ANTICIPATION OF LONG-TERM DISABILITY PROGRESSION IN PPMS USING MRI: A 15-YEAR LONGITUDINAL STUDY

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INTRODUCTION AND AIMS

Now that treatment strategies for primary progressive multiple sclerosis (PPMS) start to appear for a clinical use,[1,2] there is an increasing necessity to identify those PPMS patients who will have a more severe clinical outcome in the long-term, to optimize treatment decisions and patient management.

An observational cohort study of 54 PPMS patients is ongoing at our Unit, with clinical and brain and spinal cord MRI evaluations at baseline and after 15 months (FU1).[3] A clinical re-evaluation was done after 5 years (FU2).[4] A lower level of disability and a more severe baseline gray matter (GM) damage identified PPMS patients with an increased risk of disease progression at FU2.

Here, we report the results of the 15-year (FU3) clinical follow-up of these patients.

Aims

To investigate the added value of conventional and DT MRI measures of brain and cervical cord damage in predicting the long-term clinical evolution of PPMS in comparison to simple clinical assessment.

METHODS

Study population: **54 PPMS** patients (F/M = 27/27; mean age at study entry=51.3 years, range=25-68 years; median disease duration at study entry=10.0 years, range=2-26) were enrolled.

Clinical and MRI protocol: **1.5 T brain and cord conventional and DT MRI** scans and clinical evaluation with EDSS assessment were performed at baseline and after a median follow-up of **15.0 months (FU1, n=54)**. The following sequences were acquired: a) axial dual-echo turbo spin echo (TSE), b) axial T1-weighted conventional SE, c) axial echo-planar pulsed-gradient spin-echo (PGSE), d) cervical cord 3D T1-weighted MP-RAGE.

Clinical re-assessment after a median **FU of 56 months** (**FU2**, n=52) and after a median FU of **15.1 years** (**FU3**, n=49) was then repeated.

Statistical analysis: The following analysis were performed:

- **Univariate analysis of prediction**, after adjusting for FU duration, to detect MRI/clinical variables associated with a significant worsening of Expanded Disability Status Scale (EDSS) at FU3.
- **Linear regression models** to screen the clinical ad MRI variables as independent predictors of EDSS change at FU3 (p value for inclusion <0.10) five models were implemented. The discriminating ability of the five models was tested with the **leave-one-out cross-validation method**.

RESULTS

Study population:

Of the original cohort of 54 PPMS, 5 patients did not undertake the 15-year visit (unwilling to attend or unreachable), 2 patients had died between FU2 and FU3 for reasons due to MS (pneumonia) and received an EDSS of 10.

Median EDSS scores were 6.0 (IQR=4.5-6.5) at baseline and 7.5 (IQR=7.0-8.0) at FU3 (p<0.001).

At baseline, 36 patients were not receiving any DMT, 9 received azathioprine, 4 mitoxantrone and 5 methotrexate. At FU3 44 patients were not receiving any DMT (2 patients had stopped azathioprine, 2 mitoxantrone and 4 methotrexate**).**

At 15-year follow-up, 44 (89.8%) patients worsened and 5 (10.2%) remained stable.

MRI analysis: Table 1 summarizes the main brain and spinal cord MRI findings at baseline and at 15-month follow-up (FU1) from PPMS patients.

Table 1. Brain and spinal cord MRI findings at baseline and 15-month follow-up (FU1) from PPMS patients.

	Baseline Mean (SD)	FU1 Mean (SD)	p-value*
T2 LV (ml)	16.8 (9.4)	17.3 (16.3)	**0.004**
T1 LV (ml)	6.6 (6.3)	7.3 (7.2)	**0.003**
New T2 lesions (range)	-	1.6 (0-9)	-
New T1 lesions (range)	-	0.8 (0-7)	-
NBV (ml)	1373 (90)	-	-
PBVC (%)	-	-1.14 (1.13)	-
Cervical cord CSA (mm^2)	64.4 (9.4)	61.7 (10.6)	**0.02**
Average lesion MD ($mm^2/s \times 10^{-3}$)	1.09 (0.11)	1.10 (0.11)	0.15
Average lesion FA	0.26 (0.03)	0.26 (0.03)	0.57
Average NAWM MD ($mm^2/s \times 10^{-3}$)	0.87 (0.05)	0.86 (0.05)	0.09
Average NAWM FA	0.26 (0.02)	0.26 (0.03)	0.45
Average GM MD ($mm^2/s \times 10^{-3}$)	1.09 (0.08)	1.09 (0.08)	0.45

Abbreviations: LV=lesion volume; NBV=normalized brain volume; PBVC=percentage brain volume change; CSA=cross-sectional area; FA=fractional anisotropy; MD=mean diffusivity; NAWM=normal-appearing white matter; GM=gray matter.

*Non parametric t test.

Univariate analysis of prediction: Table 2 reports the results of the univariate analysis of correlations between clinical/MRI variables and delta-EDSS at FU3.

Table 2. Univariate correlations between clinical/MRI quantities (independent variables) and EDSS change at 15-year follow-up (FU3) (dependent variable).

Independent variable	EDSS change at FU3 Pearson correlation	p value
Age	-0.28	0.05
Disease duration (log)	**-0.33**	**0.02**
Baseline EDSS	**-0.61**	**<0.001**
Delta EDSS at FU1	**0.51**	**0.002**
Delta EDSS at FU2	**0.71**	**<0.001**
Baseline T2 LV (log)	0.24	0.09
T2 LV percentage change	0.10	0.49
Baseline T1 LV (log)	0.17	0.26
T1 LV percentage change	0.11	0.46
Number of new T2 lesions	**0.41**	**0.004**
Number of new T1 lesions	**0.35**	**0.015**
NBV	-0.21	0.16
PBVC	-0.21	0.14
Cervical cord CSA	0.06	0.67
Cervical cord CSA percentage change	**-0.35**	**0.025**
Average lesion MD	0.04	0.78
Average lesion MD percentage change	-0.23	0.12
Average lesion FA	0.10	0.47
Average lesion FA percentage change	0.04	0.8
Average NAWM MD	**0.33**	**0.03**
Average NAWM MD percentage change	0.10	0.52
Average NAWM FA	**-0.32**	**0.03**
Average NAWM FA percentage change	-0.11	0.47
Average GM MD	**0.30**	**0.04**
Average GM MD percentage change	-0.14	0.36

Linear regression models: The results of the five linear regression models implemented are summarized in Table 3. **Integrating clinical and MRI variables at FU1 predicted EDSS changes at FU3 better than clinical factors at FU2 (R^2=61% vs R^2=57%). The use of such a model allowed predicting long-term EDSS change with a precision within 1 point in 38 of 49 patients (77.6%).**

Table 3. Results of the linear regression models used to screen the clinical ad MRI variables as independent predictors of EDSS change at 15-year follow-up (FU3).

Time	Factors			
	Clinical		Clinical and MRI	
	Variables (coefficient, p)	R^2	Variables (coefficient, p)	R^2
Baseline	Age (-0.03-0.09)	0.42	Baseline GM MD (4.59, 0.023)	0.45
	Baseline EDSS (-0.63, <0.001)		Baseline EDSS (-0.68 , <0.001)	
FU1	Baseline EDSS (-0.49, 0.001)	0.47	**7.3 (7.2) Baseline EDSS (-0.54, <0.001)**	**0.61**
	FU1 EDSS change (0.51, 0.047)		**FU1 EDSS change (0.39, 0.09)**	
	Age (-0.03, 0.08)		**FU1 new T1-hypointense lesions (0.28, 0.003)**	
	-		**PBVC (-0.24, 0.05)**	
			Baseline GM MD (3.86, 0.03)	
FU2	Baseline EDSS (-0.35, 0.01)	0.57	-	
	FU2 EDSS change (0.67, <0.001)			

CONCLUSIONS

The integration of clinical and imaging measures obtained at baseline and after a relatively short follow-up (15 months) resulted in an earlier prognostication of long-term clinical worsening in PPMS than only clinical evaluation.

The integrated model allowed to identify around 78% of patients with 15-year clinical deterioration 4 years before than with simple clinical evaluation.

DISCLOSURES

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