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RESEARCH

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P300 event-related potentials in patients with multiple sclerosis

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Abstract

Background Cognitive impairment (CI) is a common and disabling symptom during the disease even in the earliest "preclinical" phase of patients with MS (pwMS). This study aims to assess cognitive function by measuring P300 event-related potential (ERP) and to look into the relationship between P300 abnormalities with the severity of the physical disability, education level, and disease duration.

Methods Fifty pwMS (28 females and 22 males) aged 20–54 years and fifty healthy subjects comprised of 21 females and 29 males aged 18–50 years serves as the control group was studied. All participants underwent medical history, neurological examination, cognitive functions using the Montreal Cognitive Assessment scale (MoCA) and the P300 ERP.

Results In this study, 48% of pwMS had CI. They had a longer P300 latency and a lower amplitude. Those with impaired cognition had a longer duration of illness and higher Expanded Disability Status Scale (EDSS), whereas those with intact cognition had a higher education level. P300 latency was correlated positively with EDSS and disease duration, but negatively with education level. P300 amplitude was found to be negatively correlated with EDSS, and disease duration but positively to the education level.

Conclusions P300, as a non-invasive test, would support the presence of CI in pwMS patients and could be used for screening in daily practice. P300 has a strong relationship with illness duration, disease subtypes, EDSS, and education level.

Keywords Multiple sclerosis, Cognition, P300

Introduction

Multiple sclerosis (MS) is a chronic, progressive, inflammatory, demyelinating autoimmune disorder caused by autoantibodies and immune cells destroying the myelin sheath [1]. MS causes a wide range of symptoms, including motor, cognitive, and neuropsychiatric issues, due to the widespread development of myelin destruction [2].

Cognitive impairment (CI) is a common and disabling symptom of all phenotypes of MS patients [3, 4], with a prevalence ranging from 34 to 65% of pwMS during the disease, even in the earliest "preclinical" phase [5, 6].

It has been established that the main risk factors for CI are greater physical disability, as measured by the Expanded Disability Status Scale (EDSS), older age, and disease duration [3, 7].

Various neuropsychological testing batteries have been developed to target the key areas of MS cognitive dysfunction in clinical practice, though their use is limited due to the long administration time, practice effect, and physical disability [8]. P300 event-related brain potentials (ERPs) have been used as neurophysiological markers in the assessment of cognition in pwMS in addition to neuropsychological tests [9, 10] and, more recently, in clinical practice [11]. Their measurement can shed light on

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cognitive processing stages, such as encoding, selecting, memorizing, and decision-making.

Given that cognitive disorders are among the most common problems in pwMS, the current study sought to assess the P300 based on age, gender, level of education, length of illness, EDSS, and total MoCA scores (as important individual characteristics).

Methods

Between November 2021 and November 2022, a case–control study was conducted at the MS clinic at Baghdad Teaching Hospital/Medical City. The IRB (Institute Review Board) of Al-Nahrain University's College of Medicine approved the study, and all participants provided informed consent.

Subjects

Fifty pwMS were included in this study after meeting the disease's McDonald Criteria [12]. They were made up of 28 females and 22 males ranging in age from 20 to 54. Their illness lasted anywhere from a year to more than 20 years. Patients with relapsing–remitting MS and secondary-progressive MS phenotypes were investigated. The patients had to be able to read and write to be included in the study, and none of them were taking any medications that had a significant impact on their cognitive performance. All of the patients were receiving immunomodulation therapy, such as interferon or glatiramer acetate. Patients with a history of impaired hearing function, a diagnosed psychiatric disorder, or a CI before MS diagnosis were barred from participating in the study.

Fifty healthy subjects consisting of 29 males and 21 females aged 18–50 years serve as the control group.

Methods

History and clinical examination

For all patients, a detailed history and neurological examination were performed:

Expanded disability status scale

Kurtzke's [13] Expanded Disability Status Scale (EDSS) is used to assess the level of disability in pwMS. In a 20-step scale, EDSS scores range from 0 (normal) to 10 (death due to MS) (with 0.5-unit increments). EDSS steps 1.0–4.5 refer to fully ambulatory patients, with the precise step number determined by the functional system score(s), whereas EDSS steps 5.0–9.5 are primarily defined by ambulation impairment [14].

Assessment of cognitive function

The Montreal cognitive assessment (MoCA) score was used to assess cognitive function. It evaluates multiple cognitive domains and is scored out of 30 points. A normal MoCA score range is between 0 and 30, with a score of 26 or higher considered normal [15, 16].

Measurement of P300

In a silent room, P300 was elicited using a Key point electromyography machine (Medtronic, Denmark) and an auditory "oddball" paradigm. Under the 10–20 International System, standard Ag/AgCl electrodes positioned at Cz, referenced at the mastoid process, and a forehead ground was used.

Subjects were instructed to mentally count rare tones while lying comfortably on the couch with their eyes closed, and they were then asked to report the number of rare tones counted at the end of each run. To determine performance accuracy, each patient's count was compared to the actual number of target tones provided at the end of each session. Two or three trials were conducted to ensure the consistency of the waveform, with each trial lasting until 200 artifact-free infrequent stimuli responses were recorded and averaged. The P300's latencies and amplitudes were measured.

The impedance was kept at 5K or less, the bandpass filter was set between 1 and 30 Hz, and the analysis time was set at 1024 ms with a 100 ms pre-stimulus baseline record.

Statistical analysis

SPSS statistical software, version 25, was used for all statistical analyses (IBM Corporation, USA). The quantitative variables were presented as means with standard deviations (SD) and were analyzed using an independent Student t test. The Chi-square test was used to analyze categorical variables that were expressed as counts and percentages. Pearson's correlation analysis was used to examine correlations between different quantitative variables. A statistically significant level of statistics was considered for all tests when $p < 0.05$.

Results

Table 1 displays the study population's basic demographic information. There was no statistically significant difference between the studied groups in terms of age, gender, or employment. On the contrary, pwMS had significantly lower education levels and total MoCA scores than controls ($p < 0.001$). Table 2 shows that pwMS had significantly longer P300 latency and smaller amplitude than controls (p 0.001, respectively) ($p < 0.001$, respectively).

The duration of illness and the EDSS were significantly higher in those with impaired cognition ($p = 0.001$, $p < 0.001$, respectively) when pwMS were divided into those with intact and those with impaired cognition based on the cutoff value of 26 of the MoCA score. Those

Table 1 Demographic characteristics of the study population

Variable	Patients *N* = 50	Controls *N* = 50	*p* value
Age, years			
Mean ± SD	35.06 ± 8.97	33.3 ± 5.56	0.318
Range	20–54	18–50	
Gender			
Male (number, %)	22(44%)	21(42%)	0.840
Female (number, %)	28(56%)	29(58%)	
Employment			
Yes	22(44%)	31(62%)	0.071
No	28(56%)	19(38%)	
Education level, years			
Mean ± SD	13.03 ± 3.48	15.6 ± 2.32	**< 0.001**
Range	8–24	10–20	
Total MoCA score			
Mean ± SD	24.58 ± 4.29	28.14 ± 0.73	**< 0.001**
Range	14–30	27–30	

Significant values (*p* value < 0.05) are given in bold

Table 2 P300 parameters of the study population

Variables	Patients *n* = 50	Controls *n* = 50	*p* value
P300 latency (ms)			
Mean ± SD Range	340.32 ± 39.34 294–417	308.82 ± 7.86 291–322	**< 0.001**
P300 amplitude (μV)			
Mean ± SD	7.76 ± 2.59	9.83 ± 0.95	**< 0.001**
Range	2.08 ± 12.0	8–12	

Significant values (*p* value < 0.05) are given in bold

with impaired cognition had significantly lower education levels and total MoCA scores (Table 3).

Table 4 shows that in pwMS with impaired versus intact cognition, the P300 latency was significantly prolonged, while the amplitude was significantly lower ($p < 0.001$, respectively).

Table 5 and Figs. 1, 2 and 3 demonstrate Pearson's correlation between P300 ERP and demographic features (age, disease duration, EDSS, education level, and MoCA scores).

Age and P300 latency were found to have a significant positive correlation ($r = 0.432$, $p < 0.001$). On the other hand, there was a significant negative correlation with P300 amplitude ($r = -0.415$, $p < 0.001$). Similarly, disease duration was found to be positively related to P300 latency and negatively related to P300 amplitude ($r = 0.750$, $p < 0.001$, and $r = -0.838$; $p < 0.001$, respectively). Likewise, there was a significant positive correlation between EDSS and P300 latency ($r = 0.861$, $p < 0.001$)

Table 3 Demographic and clinical data of patients with multiple sclerosis according to MoCA score

Variable	Cognition		*p* value
	Impaired (*n* = 24)	Intact (*n* = 26)	
Age, years			
Mean ± SD	36.88 ± 9.77	33.24 ± 7.87	0.153
Range	20–54	20–50	
Gender			
Male (number, %)	11(44%)	11(44%)	1.0
Female (number, %)	14(56%)	14(56%)	
Disease duration, years			
Mean ± SD	9.0 ± 6.11	4.46 ± 2.36	**0.001**
Range	1–22	1–10	
EDSS			
Mean ± SD	5.0 ± 2.12	2.58 ± 1.05	**< 0.001**
Range	1.5–8	1–5	
Employment			
Yes (number, %)	8(32%)	14(56%)	0.087
No (number, %)	17(68%)	11(44%)	
Education level, years			
Mean ± SD	10.84 ± 2.39	15.2 ± 3.03	**< 0.001**
Range	8–16	9–24	
Total MoCA score			
Mean ± SD	21.04 ± 3.25	28.12 ± 0.97	**< 0.001**
Range	14–25	27–30	

Significant values (*p* value < 0.05) are given in bold

Table 4 P300 parameters in patients with multiple sclerosis according to their cognition

Variables	Cognition		*P* value
	Impaired (*n* = 24)	Intact (*n* = 26)	
P 300 latency (ms)			
Mean ± SD	372.92 ± 30.22	307.72 ± 5.76	**< 0.001**
Range	300–417	294–318	
P 300 amplitude (μV)			
Mean ± SD	5.95 ± 2.34	9.58 ± 1.11	**< 0.001**
Range	2.08 ± 9.8	8.1–12	

Significant values (*p* value < 0.05) are given in bold

but it was negatively correlated with P300 amplitude ($r = -0.915$, $p < 0.001$).

Educational level, on the other hand, has a negative correlation with P300 latency and a positive correlation with P300 amplitude ($r = -0.623$; $p = 0.002$ and $r = 0.555$; $p < 0.001$, respectively). P300 wave latency was also found to be negatively related to the total MoCA

Table 5 Pearson's correlation between demographic data and P300 parameters

Variables	P300 latency		P300 amplitude	
	r	*p*	*r*	*p*
Age, years	0.432	< 0.001	0.415	0.001
Disease duration, years	0.750	< 0.001	-0.838	< 0.001
EDSS	0.861	< 0.001	-0.915	< 0.001
Education level	− 0.623	0.002	0.555	< 0.001
Total MoCA score	− 0.963	< 0.001	0.932	< 0.001

score ($r = -0.963$, $p < 0.001$) and positively related to P300 amplitude ($r = 0.932$, $p < 0.001$).

Discussion

In this study, 48% of pwMS had CI, which is within the range reported elsewhere, indicating widespread focal white matter lesions that are primarily related to impaired information processing speed, implying MS-related CI as a disconnection syndrome [17].

Gender had no significant impact on the cognitive function of the participants, according to the current study's findings, which are consistent with the findings of other researchers [18–20], but contradict the findings of Benedict et al. [21], who identified the male gender as one of the risk factors for CI in pwMS, and Shayganne-jhad et al. [22] who reported more cognitive complications in women than men. The lack of consistency could be attributed to the study's small sample size, different MS disease types, disease duration, and cognitive test type.

Age of pwMS did not affect cognitive function in this study, which is consistent with the findings of Hassan-shahi et al. [20] but differs from the findings of other researchers [18, 19, 23], who reported a decrease in cognitive level with aging or a significant relationship between age and learning, memory, and executive functions based on different batteries. The inconsistency with the latter results could be attributed to the study of different age groups, evaluation of older ages, or differences in cognitive tests.

In the current study, CI was significantly related to the duration of illness, as evidenced by a significant association between disease duration and prolonged P300 latency, lower P300 amplitude, and low MoCA score, all of which reflect changes in the central nervous system over time [24, 25]. Patients' cognitive abilities deteriorated over time, as measured by assessments of their

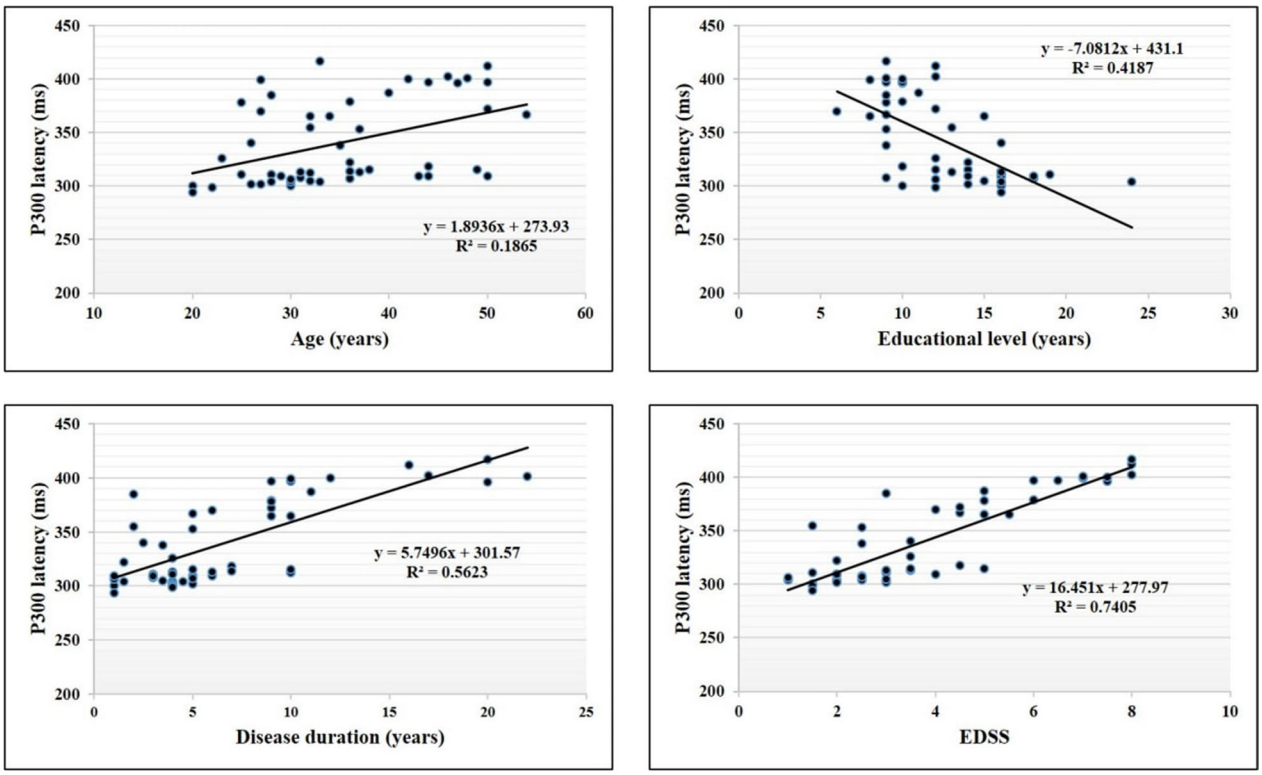

Fig. 1 Scatter plot and regression line between P300 latency and age (top left); disease duration (bottom left); educational level (top right), and EDSS (bottom right)

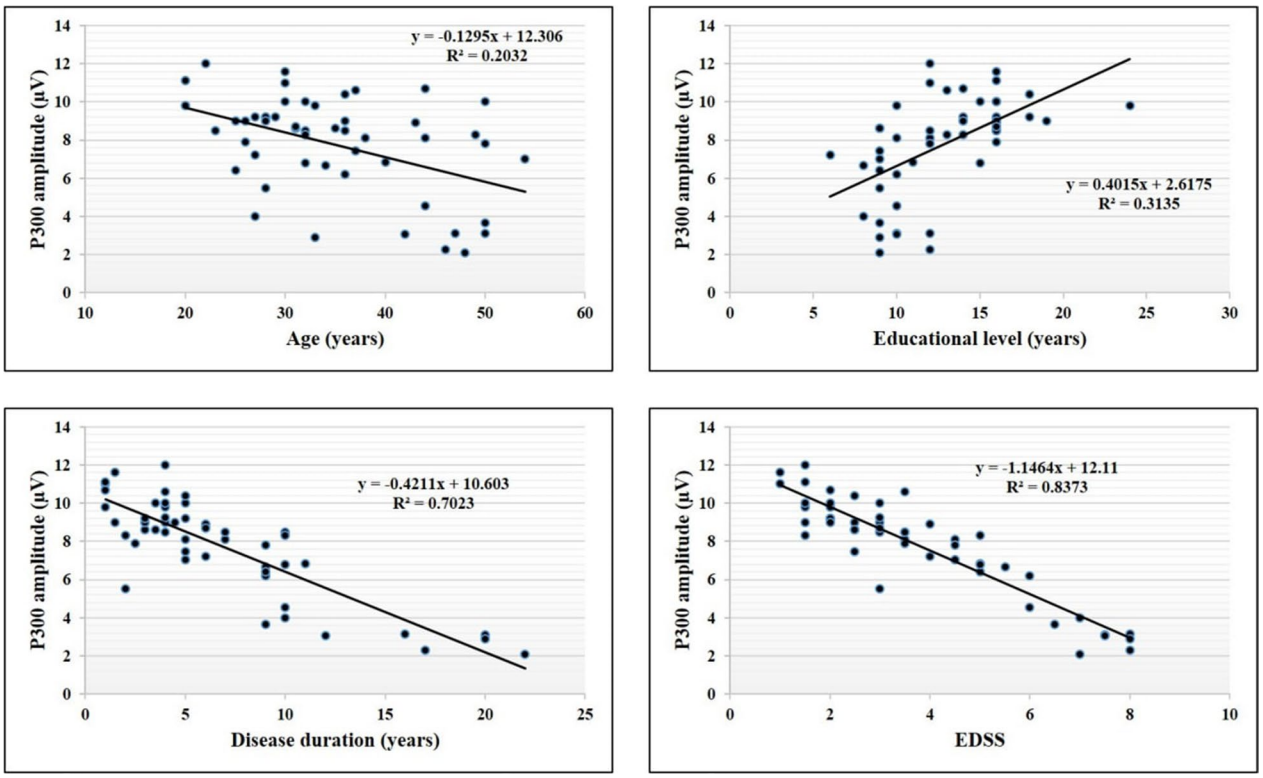

Fig. 2 Scatter plot and regression line between P300 amplitude and age (top left); disease duration (bottom left); educational level (top right), and EDSS (bottom right)

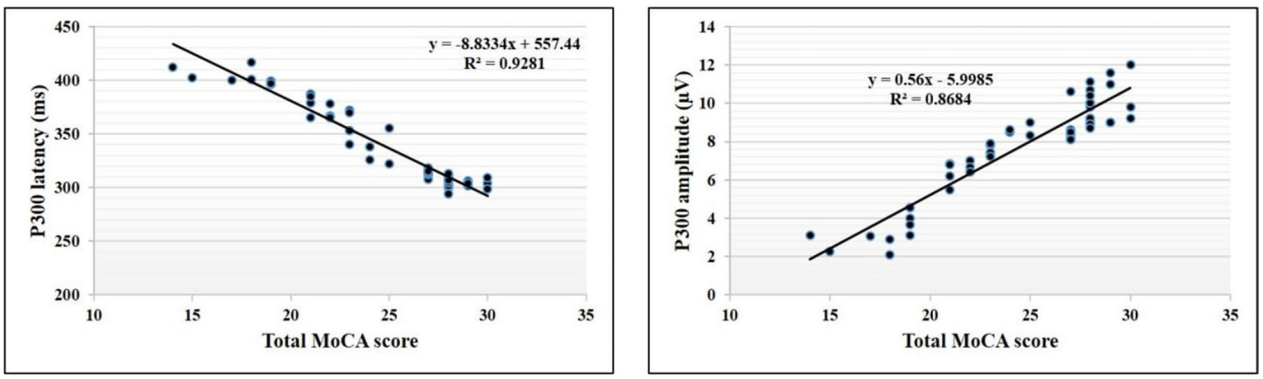

Fig. 3 Scatter plot and regression line between P300 latency and total MoCA score (left); P300 amplitude and total MoCA score (right)

short-term verbal memory, abstract reasoning, and linguistic abilities [7, 26–28]. In contrast to our findings, other studies demonstrate weak or no correlation between CI and disease duration [29, 30].

In this study, low educational attainment was linked to poor cognitive performance in pwMS. This finding is consistent with the findings of Shaygannejhad and colleagues [22], who discovered a significant relationship between cognitive disorders and educational level. It was reported that the higher education groups had the highest scores on the correct answer to the Judgment of Line Orientation Test [31] and a lower level of education was most important for CI even in patients without gray matter atrophy [32, 33]. In contrast to these findings, some research groups have stated that education level does not act as a predictor of cognitive dysfunction [19, 20, 34], which could be due to differences in cognitive assessment tools, sample populations, and sizes.

Our findings show a strong relationship between CI and individual physical state (as measured by the EDSS), which is consistent with other studies [7, 35–37].

The current study found that P300 ERP at Cz (central lobe) was significantly different in pwMS compared to the control group. The prolonged latency reflects the length of time it takes for information to be processed, whereas the reduced amplitude reflects a disruption in the activities of some centers (frontal and parietal cortex, thalamus, and temporomesial cortex) or temporal dispersion of information processing [38].

In people with MS, P300 REP was linked to disease duration, EDSS, education level, and MoCA score. Other studies have confirmed and described these findings [10, 39, 40]. However, they differed from studies that found pwMS to have normal P300 latencies [41, 42], unaffected amplitude [43], or no statistical correlations between P300 latency and/or amplitude and disease duration [44]. This difference could be attributed to the inclusion of more patients with lower physical disabilities or to the fact that the disease manifested itself in individual patients at different ages.

Total MoCA scores of pwMS were positively correlated with P300 amplitude and negatively correlated with P300 latency, which is consistent with Tag El-din and colleagues' findings [45].

The strong correlation between P300 ERP and EDSS and disease duration supports Ateş and colleagues' findings [46]. Furthermore, Triantafyllou and colleagues [47] discovered a significant relationship with EDSS but not with disease duration. Rasoulifard et al. [48] discovered a significant correlation between P300 latency but not amplitude, disease duration, or EDSS.

Patients with more severe physical disabilities (EDSS) had more cognitive dysfunctions, longer latencies, and lower amplitudes of P300 ERPs, according to the findings of this study. These findings were also reported by Kocer et al. [49].

The small sample size, the inclusion of only relapsing–remitting and secondary-progressive MS phenotypes, the difference in educational level, and the wide range of disease duration are among the limitations of our study. Consequently, longitudinal research may be required in the future for additional evaluation.

Conclusion

Our study concludes that (1) P300, as a non-invasive test would support the presence of CI in pwMS and can be used for screening in daily practice. (2) P300 is significantly related to illness duration, education level, and EDSS. Based on the findings, which show frequent changes in P300 in pwMS, we recommend that CI be diagnosed early to plan additional supportive treatment.

Abbreviations

CI	Cognitive impairment
EDSS	Expanded disability status scale
ERPs	Event-related potentials
MoCA	Montreal Cognitive Assessment test
MS	Multiple sclerosis
pwMS	Patients with multiple sclerosis
RRMS	Relapsing–remitting multiple sclerosis
SPMS	Secondary progressive multiple sclerosis

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Author contributions

I am the author for preparation of this manuscript, I did the neurophysiological tests, made the design of the study, and I approved the final version for submission.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article. The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the IRB (Institute Review Board) and written consent for participation from all subjects was ensured.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interest.

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