

Cognitive Event-Related Potentials—The P300 Wave Is a Prognostic Factor of Long-Term Disability Progression in Patients With Multiple Sclerosis

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Purpose: Multiple sclerosis (MS) is a chronic disorder with a variable course. The aim of our study was to find out whether cognitive event-related potentials are prognostic for patient disability at the 15-year follow-up.

Methods: In the observed cohort of patients with MS, we examined the event-related potentials at baseline (2003). Functional status (Expanded Disability Status Scale score) was then assessed 15 years later, and the prognostic model was developed using binary logistic regression analysis. The independent variables included demographic (age, sex, and education), clinical (disability in 2003), radiologic (MRI lesion load), and event-related potentials parameters. The prognostic accuracy of the proposed model was evaluated by calculating the area under the receiver-operating characteristics curve.

Results: The study sample consisted of 85 patients with MS. The mean age was 35.5 (SD, 11.2) years, and the median disability

score was 3.0 (1–7) in 2003 and 5.0 (1.5–9.5) in 2018. The significant prognostic factors of poor Expanded Disability Status Scale are higher baseline Expanded Disability Status Scale, longer MS duration, and prolonged P300 latency. The sensitivity and specificity of the cutoff at 5.0 for the disability score were 94% and 89%, respectively, with the area under the receiver-operating characteristics curve 0.94 (95% confidence interval, 0.889–0.984; $P < 0.001$).

Conclusions: The results show that out of event-related potentials, the P300 wave latency is a prognostic of long-term disability progression in patients with MS.

Key Words: Multiple sclerosis, P300, Event-related potential, Prognostic factors, Disability.

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Multiple sclerosis (MS) is a chronic autoimmune disorder with individual different disease activity. The research focuses on the identification of clinical and paraclinical prognostic factors for disability progression to optimize the strategy of a patient's treatment.

Event-related potential (ERP), with its parameter P300 wave, is considered to be an electrophysiologic index of cognitive function.^{1–5} The P300 (also known as P3 or P3b) is a large, positive wave that typically peaks at 300 ms or more after the onset of a task-relevant stimulus.^{5,6} The amplitude of a P300 wave corresponds to the volume of the nerve structures activated during data processing. The P300 is an endogenous potential that represents cerebral electrical processes related to expected stimuli, decision-making, and executive function. The auditory P300 is a brain response to certain auditory stimuli. The auditory

P300 is elicited by a discrimination task, the so-called “oddball” paradigm, which consists of a series of untargeted and targeted auditory stimuli. The subject should evaluate the occurrence of the target stimulus. Attention, decision-making, and memory are involved during the task.^{5,6}

In 1984, Tourtellotte et al.⁷ studied the P300 wave in patients with MS in association with a cognitive deficit. P300 latency and amplitude has been marked as a neurophysiologic indicator of cognitive functioning in MS. The relationships between P300 data and neurophysiologic tests, clinical variables, and MRI data has been described.^{1,8–13} Ellger et al.¹⁴ found longer P300 latencies in secondary progressive MS. P300 latency is related to attention and memory deficit,^{8–10,15} a higher Expanded Disability Status Scale (EDSS) score,^{4,5,11,14,15} disease duration,^{8,9,15,16} and MRI lesion burden.^{8,10,13,17} In our previous study on a group of 110 patients with MS, auditory P300 latency was prolonged in 69% of patients compared with the 130 healthy controls. P300 latency correlated with the patients' cognitive dysfunction and their quality of life.¹⁵

Several ERP studies have evaluated the effect of drugs on cognition and ERPs in patients with MS. No significant changes were observed after interferon-beta therapy,^{8,18,19} but after administration of methylprednisolone, significantly improved P300 latency was described.²⁰ In addition to MS,^{1,8–11} the P300 component of the auditory ERP is relevant to dementia and mild cognitive impairment,^{21,22} locked-in syndrome,²³ amyotrophic lateral sclerosis,²⁴ depression, and schizophrenia.²⁵

The authors have no conflicts of interest to disclose.

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Multimodal evoked potentials (EPs) (visual, somatosensory, and motor EP) can be used for monitoring and prognosis in patients with MS.^{26–28} The prognostic importance of auditory ERPs in long-term disability progression has not yet been studied.

The aim of our work was to determine whether ERPs have a prognostic significance for a patient's future disability. Using retrospective analyses, we evaluated a cohort of patients with MS and the relationship between auditory ERPs and disability progression after 15 years.

METHODS

Participants

All patients were treated in 2003 at the Department of Neurology of Louis Pasteur University Hospital in Košice. The inclusion criteria were the following: (1) diagnosis of MS based on the revised 2001 McDonald criteria, (2) being older than 18 years, and (3) the ability to give written informed consent. The exclusion criteria were the following: (1) major hypacusis or deafness and (2) relapse and/or corticosteroid use within 30 days preceding the study assessments. The study was approved by the Hospital Ethics Committee and was performed in accordance with Good Clinical Practice standard and the Declaration of Helsinki. Of the original patient cohort examined using auditory ERPs in 2003 ($N = 110$), 85 people could still be observed regarding disability in 2018 (30 men, 55 women). Of these, 54 had relapsing-remitting MS, 25 secondary progressive MS, and six primary progressive MS in 2003.

Disability was assessed using the EDSS.²⁹ Diagnosis and clinical phenotypes of MS were established on the basis of the diagnostic criteria.^{30,31} The mean age (2003) of patients was 31.18 ± 9.68 years (17–59), and the mean disease duration in 2003 was 6.7 ± 6.45 years (6 months–30 years). Disease duration was considered the time from the first symptoms of MS to the date of the ERPs examination. Conventional MRI scans acquired within the past 6 months before the study assessment were available for 110 patients (1.5-T devices). MRI lesion load was calculated as the total number of T2 lesions. Seven patients had a primary education (8%), 56 a secondary one (66%), and 22 patients had a university education (26%). A total of 24 patients terminated their treatment and monitoring in our MS centre for various reasons (mainly because of a high degree of disability and transportation problems), and one patient died (colon cancer) (Fig. 1).

Electrophysiological Assessment

A Medelec Synergy machine was used to measure auditory ERPs by means of an auditory oddball paradigm. The P300 recording was carried out in accordance with the published ERP guidelines.^{5,6} Based on the 10 to 20 system, ERPs were recorded at the Fz, Cz, and Pz scalp locations (linked earlobe electrodes were used as the reference electrodes), with Ag/AgCl electrodes used. The impedance of the electrodes was below 5 k Ω . The ERP was amplified (bandpass of 0.1–140 Hz), and the records at a sampling rate of 256 Hz were kept for subsequent offline analysis.

A prestimulus baseline was 100 ms, and the average epoch was 1,000 ms. While being tested, the patients were in a sitting position in a sound-attenuated dimly lighted room and listening to a binaural tone sequence. The tests were performed between 10 AM and 1 PM. The binaural audiometric thresholds were determined at 1,000 Hz. The two sound type stimuli at 70 dB sound pressure level were passed randomly through the headphones bilaterally. The ERPs were averaged separately via two channels. One channel registered the processing of a target (rare high-pitched) tone with a 2,000 Hz frequency, and the second channel registered a nontarget (frequent low-pitched) tone with a 1,000 Hz frequency. The increase and decrease in the sound stimulation was 5 ms; the stimulus duration lasted 50 ms, and the interstimulation interval was 1,400 ms. The probability of the nontarget sound was 85% and 15% for the target sound. The subjects were instructed to push a button as soon as they detect the target sound. Individual trials with eye blink artifacts (more than 250 μ V of peak-to-peak amplitude) were excluded. Two subsequent, equal 200-tone series (with 2-minute pause) were carried out on each patient. Averages of the ERPs were made separately for each trial type (Fig. 2).

Amplitude (μ V) was calculated as the peak-to-peak N200–P300 distance. In the case of a double peak, an intersecting line linking the two peaks was used. Latency (milliseconds) was defined as the time between a P300 peak and rare stimuli. Peak amplitudes were measured in relation with the prestimulus baseline. The N200 (approximately 200 ms) was the lowest negative peak between P200 and P300 after rare (target) stimuli. The P300 was the most prominent positive peak between 280 and 550 ms after the rare (target) stimuli. The P300 latency and amplitude were measured in the patient cohort in 2003 and compared with demographic (age, sex, and education), clinical (disability in 2003 and disease phenotypes), and radiologic (brain MRI lesion load in 2003) data and disability (EDSS) in 2018.

Statistical Analysis

Descriptive statistics were compiled to provide basic information about the patients. Inferential statistics (e.g., the Wilcoxon signed-rank test) were used to analyse the associations between variables, as appropriate. Thereafter, binary logistic regression analysis was performed. The EDSS score measured in 2018 was dichotomized (less than 5.0; 5.0 and more) and used as a dependent variable. The model of independent variables included demographic (age, sex, and education), clinical (disability in 2003, disease duration in 2003, and MS phenotype: relapsing-remitting MS, secondary progressive MS, or primary progressive MS), radiologic (MRI lesion load), and ERPs parameters. The conditional backward method was used to select the model with the best predictors; consequently, the sensitivity and specificity of this model were tested using receiver-operating characteristics (ROC) curves. To find the best model for clinical practice, we performed additional ROC analysis for the same model but plotted the curves separately for patients with P300 latency below 320 ms and at 320 ms or above (this cutoff was selected according our previous experience with healthy controls).¹⁵

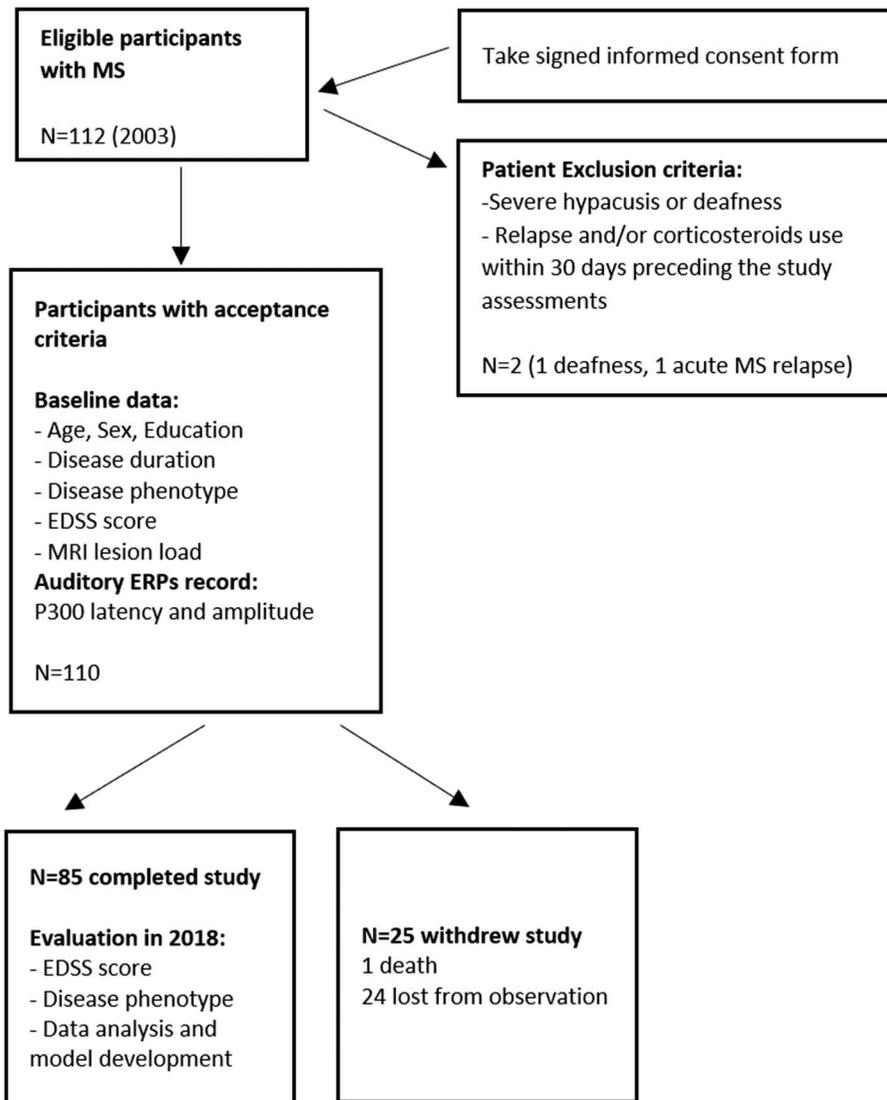


FIG. 1. A schematic flowchart diagram showing the procedure by which data were tested in patients with MS. MS, multiple sclerosis.

Statistical analyses were performed at the 0.05 level of significance using the IBM SPSS (Statistical Package for the Social Science) software version 23.0.

RESULTS

The demographic, clinical, and ERPs characteristics of the study participants are provided in Table 1. There was a change of disease phenotype in 16 patients, from relapsing remitting

MS to secondary progressive MS, over 15 years. Of the original 110 patients in 2003, 55 patients (64.7%) were treated with interferon-beta and 31 (35.3%) continued to use some form of disease modifying treatment drugs in 2018. The EDSS score after 15 years increased by 2.17 ± 1.29 points. As expected, the EDSS baseline score and the score after 15 years were significantly related (related samples Wilcoxon signed-rank test standardized test statistics 7.933; $P < 0.001$). The best model of prognostic factors of EDSS after 15 years is shown in Table 2.

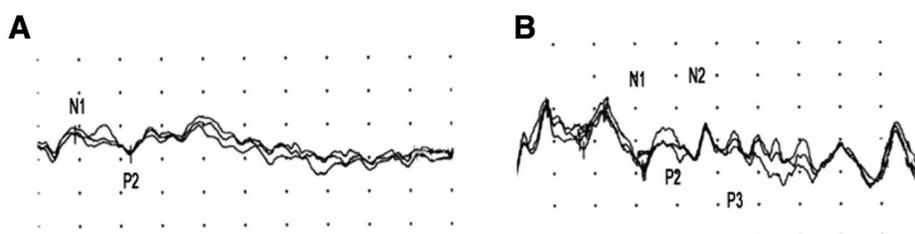


FIG. 2. Event-related potential waveforms of the two groups for nontarget stimuli (A) and target stimuli (B) for the oddball task. Negativity is upward.

TABLE 1. Demographic, Clinical, and ERPs Characteristics of the Patient Group

Parameters (N = 85)	Mean	SD	Range
Age in 2003 (years)	34.18	9.68	18–59
Gender: Female, 64.7%			
Disease duration in 2003 (years)	6.70	6.45	0.5–30
EDSS score			
2003	3.03	1.50	1.0–7.0
2018	5.21	2.11	1.5–9.5
EDSS score difference (2003–2018)	2.17	1.29	0–6.0
P300 latency (ms)	380.13	41.28	304–489
P300 amplitude (µV)	6.75	2.72	2.3–15.3

EDSS, Expanded Disability Status Scale; ERP, event-related potential.

The significant prognostic factors of poor EDSS are higher baseline EDSS, longer MS duration, and prolonged P300 latency. The other variables described in Table 2 are not significant; however, they do increase the fit of the model. The specificity and sensitivity of the model were tested by ROC analysis. The sensitivity and specificity of the predictive model were 94% and 89%, respectively, with an area under the ROC curve of 0.94 (95% confidence interval, 0.889–0.984; $P < 0.001$) (Fig. 3). In addition, we performed the same ROC analysis separately for patients with normal P300 latency (below 320 ms) and pathologic P300 latency (320 ms and above). The models are presented in Fig. 4 and fit perfectly in the subgroup of normal P300 latency patients (area under the curve, 1.0; 95% confidence interval, 1.00–1.00; $P < 0.001$) and excellent in the subgroup of pathologic P300 latency patients (area under the curve, 0.93; 95% confidence interval, 0.867–0.979; $P < 0.001$).

DISCUSSION

This study aimed to explore whether ERPs are prognostic for patient disability at the 15-year follow-up. As expected, we

found a significant increase in disability after the 15-year follow-up. The main finding is that longer disease duration, higher baseline disability, and prolonged P300 latency are prognostic factors of a severe disability score (EDSS ≥ 5.0) over the subsequent 15 years. The ROC analysis showed very high sensitivity and specificity of this prognostic model, 94% and 89%, respectively. Closer analysis showed that P300 latency at 320 ms and above is a strong prognostic factor for poor disability over the 15-year follow-up compared with P300 latency below 320 ms. An EDSS score of 5.0 represents an important disability milestone, with irreversibly severe impairment, when the patient loses the ability to walk independently.

Our analyses show that prolonged P300 latency is a prognostic factor for severe disability progression over the subsequent 15 years. This could be attributed to the fact that P300 latency does not only reflect cognitive function and speed processing but also diverse pathogenic changes in the MS brain (e.g., atrophy and neuronal signaling pathways disconnection). Disability in MS expresses the overall neuropsychologic disease-induced changes and is the most important factor influencing a patient’s quality of life. The main pathologic feature of MS is inflammation, which interacts negatively with cerebral cortical and subcortical neuronal activity. It is a possible explanation for abnormal ERPs as a consequence of the disruption of network connections giving rise to conduction block and neurodegeneration.

The composite score of multimodal EPs (visual EP, somatosensory EP, brainstem auditory evoked potentials, and motor EP) may predict future disability progression.^{28,32} Our results point to ERPs as a simple and useful prognostic tool, easily examined in people with MS suffering from a severe motor or visual deficit; in addition, P300 measures are relatively inexpensive to obtain.²

A third significant prognostic factor in long-term disability progression is the baseline EDSS score. A patient with a higher baseline EDSS will be more disabled than those with a lower score. Disability represents an irreversible deficit which increases at different rates over time in MS and logically explains our finding. This finding was previously well-documented in the study of Bergamaschi.³³

TABLE 2. Logistic Regression of Dichotomized EDSS in 2018 Versus Demographic, Clinical, Radiologic, and ERPs Parameters

Variables in the Equation	B	SE	Sig	Exp (B)	95% CI for EXP (B)	
					Lower	Upper
Sex	-1.770	1.035	0.087	0.17	0.02	1.295
Age 2003	-0.131	0.087	0.130	0.87	0.74	1.040
MS form 2003			1.000			
RMS 2003	21.873	8334.190	0.998	3156828983.597	0.000	—
PMS 2003	20.438	11491.578	0.999	751474054.21	0.000	—
EDSS 2003	1.120	0.557	0.044	3.06	1.028	9.139
MS duration 2003	0.189	0.093	0.042	1.21	1.007	1.451
P300 latency (ms)	0.056	0.024	0.021	1.06	1.008	1.110
Constant	-20.442	7.818	0.009	0.000	—	—

CI, confidence interval; EDSS, Expanded Disability Status Scale; ERP, event-related potential; PMS, progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

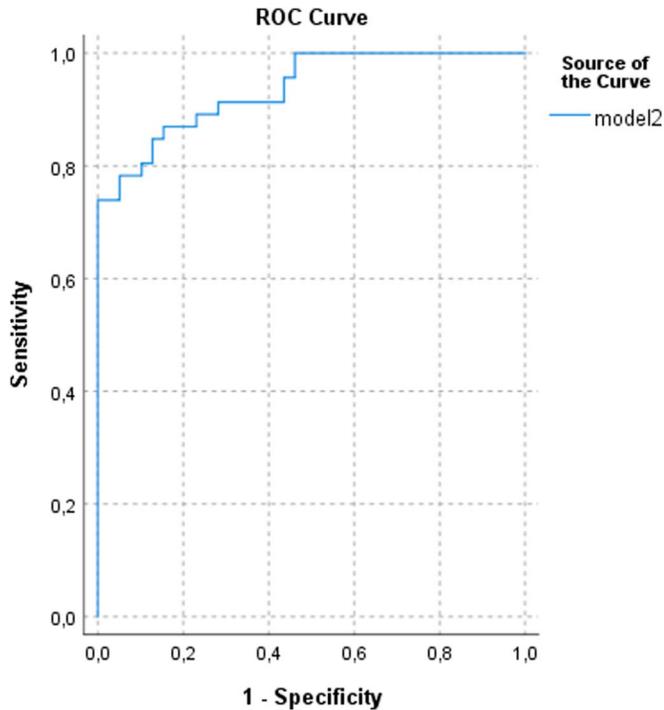


FIG. 3. The receiver-operating characteristics curve for disability progression prognostic factors. The AUC = 0.94 shows the sensitivity and specificity corresponding to different cutoff points of the disability progression prognosis (defined by patients reaching the threshold of EDSS 5.0). The best cutoff point defined by the maximum of Youden index corresponds to a sensitivity of 0.94 and a specificity of 0.89. AUC, area under the curve; EDSS, Expanded Disability Status Scale; ROC, receiver-operating characteristics.

The results in the studies with prognostic factors in MS related to disability are inconsistent. It could be explained by different cohorts and methods, variables, and the definition of disability. Disability is mostly expressed by EDSS scores, although others prefer walking ability.^{34–36} Many authors have shown that a poor prognosis is associated with male gender; later age at onset; motor, cerebellar, and sphincter dysfunction at first manifestation; a short interval between first and second relapse; a high number of relapses; and a serious residual disability at the onset.^{37,38} Paraclinical support for MS prognosis is given by MRI measures, laboratory findings, and EP examinations. The most important radiologic markers of poor disability prognosis are lesion load in cerebral and spinal MRI, gadolinium-enhancing lesions, and accelerated brain atrophy.

We found that longer disease duration and a higher baseline EDSS score negatively affect future disability. These two findings are closely related. Consistent with the findings of Leocani et al.,³² this reflects the involvement of patients with more severe disability and a progressive disease course. Our findings are in accordance with the conclusion of Hughes et al.³⁴ that EDSS increases with disease duration and is independent of relapses. Similar results were found by Briggs et al.,³⁵ who pointed out that older age and longer disease duration are longitudinal predictors of disability in MS. Our patient

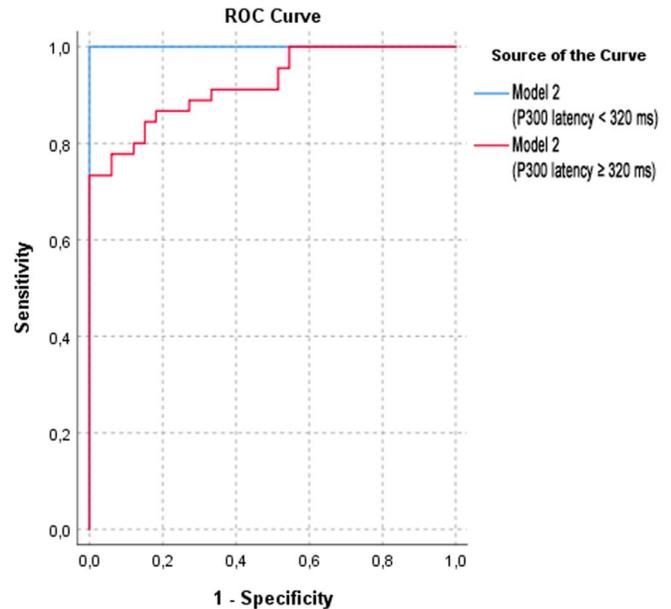


FIG. 4. Receiver-operating characteristics for the subgroups of patients of P300 latency <320 and \geq 320 ms. The AUC = 1.0 in the subgroup of P300 latency <320 and (blue) and the AUC = 0.93 in the subgroup of P300 latency \geq 320 ms (red). AUC, area under the curve; ROC, receiver-operating characteristics.

population appears to be representative of the general MS population by demographics and clinical forms, and we did observe the expected associations between longer disease duration and greater disability in accordance with Briggs et al.³⁵

Variables such as age, gender, education, disease phenotype, MRI lesion load, and P300 amplitude are not significant for disability prognosis. Our results showed that age is not related to a higher disability prognosis. Several studies have shown that younger age at disease onset is a favourable prognostic factor,^{39,40} whereas older age is an unfavourable one.^{33,41} These findings have not been confirmed by other studies.^{42,43} The differences in conclusions can be explained by the heterogeneity of the disease and individual variability of the inflammatory process at a younger age in contrast to neurodegenerative pattern determining the disability at an older age.^{42,43}

The effect of sex on the short-term and long-term prognosis of MS has been examined in numerous studies. Male gender is associated with a less favourable disability outcome than female gender,^{33,35–39,41,44} although other studies have thus far rejected this.^{43,45} When multivariate analyses with multiple variables were used, the influence of gender on long-term disability progression was lost. This is consistent with our findings.

Education is not related to a patient's future disability. The disability EDSS score consists mainly of impaired motor systems. This is one of the well-known disadvantages of the EDSS scale; nevertheless, it is the most widely used scale. The EDSS scale poorly covers items of memory, fatigue, sleep, depression, and anxiety. Cognitive items are also insufficiently covered in the EDSS scale. An increase in cognitive dysfunction over time may be associated with lower education. Similar to

those of other works, our results did not show a prognostic value of education regarding future MS disability.³⁶

Like Barkhof,⁴⁶ we did not find a significant correlation between disability progression and baseline cerebral MRI lesion load; however, many studies have shown opposite results.^{47–50} Ten or more T2 lesions in a baseline MRI scan is an unfavourable prognostic factor of high disability in patients with MS at the 10-year follow-up.⁵¹ We did not correlate the site of the MRI lesions. Infratentorial and spinal lesions are related to worsening prognosis than others.⁵² Recent data show that volumetric quantitative measures have more prognostic value than conventional MRI methods. Our findings can also be explained by the well-known clinico-radiologic paradox.⁴⁶ This means that the number of visible lesions in MRI does not reflect the patient's disability. Disability usually increases during disease; by contrast, visible new lesions may not present. Significant correlations have been found between P300 latency and lesions located in the frontal lobes and brainstem. This is supported by the findings of hemodynamic activity during the oddball task in prefrontal and temporoparietal regions.⁵³ We did not include the relapse number on purpose because it is known that relapses in MS have no significant influence on disability in the long-term disease course.^{39,54}

P300 amplitude is related to motivation, attention, and working memory; therefore, it is understandable that it does not correlate with disability development. P300 amplitude is influenced by the patient's motivation and has greater variability than latency. Similar findings have been presented by other authors.^{1–3}

Most ERP studies in the MS population have been conducted in a cross-sectional manner to analyse cognitive dysfunction.^{3,4,7,9,11} The relationship of ERPs P300 as a prognostic factor of MS long-term disability progression has not yet been published in this context.

The strengths of this study are the analysis of an MS cohort for 15 years and the evaluation of all demographic, clinical, and radiologic parameters available at the given time.

This study also has several limitations: it is useful in routine clinical practice to dichotomize clinical variables, including P300 latency. We tried to show that P300 latency above 320 ms is associated with worse clinical prognosis; however, this is just a secondary analysis based on a limited number of patients and therefore should be interpreted with caution. Further research is necessary. The other limitation was small amount of patients from only one MS centre and that the MS diagnosis was determined on the basis of criteria from 2001. Fifteen years ago, we did not have such a wide range of effective drugs available for the treatment of MS; therefore, many patients progressed in their disability faster than they would today with current treatment options. Twenty-five (23%) patients did not complete the study, and the missing data could affect our results. MRIs were performed in different centres, and we did not have better options in the MRI methods. Sociodemographic data (i.e., smoking status and body mass index), comorbidities, and socioeconomic status, all related to disability progression in MS,³⁵ were not involved in our study. We must also take into account the possibility of reverse causation because all predictors were evaluated after the onset of disease. Having more severe

MS at onset may influence variation in the prognostic markers. From this point of view, caution is needed in generalizing the findings of a too heterogeneous sample of patients. In the future, it will be necessary to validate our results in a multicentre study and with a larger cohort.

CONCLUSIONS

Our study suggests that the P300 wave latency may be considered as a useful prognostic marker of MS disability progression over the 15-year follow-up. Thus, ERPs P300 wave examination should be added to the basic EPs examination to personalize a patient's treatment. We showed that a logistic regression model combining clinical and neurophysiologic data might be a reliable tool for identifying patterns of prognosis in everyday clinical practice. Understanding the individual prognosis of disability progression may help inform about therapeutic strategies.

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