

Familial Aggregation Patterns in Multiple Sclerosis and Their Association with Disease Severity

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ABSTRACT

Introduction: Familial aggregation is a well-recognized feature of multiple sclerosis (MS). However, there is considerable heterogeneity in how disease susceptibility and clinical outcomes cluster within families. Although the relationship between parental lineage effects and MS risk has been previously investigated, their association with long-term disease severity remains poorly understood. In this study, we sought to explore patterns of familial aggregation according to maternal and paternal lineage in patients with familial MS and to evaluate whether these patterns are associated with long-term disease severity.

Methods: This retrospective observational study included 110 patients with familial MS from 50 families. Among patients in whom parental lineage could be determined, familial aggregation was classified as maternal or paternal based on comprehensive pedigree review. Clinical characteristics, disability status measured by the Expanded Disability Status Scale (EDSS), and time-adjusted disease severity assessed using the Multiple Sclerosis Severity Score (MSSS) were compared between lineages.

Results: Maternal and paternal lineages differed significantly in the distribution of affected relatives by degree of relatedness ($p=0.040$); this difference was primarily driven by a higher proportion of first-degree affected relatives in the maternal-line group. No significant differences were observed between maternal and paternal lineages in early clinical characteristics, including age at onset, sex distribution, and initial clinical symptom distribution. Although EDSS scores were comparable between groups, MSSS values were significantly higher among patients in the maternal-line group (median 4.5 vs. 1.6, $p=0.016$).

Conclusions: The parental lineage through which familial aggregation occurs in MS may be associated with long-term disease severity. These findings suggest that lineage-based approaches may offer valuable insights into the clinical profile of familial MS, while also underscoring the need for further studies integrating genetic, epigenetic, and longitudinal data.

Keywords: disease severity, familial aggregation, familial multiple sclerosis, multiple sclerosis, multiple sclerosis severity score, parental lineage

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INTRODUCTION

The etiology of multiple sclerosis (MS) is shaped by complex interactions between genetic susceptibility and environmental factors (1). Within this framework, familial aggregation has long been recognized as one of the most consistent epidemiological features of the disease (2–4). Large population-based studies conducted across different geographic regions have demonstrated that the highest recurrence risk is observed among first-degree relatives, particularly among siblings (5–10). In contrast, studies investigating maternal and paternal influences on disease susceptibility have yielded inconsistent results. While some family-based studies have suggested that clustering along the maternal lineage may be more pronounced (11,12), large-scale population-based registry analyses have reported similar recurrence risks among children of affected mothers and fathers (6,13). Moreover, the impact of familial factors on disease course and long-term disease severity remains controversial (2). Together, these findings point to substantial heterogeneity across populations and study designs.

Highlights

- Familial aggregation in MS shows heterogeneity according to parental lineage.
- Familial MS shows predominant maternal-line clustering.
- Early clinical features do not differ between maternal and paternal lineage cases.
- Maternal-line aggregation is associated with higher MSSS.

Most previous studies examining familial MS have focused on limited kinship relationships, such as parent-child or sibling pairs, and have primarily addressed disease susceptibility. In this study, familial MS cases were classified according to maternal and paternal lineages, and

the relationships between these lineages and both disease occurrence and disease severity were examined. A clearer understanding of these relationships may contribute to a more refined clinical characterization of familial MS and provide a foundation for future genetic studies. We hypothesized that parental lineage would be associated with time-adjusted disease severity, as reflected by the MSSS.

METHODS

Study design and patient selection

This retrospective observational study was conducted at the Multiple Sclerosis and Myelin Disorders Unit, Department of Neurology, Istanbul Faculty of Medicine, Istanbul University. All patients evaluated in the MS outpatient clinic between January and November 2015 were screened for study eligibility.

Inclusion and exclusion criteria

Patients were included if they had a confirmed diagnosis of MS according to the 2010 McDonald criteria, together with at least one biologically related family member who independently met the 2010 McDonald criteria for MS within the same pedigree. A uniform diagnostic standard was therefore applied to both probands and affected relatives at the time of inclusion, irrespective of the criteria originally used at the time of any relative's historical diagnosis. Adequate clinical and familial documentation was required to allow reliable lineage classification. Exclusion criteria included unverifiable MS diagnoses among relatives, incomplete clinical records, or the presence of any alternative demyelinating disorder in a family member. After applying these criteria, 110 patients from 50 families were eligible for analysis.

Degree of relatedness and consanguinity

All MS-affected relatives were classified by degree of relatedness using standard pedigree terminology. First-degree relatives included parents, siblings and offspring; second-degree relatives included aunts, uncles, grandparents, nieces and nephews; and third-degree relatives consisted of cousins. This classification enabled quantification of familial aggregation and approximation of genetic load.

Consanguinity was assessed through pedigree review and patient report. Because consanguinity may increase shared genetic load in familial neurological disorders, it was analyzed as a separate variable.

Maternal and paternal lineage assignment

Lineages were defined according to the biological side of the family in which MS occurred. The maternal lineage included the mother and relatives on the maternal side of the family, whereas the paternal lineage included the father and relatives on the paternal side.

Lineage assignment was based only on affected relatives whose position in the pedigree could be clearly attributed to either the maternal or paternal branch of the proband. An affected mother or father, as well as affected relatives whose position within a specific parental branch could be clearly established from the pedigree, were considered informative for lineage assignment. In contrast, affected siblings in the same generation as the proband, as well as affected offspring and nieces/nephews in subsequent generations, were not used for lineage classification because these relationships alone did not indicate whether familial aggregation occurred through the maternal or paternal branch. When affected relatives were present on both the maternal and paternal sides of the family, lineage was assigned according to the parental branch containing the affected relative most closely related to the proband.

Analytical sample for lineage-specific comparisons

Among the 110 patients with familial MS, pedigree information allowed unambiguous assignment of familial aggregation to a single parental lineage in 49 patients. Of these, 30 were classified as having maternal-line aggregation and 19 as having paternal-line aggregation and were included in the lineage-specific comparative analyses. The remaining 61 patients were retained in the descriptive analyses of the overall familial MS cohort but were excluded from lineage-specific comparisons because they could not be classified as maternal or paternal according to the predefined lineage-assignment rules.

Clinical data collection

Clinical variables were extracted from medical records, standardized outpatient forms and updated pedigree diagrams using predefined criteria.

Age at onset was defined as the age of first neurological symptom attributable to MS. Initial symptoms were categorized as motor, sensory, brainstem, optic neuritis or other. Onset pattern was labeled monosymptomatic or polysymptomatic depending on the number of functional systems involved. Recovery following the first attack, the interval between the first two attacks and dominant relapse symptoms were recorded using standardized definitions. Multiple sclerosis subtype (relapsing-remitting, secondary progressive or primary progressive) was assigned according to established clinical criteria.

Disability was measured using the Expanded Disability Status Scale (EDSS). Disease duration was defined as the interval between symptom onset and the most recent clinical evaluation. Multiple sclerosis severity score (MSSS) was calculated using the Roxburgh algorithm, which integrates EDSS and disease duration into a standardized measure of long-term disease severity (14). All variables were independently reviewed by two neurologists, and discrepancies were resolved by consensus.

Statistical analysis

Analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program version 21.0. The distribution of continuous variables was assessed using the Shapiro-Wilk test together with visual inspection of histograms and Q-Q plots. Continuous variables are presented as mean and standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables are summarized as counts and percentages.

Comparisons between maternal and paternal lineage groups were performed using the Mann-Whitney U test for continuous variables and the chi-square, Fisher's exact, or Fisher-Freeman-Halton exact test for categorical variables, as appropriate. For principal categorical comparisons, effect sizes were additionally reported as odds ratios with 95% confidence intervals for 2×2 contrasts and as Cramer's V for contingency tables with more than two categories. For the 3×2 comparison of degree of relatedness by lineage, the Fisher-Freeman-Halton exact test was performed as a sensitivity analysis because of small expected cell counts. For the principal Mann-Whitney U comparison of MSSS between lineage groups, the rank-biserial correlation coefficient r was additionally reported as an effect-size estimate, with its 95% confidence interval calculated using Fisher's z transformation; $r \geq 0.1$, ≥ 0.3 , and ≥ 0.5 were interpreted as small, medium, and large effects, respectively. Statistical significance was defined as a two-tailed $p < 0.05$.

This study was conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational studies; the completed STROBE checklist is provided as Supplementary Material.

RESULTS

Cohort characteristics

A total of 110 patients with familial MS were included in the analysis. Baseline demographic and familial characteristics are summarized in Table 1. The cohort was predominantly female (69.1%). The median age at disease onset was 28 years (IQR: 23–34). Female patients had a median onset age of 29 years (IQR: 24–35), whereas males exhibited a lower median onset age of 25 years (IQR: 20–30). Compared with the 49 patients who could be classified by parental lineage, the 61 patients who could not be classified by parental lineage had a later median age at onset (30 vs. 25 years), higher median EDSS (4.5 vs. 2.0), higher median MSSS (4.35 vs. 2.82), and longer median disease duration (15 vs. 10 years).

A first-degree relative with MS was identified in 44.5% of patients, and consanguinity was reported in 22.7% of the cohort. As shown in Figure 1, siblings represented the largest subgroup among first-degree affected relatives, with sisters comprising the most frequently affected category.

Familial aggregation patterns by lineage

Maternal-line clustering was more common than paternal-line clustering (27.3% vs. 17.3%). Lineage-specific patterns of familial aggregation are detailed in Table 2. When all affected relatives across the first three degrees of biological relatedness were considered collectively, the distribution of affected relatives differed significantly between maternal and paternal lineages ($\chi^2=6.4$, $p=0.040$). The effect size for this association was moderate (Cramer’s $V=0.36$, $df=2$); a Fisher-Freeman-Halton exact sensitivity analysis yielded a consistent result ($p=0.046$). This difference was driven primarily by a markedly higher proportion of first-degree affected relatives within the maternal lineage (43.3% vs. 10.5%). Consanguinity rates did not differ significantly between lineages ($p=0.458$; OR 2.12, 95% CI 0.38–11.83).

Early clinical features

Early clinical characteristics did not differ significantly between maternal and paternal lineages (Table 3). Age at onset, sex distribution ($p=0.154$; OR 0.41, 95% CI 0.12–1.42 for female sex), initial symptom category ($p=0.679$; Cramer’s $V=0.22$), and mono- versus polysymptomatic onset ($p=0.612$)

Table 1. Baseline demographic and familial characteristics of the familial multiple sclerosis cohort, including sex distribution, age at onset, degree of affected relatives, consanguinity status, and maternal- versus paternal-line clustering

Variable	Total cohort (n=110)
Female sex, n (%)	76 (69.1)
Male sex, n (%)	34 (30.9)
Age at disease onset, median (IQR), years	28 (23–34)
Age at disease onset in females, median (IQR), years	29 (24–35)
Age at disease onset in males, median (IQR), years	25.0 (20–30)
Degree of relatedness, n (%)	
1 st -degree	49 (44.5)
2 nd -degree	19 (17.3)
3 rd -degree	22 (20.0)
More distant	20 (18.2)
Consanguinity, n (%)	
Present	25 (22.7)
Absent	85 (77.3)
Parental-line clustering, n (%)	
Maternal-line MS	30 (27.3)
Paternal-line MS	19 (17.3)
Not classifiable by parental lineage	61 (55.4)

Among the 61 patients who could not be classified by parental lineage, the affected relative was a first-degree relative (sibling or offspring) in 34 patients, a second-degree relative (niece or nephew) in 7, and a relative beyond the third degree in 20. IQR: interquartile range; MS: multiple sclerosis.

showed no significant group differences. These findings indicate that early disease expression was broadly similar regardless of the lineage of familial aggregation.

Disease course and severity

Lineage-related differences emerged in long-term disease severity metrics (Table 4). MS disease course subtype (relapsing-remitting versus secondary progressive) did not differ significantly between lineages ($p=0.224$; OR 4.50, 95% CI 0.50–40.75 for secondary progressive course).

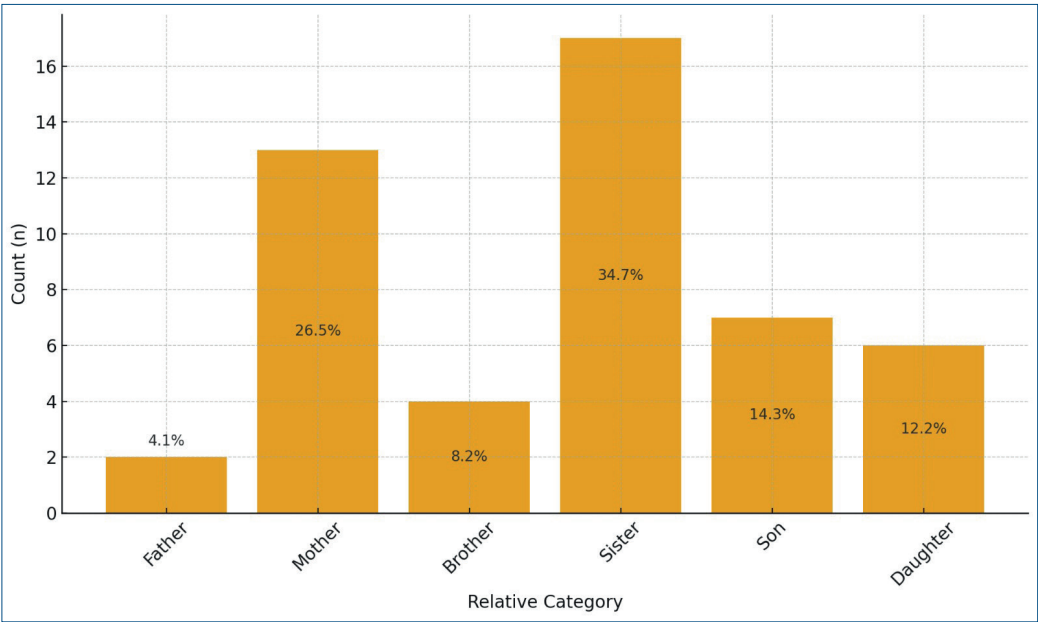


Figure 1. Distribution of first-degree relatives affected by MS among the overall familial MS cohort (n=49; 44.5% of the 110-patient cohort).

Table 2. Familial aggregation and consanguinity by maternal versus paternal lineage

Variable	Paternal lineage (n=19)	Maternal lineage (n=30)	p-value
Degree of affected relative, n (%)			0.040
1 st -degree relative	2 (10.5)	13 (43.3)	
2 nd -degree relative	5 (26.3)	7 (23.3)	
3 rd -degree relative	12 (63.2)	10 (33.3)	
Consanguinity, n (%)			0.458
Present	2 (10.5)	6 (20.0)	
Absent	17 (89.5)	24 (80.0)	

p values were calculated using χ^2 test or Fisher's exact test.

Table 3. Demographic and early clinical characteristics by maternal and paternal lineage in familial MS

Variable	Paternal lineage (n=19)	Maternal lineage (n=30)	p-value
Sex, n (%)			0.154
Female	14 (73.7)	16 (53.3)	
Male	5 (26.3)	14 (46.7)	
Age at disease onset, mean $\pm$ SD, years	22.8 $\pm$ 7.7	27.2 $\pm$ 9.0	0.168
Initial presenting symptom, n (%)			0.679
Motor	5 (26.3)	11 (36.7)	
Brainstem	4 (21.1)	7 (23.3)	
Sensory	6 (31.6)	4 (13.3)	
Optic neuritis	3 (15.8)	6 (20.0)	
Other	1 (5.3)	2 (6.7)	
Onset pattern, n (%)			0.612
Monosymptomatic	10 (52.6)	18 (60.0)	
Polysymptomatic	9 (47.4)	12 (40.0)	

p values were calculated using the Mann-Whitney U test, χ^2 test, or exact tests, as appropriate. SD: standard deviation.

Table 4. Attack features, disease course, and disability measures by familial lineage

Variable	Paternal lineage (n=19)	Maternal lineage (n=30)	p-value
Full recovery after first attack, n (%)	18 (94.7)	24 (80.0)	0.224
Interval between first two attacks, months, median (IQR)	24 (12–46)	21 (7–36)	0.488
Dominant relapse symptom, n (%)			0.098
Motor	9 (47.4)	14 (46.7)	
Brainstem	2 (10.5)	9 (30.0)	
Sensory	6 (31.6)	2 (6.7)	
Optic neuritis	2 (10.5)	5 (16.7)	
Other	0	0	
MS disease course subtype, n (%)			0.224
RRMS	18 (94.7)	24 (80.0)	
SPMS	1 (5.3)	6 (20.0)	
EDSS, median (IQR)	2.0 (1.0–3.0)	3.0 (1.5–6.0)	0.160
Disease duration, years, median (IQR)	11.0 (8.0–15.0)	10.0 (3.7–19.2)	0.429
MSSS, median (IQR)	1.6 (0.6–2.9)	4.5 (2.1–6.7)	0.016

p values were calculated using the Mann-Whitney U test, χ^2 test, or exact tests, as appropriate. EDSS: expanded disability status scale; IQR: interquartile range; MSSS: multiple sclerosis severity score; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

EDSS values tended to be higher among patients in the maternal-line group, although this difference did not reach statistical significance (median 3.0 vs. 2.0, $p=0.160$). Although EDSS scores and disease duration were comparable between lineages, MSSS values were significantly higher

among maternal-line cases (median 4.5, IQR 2.1–6.7 vs. median 1.6, IQR 0.6–2.9; Mann-Whitney $U=168$, $Z=-2.411$, $p=0.016$). The corresponding rank-biserial correlation was $r=0.41$ (95% CI 0.15–0.62), indicating a medium effect.

Overall, these findings indicate that despite comparable early clinical features, patients whose familial aggregation occurred along the maternal lineage exhibited higher time-adjusted disease severity as reflected by MSSS.

DISCUSSION

In this study, familial aggregation patterns within the MS cohort were found to differ according to parental lineage, with clustering occurring more frequently along the maternal lineage. In addition, the distribution of affected relatives by degree of relatedness differed significantly between the maternal and paternal lineages ($p=0.040$); this difference was primarily driven by a higher proportion of first-degree affected relatives in the maternal lineage. These findings indicate that familial disease burden is asymmetrically distributed between parental lineages.

No significant differences were observed between maternal and paternal lineage groups in terms of early clinical characteristics. Age at disease onset, sex distribution, presenting symptoms, and mono- versus polysymptomatic onset patterns were comparable between the groups. In contrast, MSSS values were significantly higher among patients with familial aggregation along the maternal lineage ($p=0.016$). This observation suggests that lineage-related differences may be reflected in long-term disease trajectory rather than in the initial clinical presentation.

Familial aggregation in MS has been consistently demonstrated across different populations (2). Large-scale population-based studies and family cohorts have shown that first-degree relatives carry the highest risk of developing MS (5,6). More recent quantitative analyses have further indicated that this risk pattern is preserved even when stratified by age at onset or clinical phenotype (3,7). From this perspective, the predominance of affected siblings among first-degree relatives in our cohort is consistent with previous findings from diverse geographic regions, including multiplex families from Brazil as well as cohorts reported from Australia and the United Kingdom (8–10).

Beyond overall familial risk, only a limited number of studies have examined maternal and paternal transmission patterns. In multiplex families from the Netherlands, Hoppenbrouwers and colleagues reported that maternal relationships were more frequent than paternal relationships (12). Similarly, analyses of avuncular pairs and half-sibling comparisons have demonstrated higher recurrence risks associated with the maternal lineage (11,15). Despite these epidemiological observations suggesting maternal predominance, no independent susceptibility locus has been identified on the X chromosome (16). This discrepancy implies that parent-of-origin effects may not be fully explained by classical genetic linkage and that non-genetic or epigenetic mechanisms may also contribute (1).

Indeed, not all studies have consistently supported a maternal effect. For example, Kantarci and colleagues reported that paternal effects may be more prominent in disease transmission within their cohort (17). In population-based registry analyses from Canada and Sweden, similar recurrence risks were observed among children of affected mothers and fathers (6,13). Given that most of these studies focused primarily on parent-child pairs and did not systematically evaluate broader maternal or paternal kinship networks, methodological differences may partly account for the inconsistencies reported in the literature.

Findings related to disease course and severity in familial MS are similarly heterogeneous. Several studies comparing familial and sporadic MS cases have reported no significant differences in clinical course or disability outcomes (18–21). In contrast, sibling-based analyses and large

clinical cohorts have suggested that, despite comparable cross-sectional disability levels, familial MS cases may transition to progressive phases earlier or exhibit faster disease progression (22,23). One of the few studies incorporating MSSS, conducted by Andrijauskis and colleagues, reported higher MSSS values and a tendency toward a more aggressive disease course in familial MS compared with sporadic cases (24). Conversely, Hensiek and colleagues did not identify a clear difference in disease severity between familial and sporadic MS; in a parent-of-origin analysis restricted to parent-child pairs and adjusted for country, year of birth, and clinical course, they similarly found no significant difference in MSSS between children of affected mothers and children of affected fathers ($p=0.73$) (25).

In this study, the observation that MSSS values differed despite comparable EDSS scores and disease duration is noteworthy and requires cautious interpretation. Because MSSS is derived from EDSS and disease duration using the Roxburgh decile algorithm, it reflects duration-adjusted disability severity rather than cross-sectional disability alone (14). The wider EDSS distribution in the maternal-line group (IQR 1.5–6.0 vs. 1.0–3.0) suggests that a subset of these patients reached higher disability levels within comparable disease durations, which may have translated into higher duration-adjusted severity percentiles. The numerically higher proportion of secondary progressive disease in the maternal-line group (20.0% vs. 5.3%) may also have contributed to this difference, whereas the difference in sex distribution did not reach statistical significance. Therefore, the higher MSSS observed in the maternal-line group should be interpreted as an exploratory finding that may reflect lineage-related variation in long-term disease severity, but requires confirmation in larger, preferably multicenter cohorts.

From a biological standpoint, the more pronounced aggregation along the maternal lineage has been linked to mechanisms extending beyond classical Mendelian inheritance. Sadovnick proposed that unaffected mothers may transmit a higher risk than fathers, highlighting the potential roles of parent-of-origin effects, epigenetic regulation, and X chromosome-related processes (26). Experimental and conceptual studies have further emphasized the contribution of sex chromosomes and epigenetic mechanisms in shaping immune responses and disease expression in MS (27). In addition, prenatal and intrauterine environmental factors have been proposed as modulators of long-term MS susceptibility, underscoring the possible importance of maternal biological influences (28). Although the present study does not directly test these mechanisms, the findings can be interpreted within these biological frameworks.

Consanguinity represents another important factor that may influence the genetic background of familial multiple sclerosis. In our cohort, the rate of consanguinity was 22.7%, although it did not differ significantly between maternal and paternal lineage groups. Evidence regarding the relationship between consanguinity and MS risk remains inconsistent in the literature (29,30). These findings suggest that the impact of consanguinity on MS may vary depending on population-specific genetic backgrounds and environmental factors. In our study, consanguinity did not appear to explain lineage-specific clustering; however, it should still be considered as a background factor that may contribute to shared genetic susceptibility within families.

Finally, it is noteworthy that studies systematically evaluating familial aggregation across entire maternal and paternal lineages remain scarce. Most previous investigations have focused on isolated kinship relationships and have not directly assessed whether MS clusters consistently along a single ancestral line. In the present study, lineage-specific analyses were restricted to patients in whom familial aggregation

could be assigned to either the maternal or paternal branch according to the predefined lineage-assignment rules. This approach allowed a more direct and methodologically consistent assessment of lineage-specific aggregation patterns.

Several limitations should be considered when interpreting the findings of this study. The retrospective, single-center design limits causal inference and may reduce the generalizability of the findings to populations with different genetic backgrounds, environmental exposures, or healthcare settings. The absence of molecular genetic analyses precluded direct assessment of specific genetic variants, epigenetic effects, or parent-of-origin mechanisms that might underlie lineage-specific patterns. In addition, because multiple affected individuals from the same family were included in the analysis, within-family correlation, that is, non-independence of observations, may have influenced comparisons between lineage groups and should be considered when interpreting the reported associations. Furthermore, because lineage assignment relied on affected relatives who could be clearly attributed to a specific parental branch and because the availability of such informative relatives may have varied across families, this methodological framework may have influenced the observed distribution of degrees of relatedness to some extent.

Although MSSS provides a time-adjusted measure of disease severity, the lack of prospective longitudinal follow-up data and advanced imaging biomarkers may have limited the ability to fully capture the dynamics of disability accumulation over time. In addition, the use of the 2010 McDonald diagnostic criteria represents an important limitation. The revised 2017 criteria allow for earlier and more sensitive diagnosis; therefore, the application of these updated criteria might have led to the identification of additional affected family members and potentially altered the observed patterns of familial aggregation.

Conclusions

In our cohort, clustering along the maternal lineage was observed more frequently and was associated with higher time-adjusted disease severity, despite similar early clinical features and comparable cross-sectional disability levels. These findings may be relevant to long-term prognostic considerations in patients with familial MS. Multicenter, prospective studies that integrate detailed pedigree data with genetic, epigenetic, and longitudinal clinical information may help clarify the links between familial lineage and disease progression, and ultimately enhance prognostic stratification in familial multiple sclerosis.

SUPPLEMENTARY MATERIAL

https://www.noropsikiyatriarsivi.com/uploads/NPA_29434_EN_SUPPL.pdf

Ethics Committee Approval: Ethical approval was obtained from the Institutional Ethics Committee of İstanbul Faculty of Medicine (Protocol 2017/539) for the retrospective analysis of clinical data collected during routine care between January and November 2015.

Informed Consent: The study adhered to the Declaration of Helsinki. Because only anonymized retrospective data were used, informed consent was waived. All clinical and familial information was fully de-identified before analysis to ensure confidentiality.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - ME, MK, MTS; Design - ME, MK, MTS; Supervision - ME, MK, MTS; Resource - ME, MK, MTS; Materials - ME, MK, MTS; Data Collection and/ or Processing - ME, MK, MTS, TUC, TG; Analysis and/ or Interpretation - ME, MK, MTS; Literature Search - MTS, TUC, TG; Writing - MTS, MK, ME; Critical Reviews - MTS, MK, ME.

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