The natural history of multiple sclerosis: a geographically based study

8: Familial multiple sclerosis

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Summary

We have examined the demographics and long-term outcome of 1044 patients with sporadic and familial multiple sclerosis in a population-based cohort from London, Ontario. The mean follow-up was 25 years in duration, and by this time most patients had reached the unambiguous endpoint scores of the Kurtzke disability status scale (DSS), DSS 6, 8 or 10. An affected family member was identified in 19.8% of the total population, and this subgroup was further divided arbitrarily into the following three groups by the type and number of relatives affected: (i) first degree only; (ii) first degree plus others; (iii) second or third degree. The outcome in these groups was compared with that for those patients who, at a mean 25 year follow-up, had no relatives known to be affected. Familial cases closely resembled those remaining sporadic in both demographics and outcome, although onset in the most heavily loaded families was earlier and male/female ratio was greater. The times to DSS 6, 8 and 10 did not differ significantly when sporadic, familial and familial subgroups were compared. These results provide no clinical support for viewing familial multiple sclerosis as distinct from the sporadic form. The observed recurrence rate for siblings in a strictly defined epidemiological sample was 3.5%, much as projected. These results validate the recurrence risks which have previously been derived from age-corrected data for these first-degree relatives.

Keywords: multiple sclerosis; familial outcome

Abbreviations: DSS = Kurtzke disability status scale; PP = primary progressive; RR = relapsing–remitting; SP = secondary progressive

Introduction

The cause of multiple sclerosis remains uncertain, although recent evidence has solidified the view that both genetic and environmental factors determine susceptibility (Ebers and Sadovnick, 1994). There is very strong evidence from the classical tools of genetic epidemiology that familial aggregation is determined by multiple genes. This includes data from twins (Ebers *et al.*, 1986; Sadovnick *et al.*, 1993; Mumford *et al.*, 1994), adoptees (Ebers *et al.*, 1995), half-siblings (Sadovnick *et al.*, 1996) and the offspring of conjugal pairs (Robertson *et al.*, 1997). The gradual reduction in risk as one goes from first- to second- to third-degree relatives supports early suggestions that multiple sclerosis susceptibility is polygenic (Pratt *et al.*, 1951; Ebers *et al.*, 1982; Ebers, 1983; Ebers and Sadovnick, 1994). However, the search for specific chromosomal regions or genes which underlie the basis of familial aggregation has had limited success to date.

Although the specific factors determining susceptibility remain indeterminate, there is certainty that the clinical and pathological phenotype is variable in the extreme. There is little reason to be confident that multiple sclerosis represents a homogeneous and discrete entity. Even the age of onset can span more than five decades in large population-based samples (Weinshenker *et al.*, 1989). Nevertheless, the difference in disability outcome, which can range from non-existent in asymptomatic multiple sclerosis discovered at autopsy to a disease that is fatal in <12 months, is readily demonstrable in multiple sclerosis surveys.

It would not be surprising if it were concluded that genes play a role in outcome, although little direct evidence has

been put forward to support this view. If multiple sclerosis is a heterogeneous group of disorders, the resolution of the problem of susceptibility will be difficult by conventional methods. The identification of discrete subgroups of multiple sclerosis would have implications both for genetic studies and for the understanding of factors determining outcome. The subdivision of patients by clinical or demographic features is a familiar approach and is easily done, although it lacks established biological meaning.

We report a comparison of the long-term outcome in familial and sporadic multiple sclerosis based on a large population-based sample in which we search for heterogeneity in outcome. Observations of this population have been reported previously with respect to short- and intermediate-term outcome up to 1984 (Weinshenker *et al.*, 1990). For patients with familial and sporadic multiple sclerosis derived from the same population-based sample, we report here an evaluation of the long-term clinical outcome up to 1997. Long-term observations provide three clear advantages in such a comparison. Since multiple sclerosis has a relatively discrete age of onset curve, in which risk is strongly related to age, the recognition of familial and non-familial cases becomes much more definitive with time, and the recurrence risk for colineal relatives requires little or no correction for age. In addition, long-term survival curves of populations destined to differ in outcome have had the opportunity to diverge, thereby enhancing the opportunity to show differences. Finally, disability outcomes in the long term are advanced, unambiguous and of undeniable clinical relevance. In this population, more than half of the patients were confined to bed or chair, or were dead.

The observations reported here serve the following purposes: (i) they establish the frequency of familial multiple sclerosis in a large population base; (ii) they test the hypothesis that familial multiple sclerosis is different phenotypically from sporadic disease; (iii) they document the clinical outcome for familial multiple sclerosis in this population-based sample; and (iv) they test the validity of age-correction of empirical recurrence risks in families by identifying actual rates of recurrence in relatives of both sporadic and familial cases.

Methods
Study population
From 1972 to 1984, a cohort of 1099 consecutive patients was followed at the multiple sclerosis clinic at University Campus, London Health Sciences Centre, London, Ontario. With continued follow-up now reaching a mean of 25 years, the long-term natural history of multiple sclerosis in this population continues to be described (Cottrell *et al.*, 1999*a*, *b*; Kremenchutzky *et al.*, 1999). From the original cohort, 1044 patients were evaluated for outcome. Some 55 patients were excluded for the following reasons: (i) 15 duplicates were not recognized initially because of name changes; and

(ii) 40 patients were found not to have multiple sclerosis. The great majority of the latter represented possible cases in whom multiple sclerosis was initially thought to be the most likely diagnosis but who proved to have other conditions on follow-up. (Cottrell *et al.*, 1999*a*).

This patient population was seen on a more or less yearly basis, although this proved to be increasingly difficult with increasing disability of the patients, and largely ceased when they became bed-bound. Efforts were made to follow them up in nursing homes where possible, although this was usually restricted to a single occasion. It was possible to trace the great majority of these patients at the most recent systematic follow-up in 1997, although some of the highest disability levels had to be determined by history for the most disabled patients. Almost a third of the patients had died by the time of this final evaluation.

During the nearly three decades of the clinic's operation, patients have been routinely and serially asked about the occurrence of multiple sclerosis among their family members. At the time of the last systematic global follow-up between the years 1995 and 1997, all surviving patients were again questioned about the existence of multiple sclerosis in their families. This was of doubtful value in those who had lost cognitive function to a degree that made it difficult for them to comply, and was of low yield and/or unverifiable in those who had little or no contact with their families. Accordingly, familial rates reported were certain to be underestimated to some extent, the more so for the more distant relatives.

A more detailed description of the general methods used in following this population has been described elsewhere (Weinshenker *et al.*, 1990; Cottrell *et al.*, 1999*a*). For the purposes of this study, however, patients reporting an affected family member were asked for further documentation (i.e. records), with the consent of such a member when this was possible. For patients or affected relatives who had died, medical records were obtained. Affected relatives were also seen frequently at the clinic, although they were only rarely part of the 1044 patient cohort, most often because they were seen before or after the accrual period of 1972–84, or lived elsewhere.

As in other papers in this series, a separate analysis was performed for the Middlesex County cohort, a restricted epidemiological subgroup (Hader *et al.*, 1988) with high ascertainment and almost complete follow-up. At 25 years, only seven out of the 203 patients in this subgroup were untraceable. The low rate of out-migration of area families was helpful. Pedigree size and age of relatives were identified for all probands.

The diagnostic criteria were those of Poser and colleagues (Poser *et al.*, 1983). Other heredofamilial disorders, especially system degenerations commonly confused with multiple sclerosis, are seen on a weekly basis in the multiple sclerosis clinic. A low threshold for recognizing such disorders has existed since the early days of operation of the clinic. In an early study on multiple sclerosis sib-pairs, we restricted analysis to those having at least one affected individual with

Table 1 *Demographic characteristics of total multiple sclerosis population, classified by sporadic or familial status*

	Sporadic	First degree plus	First degree	Second/third degree
n	836	27	85	96
Males	285 (34%)	11 (41%)	33 (39%)	30 (31%)
Females	551 (65%)	16 (59%)	52 (61%)	66 (69%)
Sex ratio (M/F)	0.52	0.69	0.63	0.45
Seen at onset				
No	704 (84%)	24 (89%)	67 (79%)	64 (67%)
Yes	132 (16%)	3 (11%)	18 (21%)	31 (33%)
Mean age at onset (years)	30.6	30.3	31.6	29.3
Mean duration of multiple sclerosis (years)	23.8	28.4	24.2	25.0

Table 2 *Initial presenting symptoms of familial and sporadic multiple sclerosis groups (%)*

	Sporadic	First degree plus	First degree	Second/third degree	*P**
Optic neuritis	17	30	18	18	0.36
Diplopia	12	4	9	7	0.10
Limb ataxia	4	4	6	3	0.98
Gait disturbance	14	7	14	7	0.13
Sensory					
Trunk	43	52	40	46	0.67
Face	5	0	6	5	0.92
Motor					
Insidious	13	19	14	13	0.78
Acute	6	4	8	9	0.14
Transverse myelitis	1	0	5	2	0.11[†]
Bladder disturbance	3	0	0	2	0.07
Lhermitte sign	8	7	5	17	0.16
Vertigo	3	4	2	1	0.26

* *P* value from χ^2 comparison of sporadic with non-sporadic; [†] Fisher exact test comparison of sporadic with non-sporadic (χ^2 test not valid here).

Table 3 *Clinical course of familial and sporadic multiple sclerosis subgroups (%)*

	Sporadic	First degree plus	First degree	Second/third degree
RR	28	19	25	32
SP	51	67	54	49
PP	21	15	21	19

$\chi^2 = 4.10$; $P = 0.66$.

optic neuritis, internuclear ophthalmoplegia or oligoclonal banding in the CSF (Ebers *et al.*, 1982), but we did not demand this from patients in this series since diagnostic ambiguities were pointedly resolved as a background for collecting natural history data.

The total multiple sclerosis population was somewhat arbitrarily divided into the following categories, as previously described (Weinshenker *et al.*, 1990): (i) sporadic multiple sclerosis: no affected relatives identified; (ii) first degree: a single affected first-degree relative; (iii) first degree plus: multiple affected relatives including at least one first-degree relative, as previously described; (iv) second or third degree: one or more affected second- or third-degree relatives.

Statistical analysis

All analysis was performed using SAS (SAS Institute, Cary, NC, USA). Survival analysis was performed with SAS/LIFE TEST using the life table (actuarial) method with intervals of 1 year. In this analysis, patients who had not yet reached the given Kurtzke disability status scale (DSS) level but who had been followed for a known period of time were included as right-censored. The log-rank statistic was used to test the significance of the equality of survival distributions.

Results

Demographic characteristics

The demographic characteristics of the four subgroups of multiple sclerosis patients derived from the original cohort are summarized in Table 1. Eight hundred and thirty-six patients had sporadic disease and 208 had familial multiple sclerosis according to the definitions which have been outlined. There was a relative excess of males in the first-degree group and even greater excess in the first-degree plus group, although this fell short of statistical significance. The mean age of onset was similar among the four groups, as was the mean duration of multiple sclerosis. Small numbers

Table 4 *Multiple sclerosis attacks and disease progression in familial and sporadic patients*

	n	Sporadic % (SD)	First degree plus	First degree	Second/third degree	P
Attack recurrence rate						
First year	702	26.4 (1.9)	10.0 (6.7)	35.1 (6.3)	32.4 (5.7)	0.12*
Second year	646	24.9 (1.9)	22.2 (9.8)	38.5 (6.7)	37.1 (6.1)	0.05*
Interval between first and second attacks (years)	695	3.9 (0.38)	6.3 (1.4)	3.0 (0.45)	3.7 (0.64)	0.07†
Onset of progressive deficit (years)	513	9.9 (0.38)	14.4 (1.4)	10.3 (1.0)	10.0 (1.2)	0.15†

Primary progressive patients were excluded from this analysis. * P values are derived from χ^2 test; † P values are derived from one-way ANOVA. Attack recurrence rate is defined as (number of patients with more than one attack)/(number of patients with at least one attack in the first year). For the second year, this parameter is defined as (number of patients with an attack in the first and second years)/(number of patients with at least one attack in the first year).

of patients in each group remained as possible cases. In all groups, these were patients in whom follow-up was truncated by death or loss to follow-up. The Middlesex County cohort enjoyed a 97% follow-up rate (mean 25.9 ± 8.6 years) and only one patient remained 'probable'.

Initial presentation and clinical course

The initial symptom(s) among the four groups did not differ substantially. Optic neuritis was somewhat more common among the first-degree plus group but not more common when the first-degree group was compared with the second-/third-degree subgroup (Table 2). The relative frequencies of clinical course were also rather similar among the different groups subclassified as having primary progressive (PP), secondary progressive (SP) and relapsing–remitting (RR) multiple sclerosis, although the percentage of patients with primary progressive disease was slightly lower in the first degree plus subgroup (Table 3).

Early relapse and disease progression

Following the initial exacerbation, the likelihood of relapse in the first and second year of disease, the interval between the first and second attack and the time to onset of progressive deficit in those patients with secondary progressive disease were identified for each of the four subgroups (Table 4). The likelihood of a second attack in the first 2 years was lower in the primary plus subgroup, the interval between the first and second attack was greater, and there was a longer time to onset of progressive deficit in this group. These differences approach statistical significance or are of borderline significance (Table 4) only when correction for multiple comparisons is forgone.

Outcome

Initially we compared survival curves for each of the four subgroups as given in Fig. 1 for times to DSS 3, 6, 8 and 10. Visually, these show little difference within any pair of comparisons or when survival curves are compared for all familial cases versus all sporadic cases (Fig. 2). Next we compared patients with the clinical phenotypes of RR and PP disease between and among familial groups. Survival curves for time to DSS 3, 6, 8 and 10 for (i) familial RR versus sporadic RR, and (ii) familial PP versus sporadic PP were derived (the data are not shown but are available from author G.C.E.). Little difference was noted among these pairwise comparisons. The number of patients for each comparison and the P values for differences between them are given in Table 5.

Middlesex County cohort

In the Middlesex County cohort ($n = 203$) there were 16 affected siblings among full brothers (mean age 56.23 years, range 31–95 years) and sisters (mean age 56.00 years, range 27–80 years) (total sibs, $n = 451$) of clinic probands. This gives an observed recurrence risk of 3.5% and, with a slight adjustment for remaining risk, suggests a final rate of ~4.0%. The breakdown for this cohort among the four identified subgroups is given in Table 6. The overall observed familial rate of 22.8% (Table 6) is slightly higher than the overall rate of 19.9% for the entire population, perhaps because of slightly better follow-up in this cooperative subgroup (Ebers, 1983).

Discussion

We have examined long-term outcomes in 1044 multiple sclerosis patients from a largely population-based sample having a mean follow-up of 25 years. The extended clinical follow-up of this population has allowed the evolution of widely diverging survivals for times to DSS 3, 6 and 8 and death from multiple sclerosis. Furthermore, at least for colineal relatives, much of the risk for being identified as having multiple sclerosis had elapsed. These factors should have enhanced the ability to detect differences in outcome between familial and sporadic disease, a comparison which was the primary focus of this study. The results establish a
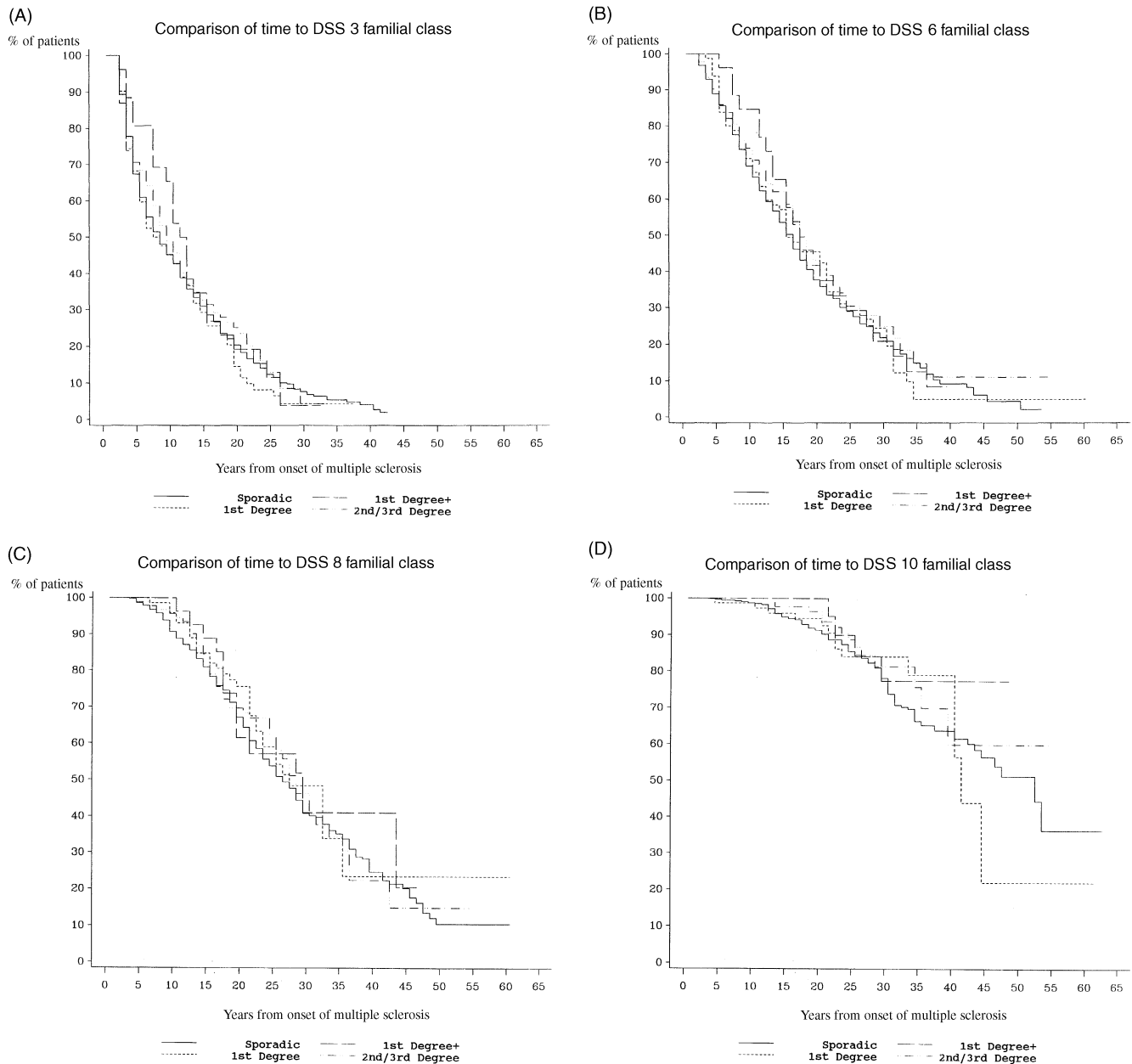
Fig. 1 Survival analysis of disability comparing sporadic, first-degree plus, first-degree and second-/third-degree groups to (**A**) DSS 3, (**B**) DSS 6, (**C**) DSS 8 and (**D**) DSS 10.

natural history for the ~20% of patients identified as having familial disease. These observations, from a sample in which detailed natural history observations have been made previously, indicate that patients with familial disease have a clinical course which differs little from those whose disorder remains sporadic even after several decades of follow-up. Accordingly, they provide little or no support for the hypothesis that familial multiple sclerosis is a disorder distinct from the more common sporadic variety.

The high familial rate identified in this study (22.8% in the Middlesex County cohort) supports the indications from previous population-based studies in which relatively high familial risks were derived from age of onset curves compiled

from general multiple sclerosis population data (Sadovnick *et al.*, 1988; Robertson *et al.*, 1996*a*; Carton *et al.*, 1997). Given the relatively low concordance of age of onset in non-twin sibs with familial disease (Doolittle *et al.*, 1990; Bulman *et al.*, 1991) it would be expected that population-based correction would suffice. However, the sib-pair data were based on smaller numbers, and it should be apparent that even in a study with a long follow-up there is potential for ascertainment to bias results towards age of onset concordance. For example, it can be appreciated that concordant pairs with late onset in one member would tend to be under-represented. This problem would be most evident with short follow-up and the effect should wane with time,
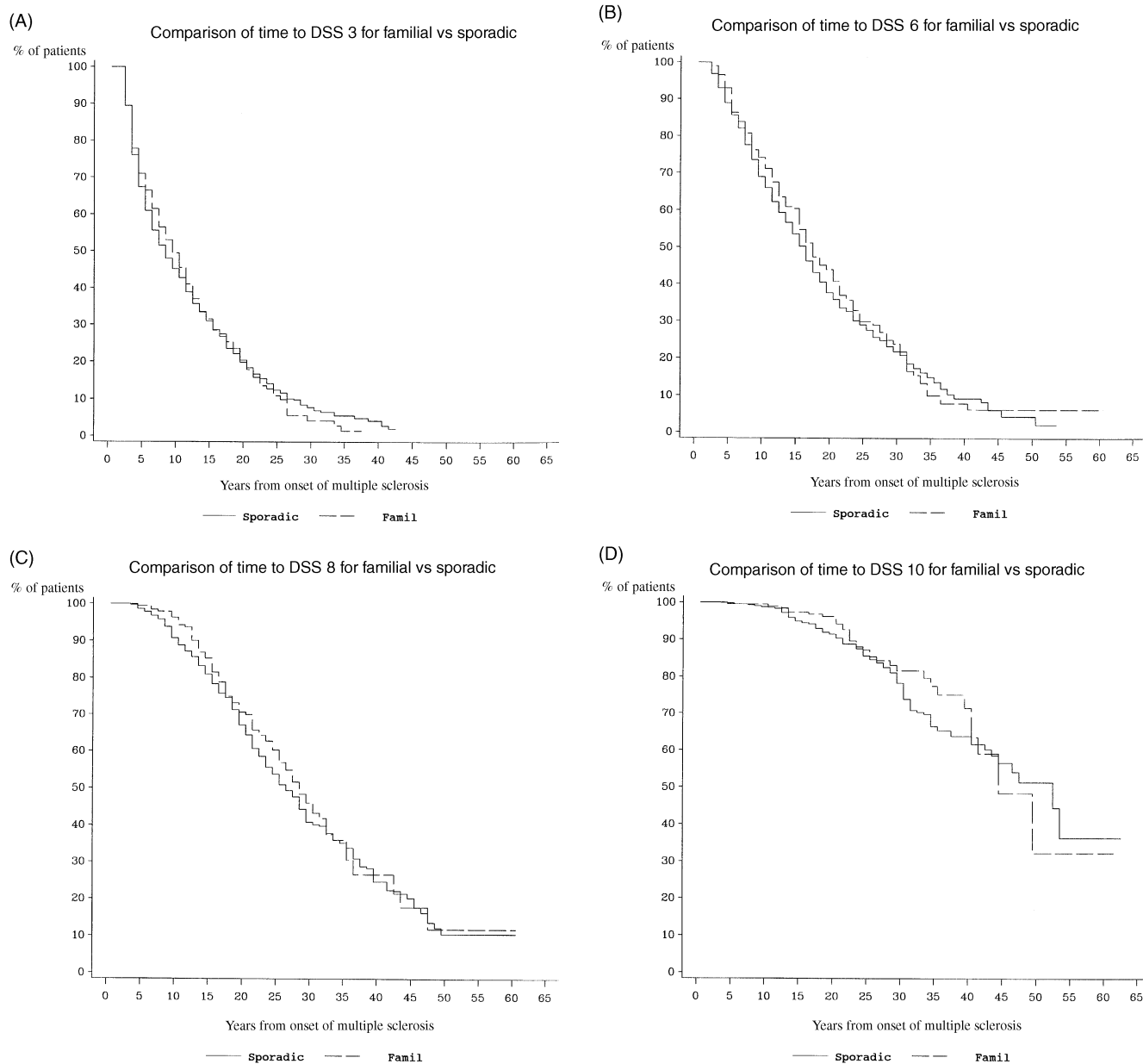
Fig. 2 Survival analysis of disability of total familial subgroup compared with sporadic multiple sclerosis patients to (**A**) DSS 3, (**B**) DSS 6, (**C**) DSS 8 and (**D**) DSS 10.

assuming similar likelihood of ascertainment over the period of observation. Examination of the Middlesex County cohort, in which long-term follow-up has been the most comprehensive, serves to specifically validate previous descriptions of recurrence risk for first-degree relatives derived from different populations within Canada. In this and three other Canadian sites, familial recurrence risks of ≥20% have now been found (Hader, 1997; Sadovnick, 1988; T. J. Murray, personal communication).

We recognize limitations in the identification of familial rates. These are likely to be most accurate for the Middlesex County subcohort. However, in patients who had long since died, the reporting of familial occurrence stopped at the time of their last evaluation in the clinic, although the awareness

of their death may not have come until many years later. Since very few patients were lost to follow-up in Middlesex County, there was no bias or selection for familial multiple sclerosis, and these results should give the closest approximation to the actual risks for sibs and for offspring. We have not attempted to ascertain the recurrence risks for parents, given the diagnostic difficulties inherent in going back one or two generations. The first neurologist in London, Ontario did not arrive until the early 1950s. Although several studies show that there are clinical, pathological and MRI features which are relatively different between PP, RR and SP multiple sclerosis (Thompson *et al.*, 1997), we found little correlation of phenotypes within multiple sclerosis families using this simple classification. The phenotype of

Table 5 P *value test for the homogeneity of survival curves for different comparisons*

Level of disability	Comparison 1 n, P	Comparison 2 n, P	Comparison 3 n, P	Comparison 4 n, P
DSS 3	978, 0.73	978, 0.89	261, 0.28	202, 0.64
DSS 6	976, 0.77	976, 0.46	255, 0.25	206, 0.35
DSS 8	946, 0.77	946, 0.32	257, 0.74	195, 0.43
DSS 10	925, 0.71	925, 0.29	257, 0.87	185, 0.89

n = total number of patients in the analysis; P = P value for the test of homogeneity of survival curves based on the log-rank statistic. Comparisons: (1) the four subgroups; (2) familial and sporadic multiple sclerosis; (3) familial RR and sporadic RR multiple sclerosis; and (4) familial PP and sporadic PP multiple sclerosis.

Table 6 *Middlesex County cohort, classified by sporadic or familial status (FAM)*

FAM	Frequency	Per cent	Cumulative frequency	Cumulative frequency
Sporadic	156	77.2	156	77.2
First degree plus	5	2.5	161	79.7
Second degree	21	10.4	182	90.1
First/second degree	20	9.9	202	100.0

the index case had little or no influence on the phenotype of the affected relative (Kremenchutzky *et al*., 1999), confirming our earlier observations (Weinshenker *et al.*, 1990) and subsequent observations from the UK (Robertson *et al*., 1996*b*). These findings establish observation-derived risks which are applicable at least to our Canadian population.

The familial recurrence risks identified in this paper are likely to represent an underestimate, since ascertainment occurred most often through the reporting by multiple sclerosis clinic probands of the occurrence of affected relatives (either in response to repeated surveys or spontaneously). The independent ascertainment of relatives of other index cases within the London multiple sclerosis clinic system has been frequent, and commonly this is unknown to the originally ascertained individual. We have observed that there remains a mean duration between clinical onset and diagnosis of some 3–4 years, typically most evident in the later-onset cases (Cottrell *et al*., 1999*a*), and we estimate that, on average, an additional period of 4 years elapses between the diagnosis of the second member of a family to be affected and the awareness of this by the first. Although this additional period is highly variable, these observations have implications for correction for age of onset since this refinement makes the now unwarranted assumption that onset would be synonymous with recognition by all previously affected family members.

We have not corrected for doubly ascertained family members. Recalculation of proband-wise concordance rates (recurrence risk) would elevate the observed crude risks. This determination is problematic since the presence or absence of complete ascertainment is a much more graded determination in practice. Even in our strictest epidemiological sample, the Middlesex County population,

ascertainment is incomplete and correction for this could only be approximated. Finally, we are aware that examination and investigation of family members may identify another cohort of affected relations who are not known to the proband, or are even aware they have test results which are seen in multiple sclerosis (Ebers, 1983; Duquette and Charest, 1986; Lynch *et al.*, 1990; Duquette; 1991)

The outcomes were examined in several ways, including the comparison of all sporadic with all familial cases, and were similar. Such comparisons are weakly powered to show a difference when done early in the clinical course. Many patients who are described as sporadic early on will eventually have affected relatives. Similarly, benign or adverse outcomes identified in the early years of disease are only moderately predictive and commonly change when viewed in long-term retrospect. Accordingly, we view these results at 25 years as being nearly definitive for the total group of familial versus sporadic cases. Most patients in this study have reached the hard outcomes of DSS 6, and most of those who have not may never do so. Many have gone to DSS 8 and 10 and the comparative data for the familial versus the sporadic groups would appear to exclude only a small difference in clinical course. However, the power to address this question is probably not great among the four specific small subgroups of familial disease. We cannot exclude there being small subgroups with clinical outcome which could differ materially from that of sporadic patients. Furthermore, we recognize that our grouping of familial cases is somewhat arbitrary and is unfounded in any known difference in pathogenesis. However, some modest trends support the observations that, among individuals with a single affected parent and having early age of onset, a higher familial risk combined with earlier age of onset, on average, is present. These findings support previous observations (Sadovnick *et al.*, 1997). Families with high recurrence risks were found to have a lower age of onset in the proband (Sadovnick *et al.*, 1998). This does not show up in the mean onset ages of our subgroups but is present when we used the divisions applied by Sadovnick and colleagues (Sadovnick *et al.*, 1998) (data not shown). A modestly more benign outcome of the first degree plus group early in the disease occurred in the presence of an excess of positive prognostic features. These included

a higher frequency of onset with optic neuritis and a longer inter-attack interval.

Although demographic features were very similar among the different groups, the elevated male : female ratio in the group which putatively includes the most heavily genetically loaded families is consistent with previous suggestions that this should be expected in polygenic disorders (Childs and Scriver, 1986). This prediction for complex traits was theory-based. A heavier than average background of susceptibility factors in families identified by having more affected relatives should lower the threshold for the more resistant sex (males in the case of multiple sclerosis). Relatively little concordance in clinical phenotype within families was found, as previously reported (Weinshenker *et al.*, 1990; Robertson *et al*, 1996*b*; M. Kremenchutzky and G. C. Ebers, unpublished results). The distribution of phenotypes, time to onset of progressive deficit and survival curves for times to EDSS 6, 8 and 10 were remarkably similar between familial and sporadic cases. At least in this analysis there appears little rationale to justify considering adequately evaluated familial cases as a separate entity or as unsuitable for entry into clinical trials of therapeutic agents.

Acknowledgements

References

Bulman DE, Sadovnick AD, Ebers GC. Age of onset in siblings concordant for multiple sclerosis. Brain 1991; 114: 937–50.

Carton H, Vlietinck R, Debruyne J, De Keyser J, D'Hooghe MB, Loos R, et al. Risks of multiple sclerosis in relatives of patients in Flanders, Belgium. J Neurol Neurosurg Psychiatry 1997; 62: 329–33.

Childs B, Scriver CR. Age at onset and causes of disease. Perspect Biol Med 1986; 29: 437–60.

Cottrell DA, Kremenchutzky M, Rice GPA, Koopman W, Hader W, Baskerville J, et al. The natural history of multiple sclerosis: a geographically-based study: 5. The clinical features and natural history of primary progressive multiple sclerosis. Brain 1999a; 122: 641–7.

Cottrell DA, Kremenchutzky M, Rice GPA, Hader W, Baskerville, Ebers GC. The natural history of multiple sclerosis: a geographically-based study: 6. Applications to planning and interpretation of clinical therapeutic trials in primary progressive multiple sclerosis. Brain 1999b; 122: 625–39.

Doolittle TH, Myers RH, Lehrich JR, Birnbaum G, Sheremata W, Franklin GM, et al. Multiple sclerosis sibling pairs: clustered onset and familial predisposition. Neurology 1990; 40: 1546–52.

Duquette P. Familial subclinical multiple sclerosis [letter]. Neurology 1991; 41: 159.

Duquette P, Charest L. Cerebrospinal fluid findings in healthy siblings of multiple sclerosis patients. Neurology 1986; 36 : 727–9.

Ebers GC. Genetic factors in multiple sclerosis. Neurol Clinics 1983; 1: 645–54.

Ebers GC, Sadovnick AD. The role of genetic factors in multiple sclerosis susceptibility. J. Neuroimmunol 1994; 54: 1–17.

Ebers GC, Paty DW, Stiller C, Nelson RF, Seland TP, Larsen B. HLA typing in MS sibling pairs [abstract]. Lancet 1982; 2: 88–90.

Ebers GC, Paty DW, Morton N. Segregation and linkage analysis of HLA typing in familial MS [abstract]. Neurology 1983; 33 Suppl 2: 180.

Ebers GC, Bulman DE, Sadovnick AD, Paty DW, Warren S, Hader W, et al. A population-based twin study of multiple sclerosis. N Engl J Med 1986; 315: 1638–42.

Ebers GC, Sadovnick AD, Risch NJ. A genetic basis for familial aggregation in multiple sclerosis. Nature 1995; 377: 150–1.

Hader WJ. The prognosis of multiple sclerosis in Saskatoon, Saskatchewan—a twenty year follow-up [abstract]. Can J Neurol Sci 1997; 24 Suppl 1: S43.

Hader WJ, Elliot M, Ebers GC. Epidemiology of multiple sclerosis in London and Middlesex County, Ontario, Canada. Neurology 1988: 38; 617–21.

Kremenchutzky M, Cottrell D, Rile G, Hader W, Baskerville J, Koopman W, et al. The natural history of multiple sclerosis: a geographically-based study: 7. Progressive-relapsing and relapsing-progressive multiple sclerosis: a re-evaluation. Brain 1999; 122; 1941–9.

Lynch SG, Rose JW, Smoker W, Petajan JH. MRI In familial multiple sclerosis. Neurology 1990; 40: 900–3.

Mumford CJ, Wood NW, Kellar-Wood H, Thorpe JW, Millar DH, Compston DA. The British Isles survey of multiple sclerosis in twins. Neurology 1994; 44: 11–5.

Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13: 227–31.

Pratt RTC, Compston ND, McAlpine D. The familial incidence of disseminated sclerosis and its significance. Brain 1951; 74: 191–232.

Robertson NP, Fraser M, Deans J, Clayton D, Walker N, Compston DA. Age-adjusted recurrence risks for relatives of patients with multiple sclerosis. Brain 1996a; 119: 449–55.

Robertson NP, Clayton D, Fraser M, Deans J, Compston DA. Clinical concordance in sibling pairs with multiple sclerosis. Neurology 1996b; 47: 347–52.

Robertson NP, O'Riordan JI, Chataway J, Kingsley DP, Miller DH, Clayton D, et al. Offspring recurrence rates and clinical characteristics of conjugal multiple sclerosis. Lancet 1997; 349: 1587–90.

Sadovnick AD, Baird PA, Ward RH. Multiple sclerosis: updated risks for relatives. Am J Med Genet 1988; 29: 533–41.

Sadovnick AD, Armstrong H, Rice GP, Bulman D, Hashimoto L, Paty DW, et al. A population-based study of multiple sclerosis in twins: update. Ann Neurol 1993; 33: 281–5.

Sadovnick AD, Ebers GC, Dyment AD, Risch NJ and the Canadian Collaborative Study Group. Evidence for genetic basis of multiple sclerosis. Lancet 1996; 347: 1728–30.

Sadovnick AD, Dyment D, Ebers GC. Genetic epidemiology of multiple sclerosis. [Review]. Epidemiol Rev 1997; 19: 99–106.

Sadovnick AD, Yee IM, Ebers GC, Risch NJ. Effect of age of onset and parental disease status on sibling risks for MS. Neurology 1998; 50: 719–23.

Thompson AJ, Polman CH, Miller DH, McDonald WI, Brochet B, Filippi M, et al. Primary progressive multiple sclerosis. [Review]. Brain 1997; 120: 1085–96.

Weinshenker BG, Bass B, Rice GPA, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study. 1. Clinical course and disability. Brain 1989; 112: 133–46.

Weinshenker B, Bulman D, Carriere W, Baskerville J, Ebers GC. A comparison of sporadic and familial multiple sclerosis. Neurology 1990; 40: 1354–8.