Multiple sclerosis in Finland: incidence trends and differences in relapsing remitting and primary progressive disease courses

M-L Sumelahti, P J Tienari, M Hakama, J Wikström

Objective: To compare the secular trends and geographical differences in the incidence of relapsing-remitting (RRMS) and primary progressive multiple sclerosis (PPMS) in Finland, and to draw inferences about aetiological differences between the two forms of the disease.

Methods: New multiple sclerosis cases in southern Uusimaa and the western districts Vaasa and Seinäjoki of Finland in 1979–1993 were verified from hospital records and classified into RRMS and PPMS. Patients met the Poser criteria for definite multiple sclerosis or otherwise satisfied the criteria for PPMS. Disease course was categorised by the same neurologist. Crude and age adjusted incidence in 1979–1993 was estimated.

Results: During 1979–1993 the age adjusted incidence was 5.1 per 100 000 person-years in Uusimaa, 5.2 in Vaasa, and 11.6 in Seinäjoki. The rates in Uusimaa remained stable, while a decrease occurred in Vaasa and an increase in Seinäjoki. Between 1979–86 and 1987–93 the incidence of PPMS increased in Seinäjoki from 2.6 to 3.7 per 100 000 and decreased in Vaasa from 1.9 to 2.2 per 100 000; the trends were similar for RRMS.

Conclusions: There are significant differences in secular trends for multiple sclerosis incidence in Finland by geographical area, but these are similar for PPMS and RRMS. The recent changes point to locally acting environmental factors. The parallel incidence trends for RRMS and PPMS suggest similar environmental triggers for the two clinical presentations of multiple sclerosis.
Incidence calculations

The calculations were based on definite cases of multiple sclerosis. Incidence was calculated from 1 January 1979 to 31 December 1993 per 100,000 person-years in age groups from 10 to 69 years and in calendar time intervals. The significance of the trend was assessed by classifying the total time period into five year age groups (1979–1986 and 1987–1993) to reduce random variation caused by small numbers. As the crude rates may be misleading when comparing two calendar periods, the rates were standardised for age by an indirect method. The standard rates in each district were those of 1979–1986 in each age group. The resulting standardised rate (SIR) is the ratio of the observed cases in 1987–1993 to those expected if the age specific rates had been those of 1979–1986. Confidence intervals (CI) were calculated assuming that the observed number of cases followed a Poisson distribution.

RESULTS

In 1979–1993 the total number of cases was 1066, 828 (78%) in the RRMS group and 238 (22%) in the PPMS group. The number of cases was 736 in Uusimaa, 240 in Seinäjoki, and 90 in Vaasa. The clinical and pathological characteristics of the material are presented in table 1. CSF intrathecal IgG synthesis, which was found in over 90% of the cases tested, showed no significant differences between PPMS and RRMS groups or between the districts. A lower female to male ratio (F/M) was observed among PPMS cases in each district (1.2–2.0) than among RRMS cases (1.8–2.7). The F/M ratio was especially low for PPMS in Seinäjoki (1.2), as was the ratio for all cases (1.6). Mean age at diagnosis was greater for PPMS (40.5 years) than for RRMS (37.5 years), and the age at diagnosis was generally greater in the western districts of Vaasa and Seinäjoki than in Uusimaa. At onset there was a higher proportion of motor symptoms in Seinäjoki (30%) than in the other districts, and the ratios of motor symptoms to other symptoms by disease course were higher for PPMS in Seinäjoki (0.9) and lower for RRMS in Uusimaa (0.1). The incidences of total multiple sclerosis, RRMS, and PPMS were similar in Uusimaa and Vaasa, but twofold higher in Seinäjoki. The difference in incidence between the RRMS and PPMS groups was somewhat larger (4.6) in Seinäjoki and about the same in Uusimaa and Vaasa (3.1 and 2.8) (table 2). Trends by five year age groups were stable in Uusimaa but showed an increase in Seinäjoki and a decrease in Vaasa. This trend was similar for RRMS and PPMS (fig 2). Owing to small numbers, especially in Vaasa district (n=90), the time period 1979–1993 was divided into two periods only (1979–1986 and 1987–1993). The incidence of PPMS increased in Seinäjoki from 2.6 to 3.7 per 10^5 person-years and decreased in Vaasa from 1.9 to 0.2. The trends were similar for RRMS. The decrease in total and PPMS incidences in Vaasa was statistically significant, but not the decrease in RRMS. Similarly, the increase in Seinäjoki was statistically significant for total multiple sclerosis and PPMS but not for RRMS (table 2).

DISCUSSION

Over successive studies from the 1960s, Finland has been shown to belong to a high risk region for multiple sclerosis. The early observation of a high risk in the western district of Seinäjoki became more evident in the early 1990s, when an incidence of 13/10^5 person-years was four times higher than the rates in neighbouring Vaasa (3/10^5) and southern Uusimaa (5/10^5). The rate in Seinäjoki was among the highest reported worldwide. In the present study we show that the secular trend in 1979 to 1993 was increasing in Seinäjoki, decreasing...
Table 2 Number of cases of multiple sclerosis, incidence per 100 000 person-years in the age group 10 to 69 years, and standardised incidence ratios by calendar time, district, and disease course, 1979 to 1993

<table>
<thead>
<tr>
<th>District</th>
<th>Disease course</th>
<th>Calendar time</th>
<th>1979 to 1986</th>
<th>N</th>
<th>I</th>
<th>SIR</th>
<th>CI</th>
<th>1987 to 1993</th>
<th>N</th>
<th>I</th>
<th>SIR</th>
<th>CI</th>
<th>1979 to 1993</th>
<th>N</th>
<th>I</th>
<th>SIR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uusimaa</td>
<td>RRMS</td>
<td>301</td>
<td>4.1 Reference</td>
<td>290</td>
<td>4.2</td>
<td>1.0</td>
<td>0.9 to 1.2</td>
<td>591</td>
<td>4.1</td>
<td>3.8 to 4.5</td>
<td></td>
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<tr>
<td>PPMS</td>
<td>75</td>
<td>1.0 Reference</td>
<td>70</td>
<td>1.0</td>
<td>1.0</td>
<td>0.8 to 1.3</td>
<td>145</td>
<td>1.0</td>
<td>0.8 to 1.2</td>
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<tr>
<td>Total</td>
<td>376</td>
<td>5.1 Reference</td>
<td>360</td>
<td>5.2</td>
<td>1.0</td>
<td>0.9 to 1.1</td>
<td>736</td>
<td>5.1</td>
<td>4.8 to 5.5</td>
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<tr>
<td>Vaasa</td>
<td>RRMS</td>
<td>42</td>
<td>4.2 Reference</td>
<td>27</td>
<td>3.1</td>
<td>0.7</td>
<td>0.5 to 1.1</td>
<td>69</td>
<td>4.0</td>
<td>3.0 to 4.9</td>
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<tr>
<td>PPMS</td>
<td>19</td>
<td>1.9 Reference</td>
<td>2</td>
<td>0.2</td>
<td>0.1</td>
<td>0.02 to 0.4</td>
<td>21</td>
<td>1.2</td>
<td>0.7 to 1.7</td>
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<tr>
<td>Total</td>
<td>61</td>
<td>6.0 Reference</td>
<td>29</td>
<td>3.3</td>
<td>0.5</td>
<td>0.4 to 0.8</td>
<td>90</td>
<td>5.2</td>
<td>4.1 to 6.3</td>
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<tr>
<td>Seinäjoki</td>
<td>RRMS</td>
<td>83</td>
<td>6.8 Reference</td>
<td>85</td>
<td>7.9</td>
<td>1.2</td>
<td>0.9 to 1.4</td>
<td>168</td>
<td>8.5</td>
<td>6.9 to 9.3</td>
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<tr>
<td>PPMS</td>
<td>32</td>
<td>2.6 Reference</td>
<td>40</td>
<td>3.7</td>
<td>1.4</td>
<td>1.02 to 1.9</td>
<td>72</td>
<td>3.5</td>
<td>2.7 to 4.3</td>
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<tr>
<td>Total</td>
<td>115</td>
<td>9.4 Reference</td>
<td>125</td>
<td>11.6</td>
<td>1.2</td>
<td>1.03 to 1.5</td>
<td>240</td>
<td>11.6</td>
<td>10.1 to 13.1</td>
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CI, confidence interval; I, incidence; N, number of cases; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SIR, standardised incidence ratio.

...
cases in our incidence data—78% in the RRMS group and 22% in the PPMS group—follows the common pattern, as do the demographic features: PPMS is commonly observed among men and is associated with a later age of onset and the likelihood of initial motor symptoms. Given the recent increase in incidence among men in Seinäjoki, and a lower F/M ratio compared with other districts, it would be reasonable to suppose that PPMS risk is associated with male sex in Seinäjoki. This was not, however, the case, as the risk for PPMS was high for both sexes (data not shown).

The causes of a locally high and increasing risk of multiple sclerosis, an overall high male risk, a high risk for both disease types in Seinäjoki, and a contrasting trend in Vaasa remain unexplained. In spite of the language difference between the partly Swedish-speaking Vaasa and Finnish speaking Seinäjoki, the genetic background is similar. In the multiple sclerosis population, cases have been characterised for HLA in the district of Seinäjoki and have been found to have increased frequencies for B7, B12, and DR2 among both patients and their healthy relatives. Families were later studied for the myelin basic protein (MBP) gene on chromosome 18, a candidate gene in multiple sclerosis. Genetic linkage and association analyses suggested that a genetic predisposition to multiple sclerosis is closely linked to the MBP gene in this population. In spite of these observations, our findings of a sustained increase in the incidence of the disease point to environmental factors, as genetic change in populations is slow. The environmental causes are generally suspected to be of viral origin but remain largely unknown at present.

The large regional differences in the incidence of multiple sclerosis in Finland in 1989–1993 result from diverging trends in incidence that are largely parallel for both types of disease course. In the originally high risk area of Seinäjoki the incidence of both types of course was still increasing from the late 1970s to the early 1990s. In Uusimaa, the incidence of both types has remained stable. In Vaasa, an intermediate incidence in 1979–1983 decreased to a low level for both PPMS and RRMS. This finding is of aetiological importance, as diagnostic practices have remained the same. The sharply diverging incidence trends in Seinäjoki and Vaasa point towards recent changes in environmental factors, and the parallel incidence trends for PPMS and RRMS in all three districts suggest that there are similar environmental triggers for both clinical types of multiple sclerosis.

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