EARLY PREDICTORS OF LONG-TERM CLINICAL OUTCOMES IN PEDIATRIC MULTIPLE SCLEROSIS: A 12-YEAR STUDY

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INTRODUCTION and PURPOSE

Identifying predictors of long-term outcomes in pediatric multiple sclerosis (MS) is crucial for tailoring an early and effective treatment, but only a few longitudinal studies have explored clinical and conventional magnetic resonance imaging (MRI) predictors of relapse risk and disability progression in pediatric MS [1]. Key factors associated with the risk of a second clinical attack include female sex, older age at onset, multifocal presentation, and optic nerve involvement. Predictors of long-term disability accumulation include older age at onset, multifocal onset, spinal cord/infratentorial involvement, higher relapse rate, and greater T2-hyperintense white matter (WM) lesion burden. Clinical and conventional MRI assessments do not fully capture the smoldering pathological processes that begin early also in pediatric MS, thus the integration of advanced MRI measures may improve early disease characterization, prognostication, and personalized treatment planning in pediatric MS.

In this study we aimed to identify early clinical and MRI predictors of long-term clinical outcomes in pediatric MS, by integrating clinical and conventional MRI measures (e.g., brain and spinal cord lesions) with advanced MRI techniques, including volumetric analysis, choroid plexus metrics, and microstructural assessment of normal-appearing white matter (NAWM).

METHODS

- **Subjects.** 70 pediatric-onset MS patients and 23 age- and sex-matched healthy controls (HC).
- **Clinical assessment (baseline and follow-up).** (A) Expanded Disability Status Scale (EDSS) score; (B) definition of MS clinical phenotypes (relapsing-remitting or secondary progressive); (C) recording of relapses; (D) ongoing disease-modifying treatment (DMT): (moderate-efficacy [ME-DMT]: interferon-beta, glatiramer acetate, teriflunomide and dimethyl fumarate); high-efficacy [HE-DMT]: cyclophosphamide, mitoxantrone, cladribine, natalizumab, fingolimod, alemtuzumab, ocrelizumab).
- **Clinical assessment (follow-up).**
  - **6-month confirmed disability worsening (6m-CDW)**: 1.5-point increase (if baseline EDSS score=0), 1.0-point increase (if baseline EDSS score<5.5), or 0.5-point increase (if baseline EDSS score≥5.5) and confirmed 6 months apart.
- **MRI acquisition and analysis.**
  - **Brain 3T MRI**: (A) dual-echo turbo spin echo: brain T2-hyperintense WM lesion volume (total, periventricular, juxtacortical, infratentorial, deep WM) *[Jim 8.0, Xinapse Systems and in-house implemented method]*; (B) three dimensional (3D) T1-weighted: normalized brain, thalamic, cortical and lateral ventricle volumes *[FSL-SIENAx2 software]*; normalized choroid plexus volume *[Jim 8.0, Xinapse Systems]*; 3D double inversion recovery (DIR): cortical lesion number *[Jim 8, Xinapse Systems]*; diffusion-weighted imaging: normal-appearing WM (NAWM) fractional anisotropy (FA), mean (MD), axial (AD) and radial (RD) diffusivities *[FSL and and in-house implemented method]*.
  - **Spinal cord MRI**: the presence of spinal cord lesions was retrospectively evaluated close to the time of MRI acquisition by reviewing medical records.

RESULTS

Demographic, clinical and MRI variables in pediatric MS patients compared to HC.

Table 1 shows the main clinical and MRI characteristics of healthy controls and pediatric MS patients at baseline.

Variable		HC (n=23)	Pediatric MS (n=52)	p
Sex, No. Male (%) / Female (%)		13 (56) / 10 (44)	19 (37) / 33 (63)	0.132
Median age at baseline (IQR) [years]		14.1 (11.8;16.2)	15.1 (14.0;16.7)	0.155
Median age at disease onset (IQR) [years]		-	13.5 (11.4;15.0)	-
Median disease duration (IQR) [years]		-	1.4 (0.5;2.7)	-
Type of onset, No. (%) Monofocal: optic neuritis / hemispheric infratentorial / spinal Multifocal		-	42 (81): 4 (10) / 9 (21) / 20 (48) / 9 (21) 10 (19)	-
Median EDSS score at baseline (IQR)		-	1.5 (1.0;1.5)	-
Median number of previous relapses (IQR)		-	1 (1;2)	-
Median follow-up duration (IQR) [years]		-	12.3 (10.1;14.3)	-
Median EDSS score at last FU (IQR)		-	1.0 (0.0;2.0)	-
No. of patients with EDSS worsening at last FU (%)		-	18 (35)	-
No. of patients with 6m-CDW during FU (%)			11 (21)	
No. of patients with >1 clinical relapse during FU (%)		-	36 (69)	-
Estimated ARR during FU (95% CI)		-	0.13 (0.10;0.17)	-
DMTs at baseline (%): ME-DMT/ HE-DMT		-	43 (83) / 9 (17)	-
No. of switchers to HE-DMT (%)		-	25/43 (58)	-
Median brain T2-hyperintense WM lesion volume (IQR) [mL]*		0.0 (0.0;0.1)	3.2 (1.6;6.6)	<0.001
Median number of T2-hyperintense WM lesions (IQR)	Periventricular	-	9 (5;15)	-
	Juxtacortical	-	13 (6;34)	-
	Infratentorial	-	2 (1;6)	-
	Deep WM	-	5 (2;8)	-
Median number of cortical lesions (IQR)		-	0 (0;1)	-
No. of patients with >1 spinal cord lesion (%)		-	29 (56)	-
EM	NBV (SE) [mL]	1717 (7)	1687 (8)	0.004
	NCV (SE) [mL]	731 (7)	706 (5)	0.008
	Normalized thalamic volume (SE) [mL]	23.0 (0.2)	22.2 (0.2)	0.023
	Normalized choroid plexus volume (SE) [mL]	2.14 (0.09)	2.74 (0.09)	<0.001
	Normalized lateral ventricle volume (SE) [mL]	14.7 (1.3)	21.9 (1.7)	0.001
	NAWM FA# (SE)	0.336 (0.003)	0.323 (0.002)	<0.001
	NAWM MD# (SE)	0.811 (0.003)	0.820 (0.003)	0.026
	NAWM AD# (SE)	1.118 (0.003)	1.116 (0.003)	0.638
	NAWM RD# (SE)	0.657 (0.004)	0.671 (0.004)	0.009

Table 1.

Comparisons performed by Fisher's exact test (sex) and Mann-Whitney (age) tests. Age- and sex-adjusted linear models were performed for MRI features. ARR was estimated with a negative binomial regression. *T2-hyperintense white matter lesion volume was log transformed. #MD, AD and RD are expressed in units of mm²/s × 10⁻³. FA is a dimensionless index.

Abbreviations: AD=axial diffusivity; ARR=annualized relapse rate; 6m-CDW=6-month confirmed disability worsening; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; FA=fractional anisotropy; HC=healthy controls; HE=high efficacy; IQR=interquartile range; MD=mean diffusivity; ME=moderate efficacy; mL=milliliter; n=number; NA=normal appearing; NBV=normalized brain volume; NCV=normalized cortical volume; RD=radial diffusivity; SE=standard error; WM=white matter.

Longitudinal findings in in pediatric MS patients.

- The **median** (interquartile range [IQR]) **follow-up duration** was **12.3** (10.1;14.3) **years**.
- **Twenty-six (50%)** of patients had the **first clinical relapse** within the **first 4.7** (95% confidence interval [CI]=2.6;7.0) **years from baseline** (**Figure 1**).
- The estimated **annualized relapse rate** was **0.13** (95% CI=0.10;0.17).
- Twenty-five (58%) out of the 43 patients treated with ME-DMTs switched to a HE-DMTs for efficacy.

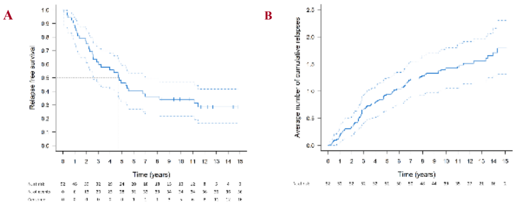

Figure 1. (A) Kaplan-Meier curves showing the probability estimates of surviving relapses. (B) Average cumulative number of relapses over the follow-up. Dotted lines are 95% pointwise confidence intervals.

- Over the follow-up, **11 (21%)** out of 52 patients had a **6m-CDW event** (**Figure 2**).
- No patient converted to secondary progressive MS.
- At last follow-up, **no significant overall EDSS changes** were observed (median EDSS at baseline [IQR]=1.5 [1.0;1.5], at follow-up=1.0 [0.0;2.5], p=0.785).
- At last follow-up, **18 (35%)** out of 52 patients had **EDSS worsening**.
- At **5** and **10 years** of follow-up, **88%** (95% CI=76;95) and **84%** (95% CI=71;92) of pediatric MS patients remained **free from 6m-CDW**.

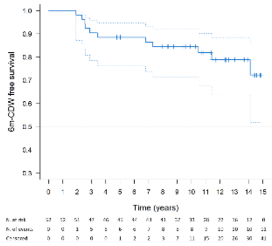

Figure 2. Kaplan-Meier curves showing the probability estimates of 6m-CDW events. Dotted lines are 95% pointwise confidence intervals.

Predictors of shorter time to first relapse. **Table 2** shows univariable and multivariable Cox regression models using time to first clinical relapse as outcome in pediatric MS.

		Time to first clinical relapse: Univariable analysis HR (95% CI)	p	Multivariable analysis HR (95% CI)	p
Sex (male vs female)		0.81 (0.41;1.61)	0.549		
Age at baseline		0.92 (0.81;1.04)	0.174		
Age at disease onset		0.94 (0.85;1.05)	0.271		
Disease duration		1.0 (0.85; 1.18)	0.962		
EDSS score at baseline		1.63 (1.02;2.58)	0.039		
No. of previous relapses		1.18 (0.82;1.68)	0.369		
Previous treatment (yes vs no)		0.61 (0.13;2.89)	0.530		
Treatment status (HE-DMT vs ME-DMT)		0.60 (0.25;1.46)	0.259	0.20 (0.06;0.68)	0.010
Brain T2-hyperintense WM LV*		1.05 (1.01;1.10)	0.019		
No. of T2-hyperintense WM lesions	Periventricular	1.06 (1.01;1.11)	0.027		
	Juxtacortical	1.01 (1.00;1.02)	0.149		
	Infratentorial	1.10 (1.02;1.18)	0.009	1.09 (1.02;1.18)	0.016
	Deep WM	1.00 (0.96;1.06)	0.845		
No. of cortical lesions		1.27 (0.97;1.65)	0.077		
Cord lesions (yes vs no)		2.13 (1.06;4.30)	0.035	2.45 (1.18;5.10)	0.017
NBV°		0.94 (0.88;1.00)	0.047		
NCV°		0.97 (0.89;1.05)	0.448		
Thalamic volume		0.72 (0.58;0.89)	0.003	0.77 (0.60;0.99)	0.046
Normalized choroid plexus volume		1.67 (1.04;2.69)	0.034	1.58 (0.93;2.68)	0.088
NAWM FA#		0.76 (0.59;0.97)	0.031		
NAWM MD#		1.13 (0.98;1.30)	0.091		
NAWM AD#		1.05 (0.92;1.20)	0.482		
NAWM RD#		1.14 (1.01;1.29)	0.041		

Table 2.

HRs, related 95% CI and p-values from extended Cox regression models are reported. Treatment status, modelled as a time-varying covariate, was included in all analyses. *HR is computed for a 10% increase in T2-hyperintense white matter lesion volume. °HR is computed for a 10-unit increase in the predictor. #HR is computed for a 0.01-unit increase in the predictor. MD, AD and RD are expressed in units of mm²/s × 10⁻³. FA is a dimensionless index.

Abbreviations: AD=axial diffusivity; CI=confidence interval; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; FA=fractional anisotropy; IQR=interquartile range; MD=mean diffusivity; ml=milliliter; NA=normal appearing; NBV=normalized brain volume; NCV=normalized cortical volume; RD=radial diffusivity; WM=white matter.

Predictors of recurrent relapses. **Table 3** shows univariable and multivariable Andersen-Gill models for recurrent relapses risk in pediatric MS.

		Recurrent relapses: Univariable analysis HR (95% CI)	p	Multivariable analysis HR (95% CI)	p
Sex (male vs female)		0.90 (0.52;1.56)	0.712		
Age at baseline		0.93 (0.82;1.05)	0.256		
Age at disease onset		0.95 (0.87;1.04)	0.283		
Disease duration		1.01 (0.90;1.14)	0.864		
EDSS score at baseline		1.67 (1.32;2.11)	<0.001	1.29 (0.96;1.73)	0.086
No. of previous relapses		1.04 (0.74;1.47)	0.813		
Previous treatment (yes vs no)		1.30 (0.35;4.86)	0.693		
Treatment status (HE-DMT vs ME-DMT)		0.43 (0.21;0.91)	0.027	0.21 (0.11;0.41)	<0.001
Brain T2-hyperintense WM LV*		1.06 (1.02;1.09)	<0.001	1.04 (1.01;1.06)	0.013
No. of T2-hyperintense WM lesions	Periventricular	1.08 (1.03;1.12)	<0.001		
	Juxtacortical	1.02 (1.01;1.02)	<0.001		
	Infratentorial	1.08 (1.03;1.13)	0.002		
	Deep WM	1.02 (0.98;1.06)	0.300		
No. of cortical lesions		1.17 (1.00;1.36)	0.051		
Cord lesions (yes vs no)		1.85 (1.00;3.40)	0.049	1.52 (0.95;2.44)	0.081
NBV°		0.96 (0.92;1.01)	0.149		
NCV°		0.98 (0.90;1.06)	0.640		
Thalamic volume		0.83 (0.70;0.98)	0.030		
Normalized choroid plexus volume		1.46 (1.06;2.02)	0.019	1.35 (1.00;1.83)	0.054
NAWM FA#		0.80 (0.67;0.95)	0.012		
NAWM MD#		1.14 (1.02;1.29)	0.026		
NAWM AD#		1.07 (0.96;1.20)	0.213		
NAWM RD#		1.14 (1.03;1.26)	0.013		

Table 3.

HRs, related 95% CI and p-values from Andersen-Gill models are reported. Treatment status, modelled as a time-varying covariate, was included in all analyses. *HR is computed for a 10% increase in T2-hyperintense white matter lesion volume. °HR is computed for a 10-unit increase in the predictor. #HR is computed a 0.01-unit increase in the predictor. MD, AD and RD are expressed in units of mm2/s × 10-3. FA is a dimensionless index.

Abbreviations: AD=axial diffusivity; CI=confidence interval; DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; FA=fractional anisotropy; IQR=interquartile range; MD=mean diffusivity; ml=milliliter; NA=normal appearing; NBV=normalized brain volume; NCV=normalized cortical volume; RD=radial diffusivity; WM=white matter.

Predictors of time to 6m-CDW event. **Younger age** (HR=0.82, 95% CI=0.68;0.98) and **lower NAWM FA** (HR=0.67, 95% CI=0.51;0.88) were risk factors independently shortening time to a 6m-CDW event.

Predictors of EDSS worsening at follow-up. A **lower NAWM FA** predicted a greater EDSS worsening at the last follow-up (β=-0.26, 95% CI=-0.50;-0.03).

CONCLUSIONS

- **Higher infratentorial lesion count, the presence of spinal cord lesions, lower thalamic volume, and greater CP volume at baseline predicted shorter time to first relapse**
- **Higher EDSS score, higher brain T2-hyperintense WM LV, the presence of spinal cord lesions, and higher CP volume were associated with increased risk of recurrent relapses**
- **HE-DMT significantly reduced the risk of relapses and delayed the time to first relapse, highlighting the benefit of early aggressive therapy**
- **Younger age and lower NAWM FA predicted earlier 6-m CDW, with lower NAWM FA being also associated with greater EDSS worsening at long-term follow-up**
- **Our findings underscore the prognostic value of integrating advanced MRI metrics (e.g., NAWM microstructure, thalamic atrophy, CP volume) with clinical measures in pediatric MS**
- **Early identification of high-risk patients can inform tailored treatment strategies, potentially improving long-term clinical outcomes**

REFERENCES

[1] Margoni et al., Expert Rev Neurother. 2022.

DISCLOSURES

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