Pediatric multiple sclerosis

Cognition and mood

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ABSTRACT

In comparison with the large body of evidence on cognitive functioning in adults with multiple sclerosis (MS), there is limited information on cognition in pediatric-onset MS (POMS). Unique vulnerabilities in POMS can derive from having a disease that occurs during key periods of age-expected brain growth, active myelination in the CNS, and maturation of neural networks during the learning curve and key formative years in the academic career of the patient. Therefore, the consequences of MS on developing cognitive faculties can be assessed only in the pediatric population and cannot be simply extrapolated from studies carried on in the adult population. Until the last decade, research in the pediatric population was mainly represented by small clinical series, often limited by the narrow scope of neuropsychological assessment and lack of adequate control groups. Over the last decade, however, cognitive functioning and mood-related difficulties have become an increasing concern as awareness of this population has grown. A few specialized MS centers have begun performing more systematic research in the field in order to assess the prevalence of cognitive impairments and mood-related difficulties in patients with POMS, to better characterize the neuropsychological pattern and determine the functional consequences of these problems. This chapter summarizes our current understanding of cognitive and mood-related difficulties in POMS and highlights perceived gaps in knowledge and priorities for future research. ***Neurology*® 2016;87 (Suppl 2):S82–S87**

GLOSSARY

BNBC = Brief Neuropsychological Battery for Children; **CIS** = clinically isolated syndrome; **CL** = cortical lesions; **EDSS** = Expanded Disability Status Scale; **FC** = functional connectivity; **fMRI** = functional MRI; **GM** = gray matter; **MS** = multiple sclerosis; **POMS** = pediatric-onset multiple sclerosis; **SDMT** = Symbol Digit Modalities Test; **WM** = white matter.

Patients with pediatric-onset multiple sclerosis (POMS) may be particularly vulnerable to inflammation, demyelination, and axonal damage associated with multiple sclerosis (MS).[1] The concurrence of these changes with myelination in the developing CNS that can go on through the third decade of life can damage networks involved in cognition.[2] Research suggests loss of myelin in POMS can adversely affect cognition and academic skills.[2,3] Whether brain plasticity and compensatory abilities can mitigate against disease-related pathologic changes remains unclear: answers will ultimately emerge through careful long-term studies of cognitive outcomes in POMS.

PREVALENCE, NEUROPSYCHOLOGICAL PROFILE, AND CLINICAL CORRELATES Across differing test batteries and definitions of cognitive impairment, cognitive impairment is consistently reported in approximately one-third of patients with POMS (table 1). In interpreting different thresholds used to classify cognitive impairment, it is useful to note that the 5th percentile equates to 1.67 SD.

In a US study of 37 POMS cases,[4] 35.1% of the patients showed cognitive impairment, defined by performance falling 1.5 or more SDs below normative data on at least 2 cognitive tasks. The most common impairments were complex attention (29.7%), poor naming (18.9%), receptive language problems (13.5%), immediate recall of visual information (8.1%), and delayed recall of visual (11%) and verbal (18.9%) information. Expanded Disability Status Scale (EDSS) was the strongest predictor of impairment followed by the

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Table 1 Key cross-sectional studies of cognitive functioning in pediatric-onset multiple sclerosis (MS)

Study authors	Region	MS sample size	Healthy control sample size	Impairment definition	Impairment rate, %	Most frequent areas of impairment (>20% of sample)
MacAllister et al.[4]	US (single center)	37	—	Two or more test scores >1.5 SDs below published normative means	35.1	Complex attention
Amato et al.[5]	Italy (multicenter)	63	57	<5th percentile of healthy control performance on at least 3 test scores	31	Verbal and visual memory, complex attention, executive functions, aspects of language function
Till et al.[8]	Canada (single center)	35	33	≥3 scores >1.5 SDs below normative mean	29.4	Attention and processing speed, visuomotor integration
Julian et al.[9]	US (multicenter)	187	—	≥33% of test scores >1 SD below normative mean	35	Fine motor speed, visuomotor integration, information processing speed

number of relapses. Thirteen out of 37 patients (35.1%) required some type of aid or adaptation in their school curriculum.

In an Italian multicenter study,[5] POMS cases (n = 63) were compared to matched healthy controls (n = 57) on an extensive battery. Cognitive impairment was defined by scores falling below the 5th percentile of healthy control performance on at least 3 tests. Verbal and Performance IQ scores were lower in the pediatric MS group as compared to healthy controls and cognitive impairment was noted in 19 patients with MS (31%). The most frequently observed cognitive deficits were on tests of verbal ability (39%–53%), visuospatial memory (18%–56%), complex attention (28%–50%), and aspects of executive functions (41%). Semantic and phonemic verbal fluencies were reduced in 22% and 17% of the cases, respectively, whereas 2 verbal comprehension tasks were failed by 28% and 39% of the patients. In a logistic regression analysis, IQ predicted cognitive impairment. When the IQ was included as a dependent variable, younger age at disease onset represented the only significant predictor.

Parents reported that the disease had a deleterious functional impact.[5] For one-third of patients, cognitive problems negatively affected school, daily, and social activities. Longitudinal data of this cohort over 5 years demonstrated declines for most participants, associated with adverse consequences on school achievements and social life.[6,7]

A study of 35 Canadian patients with POMS and a similar number of controls[8] showed reduction in functioning predominantly on measures of attention and processing speed (38%), visuomotor integration (23.5%), and expressive vocabulary (9.7%). Full-scale IQ and verbal IQ were significantly reduced in the MS vs control group, though only 5 of the 35 patients (14.3%) were reported to have a full-scale IQ that was below average (i.e., IQ <85). Higher IQ was moderately associated with shorter MS duration and older age at disease onset. Finally, higher full-scale IQ was moderately correlated with lower EDSS score.

The largest series published so far is from the US network of MS centers,[9] which defined cognitive impairment as a ratio score greater than one-third of impaired test scores relative to completed test scores, using published normative data for the tests. Impairment was noted among 35% of patients with relapsing-remitting MS and 18% of patients with clinically isolated syndrome (CIS). Impairment was predicted by a diagnosis of MS and overall neurologic disability on the EDSS. The tests most frequently compromised involved fine motor coordination (54%) and visuomotor integration (50%), followed by speeded information processing (35%).

Finally, patients with POMS have been shown to have poorer performance on measures of social cognition, such as facial recognition of affective state, identification of beliefs, and knowledge of others.[10]

In sum, approximately 30% of patients with pediatric MS have cognitive impairments characterized by deficits similar to that of adult-onset MS, except that patients with POMS are more likely to show problems with linguistic skills and general intelligence, possibly associated with younger age at MS onset.

LONGITUDINAL STUDIES Information about the long-term outcome in POMS is scarce.[11] Most but not all longitudinal studies to date[6,7,12–15] report cognitive worsening, with frequencies varying greatly across studies (table 2).

In a study[14] that used the Reliable Change Index to determine individual changes on test scores over a 15-month interval, improvements in cognitive functioning were reported on 18% of cognitive measures in the MS group as compared with 86% of measures in the control group. These results highlight a lack of maturational-expected improvements in the patients with MS relative to age-matched healthy peers. Deterioration in functioning, defined as significant decline on 3 or more tests, was observed in 7 of 28 patients (25%) as compared to only 1 of 26 controls (4.6%).

In a cohort of 35 patients with POMS, growth curve modeling was used to assess changes in cognitive maturation.[12] Results showed that younger age at disease onset was associated with a higher

Table 2 Longitudinal follow-up of samples from cross-sectional reports

Study authors	Region	MS sample size at follow-up	Healthy controls sample size at follow-up	Duration of follow-up	Definition of decline	Rate of decline in MS sample, %	Notes
MacAllister et al.[13]	US (single center)	12/37	—	Up to 3 y	>No. of test scores in impaired range from baseline	42	
Amato et al.[6,7]	Italy (multicenter)	56/63	—	Mean of 2 y	≥2 points in a total of scores weighted according to SDs from the normative means	75 at 2 y	Amato et al.[7] reported overall decline rate on a cognitive change index of 56% from baseline in 48 of the original cohort of 64 patients with a second repeat assessments on average of 4.7 y
Till et al.[14]	Canada (single-center)	28/35	26/33	15 mo	>1.5 decline on 3 or more tests	25	Analysis using reliable change indices indicate failure to make age-expected gains relative to controls followed for same period
Charvet et al.[15]	US (multicenter)	62/187	—	Mean of 1.64 y	>1 SD decline on 2 or more tests	13	

Abbreviation: MS = multiple sclerosis.

likelihood of cognitive decline on measures of processing speed and working memory. The Italian cohort was assessed at baseline[5] and again after 2[6] and 5 years.[7] Comparing results at baseline and after 5 years (when we used the same versions of the tests), we found deterioration of the cognitive impairment index in 56%, improvement in 25%, and stability in 18.8% of the patients. Functions most prone to deteriorate were visual spatial learning and memory, verbal fluency, and expressive language. Younger age at the onset of the disease and lower educational level were associated with cognitive impairment; however, these relationships were no longer significant in the multivariate analysis.

In a US study[15] that included 62 patients with MS and 5 patients with CIS, cognitive retesting after 1.6 years showed that most patients remained stable. A total of 13% deteriorated and 20% improved on 2 or more tasks. Differences in the characteristics of the patients and assessment tools may, at least in part, explain these differing results.

On the whole, while cognitive impairment seems to be frequent, many patients may exhibit stable or improved cognitive functioning over time. On the other hand, young patients with MS should be regularly followed up to monitor cognitive maturation and to screen for the possible late emergence of cognitive problems.[15]

MRI CORRELATES OF COGNITIVE IMPAIRMENT IN PEDIATRIC MS As with adult MS, white matter (WM) T2 lesion volume shows stronger correlations with specific neuropsychological outcomes than does T1 lesion volume (so-called black holes).[8] Using lesion probability mapping, Rocca et al.[16] showed that cognitively impaired relative to cognitively preserved patients were more likely to harbor lesions in the right thalamus, middle and posterior corpus callosum, and bilateral parieto-occipital WM, implicating a posterior pattern of pathology that contributes to cognitive impairment in POMS.

Using diffusion tensor imaging, Rocca et al.[17] found an abnormal development of WM in POMS, although the study did not specifically address cognition.

Moreover, microstructural WM damage in the corpus callosum, particularly the genu and anterior body, has been shown to associate with reduced visual-perceptual speed[18] and less efficient cognitive control.[19] Factoring out processing speed, a robust association was reported between arithmetic score and fractional anisotropy (a measure of WM integrity) in WM of the corpus callosum and in right frontal and parietal regions,[20] consistent with the important role of WM pathways underlying mathematical competence. Fractional anisotropy values were lower in the pediatric patients with MS as compared with controls in all regions of the brain, except for the frontal lobes. The well-established caudo-rostral pattern of myelination through childhood[3] has been suggested to confer some protection of the late maturing frontal lobes from MS-related WM insult.[18] The role of cerebellum in cognitive processes is increasingly investigated. Cognitive impairment in POMS has been correlated with smaller cerebellar posterior lobe volume and increased lesion burden in the posterior fossa.[21]

Gray matter (GM) involvement can also contribute considerably to cognitive dysfunction in this population. In one study, global brain volume loss in GM was correlated with lower estimated IQ and reduced information processing speed.[8] In another study,[16] more severe damage to GM, especially in the right precuneus and left middle temporal gyrus, was found in cognitively impaired as compared with cognitively preserved patients. In contrast with adult MS studies,

using double inversion recovery sequences, the number and volume of cortical lesions (CL) did not differ between cognitively preserved (CL 12%) and impaired (CL 15%) pediatric patients.[22]

In a study of 35 patients with POMS,[8] the volume of thalamus, which has a key integrative role in diverse cognitive abilities and is vulnerable to pathologic involvement in pediatric MS, emerged as the most robust MRI predictor of global functional outcomes, as well as measures of mental processing speed, visuomotor integration, and vocabulary. Only regional structures (thalamic volume and corpus callosum area), and not global atrophy measures, differentiated patients with POMS identified as having cognitive impairment from those without.[20]

Regarding memory outcomes, performance on a word list learning task was shown to correlate with whole brain volume and hippocampal volume, despite a relative sparing of this deep GM structure in the context of significant reduction in whole brain volume.[23] Moreover, Rocca et al.[24] found that hippocampal subregions involvement contributed to global cognitive impairment and to deficits of selected cognitive tests in POMS with cognitive impairment.

Functional MRI (fMRI) studies have also begun to shed light on the concepts of preserved functional reserve and changes to cognition-relevant networks in POMS.[25] Using resting-state fMRI, Rocca et al.[26] showed that patients with POMS as compared with controls demonstrated decreased functional connectivity (FC), mainly in posterior brain regions, suggesting an impaired maturation of large-scale brain connectivity. In addition, increased FC of the medial frontal gyrus (implicating the attention network) was also observed. Interestingly, increased FC in this frontal region was inversely correlated with T2 lesion volume and more pronounced in cognitively preserved patients with MS, suggesting a possible mechanism that may serve to counteract the impact of structural damage when the extent of damage is modest.

In one longitudinal study,[14] 28 patients with POMS underwent serial MRI and cognitive assessment over a 15-month interval. Results showed that an increase in T1 and T2 lesion volume predicted a slowing of psychomotor speed on a visual attention task. Future, longer-term longitudinal studies are needed to examine changes in regional and global brain growth to determine whether loss of volume or connectivity in patients with POMS differs as a function of MS disease activity during key epochs of brain maturation.

ASSESSMENT STRATEGIES Cognitive assessment during pediatric age is complicated by different developmental trajectories that correspond to different sets of tests or normative groups for different ages. Moreover, available cognitive data are too sparse to permit adequate pooling of data to identify the measures that are most discriminating and meet psychometric standards for reliability and validity. Assessment is further complicated by the wide range of abilities that can be affected by pediatric MS and would require a comprehensive battery. An alternative is to consider brief screening and abbreviated measures. A 30-minute screening tool, the Brief Neuropsychological Battery for Children (BNBC), was developed based on a discriminant analysis of the measures used in the initial Italian study.[27] The tests include the vocabulary test from the Wechsler Intelligence Scale for Children, Symbol Digit Modalities Test (SDMT), Trail-Making Tests A/B, and 2 measures from the Selective Reminding Test. Low performance (<5th percentile relative to control data) on at least one test on the BNBC yielded a sensitivity of 96% and specificity of 81% in detecting cognitive impairment.[27]

In a US study of over 200 pediatric MS cases,[9] the Grooved Pegboard had the highest rate of impairment, followed by the Beery-Buktenica Developmental Test of Visual-Motor Integration. Although a short neuropsychological test battery was proposed for international use,[28] we lack data to confidently know which tests are most appropriate for multicenter research studies.

The SDMT is a widely used screening measure to identify and longitudinally follow those at risk for cognitive impairment.[29] It can be administered in children as young as 8 years, is brief (90 seconds), and has alternate forms for repeat testing.[30] When consecutively administered to patients with POMS in an outpatient center,[31] in a sample of 31 cases, the SDMT showed 77% sensitivity and 81% specificity for detecting neuropsychological impairment and had 100% sensitivity when administered twice in less than 2 months.

FATIGUE AND MOOD DISORDERS Due to the high frequency of fatigue in adult MS, it is of interest to consider its impact in POMS. Of 48 pediatric patients with MS followed over 5 years in the Italian cohort,[7] 20% had severe fatigue using the fatigue severity scale (cutoff of ≥4.0). However, measures developed for pediatric use showed that 51% of parents consider their child's fatigue as severe, whereas only 32% of patients on self-report measures indicated severe fatigue.[32] In another study,[33] percentages of fatigued patients ranged from 9% to 14% according to self-reports, and from 23% to 39% according to parent reports. In this study, fatigue was significantly related with self-reported depressive symptoms; cognitive fatigue, in particular, was associated with impaired performance on a series of cognitive tasks assessing executive functions, memory, attention, and processing speed.[33] Although

one study showed no differences in quality of life indices and fatigue between controls and individuals with pediatric MS,[34] others who have compared healthy controls and patients with pediatric MS have found elevations in fatigue, sleep disturbance, and emotional distress in the MS group.[35]

Mood disturbance and behavioral problems in general are more commonly reported by the parents rather than the children or adolescents.[36] Parents noted behavioral problems in 39% of 48 pediatric-onset cases followed for a mean of 5 years.[7] Psychiatric interviews revealed affective disorders in 30% of unselected children.[7] Another study[14] using the Behavior Assessment System for Children, Second Edition, found that 29% of parents rated depression in their children with MS, whereas none of the parents of healthy controls had such reports. Finally, a study[37] comparing self-reported outcomes of fatigue, depression, and quality of life in pediatric-onset and adult-onset patients found similar quality of life measures in the 2 groups.

Overall, patients with cognitive impairment are at greater risk for mood disorders.[38] Behavioral problems are also associated with fatigue and lower full-scale IQ.

The behavioral, cognitive, and physical changes of pediatric MS clearly take a toll. Grade retention can occur,[7,39] while other aspects of academic functioning, social functioning, and engaging in hobbies[7,35,39] can all be adversely affected. Early detection can hopefully lead to the provision of support services, efforts at cognitive remediation, and counseling. Studies on these aspects, however, are still limited and more information and guidance on assessment and treatment of mood disorders in patients with POMS is needed.

Future research should include further characterization of the neuropsychological profile in relation to age, risk factors, and the potential protective role of cognitive reserve and intellectual enrichment; cognitive and functional outcomes in adult life; potential role of treatment with disease-modifying drugs in preventing/delaying cognitive problems; better understanding of brain changes underlying cognitive impairment and compensatory mechanisms; consensus on definitions of cognitive impairment; development of test batteries that can facilitate international comparisons and collaborative research; and interventions that can preserve cognitive function and improve behavioral outcomes and quality of life.

AUTHOR CONTRIBUTIONS

All authors contributed to drafting the chapter and providing critical revision.

STUDY FUNDING

This supplement is made possible by funding from the MS Cure Fund, Danish MS Society, German MS Society, Italian MS Association, MS International Federation, MS Research Foundation (Netherlands), National MS Society (USA) and Swiss MS Society.

DISCLOSURE

M. Amato has received research grants and honoraria as a speaker and member of advisory boards by Bayer, Biogen Idec, Merck Serono, Novartis, Sanofi Genzyme, Teva, and Almirall. L. Krupp received honoraria or consultation fees from Biogen, Novartis, Teva Neurosciences, Pfizer, Projects in Knowledge, Providence Health Services, and Multicell, and royalty payments from Avanir Pharmaceuticals, Abbvie Inc., Osmotica Pharmaceutical Corp., and Demos Medical Publishing; and received research funding from Novartis, Teva Neurosciences, Biogen Idec, Genentech, National Multiple Sclerosis Society, Department of Defense, National Institutes of Health, and the Lourie Foundation. L. Charvet has received research funding form Novartis AG. I. Penner and C. Till report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received August 19, 2015. Accepted in final form March 1, 2016.

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