PAPER

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

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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 10^5 and decreased in Vaasa from 1.9 to 0.2 per 10^5; 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.

The clinical spectrum of disease progression in multiple sclerosis is heterogeneous.[1 2] In most series about 70–90% of patients have a relapsing-remitting disease course (RRMS), which may later convert to a progressive phase (secondary progressive multiple sclerosis, SPMS). Approximately 10–30% of patients have a progressive course from the onset (primary progressive multiple sclerosis, PPMS),[2–6] with a worse prognosis than for RRMS.[7] In addition to differences in the natural course,[3 6] there is increasing support for pathogenic differences between RRMS and PPMS from neuroimaging[8] and neuropathological observations.[9] There is also some evidence that the HLA class II associations may be different.[10–12] Given these differences, RRMS and PPMS may also be aetiologically distinct, and this should be reflected in the circumstances of their occurrence.

Significant geographical and temporal differences and an increasing occurrence are common observations in multiple sclerosis epidemiology in high risk regions,[13] and have been reported in Finland.[14–19] Finland belongs to a high risk region for multiple sclerosis,[13] with prevalences of from 100 to 200 per 100 000 population in different areas.[18] The western district Seinäjoki has for a long time stood out as a high risk focus of the disease,[15 16] with a prevalence of 200/10^5 in 1993 and an incidence of 12 per 100 000 person-years in 1979 to 1993.[17 18] This is among the highest ever reported and is twice as high as the rates in two other areas in Finland, the western region of Vaasa and southern Uusimaa. A familial clustering of multiple sclerosis cases has been observed in Seinäjoki.[19]

The similar high multiple sclerosis incidences of 8/10^5 and 10/10^5 that were present in Seinäjoki and Vaasa in 1979 to 1983[17] showed a marked change between 1984 and 1993, with a significant increase in Seinäjoki and a decrease in Vaasa. No change was observed in southern Uusimaa. In the present study we compare the occurrence of multiple sclerosis broken down by type (RRMS and PPMS), and analyse the temporal variations in incidence and the clinical and demographic characteristics of the two forms of multiple sclerosis in Finland. This allowed us to investigate whether there are geographical and secular differences in the two disease courses which would point to aetiological differences. Such a hypothesis is feasible because there are several clinical and pathological differences between primary progressive and relapsing remitting multiple sclerosis.[3 6 8 9]

METHODS

Demographic data and population

Finland is situated in northern Europe between latitudes 60° and 70°. The total population was 5.1 million in 1993. The study districts of Uusimaa, Vaasa, and Seinäjoki are shown in fig 1. At the end of 1993 the populations were 1 277 932, 197 042, and 179 079, respectively, in the three districts. The annual increase in the Finnish population has been 0.4% from 1979. The population structure was affected by the migration of young adults into Uusimaa. However, the largest age group continues to be 40–49 years in all districts.

The western district is divided into two health care districts, where two central hospitals provide the neurological services. CSF and evoked potential examinations are equally available, but MRI has only been available in Seinäjoki since 1993. In southern Uusimaa the diagnostic facilities in the 1970s and 1980s were better; however, the situation became equal in the three areas during the 1990s. In Finland, all multiple sclerosis diagnoses from 1960s have been made by a neurologist in the neurological units of university or central hospitals, following the same diagnostic principles.

For the purpose of this study, patients with multiple sclerosis in the health care districts of Uusimaa, Vaasa, and Seinäjoki were ascertained from hospital registers by the diagnoses multiple sclerosis or morbus demyelinans (340 and 341 in the

Figure 1 Map of Finland showing the hospital districts under study (Uusimaa in the south and Vaasa and Seinäjoki in the west).

International Classification of Diseases, versions 8 and 9). Patients were re-evaluated to meet the criteria of Poser[20] or otherwise they met the criteria for PPMS.[21] Disease course was classified retrospectively (by M-LS) into RRMS and PPMS groups.[22] In our study, PPMS was defined as disease that showed steady progression during the first year from the primary symptoms.[2 5 21] The RRMS group included cases with secondary progression after an initial relapsing-remitting course.

Incidence calculations

The calculations were based on definite cases of multiple sclerosis.[20] Incidence was calculated from 1 January 1979 to 31 December 1993 per 100 000 person-years in age groups from 10 to 69 years[23] and in calendar time intervals. The significance of the trend was assessed by classifying the total time period into two subgroups only (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.[24] 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 Seinäoki (0.9) and lower for RRMS in Uusimaa (0.1).

Table 1 Clinical and pathological characteristics of patients with multiple sclerosis diagnosed in 1979–1993 in Uusimaa, Vaasa, and Seinäjoki districts

Characteristic	Uusimaa	Vaasa	Seinäjoki
CSF IgG positivity (% of tested patients)			
All	91	94	92
RRMS	91	95	91
PPMS	94	88	94
Female to male ratio			
All	2.4	2.2	1.6
RRMS	2.7	2.3	1.8
PPMS	1.6	2.0	1.2
Mean age at diagnosis (years)			
All	35.7	39.7	39.3
RRMS	35.4	38.7	38.4
PPMS	36.6	43.5	41.5
Symptoms at onset (%)			
Motor	16	18	30
Pure motor	13	8	16
Paraparesis	3	10	14
Other	84	82	70
Brain stem	19	16	21
Sensory	27	39	18
Optic neuritis	18	11	15
Miscellaneous*	20	16	16
Ratio of motor to other symptoms			
RRMS	0.1	0.2	0.3
PPMS	0.5	0.4	0.9
Total	0.2	0.2	0.4

*Cerebellar, bladder, autonomic.
PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

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.[13] The early observation of a high risk in the western district of Seinäjoki[14] 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).[17] The rate in Seinäjoki was among the highest reported worldwide.[25 26] 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

		Calendar time									
		1979 to 1986			1987 to 1993				1979 to 1993		
District	Disease course	N	I	SIR	N	I	SIR	CI	N	I	CI
Uusimaa	RRMS	301	4.1	Reference	290	4.2	1.0	0.9 to 1.2	591	4.1	3.8 to 4.5
	PPMS	75	1.0	Reference	70	1.0	1.0	0.8 to 1.3	145	1.0	0.8 to 1.2
	Total	376	5.1	Reference	360	5.2	1.0	0.9 to 1.1	736	5.1	4.8 to 5.5
Vaasa	RRMS	42	4.2	Reference	27	3.1	0.7	0.5 to 1.1	69	4.0	3.0 to 4.9
	PPMS	19	1.9	Reference	2	0.2	0.1	0.02 to 0.4	21	1.2	0.7 to 1.7
	Total	61	6.0	Reference	29	3.3	0.5	0.4 to 0.8	90	5.2	4.1 to 6.3
Seinäjoki	RRMS	83	6.8	Reference	85	7.9	1.2	0.9 to 1.4	168	8.1	6.9 to 9.3
	PPMS	32	2.6	Reference	40	3.7	1.4	1.02 to 1.9	72	3.5	2.7 to 4.3
	Total	115	9.4	Reference	125	11.6	1.2	1.03 to 1.5	240	11.6	10.1 to 13.1

CI, confidence interval; I, incidence; N, number of cases; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SIR, standardised incidence ratio.

in Vaasa, and stable in Uusimaa for the disease as a whole, as well as for the PPMS and RRMS subtypes.

The populations of western and southern districts of Finland differ economically as well as in their migration pattern, immigration being greatest in the urbanised Uusimaa but stable in the more rural populations of Vaasa and Seinäjoki. Owing to the longstanding isolation of Finland and a low migration rate within the country until recently, large areas have remained genetically isolated. The population density in the country as a whole is low and even now the growth of the gene pool is restricted.[27 28] This is shown in the HLA distribution, as allelic differences in HLA can still be found across the country. Variations in the frequencies of A9, B35, and Cw4 are common in Finland.[29]

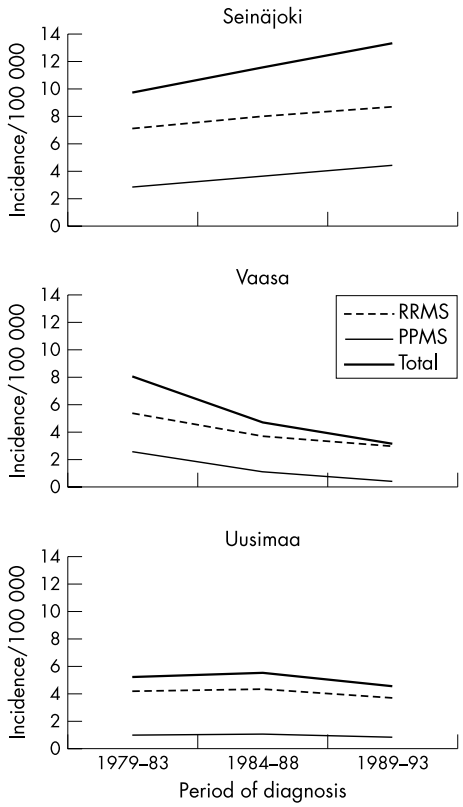

Figure 2 Incidence trends per 100 000 person-years in the disease course of all multiple sclerosis cases, relapsing-remitting multiple sclerosis (RRMS), and primary progressive multiple sclerosis (PPMS) in Seinäjoki, Vaasa, and Uusimaa in 1979–1993.

Medical practice in Finland is by and large homogeneous. Neurological facilities in the Finnish health care system are provided in the local or central hospitals of each health care district. Thus multiple sclerosis is diagnosed almost exclusively at the neurological units of these hospitals. Populations under study are reasonably large, representing an industrialised population in Uusimaa and rural populations in Vaasa and Seinäjoki. To improve the comparability between the districts, the time point of definite diagnosis was classified retrospectively, and the diagnostic tests were recorded. The diagnosis was mainly clinical in over 80% of the cases.[17] Classification of disease course was done by the same neurologist (M-LS) which should reduce potential inter-rater classification bias.[4 22] Because of the commonly recognised classification problems in multiple sclerosis,[30 31] we decided to use only two disease course categories, relapsing remitting and primary progressive, the former category including patients who later converted into the secondary progressive form.

Our population sample showing different incidence trends in the three districts provided an opportunity to test the hypothesis that the RRMS and PPMS subtypes could have a different aetiology[32] in stable and homogeneous study populations. The fact that trends in the incidence of the two disease subtypes moved in parallel in three districts in which there were diverging trends suggests that the environmental triggers for these two presentations of multiple sclerosis are similar. Our results thus contrast with earlier findings in western Norway,[33] where the incidence of PPMS remained stable while there was an increasing incidence of RRMS and progressive-relapsing multiple sclerosis during 1953 to 1982. However, these data were based on a much smaller number of patients, and the incidence trends were later shown to be similar for both disease courses.[34] The fluctuating trends typical in high risk regions for multiple sclerosis were also observed in our study and were shown to be similar for both disease courses. Such fluctuations can most readily be accounted for by environmental exposures.

The age adjusted incidence of PPMS in 1987–1993 was remarkably high in Seinäjoki ($3.7/10^5$) compared with Uusimaa ($1.0/10^5$) and Vaasa ($0.2/10^5$), indicating a long term high risk for PPMS in Seinäjoki. To our knowledge such large regional differences in PPMS occurrence have not been found before within a single population sample.[4 5] We do not believe this finding is hampered by diagnostic misclassification[6] (for example, chronic spastic paraparesis), and this interpretation is supported by the 94% positive CSF IgG findings among the 96% of PPMS cases tested in Seinäjoki. The distribution of

cases in our incidence data—78% in the RRMS group and 22% in the PPMS group—follows the common pattern,[5] 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.[3 6 8] Given the recent increase in incidence among men in Seinäjoki, and a lower F/M ratio compared with other districts,[17] 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,[17] 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.[27] 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.[35] 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.[36] 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[37] 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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