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The age-range of risk of developing multiple sclerosis

Evidence from a migrant population in Australia

S. R. Hammond,[1] D. R. English[2] and J. G. McLeod[1]

[1]*Department of Medicine, University of Sydney and* [2]*Department of Public Health, University of Western Australia, Nedlands, Australia*

Correspondence to: Professor J. G. McLeod, Department of Medicine, University of Sydney, NSW 2006, Australia

Summary

The prevalence of multiple sclerosis in the Australian-born population in five different regions of Australia has a strong correlation with latitude, the disease becoming increasingly prevalent with increasing south latitude. In this study, the prevalence in the migrant population from the UK and Ireland (UKI) in the different regions also showed a significant correlation with latitude, but this relationship was strongly influenced by the high prevalence in Hobart. Except for Hobart, the prevalence in migrants was considerably less than that in their countries of origin. The prevalence of multiple sclerosis among those migrating before the age of 15 years from the high-risk UKI to lower-risk Australia was not significantly different to that among those migrating at or after that age, and this finding was confirmed in a case-control study which demonstrated little association between age at migration and risk of developing multiple sclerosis. These findings suggest that the risk from environmental factors in multiple sclerosis may operate over a period of many years and not only in childhood and early adult life.

Keywords: multiple sclerosis; migration studies; prevalence; age-risk; case-control study

Abrreviations: SD = statistical division; UKI = UK and Ireland

Introduction

A number of migration studies have suggested that the risk of developing multiple sclerosis is largely determined before the age of 15 years (Alter *et al*., 1966, 1971, 1978; Dean and Kurtzke, 1971; Detels *et al*., 1978; Dean and Elian, 1997) or at least within the first 2 decades (Kurtzke *et al*., 1985). Australia is a particularly suitable country in which to study the effects of migration on the risk of developing multiple sclerosis, because, in recent years, large numbers of people have immigrated there from countries where the prevalence of multiple sclerosis is considerably higher than that in native-born Australians. Moreover, since a very thorough and extensive study of the epidemiology of multiple sclerosis was undertaken in Australia with a prevalence day in 1981 that coincided with a national census, it seemed opportune to base a migration study on these data (Hammond *et al*., 1987, 1988*a*, *b*, *c*, 1989*a*, *b*; McLeod *et al*., 1994). The main source of migrants has been the UK and Ireland (UKI) which are known to be in a high-risk zone for multiple sclerosis (Kurtzke 1975, 1980). Prevalence rates in excess of 110 per 100 000 of population have been recorded in Scotland (Phadke and Downie, 1987), Wales, (Swingler and Compston, 1986), south London (Williams and McKeran, 1986) and Cambridgeshire (Robertson *et al*., 1996) and a slightly lower figure in the Southampton region (Roberts *et al*., 1991). Such figures considerably exceed those found in recent epidemiological surveys of Australia (Hammond *et al*., 1987, 1988*a*, *b*, 1989*a*; McLeod *et al*., 1994).

The Australian surveys also established that there was a strong association between multiple sclerosis frequency and latitude, with prevalence increasing more than sixfold between tropical Queensland in the north (Hammond *et al*., 1987) and the statistical division (SD) of Hobart, Tasmania, in the south (Hammond *et al*., 1988*a*). These findings were supported by mortality data (Hammond *et al*., 1989*a*).

In the present study, the age range of risk of developing multiple sclerosis was investigated with three analyses. First, the relationship between multiple sclerosis prevalence and latitude was compared in the Australian-born and UKI-born populations for areas of Australia. Data from the 1981 national census indicated that in each area of Australia ~80% of the UKI-born migrants were from England and that ~70% of them had migrated at or over the age of 15 years. Hence, if the risk of acquiring multiple sclerosis is largely decided by the age of 15 years, the latitude gradient of multiple

sclerosis in Australia should have been more evident for native-born Australians than for UKI-born migrants. Secondly, the prevalence of multiple sclerosis in UKI-born patients according to whether they migrated before the age of 15 or at 15 years or older was analysed. Thirdly, the effects of age at migration to Australia and duration of residence in Australia on the risk of acquiring multiple sclerosis were examined in a case-control study by comparing UKI-born migrants who developed multiple sclerosis with a matched control group.

Methods

Population figures by birthplace were available from each of the survey areas from the national census taken on June 30, 1981; this date was chosen as the prevalence date for the survey.

The methods of case ascertainment and determination of prevalence rates of multiple sclerosis were similar in each survey area and have been fully described elsewhere (Hammond *et al*., 1987, 1988*a*; McLeod *et al*., 1994). Permission for the neurologists conducting the survey to contact patients was obtained in each area, and subsequently these patients were personally interviewed and examined to document the history and to confirm the diagnosis. Patients who were born in the UK or Ireland and whose disease onset occurred prior to migration to Australia were excluded from analyses in the present study, since they provide no information about how the risk of disease is affected by migration to a low-risk area.

Prevalence of multiple sclerosis by country of birth and place of residence in Australia

The purpose of this analysis was to compare the trends in prevalence of multiple sclerosis by latitude in the Australian-born and UKI-born populations; a latitude gradient in prevalence among the UKI-born population would suggest that the Australian environment had affected their risk of disease.

This analysis was confined to the Australian-born and UKI-born populations of five survey areas, namely the states of Queensland, Western Australia, New South Wales, South Australia and the Hobart SD in the state of Tasmania. Forty-two per cent of migrants were born in the UKI. For the purpose of examining the relationship between multiple sclerosis prevalence and latitude, a mean latitude was calculated for the four states from the population distribution in their respective SDs at the 1981 census.

In each area, directly standardized prevalence rates per 100 000 were calculated from the age-specific rates (in 10-year groups) standardized to the age distribution of the whole Australian population in 1981 (Hammond *et al*., 1987, 1988*a*, *b*, *c*). Prevalence was calculated for all ages, and age-standardization was based on the age groups 0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69 and 70+ years. In addition, prevalence ratios (relative to the prevalence in Queensland) and their 95% confidence intervals were calculated from a Poisson regression model (Frome, 1983) in which the number of cases was considered to be the (Poisson) response variable and the population size was declared to be an offset term. Prevalence was modelled as a function of age (in the same categories as described above except that the age group 0–9 years was omitted as no patient was less than 10 years of age in 1981), sex, place of residence in Australia and country of birth.

Trends in multiple sclerosis prevalence by latitude were examined by fitting a single linear term for latitude in the regression model. Adding a country of birth by a latitude interaction term tested the hypothesis that the trends were the same in the Australian- and UKI-born populations.

Prevalence of multiple sclerosis among UKI-born migrants by age at migration to Australia

To facilitate comparisons with the findings of previous multiple sclerosis migration studies, the prevalence among the UKI-born population in each area was calculated for two categories of age at migration to Australia: <15 and >15 years of age. Because Hobart is a high-risk area for multiple sclerosis (Hammond *et al*., 1988*a*) patients in this city were not included in this analysis or the case-control study. Age at migration of the patients was obtained at interview; four patients with unknown age at arrival in Australia were excluded. The analysis was restricted to patients who were 20–49 years of age. Only two UKI-born patients were <20 years of age. The upper age limit was necessary because of limitations in available census data. Census tables were provided that cross-classified duration of residence in 1981 with age in 1981. Age in 1981 was tabulated in 5-year intervals, while duration of residence was tabulated in single years to 34 years, but in a single group for those migrants with residences of 35 years or more. Thus, it was impossible to assign the age at migration as <15 or >15 years for migrants 50 years of age or older who had been in Australia at least 35 years.

Within the age group 20–49 years, there was uncertainty about whether migrants arrived in Australia before age 15 or at age 15 years or older for ~5% of the population because of the grouping of age in 5-year intervals. For example, there were 201 migrants in New South Wales in the age group 45–49 years who had resided in Australia for 34 years (i.e. had ages of arrival from 11 to 15 years). To estimate the age at arrival, it was assumed that the age distribution within each interval was uniform, and a new table was constructed giving duration of residence by age in single years. For example, 40 of the migrants mentioned above were considered to be 45 years of age, another 40 migrants to be 46 years of age, etc. The calculated age had to be at least as great as the duration of residence in Australia (e.g. for the age group

15–19 years and period of residence 17 years, the group was divided evenly into ages 17, 18 and 19 years). Finally, the age at arrival was calculated by subtracting the period of residence in Australia in 1981 from the age (in single years) in 1981.

The prevalence in each survey area was adjusted, in 10-year age groups, to the age distribution of the Australian population in 1981. No adjustment was made for sex, since the distribution of age at migration did not differ by sex. The prevalence ratio for age at migration (>15 relative to <15 years) was obtained from a Poisson regression analysis with adjustment for age. Place of residence was not included in the model because it was not associated with age at migration.

This analysis had a potential for bias towards finding a higher prevalence among those migrating before age 15 years because, for the onset of disease to have occurred in Australia and for patients to have been diagnosed before the prevalence survey, they had most probably lived in the country for some time. Clearly, patients with long duration of residence in Australia are likely to have arrived early in life. To reduce this potential bias, a second analysis was restricted to those aged 30–49 years.

Case-control study of age at migration and duration of residence in Australia

The purpose of this analysis was to avoid any bias associated with long duration of residence in Australia caused by the delay between onset of disease and the prevalence survey. The cases for this analysis were the same as those used in the analysis of prevalence by age at migration and did not include migrants to the high-risk region of Hobart. Controls were identified from the cross-classified tables of duration of residence by single years of age discussed above. Twenty controls were selected at random for each case, individually matched by state of residence in Australia and exact age. They were also required to be resident in Australia at the time of disease onset in the matched case.

To determine the effect of length of residence in Australia on the prevalence of multiple sclerosis, the period of residence prior to disease onset for each case was calculated by subtracting the age at migration from the age at onset. This variable was also calculated for controls, in whom the length of residence was taken to be the difference between the total period of residence and the duration of disease of the matched case. In the analysis, length of residence was divided into four groups based upon quartiles of the distribution in controls.

The data were analysed by conditional logistic regression (Breslow and Day, 1980) to obtain prevalence odds ratios for age at migration and length of residence prior to onset of disease.

Because multiple sclerosis is a rare disease, the prevalence odds ratios thus obtained are good estimates of the corresponding prevalence ratios.

Results

Prevalence of multiple sclerosis by country of birth and place of residence in Australia

The prevalence of multiple sclerosis in the Australian-born population increased steadily with increasing south latitude ($P < 0.001$ for log linear term), although the prevalence in South Australia was lower than expected (Table 1). A similar relationship for latitude was also seen in the UKI population ($P < 0.001$ for log linear term), but it should be noted that this finding is strongly influenced by the high prevalence of multiple sclerosis in the relatively small numbers of migrants to Hobart. We tested whether the latitude gradients were the same in Australian-born and UKI-born populations by fitting an interaction between country of birth and survey area, but the interaction was not significant ($P = 0.09$).

When the variable sex was removed from the regression model for the UKI-born patients, the prevalence ratios for each place of residence in Australia did not change appreciably. In addition, there was no interaction between sex and place of residence ($P = 0.93$). Sex was therefore omitted from the regression analysis of prevalence in the UKI-born population, in which age at migration was included as a variable.

Prevalence of multiple sclerosis by age at migration

Of the 331 patients from the UKI with disease onset after migration to the four mainland states, 208 were aged 20–49 years in 1981.

Although the prevalence of multiple sclerosis was higher in those who migrated before the age of 15, the finding is subject to bias in this direction (see Methods) and there was no significant difference between the two groups (Table 2).

Case-control study of age at migration and duration of residence in Australia

There appeared to be little association between age at migration and risk of developing multiple sclerosis (Table 3). The prevalence odds ratio for those migrating at or after the age of 15 years was less than that for those migrating before the age of 15 years, but the difference could have been due to chance alone ($P = 0.55$). No persuasive evidence for a relationship between duration of residence in Australia and risk of multiple sclerosis was seen (Table 4).

Discussion

Most studies of migrant populations that relate alterations in the risk of developing multiple sclerosis to the age of migration have suggested that the critical age is ~15 years (Alter *et al*., 1966, 1971, 1978; Dean and Kurtzke, 1971; Detels *et al*., 1978; Dean and Elian, 1997). Thus, populations migrating before the age of 15 from high- to low-risk zones acquired the low-risk status of the country to which they had

Table 1 *Prevalence of multiple sclerosis for all ages in each survey area in 1981 by country of birth*

Survey area	Latitude °S	Patients	Prevalence*	Prevalence ratio†	95% confidence interval
Australian-born					
Queensland	25.1	324	17.7	1.00	–
Western Australia	31.3	181	23.4	1.30	1.09–1.56
New South Wales	33.4	1572	42.2	2.32	2.06–2.61
South Australia	34.9	282	31.9	1.77	1.50–2.07
Hobart SD	42.8	94	68.4	3.84	3.05–4.83
UKI-born					
Queensland	25.1	50	24.7	1.00	–
Western Australia	31.3	62	25.9	1.00	0.69–1.46
New South Wales	33.7	161	36.6	1.36	0.99–1.86
South Australia	34.9	48	23.0	0.91	0.61–1.36
Hobart SD	42.8	18	121.5	4.71	2.75–8.07

The age group 0–9 years was excluded from this analysis because it had no cases. *Adjusted for sex and for age in 10-year groups to the age distribution of the 1981 Australian population; †adjusted for sex and for age in 10-year groups in a Poisson regression model.

Table 2 *Prevalence of multiple sclerosis by age at migration among migrants to Australia from the UKI aged 20–49 years*

	Age at migration to Australia (years)				Prevalence ratio†	95% confidence interval
	<15		>15			
	Patients	Prevalence*	Patients	Prevalence		
Age 20–49 years in 1981						
Queensland	11	43	14	21	–	–
Western Australia	9	64	27	28	–	–
New South Wales	30	73	86	65	–	–
South Australia	7	38	24	33	–	–
All areas	57	60	151	44	0.83	0.59–1.17 ($P = 0.29$)
Age 30–49 years in 1981‡						
Queensland	10	66	14	35	–	–
Western Australia	7	98	27	47	–	–
New South Wales	19	95	80	92	–	–
South Australia	4	53	24	54	–	–
All areas	40	83	145	65	0.90	0.62–1.30 ($P = 0.57$)

*Adjusted in 10-year age groups to the age distribution of the 1981 Australian population. †Ratio of prevalence in the >15-years group to prevalence in the <15-years group, adjusted for age in 10-year groups in a Poisson regression model. State of residence was not included in the regression model because it was not associated with age at migration. ‡This subgroup of 185 of 208 migrants has been analysed separately to reduce bias towards finding a higher prevalence in those migrating before age 15 years (see Methods).

Table 3 *Prevalence odds ratios for multiple sclerosis by age at migration among migrants to Australia from the UKI (age 20–49 years in 1981)*

Age at migration (years)	Cases	Controls	Odds ratio	95% confidence interval	*P*-value
<15	61 (29%)	1193 (29%)	1.00	–	–
>15	147 (71%)	2967 (71%)	0.96	0.67–1.37	0.81
Total	208	4160	–	–	–

migrated, but took the high-risk status with them if they migrated after the age of 15 years. Dean and Elian found that immigrants to England from India and Pakistan at an age younger than 15 years had a higher risk of developing multiple sclerosis than those immigrating after that age (Dean and Elian, 1997). This finding necessarily implies that the risk of acquiring multiple sclerosis is largely determined by the age of 15 years. A similar conclusion has been reached by studies using other types of data (Schapira *et al*., 1963; Kurtzke, 1965; Beebe *et al*., 1967). However, the study of Detels and colleagues suggested that the risk of acquiring multiple sclerosis of those migrating southwards from the higher-risk northern regions of the USA could still be modified if they migrated after the age of 15 years, although the effect was not as marked as for those migrating before that age (Detels *et al*., 1978). Furthermore, in an earlier

Table 4 *Prevalence odds ratios for multiple sclerosis by duration of residence in Australia prior to onset of disease among migrants to Australia from the UKI*

Duration of residence (years)	Cases	Controls	Odds ratio	95% confidence interval	*P*-value
0–4	59 (28%)	1198 (29%)	0.88	0.60–1.30	–
5–9	51 (25%)	1083 (26%)	0.84	0.57–1.26	–
10–14	37 (18%)	770 (18%)	0.87	0.56–1.37	–
>15	61 (29%)	1109 (27%)	1.00	–	0.52
Total	200	4000	–	–	–

migrant study based on mortality statistics, Detels and colleagues concluded that aetiological factors may still be operative as late as the third to fourth decade of life in high-risk areas (Detels *et al*., 1972). Analysis of the data from the multiple sclerosis studies of the Faroe Islands (Kurtzke and Hyllested, 1979, 1986; Fischman, 1981) has also suggested that the age range of acquisition of multiple sclerosis may be considerably wider, and a recent review and analysis of published data (Gale and Martyn, 1995), along with our findings that migrants to Australia from UKI who migrated after age 15 years had a lower prevalence of multiple sclerosis, support this view.

Some of the difficulties of studying multiple sclerosis in migrant populations have been described previously. These factors include the probability that migrants are unlikely to be typical of the general population of a country which they have left in age, social class or general health; there may be restrictions on race, age and education of migrants to the country to which they emigrate, and the accuracy of studies depends on having adequate numbers of migrants and taking note of their ages at immigration, their length of stay in the new land, and their ages at prevalence day (Kurtzke, 1976; Poser, 1994; Gale and Martyn, 1995). Some of these difficulties have been overcome in the present study by confining it to migrants from the UKI from which stock most of the Australian population was derived in 1981, controlling adequately for age, and noting ages at immigration and length of stay. No doubt there was some bias in selection of migrants, but exclusion on medical grounds would have applied only to people with significant neurological disabilities, and we have not considered cases who had established multiple sclerosis on entry to Australia. It may be noted that the number of cases of multiple sclerosis in migrants is relatively small (208 under the age of 50 years), but it is adequate for statistical analysis, and the confidence intervals around the ratios (comparing ages <15 with >15 years) were narrow.

About 70% of the UKI-born population in each survey area in Australia migrated after the age of 15 years. If the risk of multiple sclerosis is largely decided by this age, they should have brought with them their high-risk multiple sclerosis status, and the prevalence of multiple sclerosis in the group should have been the same in each survey area. On the other hand, those who migrated before the age of 15 years should have developed multiple sclerosis at the same rate as the respective Australian-born populations in each area and would therefore have shown the clear relationship of latitude exhibited by native-born Australians. Thus, multiple sclerosis in the UKI-born population should have shown a slight frequency gradient with latitude but one which was considerably less than that observed in the Australian-born population (Table 1). There was a similar prevalence in all mainland states, but the prevalence in Hobart was substantially higher. Although the numbers are small, the difference was statistically significant.

A further expectation for the UKI-born population in each survey area was that the prevalence of multiple sclerosis among them would not be substantially lower than that among their non-migrating countrymen, since 70% migrated after the age of 15 years at which age it has been proposed the disease is established. In a survey in southern England (Williams and McKeran, 1986) a crude multiple sclerosis prevalence of 115 per 100 000 was found, which, after adjustment for age and sex to the distribution of the 1981 Australian population, gave a figure of 99.4 per 100 000 (95% confidence interval 86.2–114.66). With the notable exception of the Hobart SD, this figure clearly exceeded the prevalence rate found in the UKI-born populations in each survey area of Australia. The considerable difference in multiple sclerosis frequency between migrants from the UKI to Australia and non-migrants is also supported by mortality data. Multiple sclerosis mortality in the UKI-born migrant population dying in Australia between 1961 and 1981 was found to be similar to that of the Australian-born population and very much lower than that found in the UKI (Hammond *et al*., 1989*a*; Dean and Elian, 1993).

Immigrants moving from a high-risk country for multiple sclerosis to one of lower risk have generally shown a prevalence rate intermediate between their country of origin and the host country, and part of the difference is thought to relate to a decreased likelihood of migration amongst people with established multiple sclerosis (Acheson, 1985). Could such a phenomenon explain the findings of the UKI-born populations in Australia in the present study? Although the numbers are small, the similarity between multiple sclerosis prevalence in the UKI-born population in the Hobart SD and that found in the UKI argues against this postulate, and there is no evidence that this factor would differ markedly in different areas of Australia. The possibility that the higher prevalence of multiple sclerosis in UKI-born migrants in

Hobart SD is due to differential immigration, with a preponderance of Scots in Hobart, has been addressed since it is known that multiple sclerosis has a higher frequency in Scots and that they have a significantly higher likelihood of carrying the multiple sclerosis-associated HLA-DR2 antigen (Swingler and Compston, 1986). There was no difference between the proportions of those with probable Scottish origin or in the frequency of HLA-DR2 in the different survey areas (Hammond *et al*., 1989*b*; Miller *et al*., 1990).

The most likely explanation for the low prevalence of multiple sclerosis among UKI-born migrants to Australia is that the risk of developing multiple sclerosis, rather than it being largely decided by the age of 15 years, actually spans a much wider age range, as suggested by some other studies (Detels *et al*., 1972, 1978; Kurtzke and Hyllested, 1979, 1986; Fischman, 1981). Such a situation would mean that a much larger proportion of the UKI-born migrant population was subject to the lower risk of developing multiple sclerosis in Australia than that found in their non-migrating countrymen.

A constraint on the present study, which was inherent in the fact that its data were derived from a point prevalence survey, was the need to use prevalence measures as estimators of incidence measures, although there was little evidence to suggest that this factor had any influence over the results pertaining to age at migration and prevalence by place of residence.

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