Early Predictors of 9-Year Disability in Pediatric Multiple Sclerosis

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Objective: The purpose of this study was to assess early predictors of 9-year disability in pediatric patients with multiple sclerosis.

Methods: Clinical and magnetic resonance imaging (MRI) assessments of 123 pediatric patients with multiple sclerosis were obtained at disease onset and after 1 and 2 years. A 9-year clinical follow-up was also performed. Cox proportional hazard and multivariable regression models were used to assess independent predictors of time to first relapse and 9-year outcomes.

Results: Time to first relapse was predicted by optic nerve lesions (hazard ratio [HR] = 2.10, $p = 0.02$) and high-efficacy treatment exposure (HR = 0.31, $p = 0.005$). Predictors of annualized relapse rate were: at baseline, presence of cerebellar ($\beta = -0.15$, $p < 0.001$), cervical cord lesions ($\beta = 0.16$, $p = 0.003$), and high-efficacy treatment exposure ($\beta = -0.14$, $p = 0.01$); considering also 1-year variables, number of relapses ($\beta = 0.14$, $p = 0.002$), and the previous baseline predictors; considering 2-year variables, time to first relapse (2-year: $\beta = -0.12$, $p = 0.01$) entered, whereas high-efficacy treatment exposure exited the model. Predictors of 9-year disability worsening were: at baseline, presence of optic nerve lesions (odds ratio [OR] = 6.45, $p = 0.01$); considering 1-year and 2-year variables, Expanded Disability Status Scale (EDSS) changes (1-year: OR = 26.05, $p < 0.001$; 2-year: OR = 16.38, $p = 0.02$), and ≥ 2 new T2-lesions in 2 years (2-year: OR = 4.91, $p = 0.02$). Predictors of higher 9-year EDSS score were: at baseline, EDSS score ($\beta = 0.58$, $p < 0.001$), presence of brainstem lesions ($\beta = 0.31$, $p = 0.04$), and number of cervical cord lesions ($\beta = 0.22$, $p = 0.05$); considering 1-year and 2-year variables, EDSS changes (1-year: $\beta = 0.79$, $p < 0.001$; 2-year: $\beta = 0.55$, $p < 0.001$), and ≥ 2 new T2-lesions (1-year: $\beta = 0.28$, $p = 0.03$; 2-year: $\beta = 0.35$, $p = 0.01$).

Interpretation: A complete baseline MRI assessment and an accurate clinical and MRI monitoring during the first 2 years of disease contribute to predict 9-year prognosis in pediatric patients with multiple sclerosis.

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During the last decades, pediatric multiple sclerosis (MS; ie, clinical onset before age 18 years) has been increasingly recognized, representing from 3 to 10% of the total MS population.[1–3] However, only a few longitudinal studies[4,5] have been conducted in these patients.

A higher clinical activity, with higher relapse rate especially during the first years from disease onset,[6,7] paralleled by a higher magnetic resonance imaging (MRI) activity,[8] was reported for pediatric-onset compared with patients with adult-onset MS. In details, patients with MS with disease onset in childhood or adolescence not only experienced more frequent involvement of infratentorial regions on MRI, but also had higher lesion burden both at disease onset and on follow-up.[8] However, little is

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known about how these early clinical and MRI features may influence the long-term clinical outcome of these patients.

In pediatric patients with a clinically isolated syndrome (CIS), some clinical factors contributed to predict the conversion to clinically defined MS.[5] In particular, multifocal onset and female sex were associated with a higher risk of a short-term second clinical attack, whereas exposure to disease modifying treatments (DMTs) was protective.[5] In the same cohort, the occurrence of a relapse after MS diagnosis was the only significant predictor of the Expanded Disability Status Scale (EDSS) score worsening after 10 years.[5]

In adult patients with MS, MRI has a fundamental role not only in disease monitoring but also in predicting clinical course, but data are lacking for pediatric patients. For adult patients at their first demyelinating attack, asymptomatic infratentorial,[9–11] spinal cord,[10,12,13] and gadolinium-enhancing (Gd)-lesions[10,14] were associated with the development of clinical disability (measured using the EDSS) over the first 5 to 7 years after a first clinical attack.

Considering the paucity of approved DMT in pediatric patients with MS as well as safety concerns about new highly active drugs, it appears extremely relevant to identify risk factors for disease progression in these patients.

Against this background, the aim of this study was to identify early (at disease onset and within the first 2 years of disease) clinical and MRI predictors of disease course in pediatric patients with MS, by studying a large cohort of these patients. Easily obtainable and reproducible MRI measures were investigated (number and distribution of T2-hyperintense lesions, number and distribution of Gd-lesions, including the cervical cord; presence of tumefactive lesions, and number of black holes), in order to guarantee immediate clinical applicability.

Methods

Ethics Committee Approval

Approval was received from the local ethical standards committee on human experimentation, and written informed consent was obtained from all participants and their parents prior to study enrollment.

Subjects

A cohort of 123 pediatric patients with relapsing–remitting MS,[15–17] followed at San Raffaele Hospital, Milan, Italy, Unit of Neurology, was analyzed. We included pediatric patients with MS at their first demyelinating attack with an available neurological evaluation and 1.5 Tesla brain and cervical cord MRI scan within 3 months from disease onset. Exclusion criteria were: clinical presentation with symptoms of encephalopathy referable to acute disseminated encephalomyelitis according to published operational criteria[15] and a history of other neurological/medical disorders in addition to MS.

Clinical Assessment

Neurological evaluations (with EDSS score rating) at disease onset and after 1 and 2 years were collected, together with the last available clinical visit (median follow-up duration = 9.4 years, interquartile range = 6.9–12.9 years). DMT exposure and relapses during the whole follow-up period were recorded. DMT were grouped into moderate-efficacy (any preparation of interferon-beta and glatiramer acetate) and high-efficacy (natalizumab and immunosuppressants) treatments. Disability worsening was classified as a confirmed (at a following visit 12 months apart)[18] EDSS increase of at least 1.5, 1.0, and 0.5 points for baseline EDSS scores of 0, 1.0 to 5.0, and more than 5.5, respectively.

MRI Assessment

Brain (n = 123) and cervical cord (n = 115) 1.5 Tesla MRI scans obtained in a clinical setting for diagnostic and follow-up purposes were evaluated by an experienced neurologist. In particular, the MRI scan performed at disease onset (baseline), and – when available – yearly brain MRI scans at 1 and 2 years, were analyzed. The number, distribution, and feature (tumefactive vs non-tumefactive appearance) of T_2-hyperintense lesions were recorded on baseline images, together with the number of new lesions on 1-year and 2-year scans. For this purpose, multiplanar fluid attenuation inversion recovery (FLAIR) and T_2-weighted images of the brain, and short tau inversion recovery (STIR), and/or T_2-weighted images of the cervical cord were used. The number of black holes at baseline, and the number and distribution of Gd-lesions on baseline, at 1-year and 2-year scans were measured on post-contrast, turbo-spin echo T_1-weighted scans. Regarding the distribution of lesions, the involvement of the following central nervous system (CNS) regions was evaluated (Fig 1): periventricular white matter (WM; 2 cutoffs were used: at least 1 and 3 or more lesions according to the better accuracy observed of 3 or more lesions in identifying patients with MS),[19,20] deep gray matter (GM), cortical/juxtacortical GM/WM, brainstem, cerebellum, optic nerve (as evaluable in conventional T_2-weighted sequences), and cervical cord.

Statistical Analysis

Chi-squared and Mann–Whitney *U* tests were used as appropriate to investigate differences in demographic,

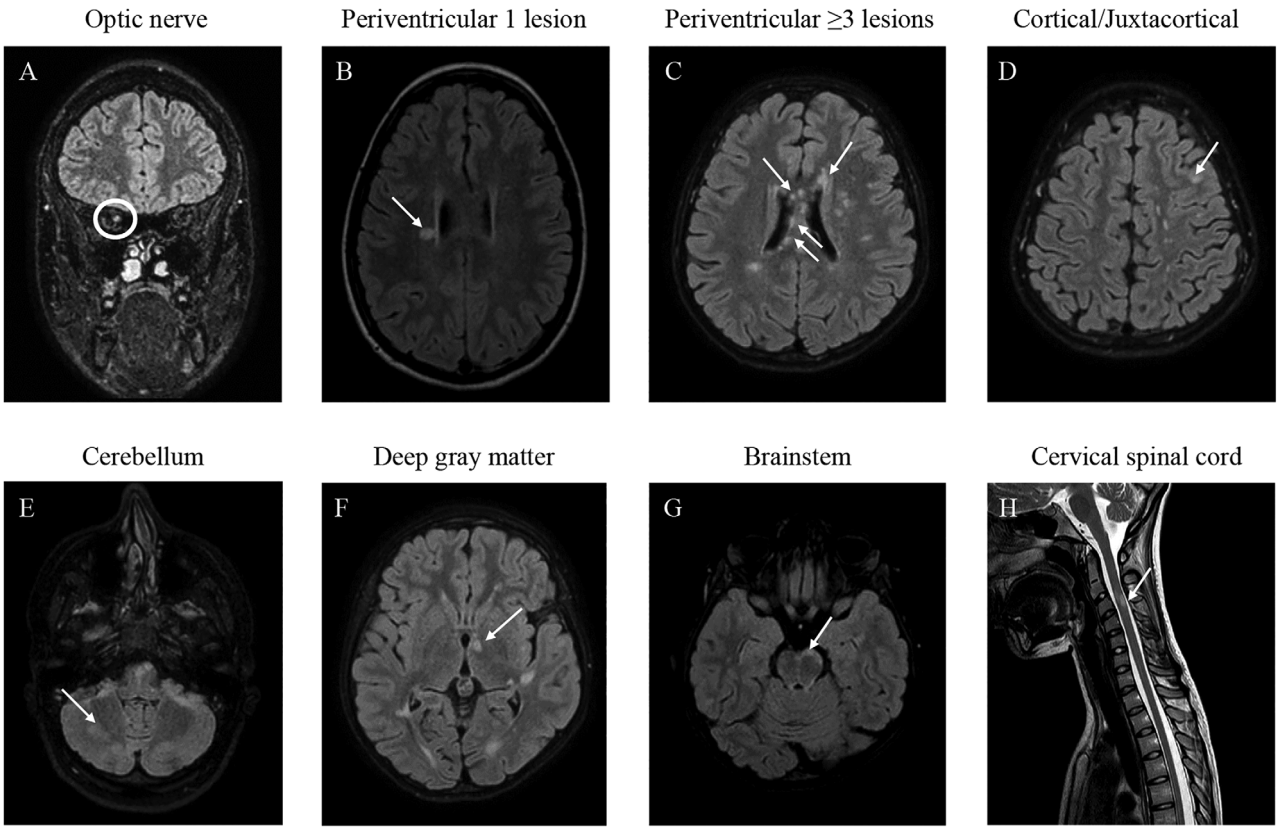

FIGURE 1: Lesion distribution. The pictures are representative of the 7 brain regions considered in the study. Lesions located in the following compartments (highlighted by *white circles* and *arrows*) were detected on fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequences: (A) optic nerve; (B) periventricular region (1 lesion); (C) periventricular region (3 or more lesions); (D) cortical/juxtacortical region; (E) cerebellum; (F) deep gray matter; (G) brainstem; and (H) cervical cord.

clinical, and MRI measures at baseline, 1-year, and 2-years, between patients who had worsened and those who had not at last follow-up. The same comparison was also performed for clinical measures at last follow-up. Differences in demographic, clinical, and MRI measure between patients who dropped out and those who remained throughout the follow-up period, as well as between patients starting moderate and high-efficacy DMT, were also analyzed.

Stepwise Cox proportional hazard models were used to identify the independent predictors of time to first relapse. Multivariable linear regression models were used to identify independent predictors of annualized relapse rate (ARR) and of EDSS score at last follow-up. Multivariable logistic regression models were used to investigate independent predictors of disability worsening at last follow-up. Separate models were built using clinical and MRI data available at each of the follow-up time points. Baseline EDSS, age at onset, sex, and the exact interval in years between onset and the last follow-up visit were included in the models as potential confounders. A stepwise variable selection procedure was used. This procedure is a combination of forward and backward selection where, in each step, every variable is considered for addition to or subtraction from the set of covariates based on an F-test with a p value for inclusion of 0.15.

In summary, 3 different models were constructed for each outcome variable:

1. Baseline model (n = 123): baseline clinical and MRI (brain and cervical cord) variables were included. MRI measures were number, location, and feature of T_2-lesions, number and distribution of Gd-lesions, and number of black holes;
2. 1-year model (n = 115): baseline predictors plus the number of relapses and time to first relapse within the first year, and the change in EDSS score and brain MRI variables (new T_2- and Gd-lesions) after 1 year were included in the model;
3. 2-year model (n = 105): baseline and 1-year predictors, plus the number of relapses and time to first relapse within the first 2 years, and the change in EDSS score and brain MRI variables (new T_2- and Gd-lesions) after 2 years were included.[2]

For each multivariable linear regression model, R is reported, as the proportion of the variance of dependent variable determined by the independent variable(s) included in the model. For multivariable logistic regression models, the model fit is reported using model C-statistic and accuracy. Statistical analysis was performed with R software (version 3.6.1). Statistical significance is reported as $p < 0.05$.

Data Availability

The data set used and analyzed during the current study is available from the corresponding author on reasonable request.

Results

Clinical Features and Course

One hundred twenty-three (89 girls and 34 boys) pediatric patients with MS with baseline clinical and MRI evaluations were included. Of them, 115 underwent clinical and MRI follow-up evaluations exclusively after 1 year, and 105 after 1 and 2 years. No significant differences in demographic, clinical, and MRI features were observed between patients who dropped out and those who remained in the follow-up period (data not shown). Over the 9-year follow-up period, 13 of 123 (11%) pediatric patients experienced disability worsening and one of them developed secondary progressive MS, whereas no significant EDSS changes were observed in the whole group (EDSS at last follow-up 1.0, range = 0.0–7.0, $p = 0.89$). Figure 2 summarizes EDSS scores in patients worsened and not worsened at last clinical follow-up.

Baseline Clinical and MRI Features

Baseline clinical and MRI features of the study cohort are summarized in Table 1. Optic nerve involvement was observed in 15 of 19 (74%) patients experiencing clinically manifest optic neuritis and in 10 of 104 (10%) patients asymptomatic for optic neuritis. No significant differences were found between patients worsened and not worsened at follow-up except for the mean number of cervical cord Gd-lesions. Table 2 summarizes the main clinical and MRI changes occurring after 1 and 2 years of follow-up. All the patients enrolled started a DMT at diagnosis (63% interferon-beta, 13% glatiramer acetate, 19% natalizumab, and 5% immunosuppressant). Compared with pediatric patients with MS starting moderate-efficacy DMT, patients starting high-efficacy DMT were older ($p = 0.01$), had higher EDSS score ($p = 0.006$), and more extensive brain and cervical cord involvement at MRI (p ranging from <0.001 to 0.04; see Table S1 in Supplementary Material for all comparisons). Four patients switched from moderate to high-efficacy DMT during the first 2-year follow-up period. During the 9-year follow-up period, 30 of 123 (24%) patients switched to higher-efficacy treatment, of which 5 patients worsened clinically.

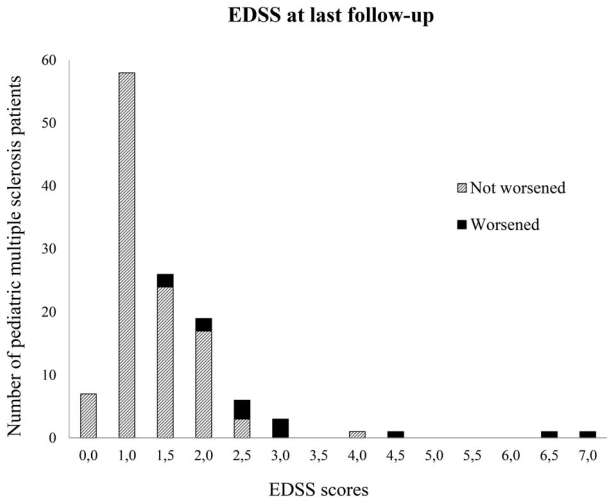

FIGURE 2: EDSS score at longest follow-up in pediatric patients with multiple sclerosis (MS). Pediatric patients with MS not worsened at last follow-up are represented in histograms with gray filling, whereas those worsened at follow-up are represented in histograms with black filling. EDSS = Expanded Disability Status Scale.

One-Year Clinical and MRI Features

During the first year from the disease onset (n = 115), 31 patients (27%) had at least one clinical relapse, 5 patients (4%) had disability worsening, 51 patients (44%) at least one new T_2-lesion, and 29 patients (25%) had at least one Gd-lesion on brain MRI.

Two-Year Clinical and MRI Features

During the second year from the disease onset (n = 105), 24 patients (23%) had at least one clinical relapse, 5 patients (5%) had disability worsening, 53 patients (50%) had at least one new T_2-lesion, and 30 patients (29%) had at least one Gd-lesion on brain MRI. Totally, during the first 2 years from the disease onset (n = 105), 38 patients (36%) had at least one clinical relapse, 10 patients (10%) had disability worsening, 53 patients (50%) had at least one new T_2-lesion, and 30 patients (29%) had at least one Gd-lesion on brain MRI.

Worsened patients at 9-year follow-up had a higher number of new brain T_2-lesions and greater EDSS change at 1 and 2 years compared with not worsened ones. No significant differences were found in terms of relapses. See Table 2 for all comparisons.

Early Predictors of Time to First Relapse and ARR

The median time from disease onset to first relapse was 1.7 years (range = 0.2–13.7). Optic nerve involvement

TABLE 1. Main Baseline Clinical and MRI Features of the Study Cohort Grouped by Clinical Status at 9 yr Follow-up

	All pediatric patients with multiple sclerosis	Pediatric patients with multiple sclerosis not worsened at FU	Pediatric patients with multiple sclerosis worsened at FU	*p*
Number of patients	123	110	13	-
Girls/boys	89/34	78/32	11/2	0.47
Mean age (range), yr	14.4 (7.3–17.9)	14.4 (7.3–17.9)	14.3 (9.8–17.0)	0.91
Median EDSS (range)	1.5 (0.0–6.0)	1.5 (1.0–4.0)	1.0 (0.0–6.0)	0.15
Treatment, n (%) IFN/GA/NAT/IS	77 (63)/16 (13)/23 (19)/7 (5)	68 (62)/13 (12)/23 (21)/6 (5)	9 (69)/3 (23)/0 (0)/1 (8)	0.26
Clinical presentation, n (%)				
Polyfocal	35 (28)	30 (29)	5 (38)	0.88
Visual	14 (11)	10 (9)	4 (31)	0.12
Brainstem	32 (26)	31 (29)	1 (8)	0.13
Sensitive	30 (24)	28 (25)	2 (15)	0.92
Pyramidal	9 (7)	8 (6)	1 (8)	0.67
Cerebellar	2 (2)	2 (2)	0 (0)	1.00
Mean number of brain T_2-lesions (range)	30.5 (3–180)	29.5 (3–167)	42.0 (3–180)	0.55
T_2-lesion location, n (%)				
Optic nerve	25 (20)	20 (18)	5 (38)	0.10
Periventricular (1 lesion)	99 (80)	89 (81)	10 (77)	1.00
Periventricular (> = 3 lesions)	84 (68)	75 (68)	9 (69)	0.70
Cortical/juxtacortical	69 (56)	62 (56)	7 (54)	1.00
Deep gray matter	38 (31)	34 (31)	4 (31)	1.00
Cerebellum	63 (51)	54 (49)	9 (69)	0.13
Brainstem	68 (55)	59 (54)	9 (69)	0.21
Cervical spinal cord	67 (63)	61 (55)	6 (46)	0.80
Presence of black holes, n (%)	51 (41)	47 (43)	4 (31)	0.66
Mean number of black holes (range)	3.2 (0–35)	3.1 (0–35)	4.1(0–21)	0.66
Presence of tumefactive lesions, n (%)	25 (20)	23 (21)	2 (15)	1.00
Presence of brain Gd+ lesions, n (%)	71 (58)	65 (59)	6 (46)	0.78
Mean number of brain Gd+ lesions (range)	3.0 (0–23)	3.0 (0–23)	5.5 (0–20)	0.87
Presence of cervical spinal cord Gd+ lesions, n (%)	24 (21)	24 (23)	0 (0)	0.17
Mean number of cervical spinal cord lesions (range)	1.1 (0–6)	1.0 (0–5)	1.4 (0–6)	0.55
Mean number of Gd+ cervical spinal cord lesions (range)	0.2 (0–3)	0.3 (0–3)	0 (NA)	0.05

EDSS = Expanded Disability Status Scale; FU = follow-up; GA = glatiramer acetate; Gd+ = gadolinium enhancing; IFN = interferon; IS = immunosuppressant; MRI = magnetic resonance imaging; NA = not applicable; NAT = natalizumab.

TABLE 2. Main Clinical and Brain MRI Changes Over the Follow-up Period Grouped by Clinical Status at 9 year

	All pediatric patients with multiple sclerosis	Pediatric patients with multiple sclerosis not worsened at FU	Pediatric patients with multiple sclerosis worsened at FU	*p*
Median follow-up duration (IQR), yr	9.4 (6.9–12.9)	8.3 (6.8–13.6)	10.0 (8.1–10.7)	0.32
Mean time to first relapse (SD), yr	2.3 (2.5)	2.3 (2.5)	2.2 (2.4)	0.23
Annualized relapse rate (SD)	0.3 (0.4)	0.3 (0.4)	0.3 (0.3)	0.75
Median EDSS at follow-up (range)	1.0 (0.0–7.0)	1.0 (0.0–4.0)	2.5 (1.0–7.0)	<0.001
Mean number of 1-yr new T_2 lesions (range)	1.4 (0–15)	1.3 (0–15)	2.0 (0–6)	0.05
Mean number of 1-yr new Gd+ lesions (range)	0.6 (0–10)	0.5 (0–5)	1.3 (0–10)	0.54
Mean number of 1-yr relapses (range)	0.3 (0–3)	0.3 (0–3)	0.5 (0–2)	0.33
1-yr EDSS change (range)	−0.3 (−3–2)	−0.4 (−3–1.5)	0.4 (−1–2)	<0.001
Mean number of 2-yr new T_2 lesions (range)	2.0 (0–15)	1.9 (0–15)	3.1 (0–7)	0.01
Mean number of 2-yr new Gd+ lesions (range)	0.8 (0–13)	0.7 (0–8)	2.1 (0–13)	0.38
Mean number of 2-yr relapses (range)	0.7 (0–6)	0.7 (0–6)	0.9 (0–2)	0.10
2-yr EDSS change (range)	−0.2 (−2.5–2)	−0.4 (−2.5–1)	0.7 (−0.5–2)	<0.001

EDSS = Expanded Disability Status Scale; FU = follow-up; Gd+ = gadolinium enhancing; IQR = interquartile range; MRI = magnetic resonance imaging; SD = standard deviation.

(hazard ratio [HR] = 2.10, 95% confidence interval [CI] = 1.12–3.91, p = 0.02) and high-efficacy DMT exposure (HR = 0.31, 95% CI = 0.12–0.72, p = 0.005) were the independent predictors of time to first relapse (Fig 3). Among patients with MRI optic nerve involvement but asymptomatic for optic neuritis, only 1 of 10 (10%) patients experienced clinically manifest optic neuritis as first relapse. At baseline, the presence of cerebellar lesions and the exposure to high-efficacy DMT predicted lower ARR, whereas that of cervical cord lesions was associated with higher ARR. In the 1-year model, the same baseline variables were confirmed as predictors of ARR. Furthermore, a positive association between the number of relapses during the first year of disease and ARR was observed. In the 2-year model, the time to first relapse and the number of relapses during the first 2 years were the independent predictors of ARR, together with the baseline predictors except for high-efficacy DMT exposure. Table 3 summarizes the results of ARR models.

Early Predictors of 9-Year Disability Worsening

At baseline, the presence of lesions in the optic nerve and brainstem was associated with a higher probability of 9-year EDSS worsening. In the 1-year model, EDSS change during the first year of disease was the only independent predictor of 9-year disability worsening (Table 4). In the 2-year model, EDSS change during the first 2 years of disease as well as the detection of at least 2 new brain T_2-lesions during the same period were the independent predictors of 9-year disability worsening.

Early Predictors of EDSS Score at 9-Year Follow-up

At baseline, EDSS score, the presence of brainstem lesions, and the number of cervical cord lesions predicted a higher 9-year EDSS score; whereas the presence of brain or cervical cord Gd-lesions was associated with a lower 9-year disability (Table 5). In the 1-year model, baseline EDSS score, brainstem, and brain Gd lesions (these last ones, although not-reaching statistical significance) confirmed their role. Furthermore, 1-year EDSS change and detection of at least 2 new brain T_2-lesions were associated with higher EDSS score at 9 years. In the 2-year model, the EDSS change at 2 years joined the 1-year model predictors.

Discussion

This longitudinal study was aimed to assess the relevance of specific early clinical and MRI features for 9-year

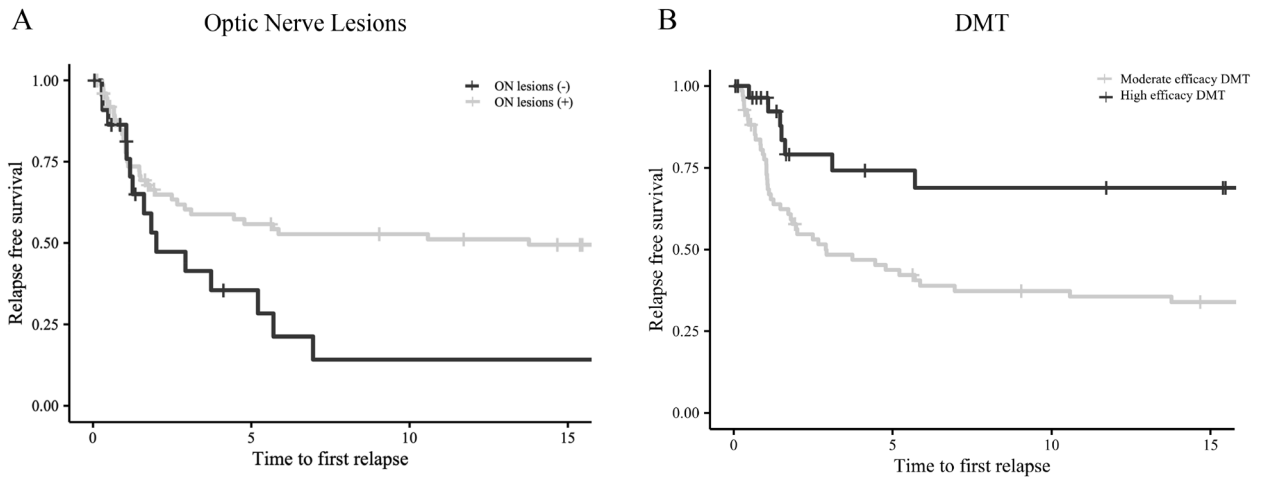

FIGURE 3: Risk of a first relapse in pediatric patients with multiple sclerosis (MS) with and without optic nerve lesions. (A) Survival curves of time from disease onset to first relapse in pediatric patients with MS with and without optic nerve lesions. Pediatric patients with MS with optic nerve lesions are represented in black, whereas patients without optic nerve lesions are represented light gray. (B) Survival curves of time from disease onset to first relapse in pediatric patients with MS on moderate- and high-efficacy disease modifying treatments (DMTs). Pediatric patients with MS on moderate-efficacy DMT are represented in light gray, whereas patients on high-efficacy DMT are represented in black. DMTs = disease modifying treatments; ON = optic nerve.

clinical outcomes in pediatric patients with MS. The purpose was to aid in the definition of prognosis and in the selection of a personalized treatment plan as soon as possible.

Time to first relapse was selected as the first outcome measure, considering the existing differences between pediatric and adult patients with MS: in particular, the higher disease activity as well as the longer time to

TABLE 3. Multivariable Linear Regression Models Investigating Early Clinical and MRI Predictors of Annualized Relapse Rate in Pediatric Patients With Multiple Sclerosis

	Coefficient	95% CI	*p*	R^2 (adjusted R^2)
Baseline (n = 123)				0.17 (0.15)
Presence of cerebellar lesions	−0.15	−0.25 to 0.05	<0.001	
Presence of cervical spinal cord lesions	0.16	0.05 to 0.26	0.003	
High- versus moderate-efficacy DMT	−0.14	−0.25 to −0.03	0.01	
Baseline – 1 yr **(n = 115)**				0.26 (0.22)
Number of 1-yr relapses	0.14	0.05 to 0.23	0.002	
Presence of cerebellar lesions[a]	−0.16	−0.26 to −0.06	0.002	
Presence of cervical spinal cord lesions[a]	0.15	0.05 to 0.25	0.004	
High- versus moderate-efficacy DMT	−0.12	−0.23 to 0.01	0.04	
Baseline - 2 yr **(n = 105)**				0.26 (0.22)
Time to first relapse	−0.12	−0.20 to −0.02	0.01	
Number of 2-yr relapses	0.06	0.01 to 0.12	0.02	
Presence of cerebellar lesions[a]	−0.12	−0.22 to −0.01	0.03	
Presence of cervical spinal cord lesions[a]	0.10	0.00 to 0.21	0.04	

CI = confidence interval; DMT = disease modifying treatments; MRI = magnetic resonance imaging.
[a]At baseline.

TABLE 4. Multivariable Logistic Regression Models Investigating Early Clinical and MRI Predictors of EDSS Worsening after 9 yr

	Odds ratio	95% CI	*p*	C-statistic	Accuracy
Baseline (n = 123)				0.79	91%
Presence of optic nerve lesions	6.45	1.48 to 30.49	0.01		
Presence of brainstem lesions	6.17	0.97 to 122.48	0.10		
Baseline - 1 yr (n = 115)				0.90	93%
1-yr EDSS change	13.40	3.27 to 96.81	<0.001		
Baseline - 2 yr (n = 105)				0.96	90%
1-yr EDSS change	26.05	4.32 to 345.76	<0.001		
2-yr EDSS change	16.38	1.99 to 228.36	0.02		
> = 2 new T_2 lesions in 2 yr	4.91	0.73 to 46.58	0.02		

CI = confidence interval; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging.

TABLE 5. Multivariable Linear Regression Models Investigating Early Clinical and MRI Predictors of EDSS Score at 9 yr

	Coefficient	95% CI	*p*	R^2 (adjusted R^2)
Baseline (n = 123)				0.42 (0.39)
Baseline EDSS	0.58	0.41 to 0.75	<0.001	
Presence of brainstem lesions	0.31	0.01 to 0.61	0.04	
Number of cervical spinal cord lesions	0.22	−0.02 to 0.46	0.05	
Number of Gd+ cervical spinal cord lesions	−0.41	−0.77 to −0.05	0.02	
Presence of brain Gd+ lesions	−0.29	−0.60 to 0.01	0.05	
Baseline - 1 yr (n = 115)				0.66 (0.64)
Baseline EDSS	0.96	0.80 to 1.12	<0.001	
1-yr EDSS change	0.71	0.54 to 0.89	<0.001	
> = 2 new T_2 lesions in 1 yr	0.28	0.03 to 0.52	0.03	
Presence of brain Gd+ lesions[a]	−0.22	−0.46 to 0.03	0.08	
Brainstem lesions[a]	0.17	−0.07 to 0.41	0.15	
Baseline - 2 yr (n = 105)				0.73 (0.71)
Baseline EDSS	0.97	0.83 to 1.13	<0.001	
1-yr EDSS change	0.79	0.62 to 0.96	<0.001	
2-yr EDSS change	0.55	0.21 to 0.88	<0.001	
> = 2 new T_2 lesions in 2 yr	0.35	0.11 to 0.60	0.01	
Presence of brain Gd+ lesions[a]	−0.19	−0.44 to 0.06	0.13	

CI = confidence interval; EDSS: Expanded Disability Status Scale; Gd+ = gadolinium enhancing; MRI = magnetic resonance imaging.
[a]At baseline.

clinical worsening in pediatric patients with MS.[1] In the present study, optic nerve involvement on brain MRI was the only independent predictor of a shorter time to first relapse. Apparently, this result may contrast with previous findings that patients with CIS presenting with optic neuritis have a lower number of asymptomatic brain lesions on MRI, and thus a better prognosis, compared with other CIS presentations.[21,22] However, our finding has a number of explanations. First, we only included patients with a diagnosis of MS, and by consequence an abnormal brain MRI scan. Indeed, in the previous studies, the benign prognosis of patients presenting with optic neuritis was driven by the subgroup without significant brain MRI lesions, which was not obviously represented in our study.[22,23] Second, optic nerve involvement on MRI may have different implications, compared with clinically manifest optic neuritis.[24,25] Importantly, these results do not seem to be affected by selection bias, given that only one patient (out of 10) with MRI optic nerve involvement but asymptomatic for optic neuritis experienced clinically manifest optic neuritis as the first relapse.[26] Finally, optic nerve involvement on MRI at the time of diagnosis may be associated with a shorter asymptomatic period, because the lesion is usually clinically manifest, and earliest phases of disease have been associated with a higher clinical activity in pediatric patients with MS.[6]

The exposure to high-efficacy DMT was the only independent predictor of longer time to first relapse. This is not surprising given the differences in efficacy profile and time needed to obtain clinical and MRI benefits reported for the distinct DMT classes.[27–29] This result is also particularly encouraging, as these patients had more severe clinical and MRI disease parameters at onset, compared with patients receiving moderate-efficacy DMT.

The second outcome variable, ARR over the first 9 years of disease, was in part predicted by baseline lesion distribution. In details, cerebellar lesions were associated with lower ARR, whereas cervical cord lesions were associated with higher ARR. These associations also remained significant when short-term follow-up variables were included in the multivariable models. Considering the typical involvement of infratentorial regions and higher ARR of pediatric compared with adult patients with MS,[30] the association of lesions in the cerebellum with lower ARR may be puzzling. However, recent studies demonstrated that the cerebellum differentiates itself from other infratentorial structures in MS, by showing similar lesion frequencies compared with supratentorial regions.[31] This finding, considering the preferential lesion location in pediatric patients with MS in those regions with more complete myelin maturational processes,[30] could be attributed to a later cerebellar maturation (compared with the remaining infratentorial structures) occurring during late childhood and adolescence.[31–33] In this perspective, it is tempting to speculate that the relationship between cerebellar lesions and lower ARR could be due to later myelination in the cerebellum.[31] Indeed, the later myelination may protect this region at younger ages, which have been associated with a higher ARR compared with adolescence, when brain maturation is more advanced, and disease features become more similar to adults (eg, lower ARR). The association between spinal cord lesions and ARR confirms the results of previous studies in adult patients with MS, in which the presence of asymptomatic spinal cord lesions was significantly predictive of an increased risk of future relapse.[34] Furthermore, the presence of asymptomatic spinal cord lesions was previously found to be a significant predictor of a first clinical attack in radiologically isolated syndrome[35–37] and of conversion to clinically defined MS in patients with CIS.[36]

In addition, some short-term follow-up measures significantly contributed to explain 9-year ARR. We found a consistent association between the number of relapses over the first 2 years and time to first relapse with ARR. These data suggest the persistence of inflammatory activity over the first years of disease in spite of DMT be highly indicative of a more active disease, with a higher ARR over 9 years. In light of these findings, close observation of clinical and radiological disease activity during the first 2 years of disease helps in the definition of an early personalized therapeutic strategy, considering long-term benefits and risks ratio.[38] Once again, a protective role was found for high-efficacy DMT exposure over the first year of disease. However, this effect was lost in the 2-year model, underscoring the existence of an early critical window in which the biology of disease can be modified for longer-term benefit.[39] Moreover, the protective role of high-efficacy DMT exposure might partially be conveyed by the number of relapses in the first 2 years of disease.

With the aim of exploring disability accrual, we investigated the 9-year EDSS worsening and score. According to recent data suggesting that disability regression post progression is quite frequent among younger patients with MS,[18] we considered 12-month confirmed disability in order to reduce a potential overestimation of disability accrual. Our results confirmed the predictive role of baseline EDSS score and of clinically eloquent site involvement (such as the optic nerve, brainstem, and spinal cord) for these 9-year outcomes. Regarding the former, the notion that higher baseline EDSS scores are associated with a higher risk of subsequent clinical worsening has also been reported for adult patients with MS.[40] Regarding the latter, different explanations may be valid for each CNS regions. For the optic nerve, there are no previous

studies aimed at directly exploring the prognostic value of MRI abnormalities of this compartment. Nevertheless, both symptomatic and asymptomatic lesions of the optic nerve were associated with retinal neuro-axonal loss on optical coherence tomography in patients with CIS.[25] In turn, different optical coherence tomography metrics have been associated with long-term clinical disability.[41,42] Accordingly, our results provided an evidence of a direct association of MRI lesions in this clinically eloquent area with long-term disability, underscoring the role of neuroaxonal degeneration in clinically eloquent areas of the CNS as an important driver of disability in MS.[43–46] In line with this hypothesis, we found an association between 9-year disability worsening and baseline brainstem (presence of lesions) and spinal cord (number of not enhancing lesions) involvement, which contain long-distance WM pathways critical for balance and locomotion. Although there are no available longitudinal studies in pediatric patients, a significant association was found between lesions in the brainstem and spinal cord with short-term[9–13,47] and long-term[47] EDSS changes in adult patients with CIS.

In the opposite direction, we found that Gd-lesions on baseline MRI have a protective role against 9-year disability in pediatric-onset patients with MS. This result, in line with recent long-term studies,[40,48] contrasts with findings observed in adult patients with MS, in whom Gd-lesions were a negative prognostic factor for long-term clinical disability.[47] However, pediatric patients with MS are known to have more frequent Gd-lesions than adults,[8] with a frequency that reduces with age.[49] This trend is paralleled by a decrease in remyelination capability with age,[50–52] which underlays the shorter time needed to reach clinical disability in adult patients compared with pediatric patients.[1] Of course, a more severe acute inflammatory activity at disease onset could stimulate myelin repair and delay chronic inflammation processes typical of the progressive phase of disease.[53] As a matter of fact, increased levels of neural growth factors[54] and increased regulatory T lymphocyte levels[55] have been found during relapses. In this perspective, our findings underscore once again the pathophysiological differences between pediatric and adult patients with MS. In addition, they point at the existence of an early critical window, in which treatment strategies need to be optimized as soon as possible, in order to protect patients' brain from the establishment of chronic neuroinflammatory processes, which probably represent the main determinant of disability accrual.

Finally, we also explored the role of a short-term follow-up in the prediction of 9-year clinical disability. As we could expect, the same as for baseline EDSS, it was also its short-term increase that provided a significant contribution in determining 9-year outcome. These results, together with the association found between 9-year clinical disability and the detection of at least 2 new T_2-lesions at 2 years, underscore the relevance of clinical and MRI monitoring during the first years of disease in predicting long-term disease evolution.[56] It is interesting to observe that, opposite to data in adult patients with MS, there was no association between high-efficacy DMT exposure and 9-year disability in pediatric patients with MS. This finding underscores the existence of distinctive pathophysiological mechanisms of damage and repair in pediatric MS, which likely explain the more favorable clinical course in spite of higher disease activity.

This study has a few limitations. First, an inherent limitation to all longitudinal observational studies is drop-out of subjects over time, although it was relatively low in the present study. The second one is represented by the absence of a standardized MRI protocol, which did not allow us to quantify brain and spinal cord atrophy, known to play an important role in determining clinical disability. In addition, optic nerve lesion assessment was performed on conventional brain MRI sequences, which have suboptimal sensitivity despite their common use for this purpose in a real-world setting. Third, we have no cognitive data for our cohort. Further long-term longitudinal studies, including cognitive data, should improve the identification of early prognostic predictors, given the paramount importance of long-term cognitive outcomes for pediatric patients with MS.

In conclusion, by using clinical and easy obtainable MRI measures, we identified early predictors of 9-year disease course. High-efficacy DMT exposure over the first year of disease reduced disease activity over the 9-year follow-up. Baseline cervical cord, brainstem, and optic nerve involvement by lesions have a major role in predicting 9-year outcomes, both in term of disease activity and disability worsening, underscoring the need for complete CNS MRI assessment at baseline. In addition, an accurate clinical and MRI monitoring during the first 2 years of disease has proven to represent a powerful tool for counseling patients about long-term prognosis and personalizing treatment strategies.

Author Contributions

E.D.M. and M.F. contributed to study concept, drafting/revising the manuscript, data collection and analysis. L.M., B.C., F.S., and C.Z. contributed to patients' enrollment and data collection and analysis. R.B., M.P.A., V.M., and M.A.R. contributed to drafting/revising the manuscript, data collection, and analysis.

Potential Conflicts of Interests

Nothing to report.

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