Recovery From Central Nervous System Acute Demyelination in Children

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abstract

BACKGROUND: Few prospective studies have systematically evaluated the extent of recovery from incident acquired demyelinating syndromes (ADS) of the central nervous system in children.

METHODS: In a national cohort study of pediatric ADS, severity of the incident attack and extent of recovery by 12 months were evaluated. Annual evaluations were used to determine current diagnoses (monophasic ADS or multiple sclerosis [MS]) and new deficits.

RESULTS: Of 283 children, 244 (86%) required hospitalization for a median (interquartile range [IQR]) of 6 (3–10) days, and 184 had moderate or severe deficits; 41 children were profoundly encephalopathic, 129 were unable to ambulate independently, and 59 with optic neuritis (ON) had moderately or severely impaired vision. Those with transverse myelitis (TM) and patients with monophasic disease were more likely to have moderate or severe deficits at onset. Twenty-seven children (10%) did not experience full neurologic recovery from their incident attack; 12 have severe residual deficits. Monophasic illness, TM, and moderate or severe deficits at onset were associated with poor recovery. After a median (IQR) follow-up of 5.06 (3.41–6.97) years, 59 children (21%) were diagnosed with MS; all recovered fully from their incident ADS attacks, although 6 subsequently acquired irreversible deficits after a median (IQR) observation period of 5.93 (4.01–7.02) years.

CONCLUSIONS: ADS is a serious illness, with 86% of affected Canadian children requiring hospitalization. More than 90% of children recovered physically from their ADS event, including those children experiencing onset of MS. However, permanent visual or spinal cord impairment occurred in some children with ON or TM.

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WHAT'S KNOWN ON THIS SUBJECT: Most prospective cohort studies of acquired demyelinating syndromes in children have focused on the genetic, environmental, and neuroimaging predictors of multiple sclerosis. Less is known regarding the severity of the incident demyelinating event and predictors of residual attack–related physical disability.

WHAT THIS STUDY ADDS: In a national, prospective longitudinal study, incident acquired demyelinating syndromes in children were characterized in terms of physical deficits and acuity at onset, and recovery over the first 12 months. Follow-up evaluations up to 10 years' postonset were analyzed.

Acquired demyelinating syndromes (ADS) of the central nervous system (CNS) include optic neuritis (ON), transverse myelitis (TM), other monofocal demyelination (neurologic deficits referable to a single CNS lesion), acute disseminated encephalomyelitis (ADEM [defined according to polyfocal deficits accompanied by encephalopathy]), or polyfocal demyelination (deficits localized to >1 CNS location) without encephalopathy.[1] Most prospective cohort studies of ADS in children have focused on the genetic, environmental, and neuroimaging predictors of multiple sclerosis (MS).[2–5] Relatively less is known regarding the severity of the acute incident demyelinating event and the predictors of residual attack–related physical disability.

In a national, prospective longitudinal study, we characterized incident ADS in children in terms of physical deficits at onset, clinical management, duration of hospitalization, and recovery over the first 12 months. Follow-up evaluations up to 10 years' postonset were analyzed to ascertain final diagnosis (MS or monophasic demyelination), evaluate stability of recovery beyond 12 months, and note new deficits among patients with MS.

METHODS

As detailed previously,[2] children aged <16 years who met the criteria for ADS (Supplemental Table 4) were enrolled at 1 of 16 Canadian pediatric or 7 regional health care facilities within 90 days of symptom onset. Ethics approval was obtained at all sites. Parents or legal guardians signed informed consent forms, and younger children provided assent.

Patients were removed from the analysis if they withdrew after enrollment and requested data destruction or if they met the diagnostic criteria for neuromyelitis optica or nondemyelinating disorders.[6] All 283 children included in this analysis were seronegative for antibodies directed against aquaporin-4.[7] Clinical diagnosis data were censored as of the last study visit.

Site investigators attended training sessions and used standardized case report forms to record physical examination findings (Supplemental Appendix), as well as a priori criteria independent of MRI findings to confirm each patient's categorization according to the ADS presentations (Supplemental Table 4). One investigator (B.B.) reviewed all case report forms for accuracy of the ADS designation, and trained staff entered data centrally. Nerve or spinal cord involvement occurring in the context of ADEM or polyfocal demyelination was described as a component of these ADS presentations. Relapses were defined as new neurologic deficits persisting for 24 hours, confirmed by neurologic examination. When available, total white blood cell count in cerebrospinal fluid, protein, and presence in the cerebrospinal fluid of oligoclonal bands were recorded.

All participants were offered standardized research brain MRI studies at baseline; 3, 6, and 12 months; and annually thereafter. Brain and spine scans performed were also evaluated. All scans were anonymized and analyzed centrally. MRI scans that could not be assessed due to artifact from excessive patient motion or dental hardware were excluded. T2 lesions were defined as regions of increased T2 intensity >3 mm in cross-sectional diameter, and their presence or absence on baseline MRI of the brain and spine were noted. Lesions with regional mass effect or perilesional edema were reviewed to exclude malignancy. Longitudinally extensive transverse myelitis (LETM), defined as lesions extending 3 spinal segments, was noted on MRI. Serial scans were evaluated for the presence of new T2 or T1 gadolinium-enhancing lesions according to criteria for lesion dissemination in time.[8]

Neurologic impairment was assessed quarterly in the first year, and annually thereafter, by using a descriptive scale of clinical severity within the same 8 functional systems (mobility, cognition, vision, pyramidal, cerebellar, brainstem, bowel and bladder, and sensory functions) (Supplemental Appendix) as on the Expanded Disability Status Scale.[9] This scale was not used because most of the pediatric neurologists were not sufficiently familiar with its adjudication. Treatments, the requirement for hospitalization, and the corresponding length of stay were recorded for each child.

Extent of recovery is reported for examinations at all time points within the first 12 months. Evaluations beyond 12 months' postonset were used for this analysis to ascertain diagnoses (MS versus monophasic ADS), comment on stability of recovery, and to note clinical deficits that occurred due to subsequent relapses in the patients with MS. We chose 12 months to maximize retention of participants and to reduce the likelihood of deficits due to subsequent attacks or early progressive disability in MS patients (secondary disease progression in pediatric-onset MS typically does not occur within the first years after onset).[10]

Cognition was dichotomized according to the presence or absence of encephalopathy. Physical deficit severity was categorized (defined in Supplemental Table 5) for each patient, and overall severity was graded according to the most severe deficit observed in 1 of the following: mobility (pyramidal and cerebellar gait dysfunction), vision, or bowel and bladder function. Of the remaining domains, sensory deficits are not reported in terms of severity because they are too subjective, and isolated brain stem dysfunction

occurred too rarely to contribute to an evaluation of severity. If patients experienced bilateral ON, the visual loss of the more severely affected eye was reported. Patients were considered to have experienced full physical recovery if they had normal gait, were considered to be back to baseline cognitively with resolution of encephalopathy (formal cognitive evaluations were not performed), if they had a corrected visual acuity of 20/20 in both eyes (as measured by using high-contrast visual acuity testing), and if they did not experience any difficulties with bowel or bladder control. Partial recovery was recorded if patients improved but did not experience full recovery.

Diagnoses of MS were conferred according to the 2005 McDonald criteria[8] (Supplemental Table 4). The 2010 McDonald criteria were applied to baseline scans.[11] Deficits arising from subsequent attacks were recorded for all patients with MS.

Continuous variables were summarized as mean ± SD or median (interquartile range [IQR]) as appropriate; categorical variables were described as frequency (percent). P values $<.05$ were considered significant. For univariate analyses, χ^2, Fisher's exact, and Wilcoxon or Kruskal-Wallis tests were performed as appropriate. Statistical analyses were performed with Stata version 12 (Stata Corp, College Station, TX).

RESULTS

Characteristics of Participants

Between September 1, 2004, and June 30, 2010, a total of 332 children were enrolled, and 283 were included in this analysis (Fig 1). Table 1 and Fig 2 detail the demographic, diagnostic, and clinical features of these patients. Although puberty was not formally assessed, Table 1 includes an evaluation of a gender ratio according to ADS presentation, and Fig 2 illustrates ADS presentation as a function of age <12 years or ≥12 years (a reasonable approximation of puberty) and outcome.

Lumbar puncture was performed in 213 (75%) children (Table 1). Clinicians were more likely to obtain

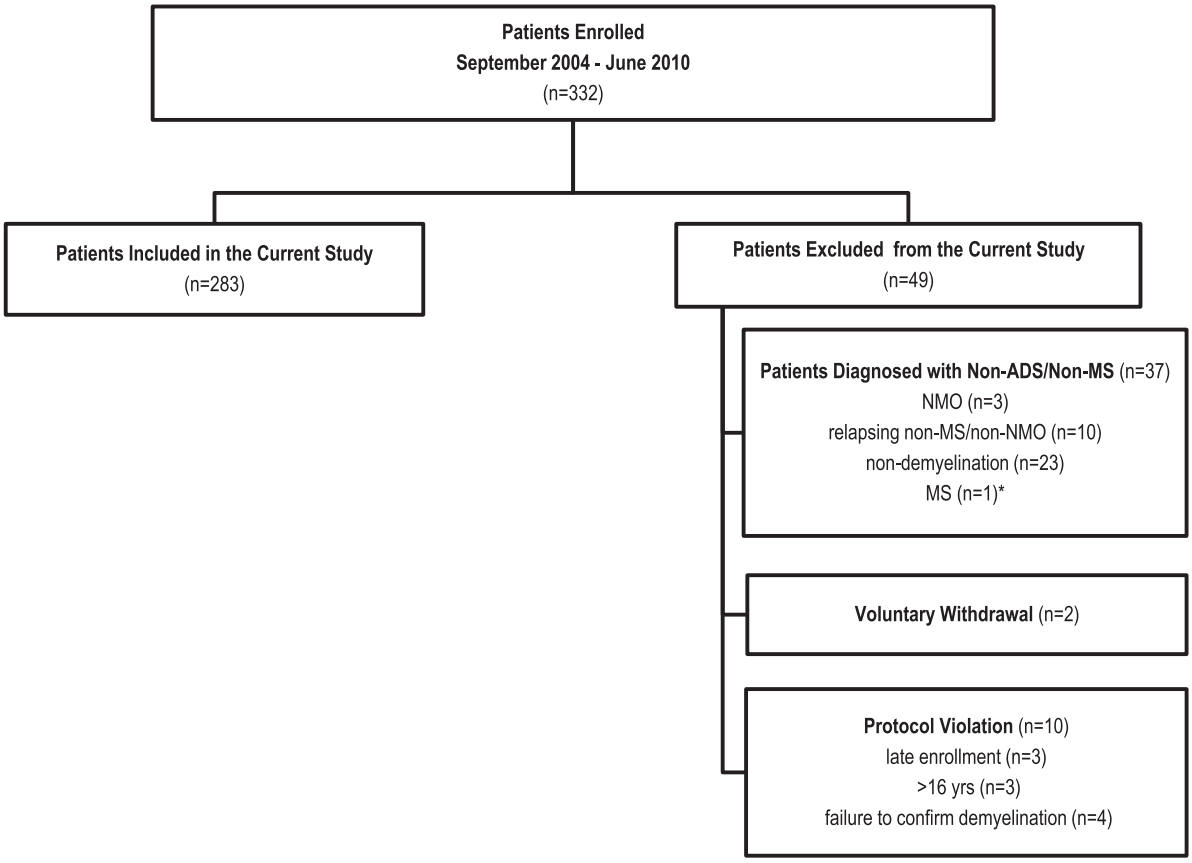

FIGURE 1

Study participants. Of 332 patients enrolled, 283 were analyzed in the current study. [a]One patient with MS was excluded because of severe and atypical attacks that have prompted investigation for an alternative diagnosis. Four of the patients who were included in the MS cohort in our previous research[2] were excluded from the present analysis: 2 children withdrew and asked that all of their data be destroyed; 1 child with severe CNS demyelination initially meeting criteria for MS developed progressive neurologic deterioration, and autopsy confirmed a mitochondrial encephalopathy associated with white matter lesions; and 1 child initially classified as having MS has developed new-onset systemic autoimmune features and is being assessed for systemic lupus erythematosus.

TABLE 1 Characteristics of the Cohort

Characteristic	All (N = 283)	Monofocal ON (n = 69)	Monofocal TM (n = 62)	Monofocal Other[a] (n = 31)	Polyfocal (n = 52)	ADEM (n = 69)	P
Demographic							
Age at onset, y	10.4 (5.8–13.6)	11.9 (9.1–13.3)	11.1 (7.8–13.6)	13.6 (5.7–14.8)	11.8 (7.5–14.3)	5.2 (2.9–7.8)	<.001
Female patients	146 (51.6)	40 (58.0)	31 (50.0)	19 (61.3)	24 (46.2)	32 (46.4)	.45
Male patients	137 (48.4)	29 (42.0)	31 (50.0)	12 (38.7)	28 (53.8)	37 (53.6)	
Gender ratio for patients aged ≥12 y (F:M)	1:1	1.1:1	1:1.9	2.2:1	1:1.2	3:1	.12
Gender ratio for patients <12 y (F:M)	1.1:1	1.6:1	1.8:1	1.1:1	1:1.2	1:1.3	.21
Born in Canada	265 (93.6)	65 (94.2)	56 (90.3)	29 (93.6)	50 (96.2)	65 (94.2)	.79
Non-white	25 (8.8)	4 (5.8)	7 (11.3)	4 (12.9)	6 (11.5)	4 (5.8)	.49
Family history of MS	49 (17.3)	14 (20.3)	10 (16.1)	8 (25.8)	9 (17.3)	8 (11.6)	.45
Laboratory features							
CSF white blood cell count	213/283 (75.3)	36/69 (52.2)	49/62 (79.0)	25/31 (80.6)	40/52 (76.9)	63/69 (91.3)	<.001
Cells per μL	44.0 ± 70.9	32.1 ± 55.9	45.5 ± 84.7	23.8 ± 63.4	51.5 ± 73.1	53.1 ± 67.7	.003
CSF OCBs	41/162 (25.3)	6/32 (18.8)	7/42 (16.7)	9/20 (45.0)	15/34 (44.1)	4/34 (11.8)	.004
Brain MRI abnormal	176/269 (65.4)	28/66 (42.4)	39/56 (69.6)	26/30 (86.7)	42/51 (82.4)	63/66 (95.4)	<.001
Brain MRI normal	93/269 (34.6)	38/66 (57.6)	17/56 (30.4)	4/30 (13.3)	9/51 (17.6)	3/66 (4.6)	
Spine MRI LETM	44/83 (53.0)	0/4 (0.0)	25/41 (61.0)	0/3 (0)	10/18 (55.6)	9/17 (52.9)	.06
Spine MRI focal lesions	23/83 (27.7)	0/4 (0.0)	14/41 (34.1)	0/3 (0)	6/18 (33.3)	3/17 (17.6)	<.001
Initial management							
Hospitalized	244 (86.2)	45 (65.2)	59 (95.2)	24 (77.4)	48 (92.3)	68 (98.6)	<.001
Not hospitalized	39 (13.8)	24 (34.8)	3 (4.8)	7 (22.6)	4 (7.7)	1 (1.4)	
Length of stay, d	6 (3–10)	4 (0–6)	8 (4–14)	6 (0–10)	6 (5–10)	9 (6–14)	<.001
Recovery and baseline clinical severity							
Mild deficits at baseline	99 (35.0)	25 (36.2)	12 (19.4)	23 (74.2)	22 (42.3)	17 (24.6)	<.001
Moderate or severe deficits at baseline	184 (65.0)	44 (63.8)	50 (80.6)	8 (25.8)	30 (57.7)	52 (75.4)	
Received any treatment at baseline[b]	236 (83.4)	53 (76.8)	58 (93.6)	21 (67.7)	42 (80.8)	62 (89.9)	.005
No treatment	47 (16.6)	16 (23.2)	4 (6.4)	10 (32.3)	10 (19.2)	7 (10.1)	
Diagnosis							
MS outcome	59 (20.8)	14 (20.3)	8 (12.9)	14 (45.2)	22 (42.3)	1 (1.4)	<.001
Monophasic ADS	224 (79.2)	55 (89.7)	54 (87.1)	17 (54.8)	30 (57.7)	68 (98.6)	
McDonald 2010 MS diagnosis at baseline (n = 46)[c]	49/156 (31.4)	12/50 (24.0)	6/37 (16.2)	10/22 (45.4)	21/42 (50.0)	0/5 (0)	.003

Data are median (IQR), n (%), or n/N (%), unless otherwise stated. CSF, cerebrospinal fluid; F:M, female:male; OCBs, oligoclonal bands.

[a] Refers to neurologic deficits referable to the brain stem (ie, internuclear ophthalmoplegia) or cerebrum (ie, unilateral motor or sensory deficits).

[b] Of the 234 children treated at ADS onset, 228 received ≥1 dose of corticosteroids, 210 received intravenous corticosteroids, 168 were prescribed oral prednisone (typically after a course of intravenous corticosteroids), 36 were treated with intravenous immunoglobulin (6 without corticosteroids), and 4 children underwent plasma exchange.

[c] Of the 59 patients diagnosed with MS, 48 had brain MRI scans with gadolinium suited for evaluation of the 2010 McDonald diagnostic criteria for MS as applied to baseline imaging. Three additional patients met the baseline 2010 criteria for diagnosis of MS, but have not had clinical or serial MRI evidence of new disease and for the purposes of the present article are considered with the monophasic ADS group.

spinal fluid in children with ADEM. Brain MRIs were available for 269 children and MRI spine scans for 83 children. The frequencies of cerebrospinal fluid oligoclonal bands and MRI abnormalities varied according to ADS presentation.

Clinical Severity

Hospitalization was required for 244 children (86.2%), with a median (IQR) length of stay of 6 (3–10) days. Children with ADEM had the longest hospital stays, whereas children with ON had the shortest hospital stays (Table 1). Length of stay during the incident attack was longer among patients with monophasic ADS (median [IQR]: 7 [5–12] days) compared with children subsequently diagnosed with MS (median [IQR]: 4 [0–7] days; $P < .001$). Of 283 children, 236 (83.4%) were treated with corticosteroids, intravenous immunoglobulin, or plasma exchange (Table 1).

Severe deficits in ≥1 feature of vision, motor, bladder and bowel function, or cognition were detected at ADS onset in 133 (47.0%) of 283 children, whereas 51 (18.0%) children had ≥1 moderate deficit, and 79 (27.9%) children had at least 1 mild deficit (Supplemental Fig 3A). Twenty (7.1%) children had a normal examination at study enrollment (days from onset, median [range]: 9 [4–23]); all had at least 1 deficit at onset verified according to records review of their presenting examination.

Sixty-nine (24.4%) of 283 patients met the diagnostic criteria for ADEM at presentation, 11 of whom experienced concurrent TM and 4 of

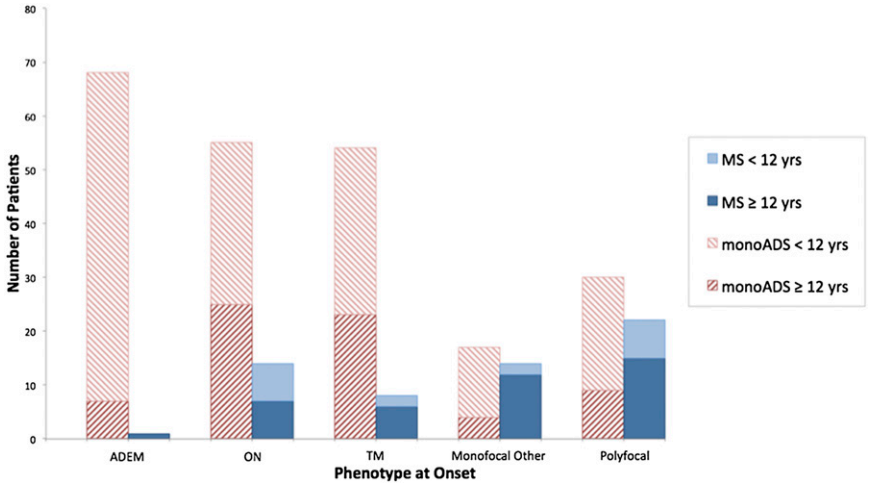

FIGURE 2

Impact of age on presentation and outcome. Each of the clinical ADS presentations is further delineated according to outcome (MS in blue, monophasic ADS in red) and according to age at ADS. Optic nerve or spinal cord involvement occurring in the context of ADEM or polyfocal demyelination is described as a component of these ADS presentations. Children with ADEM were younger (n = 69; median [IQR] age: 5.2 [2.9–7.8] years) than children with non-ADEM presentations (n = 214; median [IQR] age: 11.8 [8.1–14.0] years; $P < .001$). Isolated ON and presentations with monofocal deficits extrinsic to the optic nerve or spinal cord (monofocal/other) occurred more often in female patients (female:male ratio: 1.4 for ON; 1.2 for monofocal/other), whereas a male preponderance was noted in children with polyfocal deficits without encephalopathy (female:male ratio: 0.9) and in children with ADEM (female:male ratio: 0.9). Female and male patients were equally represented in the monofocal TM group.

whom experienced concurrent ON. Ataxia was the most commonly documented localized neurologic deficit, present in 30 (43.5%) of 69 children. However, in many encephalopathic children, it was difficult to determine whether gait impairment was predominantly related to ataxia, pyramidal, or sensory involvement. Bladder impairment was difficult to assess while children were encephalopathic, but 5 children required catheterization. Accurate visual acuity could not be measured during acute illness; however, all children had normal vision on examination 3 months' postonset. Spinal cord imaging was available for 17 (24.6%) of the 69 children, of whom 12 (70.6%) had spinal lesions; 9 (75.0%) of these 12 patients had LETM.

TM was diagnosed in 102 children based on clinical localization, 62 (60.8%) of whom had monofocal TM. Spinal cord imaging performed within 30 days of symptom onset was available for 60 (58.8%) patients; 57 (95.0%) had spinal cord lesions. LETM was noted in 36 (60.0%) of 60 children; 1 was diagnosed with MS.

Monofocal deficits extrinsic to the optic nerve or spinal cord occurred in 31 (11.0%) children. Neurologic deficits were localized to the brain stem or cerebellum in 22 children, 18 of whom manifested with ataxia. Focal motor deficits were reported by 25 children, and sensory deficits were reported by 11 children.

Polyfocal deficits without encephalopathy occurred in 52 (18.4%) children. At onset, 31 (59.6%) of 52 children had deficits referable to the spinal cord (polyfocal with TM), with severe mobility impairment in 10 patients and mild to moderate impairment in 16. Bladder dysfunction was reported in 15 children. Twenty-one patients experienced polyfocal deficits and ON, with severe visual loss in 11 children, and mild to moderate impairment in 5. Spinal cord imaging was abnormal in 16 (88.9%) of 18 scanned, with 10 (55.6%) children exhibiting LETM.

Younger age at symptom onset, an ADEM phenotype, and TM were associated with an increased risk of moderate or severe deficits at onset (Table 3). Within the TM group, LETM did not predict a worse clinical onset.

Patients were followed up for a median (IQR) of 5.06 (3.41–6.97) years from onset. Among the 283 participants, 224 have experienced a monophasic course, 2 children died of their acute illness (1 due to complications of prolonged ventilator support in the context of ADEM with TM, and 1 child with severe TM died of pneumonia), and 59 (20.8%) were diagnosed with MS. Children who were ultimately diagnosed with MS were less likely to have experienced moderate or severe deficits at onset (P = .007) compared with children with monophasic disease (Table 3), which remained true even when children with ADEM were excluded.

Supplemental Figs 3A and 3B compare clinical severity at onset and the extent of recovery of the 281 children who were examined beyond their initial enrollment in the study (2 patients declined all follow-up) and provide detailed information regarding the 27 (10.0%) children who did not recover completely from their incident attack. Residual impairment from the incident ADS event was more common in female subjects (female:male ratio of 2.2:1), in children with TM, in children with more severe deficits at onset, and in those with a monophasic illness (Table 2). Among the 27 children who did not experience complete recovery, all exhibited moderate or severe deficits at presentation. However, 156 children with moderate to severe deficits at onset recovered fully. All 99 children who experienced mild deficits at presentation experienced full resolution of symptoms. Eighty-nine (90.8%) of 98 children with ON recovered fully compared with 82

TABLE 2 Clinical Recovery After Incident

Variable	Full Recovery	Incomplete Recovery	*P*
Recovery and demographics			
All (*N* = 281)[a]	254/281 (90.4)	27/281 (9.6)	
Duration of follow-up, y	5.1 (3.9–7.0)	4.1 (2.3–6.1)	.06
Age at onset, y	10.5 (5.8–13.7)	9.0 (5.8–12.5)	.29
Female patients (*n* = 145)	126/145 (86.9)	19/145 (13.1)	.09
Male patients (*n* = 136)	128/136 (94.1)	8/136 (5.9)	
Recovery and presenting features			
Brain MRI abnormal (*n* = 176)[b]	168/176 (95.4)	8/176 (4.6)	.001
Brain MRI normal (*n* = 91)	75/91 (82.4)	16/91 (17.6)	
Polyfocal (*n* = 52)	49/52 (94.2)	3/52 (5.8)	0.02
Monofocal (*n* = 160)	138/160 (86.2)	22/160 (18.8)	
ADEM (*n* = 69)	67/69 (97.1)	2/69 (2.9)	
TM (*n* = 101)[c]	82/101 (81.2)	19/101 (18.8)	<0.001
No spinal cord symptoms at onset (*n* = 180)	172/180 (95.6)	8/180 (4.4)	
ON (*n* = 97)[d]	89/97 (91.8)	8/97 (8.2)	0.54
No clinical evidence of ON at onset (*n* = 184)	165/184 (89.7)	19/184 (10.3)	
Recovery in patients with TM			
No visible spine lesion (*n* = 3 of 59 with spine MRI)[e]	3/3 (100.0)	0/3 (0)	0.09
Focal lesions (*n* = 20 of 59)	18/20 (90.0)	2/20 (10.0)	
LETM (*n* = 36 of 59 with spine MRI)	27/36 (75.0)	9/36 (25.0)	
Recovery and baseline clinical severity			
Mild deficits at baseline (*n* = 98)	98/98 (100.0)	0/98 (0.0)	<0.001
Moderate or severe deficits at baseline (*n* = 183)	156/183 (85.2)	27/183 (14.8)	
Any treatment at baseline (*n* = 234)[f]	207/234 (88.5)	27/234 (11.5)	0.06
No treatment (*n* = 47)	47/47 (100.0)	0/47 (0)	
Diagnosis			
MS outcome (*n* = 59)	59/59 (100.0)	0/59 (0)	0.001
Monophasic ADS (*n* = 222)	195/222 (87.8)	27/222 (12.2)	
McDonald 2010 MS diagnosis at baseline (*n* = 46)[g]	46/46 (100.0)	0/46 (0)	0.02

For the purposes of this table, recovery at the final visit available was used to determine final recovery. Of the 59 children with MS, all had full neurologic recovery from their initial attack; any deficits after this point were considered secondary to further relapses and are not part of the present table. Data are presented as median (IQR), *n/N* (%), or *n* (%) unless otherwise stated.

[a] Two children were not available for follow-up examinations.

[b] Of the 281 with outcome data, 267 had baseline brain MRI studies for evaluation.

[c] TM was diagnosed in 101 children, 61 with monofocal TM, 9 had TM in the context of ADEM, and 31 had TM as a component of their polyfocal deficits.

[d] ON was diagnosed in 92 children, 68 with monofocal ON, 3 with ON and ADEM, and 21 had ON as part of a polyfocal presentation.

[e] Of 101 children meeting criteria for TM, 59 had spine MRI scans available for analysis. Spinal cord imaging was not part of our formal study methods, and all spine MRI scans were obtained clinically.

[f] Of the 234 children treated at ADS onset, 228 received ≥1 dose of corticosteroids, 210 received intravenous corticosteroids, 168 were prescribed oral prednisone (typically after a course of intravenous corticosteroids), 36 were treated with intravenous immunoglobulin (6 without corticosteroids), and 4 children underwent plasma exchange.

[g] Of the 59 patients diagnosed with MS, 48 had brain MRI scans with gadolinium suited for evaluation of the 2010 McDonald diagnostic criteria for MS as applied to baseline imaging. Three additional patients met the baseline 2010 criteria for diagnosis of MS, but have not had clinical or serial MRI evidence of new disease and for the purposes of the present article are considered with the monophasic ADS group.

(80.4%) of 102 patients with TM (P = .002). Among the 22 children who had optic nerve and spinal cord involvement, 20 (90.9%) experienced full recoveries.

Of the 281 children who agreed to follow-up examination, 254 experienced complete recovery; 209 had a normal examination by 3 months (19 were not examined at 3 months), and 248 had a normal examination by 12 months. Seven children who experienced severe deficits at onset continued to improve beyond 12 months; 4 patients with TM regained normal mobility between 2 and 5 years' postonset, 2 patients with ON regained normal visual acuity between 12 and 24 months' postonset, and 1 child with TM regained normal bladder and bowel functioning by 3 years. Mobility deficits have not resolved after 6 years of follow-up, however.

MS Outcome

All 59 children diagnosed with MS recovered full mobility, normal vision, and bowel and bladder control after their incident attack; 57 children had reached full recovery by 3 months, and all had normal neurologic examinations by 12 months. Of these 59 patients, 42 have experienced ≥2 clinical attacks and 17 were diagnosed on the basis of MRI evidence of dissemination in time and have not experienced further clinical attacks after a median (IQR) of 5.2 (4.0–7.0) years of follow-up. The median number of relapses experienced by the 59 MS patients was 2.0 (IQR: 0–3.0).

Fifty-three (89.8%) of these 59 children continue to have normal neurologic examinations at their most recent visit (median [IQR]: 5.9 [4.0–7.0] years' postonset). Of the 6 children with abnormal examinations at their most recent visit, all demonstrated full recovery from their incident attack, with deficits acquired after subsequent relapses and have persisted for at least 1 year. The median (IQR) number of clinical relapses among the 6 patients with deficits on most recent examination was 3 (2–4). The median (IQR) number of clinical relapses in all 59 MS patients was 2 (0–3).

DISCUSSION

Acute demyelination in children is a serious illness, with >86.2% of children requiring hospitalization for a median of 6 days and collectively requiring 2787 days in the hospital. The children recovered well, although residual visual, motor, bowel, and bladder deficits occurred in children who presented with severe ON or TM. Twenty percent of children with ADS were diagnosed with MS within the first 12 months, and more than one-

TABLE 3 Correlates of Clinical Severity at Presentation

Variable	Mild Deficits at Onset[a]	Moderate or Severe Deficits at Onset	*P*
Severity and demographics			
No. of patients (*n* = 283)	99/283 (35.0)	184/283 (65.0)	
Age at onset (*n* = 283)	12.3 (6.2–14.4)	9.6 (5.6–13.1)	.007
Female patients (*n* = 146)	54/146 (37.0)	92/146 (63.0)	.54
Male patients (*n* = 137)	45/137 (32.8)	92/137 (67.2)	
Hospitalized at onset	72/244 (29.5)	172/244 (70.5)	<.001
Not hospitalized at onset	27/39 (69.2)	12/39 (30.8)	
Length of stay (days)	5 (0–7)	8 (5–14)	<.001
Severity at onset and presenting phenotype			
Polyfocal (*n* = 52)	22/52 (42.3)	30/52 (57.7)	.09
Monofocal (*n* = 162)	60/162 (37.0)	102/162 (63.0)	
ADEM (*n* = 69)	17/69 (24.6)	52/69 (75.4)	
TM (*n* = 102)[b]	22/102 (21.6)	80/102 (78.4)	<.001
No spinal cord symptoms at onset (*n* = 181)	77/181 (42.5)	104/181 (57.5)	
ON (*n* = 98)[c]	34/98 (34.7)	64/98 (65.3)	.99
No clinical evidence of ON at onset (*n* = 185)	65/185 (35.1)	120/185 (64.9)	
Severity at onset in patients with TM			
No visible spine lesion (*n* = 3 of 60 with spine MRI)[d]	1/3 (33.3)	2/3 (66.7)	.18
Focal lesion(s) (*n* = 21 of 60)	5/21 (23.8)	16/21 (76.2)	
LETM (*n* = 36 of 60 with spine MRI)	4/36 (11.1)	32/36 (88.9)	
Diagnosis			
MS outcome (*n* = 59)	35/59 (59.3)	24/59 (40.7)	<.001
Monophasic ADS (*n* = 224)	64/224 (28.6)	160/224 (71.4)	

Data are presented as median (IQR), *n/N* (%), or *n* (%) unless otherwise stated.

[a] Patients with a normal examination at the time of study entry were classified as mild given that their presenting clinical deficits (as documented by intake examination before enrollment) had already resolved.

[b] TM was diagnosed in 102 children, 62 with monofocal TM, 9 had TM in the context of ADEM, and 31 had TM as a component of their polyfocal deficits.

[c] ON was diagnosed in 93 children, 69 with monofocal ON, 3 with ON and ADEM, and 21 had ON as part of a polyfocal presentation.

[d] Of 102 children meeting criteria for TM, 60 had spine MRI scans available for analysis. Spinal cord imaging was not part of our formal study methods, and all spine MRI scans were obtained clinically.

half of these children experienced a second clinical attack in the first year.

Our findings are similar to the 90% recovery reported for 296 pediatric ADS patients in the KIDMUS study in France.[4] In a cohort of 88 German children with MS, 80 had complete recoveries after their incident attacks.[12] We previously assessed 36 children with ON and found that full visual recovery occurred in 39 of 47 affected eyes, despite 69% having a visual deficit worse than or equal to 20/200 at onset.[13]

Clinical recovery occurred quickly in our patients, with normalization of the neurologic examination by 3 months in nearly all children; a small number of children demonstrated further improvement at 12 months, and 7 children improved further beyond 12 months. ADS severity at onset was associated with the risk of residual deficits; however, most children with severe deficits recovered. Although the diagnosis of MS is considered a poor outcome, patients with MS had milder deficits at onset compared with children with monophasic disease, and all recovered from their incident attack. Consistent with these findings, data from patients with adult-onset MS have shown that MS patients initially presenting with TM have milder deficits than adults with monophasic TM.[14]

Younger children were more likely to experience a severe presentation, as also noted in the study from Germany.[12] Although some of this relationship was driven by the higher frequency of ADEM at younger ages, younger age remained associated with severity at onset even when the children with ADEM were excluded. However, age at onset did not predict residual physical impairment from the acute attack, which may suggest a strong capacity for neurologic repair of acute lesions in the youngest patients.

Of the 102 patients with TM in our study, 15 (14.7%) were left with residual motor impairment, 8 (7.8%) of whom require a wheelchair and 13 (12.7%) have residual bladder impairment. We previously described 38 children with TM (none included in the present analysis); 6 (16%) experienced residual motor impairment and 8 (22%) experienced residual bladder impairment.[15] In a European study of 95 children with TM, 28 (30%) experienced a poor outcome (defined as Expanded Disability Status Scale score ≥4).[16] Of 47 children reported from the Johns Hopkins Myelitis Center,[17] ten (21%) patients required a walker or other support and 22 (50%) of 44 required bladder catheterization. The slightly higher proportion of TM patients with severe deficits in the Hopkins center may reflect referral bias to a dedicated TM program. Of interest in our study was that LETM did not predict more severe disability; however, we excluded 3 children with neuromyelitis optica in whom LETM is typically clinically severe.

Given the common practice of corticosteroid therapy (provided to 82% of our cohort), we cannot evaluate the contribution of corticosteroid exposure to outcome. Although randomized trials would provide evidence to support or refute the role of corticosteroids in acute management of ADS, endorsement of such a study is unlikely given the severity of acute illness and the strong international consensus

regarding at least its short-term benefit.[18,19]

There are limitations to our study. First, children with mild symptoms of ADS may have been missed; our research thus delineates the clinical severity and outcome of children unwell enough to seek medical attention. Our national network mitigates concerns regarding referral to specialized MS centers, and our network has >95% ascertainment of all children with ADS seen by Canadian pediatric health care providers.[20] We did not collect detailed information regarding rehabilitation and could not evaluate how this factor contributed to participant recovery. We used a structured clinical examination form at all study visits but did not use the more conventional Expanded Disability Status Scale because this tool is not familiar to most pediatric neurologists. Because we did not assess cognitive performance by using formal neuropsychological measures, we thus have likely underappreciated this aspect of ADS. The impact of ADS on patient function may be underestimated by using standardized physical examinations, which do not query patient-perceived health-related quality of life and do not evaluate participation and activity limitations, cognitive function, or brain volume changes. Areas of active research include more sensitive and comprehensive outcome metrics that may serve as sensitive tools to detect the sequelae of ADS and the potential for new deficits in MS.

ADS in children and adolescents are often severe at onset, although recovery of gait, vision, and bladder and bowel function occurs in most patients. Residual neurologic deficits from incident ADS occur in children with severe monophasic ON or TM. Although return to normal physical function occurs in pediatric MS patients early in the disease, the impact of MS on cognition has been well recognized,[21–24] and the risk for future disability remains.

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ABBREVIATIONS

ADEM: acute disseminated encephalomyelitis
ADS: acquired demyelinating syndromes
CNS: central nervous system
IQR: interquartile range
LETM: longitudinally extensive transverse myelitis
MS: multiple sclerosis
ON: optic neuritis
TM: transverse myelitis

and Yager served as site investigators; Ms C. Phan contributed to the core design of the report. All listed authors made substantial contributions to the acquisition and interpretation of data, were responsible for reviewing all aspects of the data, and provided in-depth edits to the final report. All listed authors approved of the final report and have agreed to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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