Familial effects on the clinical course of multiple sclerosis

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Abstract—Background: Familial factors influence susceptibility to multiple sclerosis (MS) but it is unknown whether there are additional effects on the natural history of the disease. **Method:** We evaluated 1,083 families with ≥ 2 first-degree relatives with MS for concordance of age at onset, clinical course, and disease severity and investigated transmission patterns of these clinical features in affected parent-child pairs. **Results:** There is concordance for age at onset for all families (correlation coefficient 0.14; $p < 0.001$), as well as for affected siblings (correlation coefficient 0.15; $p < 0.001$), and affected parent-child pairs (correlation coefficient 0.12; $p = 0.03$) when each is evaluated separately. Concordance for year of onset is present among affected siblings (correlation coefficient 0.18; $p < 0.001$) but not the parent-child group (correlation coefficient 0.08; $p = 0.15$). The clinical course is similar between siblings (kappa 0.12; $p < 0.001$) but not affected parents and their children (kappa -0.04 ; $p = 0.09$). This influence on the natural history is present in all clinical subgroups of relapsing-remitting, and primary and secondary progressive MS, reflecting a familial effect on episodic and progressive phases of the disease. There is no concordance for disease severity within any of the considered family groups (correlation coefficients: all families analyzed together, 0.02, $p = 0.53$; affected sibling group, 0.02, $p = 0.61$; affected parent-child group, 0.02, $p = 0.69$). Furthermore, there are no apparent transmission patterns of any of the investigated clinical features in affected parent-child pairs and no evidence for anticipation or effects of genetic loading. **Conclusion:** Familial factors do not significantly affect eventual disease severity. However, they increase the probability of a progressive clinical course, either from onset or after a phase of relapsing remitting disease. The familial effect is more likely to reflect genetic than environmental conditions. The results are relevant for counseling patients and have implications for the design of studies seeking to identify factors that influence the natural history of the disease.

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The clinical and paraclinical expression of multiple sclerosis (MS) differs between individuals. These patterns may merely reflect chance variations in CNS involvement. Alternatively, additional genetic or environmental factors could influence the core pathologic process and produce identifiable phenotypic variations. A final possibility is that the entity MS could constitute more than one disease, the diverse phenotypes representing true heterogeneity.

Epidemiologic and family studies implicate genetic and environmental factors in determining sus-

ceptibility to MS.^{1–5} Evidence that these risk factors also influence phenotypic expression is less secure. The recurrence risk in relatives of individuals with MS is significantly increased compared to the background population. Knowledge of familial influences on disease expression therefore has significant implications for counseling families with several affected family members.

Many investigators have assumed that phenotypic variations in MS depend on differences in genetic background and have therefore stratified samples in

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order to search for disease modifying genes.⁶ However, if stratifications are unnecessary or uninformed, this maneuver will lead to loss of power during analysis.

If genetic risk factors do indeed influence aspects of the natural history, it follows that certain clinical characteristics of MS should cluster in families having several affected individuals. The available surveys provide conflicting results, due either to methodologic variations or the use of sample sizes that are too small for definitive analysis.⁷⁻¹¹

Here we report the assessment of familial concordance for clinical features of MS in a large cohort comprising 1,083 multiplex families of European origin.

Methods. *Clinical resource.* We invited all groups participating in the Genetic Analysis of MS in EuropeanS (GAMES)¹² to contribute clinical data from multiplex families. Any combination of first-degree relatives concordant for MS, but not more distant family members, was included in the analysis. The probands were 2,310 individuals from 1,083 families. A total of 564 of these families have been included in previously published surveys on intrafamilial clinical concordance in affected siblings.^{8,10,11} The 2,310 cases included probands selected on the basis that they met the McDonald diagnostic criteria¹³ ($n = 1,293$); fulfilled the Poser criteria¹⁴ for clinically definite ($n = 118$), laboratory supported definite ($n = 126$), or clinically probable ($n = 121$) MS; matched Goodkin's diagnostic criteria¹⁵ ($n = 416$); had MS proven at autopsy ($n = 3$); or had the diagnosis confirmed by a neurologist, even though details of criteria used to support that opinion were not available ($n = 233$). The clinical data were based on assessments made by a specialist in neurology. All the probands gave informed consent for participation; ethical approval for including individuals in the clinical assessments and obtaining blood samples for previous genetic analyses^{11,12} was obtained from local committees.

Clinical variables. In addition to basic demographic details, information was collected on the year of assessment, age at disease onset (first symptom thought to be caused by MS), age at diagnosis, previous or current use of disease modifying therapies, clinical course, and Kurtzke expanded disability status scale (EDSS) scores.¹⁶

Disease severity was assessed using the Multiple Sclerosis Severity Score (MSSS).¹⁷ Briefly, the MSSS uses an algorithm that relates scores on the Kurtzke EDSS to the distribution of disability in patients with comparable disease durations in order to derive a rank-based score from 0 to 10 (with two decimal places). Thus, for any given disease duration, current disability can be ranked and allocated to a particular decile. Scores in the middle range represent average disabilities for that disease duration, whereas those with higher or lower scores have more or less accelerated rates of progression.

The clinical course was recorded in the categories relapsing-remitting, secondary progressive, and primary progressive MS, which were defined according to the criteria of Lublin and Rheingold.¹⁸ The diagnosis of definite, probable, and possible primary progressive MS incorporated findings from MRI and CSF examination¹⁹; however, patients assessed before these new criteria were introduced or in whom particular laboratory investigations were not available for review were included if, in all other respects, they fulfilled the criteria for primary progressive MS.

Statistical analysis. Kappa and intraclass correlation coefficient (ICC) were used to measure pairwise concordance. The first was used for the categorical (disease course) and the second for continuous outcome variables (disease progression and age at onset). A Kappa statistic or ICC close to 1 indicates that a pair of relatives is alike with respect to the outcome variable, whereas a value of 0 indicates that a pair is no more alike than random unrelated couples generated from the sample. Whenever a family contained >2 affected members, all possible pairs were formed and then weighted according to the number of independent pairs

in that family; for example, a family containing three members would be considered as three pairs, each receiving a 2/3 weighting.

Disease course was treated both as having three patterns (primary progressive, secondary progressive, and relapsing remitting), and also as a binary variable in various combinations (primary progressive vs not primary progressive; relapsing remitting vs primary or secondary progressive; relapsing-remitting vs secondary progressive [excluding primary progressive]; primary progressive vs secondary progressive [excluding relapsing-remitting]).

Crude estimates of Kappa and ICC are subject to confounding.⁷ For example, subjects with more recent dates of birth recruited into the study will have early ages at onset. Since siblings are more likely to have close dates of birth than unrelated individuals, a spurious association for age at onset is created. Conversely, parents and children will have very different dates of birth, thereby reducing any association for age at onset. Individuals with primary progressive MS have a later age at onset and are more likely to be male than probands with bout onset disease.¹⁹ Furthermore, most individuals with relapsing-remitting MS will eventually develop secondary progressive disease and disease duration therefore has to be considered in the analysis. Kappa and ICC estimates were adjusted for these potential confounders using the method of Lipsitz et al.²⁰ for categorical outcome variables, and by regressing out the confounders before calculating the ICC for continuous outcome variables. All analyses were adjusted for gender, year of birth, and country. In addition, disease course was adjusted for age at onset and duration of disease. Year at onset was adjusted for disease course. Disease progression was adjusted for duration and course. CIs and p values were calculated using Bootstrapping.

The effects of inheritance patterns on the natural history, the influence of parent of origin, and evidence for genetic loading in families with multiple affected cases were examined by multiple regression analysis.

Results. *Demographic features and family structures.* Fourteen groups from 11 countries contributed data relating to 2,310 individuals from 1,083 MS multiplex families (table 1). There were 757 families with 2 affected siblings, 199 families with an affected parent and child, 72 families with ≥ 3 affected siblings, and 55 families with more complicated structures (table 2).

Since most of the data were obtained retrospectively, some clinical information was not available. Details of age at onset were available for 2,158 individuals. Assessments of the clinical course and disease progression were made in 2,254 and 1,739 cases. Most of the missing data for disease progression were due to disability in the US cohort not having been measured in the standard ranked EDSS measurements, but rather in four grouped EDSS categories. Of the 302 index cases with primary progressive MS, 83 had definite, 80 probable, and 14 possible primary progressive disease; laboratory investigations were missing in 125 of these 302 cases. The exclusion of families from analyses requiring those clinical features that were missing reduced the sample size for some subgroup analyses.

Age and year at onset. There was concordance for age at onset within all families before and after adjusting the analysis for the potential confounding effects of gender, year of birth, country of origin, and disease course (correlation coefficient 0.24: 95% CI 0.20 to 0.35, $p < 0.001$; and 0.14: 95% CI 0.10 to 0.24, $p < 0.001$). A significant correlation was also observed when the affected sibling group was analyzed alone, before and after adjustment for the same confounders (correlation coefficient 0.31: 95% CI 0.28 to 0.42, $p < 0.001$; and 0.15: 95% CI: 0.10 to 0.25, $p < 0.001$). However, intrafamilial concordance was only demonstrated within the affected parent-child group after adjustment for these potential confounding factors (correlation

Table 1 Basic demographic and clinical details of included probands

Country	N	Age, y	Male	Female	Age at onset, y	Age at diagnosis, y	Mean EDSS	RR	SP	PP
United Kingdom	1,114	46.4	335	779	29.9	35.9	4.3	549	358	151
Nordic 1	118	47.6	51	67	29.1	35.1	4.9	36	58	24
Nordic 2	40	55.8	14	26	33.5	37.2	5.3	19	8	13
Nordic 3	48	44.3	19	29	28.3	34.6	3.8	28	14	6
Nordic 4	48	48.3	19	29	30.4	32.9	4.6	23	14	11
Nordic 5	18	49.6	7	11	31.5	36.8	3.2	13	3	2
Germany	6	38.9	5	1	24.6	28.3	3.9	3	2	1
Italy	10	37.8	5	5	26.6	27.7	3.6	5	3	2
Turkey	102	39.6	27	75	29	31.6	3.6	70	26	6
United States	416	45.4	115	301	30.3	34.4	N/A	233	145	36
Australia	114	50.5	26	88	N/A	36.9	N/A	74	19	20
Belgium	19	45.3	7	12	28.3	32.4	5.2	8	9	2
Hungary	26	40.5	7	19	26.2	29.5	2.7	20	2	4
Sardinia	231	43	73	158	29.4	34.1	3.9	152	53	26
Total	2,310	46	710	1,600	29.9	35.3	4.2	1,233	714	302

EDSS = Expanded Disability Status Scale; RR = relapsing-remitting; SP = secondary progressive; PP = primary progressive; Nordic 1 = Denmark; Nordic 2 = Sweden (Huddinge); Nordic 3 = Norway (Bergen); Nordic 4 = Norway (Oslo); Nordic 5 = Sweden (Göteborg); N/A = not available.

coefficient before adjustment -0.05 ; 95% CI -0.14 to 0.13 , $p = 0.96$; and after adjustment 0.12 ; 95% CI 0.01 to 0.30 , $p = 0.03$; figure).

In the year of onset analysis, adjusted for gender, year of birth, country, and disease course, we found significant concordance when all families (correlation coefficient 0.16 , 95% CI: 0.12 to 0.26 ; $p < 0.001$) and the affected sibling

group (correlation coefficient 0.18 , 95% CI: 0.13 to 0.29 ; $p < 0.001$) were evaluated. However, concordance for year of onset was not observed in the affected parent-child group (correlation coefficient 0.08 , 95% CI: -0.04 to 0.27 ; $p = 0.15$; figure).

Clinical course. For the analysis of clinical course concordance, we first considered probands in three disease

Table 2 Family structures of included probands

Country	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	Total
United Kingdom	326	138	19	3	22	—	2	10	—	2	2	524
Nordic 1	59	—	—	—	—	—	—	—	—	—	—	59
Nordic 2	20	—	—	—	—	—	—	—	—	—	—	20
Nordic 3	24	—	—	—	—	—	—	—	—	—	—	24
Nordic 4	24	—	—	—	—	—	—	—	—	—	—	24
Nordic 5	9	—	—	—	—	—	—	—	—	—	—	9
Germany	0	3	—	—	—	—	—	—	—	—	—	3
Italy	3	2	—	—	—	—	—	—	—	—	—	5
Turkey	30	16	1	—	1	1	—	—	—	—	—	49
United States	125	2	32	6	4	1	1	5	1	1	—	178
Australia	51	—	4	—	—	—	—	—	—	—	—	55
Belgium	7	1	1	—	—	—	—	—	—	—	—	9
Hungary	3	6	1	—	—	—	1	—	—	—	—	12
Sardinia	75	31	4	1	—	—	—	1	—	—	—	112
Total	757	199	62	10	27	2	4	16	1	3	2	1,083

F1 = two affected siblings; F2 = affected parent and child; F3 = three affected siblings; F4 = four affected siblings; F5 = affected sibling pair plus parent; F6 = affected trio plus child; F7 = affected individuals from three successive generations; F8 = affected sibling pair plus child; F9 = two affected siblings plus two affected children; F10 = three affected siblings plus parent; F11 = conjugal parents plus child; Nordic 1 = Denmark; Nordic 2 = Sweden (Huddinge); Nordic 3 = Norway (Bergen); Nordic 4 = Norway (Oslo); Nordic 5 = Sweden (Göteborg).

Figure. Intrafamilial correlation for various clinical features of all included families, as well as affected parent-child and sibling pairs analyzed separately. The analyses for age and year at onset are adjusted for gender, year of birth, country of origin, and disease course. The analyses for disease severity as measured by MSSS are adjusted for disease course, disease duration, year of birth, gender, and country of origin. The various analyses for disease course are adjusted for disease duration, age at onset, year of birth, gender, and country of origin. The figure shows correlation coefficients kappa, with 95% confidence intervals. * $p < 0.05$; ** $p < 0.001$.

categories: relapsing-remitting (1,233 individuals), secondary progressive (714 individuals), and primary progressive (302 individuals). The observed and expected intrafamilial concordance rates within these three groups are summarized in table 3.

There was concordance for disease course when all families with ≥ 2 affected first-degree relatives were analyzed together, before and after adjusting for country of origin, age at onset, year of birth, gender, and disease duration (kappa 0.14: 95% CI 0.09 to 0.18, $p < 0.001$; and 0.08: 95% CI 0.04 to 0.14, $p = 0.006$). Stratification of families into affected sibling and parent-child groups showed that this effect was only derived from the affected siblings, where concordance was stronger than in all families analyzed together, with and without adjustment for potential confounding factors (kappa 0.20: 95% CI 0.14 to 0.25, $p < 0.001$; and 0.12: 95% CI 0.06 to 0.19, $p < 0.001$; see the figure). Conversely, no concordance for disease course was demonstrated when the affected parent-child group was analyzed separately (unadjusted analysis: kappa -0.14 : 95% CI -0.25 to -0.02 , $p = 0.02$; and adjusted analysis: -0.04 : 95% CI -0.12 to 0.01 , $p = 0.09$; see the figure).

The results of this global analysis leave open the question of whether the concordance in affected siblings is derived from all subgroups, defined on the basis of clinical course. We therefore reconsidered these groups in various

combinations, classified on the basis of bouts, and disease progression from onset or after a period of relapses. We first analyzed all relapsing-remitting and secondary progressive case probands as a bout-onset group and compared these with primary progressive cases. We then grouped all progressive cases (primary and secondary) and compared these with the relapsing-remitting individuals in order to assess the independent effect of progression, whatever its clinical context. We compared individuals with bout onset who continued to manifest a relapsing-remitting course with those who had developed secondary progressive MS (excluding primary progression). Finally, after excluding all relapsing-remitting cases from the analysis, we compared only primary and secondary progressive disease courses. The results of these analyses are shown in the figure. Only data that were adjusted for the same covariables are described; however, no one of these adjustments did in fact influence the direction or significance of results.

Taken together, these analyses show that, although the intrafamilial correlation is strongest for the comparison of bout-onset vs primary progressive MS, concordance for the disease course in affected siblings is also observed when all cases with disease progression are compared with relapsing remitting MS that has not matured to the stage of secondary progression, and when those in whom the pro-

Table 3 Expected and observed concordance rates and number of concordant pairs (N) for clinical course in the considered family groups

		All families	Affected sibling group	Affected parent-child group
Relapsing-remitting	Observed; Expected	0.34 (N = 146); 0.30 (N = 117)	0.37 (N = 351); 0.31 (N = 293)	0.23 (N = 53); 0.27 (N = 63)
Secondary progressive	Observed; Expected	0.12 (N = 404); 0.10 (N = 356)	0.13 (N = 122); 0.09 (N = 88)	0.10 (N = 24); 0.13 (N = 29)
Primary progressive	Observed; Expected	0.032 (N = 38); 0.017 (N = 26)	0.038 (N = 36); 0.018 (N = 17)	0.009 (N = 2); 0.012 (N = 3)

Table 4 Clinical variables in the defined groups of affected relatives

	Number	Mean severity (MSSS)	Mean age at onset, y	Percentage RR/SP/PP
Parents	245	5.8	35.1	29/54/17
Children of affected parents	246	4.5	25.7	74/19/7
Affected fathers	58	5.5	37.1	34/41/25
Affected mothers	187	5.9	34.4	28/58/14
Children of affected fathers	59	4.9	25.3	74/20/6
Children of affected mothers	187	4.4	27.5	75/16/9
Individuals with 1 affected first-degree relative	1,905	5.7	30.7	55/31/14
Individuals with >1 affected first-degree relatives	405	4.8	29.8	59/30/11

RR = relapsing-remitting; SP = secondary progressive; PP = primary progressive.

gressive course was preceded by a period of relapses are compared with individuals having progression from disease onset. When primary progressive cases not fulfilling criteria for definite or probable primary progressive MS are excluded, there was a slight increase in the strength of correlations observed for the bout onset vs primary progressive category analysis (kappa 0.13: 95% CI 0.03 to 0.24 for all families; kappa 0.17: 95% CI 0.04 to 0.30 for the affected sibling group, data not shown in the figure), while the same maneuver led to a slight reduction of the correlation in the comparison primary vs secondary progressive cases (kappa 0.14: 95% CI -0.04 to 0.29; $p = 0.13$ for all families analyzed together; and kappa 0.18: 95% CI 0.02 to 0.40; $p = 0.03$ for the affected sibling group; data not shown in the figure).

Severity. Since disease severity in MS is increased in individuals with a primary progressive clinical course, and in males, we adjusted our analysis of disease severity, measured by the MSSS, for the covariates clinical course and gender together with country, disease duration, and year of birth. There was no concordance for severity before and after adjustment when all families were analyzed together (correlation coefficient 0.05: 95% CI -0.02 to 0.13, $p = 0.14$; and 0.02: 95% CI -0.05 to 0.10, $p = 0.53$), in the siblings pairs (correlation coefficient 0.07: 95% CI -0.02 to 0.16, $p = 0.11$; and 0.02: 95% CI -0.07 to 0.11, $p = 0.61$), or in the parent-child group (correlation coefficient 0.03: 95% CI -0.14 to 0.17, $p = 0.86$; and 0.02: 95% CI -0.12 to 0.18, $p = 0.69$) providing no evidence for intrafamilial concordance of disease severity (figure).

Comparison of parent-child pairs. After adjustment for year of birth, age at onset in children was on average 0.8 (95% CI: -2.5 to 4.1) years earlier than in their affected parents but this was not significant ($p = 0.63$; table 4). There was no significant difference in the delay between age at onset and diagnosis in children compared to their parent(s) ($p = 0.87$).

There was no significant difference in disease severity as measured with the MSSS when affected children were compared with their affected parents ($p = 0.26$).

In the parent of origin analysis (adjusted for country, year of birth, and clinical course) we found no difference in disease severity or age at onset when children of affected mothers were compared to children of affected fathers ($p = 0.08$ for age at onset; $p = 0.73$ for severity). There was no intrafamilial concordance for disease course when father-

child or mother-child pairs were analyzed separately ($p = 0.72$ and $p = 0.25$).

Effects of multiple cases within families. Individuals from families with >2 affected first-degree relatives tended to have slower disease progression than probands from families with only two affecteds (-0.18 MSSS points: 95% CI 0.02 to 0.34, $p = 0.02$), but there was no difference for age at onset ($p = 0.87$) or disease course ($p = 0.16$; table 4).

Discussion. The aim of this study was to show, using 1,083 multiplex families with ≥ 2 affected first-degree relatives, whether familial factors influence the natural history of MS. We confirm that age at onset is similar between all affected family members, with concordance for year of onset also being observed in sibling pairs but not parent-child combinations. The clinical course is concordant in affected siblings but not the subgroup of parents and their children, although this difference does not eliminate the effect on clinical course when all families are analyzed together. This familial influence on the natural history can be attributed to an effect on disease progression, either from onset or after a period of relapsing-remitting MS. There is no family concordance for disease severity, and no evidence for a parent of origin effect or genetic loading.

Previous studies have reported clustering for age at onset in affected siblings^{8,21-23} or in families with more complex pedigrees.^{11,24} Others have not reproduced this finding.^{10,25,26} Concordance for severity between affected family members has also been reported in some^{9,10,26} but not all series.^{8,11} Again, whereas course concordance between affected siblings is described,^{8,10} not all investigators have confirmed this finding.^{9,27}

A critical explanation for the ambiguity of these previous studies is that lack of power has significantly limited the ability to draw reliable conclusions from subgroup analysis. Previous investigators considered cohorts ranging in size from 85 to 512 individuals, derived from 40 to 250 families. Thus, even the subgroups we studied included significantly larger sample sizes than the totality of most previous

surveys. Furthermore, methodologic variation is likely to account for at least some of these inconsistencies. For example, in order to characterize disease severity, some investigators simply divide the EDSS score by disease duration to derive a progression index,¹⁶ whereas others use crude cross-sectional EDSS scores with no correction for disease duration.^{7,10}

The vast majority of probands included in this survey are Caucasian and of European (particularly Northern European) descent. It is therefore possible that this sampling could have introduced genetic bias and that our findings cannot be universally applied to MS families from other ethnic/racial groups.

Our sample of families is not strictly population based, and so may be subject to recruitment bias. That said, the individual collections were obtained from investigators to whom notification of a high proportion of prevalent familial cases would be expected, and without any obvious selection for clustering of clinical characteristics. Although there may be a tendency for familial cases to more readily seek medical attention, the demographic features of our sample are similar to published population-based cohorts.²⁸⁻³⁰ Nevertheless, in order to minimize the possibility of recruitment bias, we adjusted our analyses for country of origin.

Clinical assessments, particularly from multiple sites, can be subject to inter-rater variability, and it is possible that this could have influenced our results in either direction. As most of the data were collected retrospectively, it was not feasible to reassess a cohort of probands in order to quantify this potential confounder for each group. However, we deliberately limited our clinical endpoints to include only very clearly defined features (age at onset, course, and severity) and used country of origin as a confounding factor in our analyses in order to minimize the effects of inter-rater variability as best as possible.

Assessments of age at onset are limited by the exclusion of relatives who develop symptoms after the completion of data collection. Therefore, we also adjusted our analyses for year of birth in order to control for this potential confounding factor. Individuals in whom genetic susceptibility factors are loaded (i.e., familial cases) are expected to develop MS earlier in life, since fewer additional events are then needed for disease expression to manifest. However, most large studies^{24,28} have not shown a difference in age at onset between sporadic and familial patients with MS (although one could speculate that familial cases who have an accumulation of genetic susceptibility risk factors should have a lower age at onset). It therefore seems likely that additional familial risk factors which may not necessarily be linked to disease susceptibility influence age at onset. It is possible that these additional familial risk factors could partly also influence the inflammatory component of the disease, as has been shown in HLA DR15 positive individuals, who are more likely to be younger at onset.^{31,32}

Our analyses of concordance provide evidence that

familial factors influence the clinical course of MS. This conclusion has implications for the design of future genetic and epidemiologic studies, and informs concepts on the pathogenesis of MS.

The effect we observed on course concordance was strongest for the comparison of primary progressive vs bout-onset disease, and increased with the diagnostic certainty of primary progressive MS. However, there was also significant concordance between siblings when relapsing-remitting and secondary progressive groups were evaluated separately, when all progressive cases were compared with the relapsing-remitting group; and in direct comparison of the primary and secondary progressive cases, indicating that the categories of relapsing-remitting, secondary progressive, and primary progressive disease each contributed to the effect on course concordance. Taken together, these data provide evidence for a familial effect on progression either from onset or following a period of relapsing-remitting disease. There are differences between primary progressive and bout-onset forms of MS in sex ratio, age at onset, rates at which disability accumulates, and paraclinical abnormalities; and a significant proportion of patients whose illness is progressive from onset have superimposed relapses.^{19,33} While conversion to disease progression often occurs later in patients with relapsing-remitting MS, some individuals never enter the secondary progressive stage. Since progression is considered to reflect tissue atrophy and axonal degeneration in MS,³⁴ it follows that these putative factors may predispose to the neurodegenerative component. Our findings are best interpreted as indicating that primary progressive, relapsing-remitting disease, and secondary progressive MS represent a continuous spectrum of disease phenotypes in which risk factors drive the relative balance, at any one time, of inflammatory and degenerative contributions to tissue injury. Individuals with a low threshold for neurodegeneration would more probably manifest disease progression, whereas individuals with a lower risk of this component but more inflammatory activity would tend to the relapsing-remitting phenotype.

For affected individuals, disease severity is arguably the most relevant aspect of the illness and, particularly in multiplex families, newly diagnosed individuals understandably want to know whether the family experience has predictive value for their own illness. The issue of how to best evaluate disease severity has received much recent attention, particularly in the context of new disease-modifying therapies. The EDSS,¹⁶ which measures impairment and disability in a single score, is still the most widely used clinical rating scale of severity, even though it is insensitive to clinical changes that do not affect mobility (such as cognitive or upper limb function).³⁵ The recently developed MSSS used in our survey ranks disability in the individual by reference to a very large number of other patients having the same

disease duration and corrects the EDSS for disease duration in cross-sectional studies.¹⁷

Disease progression is often considered to be the harbinger of severity, but we found no evidence that clinical severity is more likely to be similar between two affected family members than a pair of unrelated individuals with MS. It is possible that an effect on disease severity would have emerged with even larger sample sizes or other methods of severity assessment that include MRI data, upper limb, or cognitive function. However, within the limits of the current study where many data were collected retrospectively it was not feasible to use these methods of severity assessments. Although we did observe intrafamilial concordance for clinical course in affected sibpairs, the overall size of this effect is very modest and not associated with clustering of severity in affected siblings. Affected children were no more or less likely to experience severe disease than their affected parent. Furthermore, the gender of the affected parent did not influence disease severity in their affected children. These conclusions have significant implications for the counseling of patients: affected family members should not draw personal conclusions for their own prognosis and expected disease severity from observing the condition of their affected relative(s).

It is important to resolve the issue of whether familial effects can be attributed solely to genetic risk factors or reflect the importance of a shared environment. Our position is that these familial patterns are more likely to implicate genetic than environmental risk factors in mediating predisposition to inflammatory and neurodegenerative aspects of the disease. However, two observations could be interpreted as indicating a more important and independent contribution from environmental conditions. Previous investigators have argued that concordance for age at onset implies a genetic contribution to disease susceptibility, whereas exposure to a shared environment would result in concordance for year of onset between affected family members. In addition to the similar age at onset, we found significant concordance for year at onset in affected siblings. The evidence for course concordance only in sibling pairs, but not other first-degree relatives, could also be interpreted as indicating a contribution from environmental factors (which are effective in childhood/teenage years) in determining course concordance. Siblings may have less genetic sharing than must occur between parents and their children, but they are more likely to share environmental exposure during development.

Overall, the results of this study provide evidence that familial factors significantly influence both susceptibility and the clinical course, but not the eventual severity, of MS. These data have significant implications for the counseling of patients with affected family members. They indicate that the analysis of genetic studies should be stratified (according to clinical course rather than severity) in order to

separate effects that increase susceptibility to MS from those that determine the pattern of tissue injury and its clinical expression as disease progression. The independent effect on disease progression further supports the concept that the natural history of MS depends on a complex interplay of inflammatory activity in the CNS and axon degeneration.

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NeuroImages

Figure. (A) The noncontrast CT of the cervical spine revealed amorphous calcification of the prevertebral space at the C1-C2 level (arrow) with the expansion of the retropharyngeal space (). The axial and coronal non-contrast CT of the neck (B and C) showed calcification at the tendon of the longus colli muscle (arrows).*

Neck pain and calcium deposition

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A 43-year-old man had acute neck pain, sore throat, dysphagia, and low-grade fever upon awakening. His examination was unremarkable except for significantly limited cervical range of motion

due to pain. CT demonstrated calcification anterior to C1-C2 with thickened prevertebral soft tissues due to effusion (figure). Retropharyngeal calcific tendinitis is an uncommon condition caused by deposition of calcium hydroxyapatite crystal in the longus colli tendon which provokes local inflammation.^{1,2} The pathophysiology of the deposition is unknown. Retropharyngeal calcific tendinitis is often misdiagnosed as retropharyngeal abscess but the characteristic calcium deposition is diagnostic. It is self-limiting and the calcium deposition usually resolves completely.¹

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