The evolving contribution of MRI measures to the prediction of clinical outcomes in MS

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BACKGROUND

Initially ~85% of people with multiple sclerosis (MS) follow a relapsing-remitting trajectory,[1] of whom ~60% will transition to secondary progressive (SPMS) within ~20 years[2-3] during which most disability accrues.[4-5] There is growing evidence that earlier commencement of disease modifying therapies (DMTs) may reduce the risk of, or at least delay, SPMS onset.[6-7] However, this needs to be carefully balanced against the risk of serious harm that accompanies DMT use.

Magnetic resonance imaging (MRI) prognostic markers associated with favourable outcomes include lower white matter (WM) lesion counts[8] and volumes[9] the absence of lesions in the posterior fossa and spinal cord[10], and slower brain atrophy.[11] With increasing disease duration (and age), WM lesion formation diminishes and brain atrophy increases, and this shifting balance reflects the transition from RRMS to SPMS.[12] However, it is not known whether these two elements of MS pathology remain equally, and consistently, relevant to ultimate clinical outcomes in MS or differ in their long-term relevance over the disease course.

Predicting the disease trajectory of MS, and those at risk of SPMS, is made more challenging as most individuals only develop SPMS ~15 years or more from first symptom onset, and so we need follow-up data that is sufficiently long-term that the majority of those who are likely to develop SPMS have done so.

AIMS AND OBJECTIVES

Using the data from our recently completed 30-year longitudinal clinical and MRI follow-up study, we sought to determine:

(1) Whether WM lesions and brain atrophy measures were equally relevant to the development of SPMS throughout the MS disease course;

(2) If not, how long after disease onset did the balance between them shift; and

(3) Whether optimised prognostic models should therefore include different features dependent on disease duration.

METHODS

A cohort of 132 participants were prospectively recruited between 1984-87 after first presentation with a clinically isolated syndrome. Clinical and MRI assessments performed at 5 (n=92), 10 (n=66), 14 (n=55), 20 (n=75) and 30 (n=63) years were used in our analysis. By 30 years, 27 (26.2%) remained CIS, 34 (33.0%) had RRMS, 26 (25.2%) had SPMS, and 16 (15.5%) had died due to MS.

We previously described image acquisition and analysis protocols[10,11]; baseline, 1- and 5-year 0.5T MRI images were obtained on film (and subsequently digitised), while remaining timepoints were obtained digitally (10, 14, 20-years at 1.5T, 30 years at 3T). Lesions were marked and their location assessed by consensus.

Linear atrophy measures were used as volumetric methods were not suitable for 0, 1-, 5- or 10-year scans. Third ventricular width (TVW) was measured by drawing a midpoint line running parallel to the long axis of the ventricle on axial PD/T2 (1, 5, 10, 14, 20 year) or T2 (30 year) MRI scans. Medullary width (MEDW) was measured on midsagittal imaging normal to the craniocaudal cord orientation. Sagittal scout MRI were used at baseline, 1 and 5 years; axial sagittal reconstructed MRI at 10 years; volumetric T1 and cervical spine MRI at 14 and 20 years; and volumetric T1 brain and spine at 30 years.

Binary logistic regression models were built exploring predictive effects of lesion accrual and linear atrophy measures at each timepoint on SPMS development by 30 years. All models were adjusted for age and gender, and built considering either single timepoint data, or longitudinally considering timepoint data adjusted for baseline measures.

RESULTS

In cross-sectional (single timepoint) models indicated that whole brain lesion counts were most contributory to an eventual SPMS diagnosis in the first 5 years from first symptom onset, after which their influence appeared to progressively diminish (Table 1).

Conversely, single timepoint models considering TVW linear atrophy measures increased contributory effects over time, reaching clinical significance from 10 years and peaked in contributory effect at 14 years.

Single timepoint models considering medullary thinning (1/MEDW as an inverse function of preserved medullary width) also increased in contributory effects over time towards SPMS development by 30 years (significant at the 5, 14, and 20-year timepoints).

When adjusted for baseline measures, lesion count models also diminished in contributory effect over time, while linear atrophy models increased.

Table 1 – Total lesion counts, lesion counts separated by location and linear atrophy models predicting 30-year SPMS outcomes

	Timepoint	0 year	1 year	5 year	10 year	14 year	20 year
Total Lesion Count	n	103	86	81	62	52	63
	OR (95% CI)	1.04 (1.01-1.07)	1.07 (1.03-1.11)	1.06 (1.03-1.09)	1.04 (1.02-1.07)	1.03 (1.01-1.05)	1.02 (1.01-1.04)
	p=	0.004*	0.001*	<0.001*	0.001*	0.001*	0.001*
	pseudoR²	0.177	0.354	0.485	0.489	0.482	0.305
Periventricular Lesions	n	97	82	81	62	52	71
	OR (95% CI)	1.04 (1.01-1.07)	1.07 (1.03-1.11)	1.06 (1.03-1.09)	1.04 (1.02-1.07)	1.03 (1.01-1.05)	1.02 (1.01-1.04)
	p=	<0.004*	0.001*	<0.001*	0.001*	0.001*	0.001*
	pseudoR²	0.177	0.354	0.485	0.489	0.482	0.305
Deep White Matter Lesions	n	97	82	81	62	52	71
	OR (95% CI)	1.06 (1.02-1.10)	1.10 (1.04-1.17)	1.07 (1.03-1.11)	1.06 (1.02-1.10)	1.05 (1.02-1.08)	1.03 (1.01-1.05)
	p=	0.006*	0.001*	<0.001*	0.001*	0.001*	0.002*
	pseudoR²	0.17	0.328	0.441	0.45	0.429	0.248
Juxtacortical Lesions	n	97	82	81	61	50	69
	OR (95% CI)	1.54 (1.13-2.11)	1.49 (1.11-2.01)	1.24 (1.06-1.46)	1.09 (1.01-1.17)	1.10 (1.02-1.18)	1.08 (1.01-1.15)
	p=	0.007*	0.008*	0.007*	0.025*	0.016*	0.021*
	pseudoR²	0.157	0.222	0.261	0.218	0.269	0.147
Infratentorial Lesions	n	96	82	78	55	47	64
	OR (95% CI)	3.03 (1.48-6.20)	5.10 (2.01-12.93)	2.30 (1.39-3.81)	1.96 (1.18-3.26)	1.90 (1.25-2.89)	1.45 (1.12-1.89)
	p=	0.002*	<0.001*	0.001*	0.01*	0.003*	0.005*
	pseudoR²	0.259	0.445	0.417	0.474	0.505	0.299
TVW	n	87	76	70	61	47	70
	OR (95% CI)	1.22 (0.77-1.93)	1.55 (0.90-2.65)	1.58 (0.96-2.59)	**1.93 (1.24-3.00)**	**2.49 (1.42-4.37)**	**1.62 (1.21-2.17)**
	p=	0.409	0.112	0.072	**0.004***	**0.001***	**0.001***
	pseudoR²	0.032	0.107	0.126	**0.321**	**0.508**	**0.263**
1 / MEDW	n	60	52	**70**	53	**47**	**64**
	OR (95% CI)	1.05 (0.56-1.95)	1.13 (0.62-2.02)	**3.31 (1.56-7.04)**	1.39 (0.65-2.97)	**2.60 (1.13-6.02)**	**7.19 (1.87-27.78)**
	p=	0.880	0.696	**0.002***	0.398	**0.025***	**0.004***
	pseudoR²	0.031	0.043	**0.301**	0.108	**0.224**	**0.26**

CONCLUSIONS

Lesion accrual appears to have the greatest clinical relevance to the SPMS development in the first 5 years following symptom onset, whilst linear brain atrophy measures appear to increase in relevance over time (reaching statistical significance from 10 years onwards). Our findings corroborate existing knowledge that early lesion formation plays a significant role in determining disease trajectory, while neurodegenerative mechanisms appear to become more relevant closer to SPMS onset. They also suggest that the same prognostic model may not be optimal throughout the clinical course of MS.

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