ORIGINAL COMMUNICATION

Prognostic value of multimodal evoked potentials in multiple sclerosis: the EP score

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Abstract Evoked potentials (EPs) have long been used as diagnostic tools in multiple sclerosis (MS), although their importance decreased as magnetic resonance imaging (MRI) became available. However, the prognostic value of EPs in MS has not been completely established. The aim of the study was to analyze the prognostic significance of EPs in a cohort of MS cases. From the Verona University Hospital MS Clinic database we retrospectively identified 80 MS patients who underwent a complete neurophysiological evaluation, including visual, brain stem, somatosensory and motor EPs and who were followed for at least 5 years after the study. EPs abnormalities were quantified through an index of global EPs alteration (EP score). The relationship between EP score and disability in terms of Expanded Disability Status Scale (EDSS) was analyzed by the Kaplan–Meier survival method and Spearman ρ correlation coefficient. ROC curves were used to determine the best EP score cut off to predict different EDSS endpoints. For each endpoint, sensitivity, specificity, positive and negative predictive value of EP score were calculated. We found a significant correlation ($p < 0.001$) between EP score and EDSS score at the time of neurophysiological study and at 1, 3 and 5 years of follow-up, particularly for motor and somatosensory EPs. Kaplan–Meier curves confirmed an increased risk of disability in those patients with EP score higher than the median value. EP score of 8 or 9 showed the highest sensitivity and specificity in predicting EDSS 4.0 and 6.0. EPs are reliable procedures to predict disability in MS patients. The correlation between EPs abnormalities and EDSS is higher than between conventional MRI and EDSS.

Introduction

The disability secondary to multiple sclerosis (MS) is known to be highly variable among patients, and hardly predictable. This feature can be interpreted as a consequence of the different pathological mechanisms underlying MS [1], combining inflammation and neurodegeneration, demyelination and axonal damage, and is related to the variable clinical course both across different patients and within the single patient at different disease phases [2].

The availability of magnetic resonance imaging (MRI) conventional techniques in recent decades changed the diagnostic attitude toward MS, and neuroimaging has become the main component of MS diagnostic criteria since 2001 [3–5]. However, recent studies [6] also confirm the poor correlation between conventional MRI and disability—the "clinical-radiological paradox" of MS [7]. The most widely used MRI parameter of damage in MS, i.e. T2 lesion burden, presents a poor correlation with the disability graded by the Expanded Disability Status Scale (EDSS) [8], with Pearson correlation coefficients r between 0.2 and 0.5 [9–11]. In a recent study, Li et al. [12] showed that the T2 lesion burden is related to EDSS only for scores between 2.0 and 4.0.

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The importance of evoked potentials (EPs) in MS diagnosis decreased in the last decades, as MRI became largely available. Nevertheless, in 1998 O'Connor et al. [13] showed that the number of pathological EPs presented a stronger correlation with EDSS than the T2 lesion load in 50 MS patients with relapsing-remitting (RR) course. In 2001, Fuhr et al. [14] confirmed a good correlation between a Z-score based on latency of visual and motor EPs (VEPs and MEPs) and EDSS (Spearman ρ 0.62–0.72) in 30 patients (25 with RR and 5 with secondary progressive [SP] MS), and also with the increase of EDSS in the 2 years after the neurophysiological evaluation, suggesting for the first time the potential prognostic value of EPs. Leocani et al. [15] confirmed an increased risk of EDSS progression in patients with a higher degree of EPs abnormality, graded on a scale from 0 to 36, in a group of 64 MS patients (40 RR, 19 SP, and 5 primary progressive, [PP]). In the same year, Kallman et al. [16] showed a correlation between the alteration of multi-modal EPs and the EDSS score after 5 and 10 years (Spearman ρ 0.57 and 0.51) in 44 patient (23 RR, 15 SP, and 6 PP) who underwent EPs study in the first 2 years of disease.

The aim of our study is to verify the prognostic value of EPs in a series of 80 MS patients with different clinical courses and variable time elapsed from first symptom to neurophysiologic evaluation through an ad hoc scale, that we called *EP score*.

Methods

Patients

From the Verona University Hospital MS Clinic database, we retrospectively identified all MS subjects (McDonald) [3] who underwent a complete EPs evaluation at the neurophysiology section of our department and were followed for at least 5 years from the time EPs were performed. Complete EPs evaluation included: bilateral VEPs, bilateral brainstem auditory EPs (BAEPs), somatosensory EPs (SEPs) from lower limbs, MEPs from lower and upper limbs, for a total number of 10 EPs (5 for each side).

From medical records we collected information about: time elapsed from the onset of the disease to neurophysiological evaluation, clinical course of the disease at the time of the EPs and during follow-up, EDSS at the time of neurophysiological evaluation, after 1, 3, 5 years and at last follow-up, and the interval between the date of EPs and the date EDSS score of 4.0 and 6.0 were reached. As usually adopted in MS clinical trials, EDSS progression was defined as the increase of ≥ 1.0 points if basal EDSS ≤ 5.0 or 0.5 point if basal EDSS ≥ 5.5.

EP

The abnormality of EPs was quantified through a scale that we called *EP score*. For each patient, the global EP score is the sum of ten 4-graded scores derived from the evaluation of each EP. The 4 grades are: 0 = normal EP; 1 = increased latency with normal amplitude and morphology of major potentials; 2 = decrease in amplitude or altered morphology of major potentials; 3 = absence of a major potential (modified, from Leocani et al.) [15]. EPs were obtained according to previously published guidelines (Deuschl and Eisen) [17]. A complete revision of all patients' neurophysiological evaluation (NPE) reports verified that EPs acquisition protocol was consistent with Deuschl and Eisen guidelines also for patients evaluated before 1999. When analyzing EPs, not only the absolute values of latencies and amplitudes, but also waves symmetry were considered. Destructured or dispersed potentials were considered abnormal. For VEPs, N75-P100 wave presence, amplitude and morphology and P100 peak latency were considered. P100 latency was considered increased if greater than 110.0 ms or if there was a difference greater than 7.0 ms between the two sides. N75-P100 wave amplitude was considered decreased if lower than 5.0 μV or if less than 50% of the contralateral. For BAEPs, the presence, amplitude and morphology of waves from I to V and the I–III and III–V intervals were analyzed. BAEPs latency were considered increased if I–III interval, III–V interval, or both were greater than 2.25 ms. Waves amplitude was considered decreased if less than 50% of the contralateral. For SEPs from the lower limbs, the presence of the P40-N50 complex, P40 wave latency, amplitude and morphology, and N22-P40 interval were analyzed. P40 latency was considered increased if greater than 43.5 ms, if there was a difference greater than 5.0 ms between the two sides, or if the N22-P40 interval was greater than 20.0 ms. P40 amplitude less than 0.5 μV or less than 50% of the contralateral was considered decreased. For MEPs, the presence, amplitude and morphology of the response to the cortical stimulus and the central conduction time were analyzed. The triple stimulation technique was used to minimize MEPs amplitude variability. The amplitude of the response to the cortical stimulus was considered decreased if it was less than 50% of the contralateral. It was considered equivalent to amplitude decrease if muscle facilitation or cortical stimulus intensity greater than 20% of the contralateral was needed to obtain a response. Central conduction time was considered increased if greater than 10.0 ms at upper limbs and greater than 18.0 ms at lower limbs.

Statistical analysis

Quantitative data are expressed by median and range. The relationship between EP score and disability (EDSS) was analyzed by the Spearman correlation coefficient (ρ) as the two variables are both ordinal scales. ROC curves were used to determinate the best EP score cut off for different endpoints: EDSS ≥ 4.0 at 5 years or at last follow-up, EDSS ≥ 6.0 at 5 years or at last follow-up, EDSS progression at 5 years or at last follow-up. For each endpoint sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) (with 95% CIs) of EP were calculated. Kaplan–Meier survival curves were plotted for endpoint EDSS ≥ 4.0 or 6.0 and log rank test was performed. A level of significance $\alpha = 0.05$ was adopted (two-tailed).

Results

We identified 80 patients who fulfilled the inclusion criteria of the study. The characteristics of cases are summarized in Table 1. The EP score in our sample had a median value of 8 (range 0–24): in 32.5% of patients EP score was <5 and in 30% >10, while the 25th and 75th percentile were 3 and 12, respectively.

Figure 1 shows the best-fit linear regression line, including the 95% prediction interval, of the relationship between EP and EDSS (a) after 5 years since neurophysiological evaluation, and (b) at last follow-up. At each time point the relationship was highly significant ($p < 0.001$). Moreover, Spearman correlation coefficients (ρ) for EP and EDSS were 0.55 at the time of neurophysiologic evaluation, 0.75 after 1 year, 0.80 after 3 years, 0.82 after 5 years, and 0.78 at last follow-up ($p < 0.001$). When we analyzed the relationship between EP score and EDSS by type of EP we found that after 5 years of follow-up every type of EPs was still highly correlated to EDSS score, with ρ coefficients of 0.45 for MEP (upper limbs), 0.46 for BAEP, 0.60 for VEP, 0.62 for MEP (lower limbs) and 0.69 for SEP (lower limbs) ($p < 0.001$).

Then we analyzed the relationship of EP score to the length of time required to reach disability using the Kaplan–Meier survival analysis. Stratifying cases by EP score ≤ 8 (median value) and >8 at the time of neurophysiological evaluation and establishing EDSS 4.0 and 6.0 as endpoints, we found that the difference between the two curves was highly significative (log-rank test: $p < 0.001$) (Fig. 2). The median time to reach the first step of disability (EDSS 4) was 3.8 years in cases with EP score >8 versus 13.5 years in cases with lower EP score; none in the latter group reached the EDSS score of 6 during the follow-up, while the median time to reach

Table 1 General characteristics of the 80 MS patients

Sex	
Female	53 (66.3%)
Males	27 (33.7%)
Age at first symptom	
Median	30 years
Range	14–54 years
Time from first symptom to NPE*	
Median	4 years
Range	0–34 years
Duration of follow-up	
Median	8 years
Range	5–17 years
Clinical course at NPE*	
RR	62 (77.5%)
PP	14 (17.5%)
SP	4 (5.0%)
Clinical course at last follow-up	
RR	47 (58.8%)
SP	19 (23.7%)
PP	14 (17.5%)
EDSS at NPE*	
Median	3.0
Range	0.0–6.5
Patients on relapse at NPE*	
On relapse	19 (23.75%)
Not on relapse	61 (76.25%)
EDSS at last follow-up	
Median	4.0
Range	0.0–8.0

* *NPE* neurophysiological evaluation

this milestone of disability was about 7 years in the former group.

Since our sample, as often happens in MS outpatients, was heterogeneous in clinical course, disability, and time elapsed from first symptom to neurophysiologic evaluation, we verified whether these differences influenced the association between EP score and disability [16] stratifying cases by EDSS and clinical course at the time of neurophysiologic evaluation, and by the interval between disease onset and neurophysiologic evaluation.

In thirty cases EDSS score was ≤ 2.0 at the time of neurophysiological examination, in 32 ranged from 2.5 to 3.5 and in 18 cases was ≥ 4.0. We found a statistically significant correlation between EPs and EDSS score in all the three groups of cases and for different points in time (Table 2).

When the patients were analyzed by clinical course at the time of neurophysiological evaluation (RR vs. PP, 62 and 14 patients, respectively), the correlation between EPs
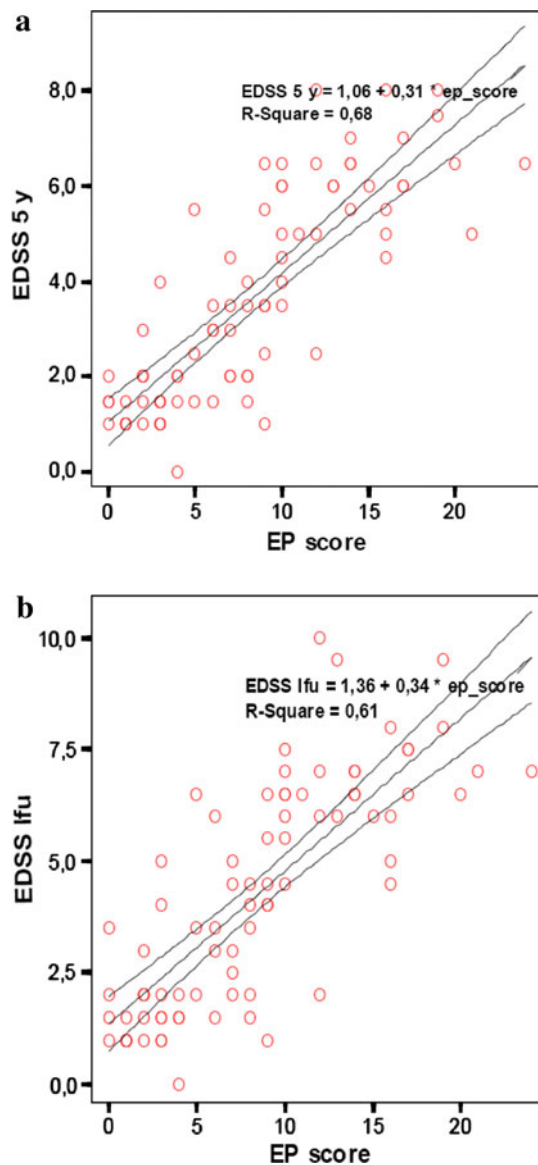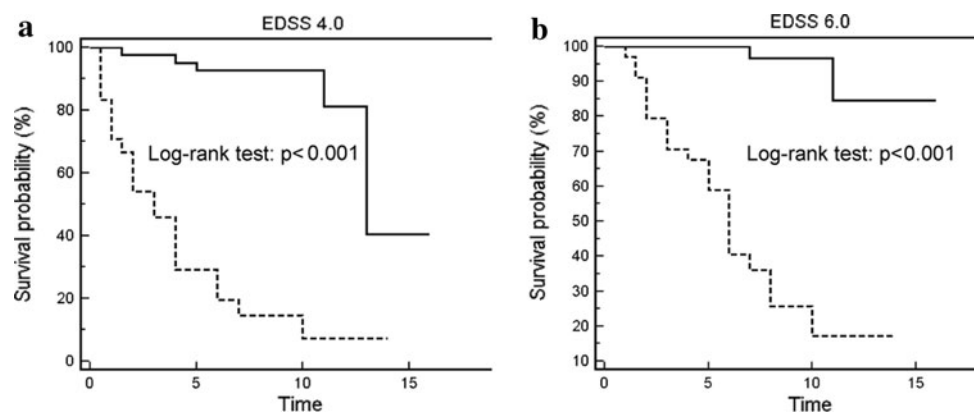
Fig. 1 Best-fit linear regression line, including the 95% prediction interval, of the relationship between EP score and EDSS after 5 years since neurophysiological evaluation (**a**) and at last follow-up (**b**)

and EDSS was evident in RR patients, the larger group, while in PP subjects it was statistically significant only after 5 years and at the last visit of follow-up (Table 2). In PP cases the difference in survival curves by EPs score and EDSS 4.0 and 6.0 as endpoints was weakly significant (log-rank test, $p = 0.03$).

Twenty-four patients underwent EPs within 2 years from the onset of the disease, 30 after 2–6 years from onset, and 26 more than 6 years after the first symptom. We found that the correlation between EP score and EDSS was highly significant ($p < 0.001$) in all the three groups of patients, independently on the time in which EPs were performed (Table 2).

Moreover, to verify the possible influence of relapses on NPE, we stratified our sample in 2 groups: 19 subjects in which the NPE was performed during a relapse and 61 in which NPE was not performed during a relapse. In patients not on relapse the correlation was evident throughout the follow-up ($p < 0.001$), while in the 19 subjects who underwent the NPE during a relapse the correlation was weaker, but still statistically significant ($p < 0.05$) at all steps except at 5 years ($p = 0.09$).

Finally, we determined the best EP score cut-off value of sensitivity and specificity, PPV and NPV for different endpoints: EDSS ≥ 4.0 or ≥ 6.0 and EDSS progression after 5 years and at last follow-up. We found that for the endpoints of EDSS ≥ 4.0 at last follow-up, and EDSS progression at 5 years or at last follow-up the best EP cut-off was 8, while for EDSS ≥ 4.0 at 5 years and EDSS ≥ 6 at 5 years and at last follow-up the best EP cut-off was 9 (Table 3).

Discussion and conclusions

In recent years, several studies have suggested a prognostic value of EPs in MS, showing a good correlation between EPs and disability [13–16]. This retrospective study was aimed at determining the prognostic value of EPs using the

Fig. 2 Survival curves for EP and EDSS 4.0 (**a**) and 6.0 (**b**) as endpoint (*broken lines*: cases with EP score > median value 8, *continuous lines*: cases with EP score ≤ median value 8). Time in years from neurophysiologic evaluation (T_0)

Table 2 Correlation between EP score and EDSS at different points of time by characteristics at NPE (disability, clinical course, and interval between disease onset and NPE)

Variable	Correlation between EP score and EDSS score									
	At time of NPE		After 1 year		After 3 years		After 5 years		At last follow-up	
	ρ	p value	ρ	p value	ρ	p value	ρ	p value	ρ	p value
EDSS at NPE										
≤2 (n = 30)	0.06	0.74	0.59	0.001	0.59	0.001	0.66	<0.001	0.55	0.002
2–3.5 (n = 32)	0.23	0.20	0.70	<0.001	0.78	<0.001	0.75	<0.001	0.71	<0.001
≥4 (n = 18)	0.23	0.36	0.66	0.03	0.56	0.02	0.72	0.001	0.64	0.004
Clinical course at NPE										
RR (n = 62)	0.54	<0.001	0.75	<0.001	0.79	<0.001	0.81	<0.001	0.77	<0.001
PP (n = 14)	0.38	0.21	0.51	0.06	0.49	0.08	0.63	0.02	0.60	0.02
Interval between MS onset and NPE										
<2 yrs (n = 24)	0.46	0.023	0.77	<0.001	0.83	<0.001	0.77	<0.001	0.74	<0.001
2–6 yrs (n = 30)	0.75	<0.001	0.81	<0.001	0.85	<0.001	0.88	<0.001	0.86	<0.001
>6 yrs (n = 26)	0.33	0.09	0.72	<0.001	0.80	<0.001	0.79	<0.001	0.73	<0.001
Relapse at NPE										
Yes (n = 19)	0.59	0.007	0.48	0.03	0.57	0.011	0.39	0.09	0.46	0.045
No (n = 61)	0.70	<0.001	0.78	<0.001	0.83	<0.001	0.85	<0.001	0.82	<0.001

NPE Neurophysiologic evaluation; ρ Spearman correlation coefficient

EP score (modified from Leocani et al.) [15]. This scale, besides considering alteration of EPs latencies, expression of demyelinating damage typical of MS, quantifies also amplitude and morphological abnormalities, expressions of axonal and secondary neural damage that is considered the most important factor determining disability, as confirmed by recent MRI studies [18, 19].

In our cases, the correlation between EPs abnormalities and disability quantified through EP score and EDSS, respectively, was stronger compared to that usually reported for conventional MRI [6, 7, 9–12]. Our results confirm the findings of Fuhr et al. [14] and Leocani et al. studies [15], in which the follow-up of patients was shorter (about 2 and 3 years) than in the present study (median 8 years).

In their study, Kallman et al. [16] showed an important correlation between EPs abnormalities and EDSS after 5 and 10 years in the group of subjects who underwent neurophysiological evaluation in the first 2 years after symptoms onset, but not in those subjects in which EPs were performed more than 2 years after onset. When we analyzed EPs and EDSS in patients stratified by time elapsed from first symptom and neurophysiologic evaluation, however, we found a similar correlation in all the groups, suggesting that the possible prognostic value of EP score was independent of the time in which EPs were performed (Table 2).

Moreover, we observed that the correlation between EP score and disability was more evident during the follow-up than at the time of the complete neurophysiological evaluation. A possible explanation of this finding is that in our sample the complete EPs study was performed for diagnostic purpose and often during a relapse, as usually happens in everyday practice, so that the sample was not homogeneous at this time.

Among EPs, SEPs and MEPs from lower limbs were the ones showing the best correlation with EDSS during follow-up, because of the preponderant weight of walking impairment and spinal cord dysfunction in determining disability level measured through the EDSS score.

As shown in Table 2, the correlation between EP score and EDSS was statistically significant in the three subgroups of patients stratified by EDSS score at the time of neurophysiological evaluation (≤2.0, 2.5 to 3.5, ≥ 4.0). The presence of an evident correlation in subgroups with different levels of disability at the time of NPE confirms that the prognostic information provided by EP score is not available from clinical evaluation alone. The weak correlation between EP score and EDSS observed in our PP patients may depend on the small number of cases with this type of clinical course and their clinical homogeneity, that makes difficult to differentiate subjects with a more or less severe disease in this subgroup. Nevertheless, the Spearman correlation analysis at 5 years and at the last follow up, and the Kaplan–Meier survival analysis confirm the prognostic value of EP score also in this group of cases.

When we stratified our sample for presence or absence of relapse at the time of NPE we found that the correlation between EP and EDSS scores was weak in subjects on relapse, likely because EPs abnormality observed in such patients might be due to acute reversible demyelination not

Table 3 Sensitivity, specificity, PPV and NPV (with 95% CI) of EPs best cut-off values for the different endpoints: EDSS ≥4.0 at 5 years or at last follow-up, EDSS ≥6.0 at 5 years or at last follow-up, EDSS progression at 5 years or at last follow-up

Endpoint	EPs cut off value (≥)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
EDSS ≥4.0 at 5 yrs	6	90.0 (68–98)	66.7 (51–80)	54.5 (36–72)	93.7 (79–99)
	7	85.0 (62–97)	75.6 (60–87)	60.7 (41–78)	91.9 (78–98)
	8	85.0 (62–97)	84.4 (70–93)	70.8 (49–87)	92.7 (80–98)
	9	**80.0 (56–94)**	**93.3 (82–98)**	**84.2 (60–96)**	**91.3 (79–97)**
	10	65.0 (41–84)	97.8 (88–100)	92.9 (66–99)	86.3 (74–94)
EDSS ≥4.0 at last follow-up	6	88.5 (70–97)	74.4 (58–87)	69.7 (51–84)	90.6 (75–98)
	7	84.6 (65–95)	84.6 (69–94)	78.6 (59–92)	89.2 (75–97)
	8	**80.7 (61–93)**	**92.3 (79–98)**	**87.5 (68–97)**	**87.8 (74–96)**
	9	65.4 (44–83)	94.9 (83–99)	89.5 (67–98)	80.4 (66–91)
	10	50.0 (30–70)	97.4 (86–100)	92.9 (66–99)	74.5 (60–86)
EDSS ≥6.0 at 5 yrs	8	100.0 (77–100)	67.7 (55–79)	41.2 (25–59)	100.0 (91–100)
	9	**92.9 (66–99)**	**75.8 (63–86)**	**46.4 (27–66)**	**97.9 (89–100)**
	10	71.4 (42–91)	83.9 (72–92)	50.0 (27–73)	92.9 (83–98)
	12	71.4 (42–91)	88.7 (78–95)	58.8 (33–81)	93.2 (83–98)
EDSS ≥6.0 at last follow-up	8	92.0 (74–99)	78.4 (65–89)	67.6 (49–83)	95.2 (84–99)
	9	**88.0 (69–97)**	**88.2 (76–95)**	**78.6 (59–92)**	**93.7 (83–99)**
	10	68.0 (46–85)	94.1 (84–99)	85.0 (61–97)	85.7 (74–94)
	11	64.0 (42–82)	94.1 (84–99)	84.2 (60–94)	84.2 (72–92)
EDSS progression at 5 yrs	6	89.5 (75–97)	66.7 (50–80)	70.8 (56–83)	87.5 (71–96)
	7	84.2 (69–94)	73.8 (58–86)	74.4 (59–86)	83.8 (68–94)
	8	**81.6 (66–92)**	**83.3 (69–93)**	**81.6 (66–92)**	**83.3 (69–93)**
	9	73.7 (59–87)	90.5 (77–97)	87.5 (71–96)	79.2 (65–89)
EDSS progression at last follow-up	6	83.3 (70–92)	75.0 (57–88)	83.3 (70–92)	75.0 (57–88)
	7	77.1 (63–88)	81.2 (64–93)	86.0 (72–95)	70.3 (53–84)
	8	**75.0 (60–86)**	**93.7 (79–99)**	**94.7 (82–99)**	**71.4 (55–84)**
	9	64.6 (49–78)	96.9 (84–99)	96.9 (84–99)	64.6 (49–78)

Bold values indicates the best cut-off values combinations of sensitivity, specificity, PPV and NPV for each endpoint

associated with irreversible neurological disability. On the contrary, the evident correlation between EP and EDSS scores in patients assessed during the remission phase suggests the prognostic value of EPs when performed.

Finally, we determined the best cut off values for identifying patients at greater risk of disability or disability progression (Table 3). The EP score cut off of 8 or 9 has a good sensibility, specificity, PPV and NPV values for each endpoint except EDSS ≥6.0 at 5 years for which specificity and PPV are lower, probably because this is the threshold of irreversible disability and the index of the most severe clinical course.

Our study was limited by the retrospective design and the quantification of disability in terms of global EDSS score only. Prospective studies conducted with an EPs standardized protocol and including the assessment of each neurological functional system at the various follow-up time points would be very helpful in obtaining prognostic information in MS patients.

In conclusion, our study confirms the value of EP, particularly SEPs and MEPs, in predicting neurological disability in MS. Notably, the association between EPs' alteration and disability was independent of the timing of neurophysiological assessment and was maintained through all follow-up duration. Should neuroprotective therapies for multiple sclerosis be available in the future, the EP score might be a useful tool to support treatment decisions.

References

1. Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H (2000) Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 47:707–717

2. Lublin FD, Reingold SC, For the National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis (1996) Defining the clinical course of multiple sclerosis: results of an international survey. Neurology 46:907–911

3. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinski JS (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol 50:121–127

4. Polman CH, Reingold SC, Edan G, Filippi M, Hartung H-P, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS (2005) Diagnostic criteria for multiple sclerosis: 2005 revision to "McDonald Criteria". Ann Neurol 58:840–846

5. Swanton JK, Fernando K, Dalton CM, Miskiel KA, Thompson AJ, Plant GT, Miller DH (2006) Modification of MRI criteria for multiple sclerosisin patients with clinically isolated syndromes. J Neurol Neurosug Psychiatry 77:830–833

6. Bakshi R, Neema M, Healy BC, Liptak Z, Betansky RA, Buckle GJ, Gauthier SA, Stankiewicz J, Meier D, Egorova S, Arora A, Guss ZD, Glanz B, Khoury SJ, Guttman RG, Weiner HL (2008) Predicting clinical progression in multiple sclerosis with the magnetic resonance disease severity scale. Arch Neurol 65:1449–1453

7. Barkhof F (2002) The clinico-radiological paradox in multiple sclerosis revisited. Curr Opin Neurol 15:239–245

8. Kurtzke JF (1983) Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33:1444–1452

9. Gawne-Cain ML, O'Riordan JI, Coles A, Newell B, Thompson AJ, Miller DH (1998) MRI lesion volume measurement in multiple sclerosis and its correlation with disability: a comparison of fast fluid attenuated inversion recovery (fFLAIR) and spin echo sequences. J Neurol Neurosug Psychiatry 64:197–203

10. Nijeholt GT, van Walderveen MA, Castelijns JA, van Waesberghe JH, Polman C, Scheltens P, Rosier PF, Jongen PJ, Barkhof F (1998) Brain and spinal cord abnormalities in multiple sclerosis. Correlation between MRI parameters, clinical subtypes and symptoms. Brain 121:687–973

11. Charil A, Zijdenbos AP, Taylor J, Boelman C, Worsley KJ, Evans AC, Dagher A (2003) Statistical mapping analysis of lesion location and neurological disability in multiple sclerosis: application to 452 patient data sets. Neuroimage 19:532–544

12. Li DKB, Held U, Petkau J, Daumer M, Barkhof F, Fazekas F, Frank JA, Kappos L, Miller DH, Simon JH, Wolinsky JS, Filippi M, For the Sylvia Lawry Centre for MS research (2006) MRI T2 lesion burden in multiple sclerosis. A plateauing relationship with clinical disability. Neurology 66:1384–1389

13. O'Connor P, Marchetti P, Lee L, Perera M (1998) Evoked potential abnormality scorse are a useful measure of disease burden in relapsing-remitting multiple sclerosis. Ann Neurol 44:404–407

14. Fuhr P, Borggrefe-Chappuis A, Schindler C, Kappos L (2001) Visual and motor evoked potentials in the course of multiple sclerosis. Brain 124:2162–2168

15. Leocani L, Rovaris M, Boneschi FM, Medaglini S, Rossi P, Martinelli V, Amadio S, Comi G (2006) Multimodal evoked potentials to assess the evolution of multiple sclerosis: a longitudinal study. J Neurol Neurosurg Psychiatry 77:1030–1035

16. Kallman BA, Fackelmann S, Toyka KV, Rieckmann P, Reiners K (2006) Early abnormalities of evoked potentials and future disability in patients with multiple sclersosis. Mult Scler 12:58–65

17. Deuschl G, Eisen A (1999) Recommendations for the practice of clinical neurophysiology: guidelines of the international federation of clinical neurophysiology. Electroencephalogr Clin Neurophysiol 52(Suppl):192–211

18. Fisher E, Lee JC, Nakamura K, Rudick RA (2008) Gray matter atrophy in multiple sclerosis: a longitudinal study. Ann Neurol 64:255–265

19. Fisniku LK, Chard DT, Jackson JS, Anderson VM, Altmann DR, Miszkiel KA, Thompson AJ, Miller DH (2008) Gray matter atrophy is related to long-term disability in mutiple sclerosis. Ann Neurol 64:247–254