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ARTICLE

Pediatric Multiple Sclerosis Severity Score in a large US cohort

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Abstract

Objective

To characterize disease severity and distribution of disability in pediatric-onset multiple sclerosis (POMS) and to develop an optimized modeling scale for measuring disability, we performed a multicenter retrospective analysis of disability scores in 873 persons with POMS over time and compared this to previously published data in adults with multiple sclerosis (MS).

Methods

This was a retrospective analysis of prospectively collected data collected from 12 centers of the US Network of Pediatric MS Centers. Patients were stratified by the number of years from first symptoms of MS to Expanded Disability Status Scale (EDSS) assessment and an MS severity score (Pediatric Multiple Sclerosis Severity Score [Ped-MSSS]) was calculated per criteria developed by Roxburgh et al. in 2005.

Results

In total, 873 patients were evaluated. In our cohort, 52%, 19.4%, and 1.5% of all patients at any time point reached an EDSS of 2.0, 3.0, and 6.0. Comparison of our Ped-MSSS scores and previously published adult Multiple Sclerosis Severity Scores (MSSS) showed slower progression of Ped-MSSS with increasing gaps between higher EDSS score and years after diagnosis. Decile scores in our POMS cohort for EDSS of 2.0, 3.0, and 6.0 were 8.00/9.46/9.94, 7.86/9.39/9.91, and 7.32/9.01/9.86 at 2, 5, and 10 years, respectively. Notable predictors of disease progression in both EDSS and Ped-MSSS models were ever having a motor relapse and EDSS at year 1. Symbol Digit Modalities Test (SDMT) scores were inversely correlated with duration of disease activity and cerebral functional score.

Conclusions

Persons with POMS exhibit lower EDSS scores compared to persons with adult-onset MS. Use of a Ped-MSSS model may provide an alternative to EDSS scoring in clinical assessment of disease severity and disability accrual.

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Glossary

ARMSSS = Age-Related Multiple Sclerosis Severity Score; **CI** = confidence interval; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **FS** = functional score; **IQR** = interquartile range; **MOG** = myelin oligodendrocyte glycoprotein; **MS** = multiple sclerosis; **MSSS** = Multiple Sclerosis Severity Score; **Ped-MSSS** = Pediatric Multiple Sclerosis Severity Score; **POMS** = pediatric-onset multiple sclerosis; **SDMT** = Symbol Digit Modalities Test.

Onset of multiple sclerosis (MS) in childhood or adolescence occurs in approximately 5% of all persons with MS.[1] Recognition of the frequency and clinical care needs of persons with pediatric-onset MS (POMS) has grown over the last decade. Natural history studies have suggested that POMS has a relatively benign disease course compared to adult-onset MS,[1] but these studies only considered disability as measured by the Expanded Disability Status Scale (EDSS), a measure weighted towards locomotor deficits. There is also growing recognition that persons with POMS have substantial cognitive dysfunction early in their disease course.[2–6] It is also now well-accepted that patients with POMS have increased relapse rates compared to adults.[7,8] Data emerging from international cohorts show that persons with POMS take longer to reach common EDSS checkpoints such as 4.0 (impaired gait) and 6.0 (use of assistive device). For this reason, such models may be insufficient in the assessment of disease severity in POMS.[9,10]

New treatments are available for POMS, but standardized outcomes and endpoints for these therapies remain a subject of debate.[11,12] Higher-efficacy disease-modifying therapies (DMTs) are accompanied by increasing safety issues, making it necessary to identify the patients who may benefit most from these interventions. Thus there is a need to better characterize disease severity and prevention in patients with POMS in a modern cohort, accounting for disease duration, with the goal of creating an optimized disease and disability modeling scale in this unique population.

We sought to retrospectively analyze disability scoring in a multicenter cohort[13] of persons with POMS and describe the distribution of EDSS scores, according to disease duration, using an algorithm similar to the Multiple Sclerosis Severity Score (MSSS) published by Roxburgh et al.,[14] and later Kister et al.,[15] which we refer to as the Pediatric Multiple Sclerosis Severity Score (Ped-MSSS). Further, we sought to assess the distribution of a validated cognitive measure, the Symbol Digit Modalities Test (SDMT),[16,17] to capture the cognitive function component of the disease severity in POMS.

Methods

Standard protocol approvals, registrations, and patient consents

This study examined a cohort of study participants with longitudinal data previously enrolled (May 2011 to July 2018) by the US Network of Pediatric MS Centers, with all 12 sites having prior institutional review board approval. Written informed consent was obtained from all participants or guardians of participants. Selection of the centers and confirmation of diagnosis has been described previously.[13]

Participants

Eligibility criteria included diagnosis of POMS (per McDonald 2010 and 2017 criteria and the International Pediatric MS Study Group's 2013 guidelines),[18,19] age ≤18 years at onset of symptoms, and at least 1 EDSS recording within the documented time from symptom onset or initial presentation. Patients were excluded if they had a diagnosis of clinically isolated or radiographically isolated syndrome or any other non-MS disorder (supplementary table e-1, available at Dryad, 10.5061/dryad.x0k6djhfm). Patients with known anti–myelin oligodendrocyte autoantibodies were included in this cohort if they met the above criteria for MS alone.

Demographic information

Parents of each participant completed a detailed questionnaire about their child's demographic information, which was extracted along with EDSS and SDMT data. Historical birth, family, medical, and surgical history were also extracted as part of this study from both questionnaires and patient medical records.

Definition of relapse and relapse type

Relapses in this cohort could be clinical or a combination of clinical and radiographic. Relapse subtypes were defined by having neurologic dysfunction in that grouping resulting in an EDSS functional score above 0 (e.g., vision subtype required visual dysfunction). Patients may have had more than one subtype present during a relapse.

Pediatric MSSS

An MSSS score was derived by adjusting disability and disease duration using the formula proposed by Roxburgh et al.[14]:

$$\text{MSSS is calculated as: } \frac{\text{Rank Average}}{N+1} \times 10.$$

Participants were stratified by the number of whole years from first event symptoms to EDSS assessment. Each year was analyzed with the one on either side. For example, for the 2-year disease duration group, the closest EDSS to 2 years of disease duration was selected from all the EDSS scores from 1 to 3 years of disease duration. This output score was then converted to a decile of the EDSS (defined as 10 equal distributions of resultant scores) within the range of patients who had the same disease duration. Any score obtained within 30 days of an MS attack were omitted. For comparison, the

authors also performed an analysis of our cohort using a previously established Age-Related Multiple Sclerosis Severity Score (ARMSSS). This score was calculated using previously established methodology.[20]

SDMT scores

The oral form of the SDMT (forms A and B) was obtained as part of clinical care at all centers and data were collected in a standardized fashion. To assess whether cognitive dysfunction was a function of EDSS, these data were compared to determine a correlation coefficient in a cross-sectional manner. Any score obtained within 30 days preceding or following an MS attack or treatment with steroids was omitted.

Statistical analysis

Frequencies and averages for the primary and secondary outcome measures were summarized. Time to first having an EDSS score of 2.0, 3.0, and 6.0 from disease onset was determined for each participant. Those who never reached scores of 2.0, 3.0, and 6.0 were censored to the time of their most recent EDSS score. The product-limit survival estimates were plotted using PROC LIFETEST in SAS to display the time in years to EDSS scores of 2.0, 3.0, and 6.0. For comparison, the time until first EDSS MSSS of 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 were also determined and plotted.

Linear regression analyses were calculated using PROC GENMOD in SAS to predict EDSS at year 5 and EDSS MS severity decile at year 5 adjusting for all our primary outcome measures. The variance inflation factors and residuals were reviewed as part of the modeling diagnostics.

Data availability

Data not published within this article are available in a public repository (doi:10.5061/dryad.x0k6djhfm).

Results

In total, 987 patients were screened for inclusion in our study. Of these, 114 patients were excluded for meeting one or more of our predefined exclusion criteria, leaving 873 patients for study and accounting for 4,373 unique clinical encounters. The mean age at diagnosis was 13.6 years (median 14.6, interquartile range [IQR] 12.3–16.1, range 1.8–18.0). The mean duration of follow-up (disease duration) was 4.3 years (median 3.5, IQR 1.7–5.9, SD 3.4, range 0.1–21.5). Demographic data are presented in table 1 with additional supplementary demographic data presented in supplementary table e-2 (available at Dryad, 10.5061/dryad.x0k6djhfm). Among our POMS cohort, the majority of EDSS scores were skewed towards lower scores, with a mean of 1.3 (range 0–7.5, IQR 0–2.0). Further, 52%, 19.4%, and 1.5% of all patients at any time point reached an EDSS of 2.0, 3.0, and 6.0, respectively. Survival plot of disease severity by EDSS score is displayed in figure 1. The mean time from diagnosis to reach these EDSS milestones was 2.6 (n = 454, SD 3.0, range 0.1–15.5), 3.1 (n = 169, SD 3.6, range 0.1–15.5), and 3.9 (n = 13, SD 3.0, range 0.6–8.7) in patients who ever achieved the corresponding score. Only 72 patients in our cohort were tested for myelin oligodendrocyte glycoprotein (MOG) antibody. Of this group, only 10 patients were positive and 80% of those testing positive for MOG antibody had onset of symptoms before 8 years of age.

The distribution of our Ped-MSSS values is displayed in figure 2, which presents disease duration–adjusted mean ranks by decile in a format similar to adult-based MSSS scales by Roxburgh et al.[14] and later Kister et al.[15] Distribution of scores, as predicted, were heavily clustered towards EDSS values ≤2.0, accounting for 85% of all cases in our cohort at both 1 and 5 years. Decile scores in our POMS cohort for EDSS of 2.0, 3.0, and 6.0 were 8.00/9.46/9.94, 7.86/9.39/9.91, and 7.32/9.01/9.78 at 2, 5, and 10 years, respectively; by comparison, adult data published by Roxburgh et al.[14] reported decile scores of 5.24/7.27/9.59, 3.90/5.79/8.83, and 2.34/3.79/7.39 at 2, 5, and 10 years. Of note, the lowest decile score at an EDSS of 2.0 in our cohort, at any time point, was 6.94. Both EDSS score and Ped-MSSS score 2 years after diagnosis were predictive of the most recent respective EDSS or Ped-MSSS score in patients with more than 5 years of follow-up (r value 0.52 for EDSS and 0.50 for Ped-MSSS). For comparison, ARMSSS scoring in our cohort was evaluated to determine whether this methodology compared to the Ped-MSSS distribution. The results of this assessment are presented in supplementary table e-3 (available at Dryad, 10.5061/dryad.x0k6djhfm). The ARMSSS and Ped-MSSS deciles were nearly identical with regards to distribution, with skew towards EDSS scores <2.0.

Subanalysis of EDSS functional score (FS) subgroups was performed to determine the relative distributions given clustering of lower EDSS scores in our cohort. Full FS data sets are presented in supplementary table e-4 (available at Dryad, 10.5061/dryad.x0k6djhfm). At EDSS points between 1.0 and 1.5, visual, pyramidal, and sensory scores were the most frequently occurring FS abnormalities, compared to EDSS ≥2.0, where visual, pyramidal, cerebellar, and sensory scores predominated. The average FS contributions to composite EDSS score are displayed in figure 3.

Linear regression models of prediction of disease severity are presented in table 2. Notable predictors of disease progression in both models were ever having a motor relapse (effect 0.41, 95% confidence interval [CI] 0.01–0.80, and effect 1.20, 95% CI 0.23–2.17, respectively) and EDSS at year 1 (effect 0.35, 95% CI 0.20–0.51, and effect 0.63, 95% CI 0.25–1.02, respectively). The Ped-MSSS scoring model identified ever having a sensory relapse as additional predictor of disease severity (effect −0.94, 95% CI −1.88 to −0.01). The Ped-MSSS scoring model showed trends for ethnicity (Hispanic or Latino) to be associated with disease severity. There was no correlation between the type of first DMT and EDSS or Ped-MSSS at year 5. The mean EDSS between patients on injectable therapies (such as interferon) was 1.3 and the mean EDSS of patients on oral or IV therapies was 1.2. Mean time to DMT differed by type of treatment: 0.8 years for injectable therapies and 2.8 for oral and IV therapies.

Table 1 Population demographics

	Overall (n = 873), n (%) or mean (Q1, Q3)
Sex	
Male	294 (34)
Female	579 (66)
Race	
White	558 (68)
Black	169 (21)
Other	95 (12)
Ethnicity	
Hispanic or Latino	260 (31)
Not Hispanic or Latino	571 (69)
First body mass index	25.5 (20.7, 29.0)
Last body mass index	26.5 (21.4, 29.7)
Breastfed	
No	229 (35)
Yes	430 (65)
Tobacco exposure	
No	613 (77)
Yes	188 (23)
Mother's education	
None	97 (13)
High school or Associate's	423 (55)
Bachelor's or graduate	251 (33)
Age at first event	13.6 (12.3, 16.1)
Age at first MS diagnosis	14.4 (13.2, 16.7)
MS onset in relation to puberty	
Prepubertal	124 (18)
Postpubertal	565 (82)
No. of events	1.7 (0.0, 2.0)
No. of events in first 2 years	1.0 (0.0, 1.0)
Relapse rate	0.5 (0.0, 0.7)
Ever vision relapse subtype	508 (58)
Ever motor relapse subtype	534 (61)
Ever sensory relapse subtype	562 (64)
Ever coordination relapse subtype	419 (48)
Ever bladder/bowel relapse subtype	138 (16)
Ever constitution relapse subtype	385 (44)
Ever meningismus relapse subtype	18 (2)
Ever cognitive relapse subtype	129 (15)
Ever encephalopathy relapse subtype	65 (7)
Ever behavioral relapse subtype	79 (9)
Time to first DMT, y	1.7 (0.3, 2.3)
First DMT	
Injectable	475 (63)
Oral	170 (23)
Intravenous	94 (13)
Other	12 (2)
Ever autoimmune disease (other than MS)	89 (10)
Family ever autoimmune disease	608 (70)
EDSS at 1 year	1.3 (0.0, 2.0)
EDSS at 5 years	1.3 (1.0, 2.0)

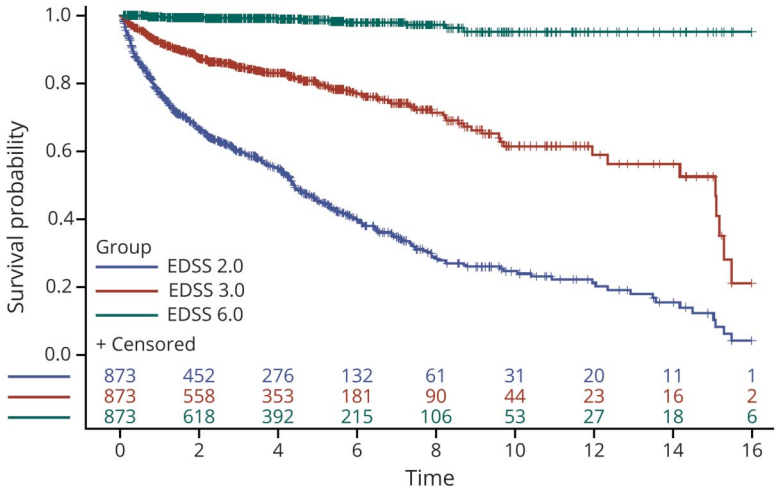
Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis.

Of the 873 patients included in this study, 500 had an SDMT analysis at any time point. The remaining 373 patients either had no SDMT assessment or had the test performed in an ineligible window (such as within 30 days of relapse). The average number of SDMT administrations was 2.8 (SD 1.9, range 1–11). There were 1403 SDMT recordings with a mean value of 55.5 (SD 14.2). As shown in figure 4, there was a modest correlation between SDMT score and EDSS at 5 years ($r = -0.34$). Additional data on earlier time courses are supplied in supplementary table e-5 (available at Dryad, 10.5061/dryad.x0k6djhfm). When the EDSS cerebral FS was compared to SDMT data, there was a statistically significant inverse trend indicating that lower SDMT scores matched higher cerebral functional scores across all EDSS levels ($r = -0.15$).

Discussion

Our study presents a continuous measure of disease severity (Ped-MSSS) by disease duration in the largest cohort of patients with POMS. When compared to prior studies in adults, our cohort had dramatically different deciles of disease severity at commonly used EDSS checkpoints. At EDSS milestones of 2.0, 3.0, and 6.0, our cohort differed greatly from established adult data, with much higher Ped-MSSS scores compared to MSSS scores at similar disease duration time points.[14] This finding is consistent with data emerging from smaller and more homogenous cohorts of patients with POMS.[10] Because EDSS progresses more slowly in POMS than adult cohorts,[9] conversion of scores to a normalized, continuous, scoring model such as the Ped-MSSS may provide a superior alternative to the stepwise EDSS. This scoring system may present benefits in

Figure 1 Survival plot of patients with pediatric-onset multiple sclerosis to Expanded Disability Status Scale (EDSS) end points of 2.0, 3.0, and 6.0



Disease duration is present on the x-axis and survival probability defined on the y-axis. Across all time points, 52%, 19.4%, and 1.5% of patients reached an EDSS of 2.0, 3.0, and 6.0, respectively.

evaluating clinical disability status and response to therapeutic interventions. Finally, this model utilizes a simple algorithm similar to those reported by Roxburgh et al.[14] and later Kister et al.,[15] allowing for a distributed decile scoring of disability and easy integration into any clinic or electronic medical record system by reference to figure 2.

Disability between relapses at commonly used EDSS milestones was low in our POMS cohort, with a clustering of scores below 2.0. Due to this skew towards lower EDSS scoring and the stepwise nature of this scoring system, patients are limited to scores of 0, 1.0, 1.5, and 2.0, restricting disease status to a small number of predefined outputs. Using Ped-MSSS scoring, patients were ranked into deciles in a disease duration–adjusted manner, allowing for a continuous assessment and comparison against other patients with POMS. Presumably, use of a continuous disability scoring model should allow for improved detection of changes in disability related to interventions, such as initiation or change of DMT. Standardized and distributed scoring allows for disease severity comparison between subpopulations, which is particularly important in the appraisal of disease progression between POMS and adult-onset MS.[21] Further, studies in adults have already reported a downtrend in similarly distributed disability progression models over time with increased use of high-efficacy DMTs. These same DMTs are being increasingly utilized in patients with POMS.[22,23]

Figure 2 Pediatric Multiple Sclerosis Severity Scores (Ped-MSSS)

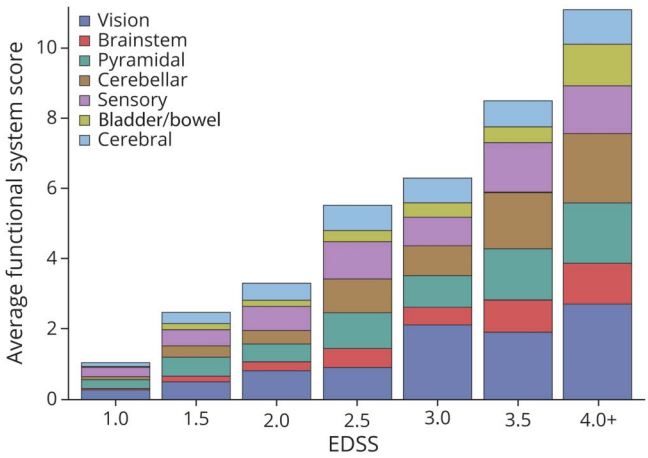
Pediatric multiple sclerosis severity scores

Years	0.0	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0
1	1.41	4.03	6.09	7.75	8.78	9.29	9.70	9.86	9.90		9.92	9.94			9.98	
2	1.58	4.47	6.58	8.00	8.91	9.46	9.77	9.88		9.93	9.94				9.97	
3	1.38	4.05	6.43	8.20	9.13	9.51	9.78	9.93					9.98			
4	1.34	3.96	6.26	8.09	9.11	9.43	9.68	9.84				9.93				
5	1.18	3.71	6.08	7.86	8.95	9.39	9.61	9.76		9.84		9.91		9.97		
6	1.22	3.61	5.91	7.92	8.92	9.23	9.58	9.75	9.83			9.90		9.96		
7	1.17	3.55	5.67	7.40	8.52	9.11	9.58	9.83	9.94							
8	1.23	3.32	5.11	6.90	8.13	8.77	9.22	9.51	9.70			9.81	9.93			
9	1.29	3.54	5.45	7.02	7.98	8.60	9.10	9.49				9.78	9.89			
10	1.41	3.59	5.49	7.32	8.38	9.01	9.44	9.65					9.86			
11	1.63	4.19	6.28	8.02	8.84	9.19		9.53	9.77							
12	1.32	3.53	5.74	7.35	8.24	8.82	9.26	9.71								
13	0.95	2.62	5.00	6.67	7.62	9.05										
14	1.11	3.06	5.28	6.94	8.06	8.89	9.44									
15	0.83	1.94	3.89		5.83	6.94	7.78	8.89								

Decile
= 1st
= 2nd
= 3rd
= 4th
= 5th
= 6th
= 7th
= 8th
= 9th
= 10th

Ped-MSSS generated from 873 patients with pediatric-onset multiple sclerosis. Score calculation is determined by accounting for disease severity (measured by Expanded Disability Status Scale) in the context of disease duration.

Figure 3 Function score (FS) contribution to composite Expanded Disability Status Scale (EDSS) score by EDSS



Subanalysis of our cohort's EDSS scores revealed that sensory, visual, pyramidal, and cerebellar FS predominated. Although cerebral phenotypes are frequently reported,[2–6] this is a subjective measure with high variability in reporting as with the lack of overt neurocognitive signs or detailed mental status assessment, scoring may be minimized. For this reason, the use of SDMT in clinical practice can be informative from both an FS scoring perspective and to obtain an objective measure of neurocognitive deficits. In patients with higher EDSS scores, cerebellar FS became increasingly contributory to the total EDSS score. This is interesting not just in that cerebellar dysfunction yields increasing disability, but also that cerebellar pathology may contribute to cognitive dysfunction in POMS. This latter finding has been reported previously in a small cohort of patients with POMS.[24] Findings in adult-onset MS also support this conclusion and have shown the cerebellar volume loss is directly associated with both cognitive and locomotor disability in MS.[25–27]

In comparing EDSS and Ped-MSSS with linear regression models, EDSS at 1 year and motor relapses predicted disease severity at 5 years. Although our cohort did not find that disease duration was predictive of disease severity, recent literature has identified that both baseline EDSS and duration of disease are predictive of response to DMT.[28] Response to DMT could be considered a surrogate for disease severity although the previously mentioned study did not assess this directly. Utilizing just EDSS scoring, no additional disease modifiers were found while using Ped-MSSS scoring, and sensory relapses and ethnicity respectively predicted and tended to predict disability at 5 years. This suggests an increased capacity of the Ped-MSSS system to capture more subtle levels of disease progression. The ability to better assess disease progression could be useful in clinical therapeutic interventions as they are released in POMS. Augmented disease progression in high-efficacy DMT clinical trials using MSSS (as opposed to EDSS) scoring in adult MS literature has been reported, underscoring the need for a companion model in POMS.[29–32]

Interestingly, Ped-MSSS decile scoring 1 year after diagnosis was predictive of the ultimate decile scoring for patients on therapy, as was EDSS. This early predictive finding is of note given the extensive longitudinal data we have on our POMS cohort. This finding has been observed previously in 2 large-scale adult populations using different methodologies and may be a candidate marker of DMT efficacy in the future should decile scoring decrease following initial assessments.[33–36] The lack of both time to DMT initiation and type of DMT initiated being predictive of disability accrual in our cohort is discrepant from previously published literature.[10,37] However, the former study by McKay et al.[10] divided DMT therapy into first- and second-line therapeutic categories (which were much more broad) as opposed to categorizing by administration mechanisms, which the authors believed was more representative of the generational therapeutic options available for persons with POMS and could explain this disparity. Further, our cohort represents patients from multiple different treatment epochs, which augments the types of patients who were placed at diagnosis on oral and IV therapies. While the mean EDSS was no different between DMT types, the time to start therapy was widely discrepant at nearly 2 years difference between injectable and oral/IV DMT classes. This finding may augment the response on disease severity of higher-efficacy therapies as patients may have already accrued subclinical insults due to care delay.

To address the major concern of cognitive dysfunction in POMS, this study also evaluated the interrelationship between EDSS scoring and SDMT z scores. A modest association between EDSS and SDMT scores was appreciated, which has also been noted among some but not all prior studies of cognitive dysfunction in POMS.[38] The cerebral FS of the EDSS was most predictive of poor SDMT performance. While unsurprising, this association is of importance in POMS given the substantial report of cognitive dysfunction.[2–6] While prior data have shown a bimodal decline in SDMT scores in patients with POMS, this was not observed in our cohort.[39] Further, studies evaluating SDMT have demonstrated that baseline lesion load and location of lesions may affect scoring, although further study is needed because this was not assessed in our protocol.[40,41]

This study leverages the largest United States–based database of persons with POMS including longitudinal data. Limitations of this study include recall bias for patients and families when self-reporting data at intake and follow-up. Because all patients in this study were evaluated at tertiary care centers, severity bias cannot be ignored. Geographic and socioeconomic bias is also present with regards to patient ability to follow-up in the centers, potentially skewing our populations towards more urban and suburban populations as well as persons of higher socioeconomic status. Although all Network physicians were trained to utilize EDSS with neurostatus EDSS training, interrater differences are likely, but were not assessed in this study. Patients with known anti-MOG antibodies were included because only a minority were tested due

Table 2 Linear regression model comparing Expanded Disability Status Scale (EDSS) scores at 5 years to Pediatric Multiple Sclerosis Severity Scores (Ped-MSSS) decile at 5 years

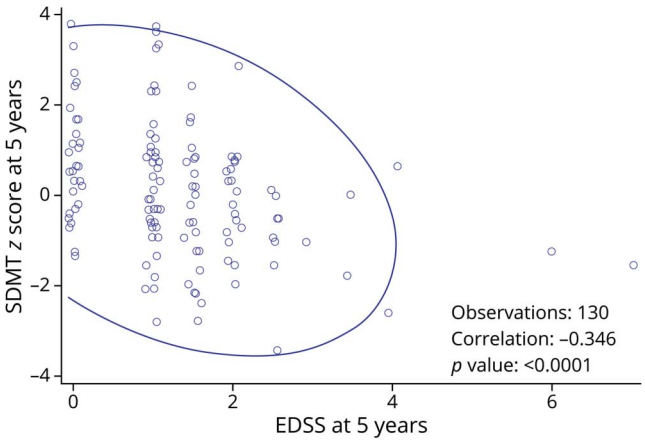
	EDSS at 5 years, effect (95% CI)	Ped-MSSS at 5 years (decile), effect (95% CI)
Tobacco exposure	0.20 (−0.32 to 0.71)	0.89 (−0.37 to 2.15)
Sex		
Female	0.22 (−0.15 to 0.59)	0.17 (−0.73 to 1.08)
Race		
White	0.10 (−0.38 to 0.57)	−0.22 (−1.38 to 0.94)
Black	−0.17 (−0.74 to 0.41)	−0.15 (−1.56 to 1.26)
Ethnicity		
Hispanic or Latino	0.25 (−0.14 to 0.65)	0.88 (−0.09 to 1.85)
Ever vision relapse subtype	0.15 (−0.20 to 0.50)	0.24 (−0.62 to 1.10)
Ever motor relapse subtype	0.41 (0.01 to 0.80)[a]	1.20 (0.23 to 2.17)[a]
Ever sensory relapse subtype	−0.28 (−0.66 to 0.10)	−0.94 (−1.88 to −0.01)[a]
Ever coordination relapse subtype	0.11 (−0.26 to 0.47)	0.66 (−0.24 to 1.55)
Ever bladder/bowel relapse subtype	−0.04 (−0.50 to 0.43)	−0.10 (−1.24 to 1.04)
Ever constitution relapse subtype	0.29 (−0.08 to 0.67)	0.49 (−0.42 to 1.41)
Ever meningismus relapse subtype	0.66 (−0.36 to 1.68)	1.83 (−0.68 to 4.34)
Ever cognitive relapse subtype	−0.34 (−0.85 to 0.17)	−0.59 (−1.85 to 0.67)
Ever encephalopathy relapse subtype	−0.45 (−1.07 to 0.17)	−1.19 (−2.72 to 0.34)
Ever behavioral relapse subtype	0.01 (−0.56 to 0.58)	0.02 (−1.39 to 1.43)
MS onset in relation to puberty		
Prepubertal	Reference	Reference
Postpubertal	0.24 (−0.23 to 0.72)	0.09 (−1.08 to 1.26)
First body mass index	−0.02 (−0.04 to 0.01)	−0.03 (−0.10 to 0.04)
EDSS at 1 year	0.35 (0.20 to 0.51)[a]	0.63 (0.25 to 1.02)[a]
High efficacy first DMT	−0.17 (−0.62 to 0.28)	−0.65 (−1.76 to 0.45)
Time to first DMT, y	−0.02 (−0.15 to 0.10)	−0.01 (−0.31 to 0.29)

Abbreviations: CI = confidence interval; DMT = disease-modifying therapy; MS = multiple sclerosis.
Results are based on multivariable models, adjusting for each of the predictors in this table. The first column demonstrates predictors of disease severity using the EDSS only whereas the second column demonstrates predictors of disease severity using our Ped-MSSS modeling.
[a] Values do not span zero.

to recent availability of the commercial test, possibly adding another confounder. Future study would be needed to determine whether disability accrual in MOG antibody–positive patients is similar to that in MOG antibody–negative patients with POMS. Interestingly, the Ped-MSSS would be ideal to study this given the predilection for MOG seropositivity in younger patients with demyelinating disorders, which is adjusted for in this model.[42] Finally, comparisons were made between the Roxburgh et al.[14] study, which was published 15 years ago, and our cohort. The data derived in both studies are from 2 different epochs in MS and POMS care and may not be the most accurate comparison, with the former study representing a skew towards higher disability scores due to data collection in a lower-efficacy treatment era. Further, longer follow-up in the Roxburgh et al.[14] cohort, generational differences in access to health care (and specifically, neurologic subspecialty care), and less inclusive diagnostic criteria in earlier epochs of MS care further compound the ability to interpret disease progression between these 2 cohorts. For this reason, our study group is in the process of making more up-to-date evaluations based on current adult cohort data at our center.

The Ped-MSSS represents an alternative, and arguably more sensitive, method of evaluating disease severity in patients with POMS. This is the first study of its kind to assess disease

Figure 4 Correlation of Symbol Digit Modalities Test (SDMT) and Expanded Disability Status Scale (EDSS) at year 5



Scatter plot representing correlation between SDMT *z* scoring and EDSS at 5 years ($r = -0.34$).

severity and disability in the context of disease duration in POMS, and the model studied has the potential to more sensitively assess changes in disease state or response to therapeutic intervention in this unique population. Further studies interrogating direct relationships to SDMT and other cognitive measures, as well as intervention-based modification of disease course, are warranted in this population.

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Anita Belman, MD	New York, NY	Site data acquisition and revision of the final manuscript for intellectual content
Leslie Benson, MD	Boston, MA	Site data acquisition and revision of the final manuscript for intellectual content
Mark Gorman, MD	Boston, MA	Site data acquisition and revision of the final manuscript for intellectual content
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Continued

Appendix *(continued)*

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T.C. Casper, PhD	Salt Lake City, UT	Major role in the acquisition of data and data analysis
Tanuja Chitnis, MD	Boston, MA	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content, obtained study funding

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