

Cognitive and Behavioral Functioning in Childhood Acquired Demyelinating Syndromes



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Abstract

Objectives: The aim of this study was to describe cognitive, academic, and psychosocial outcomes after an incident demyelinating event (acquired demyelinating syndromes, ADS) in childhood and to investigate the contribution of brain lesions and confirmed MS diagnosis on outcome. **Methods:** Thirty-six patients with ADS (mean age = 12.2 years, *SD* = 2.7, range: 7–16 years) underwent brain MRI scans at presentation and at 6-months follow-up. T₂-weighted lesions on MRI were assessed using a binary classification. At 6-months follow-up, patients underwent neuropsychological evaluation and were compared with 42 healthy controls. **Results:** Cognitive, academic, and behavioral outcomes did not differ between the patients with ADS and controls. Three of 36 patients (8.3%) were identified with cognitive impairment, as determined by performance falling ≤ 1.5 *SD* below normative values on more than four independent tests in the battery. Poor performance on a visuomotor integration task was most common, observed among 6/32 patients, but this did not differ significantly from controls. Twelve of 36 patients received a diagnosis of MS within 3 years post-ADS. Patients with MS did not differ from children with monophasic ADS in terms of cognitive performance at the 6-months follow-up. Fatigue symptoms were reported in 50% of patients, irrespective of MS diagnosis. Presence of brain lesions at onset and 6 months post-incident demyelinating event did not associate with cognitive outcome. **Conclusions:** Children with ADS experience a favorable short-term neurocognitive outcome, even those confirmed to have MS. Longitudinal evaluations of children with monophasic ADS and MS are required to determine the possibility of late-emerging sequelae and their time course. (*JINS*, 2016, 22, 1050–1060)

Keywords: Demyelination, Cognition, Pediatric, Multiple sclerosis, Brain lesions, Magnetic resonance imaging

INTRODUCTION

Acquired demyelinating syndromes (ADS) of the central nervous system (CNS) (Banwell et al., 2011) affect 0.9 per 100,000 Canadian children and adolescents per year (Banwell et al., 2009). Subtypes of ADS include acute disseminated encephalomyelitis (ADEM), demyelination isolated to the spinal cord or optic nerves (i.e., isolated transverse myelitis,

TM; or optic neuritis), and polyfocal and monofocal presentations thought to be at high likelihood of multiple sclerosis (MS; also termed clinically isolated syndromes, CIS). Most children with ADS experience a monophasic illness, while in 20–30% of children, incident ADS is the sentinel attack of MS (Banwell et al., 2011; Verhey et al., 2011).

Because of the accrual of new lesions and progressive CNS injury, children with MS are theoretically at greater risk for cognitive impairment, as compared to children with monophasic ADS in whom partial or near-complete resolution of presenting lesions occurs and who, by definition, have no new lesions over time (Banwell et al., 2011;

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Dale, Brilot, & Banwell, 2009; Tenenbaum, Chamoles, & Fejerman, 2002). Studies conducted in the United States, Canada, and Italy on five independent pediatric MS cohorts have documented relatively consistent findings of cognitive impairment in 30 to 41% of youth with MS, despite differences in sampling, assessment procedures, and criterion for determining impairment (Amato et al., 2010, 2014; Charvet et al., 2014; Julian et al., 2013; MacAllister et al., 2005; Till et al., 2011).

By comparison, cognitive impairment has been reported in 16 to 50% of children with ADEM, but this range includes estimates reported in small samples ($n = 9$; Deery, Anderson, Jacobs, Neale, & Kornberg, 2010; $n = 8$, Jayakrishnan & Krishnakumar, 2010; $n = 19$, Kuni, Banwell, & Till, 2012; $n = 22$, Suppiej et al., 2014) and using different criteria for establishing cognitive impairment; results should, therefore, be interpreted with caution. A study conducted among 44 children and adolescents with clinically isolated syndromes (some of whom may have MS) found that 8 of the 44 (18%) patients had scores falling at least one standard deviation (*SD*) below the normative mean on one-third or more of the 25 tests completed in the battery; testing in this study was conducted within the first 2 years following symptom onset (Julian et al., 2013). Less is known about the effects of monophasic TM on cognition. Even though most patients with TM do not show cerebral involvement clinically or by MRI, fine-motor coordination and attention problems (defined as performance falling 1.5 *SD* or more below normative values) have been described in approximately 20% of these patients (Harder, Holland, Frohman, Graves, & Greenberg, 2013).

Cognitive deficits in youth with MS or those with a history of ADEM can vary, but often involve attention and processing speed, visuomotor functions, and language (Amato et al., 2008; Banwell & Anderson, 2005; Julian et al., 2013; Kuni et al., 2012; MacAllister et al., 2005; Till et al., 2011). Cognitive dysfunction in pediatric MS samples has been associated with a range of clinico-demographic factors, including younger age at disease onset (Amato et al., 2008; Banwell & Anderson, 2005), longer disease duration (Banwell & Anderson, 2005), and neurologic dysfunction (as measured by the Expanded Disability Status Scale; MacAllister et al., 2005). Structural brain correlates of cognitive dysfunction in pediatric MS include reductions in the size of the thalamus and total brain volume, and to a lesser degree, T2 lesion volume (Till et al., 2011). In patients with ADEM, lower neuropsychological outcome is associated with younger age at onset, whereas brain MRI lesions at onset and MRI outcome at testing (coded as improved, unchanged, or worsened) had no effect (Suppiej et al., 2014).

To evaluate the early impact of CNS demyelination during childhood on cognitive function, we performed detailed cognitive assessments 6 months post onset in a cohort of prospectively followed children who were at least 5.5 years of age at incident demyelinating event (and, therefore, 6 years at time of testing). We further explored whether cognitive function at this early time point differed as a

function of the presence or absence of brain involvement at onset or with residual lesion volumes at 6 months. Finally, we compared the 6-month cognitive outcomes of patients who remained clinically and radiographically monophasic to those diagnosed with MS within the first 3 years of presentation.

METHODS

Participants

Children and adolescents with ADS were recruited consecutively and prospectively from two pediatric demyelinating disease clinics in Canada (The Hospital for Sick Children, Toronto, Ontario; Alberta Children's Hospital, Calgary, Alberta) between 2010 and 2013, as part of a national demyelinating disease study (detailed in Banwell et al., 2011). Both sites received approval from their respective Research Ethics Boards. Informed consent/assent was obtained from parents and participants.

Patients were included in the study sample if they received a diagnosis of acquired demyelinating syndrome according to established criteria (Krupp et al., 2013) and were between the age of 6 and 16 years at time of assessment to ensure administration of a consistent and standardized test battery. Exclusion criteria for both MS patients and HCs included (1) history of a major medical illness or an active psychiatric disorder (e.g., major depressive episode), (2) a history of physician-diagnosed head injury (defined as a physician-diagnosed concussion or witnessed post-traumatic loss of consciousness for >5 min in duration), (3) dependence on alcohol or illicit drugs as reported by the parent on a Case History form and by telephone screening with the parent, (4) limited English proficiency (defined as having difficulty with understanding instructions and/or speaking conversational English as determined at time of recruitment), and (5) insufficient visual ability to perform cognitive testing.

Of the original 61 patients with ADS enrolled at the two sites, 13 were too young (i.e., <5.5 years at presentation), leaving 48 eligible for cognitive testing. Of the 48, 12 (25%) were excluded, leaving a final sample of 36 ADS patients (Supplementary Figure 1). Reasons for exclusion included: declined or were unable to participate in cognitive testing within the planned testing window ($n = 9$); testing discontinued due to behavioral problems ($n = 1$), invalid test results due to child withdrawing from testing ($n = 1$), and language barriers ($n = 1$). Thirty-two patients were recruited from Toronto and 4 were recruited from Calgary.

Healthy controls (HCs; $n = 42$) were recruited from the same local geographic areas as the patient cohort through local advertisement. Before testing, parents of all HCs participated in a screening questionnaire administered over the phone by a research coordinator that included an extensive developmental history questionnaire. Our study sample included more controls than patients because controls, in

some cases, were assessed before the “matched” patient who sometimes did not complete the evaluation. Control participants, but not patients given that the evaluations were part of their routine clinical care, received a gift card valued at \$20.

All participants received reimbursement for parking as well as a written psychology report (and verbal feedback when warranted) by a clinical neuropsychologist (C.T., K.S., B.L.B.).

Procedure

Patients underwent a clinical evaluation by a pediatric neurologist or trained coordinator, which included a complete history and determination of current disability using a structured examination template (as described in O’Mahony et al., 2015). Neurologic impairment was evaluated using a descriptive scale that assesses the same eight functional systems as on the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). Clinical MRI scans obtained at incident demyelinating event were visually inspected and the presence or absence of T2 hyperintense lesions in the brain was adjudicated. Although research MRI scans were also obtained at onset in some patients, many children were too unwell to undergo a non-sedated research MRI at this time point. As such, T2 lesion volume analyses could not be calculated for all patients at baseline. Research-quality MRI scans from the 6-month study visit were processed, and total brain T2 lesion volumes as well as normalized brain and thalamic volumes were calculated.

Approximately 6 months post-ADS, patients completed a 3-hr neuropsychological evaluation administered by a trained psychometrist who was supervised by a clinical neuropsychologist. This time point was planned to permit evaluation of patients remote from their acute illness, but also proximate to ADS to determine whether cognitive impairment is an early consequence of demyelination. The psychometrist was aware of the participant’s group membership, but was blinded to MRI and clinical features. The evaluation was conducted in a quiet room, with breaks provided as necessary. All test results were then double scored by another person who was blind to the participant’s group status. Additionally, caregivers completed questionnaires related to their child’s behavioral and emotional functioning. These questionnaires were mailed to the families and returned at the time of the evaluation or, in some cases, completed while the child was being evaluated.

Neuropsychological Evaluation

The following cognitive domains were assessed: (i) Global cognitive functioning was estimated using the four-subtest Full Scale IQ (FSIQ) from the Wechsler Abbreviated Scales of Intelligence (WASI; Wechsler, 1999). (ii) Attention and processing speed were assessed using the: Visual Matching, Decision Speed, and Numbers Reversed subtests from the Woodcock-Johnson –third edition (WJ-III) Tests of

Cognitive Abilities (Woodcock, McGrew, & Mather, 2001), and Symbol Digits Modalities Test – oral version (SDMT; Smith, 1982). (iii) Inhibition and Inhibition/Switching were assessed using the Color Word Interference Test from the Delis-Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001). (iv) Language was assessed using the Vocabulary and Similarities subtests of the WASI (Wechsler, 1999) and the Verbal Fluency test from the DKEFS (Delis et al., 2001). (v) Visuospatial ability was assessed using the Beery-Buktenica Developmental Test of Visuomotor Integration –6th edition (VMI; Beery, 1997), and Block Design and Matrix Reasoning subtests from the WASI (Wechsler, 1999). (vi) Memory was assessed using two subtests from the Test of Memory and Learning–2nd edition (TOMAL-2; Reynolds & Voress, 2007): the Word Selective Reminding (WSR) test (total words learned over six learning trials and total words recalled after a delay) and Memory for Location. These tests were used to assess verbal and visual memory, respectively. (vii) Academic Achievement was assessed using the following subtests from the WJ-III Tests of Achievement (Woodcock, McGrew, & Mather, 2007): Calculation, Math Fluency, Spelling, Letter-Word Identification, and Reading Fluency. (viii) Bilateral fine motor dexterity was assessed using the Grooved Pegboard test (Lafayette Instrument Company Inc., 2002).

The Behavior Assessment System for Children, Second Edition (BASC-2) –Parent Rating Scale was completed by caregivers using the Child (ages 6–11 years) or Adolescent (ages 12–21 years) form ($M = 50$; $SD = 10$; Reynolds & Kamphaus, 2004) to assess internalizing and externalizing behaviors, as well as adaptive behaviors in their child. On the BASC-2, a higher score on a clinical scale (i.e., $T > 60$) indicates a higher level of dysfunction; the only exception is with regard to the Adaptive Skills scale for which a low score (i.e., $T < 40$) denotes problematic levels of adaptive skills, such as difficulty with functional communication and activities of daily living.

The Pediatric Quality of Life Multidimensional Fatigue Scale (PedsQL)–Parent Report Rating Scale was completed using the Young Child (ages 5–7 years), Child (ages 8–12 years), or Adolescent (ages 13–18 years) form (Varni, Beaujean, & Limbers, 2013) to measure subjective experiences of fatigue. The PedsQL is composed of three subscales: the General Fatigue Scale (six items), Sleep/Rest Fatigue Scale (six items), and Cognitive Fatigue Scale (six items). A 5-point Likert response scale is used across the questionnaires. Higher scores on the PedsQL indicate a better health-related quality of life and less fatigue. Due to a large proportion of incomplete PedsQL questionnaires for the control group, data are only reported for the ADS group.

Sociodemographic and Clinical Variables

Clinical variables included: (i) number of days hospitalized for ADS; (ii) age at incident demyelinating event; (iii) medication provided; (iv) time from ADS to cognitive evaluation;

(v) clinical features at ADS; (vi) neurological deficits at onset and at time of cognitive evaluation. Socioeconomic status was estimated using the Barratt Simplified Measure of Social Status (BSMSS; Barratt, 2006), which is based on average years of parental education and occupation of each parent.

MRI

T2-weighted and FLAIR images from clinically acquired brain MRI scans obtained at ADS onset were reviewed for the presence of brain lesions. A lesion was defined as a T₂-weighted or FLAIR hyper-intensity measuring ≥ 3 mm in diameter in either the axial, sagittal, or coronal plane. A lesion was required to be visualized in ≥ 2 planes. The scoring guideline is described in a prior study (Verhey et al., 2013) and is shown to have high inter-rater reliability.

Research brain MRI scans were acquired at the 6-month visit according to a standardized protocol on 1.5 Tesla scanners at each site. The MRI protocol included 3D T₁-weighted pre- and post-contrast, axial dual echo PD-/T₂-weighted, and axial and sagittal FLAIR sequences. MRI scans were reviewed for compliance with pre-determined image quality standards by trained staff at the McConnell Brain Imaging Centre at the Montreal Neurological Institute (Montreal, Canada). T₂-weighted lesions were segmented using an automated Bayesian classifier followed by manual review and correction of the results, as previously described (Ghassemi et al., 2008).

A multi-resolution, non-local patch-based segmentation technique was used to extract the brain from the T₁-weighted images (Eskildsen et al., 2012). Lateralized thalamic structures were first manually delineated on the population template and were nonlinearly warped onto each subject's T₁-weighted images (Fonov et al., 2011). Right and left thalamic volumes were combined for analysis and the resulting thalamic volume was normalized by the brain volume. Finally, brain and normalized thalamic volumes were transformed into a Z-score by subtracting the mean volumes obtained for age- (± 6 months) and sex-matched controls from the NIHPD database (publicly available NIH-funded MRI Study of Normal Brain Development; Evans & Group, 2006) and then dividing by their standard deviation, as described in prior work (Aubert-Broche et al., 2011). Before doing so, we confirmed that the normed brain volumetric data for the controls in the current study fell within the average range (i.e., Z-score close to 0), thereby ensuring that it was reasonable to compare the patient sample to the NIHPD normative dataset.

Statistical Analyses

Independent samples *t* tests or chi-squared analyses were performed to ensure the patient and control groups were matched on demographic variables. Outcomes on cognitive testing and questionnaires were characterized for each

individual by converting raw scores to standardized Z-scores (as per test manual) to control for the effect of age and to place all scores on a similar metric. Before calculating group scores, data were inspected for outliers. A Winsorization technique was applied so that data falling outside two standard deviations (*SD*) from the mean were systematically adjusted to a value of ± 2 *SD* so as to not skew the distributions. The Kolmogorov-Smirnov and Levene's tests were used to detect any violations of normality and homogeneity of variance within data sets.

Separate multivariate analyses of variance were conducted to examine differences in cognitive, academic, behavioral, and fatigue outcomes using the following comparisons: (a) all ADS *versus* HCs; (b) patients with visible brain lesions at onset of ADS ($n = 18$) *versus* no lesions at the same time point; and (c) patients with visible brain lesions at 6-months post-ADS ($n = 17$) *versus* no lesions at the same time point; and (d) patients who eventually received a diagnosis of MS ($n = 12$) compared to those with monophasic ADS ($n = 20$). Supplementary analyses compared the MS patients and monophasic ADS patients with respect to total and thalamic brain volumes and T2 lesion volumes at 6-months post-ADS. Effect sizes are reported as Cohen's *d*.

A qualitative profile analyses at the individual level was also conducted to address the expected heterogeneity in cognitive scores. Specifically, the proportion of individuals with scores falling at least 1.5 *SD* below the normative mean was examined for the entire ADS cohort *versus* HCs. Individual profiles were examined to determine whether any participants met criteria for cognitive impairment, defined as performance falling 1.5 *SD* or $< 7^{\text{th}}$ percentile below the normative mean on at least four independent tests in the battery, excluding the Grooved Pegboard test (see Table 1 for tests used to determine impairment).

To minimize false positive results, we adopted this stringent cut-off (as opposed to a cut-off of three tests as used in prior work; for example, Amato et al., 2008; MacAllister et al., 2005; Till et al., 2011) given that the probability that an individual will have a deviant test score rises as the number of tests in the battery increases (Ingraham & Aiken, 1996). In a pediatric healthy control sample, the base rate for the occurrence of four low scores was shown to be 15.1% (falling $\leq 10^{\text{th}}$ percentile) and 5.2% (falling $\leq 5^{\text{th}}$ percentile) in a sample of 7- to 16-year-old children (Brooks, Sherman, & Iverson, 2010). Finally, Spearman correlations were used to examine whether brain volumetric measures at 6-months post-ADS relate to cognitive dysfunction. To limit the number of correlational analyses and thereby reduce the likelihood of Type 2 errors, we only examined the cognitive measures for which at least 10% of the entire ADS cohort showed impairment. This criterion was also introduced to minimize range restriction issues with the correlation analyses.

An adjusted *p*-value of $< .01$ was used to determine significance for between group comparisons given the large number of comparisons made. Data were analyzed using SPSS 21.0 (SPSS Inc., Chicago, IL).

Table 1. Clinical characteristics of the ADS and control groups

Variable	Patient group Mean (SD)	Control group Mean (SD)	p Value
N	36	42	—
Sex (n female: n male)	19 : 17	21 : 21	.81
Age (years) at ADS onset ^a	11.67 (2.69), range 6.5–15.8	—	—
Age (years) at evaluation	12.2 (2.69), range 7.1–16.4	13.4 (2.50), range 7.7–17.9	.053
Parental socioeconomic status ^b	45.00 (11.27)	46.58 (14.90)	.59
Race/ethnicity, n (%)			
White	19 (54.3%)	25 (59.5%)	
Black or African American	3 (8.3%)	1 (2.3%)	
Asian	6 (16.7%)	7 (16.7%)	
American Indian	1 (2.8%)	0	
Other/mixed	3 (8.3%)	4 (9.5%)	
Unknown	4 (11.1%)	5 (11.9%)	
Neurologic Disability score ^c			
Median (SD), baseline	1.5 (2.04), range 1–8.5		
Median (SD), 6 mo. evaluation	1.0 (1.48), range 0–7.5		
Corticosteroid treatment at ADS, n (%)	27 (75%)		
T2 brain lesions at onset of ADS, n (%)	18 (50%)		
PedsQL ^d			
General Fatigue	78.03 (16.6), range: 37.5–100		
Sleep/rest Fatigue	80.6 (16.3), range: 41.7–100		
Cognitive Fatigue	78.7 (21.5), range: 37.5–100		

^aAs expected, due to the requirement to evaluate only patients older than 5.5 years at ADS onset, the proportion of children with ADEM in the present study is lower than reported in other ADS cohorts.

^bBSMSS = Barratt Simplified Measure of Social Status.

^cDetermined using a structured examination template that uses a descriptive scale to assess the same eight functional systems as on the Expanded Disability Status Scale.

^dPediatric Quality of Life Multidimensional Fatigue Scale (PedsQL) – Parent Report Rating Scale.
ADEM = acute disseminated encephalomyelitis; ADS = acquired demyelinating syndrome.

RESULTS

Clinical and Demographic Characteristics of Sample

Table 1 presents the clinical and demographic characteristics of the patient and control groups. At incident demyelinating event, 14 (38.9%) presented with optic neuritis, 12 (33%) with TM, 3 (8.3%) with ADEM, and 7 (19.4%) with other manifestations of demyelination. Of the 36 patients, 12 (33.3%) had received a diagnosis of MS using the 2010 McDonald criteria (Polman et al., 2011) within 3 years following the incident demyelinating event (and all of whom had brain lesions present at onset). Eight of the 12 patients with an eventual diagnosis of MS had new lesions detected by 6-months post-ADS; the remaining four patients developed lesions at a later time point. All ADS participants were tested for the presence of anti-aquaporin-4 antibodies. The only patient with positive results met criteria for neuromyelitis optica spectrum disorder (NMOSD; Wingerchuk et al., 2015). Patients with relapses not meeting criteria for MS (i.e., relapses localized to a single CNS site) were termed relapsing non-MS.

At the 6-month post-ADS brain scan, T2 lesions were visible on 17 of 35 (48.6%) scans. It should be noted that one patient could not undergo an MRI scan at 6 months

due to having cochlear implants; a computed tomography scan was used instead at the baseline visit. This child was not eventually diagnosed with MS nor identified as having cognitive impairment. Of the 17 patients with visible lesions at this time point, 16 patients were classified as having at least one lesion at both onset and 6-month post-ADS scan (note that a “yes” classification at both time points could signify new or residual lesions at 6 months). The one patient who was rated as not having any lesions visible at onset was later shown to have a very small lesion burden (0.03 cc), which may have simply captured a lesion not appreciated on the initial clinical scan. Sixteen of 18 patients had no T2 brain lesion at ADS onset and did not accrue any lesions at 6-months post-ADS; the remaining two patients had lesion(s) noted at ADS which resolved by 6 months.

Cognitive testing was completed between 5 and 12 months post-ADS, though for the majority, testing was conducted at 6-months post-ADS (mean = 6.44; SD = 1.63).

Fatigue scores as reported by parental observation on the PedsQL for the ADS group are also shown in Table 1. The proportion of responses falling in the mild (i.e., score between 61 to 79) and severe range (i.e., score) are as follows: general fatigue (22% and 31.8%), sleep/rest fatigue (50% and 4.5%), and cognitive fatigue (22.7% and 22.7%).

Comparison of Cognitive Performance between Entire Patient Cohort and Controls

Table 2 shows cognitive and academic outcomes for all patients (ADS and MS) versus HCs. Mean IQ in the patient group ($M = 110.1$; $SD = 18.7$; range: 76–143) and control group ($M = 112.2$; $SD = 13.3$; range: 89–146) did not differ [$F(1,72) = 0.31$; $p = .58$]. IQ scores were normally distributed and scores fell within the average to superior range, with the exception of two scores (both from MS patients) which fell within the borderline range (i.e., 5th to 9th percentile). Groups did not differ on any of the individual cognitive or academic subtests at the mean level nor at the individual level. Between-group differences showed small

effect sizes for most tests, with the exception of the Grooved Pegboard test for which lower performance was observed in the patient group relative to the control group ($d = 0.48$ and $d = 0.53$ for the non-dominant and dominant hands, respectively); however, this difference did not meet our statistical threshold after adjustment.

Within the patient group, normalized brain volume did not correlate significantly with any of the cognitive and academic outcomes.

Three patients (8.3%; two females; two eventually diagnosed with MS) and two of the HCs (4.7%; 1 female) were identified as having cognitive impairment [$\chi^2(1) = 0.025$; $p = .87$]. One patient with cognitive impairment had a diagnosis of TM and remained physically impaired at time of

Table 2. Neuropsychological outcomes across groups

	n	ADS group (n = 36)			Controls (n = 42)			F	p Value	d	
		Mean	(SD)	<1.5 SD	n	Mean	(SD)				<1.5 SD
WASI FSIQ ^a	35 ^a	0.65	1.23	1	42	0.78	0.90	0	0.31	.58	0.12
Vocabulary*	36	0.40	0.84	2	42	0.56	0.94	0	1.99	.16	0.18
Similarities*	36	0.71	0.98	0	42	0.77	0.82	0	0.07	.80	0.06
Block Design*	35	0.41	1.38	5	42	0.62	1.05	1	0.57	.45	0.17
Matrix Reasoning*	36	0.31	1.14	3	42	0.44	0.86	1	0.33	.57	0.13
Grooved Pegboard											
Dominant Hand	33	0.06	1.01	3	42	0.51	0.65	0	5.28	.02	0.53
Non-Dominant Hand	33	-0.13	0.97	1	42	0.30	0.81	1	4.35	.04	0.48
Beery VMI*	32	-0.14	1.13	6	42	0.04	0.93	2	0.62	.44	0.17
TOMAL-2											
WSR-Immediate*	35	0.18	0.91	3	42	-0.13	0.93	3	2.27	.14	0.34
WSR-Delayed	35	0.31	0.55	0	42	0.16	0.57	1	1.30	.26	0.27
Memory for Location*	33	0.14	1.07	3	42	0.40	1.14	3	0.97	.33	0.24
SDMT – Oral version*	35	1.39	1.56	0	41	1.30	1.31	1	0.06	.80	0.06
WJ-III Visual Matching*	36	-0.27	1.10	4	42	-0.06	1.15	5	0.68	.41	0.19
WJ-III Decision Speed*	34	-0.05	1.24	3	41	0.01	1.05	3	0.05	.82	0.05
WJ-III Numbers Reversed*	33	0.48	1.13	1	41	-0.01	0.94	2	4.02	.05	0.47
DKEFS											
Verbal Fluency ^b *	35	0.40	1.27	1	41	0.61	1.15	1	0.57	.45	0.17
Category Fluency	35	0.43	1.08	1	41	0.57	1.21	1	0.31	.58	0.12
Category Switching (tot. correct)	34	0.77	1.17	1	40	0.29	1.31	1	2.73	.10	0.39
Color Word Interference											
Color Naming*	35	0.30	0.91	1	40	0.23	0.99	2	0.10	.75	0.07
Word Reading	35	0.48	0.79	0	40	0.36	0.85	2	0.38	.54	0.15
Inhibition*	35	0.08	0.95	1	40	0.24	1.01	4	0.53	.47	0.16
Inhibition/Switching	34	0.16	0.86	1	40	0.41	0.80	1	1.71	.20	0.30
WJ-III Academic Achievement Scores											
Letter-Word Identification*	33	0.56	0.90	0	41	0.48	0.69	0	0.18	.70	0.10
Spelling*	31	0.32	0.98	0	40	0.55	0.77	0	1.24	.27	0.26
Calculation*	29	-0.19	1.34	2	40	-0.23	1.00	4	0.02	.90	0.03
Reading Fluency*	32	0.16	0.98	1	41	0.56	0.95	0	3.07	.08	0.41
Math Fluency*	31	-0.51	1.05	4	40	-0.11	1.46	5	1.72	.19	0.31

Note. Results shown as Z-scores (mean = 0, $SD = 1$).

^aFull-Scale IQ (four subtest score) was not computed for one patient because of incomplete administration of one PIQ subtest. Verbal IQ score was substituted instead.

^bPediatric norms used for Verbal fluency and Category fluency for children <8 years (taken from Spreen, 1991).

*Denotes that the measure was used in the determination of cognitive impairment.

DKEFS = Delis-Kaplan Executive Function System; SDMT = Symbol Digits Modalities Test; TOMAL-2 = Test of Memory and Language, 2nd Edition; VMI = Beery-Buktenica Developmental Test of Visual Motor Integration - 6th Edition; WASI = Wechsler Abbreviated Scale of Intelligence; WJ-III = Woodcock Johnson - 3rd Edition.

Table 3. BASC-2 – Parent Rating Scale results for patients in the ADS group and controls

	ADS group				Controls				F	p Value
	n	Mean	(SD)	Elevated ^a	n	Mean	(SD)	Elevated ^a		
BASC Scales (T-score)										
Externalizing Problems	30	46.10	9.25	3	33	47.27	10.69	1	0.21	.65
Internalizing Problems	30	49.27	10.55	5	33	45.69	9.42	3	1.99	.16
Behavioural Symptoms Index	30	47.03	9.61	2	33	46.28	10.12	4	0.09	.77
Adaptive Skills	30	49.93	11.63	5	33	53.09	10.79	4	1.40	.24

Note. Data unavailable for six patients.

^a“At-Risk” or “Clinically Significant” range (i.e. T score ≥ 60 for clinical scales; T score ≤ 40 for adaptive scales) is reported.

BASC = Behavior Assessment System for Children – 2nd Edition.

cognitive assessment (11.4-year-old female with a neurologic disability score of 7.5). Closer inspection of the results for this patient revealed impairment on two tasks that involve a motor component (Block Design, Beery VMI), four tasks that have a minimal motor component, and one that is a non-motor task. It is probable that the severity of motor disability in this patient increased the likelihood of achieving impaired scores, particularly on motor tasks. Note that administration of the Grooved Pegboard was discontinued for this particular patient due to her significant motor disability.

Table 3 shows overall average scores across composite scales of the BASC-2 in both the ADS and control group. No differences were observed between groups with regard to mean scores, nor in terms of proportion of individuals with clinically elevated scores on the BASC-2.

Taken together, comparison of the cognitive, academic, and behavioral outcomes between the ADS and HC groups did not reveal any significant differences.

Outcomes in Patients with Visible Brain Lesions versus No Lesions

Presence of brain MRI lesions at onset and at 6-months post-ADS did not relate to cognitive and academic outcomes, psychosocial scores, nor with fatigue symptoms endorsed by parents.

Outcomes in patients with an eventual diagnosis of MS (n = 12) compared to those with monophasic ADS (n = 20; excluding 3 patients with relapsing non-MS, and 1 child with NMOSD)

Two of the 12 MS patients (16.6%) were classified as cognitively impaired. This finding does not differ from the proportion classified as cognitive impaired in the monophasic patient group (i.e., 1 of 20; $X(1) = 1.20$; $p = .27$), even if we take into account that cognitive performance was underestimated in this one patient due to severe motor symptoms. Importantly, the observed rate of cognitive impairment among the patients with an eventual diagnosis of MS was similar to the 15.1% expected base rate for a healthy pediatric sample using a cut-off below the 10th percentile (Brooks et al., 2010). Comparison of the MS group and the

monophasic ADS group on specific cognitive outcomes also did not reveal any significant differences. While not reaching statistical significance [$F(1,30) = 6.65$; $p = .015$], a large effect size ($d = 1.06$) was found on the Semantic Fluency subtest reflecting lower performance in the MS group relative to the monophasic ADS group (MS: $M = -0.17$; $SD = 1.03$ vs. monophasic ADS: $M = 0.81$; $SD = 0.81$).

Fatigue symptoms as endorsed by parents did not differ as a function of diagnostic status (MS vs. monophasic ADS). Likewise, psychosocial outcomes in both the MS and monophasic ADS groups were within the normal range for composite indices on the BASC-2, including Internalizing and Externalizing Problems, Behavioral Symptoms Index, and Adaptive Skills, as shown in Table 3.

Patients eventually diagnosed with MS and those with monophasic ADS did not differ significantly with respect to normalized brain volume [MS: $M = -0.87$; $SD = 0.81$ vs. monophasic ADS: $M = -0.36$; $SD = 1.10$; $F(1,30) = 1.84$; $p = .19$] and normalized thalamic volume [MS: $M = -0.12$; $SD = 1.38$ vs. monophasic ADS: $M = 0.08$; $SD = 1.13$; $F(1,30) = 1.88$; $p = .67$]. As expected, lesion volume was higher in the MS group (median = 0.95 cc³; $SD = 3.18$; range: 0.05–8.69) as compared with the monophasic ADS group (median = 0.00; $SD = 0.10$; Mann-Whitney $U = 12.0$; $p < .001$).

Summary of Findings

Overall, at 6-months post-incident demyelinating event, no statistically significant differences were observed between patients with monophasic ADS and healthy controls on the cognitive, academic, and behavioral outcomes. Likewise, patients eventually diagnosed with MS did not differ from the monophasic ADS group on cognitive, behavioral, and brain volume measures. There were too few patients with relapsing non-MS or NMOSD for comparisons with those groups.

DISCUSSION

ADS in children, both monophasic and relapsing forms, has the potential for both early and longer-term CNS insult. Conceptually, early deficits reflect damage to active neural

networks, while deficits that emerge over time occur due to impairment in normal maturational processes dependent on subsequent myelination capacity and age-related increases in connectivity.

To date, cognitive studies in pediatric patients with ADS vary considerably with respect to the time of evaluation relative to presentation, rendering it challenging to delineate early from later effects. In the current study, we address the acute impact of ADS through evaluation of patients approximately 6 months post-ADS—a time point selected to ensure adequate time to recover from transient impairments and corticosteroid exposure, and at the same time, to capture functioning at an early time point post illness. At the group level, ADS did not impact overall intelligence and no significant differences were observed on cognitive, academic, or psychosocial measures as compared with age- and sex-matched healthy controls.

Only 3 of the 36 patients (8.3%) were identified as having cognitive impairment. Importantly, our findings demonstrated that only two of the twelve MS patients (16.6%) were classified as cognitively impaired, a rate that is not considerably higher than the normative rates ranging between 5.2 and 15.1% (falling $\leq 5^{\text{th}}$ and $\leq 10^{\text{th}}$ percentile, respectively; Brooks et al., 2010). In comparison, the prevalence of cognitive impairment in pediatric MS cohorts from Canada, Europe, and the United States is estimated to be approximately 30% (Amato et al., 2008; MacAllister et al., 2005; Till et al., 2011), although the true prevalence remains unclear because of differences in sampling, assessment procedures, and criterion for impairment.

Taken together, our findings suggest that cognitive impairment requires time to develop in patients with pediatric-onset MS, likely reflective of ongoing insult to developing neural networks. It is important to note that the brain, and specifically thalamic volumes of the MS patients as measured at 6 months post onset were not different from age-expected values. In our prior studies of pediatric MS patients evaluated further from onset, impaired cognitive performance correlated strongly with reduced brain and thalamic volumes (Till et al., 2011).

Children with ADS including those eventually diagnosed with MS demonstrated higher susceptibility to compromised fine motor dexterity relative to controls (as indicated by the moderate effect size; $d = 0.48\text{--}0.51$); however, these findings did not meet our statistical threshold which was adjusted for multiple comparisons. Difficulties with fine motor control and visuomotor integration have been reported in patients with clinically isolated syndrome (Julian et al., 2012), pediatric-onset MS (Julian et al., 2013; Smerbeck et al., 2011; Squillace, Ray, & Milazzo, 2015; Till et al., 2011), adult MS (Buchanan, Chakravorty, Tyry, Hatcher, & Vollmer, 2009), and ADEM (Hahn et al., 2003; Jacobs, Anderson, Neale, Shield, & Kornberg, 2004; Kuni et al., 2012).

Because fine motor function is often compromised in patients with demyelinating disease, fine motor control has been adopted as a primary component of the Multiple Sclerosis Functional Composite Measure. We recommend

attending to the fine motor status of youth with ADS for which the deficits may be subtle and remain unreported unless formally tested. Further investigation is needed to better understand the potential for critical windows for disrupting the development of fine motor coordination and visuomotor integration as well as the underlying mechanisms that may contribute to difficulties in these areas.

It is important to note that the SDMT is widely regarded as a valuable screening test for cognitive impairment in MS and has been proposed for inclusion in a revised MS functional composite (Cohen, Reingold, Polman, & Wolinsky, 2012). However, in the current study, the SDMT did not identify deficits in any of the MS or monophasic ADS patients.

Although magnetic resonance imaging (MRI) measures of global and regional brain volumes have been shown to strongly correlate with cognitive impairment in pediatric-onset MS (Till et al., 2011), the relationship between the presence and severity of brain insult at the onset of ADS and cognitive functioning remain largely unexplored. Our findings show that the presence of T2 lesions at both onset and at 6-months post-ADS did not relate to specific cognitive and academic outcomes. These findings are similar to those of a recent Italian study of 22 patients with a history of ADEM which showed that an improved (or normalized) MRI *versus* an unchanged MRI at follow-up did not predict neuropsychological scores; follow-up in this study was, on average, 6.8 years and ranged from 2 to 15 years (Suppiej et al., 2014). Longitudinal studies are needed to determine whether there are any long-term effects of brain lesions, or other effects on the brain, such as reduced brain-growth, on skill development.

Given that the assessment was conducted within the first year following the incident event, it is possible that the more widespread sequelae that are commonly reported in pediatric-onset MS and in children with monophasic demyelination have yet to manifest. These findings may reflect the use of alternate latent or compensatory pathways in the early stages of MS or a possible masking of deficits by the sample's average IQ (mean IQ for MS group = 103.8). This interpretation is supported by studies showing increased risk of cognitive impairment (Banwell & Anderson, 2005; MacAllister, Christodoulou, Milazzo, & Krupp, 2007; Till et al., 2011) and lower brain volume (Kerbrat et al., 2012) with increasing duration of disease, and highlights the need to continue to follow children with ADS and MS. Children with ADS may be vulnerable to future cognitive sequelae that remain undetected at an early time point post-ADS due to injury to developing networks that are not more formally interrogated until older ages, such as those subserving executive function.

There are several limitations to this study. ADS is rare and, even with a national program, our sample size remained too small to permit comparison of cognitive function between the different ADS presentations. Sample size was further restricted by excluding children who were younger than 5.5 years at ADS. This exclusion criterion was applied so that the same cognitive tests could be administered to all

participants. We also tested ADS participants at only two sites in our network for practical and cost related considerations of supporting a neuropsychologist and psychometrists.

By excluding the young patients, we were less likely to recruit patients with ADEM and, by virtue of an older onset age, we were more likely to include patients with a diagnosis of MS (i.e., 33%) in the current sample as compared with the 21% rate reported in our national study (O'Mahony et al., 2015). Importantly, we were able to recruit and cognitively assess 75% of patients enrolled at the two participating sites who met our inclusion criteria which minimized ascertainment bias at these sites. Moreover, comparison of the demographic characteristics of the patients included in the current analysis and those excluded did not show a difference with respect to sex, race, and socioeconomic status. However, patients who did not complete testing (but were eligible) were more likely to have a higher scores on our measure of neurologic disability, which reflected the fact that several of the non-evaluated patients were diagnosed with TM; none were eventually diagnosed with MS.

Another limitation is the use of a psychometrist who was aware of whether the participant was a patient or control. However, the psychometrist did not have access to clinical and MRI information, and thus was not influenced by any perception of onset severity or whether the patient was diagnosed with MS. Moreover, efforts were taken to reduce potential bias in test scoring by including a second, blinded scorer for all data files.

Despite these limitations, this is the first study to evaluate a broad range of cognitive, academic, and psychosocial outcomes and to include MRI measures in patients evaluated at an early time point following ADS. Overall, findings demonstrate a favorable neurocognitive outcome within the first year post-ADS in children. Longitudinal evaluation is needed to determine the development of cognitive impairment over time, an outcome that is expected with progressive disease activity in MS (Amato et al., 2014; Hosseini, Flora, Banwell, & Till, 2014; Marin, Banwell, & Till, 2013; Till et al., 2013), but has not been well-studied in patients with monophasic ADS. Longitudinal studies that combine advanced MRI technology, such as functional MRI, with neuropsychological assessment will provide exciting opportunities to understand how developing neural networks are impacted by demyelinating conditions in childhood.

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Dr. Brooks declares the following potential conflicts of interest: he receives royalties for sales of a pediatric memory battery [Sherman, E.M.S. and Brooks, B.L. (2015). *Child and Adolescent Memory Profile*. Lutz, FL; Psychological Assessment Resources Inc.], a pediatric performance validity test [Sherman, E.M.S. and Brooks, B.L. (in press); *Memory Validity Profile*. Lutz, FL; Psychological Assessment Resources, Inc.], and a pediatric textbook [Sherman, E.M.S. and Brooks, B.L.; Eds. (2012), *Pediatric Forensic Neuropsychology*. Oxford University Press]. Dr. Collins receives consulting from NeuroRx. *Funding:* All phases of this study were supported by the Multiple Sclerosis Society Scientific Research Foundation.

Supplementary Materials

To view supplementary material for this article, please visit <http://dx.doi.org/10.1017/S1355617716000308>

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