Clinical and paraclinical markers of disability progression after a first demyelinating event: a long term follow-up study

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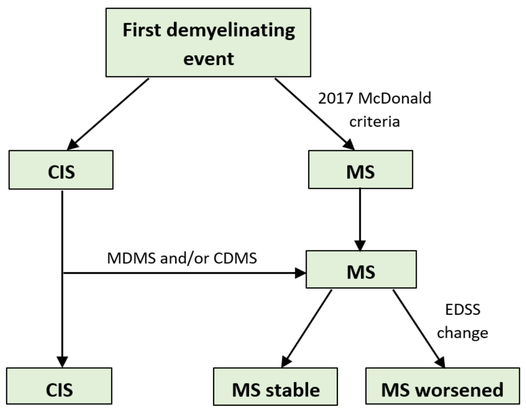
Introduction and aims

- The current paradigm in multiple sclerosis is that axonal damage occurs early in disease course, leading to accumulation of disability even in the initial years of disease, when progressive phase has not occurred yet. Since several specific drugs are able to arrest the inflammatory process, it is crucial to identify those patients who will experience such disability progression. The identification of early predictors of long term disability progression is of critical importance in everyday clinical practice, in order to initiate a personalized treatment as soon as possible.
- The aim of the current study was to explore the role of different prognostic markers of long term disability progression after a first demyelinating event, in order to find out the patients who would benefit of early treatment.

Methods

- Patients: a total of 255 patients admitted to San Raffaele hospital between 2000 and 2013 for a first demyelinating event and with a minimun follow-up of 2 years have been included in the study.
- Baseline data: during the first clinical evaluation, clinical and paraclinical characteristics have been reported, in particular those conventionally used in everyday clinical practice, such as personal and demographic data, clinical course, brain and spinal cord MRI features, CSF data and multimodal evoked potentials score (from 0 to 12).
- Serum 25-OH-vitamin D levels and smoke habits were also collected, to explore their role as possible risk factors of subsequent mild to moderate disability progression.
- Disability progression: patients diagnosed with MS were followed for a minimun follow-up of 2 years (median follow-up 11.5 years). We considered as worsened those patients who showed an increase of EDSS consistent with accumulation of disability, confirmed and sustained over time. The EDSS has been adjusted for DMT and lenght of follow-up.



- Statistics: univariate and multivariate logistic regression models were performed to define the impact of baseline characteristics on disability progression over time. The results have been reported as odds ratios (ORs). Only $p \leq 0.05$ was considered as statistically significant.

Results

Characteristic	Univariate OR (95% CIs)	p value	Multivariate OR (95% CIs)	p value
Presence of spinal T2 lesions	2.47 (1.40-4.36)	< 0.01	3.07 (1.54-6.26)	< 0.01
CSF oligoclonal bands	1.88 (0.98-4.11)	0.05	2.48 (1.02-6.51)	0.05
Female sex	1.91 (1.01-3.72)	0.05	2.46 (1.16-5.51)	0.02
Multimodal EPs score	1.22 (1.08-1.40)	< 0.01	1.34 (1.14-1.60)	< 0.01
Older age at onset	1.06 (1.03-1.10)	< 0.01	1.06 (1.01-1.10)	0.02
Multifocal clinical onset	1.30 (0.68-2.44)	0.42	-	-
Partial recovery	1.80 (1.01-3.23)	0.04	-	-
Brain T2 lesions				
2-9	0.79 (0.51-1.39)	0.65	-	-
> 9	1.92 (0.71-5.47)	0.21	-	-
Gd-enhancing lesions	1.27 (0.73-2.22)	0.39	-	-

Table 1. Baseline characteristics of patients presenting a first demyelinating event. Their role as early markers of future disability progression has been calculated as odds ratio (OR) by performing both univariate and multivariate analysis with the use of logistic regression models.

Results

After the first demyelinating event, 160 patients (63%) had relapses during follow-up while 214 (84%) developed new subclinical lesions. Multivariate logistic regression showed that the early spinal cord involvement, especially when associated with partial recovery from first clinical episode, was the most important prognostic factor for long term disability occurrence.

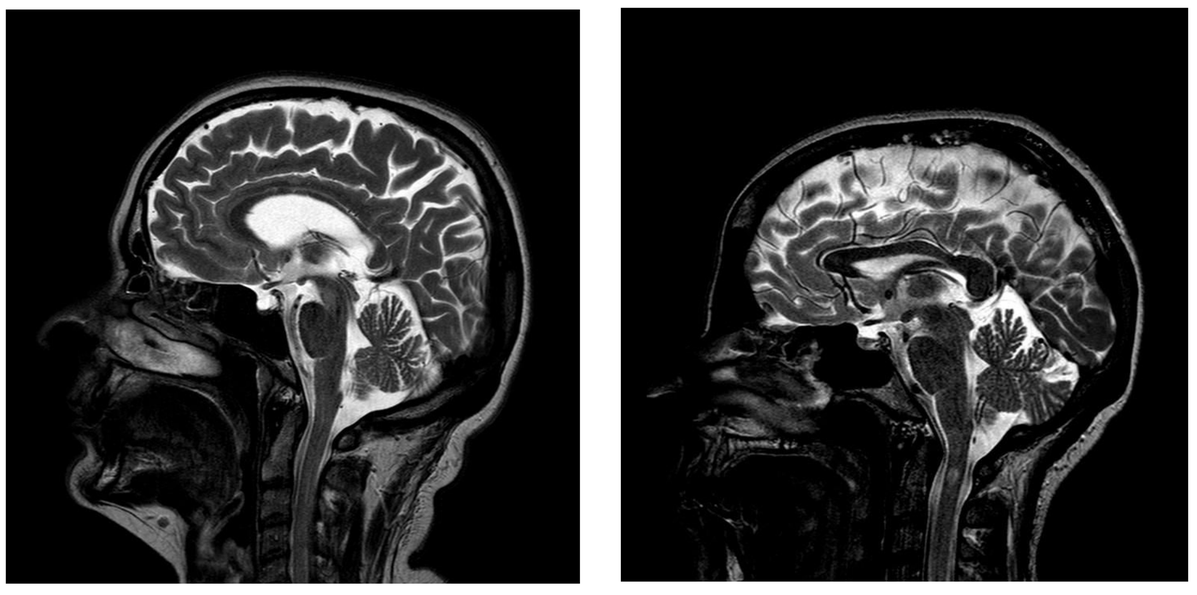


Figure 1. On the left: basal cervical MRI of a 21 year-old male patient with no disability progression after 10 years of disease (last EDSS score 1.0), showing no spinal cord alterations. On the right: basal cervical MRI of a 35 year-old female patient with disability progression after 8 years of disease (last EDSS 3.5), showing cervical white matter alterations consisent with multiple sclerosis demyelinating lesions.

In addition, other patients' characteristics like older age, female sex, presence of OCBs and elevated abnormal evoked potential scores seem to play a role as prognostic factors for disability progression over medium and long term follow-up.

OR (95% CIs)	Vitamin D deficiency	p	Smoke	p	Vitamin D deficiency and Smoke	p
Base model	1.52 (0.91-2.90)	0.07	1.46 (0.95-1.99)	0.08	1.78 (1.00-3.29)	0.05
Adjusted model	1.49 (0.98-3.14)	0.05	1.48 (0.93-2.12)	0.09	1.85 (0.98-3.76)	0.05

Table 2. Effect of modifiable factors as prognostic markers of disability progression in relapsing-remitting multiple sclerosis. Base model has been adjusted for month of blood sampling, sex, age and time of follow-up under DMTs.

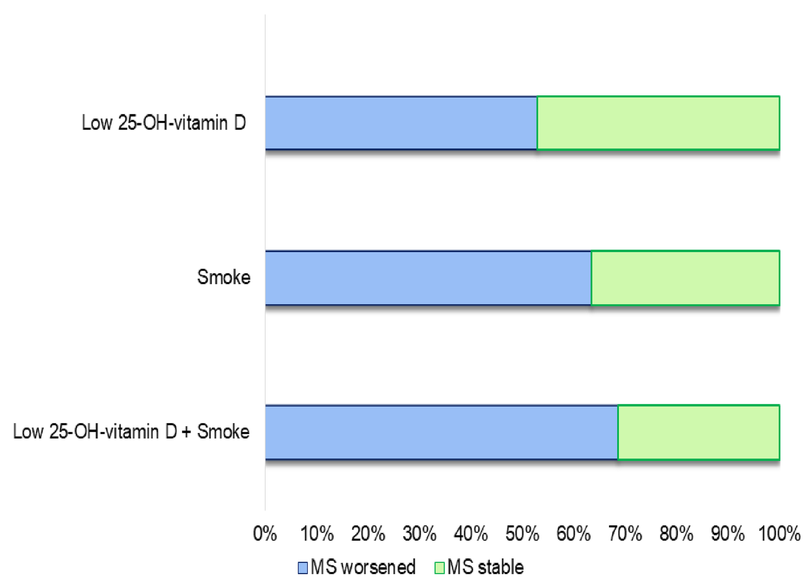


Figure 2. Distribution of modifiable factors in the stable MS group and the worsened MS group. Taken together, smoke and 25-OH-vitamin D deficiency show a synergic negative effect on disability progression over medium and long term follow-up.

Conclusions

- In the present study we observed that different clinical and paraclinical basal characteristics of patients are predictive factors of confirmed disability progression over medium and long term follow-up, in particular the presence of spinal cord lesions at disease onset.
- Among the modifiable risk factors reported by literature, low serum levels of 25-OH-vitamin D show a potential role as risk factor for neurodegeneration, especially when associated with smoking.
- All the results are indicative that it is possible to define an individual risk-profile of any patients presenting with a first demyelinating event and this information should guide the Neurologist to choose the best clinical and therapeutic approach, with the purpose of defining a more and more precise and personalized therapy since the onset of the disease.