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RESEARCH ARTICLE

Pediatric-onset Multiple Sclerosis in Families: A Distinct Phenotype

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Abstract

Objective: Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system. Pediatric-onset MS (POMS) represents a distinct subgroup with unique clinical and immunological features. Although familial predisposition contributes to MS pathogenesis, data on familial POMS remain limited. To investigate the demographic and clinical characteristics of familial POMS and compare them with those of the broader MS patient cohort.

Materials and Methods: We performed a retrospective descriptive analysis of 3,411 patients diagnosed with MS at a university hospital MS center. Of these, 523 had a family history of MS, and 251 were identified as having POMS, defined as disease onset before age 18. Data on demographic and clinical characteristics, cerebrospinal fluid (CSF) findings, treatment history, and disability scores were analyzed using IBM SPSS version 25.

Results: Among 3,411 MS patients, 251 (7.36%) had POMS. Of these, 177 (70.5%) were female and 74 (29.5%) were male. Most had a relapsing-remitting course (236 patients, 94%), while 15 (6%) developed secondary progressive MS; no cases of primary progressive MS were identified. Within the 523 familial MS cases, 51 (9.75%) had POMS. CSF analysis was available for 31 patients, 24 (77.4%) of whom showed MS-specific abnormalities; 13 (41.9%) had an elevated IgG index. Regarding treatment history, 59 patients (23.5%) received first-line therapies, 123 (49%) second-line therapies, and 69 (27.5%) third-line therapies. The mean Expanded Disability Status Scale score was 1.3.

Conclusion: This study adds to the literature on POMS by providing detailed demographic, clinical, and familial data. The findings underscore the importance of considering familial predisposition when evaluating pediatric MS and highlight the need for further research into the genetic and immunological mechanisms underlying POMS. Long-term follow-up and genetic studies are warranted to deepen understanding of this uncommon yet clinically important MS subtype.

Keywords: Familial MS, multiple sclerosis, onset multiple sclerosis, pediatric-onset multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system characterized by a complex interplay of genetic and environmental factors (1). Although most cases occur in adults, a subgroup arising in children-referred to as pediatric-onset MS (POMS)-has distinct biological and clinical features (2,3). The International Pediatric Multiple Sclerosis Study Group defines pediatric MS as disease onset before the age of 18 and highlights the importance of age-specific diagnostic criteria and management strategies (4,5). Globally, epidemiological data on POMS remain limited; according to 2013 estimates from the MS International Federation, the worldwide prevalence was 0.63 per 100,000 people (6).

The primary distinction between POMS and adult-onset MS (AoMS) lies in the clinical course. Most POMS cases follow a relapsing-remitting pattern (RRMS), characterized by episodes of neurological dysfunction followed by remission.

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Immunologically, POMS differs in cerebrospinal fluid (CSF) profiles, particularly in lower rates of oligoclonal band (OCB) positivity compared with adults. These differences suggest distinct disease pathophysiology, potentially reflecting more robust immune responses in younger patients or unique genetic predispositions.

Familial predisposition plays a significant role in MS pathogenesis. Familial pediatric MS refers to cases in which patients have a first- or second-degree relative diagnosed with the disease. Genetic susceptibility-particularly associations with the HLA-DRB1*1501 allele-along with environmental triggers such as Epstein-Barr virus infection, has been implicated in familial MS (7,8). However, studies focusing specifically on the familial aspect of POMS remain scarce, limiting our understanding of its genetic and environmental determinants. This study therefore aimed to investigate the demographic and clinical characteristics of familial POMS and to compare them with non-pediatric familial MS, thereby contributing to the existing knowledge base.

Materials and Methods

The study was approved by the Karadeniz Technical University Faculty of Medicine Clinical Research Ethics Committee (decision no.: 2014/125, date: 25.02.2015). We conducted a retrospective descriptive study of 3,411 patients diagnosed with MS at the MS center of a university hospital. POMS was defined as disease onset before 18 years of age, in accordance with the 2017 revised McDonald criteria. Familial MS cases were identified by the presence of a first- or second-degree relative with an MS diagnosis. Within the familial MS subgroup, patients were further categorized as having POMS or AoMS based on their age at disease onset.

Statistical Analysis

Demographic and clinical data were extracted from patient records and included age at onset, gender, MS subtype, disease duration, Expanded Disability Status Scale (EDSS) score, CSF findings (OCBs and IgG index status), and treatment history. Descriptive statistics were used to summarize the data. Categorical variables (gender, MS subtype, family history, CSF profile, and treatment category) were reported as frequencies and percentages, while continuous variables (age at onset, disease duration, and EDSS score) were expressed as means and ranges. Comparisons between POMS and AoMS, as well as between familial and nonfamilial cases, were performed using appropriate statistical tests. A p-value <0.05 was considered statistically significant.

All analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 3,411 MS patients were evaluated, of whom 251 were identified as having POMS, defined as disease onset before the age of 18. This corresponded to a pediatric-onset rate of 7.36% within the overall cohort (Figure 1).

Demographic analysis showed that most POMS patients were female (n=177, 70.5%) compared with male patients (n=74, 29.5%). The predominant MS subtype was RRMS (n=236, 94%), while 15 patients (6%) had secondary progressive MS (SPMS). No cases of primary progressive MS (PPMS) were observed (Table 1).

The mean age at disease onset was 15.7 years (range, 4-18), and the mean disease duration was 16.0 years (range, 1-55). The mean EDSS score was 1.3, reflecting generally mild disability at the time of evaluation.

CSF analysis was available for 31 POMS patients. Of these, 24 (77.4%) were positive for OCBs (Type 2 or Type 3), consistent with intrathecal IgG synthesis. An elevated IgG index was detected in 13 patients (41.9%).

Among 440 patients with available CSF data, an elevated IgG index was observed in 13 POMS patients (41.9%) and 259 AoMS patients (58.9%). A normal IgG index was found in 18 POMS patients (58.1%) and 181 AoMS patients (41.1%). Although

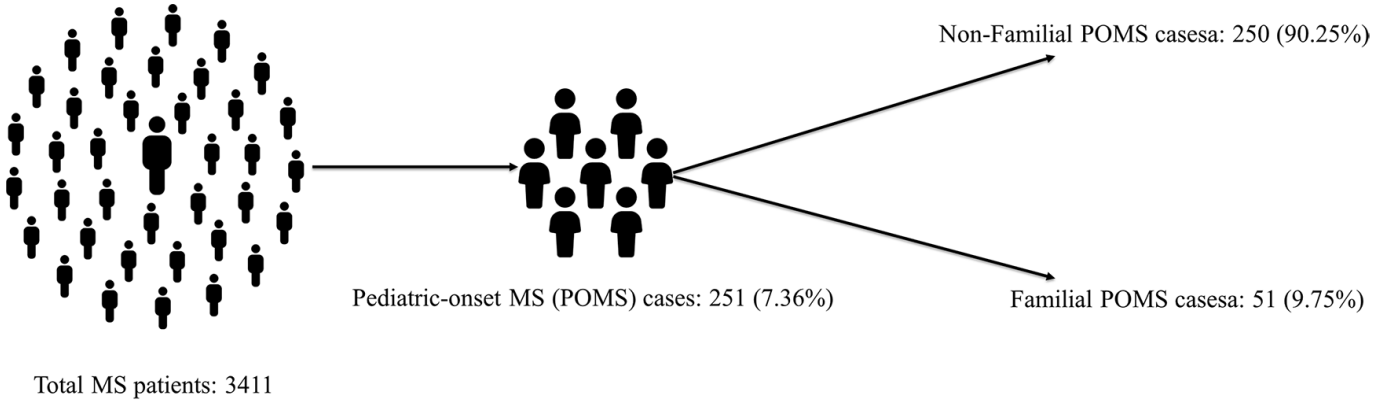

Figure 1. Distribution of familial and nonfamilial POMS cases within the total MS cohort
MS: Multiple sclerosis, POMS: Pediatric-onset MS

Table 1. Demographic and clinical characteristics of pediatric-onset MS (POMS) patients (n=251)		
Category	**Subcategory**	**n (%) or mean (range)**
Gender distribution	Female	177 (70.5%)
	Male	74 (29.5%)
MS subtypes	Relapsing-remitting MS (RRMS)	236 (94.0%)
	Secondary progressive MS (SPMS)	15 (6.0%)
CSF analysis (n=31)	OCB-positive (Type 2 or Type 3)	24 (77.4%)
IgG	Elevated IgG index (among those with abnormal CSF)	13 (41.9%)
Treatment history	First-line treatment	59 (23.5%)
	Second-line treatment	123 (49.0%)
	Third-line treatment	69 (27.5%)
Disability status	Mean EDSS score	1.3
Age at onset	Mean (range)	15.7 years (4-18)
Disease duration	Mean (range)	16.0 years (1-55)

This table summarizes the demographic and clinical characteristics of 251 POMS cases, identified among a total of 3,411 MS patients (7.36%)
MS: Multiple sclerosis, CSF: Cerebrospinal fluid, OCB: Oligoclonal band

the proportion of elevated IgG index was lower in the POMS group, the difference between groups did not reach statistical significance (p=0.065).

Similarly, the difference in OCB positivity between the POMS and AoMS groups was not statistically significant (p=0.863).

Discussion

POMS is a rare subtype of MS that occurs in individuals younger than 18 years and accounts for approximately 3%-10% of all cases. Compared with AoMS, POMS demonstrates distinct clinical features and disease courses (6,9,10). Epidemiological studies report that the incidence of POMS varies globally from 0.05 to 2.85 per 100,000 children (11,12). This variability is likely influenced by genetic predisposition, environmental exposures, and differences in diagnostic awareness and criteria across populations.

In our study, POMS represented 7.36% of the total MS cohort, consistent with previously reported prevalence rates. The increasing detection of POMS in recent years may be explained by advances in diagnostic techniques, heightened clinical awareness, and the adoption of the 2017 revised McDonald criteria. In agreement with earlier studies, most POMS patients in our cohort were female (70.5%), reflecting the well-documented female predominance in MS (2). This gender imbalance, also observed in adult MS, has been attributed to hormonal factors, genetic susceptibility, and immunological differences (10). While our findings confirm this female predominance, we were unable to assess whether the pattern varied before and after menarche, which could influence hormonal susceptibility and immune responses.

One of the most important findings of our study is the predominance of RRMS subtype in pediatric patients, accounting for 94% of cases. This observation is consistent with previous research showing that nearly all pediatric MS patients initially present with RRMS and are less likely to develop PPMS at an early stage (11,13). Although progressive forms of MS are rare in pediatric populations, the risk of transition to SPMS increases with disease duration. In our study, SPMS was observed in 6% of patients-lower than the rate reported in AoMS-supporting the view that POMS typically follows a more favorable early disease course (14). Despite higher relapse rates in the early stages, pediatric patients generally demonstrate better recovery, as reflected by the low mean EDSS score of 1.3 in our cohort. This finding aligns with prior reports suggesting that disability accumulation is slower in POMS than in AoMS (15).

CSF analysis remains an important diagnostic tool in MS, with OCBs serving as key biomarkers. Previous studies have reported lower OCB positivity rates in POMS compared with AoMS, with frequencies ranging from 40% to 80% (2,16,17). In our cohort, OCB positivity was observed in 77.4% of POMS patients and 76.1% of AoMS patients, a difference that was not statistically significant (p=0.863). These comparable OCB rates suggest that OCBs alone may not adequately reflect age-related differences in intrathecal immune responses. Although earlier reports have described lower OCB frequencies in pediatric cases, our findings underscore the potential heterogeneity of immunological profiles within both POMS and AoMS populations. Variability in diagnostic timing, assay sensitivity, and population characteristics may contribute to these discrepancies. Nonetheless, our results add to the current understanding of OCB distribution in MS and highlight the need for further research to clarify its age-dependent immunopathological relevance.

The primary focus of our study was familial MS in the pediatric population. The prevalence of familial MS varies widely, with reported rates ranging from 10% to 21% (18). In our cohort, 20.3% of POMS patients had a family history of MS, further supporting the role of genetic factors in disease susceptibility. Previous studies have identified specific genetic variants-particularly the HLA-DRB1*1501 allele-as risk factors for familial MS (7). Familial clustering suggests that POMS cases with a family history may exhibit distinct clinical and immunological profiles compared with sporadic cases. However, additional research incorporating genetic analyses is needed to clarify the exact contribution of hereditary factors to disease pathogenesis.

Despite providing insights, our study has several limitations. First, a larger dataset is required to draw more definitive conclusions. Second, the absence of genetic analyses restricts our ability to identify specific hereditary risk factors associated with POMS. Future studies utilizing genome-wide association studies and familial linkage analyses could offer a more comprehensive understanding of the genetic basis of POMS. Additionally, the lack of long-term follow-up data limits our evaluation of disease progression and treatment effectiveness in pediatric patients. Longitudinal cohort studies are needed to assess transition rates to progressive MS and to identify prognostic factors that influence outcomes in POMS.

In conclusion, our study contributes to the growing body of literature on POMS by providing insights into its demographic, clinical, and familial characteristics. The findings underscore the importance of considering familial predisposition when evaluating pediatric MS patients and highlight the need for further research into the genetic and immunological mechanisms underlying POMS. Future studies incorporating long-term follow-up and genetic analyses will enhance our understanding of this rare yet clinically significant MS subtype.

Study Limitations

Several limitations should be considered when interpreting our findings. First, the retrospective design limits the ability to establish causal relationships and relies on the accuracy and completeness of medical records. Second, the relatively small number of patients with available CSF data restricts the generalizability of immunological findings, including OCB and IgG index results. Third, the absence of genetic analyses precludes identification of specific hereditary markers underlying familial POMS. Additionally, the lack of longitudinal follow-up prevented assessment of long-term disease progression, cognitive outcomes, or sustained treatment efficacy. Finally, the single-center nature of the study may introduce selection bias and limit the generalizability of the results. Future multicenter, prospective studies incorporating genetic profiling and long-term clinical monitoring are needed to validate and expand upon these findings.

Conclusion

In summary, our study adds to the growing body of evidence on POMS, with a particular focus on familial cases. We found that POMS accounts for a substantial proportion of MS diagnoses and is predominantly characterized by an RRMS and mild early disability. Familial cases were relatively common, highlighting the potential role of genetic predisposition in disease development. Although no significant differences were observed in CSF biomarkers between pediatric and AoMS, our findings emphasize the need for further immunological and genetic investigations. Recognizing familial MS in pediatric population may enable earlier diagnosis and more tailored monitoring strategies. Continued research with larger cohorts, long-term follow-up, and integrative approaches is essential to advance understanding of the pathophysiology and clinical trajectory of familial POMS.

Ethics

Ethics Committee Approval: The study was approved by the Karadeniz Technical University Faculty of Medicine Clinical Research Ethics Committee (decision no.: 2014/125, date: 25.02.2015).

Informed Consent: We conducted a retrospective descriptive study of 3,411 patients diagnosed with MS at the MS center of a university hospital.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.A., E.S.Z., Concept: S.A., C.C., E.S.Z., Y.S., Design: S.A., C.C., E.S.Z., Y.S., Data Collection or Processing: S.A., C.C., Y.S., Analysis or Interpretation: S.A., C.C., Y.S., Literature Search: S.A., C.C., E.S.Z., Y.S., Writing: S.A., C.C., E.S.Z.

Conflict of Interest: No conflict of interest was declared by the authors.

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