Cognitive and patient-reported outcomes in adults with pediatric-onset multiple sclerosis

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Abstract
Background: Little is known about long-term cognitive and patient-reported outcomes of pediatric-onset multiple sclerosis (POMS).
Objective: The objective of this paper is to compare cognitive and patient-reported outcomes in adults with POMS vs. adult-onset MS (AOMS).
Methods: We compared standardized patient-reported measures MSQOL54, MFIS, CES-D and SDMT in adult patients with MS onset prior to and after age 18, using data gathered in the Comprehensive Longitudinal Investigations in MS at Brigham and Women’s Hospital (CLIMB) study.
Results: Fifty-one POMS and 550 AOMS patients were compared. SDMT scores were significantly lower in POMS after adjusting for age (−7.57 (−11.72, −3.43; \( p < 0.001 \)), but not after adjusting for disease duration. Estimated group difference demonstrated lower normative \( z \) scores in POMS vs. AOMS in unadjusted analysis (−0.74 (95% CI: −1.18, −0.30; \( p = 0.0009 \)) and after adjusting for disease duration (−0.60; 95%CI: −1.05, −0.15; \( p = 0.0097 \)). Findings were unchanged in a subset of POMS diagnosed prior to age 18. In unadjusted and adjusted analyses, no significant differences were observed in health-related quality-of-life, fatigue, depression or social support between POMS and AOMS.
Conclusions: Younger age of onset was associated with more impairment in information-processing speed in adults with POMS compared to AOMS, and remained significant when controlling for disease duration in age-normed analysis. The two groups were similar in terms of patient-reported outcomes, suggesting similar qualitative experiences of MS.

Keywords: Multiple sclerosis, pediatric, cognition, quality of life, outcomes

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Introduction
Multiple sclerosis (MS), a disease once thought to arise in early adulthood, is now known to manifest in childhood in a subset of patients. Pediatric-onset multiple sclerosis (POMS) is defined by the International Pediatric MS Study Group as onset of the disease before the age of 18 years with use of the McDonald criteria for validation of the diagnosis.\(^1\) The proportion of POMS patients in the total MS population is estimated to be approximately 3–5%.\(^2\) The past 10 years have seen a growing body of research on POMS with children and adolescents. However, there is still very little known about long-term outcomes for patients with POMS. This is particularly true for health-related quality of life (HRQOL), depression, and cognitive functioning in POMS patients once they reach adulthood. The current study aims to explore these factors in an adult sample of POMS patients.

HRQOL is defined as those aspects of life quality or function that are influenced by health status.\(^3\) Studies have reported that individuals with MS-related cognitive impairment are less likely to be employed, engage in fewer social activities, report greater difficulty in performing household tasks, and benefit less from rehabilitative therapies.\(^4,5\)

Young adults who grow up with a chronic illness reportedly attain fewer developmental milestones in multiple domains in comparison to healthy young
Results are mixed regarding correlates of QOL in POMS patients. One study found that greater disease severity (as measured by physician-rated Expanded Disability Status Scale (EDSS)) scores and older age or longer disease duration were related to lower QOL. Girls and nonwhite patients also experienced lower QOL than boys and white patients in the same study. However, other research indicates that only disease severity (EDSS) was predictive of reduced QOL. Results were not significant for age, disease duration, number of relapses, or disease-modifying treatment.

Depression may occur in POMS, but studies have yielded mixed results, ranging from rates of 3.8% to 36%. This wide range is possibly the result of screening methodology. We found that parents of POMS patients were more likely to rate their children as having more problems on depression scales than their children and parents of healthy controls. Depression is common among adults who have MS. The lifetime risk of major depression in adult MS has been shown to be greater than 50%.

Research examining cognitive function in POMS indicates that approximately one-third of pediatric patients meet criteria for cognitive impairment, scoring below the fifth percentile on at least three cognitive tests from standardized neuropsychological batteries, and about half of these patients score below the fifth percentile on at least two tests. Cognitive deficits in POMS are similar to those observed in adult-onset MS (AOMS) and include impairments in information-processing speed, sustained attention and concentration, complex attention, working memory, verbal learning, fine motor skills, and visuospatial processing. These studies have highlighted features unique to POMS compared to AOMS, particularly in language and verbal comprehension. It is hypothesized that these issues in children may be due to onset of the disease during a time of critical development of language.

Research into the longitudinal impact of POMS on cognitive function over a two- to three-year period has yielded mixed results. Several studies have found that a significant percentage of patients (70% in one study) show cognitive decline at two-year follow-up. However, a recent study following the largest cohort of POMS patients to date was more consistent with research on cognitive decline in AOMS and suggested stable or even improved performance on cognitive testing over a short time frame. The long-term cognitive functioning of POMS patients compared to AOMS patients remains unknown.

Research on POMS is itself in its adolescence and opportunities are only now arriving to follow patients diagnosed in childhood into adulthood. While studies have looked individually at QOL, depression, and cognitive impairment in children and adults with MS, no studies have directly compared these outcomes in adults who experienced childhood-onset vs. adults with AOMS. The present study attempts to address this gap using a large-scale longitudinal cohort study of MS patients followed at a single center (Comprehensive Longitudinal Investigations in MS at Brigham and Women’s Hospital (CLIMB) at Brigham and Women’s Boston).

Materials and methods

Participants

Adults enrolled in this study were part of the larger CLIMB study at the Brigham and Women’s Hospital and Partners MS Center between 2000 and 2009. The CLIMB study is approved by the Partners Human Research, and informed consent was obtained according to committee guidelines.

At enrollment into the CLIMB study, demographic information including age, sex, race, and ethnicity was obtained through self-report questionnaires. All data for CLIMB participants are recorded and stored in an Oracle-based database. CLIMB participants have a clinic visit every six months with a complete neurological examination, including each patient’s EDSS score and other clinical variables. Medication history was recorded based on patient report and validated by study staff annually. Approximately half of the CLIMB participants are enrolled in a subgroup, which completes an annual brief cognitive screening test, and patient-reported outcome measures including QOL, depression and fatigue questionnaires.

The last available clinic visit with corresponding questionnaire data was used for the purposes of this analysis. Two final inclusion criteria were that participants had a diagnosis of relapsing–remitting or secondary progressive MS at the last available clinic visit.
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by the 2005 revised McDonald criteria and must be younger than 55. These criteria led to a final sample size of 601 individuals.

Study staff validated all first symptom dates and details. POMS participants were selected as those with a documented first attack occurring prior to the age of 18, as detailed by available neurologist notes. The remaining individuals were classified as having AOMS.

Measures

With the exception of the Symbol Digit Modalities Test (SDMT), all of the measures listed below are administered to CLIMB patients using either an electronic form available on an iPad or paper versions. All examiners administering the measures were trained by a PhD in clinical psychology (BG).

HRQOL was assessed via self-report. The Multiple Sclerosis Quality of Life- 54 (MSQOL-54) is a 54-item measure that includes the Short Form 36 (SF-36) instrument as the core measure as well as 18 additional items on health distress (four items), sexual function (four items), satisfaction with sexual function (one item), overall QOL (two items), cognitive function (four items), energy (one item), pain (one item), and social function (one item). It is composed of 12 subscales and two summary scores: the Physical Health Composite Summary and the Mental Health Composite Summary. Mean subscale scores were used to replace missing items unless all questions for a subscale were omitted, in which case that patient was excluded from analyses.

The Modified Fatigue Impact Scale (MFIS) is a 21-item measure of the effects of fatigue on physical, cognitive, and psychosocial functioning. It asks about perceived impact of fatigue on a variety of daily activities. There are three subscales: physical, cognitive, and psychosocial and then a total scaled score based on the sum of the three subscales.

The Modified Social Support Survey (MSSS) is an 18-item measure of perceived social support including tangible support, emotional support, affective support, and positive support.

The Center for Epidemiological Studies Depression Scale (CES-D) is a 20-item measure of depression that focuses on the major components of depressive symptomatology including depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, appetite loss, and sleep disturbance.

The SDMT is a brief test of information-processing speed. It is a timed coding test. Participants are required to refer to a key at the top of the page with numbers and symbols to correctly decode as many symbols as possible under a 90-second time limit. Consistent with other studies of MS patients, the oral-response condition (answers provided orally) was used in this study to limit the influence of motor impairment. The SDMT is known to be sensitive to MS-associated cognitive impairment and also correlates with magnetic resonance imaging (MRI) measures of disease burden in MS. The SDMT has been identified as possessing the highest sensitivity (74.2%) and specificity (76.9%) in predicting cognitive impairment in MS. The SDMT is the most commonly used measure of cognitive impairment in AOMS and has recently been proven an effective cognitive screen in POMS. Version 1 of the SDMT was administered to all participants included in this study. We additionally compared our SDMT results to adjusted normalized SDMT raw scores by age and gender using published regression-based normative procedures validated in MS.

Statistical analysis. Demographic and clinical characteristics of adults enrolled in the CLIMB study with POMS and AOMS were compared using a two-sample t-test and Fisher’s exact test as appropriate. For each of the outcome measures, the two groups were first compared without adjusting for potential confounders using a t-test. Groups were then compared controlling for age and disease duration in separate linear regression models using age-normed SDMT data. All statistical tests used a two-sided 0.05 alpha level to assess statistical significance. To account for multiple comparisons with six outcome variables, a two-sided 0.0083 alpha was used.

Results

Demographics

The demographic characteristics of these groups are found in Table 1. The average age at diagnosis in our POMS group was over 21, since 62.7% of our POMS patients were not diagnosed until after age 18 but had reported earlier symptom onset. Significant differences were observed between the POMS and AOMS groups in terms of age, disease duration, age at onset, and age at diagnosis (p < 0.0001 for each comparison). These differences were expected given the definitions of the groups. The proportion of patients on a disease-modifying therapy did not differ between the two groups (88.2% of POMS and 75.6% of AOMS patients, p = 0.055). POMS patients were somewhat more likely to be Hispanic (8.0% compared with...
Table 1. Patient demographic and clinical characteristics at last clinic visit.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Pediatric-onset MS (POMS)</th>
<th>Adult-onset MS (AOMS)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>51</td>
<td>550</td>
<td></td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>32.7 ± 9.7</td>
<td>41.8 ± 7.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>78.4</td>
<td>75.6</td>
<td>0.74</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>96.0</td>
<td>94.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Ethnicity (% Hispanic)</td>
<td>8.0</td>
<td>3.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Disease duration (years, mean ± SD)</td>
<td>17.2 ± 10.3</td>
<td>10.2 ± 6.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at onset (years, mean ± SD)</td>
<td>15.5 ± 2.1</td>
<td>31.5 ± 7.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at diagnosis (years, mean ± SD)</td>
<td>21.3 ± 6.9</td>
<td>33.9 ± 7.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EDSS (mean ± SD; range)</td>
<td>2.2 ± 2.1; 0–8.0</td>
<td>1.7 ± 1.6; 0–8.5*</td>
<td>0.15b</td>
</tr>
<tr>
<td>Disease category (RR, SP)</td>
<td>41, 10</td>
<td>502, 48</td>
<td>0.022</td>
</tr>
</tbody>
</table>


Table 2. Unadjusted mean scores on self-report and cognitive measures.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Pediatric-onset MS (POMS)</th>
<th>Adult-onset MS (AOMS)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMT (N, mean ± SD)</td>
<td>43, 53.1 ± 16.1</td>
<td>405, 56.9 ± 12.4</td>
<td>0.063</td>
</tr>
<tr>
<td>PHC (N, mean ± SD)</td>
<td>51, 68.9 ± 21.6</td>
<td>519, 73.3 ± 18.5</td>
<td>0.12</td>
</tr>
<tr>
<td>MHC (N, mean ± SD)</td>
<td>51, 68.0 ± 19.1</td>
<td>525, 71.7 ± 17.4</td>
<td>0.14</td>
</tr>
<tr>
<td>MFIS (N, mean ± SD)</td>
<td>48, 27.2 ± 15.1</td>
<td>487, 25.3 ± 17.4</td>
<td>0.47</td>
</tr>
<tr>
<td>MSSS (N, mean ± SD)</td>
<td>49, 82.4 ± 19.4</td>
<td>527, 81.8 ± 20.2</td>
<td>0.85</td>
</tr>
<tr>
<td>CESD (N, mean ± SD)</td>
<td>50, 30.1 ± 9.1</td>
<td>537, 30.0 ± 8.3</td>
<td>0.95</td>
</tr>
</tbody>
</table>

SDMT: Symbol Digit Modalities Test; PHC: Physical Health Composite from Multiple Sclerosis Quality of Life-54 (MSQOL-54); MHC: Mental Health Composite from MSQOL-54; MFIS: Modified Fatigue Impact Score; MSSS: Modified Social Support Survey; CESD: Center for Epidemiological Studies Depression Scale.

3.6% in the adult-onset group), though this difference was not statistically significant (p = 0.13). Average EDSS scores in the two groups were similar (2.2 ± 2.1 in the POMS group and 1.7 ± 1.6 in the AOMS group). POMS patients were more likely to have converted to secondary progressive MS (p = 0.022), which was likely due to the longer disease duration in this group.

To account for the possibility that POMS patients diagnosed before the age of 18 might be different from POMS patients who experienced symptoms onset prior to 18 but were not diagnosed until adulthood, the subset of 19 POMS patients diagnosed before age 18 was also compared separately to the AOMS patients. Demographics are presented in Supplementary Table 1. Results were consistent with the larger sample except for disease duration not being significantly different.

**SDMT**

In the unadjusted analysis, POMS patients had a lower mean SDMT score than AOMS patients but this difference was nonsignificant (POMS = 52.1 ± 16.1 vs. AOMS 56.9 ± 12.5, p = 0.063) (Table 2). After adjusting for age, the POMS patients had significantly lower scores on the SDMT (−7.57 (−11.72, −3.43; p < 0.001) (Table 3). There was no significant difference in SDMT after adjusting for disease duration. These results remained, including a significant difference in age-adjusted SDMT (POMS < AOMS; 11.16 (17.63, −4.69; p < 0.001) in the analyses comparing the subsample of POMS patients diagnosed before age 18 to the AOMS group (Supplementary Tables 2 and 3).

We additionally compared SDMT scores to age-matched normal controls provided by Dr Benedict from a previous study completed at State University of New York at Buffalo (SUNY-Buffalo). The mean (SD) z-score in AOMS is −0.76 (1.38), and the mean (SD) z-score in POMS is −1.50 (1.48). The estimated group difference demonstrated lower normative z-scores in POMS vs. AOMS (−0.74 (95% CI: −1.18, −0.30; p = 0.0009), and was significant after adjusting for disease duration (−0.60; 95% CI: −1.05, −0.15;
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In terms of patient-reported outcomes, the POMS and AOMS groups were similar (Table 2). In unadjusted analyses, no significant differences were observed in HRQOL, fatigue, social support or depression.

After adjusting for age, a significant difference between the groups was observed on the physical health composite of the MSQOL-54 (p < 0.05), but this difference would not have remained significant after accounting for multiple comparisons. No other significant differences between the groups were observed. Again, these results remained in the analyses comparing the subsample of POMS patients diagnosed before age 18 to the AOMS group (Supplementary Tables 2 and 3).

### Discussion

This study explored HRQOL, depression, and speed of information processing in an adult sample of patients with POMS compared to patients with AOMS. While these factors have been studied individually in POMS and AOMS, POMS and AOMS patients have not previously been compared.

The SDMT was used to assess information-processing speed and was the only measure studied that was found to be significantly different between the two groups. In our initial analysis, pediatric-onset patients scored lower than adult-onset patients when scores were adjusted for age, but not when adjusting for disease duration. However, when the dataset was normalized using age-matched controls, we found that POMS SDMT scores were lower than AOMS both in unadjusted analysis and when adjusting for disease duration. The summary of these analyses suggests that using age-adjusted values, POMS showed lower SDMT scores in adulthood than did AOMS; and in a subanalysis using normative values, suggests that POMS have more impaired processing speed scores than AOMS even after adjusting for disease duration. This was irrespective of age at formal diagnosis of POMS patients, since all results remained significant in the subset of POMS diagnosed prior to age 18. Our findings suggest that in adulthood POMS may have more difficulty with processing speed as studied here, and whether this holds true for other cognitive measures needs to be further explored.

Prior studies in children with MS have demonstrated persistent or even worsening cognitive impairment over a two-year period. Patients with POMS may be particularly susceptible to cognitive problems as white-matter and gray-matter changes are found as part of the disease and the neuropathologic processes of the disease occur during primary myelinogenesis. Onset of the disease at a young age may affect ongoing maturation of white-matter pathways that can lead to neurodegeneration of neural networks involved in cognition. Although the severity and trajectory of changes in cognition may differ widely among POMS patients, the presence of demyelination over key educational and developmental years remains a concern, and may have long-term impact on scholastic and potentially work-related achievement.

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**Table 3. Comparison of AOMS patients and POMS.**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unadjusted difference (95% CI)</th>
<th>Disease duration-adjusted difference (95% CI)</th>
<th>Age-adjusted difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDMT</td>
<td>−3.84 (−7.88, 0.20)</td>
<td>−0.68 (−4.74, 3.39)</td>
<td>−7.57 (−11.72, −3.43)</td>
</tr>
<tr>
<td>PHC</td>
<td>−4.32 (−9.73, 1.09)</td>
<td>−2.59 (−8.19, 3.01)</td>
<td>−5.87 (−11.55, −0.19)</td>
</tr>
<tr>
<td>MHC</td>
<td>−3.77 (−8.84, 1.29)</td>
<td>−3.06 (−8.31, 2.20)</td>
<td>−4.04 (−9.37, 1.30)</td>
</tr>
<tr>
<td>MFIS</td>
<td>1.92 (−3.27, 7.11)</td>
<td>1.03 (−4.37, 6.43)</td>
<td>3.04 (−2.43, 8.52)</td>
</tr>
<tr>
<td>MSSS</td>
<td>0.55 (−5.35, 6.46)</td>
<td>2.32 (−3.79, 8.42)</td>
<td>−3.11 (−9.26, 3.05)</td>
</tr>
<tr>
<td>CESD</td>
<td>0.08 (−2.35, 2.50)</td>
<td>0.50 (−2.03, 3.02)</td>
<td>−0.41 (−2.95, 2.13)</td>
</tr>
</tbody>
</table>

*p < 0.05. †p < 0.001.

For each comparison, a negative difference implies that the adult onset had higher scores. AOMS: adult-onset multiple sclerosis; POMS: pediatric-onset multiple sclerosis; SDMT: Symbol Digit Modalities Test; PHC: Physical Health Composite from Multiple Sclerosis Quality of Life-54 (MSQOL-54); MHC: Mental Health Composite from MSQOL-54; MFIS: Modified Fatigue Impact Score; MSSS: Modified Social Support Survey; CESD: Center for Epidemiological Studies Depression Scale; CI: confidence interval.
Although SDMT was the only cognitive measure included in our battery, SDMT has been shown to be a sensitive measure of cognitive processing speed both in adults\textsuperscript{33,34} and children.\textsuperscript{30} In the pediatric population, SDMT showed 100\% sensitivity for detecting neuropsychological impairment when administered within two months of a comprehensive cognitive battery.\textsuperscript{30} Several studies have demonstrated that the most common impairments in POMS patients are in complex attention (specifically rapidly shifting attention between competing stimuli) and in mental-processing speed.\textsuperscript{14-18} However, the sole focus of cognitive measures on processing speed, is a limitation of this study, particularly given evidence that has emerged since the CLIMB study began that there may be cognitive impact that is unique to POMS (e.g. on language and verbal comprehension) compared to AOMS. The fact that only processing speed was examined as a measure of cognitive impairment in this study may also explain the lack of findings regarding a relation between cognitive impairment and QOL. It may be that the patients experiencing impaired processing speed were not experiencing more general cognitive impairment that was noticeable or significantly disruptive for them. Future studies should include a more comprehensive neuropsychological test battery that assesses additional cognitive domains. Better yet, these studies should focus on following POMS patients from diagnosis before age 18 into adulthood.

Measures of QOL, fatigue, and depression were not significantly different between the pediatric and adult-onset groups, regardless of age at diagnosis among POMS patients. This was unexpected, given that the early course of pediatric MS tends to be more severe than in AOMS with more frequent relapses\textsuperscript{35} and that MS-related cognitive impairment has been found to be related to QOL. Given that POMS patients showed slower processing speed than AOMS patients in the current study, they might also be expected to show lower QOL. However, both groups had a relatively mild disease severity (mean EDSS score of $<2$), which has been most strongly associated with QOL.\textsuperscript{8,36} It is notable that POMS patients are more likely than AOMS patients to have converted to secondary progressive MS at a younger age, a diagnosis associated with more severe symptoms and a worse prognosis. While the sample size did not allow for a comparison of these patients to POMS patients with relapsing–remitting MS, future studies might explore possible differences in QOL in adulthood between these groups.

It is also possible that the subjective experience of living with MS was not significantly different between POMS and AOMS patients in the current study because fewer than half of the POMS patients had been formally diagnosed before 18 years of age. Therefore, relatively few of the POMS patients in the current study had the experience of living through their adolescent years with a diagnosed chronic illness. It is possible that this shortened diagnostic period, combined with the small sample size of POMS patients diagnosed before age 18, explains the lack of difference between our POMS and AOMS groups in their report of the impact of diagnosis on QOL. It will be important for future studies comparing these same variables in POMS and AOMS patients to include more POMS patients diagnosed prior to 18 years old to address this possibility.

This study supports the need for ongoing research into the long-term course and outcomes of POMS into adulthood that includes comparisons between POMS and AOMS. While the pathology and clinical correlates of POMS and AOMS may be very similar, their long-term course may be different both clinically and in terms of impact on everyday functioning.

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Conflict of interest
None declared.

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