USE OF MULTIPLE BIOMARKERS TO IMPROVE THE PREDICTION OF MULTIPLE SCLEROSIS IN PATIENTS WITH CLINICALLY ISOLATED SYNDROMES

Martinelli V, Dalla Costa G, Messina MJ, Di Maggio G, Moiola L, Rodegher M, Colombo B, Leocani L, Furlan R, Comi G.

San Raffaele Hospital and Institute of Experimental Neurology, Milan, Italy

BACKGROUND & AIMS

- The incidence of multiple sclerosis (MS) continues to increase worldwide particularly in developed countries;
- as the current paradigm in multiple sclerosis is that axonal damage occurs early in the course of the disease, an early diagnosis represents the main purpose of the evolving diagnostic criteria and of clinicians in everyday clinical practice.
- MRI has had a major impact on the early and more precise diagnosis of the disease, but several other clinical and paraclinical markers have been reported to be associated with an increased risks of MS independently of MRI;
- the aim of the current study is to investigate whether the incorporation of different multiple clinical and paraclinal parameters in a model with the established MRI criteria improved the prediction of early MS in real-world clinical practice.

MATERIALS & METHODS

Study population:

- patients admitted to our hospital between January 1, 2000 and December 31, 2013 for a first time monophasic neurologic episode not attributable to other diseases;
- age 18-55 years;
- follow-up for at least two years with documentation regarding the development of a second clinical attack (CDMS)

Baseline data

- Demographic and clinical data (age at onset, gender, type of onset, steroid therapy at onset, duration of the symptoms and type of recovery) was retrieved from our inpatient database and medical charts;
- IgG oligoclonal bands (OBs) in serum and CSF had been examined by agarose isoelectric focusing combined with immunoblotting and avidin-biotin amplified double antibody peroxidase staining at the time of hospitalization;
- multimodal visual, auditory, somatosensory and motor evoked potentials to the four limbs were obtained and abnormalities quantified according to a conventional 4-point graded ordinal score;
- MRI scans were retrieved from our hospital archive and assessed by a neurologist with MRI experience. Number of baseline T1, T2 and gadolinium enhancing lesions were scored.

Follow-up data

- Follow-up information was retrieved retrospectively from medical records obtained from the computerized local MS patient database (iMed) or was received from the local investigator at the MS centre in the event that the patient had moved;
- the duration of follow-up was calculated as the interval between onset of the first neurological event and that of the last neurological visit;
- a diagnosis of CDMS was made when new symptoms or signs occurred according to Poser's MS criteria and only when other diagnoses had been excluded.

Statistical analysis

- Univariate and multivariate Cox models were used to assess the associations of patient demographic, clinical, MEPs and MRI characteristics with clinical outcome;
- the increased discriminative value of the biomarkers was assessed using the net reclassification improvement and the integrated discrimination improvement as described by Pencina et al. (Pencina et al 2008).

RESULTS

- 243 CIS patients who met inclusion criteria and with complete data were identified. Their median follow-up was 7.2 years (range, 5.8 to 8.3). Patients' characteristics are listed in table 1;
- during follow-up, 127 patients (52.2 %) developed CDMS: 78 (32.1 %) within the second year, and 108 (56.3 %) out of the 192 patients with a 5-year follow-up;
- patients who subsequently developed CDMS were younger, more likely to be females, more likely to report multifocal symptoms had CSF OBs, an higher overall score at multimodal evoked potentials and an higher number of T1 and T2 lesions at brain MRI than patients who did not converted to CDMS;

Table 1. Patients' Characteristics

Characteristic	Patients (n = 243)	Characteristic	Patients (n = 243)
Age at onset (years)	32.0 ± 8.8	CSF findings	
Females — %	165 (67.9)	CSF cells	5.4 ± 7.3
Multifocal type of onset — %	44 (18.1)	CSF proteins	35.4 ± 12.5
Partial recovery after CIS — %	123 (50.6)	Presence of CSF oligoclonal bands — %	169 (69.5)
Type of CIS — % †		Link Index	0.8 ± 0.4
Optic neuritis syndrome	59 (29.6)	Tourtellotte Index	3.5 ± 9.3
Brainstem syndrome	46 (23.1)	Reiber Index	1.1 ± 2.9
Spinal cord syndrome	70 (35.2)	Blood-brain barrier damage Index	0.5 ± 0.2
Other	24 (12.1)	Neurophysiological findings	
MRI findings		Abnormal visual evoked potentials — %	119 (49.0)
2010 DIS criteria fulfilled — %	166 (68.3)	Abnormal auditory evoked potentials — %	57 (23.5)
2010 DIT criteria fulfilled — % ‡	63 (25.9)	Abnormal somatosensory evoked potentials — %	132 (54.3)
T2 lesions	16.9 ± 10.5	Abnormal motor evoked potentials — %	114 (46.9)
T1 lesions	4.6 ± 5.6	Overall evoked potential score	3.9 ± 4.1
Gd-enhancing lesions	0.7 ± 1.3		

* Plus–minus values are means ± SD.
definite multiple sclerosis, DIS dissemination in space, DIT dissemination in time
† Defined in patients with a monofocal type of onset.
‡ Defined as the simultaneous presence of asymptomatic gd-enhancing lesions and non enhancing lesions

RESULTS (cont.)

Table 2. Discrimination and Calibration Estimates for Predicting Clinically Definite Multiple Sclerosis in Patients with Clinically Isolated Syndromes

	Goodness of fit, LR	P value	C Statistic (95% CI) for CDMS Risk at 2 Years	C Statistic (95% CI) for CDMS Risk at 5 Years
Risk Factors and Biomarkers				
Established MRI criteria	42.72	Ref	0.698 (0.628-0.767)	0.667 (0.607-0.728)
Established MRI criteria plus age	47.25	0.033	0.720 (0.653-0.787)	0.679 (0.618-0.740)
Established MRI criteria plus type of onset	45.42	0.100	0.703 (0.635-0.711)	0.673 (0.613-0.732)
Established MRI criteria plus type of recovery	46.21	0.062	0.708 (0.640-0.776)	0.676 (0.607-0.728)
Established MRI criteria plus T2 lesions	43.39	0.415	0.702 (0.632-0.772)	0.673 (0.612-0.735)
Established MRI criteria plus T1 lesions	46.75	0.045	0.712 (0.643-0.780)	0.673 (0.612-0.734)
Established MRI criteria plus Gd-enhancing lesions	45.07	0.125	0.708 (0.639 0.777)	0.677 (0.616-0.738)
Established MRI criteria plus CSF oligoclonal bands	57.45	< 0.001	0.715 (0.654-0.777)	0.685 (0.630-0.740)
Established MRI criteria plus Link Index	44.05	0.249	0.722 (0.654-0.791)	0.684 (0.623-0.745)
Established MRI criteria plus all significant biomarkers	63.01	< 0.001	0.740 (0.677-0.804)	0.695 (0.635-0.753)

Abbreviations: CI, confidence interval; LR, likelihood ratio; Gd, gadolinium; CSF, cerebrospinal fluid; CDMS, clinically definite multiple sclerosis.
[a] Values are likelihood ratio
[b] P values are for the comparison with the model with established risk factors.
[c] Values are C index (95% CI; a higher value indicates a better discrimination).

Table 3. Reclassification of Patients Who Developed Clinically Definite Multiple Sclerosis or Who Did Not Develop the Disease During Follow-up

Model with Established Criteria	No. of Patients			Reclassified		Net Correctly Reclassified, %
	Low Risk	Moderate Risk	High Risk	Increased Risk	Decreased Risk	
Predicted 2-Year CDMS Risk with Established Criteria and Biomarkers						
Individuals with events during follow-up (n=78)						
Predicted 2-y CDMS risk with established criteria						
Low Risk	19	4	0			
Moderate Risk	5	33	17	21	5	0.21
High Risk	0	0	0			
Individuals without events during follow-up (n=165)						
Predicted 2-y CDMS risk with established criteria						
Low Risk	108	2	0			
Moderate Risk	20	31	4	6	20	0.08
High Risk	0	0	0			
Net reclassification improvement						0.29
P value						< 0.001
Predicted 5-Year CDMS Risk with Established Criteria and Biomarkers						
Individuals with events during follow-up (n=108)						
Predicted 5-y CDMS risk with established criteria						
Low Risk	3	1	0			
Moderate Risk	8	34	28	29	17	0.11
High Risk	0	9	25			
Individuals without events during follow-up (n=84)						
Predicted 5-y CDMS risk with established criteria						
Low Risk	5	3	0			
Moderate Risk	23	28	10	13	29	0.19
High Risk	1	6	8			
Net reclassification improvement						0.30
P value						< 0.001

Abbreviations: CDMS, clinically definite multiple sclerosis
aThe reclassification of CDMS risk was evaluated by comparing predicted risk estimates based on multivariate models with established criteria and with established criteria an all biomarkers. t
cThe proportion correctly reclassified in those who experience an event during follow-up is the proportion of individuals reclassified to a higher risk minus the proportion reclassified to a lower risk; in those who do not experience an event during follow-up, the proportion of individuals reclassified to a lower risk minus the proportion reclassified to a higher risk. The net reclassification improvement is the sum of correctly reclassified individuals with and without events.

CONCLUSIONS

- About 1/3 of our patients had a second clinical attack during the first 2 years of follow-up. Our data on the conversion rate in CIS patients, observed in a real-world clinical cohort are lower than previous data reported at 2 year follow-up in the placebo arms of randomized controlled trials conducted on CIS patients, suggestive of MS (6). In fact, the patients in our cohort were not selected based on the presence of brain lesions typical of MS, and as such our results should be more representative of the situation in routine clinical practice;
- MRI DIS and DIT criteria are the best predictors of CDMS; age at onset, number of T1 lesions and presence of CSF oligoclonal bands significantly increased the accuracy of the model in identifying patients developing MS within 2 and 5 years.
- the use of multiple biomarkers led to a 29% net-reclassification improvement at 2 years ($p < 0.001$) and 30% at 5 years ($p < 0.001$);
- the simultaneous addition of several biomarkers improves the personalized risk stratification for MS in patients with clinically isolated syndromes beyond that of a model that is based only on MRI criteria.

DISCLOSURES

Vittorio Martinelli has received personal compensation for activities with Biogen Idec, Merck/Serono, Bayer,TEVA, Novartis and Sanofi Aventis as a speaker. Giancarlo Comi has received compensation for consulting services and/or speaking activities from Bayer, Serono Symposia International Foundation, Merck Serono, Teva Pharma, Sanofi-Aventis, Novartis and Biogen Idec. Gloria Dalla Costa, Giovanni Di Maggio, Bruno Colombo, Letizia Leocani, Roberto Furlan have disclosed no relevant financial relationship.