflammatory bowel disease,[13] psoriasis [14] and type 1 diabetes mellitus [15] have been reported to occur more frequently in MS patients than in the general population, although one study found that rheumatoid arthritis, ankylosing spondylitis, type 1 diabetes mellitus, primary hypothyroidism and vitiligo were not increased. [16] No increase in total autoimmune diseases was found in studies comparing the prevalences in MS patients and the general population.[16,17]

Three case–control studies have suggested an association between MS and other autoimmune diseases by showing an increased occurrence of autoimmune diseases in MS cases compared to control groups.[18–20] Midgard and colleagues conducted a hospital-based interviewer questionnaire study of hospitalised patients and found that the total combined prevalence of rheumatoid arthritis, psoriasis and goitre was significantly higher in MS patients than in controls with mainly surgical diagnoses, although the individual diseases were not.[18] Seyfert and colleagues in a prospective case–control interview study found significantly increased occurrence of total autoimmune diseases in MS patients compared with a control group of unselected clinic personnel.[19] In a recent case–control study, Karni and Abramsky reported the increased occurrence of autoimmune thyroid disease in females with MS.[20] It has also been reported that the prevalence of elevated antinuclear antibodies and other auto antibodies is increased in MS patients compared to controls.[16,19,21,22]

A familial association of MS with other autoimmune diseases has been reported in studies on individual family pedigrees [3,23] but has not been demonstrated in case–control studies.[18,24] Inflammatory bowel disease was found to be increased in the families of MS patients compared to population prevalences in two studies.[25,26]

We have conducted a case–control study using a questionnaire design to compare MS patients and the general population. Our study aimed to determine whether 11 specific autoimmune diseases individually and as a total are more common in MS patients and in their first-degree relatives than in random population controls and their first-degree relatives. The study also examined whether the type of MS (relapsing–remitting, secondary progressive or primary progressive) influences the personal and familial occurrence of other autoimmune diseases.

Methods

The cases comprised patients admitted to the Royal Brisbane Hospital Department of Neurology between 1992 and 1997 with a diagnosis of clinically definite or laboratory-supported definite MS.[27] Of 216 cases identified by the International Classification of Diseases selection code 340, 205 had medical records that were able to be obtained. Of these, 158 had a diagnosis of clinically definite or laboratory-supported definite MS from the available documentation in the medical records. The type and duration of MS were also determined. One patient from Papua New Guinea was not included, leaving 157 cases. The majority of cases were from southeast Queensland but 27 had been referred from elsewhere in the state of Queensland and three from interstate for investigation. The address used for mailing purposes was the latest available from the hospital file.

Controls were selected from persons living in the same street (but not immediate neighbours) as the cases. The names and addresses of controls were obtained from the 1997 desktop marketing system (DtMS) database, an up-to-date telephone-based electronic directory. Only residential listings were used. The surname, first initial and address of three controls for each case were randomly selected using a search and retrieval system. Using the directory, addresses for street residents of 24 cases were unable to be found (including the three interstate patients) and fewer than three controls were able to be found for 19 cases. As the cases without addresses in the sampling frame had a prevalence of autoimmune diseases almost identical to that of all the cases, they were retained in the analysis to maximise power. Where two sets of initials (persons) were listed at the same telephone number, for half of the group a questionnaire was addressed to the household and for the other half of the group the questionnaire was sent to the person whose initials were listed second. Questionnaires were sent to a total of 362 controls.

All cases and controls were mailed a standard covering letter with only minor differences in the wording stating whether they were in the case or control group. The letter addressed to members of the control group stated that controls had been randomly selected as persons without MS. In the covering letter both groups were asked to indicate if they or family members had been definitely diagnosed with a disease. A second standard covering letter and questionnaire were mailed 4 weeks later to all those who had not responded to the initial questionnaire. The importance of a reply was stressed in this letter. All cases and controls received the same questionnaire with a reply-paid envelope.

The questionnaire asked for date of birth and gender. We used a list of autoimmune diseases, which included diseases used in previous studies of this type or those for which case reports have documented concurrence with MS, and which are likely to be known to the general population. From this list, respondents indicated personal, parental, sibling or offspring occurrence of an autoimmune disease. The autoimmune diseases selected were accompanied by alternative descriptions which are listed in **Table 1**.The respondents also indicated if a parent, sibling or offspring had MS. The final questionnaire that was used had been tested on unselected hospital patients and staff and found to be easily able to be completed in less than 2 minutes.

This study was approved by the Research Ethics Committee of the Royal Brisbane Hospital. Participation in the study was voluntary and corroboration of reporting of personal or family history of an autoimmune disease was not attempted.

Data collection was performed in 1998 and early 1999. Data were entered into the Microsoft Excel package and statistical analysis performed primarily with EPI Info 6. Where counts were small, Fisher's exact test was used, and exact 95% confidence intervals were calculated and stratified data were combined by maximum likelihood methods.[28]

Results

Of the 157 questionnaires sent to cases, 13 were returned because of an incorrect address and two were returned indicating the person was deceased. Of the remainder, 117 (82%) were returned completed. Of these 117 cases, 58 had relapsing–remitting MS, 41 had secondary progressive MS and 18 had primary progressive MS, as

defined by Lublin and Reingold. [29] Of these 117 cases, there were 722 first-degree relatives comprising 304 siblings, 234 parents and 184 children. From the 362 questionnaires sent to the control group, 32 were returned because of an incorrect address and two were returned indicating the addressed person was deceased. Of the remainder, 222 (68%) were returned completed. Of these 222 controls, there were 1582 first-degree relatives comprising 651 siblings, 444 parents and 487 children.

Table 1. List of autoimmune diseases in questionnaire

Crohn's disease or ulcerative colitis – types of inflammatory bowel disease
Psoriasis – a skin disease
Rheumatoid arthritis – a type of arthritis
Diabetes mellitus type 1 – childhood onset/insulin-dependent diabetes
Systemic lupus erythematosus – lupus or SLE
Hypothyroidism – underactive thyroid
Hyperthyroidism – overactive thyroid
Ankylosing spondylitis – a type of arthritis with the lower spine usually affected
Scleroderma – a connective tissue disease
Vitiligo – a skin disease where pigment is lost
Primary biliary cirrhosis – a type of liver disease

Table 2. Age distribution

Age bracket (range in years)	Number of cases	Number of controls	Total number
<20	2	3	5
20–29	11	18	29
30–39	22	41	63
40–49	34	49	83
50–59	35	46	81
60–69	9	30	39
70–79	4	23	27
80–89	0	11	11
Total number	117	221	338

Gender

Of the cases, 83 (71%) were females, as were 133 (60%) of the controls. The proportion of females in the case group was significantly higher than in the control group (P= 0.04).

Age

The age distributions of cases and controls are shown in Table 2. Proportionally more of the controls were aged 60 years and over (29%) than were the cases (11%) (P= 0.003). One control did not enter a date of birth correctly.

Autoimmune diseases in cases and controls

Twenty-four autoimmune diseases were reported in the cases and 29 in the control group. Twenty cases and 25 controls indicated personal occurrence of one autoimmune disease and two cases and two controls reported personal occurrence of two autoimmune diseases. The excess proportion of cases with one or more autoimmune diseases (19%) compared to controls (12%) did not quite reach formal statistical significance (P= 0.10, odds ratio 1.7, confidence interval 0.9–3.2). The occurrence of specific autoimmune diseases is shown in Table 3. There were apparent

excesses of inflammatory bowel disease, psoriasis and rheumatoid arthritis, in particular, among the cases but the small numbers prevent firm comment.

Table 3. Specific autoimmune diseases in cases and controls

Disease	Number of diseases in cases	Number of diseases in controls
Inflammatory bowel disease	3	0
Psoriasis	6	7
Rheumatoid arthritis	4	1
Diabetes mellitus type 1	1	2
Systemic lupus erythematosus	2	1
Hypothyroidism	3	8
Hyperthyroidism	3	7
Ankylosing spondylitis	1	1
Scleroderma	1	0
Vitiligo	0	2
Primary biliary cirrhosis	0	0
Total	24	29

Autoimmune diseases in first-degree relatives

Forty cases (34%) and 43 controls (19%) reported at least one first-degree relative with an autoimmune disease (P= 0.003, odds ratio 2.2, confidence interval 1.3–3.7). There were a total of 53 autoimmune diseases in the first-degree relatives of the cases and 60 in those of the controls. The specific autoimmune diseases occurring in first-degree relatives are shown in **Table 4**. Ankylosing spondylitis was the only disease that occurred much more frequently in the relatives of the cases; in particular, there was no excess of inflammatory bowel disease or psoriasis.

Autoimmune diseases according to gender and age

Of 83 female cases, 15 (18%) reported personal occurrence of an autoimmune disease as did seven of 34 male cases (21%). Seven different autoimmune diseases occurred in the male cases and the numbers are too small for meaningful analysis of specific autoimmune diseases in MS cases according to gender. Sixteen of the 133 female controls (12%) and 11 of the 89 male controls (12%) indicated a personal occurrence of an autoimmune disease. The odds ratios for males (1.8) and females (1.6) were similar. First-degree relatives were not categorised by gender. The prevalence of autoimmune disease in cases was similar at all ages (range 14–22%). This also held for controls up to the age of 59 years (mean 10%) but increased substantially in older persons (mean 19%). The age-specific odds ratio for autoimmune disease was 2.3 (95% confidence interval 1.1–4.6) in the persons under 60 years of age but only 0.8 (0.2–3.7) for older persons. The summary age-adjusted odds ratio was 1.9 (1.0–3.5; P= 0.05).

Familial MS

Nine cases and one control reported a first-degree relative with MS (P= 0.0002, odds ratio 18.4, confidence interval 2.3–393).

Type and duration of MS

The numbers of cases with different types of MS reporting the personal or familial occurrence of an autoimmune disease are shown in **Table 5**. There was no significant difference among the three types of MS in the reporting of a personal or familial

occurrence of autoimmune disease. The influence of the duration of MS was analyzed by comparing the occurrence of autoimmune diseases in those with MS for less than 10 years and those with MS for greater than 10 years. There was no marked difference in the occurrence of autoimmune diseases between the two groups.

Table 4. Specific autoimmune diseases in first-degree relatives

Disease	Number of diseases in relatives of cases	Number of diseases in relatives of controls
Inflammatory bowel disease	2	4
Psoriasis	9	17
Rheumatoid arthritis	11	14
Diabetes mellitus type 1	5	4
Systemic lupus erythematosus	6	7
Hypothyroidism	6	7
Hyperthyroidism	6	4
Ankylosing spondylitis	6	1
Scleroderma	1	0
Vitiligo	1	1
Primary biliary cirrhosis	0	1
Total	53	60

Table 5. Influence of the type of MS on association with autoimmune disease

Type of MS	Number with an autoimmune disease (%)	Number with a first degree relative with an autoimmune disease (%)
Relapsing-remitting ($n = 58$)	12 (21%)	18 (31%)
Secondary progressive ($n = 41$)	5 (12%)	12 (29%)
Primary progressive ($n = 18$)	5 (28%)	10 (56%)
Total ($n = 117$)	22 (19%)	40 (34%)

Discussion

The present study has shown that the prevalence of autoimmune diseases other than MS is higher in patients with MS and their first-degree relatives than in controls and their first-degree relatives. However, these results need to be considered in the light of a number of possible errors. In a small study of uncommon diseases, chance is obviously possible. Furthermore, errors of measurement and selection may occur. Measurement errors may be due to misclassification or to reporting bias. The potential for misclassification existed for both groups, with some common diseases possibly being mistakenly listed, and less common or difficult-to-diagnose diseases having been missed. Such similarly poor measurement for cases and controls will produce lower odds ratios than truly exist. Studies of this type are also prone to reporting bias: it is possible that cases may have been more likely than controls to report a personal or familial occurrence of an autoimmune disease, either from being more likely to visit medical services or because they may have been more motivated to discuss the questionnaire with relatives or to record an uncertain autoimmune disease. However, MS cases with cognitive impairment may have been less likely to report an

autoimmune disease, and the balance of these countervailing influences on the apparent effect (odds ratio) remains speculative.

With regard to selection errors, we believe the cases used in this study reflect the general MS population in Australia to a reasonable degree. The cases sampled included patients who had been recently diagnosed as having MS (and had required a hospital admission for cerebrospinal fluid examination), cases who had been admitted for intravenous methylprednisolone therapy for relapses, and cases of advanced MS with disabling symptoms. However, it is possible that milder cases of MS were underrepresented in our group of MS cases. As we selected only cases with clinically definite or laboratory-supported definite MS, the possibility of an incorrect diagnosis of MS is unlikely. With regard to selection errors in controls, it is certainly difficult to select the optimal control group for a set of cases drawn to a tertiary referral centre, but the appropriate principle is to use persons who, if they developed MS, would be likely to be referred to our unit. On this basis we chose persons living near the cases as being more appropriate than a random sample of the whole community since the cases were clearly not a random subset of all Brisbane cases.[30] However, the age distribution of our control group was different from that of the cases, with a higher proportion of controls aged 60 and over, and there was a trend for increased occurrence of autoimmune diseases with age in our control group. This may have reduced a true positive finding, as indicated by the increase in the odds ratio with age adjustment. The even higher odds ratio (2.3) for persons under 60 may be a more accurate reflection of the overall association. On the other hand, the prevalence of autoimmune diseases is higher in females than males, [31] and the proportion of females in our group of MS cases was higher than in our control group. However, in our study there was no difference between women and men in the occurrence of autoimmune diseases in cases or controls or in the total number of subjects studied.

Our finding of an increase in the total prevalence of autoimmune disease in patients with MS is consistent with the findings of two previous studies.[18,19] In our study, although inflammatory bowel disease was significantly more common in MS patients than in controls, the numbers were small and the confidence interval was wide. Rang and colleagues also found an increased prevalence of inflammatory bowel disease in patients with MS.[13] Our study did not find an increased prevalence of other specific autoimmune diseases with MS as has been shown in other studies, [13–15,20] but this is probably because of the small numbers in our study. Our study found a statistically significant doubling of autoimmune disease in the first-degree relatives of MS patients compared with the first-degree relatives of the control group. This was not shown in the study of Midgard and colleagues, who studied a smaller number of autoimmune diseases, [18] or in the study by Souberbielle and colleagues who did not provide details of the specific familial autoimmune diseases.[24] An increased occurrence of inflammatory bowel disease in families of MS patients compared with known disease prevalence rates has previously been reported.[25, 26] This was not demonstrated in the present study, perhaps because of the small numbers. Our study found a relative risk of 18 for MS in first-degree relatives which is consistent with the findings of large familial MS studies. [32, 33] We found that the occurrence of autoimmune diseases in individuals with MS and in their first-degree relatives was independent of the type or duration of MS. In particular, patients with primary progressive MS did not differ from patients with relapsing-remitting or secondary progressive MS in the personal or familial occurrence of autoimmune diseases. Our study provides further support for an association between MS and other autoimmune

diseases. We did not include all the autoimmune diseases that have been associated with MS, for example Goodpasture's disease, [34] myasthenia gravis, [35] uveitis, [36] and alopecia areata,[19] so it is possible that we have actually underestimated the occurrence of autoimmune diseases in MS patients and their families. The increased occurrence of autoimmune diseases in patients with MS and in their families suggests that individuals with MS may have a genetic predisposition to autoimmunity in general.

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References

1. Martin R, McFarland HF. Immunological aspects of experimental allergic encephalomyelitis and multiple sclerosis. Crit Rev Clin Lab Sci 1995; 32:121–182.
2. Pender MP. Multiple sclerosis. In: Pender MP, McCombe PA (eds).Autoimmune neurological disease. Cambridge: Cambridge University Press, 1995; 89–154.
3. Bias WB, Reveille JD, Beaty TH, Meyers DA, Arnett FC. Evidence that autoimmunity in man is a Mendelian dominant trait. Am J Hum Genet 1986; 39: 584–602.
4. Baker HWG, Balla JI, Burger HG, Ebeling P, Mackay IR. Multiple sclerosis and autoimmune diseases. Aust NZ J Med 1972; 3: 256–260.
5. Trostle DC, Helfrich D, Medsger TA. Systemic sclerosis (scleroderma) and multiple sclerosis. Arthritis Rheum 1986; 29: 124–127.
6. Jawad SH, Askari A, Ward AB. Case history of a patient with multiple sclerosis and scleroderma. Br J Rheumatol 1997; 36: 502–509.
7. Taub WH, Lederman RJ, Tuthill RJ, Falk GW. Primary biliary cirrhosis in a patient with multiple sclerosis. Am J Gastroenterol 1989; 84: 415–417.
8. Pontecorvo MJ, Levinson JD, Roth JA. A patient with primary biliary cirrhosis and multiple sclerosis. Am J Med 1992; 92: 433–436.
9. Noseworthy JH, Ebers GC. Primary biliary cirrhosis and multiple sclerosis. AmJ Gastroenterol 1989; 84: 1584–1585.
10. Kinnunen E, Muller K, Keto P, Ketonen L, Helve T, Sepponen R. Cerebrospinal fluid and MRI findings in three patients with multiple sclerosis and systemic lupus erythematosus. Acta Neurol Scand 1993; 87: 356–360.
11. Khan MA, Kushner I. Ankylosing spondylitis and multiple sclerosis. Arthritis Rheum 1979; 22: 784–786.
12. Whitman GJ, Khan MA. Unusual occurrence of ankylosing spondylitis and multiple sclerosis in a black patient. Cleve Clin J Med 1989; 56: 819–822.
13. Rang EH, Brooke BN, Hermon-Taylor J. Association of ulcerative colitis with multiple sclerosis. Lancet 1982; 2: 555.
14. Cendrowski W. Multiple sclerosis and psoriasis. Wiad Lek 1989; 42: 575–578.
15. Wertman E, Zilber N, Abramsky O. An association between MS and type 1diabetes mellitus. J Neurol 1992; 239: 43–45.
16. De Keyser J. Autoimmunity in multiple sclerosis. Neurology 1988; 38:371–374.
17. Wynn DR, Rodriguez M, O'Fallon M, Kurland LT. A reappraisal of the epidemiology of multiple sclerosis in Olmsted County, Minnesota. Neurology1990; 40: 780–786.

18. Midgard R, Grønning M, Riise T, Kvåle G, Nyland H. Multiple sclerosis and chronic inflammatory diseases. Acta Neurol Scand 1996; 93: 322–328.
19. Seyfert S, Klapps P, Meisel C, Fischer T, Junghan U. Multiple sclerosis and other autoimmune diseases. Acta Neurol Scand 1990; 81: 37–42.
20. Karni A, Abramsky O. Association of MS with thyroid disorders. Neurology 1999; 53: 883–885.
21. Barned S, Goodman AD, Mattson DH. Frequency of anti-nuclear antibodies in multiple sclerosis. Neurology 1995; 45: 384–385.
22. Collard RC, Koehler RP, Mattson DH. Frequency and significance of antinuclear antibodies in multiple sclerosis. Neurology 1997; 49: 857–861.
23. McCombe PA, Chalk JB, Pender MP. Familial occurrence of multiple sclerosis with thyroid disease and systemic lupus erythematosus. J Neurol Sci 1990; 97:163–171.
24. Souberbielle BE, Martin-Mondiere C, O'Brien ME, Carydakis C, Cesaro P, Degos JD. A case-control epidemiological study of MS in the Paris area with particular reference to past disease history and profession. Acta Neurol Scand1990; 82: 303–310.
25. Sadovnick AD, Paty DW, Yannakoulias G. Concurrence of multiple sclerosis and inflammatory bowel disease. N Engl J Med 1989; 321: 762–763.
26. Minuk GY, Lewkonia RM. Possible familial association of multiple sclerosis and inflammatory bowel disease. N Engl J Med 1986; 314: 586.
27. Poser CM, Paty DW, Scheinberg L, et el. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13: 227–231.
28. Martin D, Austin H. An efficient program for computing conditional maximum likelihood estimates and exact confidence limits for a common odds ratio. Epidemiology 1991; 2: 359–362.
29.Lublin F, Reingold SC. Defining the clinical course of multiple sclerosis. Neurology 1996; 46: 907–911.
30. Rothman KJ. Modern epidemiology. Boston: Little Brown, 1986.
31. Jacobson DL, Gange SJ, Rose NR, Graham NMH. Epidemiology and estimated population burden of selected autoimmune disease in the United States. Clin Immunol Immunopathol 1997; 84: 223–243.
32. Sadovnick AD, Baird PA, Ward RH. Multiple sclerosis: updated risks for relatives. Am J Med Genet 1988; 29: 533–541.
33. Robertson NP, Fraser M, Deans J, Clayton D and Compston DAS. Age adjusted recurrence risks for relatives of patients with multiple sclerosis. Brain1996; 119: 449–455.
34. Henderson RD, Saltissi D, Pender MP. Goodpasture's disease associated with multiple sclerosis. Acta Neurol Scand 1998; 98: 134–135.
35. Somer H, Muller K, Kinnunen E. Myasthenia gravis associated with multiple sclerosis. Epidemiological survey and immunological findings. J Neurol Sci1989; 89: 37–48.
36. Biousse V, Trichet C, Bloch-Michel E, Roullet E. Multiple sclerosis associated with uveitis in two large clinic-based series. Neurology 1999; 52: 179–181.