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Behavioral Symptoms in Pediatric Multiple Sclerosis (MS): Relation to Fatigue and Cognitive Impairment

Leigh Charvet¹, Bianca Cersosimo², Colleen Schwarz^{1,2}, Anita Belman^{1,2}, and Lauren B. Krupp^{1,2}

¹New York University MS Comprehensive Care Center

²Stony Brook Medicine, Department of Neurology

Abstract

The emotional and behavioral problems associated with pediatric multiple sclerosis (MS) remain unclear. Participants with pediatric MS or clinically isolated syndrome (n=140; ages 5 to 18 years) completed self- and parent-ratings using the Behavioral Assessment System for Children, Second Edition, neurological exam, the Fatigue Severity Scale, and neuropsychological assessment. Mean self- and parent-ratings on the BASC-2 were in the typical range across all scales. However, 33.1% indicated a clinically significant problem on a least one scale. While the type of clinical problems varied across participants, attention problems, somatization and anxiety were found most common. Disease features including duration, age of onset, neurologic disability and fatigue did not distinguish those with and without clinical problems. However, cognitive functioning significantly predicted the presence of a clinical problem (p=0.02). Pediatric MS is associated with a range of nonspecific emotional and behavioral clinical problems, occurring more frequently in those patients with cognitive involvement.

Keywords

Pediatric; multiple sclerosis; behavior; cognition; fatigue; BASC-2

Introduction

The onset of multiple sclerosis (MS) during childhood and adolescence presents unique clinical challenges. Pediatric (under age 18) onset is rare with an estimated incidence of 0.2

Corresponding Author: Leigh Charvet, PhD, NYU MS Comprehensive Care Center, 240 East 38th Street, 20th Floor, New York, NY 10016, 646-501-9257 (phone), 646-754-9593 (fax), Leigh.Charvet@nyumc.org.

Author contact information:

Bianca Cersosimo, BS, Stony Brook Medicine, Department of Neurology, HSC T12-020, 100 Nicolls Rd., Stony Brook, NY 11794, Tel: 631-444-7802, Fax: 631-444-6438, Bianca.cersosimo@stonybrookmedicine.edu

Colleen Schwarz, NYU MS Comprehensive Care Center 240 East 38th Street, 20th Floor, New York, NY 10016 Tel: 631-444-2599, Fax: 631-444-6438, Colleen.schwarz@nyumc.org

Anita Belman, MD, NYU MS Comprehensive Care Center 240 East 38th Street, 20th Floor, New York, NY 10016 Tel: 631-444-2599, Fax: 631-444-6438, Anita.belman@nyumc.org

Lauren B. Krupp, MD, NYU MS Comprehensive Care Center 240 East 38th Street, 20th Floor, New York, NY 10016 Tel: 631-444-2599, Fax: 631-444-6438, Lauren.Krupp@nyumc.org

Conflict of interest statement

The Authors declare that there are no conflicts of interest.

to 0.6 per 100,000. While adult onset MS is associated with increased risk for mood disorders and other psychiatric problems, less is known concerning the psychiatric and psychosocial consequences in pediatric patients.

Initial studies of pediatric MS samples indicated that behavioral problems may be a frequent concern. Descriptive studies have found increased rates of mood disturbances, as reported by parents. These disturbances potentially increase over disease course. Using semi-structured psychiatric interviews, studies have reported elevated rates of mood and anxiety disorders as well as depressive symptoms, especially in those presenting with cognitive impairment and/or fatigue.

We sought to characterize the behavioral and emotional problems observed in a large consecutively-recruited sample of pediatric MS patients, and to test whether these problems were associated with disease features or symptoms of fatigue and cognitive impairment. Problems were identified using the parent- and self-report forms of the Behavioral Assessment System for Children, 2nd Edition (BASC-2), a multi-item inventory that addresses adaptive skills, behavioral symptoms, externalizing problems, internalizing problems, and school problems. It is used to broadly screen for areas of clinical concern in children, adolescents and young adults. Items present questions that allow participants to assess their adaptive and prosocial skills (e.g., positive school functioning) as well as problem behaviors or feelings that may indicate the presence of a clinical disorder(s) (e.g., inattention, mood disturbance). The BASC-2 is commonly used to screen and characterize these problems in youth with clinical diagnoses as well as with healthy children in atypical situations.

Methods

Participants were consecutively-recruited during outpatient clinical visits to the Lourie Center for Pediatric MS between April 2006 and May 2014. This study was IRB approved and all individuals provided written, informed consent before participating. All participants were aged 18 years and younger, with those below the age of 18 presenting with symptom onset the prior year. All participants met criteria for a diagnosis of pediatric MS or clinically isolated syndrome (CIS), with no other neurologic diagnosis. Those presenting with CIS were included as they have had a clinical event consistent with MS and are often considered to represent those in the earliest stages of the disorder. Participants with a current MS relapse, or who had received treatment with steroids within one month time of cognitive assessment were excluded.

Neurological, Cognitive and Fatigue Assessment

Neurologic assessment included confirmation of the diagnosis, date of symptom onset and a neurological examination that included the Expanded Disability Status Scale (EDSS). The majority of the participants also underwent neuropsychological evaluation at the same visit that the BASC-2 was administered. Neuropsychological evaluations used a battery of tests developed through consensus for use in the U.S. Network of Pediatric MS Centers and reported as part of the national cross-sectional study, assessing a broad range of areas including attention, executive functioning, and verbal and visual learning. Following the

methods of the original cognitive study, each test score was converted to an age-normative z score, with an average z score composite across measures representing cognitive functioning. Participants were determined to have cognitive impairment based on at least one-third of test scores falling one standard deviation or more below the age normative mean.

For a subset, fatigue was also measured using the self-reported Fatigue Severity Scale or FSS. The FSS includes nine items addressing fatigue severity and its influence on daily activities. Each item is rated along a seven-point scale, with higher ratings indicated more severe fatigue. In this manner, scores can range from 9 to 63. For adult samples, severe fatigue is suggested by scores >36, however this has not yet been validated for younger patients.

Behavioral ratings were completed using the BASC-2 self- and parent-report forms (self-report of personality or SRP and parent rating scales or PRS, respectively). Two SRP forms were used, each tailored towards a specific age group, ages 8-11 and ages 12-21. Similarly, two PRS forms were designated for parents of children whom were between the ages of 6-11 and 12-21. The length of the reports depended on the form administered, ranging from 134 to 160 items. Each item was either rated along a four point Likert Scale ("Never" to "Almost always") or a "True or False" statement. All participants were English-speaking and reading; Spanish language forms were provided to parents who were primary Spanish speakers.

The BASC-2 includes clinical and adaptive functioning scales. While there is some overlap, the individual scales vary from self- and parent-report forms, and also with age range. Each scale score is transformed to a T score (mean= 50, standard deviation or SD=10) based on the extensive age-normative database with a normal distribution. Therefore, a scale T score falling two standard deviations from the normative mean represents the second percentile, indicating only two percent or less of the normative sample to have scored in that range. Scores in this range are considered to be "clinically-significant".

Participants' BASC-2 profiles were scored (double entry) using BASC-2 ASSIST™ Software and generated using the program software referencing large normative databases (combined sex). Only participants with profiles showing acceptable validity indices were included for analyses.

Analyses

All analyses were completed using SPSS Version 22.0. A descriptive approach was used to determine whether there was any pattern of clinical concerns for the sample using the mean scores for the full group across both SRP and PRS scales. Next, the frequency of clinically significant scores was determined across individuals. Using group comparisons, we then tested whether any disease features or the symptoms of fatigue and cognitive impairment contributed to the likelihood of having a clinically significant score.

Results

Demographic and clinical factors

A total of 140 participants completed at least one report form of the BASC-2. The majority of the sample (n=108, 77.1%) met criteria for relapsing remitting MS and the remainder were diagnosed with CIS (n=32, 22.9%). Sample characteristics are demonstrated in Table 1.

Cognitive Functioning

Of the full sample with BASC-2 reports, 120 also completed the neuropsychological assessment. A total of n=38 (37.1%) were classified as having cognitive impairment (n=32 MS vs. n=6 CIS). This rate of impairment is consistent with what was found in the larger U.S. Network sample (32%). The mean composite z score (lower scores indicating greater impairment) for the full sample was $z=-0.31\pm0.77$ indicating average range of functioning overall. While the MS participants had overall lower cognitive functioning than the CIS participants, this difference was not significant (mean z score of -0.37 ± 0.78 vs. -0.12 ± 0.71 , $p=0.12$).

Fatigue

A total of n=66 participants also completed the FSS, indicating mild to moderate levels of fatigue overall (Table 2).

Behavioral symptoms at the group level—Of the 140 participants with BASC-2 data, n=128 had completed self-report forms and n=130 had parent-report forms completed, while n=119 had both self- and parent-report forms completed. Figure 1 illustrates the mean scores for each of the clinical scales for the SRP and PRS for the sample as a whole in Figures 1. As shown, no mean score on any clinical scale for self- or parent-report forms fall outside of the typical range (all mean T scores between 45 and 55).

Behavioral symptoms across individuals—At the individual profile level, there was a high frequency of scales rated in the clinically significant range. Across the sample, 29.9% and 34.1% of the SRP and PRS profiles, respectively, had at least one scale in the clinically significant range, indicating approximately one-third of the sample having a clinical concern and that the parents were slightly more likely to indicate the presence of a behavioral concern. Figure 2 shows the rates of clinically-significant scores for the self- and parent-report form composite scales.

Comparison of self- and parent- reports—Parents reported clinically significant problems at generally the same rate as were reported by the participants themselves (16.2% vs 14.7%). More than 5% of parents reported clinically significant scores in eight different scales, while participant self-reports only highlighted 6 clinically significant scales of dysfunction (Figure 2). Both parent and participant reports seemed to agree on scales of dysfunction that occurred at higher frequencies, such as problems with attention, somatization, and hyperactivity.

Predictors of BASC-2 clinical elevations—Those participants with at least one clinically significant scale elevation (SRP or PRS, $n=34$ or 33.1%) were compared to those with profiles in the typical range across demographic and clinical features. Among the demographic features, gender but not age, race or ethnicity trended towards significant association with the presence of a clinical problem: 62% of the girls vs. 28% of the boys, $\chi^2(1, N=96) = 4.17, p=0.04$ (all other p 's >0.12).

Among the clinical features, MS and CIS participants did not significantly differ in rates of clinically significant elevations for either the PRS (35.0% vs. 30.0% respectively, $p=0.72$) or SRP (28% vs. 34%, $p=0.51$). Further, between those with and without at least one clinically significant elevation, there were no significant differences in age, age of onset, disease duration, EDSS, or fatigue (all p 's >0.12). However, the clinical elevation group had significantly lower cognitive functioning (mean composite z score = -0.69 ± 0.78 vs. $-0.18 \pm 0.74, p=0.007$). Cognitive functioning (composite z score) and fatigue (FSS) were not significantly related, $r=0.09, p=0.48$, consistent with its unique association to the presence of a cognitive problem. Finally, those meeting criteria for cognitive impairment were significantly more likely to have at least one clinically significant problem, $\chi^2(1, N=113) = 5.56, p=0.02$.

Discussion

In this large and consecutively-evaluated sample, one-third (33.1%) of those diagnosed with pediatric MS or CIS had clinically significant elevations on at least one self- or parent reported BASC-2 clinical scale. However, no one scale consistently emerged to characterize the MS group's behavioral symptoms as a whole. Taken together, these findings indicate frequent clinically significant behavioral and emotional problems in pediatric MS.

Participants self-reported slightly lower rates of impairment than was reported by their parents, but both indicated similar problem areas of attention problems, somatization, and anxiety with other internalizing problems. Attention problems may indicate awareness and experience of the influence of MS on cognition, as information processing is the earliest and most common type of impairment. Anxiety and internalizing symptoms in general may indicate concern with the diagnosis and future disease course, and problems related to living with a medical diagnosis during childhood. Elevations on the somatization scale are likely to reflect, at least in part, the symptoms of MS as they are experienced.

Age, age of onset, and disease features of duration and severity (EDSS) were not associated with behavioral ratings on either self- or parent-reports. Among the symptoms measured, cognitive impairment, but not fatigue, was a significant predictor of BASC-2 impairment.

The current findings are generally consistent with prior studies that have used the BASC-2 to characterize behavioral issues in smaller samples. Only one study has found clinical elevations in the BASC-2 for an MS sample, and only in parent-report scales measuring depression and anxiety. The other two studies found all self- and parent-reports to fall within the typical range, but with elevations relative to healthy control participants. In a study focused on depression and fatigue in pediatric demyelinating disorders (children

diagnosed with MS, n=36, and acute disseminated encephalomyelitis, n=13), Parrish and colleagues found that parents reported their children to have more depressive symptoms than parents of healthy control participants (with no difference in self-reported depression ratings between the demyelinating disorder group and healthy controls). Till and colleagues compared a Canadian sample of 31 consecutively-recruited pediatric MS participants to 31 controls and found that while both groups' mean scale scores were within the typical (non-clinical) range, the MS group had more frequently reported problems. Self-reported problems included inattention/hyperactivity, lower self-reliance and parent-reported problems included depression, higher somatization and lower adaptive functioning when compared to controls. Overall, these studies suggested that behavioral problems were generally related to elevated symptoms such as fatigue, but without strong relation to other disease features including years of disease, EDSS or imaging markers.

While we found cognitive impairment to be linked to higher risk of behavioral problems, the mechanism of the risk remains unclear. Cognitive impairment is a common feature of both adult and pediatric MS, reported in approximately 30% of patients across varying samples and methods. Of the studies including both cognitive and behavioral measures, findings have been variable. In a subset of these participants who also received psychiatric interviews, those who were concurrently diagnosed with an anxiety or mood disorder had the highest frequency of cognitive impairment. Parent-reported depression has also been reported as a predictor of poorer executive functioning. However, other studies have found an absence of a strong relation between behavioral problems and cognitive performance. Future studies may be designed to specifically test hypotheses concerning the direct link between cognitive involvement of MS and the resulting emotional and behavioral problems. For example, cognitive difficulties may increase the disease burden on a daily basis, therefore raising overall stress. Or, certain types of cognitive impairment such as executive dysfunction may contribute to poorer emotional and behavioral control.

There are several limitations to the current study. No healthy control participants were available for comparison. It is important to note that prior studies have found more subtle differences between the MS and healthy control groups even when group averages were within the nonclinical range. Instead, our study focused on the frequency of clinically significant elevations in reference to the normative data provided by the BASC-2 scoring system. Also, including a comparison group with other neurological disorders as well as general medical illness would allow us to isolate any risk factors related to behavior and emotional functioning unique to pediatric MS patients. While we included fatigue measurement in a subset, it would have been useful to include these measures for the full sample. Additional symptom inventories would be helpful as well to better understand the full impact of the disease.

Despite these limitations, it is clear that nonspecific behavioral problems are a frequent occurrence in this pediatric MS sample, and that the presence of cognitive impairment elevates this risk. Future studies should focus on the specificity of the association between cognitive impairment and behavioral problems for pediatric MS or pediatric CNS disorders, as well as the overall more general effects of chronic illness in childhood. The behavioral, cognitive, and physical changes of pediatric MS clearly impact a child's life. Early detection

can hopefully lead to the provision of support services to ease burden for patients and their families.

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Figure 1.
Mean Scale Scores for Self- and Parent-Report

Figure 2.
Scales with >5% Clinically Significant Ratings

Table 1

Demographic and Clinical Characteristics

n= 140*	
Age, M ± SD, (range)	14.9 ± 2.6, (5 years 9 months to 18 years)
Female, n (%)	81 (57.6)
Race, n (%)	-
White	75 (69.4)
African American	21 (19.4)
Asian	3 (2.8)
Mixed/Other	5 (4.6)
Hispanic Ethnicity, n (%)	32 (28.1)
Disease Duration, M ± SD, (range)	1.6 ± 2.6 years (<1 to 10.1 years)
Age at symptom onset, M ± SD, (range)	12.5 ± 3.3 (2 years 4 months to 17 years)
EDSS score, median, (range)	1.0(0.0 to 6.5)

* Total n=140 with one BASC-2 report: n=128 with SRP form, n=130 with PRS, and n=119 with both SRP and PRS

Table 2
Cognitive and Fatigue Symptom Measures in Sample Subsets

Cognitive Functioning*	MS n=91	CIS n=20	Total n=120	Typical Range
Composite z score	-0.37±0.78	-0.11±0.72	-0.31±0.77	0.00±1.00
<i>Mean±SD (range)</i>	(-3.40 to 1.88)	(-1.37 to 2.20)	(-3.40 to 2.20)	(-1.00 to 1.00)
Fatigue Severity Scale	MS n=46	CIS n=20	Total n=66	Typical Range
Self-Report	30.06±14.37	32.70±13.78	30.86±14.14	20.70±6.30
<i>Mean±SD (range)</i>	(9 to 53)	(12 to 72)	(9 to 72)	(<27)

* Cognitive functioning composite z score, with lower indicating greater impairment; tests in battery were the Wechsler Abbreviated Scale of Intelligence including Vocabulary and Matrix Reasoning subtests, Wechsler Intelligence Scale for Children- Fourth edition and Wechsler Adult Intelligence Scale- Fourth Edition- Digit span, Contingency Naming Test, California Verbal Learning Test – Child or second edition, Beery-Buktenica Developmental Test of Visual-Motor Integration – 6th edition, Wechsler Abbreviated Scale of Intelligence Matrix Reasoning, Expressive One Word Picture Vocabulary Test, Wechsler Individual Achievement Test-II, Wechsler Abbreviated Scale of Intelligence, Delis-Kaplan Executive Functioning System Trail Making Test- motor speed condition, Pediatric Quality of Life Inventory- Multidimensional Fatigue Scale; see Julian et al.