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P300 in peripheral neuropathy: cognitive functions assessment and gender effect

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Abstract

Background Patients with peripheral neuropathy (PN) have subtle central pathology that might contribute to cognitive impairment. P300 is a cognitive potential that is connected to both sensory and cognitive processes. Subjects with neurocognitive disorders have considerably longer P300 latency. This study aims to investigate P300's potential as a marker of early-stage cognitive deterioration in PN patients and also, the effect of gender on P300 in patients with PN.

Results A study group of 60 subjects with PN of various etiologies and no other neurological conditions was included, in addition to, a control group of 40 volunteers with normal hearing sensitivity and no central or peripheral auditory neurological abnormalities. P300 response showed significant delayed latencies in study group when compared to control group. Male group had significant delayed P300 latencies in comparison to female group. As regard P300 amplitude, male group showed no statistically significant differences in comparison to female group.

Conclusions Although patients with PN apparently have normal cognitive function, the results in this study revealed the possibility of subtle cognitive impairment. Cognitive functions are affected in both axonal PN and demyelinating PN, however there were no differences found between the two subgroups. Auditory evoked potentials, particularly P300 can be used easily for early detection of subclinical cognitive impairment before appearance of any neurological manifestations. P300 latencies are more important than amplitudes and may be used alone or in addition to amplitudes in cognitive function assessment.

Keywords Peripheral neuropathy, Cognitive function, Gender, Auditory evoked potentials, P300

Background

The term "peripheral neuropathy" (PN) refers to a wide range of illnesses that harm and impair the nerves of the peripheral nervous system in a variety of ways [1]. It is one of the most prevalent neurological issues, especially

among the elderly [2]. According to Callaghan et al. [3], PN may impact 5% of the global population, especially in Western countries than in developing countries [4]. Around 30% of all occurrences of PN are caused by diabetes, which is a global phenomenon [5].

The differential diagnosis of PN is very important, especially with diseases with similar symptoms [6]. Although, idiopathic PN accounts for the majority of cases (about 40% of cases), PN had many other causes including: genetic, toxic, vitamin deficiency, endocrine, inflammatory and other medical conditions (like uremia and hepatic failure) [7]. These different etiologies had variable pathology to affect central nervous system (CNS) [8]. Many people with PN have comorbid cognitive impairment [9]. There is evidence that the severity

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of PN has a significant negative correlation with cognitive [10].

Few researches have examined the relationship between the various PN causes and cognitive function [10]. Some of these illnesses could be associated with lower hippocampal neurogenesis, which would then cause the hippocampus to shrink and die with subsequent impaired cognitive function [11]. So, early detection is essential for the prevention and interventions of this frequent neurodegenerative disease to enable the prescription of treatment at the earliest opportunity [12].

Event-related potentials (ERPs), in addition to neuropsychological assessments, have been found to be sensitive indicators of cognitive impairments [13]. They can reveal details regarding higher-order CNS functions like categorization and classification of multimodal inputs in addition to decoding and interpretation of complex stimuli like language and images [14].

Damage to the brain or peripheral receptors caused by physical or metabolic processes can impair the CNS's ability to receive sensory information and result in inefficient processing within and between central pathways such as delayed latency, reduced amplitude, or even absent ERP components [14].

P300 is a cognitive potential that is connected to both sensory and cognitive processes. It represents the acoustic properties of the stimuli's conscious perception, attention, and auditory discrimination (tones and speech). The P300 wave is a late, cortical, neurogenic, transient, far-field and endogenous auditory evoked potentials (AEPs) that run through the thalamus and cortex. It occurs in the form of a positive (P) wave between 220–380 ms (ms) [15]. P300 is intentionally measured when a deviant and random stimulus is found amid a group of standard stimuli [16].

Subjects with neurocognitive disorders have considerably longer P300 latency, which was similar in both cases of minor or major neurocognitive disorders [17]. Moreover, P300 amplitude and latency are thought to have important correlates to cognitive abilities [18].

In this study, we hypothesized that patients with PN have subtle central pathology that might contribute to cognitive impairment. P300 component of ERP was used to study this issue. The primary purpose of this research was to further examine the utility of P300 as a marker of early-stage cognitive impairment in patients with PN.

Methods

We evaluated the hypothesis that patients with PN have subtle central pathology that might contribute to cognitive impairment. To this finding, P300 components of the ERPs were recorded. We also examined the gender affection on P300 in these patients.

This study was performed on 100 adult subjects aging 18–45 years, divided into two groups. The study group is composed of 60 adults with PN of different etiologies and without other neurological disorders. The control group is composed of 40 normal volunteers with normal hearing sensitivity and free from any central or peripheral auditory neurological disorder. Criteria of the American Association of Electrodiagnostic Medicine and the American Academy of Physical Medicine and Rehabilitation were used [19, 20]. If two distinct aberrant nerve responses occurred in more than one limb, PN was confirmed [21] in which nerve conduction study (NCS) parameters exceed normative data by two standard deviations (SD).

Study group was further divided according to the underlying pathology of PN into two subgroups: a) Axonal PN subgroup. b) Demyelinating PN subgroup.

Inclusion criteria: subjects with bilateral normal hearing sensitivity.

Exclusion criteria: subjects who had hearing loss or had undergone ear surgery, a history of head trauma or a stroke, chronic systemic diseases (such as hypertension or uncontrolled diabetes mellitus), psychological disorders, endocrine diseases, otological disorders, a history of taking ototoxic medications, or a history of exposure to noise.

Participants were chosen from patients attending University Hospitals' Audiovestibular Unit, Otolaryngology Department, Rheumatology department and Internal Medicine department. After explaining the test process to each person in the study, written consent was obtained.

All participants underwent a thorough physical examination that included taking their medical history, an otoscopic examination, pure tone audiometry between 250 and 8000 Hertz (Hz), and speech audiometry using Interacoustic AD629 audiometer. Tympanometry and acoustic reflexes (ipsilateral) were assessed using an Interacoustic AT235.

P300 was recorded in response to two stimuli (Tone burst) of different frequencies presented in oddball paradigm. They were presented in a random order with a 10 ms rise/fall time and 30 ms plateau (10–30–10). The standard stimulus (1000 Hz), one of the two stimuli, was provided more frequently than the deviant stimulus (2000 Hz). There were 200 stimuli in total (standards plus deviants). They were presented at a rate of 1 stimulus per second (through an insert-phone ER-3A) at 70 dB SPL with alternate polarity. The gain factor was (10,000), high-pass filtered at 1.0 Hz 6/octave and low-pass filtered at 100 Hz. The analysis window was -90 ms pre-stimulus to 450 ms post-stimulus. Subjects were instructed to maintain their composure while reclining on a cozy

sofa. After that, they were told to actively (and mentally) count the deviants that had a 15% chance of occurring. According to the side being stimulated, four electrodes were employed for P300 recording: Fz (active electrode), Fpz (ground electrode), M1 and M2 (mastoids) were used as reference electrodes. For subjects in both groups, latencies and amplitudes were calculated. The electrode impedance was kept below 5 K Ω . Measurements made on the latency (ms) and the peak to following trough amplitude (μ V).

Statistical Package for the Social Studies version 22 was used to statistically examine the data that had been gathered. Mean, SD and median are used to describe quantitative data. Number and percentage formats are used to portray qualitative data. The threshold for significance was set at $p \leq 0.05$. To compare between the two groups, categorical variables were compared using the Chi-square test, while quantitative variables with normally distributed data were compared using the Student t test, and those with abnormally distributed data were compared using the Mann-Whitney test.

Results

There were 100 participants in this study, which took place between April 2020 and April 2022. There were 16 males and 24 females in the control group ($n=40$), who had an average age of 30.50 ± 7.55 years, and 30 males and 30 females in the study group ($n=60$), who had an average age of 31.62 ± 4.11 years. Age and gender did not significantly differ between the two groups ($p > 0.05$).

P300 response in the study group had significantly delayed latencies when compared to the control group (Fig. 1). As regard P300 amplitude (Fig. 2), lower amplitudes were observed in the study group in comparison to the control group however, they did not reach a significant level (Table 1).

Comparing the results of P300 response between male and female in the study group revealed significant delayed P300 latencies in male patients in comparison to female patients. As regard P300 amplitude, male patients showed no statistically significant differences in comparison to female patients (Table 2).

Comparing the results of P300 response between male and female in the control group revealed significant delayed P300 latencies in male group in comparison to female group. As regard P300 amplitude, both male and female had similar results (Table 3).

The study group was further divided into two subgroups according to the pathology of PN: a) Axonal PN subgroup (44 patients). b) Demyelinating PN subgroup (16 patients).

Regarding the axonal PN subgroup, there were significant delayed latencies of P300 when compared to the control group. As regard the P300 amplitudes, small amplitudes were observed in the axonal PN subgroup in comparison to the control group but they were statistically non-significant (Table 4).

Regarding the demyelinating PN subgroup, there were significant delayed latencies of P300 when compared to the control group. As regard the P300 amplitudes, small

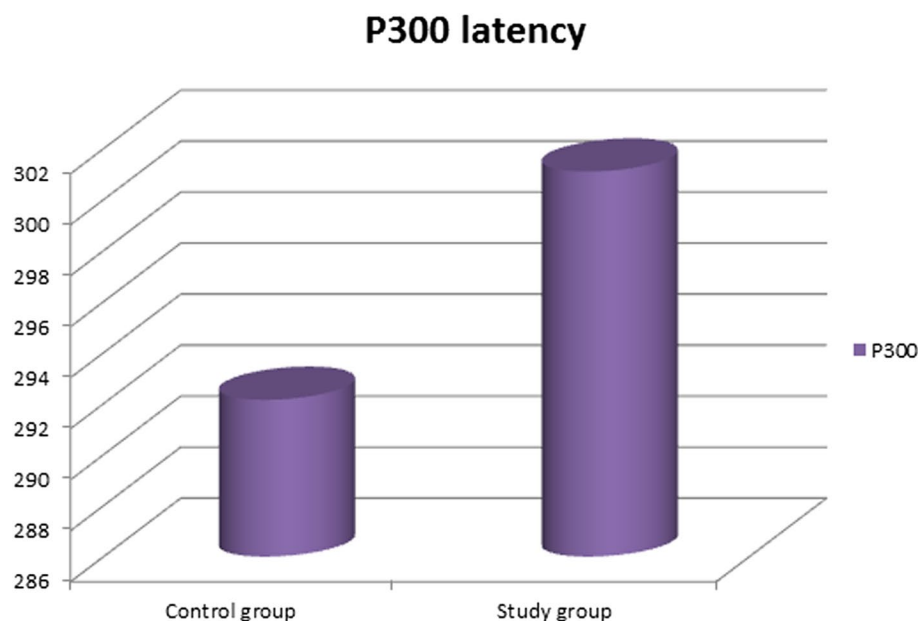


Fig. 1 Comparison between the control and the study group regarding P300 latencies. P300 response in the study group (301.1 ± 23.43) had significantly delayed latencies when compared to the control group (292.15 ± 15.87)

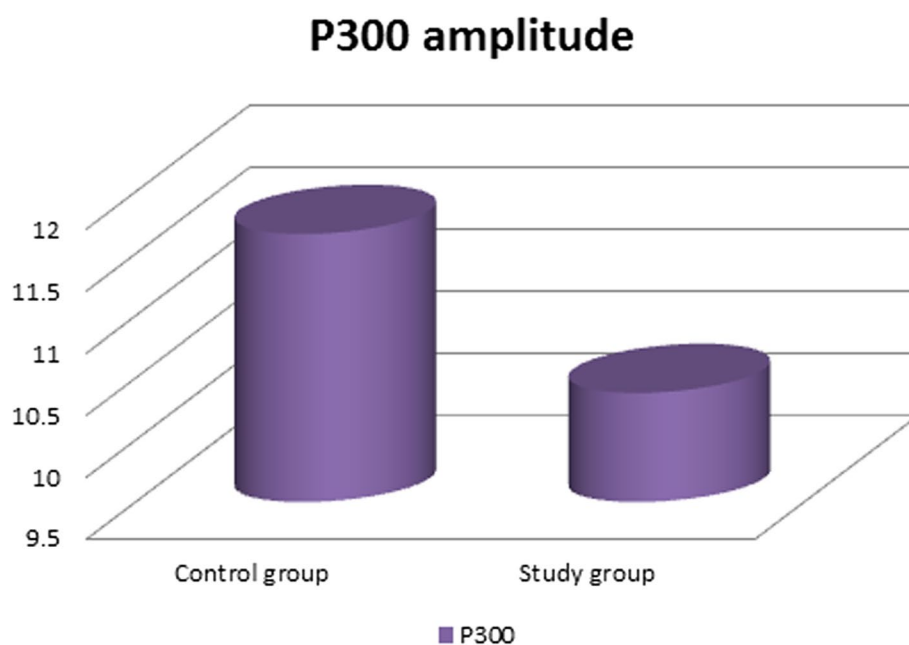


Fig. 2 Comparison between the control and the study group regarding P300 amplitudes. Lower amplitudes were observed in the study group [10.38 (3.85–69.70)] in comparison to the control group [11.66 (6.24–21.31)] however, they did not reach a significant level

Table 1 Comparison between the control and the study groups in P300 latencies and amplitudes

P300	control group (n = 40) (mean/ median) ± (SD/ min—max)	study group (n = 60) (mean/ median) ± (SD/ min—max)	t / z	P
Latency	292.15 ± 15.87	301.1 ± 23.43	2.11	0.037*
Amplitude	11.66 (6.24–21.31)	10.38 (3.85–69.70)	1.236	0.800

* Statistically significant at $p \leq 0.05$

Table 2 Gender-based difference in the study group regarding P300 latencies and amplitudes

P300	Male (n = 30) (mean/ median) ± (SD/ min—max)	Female (n = 30) (mean/ median) ± (SD/ min—max)	t / z	P
Latency	308.33 ± 22.86	293.87 ± 22.04	2.495	0.015*
Amplitude	10.47 (5.45–25.50)	10.38 (3.85–69.70)	1.305	0.871

* Statistically significant at $p \leq 0.05$

Table 3 Gender-based difference in the control group regarding P300 latencies and amplitudes

P300	Male (n = 16) (mean/ median) ± (SD/ min—max)	Female (n = 24) (mean/ median) ± (SD/ min—max)	t / z	P
Latency	300.5 ± 13.79	286.6 ± 14.90	2.98	0.005*
Amplitude	11.76 (6.24–21.31)	11.66 (6.36–18.05)	192	1.000

* Statistically significant at $p \leq 0.05$

Table 4 Comparison between control and Axonal PN groups in P300 latencies and amplitudes

P300	control group (n = 40) (mean/ median) ± (SD/ min—max)	Axonal PN (n = 44) (mean/ median) ± (SD/ min—max)	t / z	P
Latency	292.15 ± 15.87	300.36 ± 23.89	1.84	0.005*
Amplitude	11.66 (6.24–21.31)	10.61 (5.45–69.70)	884.0	0.971

* Statistically significant at $p \leq 0.05$

amplitudes were observed in the demyelinating PN subgroup in comparison to the control group but they were statistically non-significant (Table 5).

No statistically significant differences were found between the two subgroups as regard P300 latencies and amplitudes (Table 6).

According to different causes of PN, we found 29 (out of 60) patients had diabetic PN (DPN), 17 (out of 60) had leprosy, 12 (out of 60) had vasculopathy and 2 (out of 60) patients had Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) Fig. 3.

Table 5 Comparison between control and Demyelinating PN groups in P300 latencies and amplitudes

P300	control group (n = 40) (mean/ median) ± (SD/ min—max)	Demyelinating PN (n = 16) (mean/ median) ± (SD/ min—max)	t / z	P
Latency	292.15 ± 15.87	303.12 ± 22.73	2.06	0.045*
Amplitude	11.66 (6.24–21.31)	9.15 (3.85–25.50)	280.0	0.467

* Statistically significant at $p \leq 0.05$ **Table 6** Comparison between Axonal PN and Demyelinating PN groups in P300 latencies and amplitudes

P300	Axonal PN (n = 44) (mean/ median) ± (SD/ min—max)	Demyelinating PN (n = 16) (mean/ median) ± (SD/ min—max)	t / z	P
Latency	300.36 ± 23.89	303.12 ± 22.73	0.40	0.690
Amplitude	10.61 (5.45–69.70)	9.15 (3.85–25.50)	422.0	0.242

* Statistically significant at $p \leq 0.05$

According to type of nerve affection, we found 52 (out of 60) patients had sensorimotor affection and 8 (out of 60) patients had sensory affection.

Discussion

The P300 cognitive component is the best ERP at identifying the consistency of mental processes. Studies have shown that the latency of P300 is proportional to the time needed to perceive and assess the stimulus and is connected to the speed of cognitive processing and memory. It evaluates how quickly memory and attention resources are called upon, showing the amount of time needed for processing before the response is produced [22]. The P300 amplitude, meanwhile, is correlated with the novelty of stimuli and attention demands. An increase in P300 amplitude indicates higher neural circuit activation and is related to the amount of attention and memory resources used. Higher amplitudes indicate more cognitive capacity [23]. Attention, concentration and memory impairments are associated with latency variation [24] where shorter latencies are associated with improved cognitive function and indicated better attention [25]. Consequently, in clinical practice, the P300 can be utilized as an indicator to assess cognitive impairment [26].

In this study, P300 latencies in the study group were significantly delayed in comparison to the control group. According to Bevilacqua et al. [27], the increase in latency suggests a slow searching and processing of auditory information and is a sign of cognitive problems [22]. In another cognition-related condition, similar findings

were found by Oliveira et al. [28], De Salvo et al. [29], and Krishnamurti and Messersmith [30].

Oliveria et al. [28] found that there is a relationship between long-latency potentials and cognitive performance in the elderly, which was observed by the significant increase in the cognitive component (P300) latency in the elderly population.

De Salvo et al. [29] findings confirm that P300 ERPs' component could be a predictive marker for cognitive recovery of ischemic subacute stroke patients.

Krishnamurti and Mesersmith [30] show that P300 may provide valuable insights into differences in higher-order auditory processing between younger and older listeners and a potential clinical tool to evaluate central auditory changes in older listeners. Younger listeners showed shorter P300 latencies than older listeners. P300 amplitudes were greater for younger listeners than older listeners. These results indicate that aging slows down information-processing.

P300 amplitudes were found to be reduced in the study group, although they were not statistically significant. This finding could have two main justifications. First, some commercially available software determines the amplitude of P300 from the plot's midline, even though the International Federation of Clinical Neurophysiology advises measuring it from the N200 (N2) curve's lowest point. Second, the research shows that the typical P300 amplitude range varies greatly, with extreme ranges of 5 to 20 μv [31].

It is suggested that the amplitude of P300 serves as a measure of working memory capacity and attentional resources since it captures the brain's response to changes in the external input [32].

Demyelinating diseases were shown to have reduced P300 amplitude and delayed P300 latency [33]. In another cognition-related condition like iron-deficiency anemia, mild cognitive impairment is indicated by prolonged P300 latency and reduced amplitude [34].

According to the proposed theory for neural P300 generators, the oddball paradigm which requires distinguishing between the deviant and standard stimuli, triggers activity in the frontal lobe, which is important for the function of attention [35]. Following this, the temporo-parietal regions activate memory functions that depend on the integrity of the junctional area. This cascade of activation was made obvious by neuroimaging techniques like functional magnetic resonance imaging with simultaneous ERP recording [36]. According to the different transmitter P300 hypothesis, the frontal area's role of attention is driven by dopaminergic activity, whereas the temporo-parietal junction's function of working memory is mediated by norepinephrine activity [32].

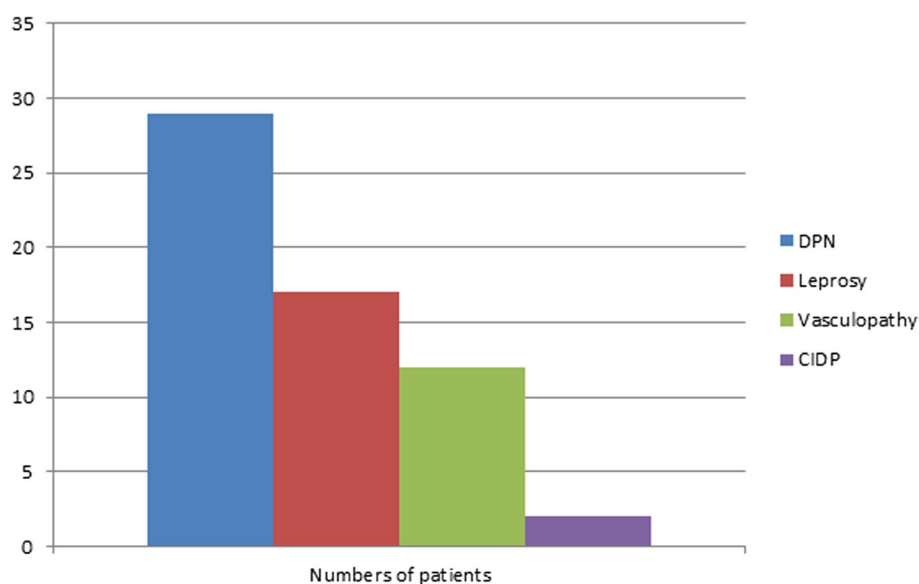


Fig. 3 Number of patient in different causes of PN. There were 29 (out of 60) patients had diabetic PN (DPN), 17 (out of 60) had leprosy, 12 (out of 60) had vasculopathy and 2 (out of 60) patients had Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Working memory and attention as measured by P300 potential are primarily dependent on cholinergic substrate [37], which is also the primary neurotransmitter responsible for the generating of P300 [38]. Therefore, the delayed latency of P300 potential may be explained by cholinergic neuron loss in various forms of cognitive impairment [39], as described by other studies [40].

Studying the gender effect on P300 latencies and amplitude in this work revealed statistically significant delayed P300 latencies in males in comparison to females. However, there are no significant differences regarding P300 amplitudes between male and female groups. This is not consistent with Melynnyte et al. [41] who revealed a substantial gender difference in the P300 amplitude, with females having higher amplitude than males. At the contrary, the authors stated that gender has little impact on the P300 latency where it showed little variation between males and females. The hormonal context, anatomy, and other methodological aspects might all contribute to the gender-related effect on P300 recording. For example, it has been demonstrated that females have greater corpus callosum diameters and more parietal lobe grey matter volume [42].

Additionally, the study's season could have an effect on P300 ERP [43] due to gender-specific seasonal mood differences [44] and seasonal variations in sex hormones like testosterone [45]. Both the winter and the summer have higher amplitudes for male, while the winter has shorter P300 latencies in female [46].

The statistically significant delayed P300 latencies in males in comparison to females in the study group could

be also explained by the higher incidence of cranial nerve palsies in males [47]. This is further supported by the well-established observations of differences between males and females in the prevalence, age of symptom onset, and severity of psychiatric disorder symptoms [48]. According to Sánchez et al. [49], the use of sex steroids has been accepted as being important in the management of neuropsychiatric diseases. For example, according to a study by Braverman et al. [50], P300 latencies were longer among males between the ages of 30 and 49 who had lower testosterone levels (but not the amplitudes). Furthermore, the influence of synthetic sex hormones on females who used estradiol and progestin combined resulted in shorter P300 latencies as well as larger P300 amplitudes [51].

Therefore, the research on the relationship between gender and evoked potential results supported our findings. First, patients with PN have subtle cognitive impairment as revealed by delayed P300 latency. Second, there is a lack of consistency in the gender effects on P300 amplitudes, with around half of the research reporting higher P300 amplitudes in females while the other studies finding no gender effects. It is highly uncommon to find reports of higher P300 amplitudes in males [41, 48–51].

The study group was further divided into two subgroups depending on the underlying pathology of PN: the axonal and demyelinating subgroups.

The distinction between axonal and demyelinating pathology is often not clear [52] and this was consistent with that of our study according to P300. Typical electrophysiological signs of demyelinating PN include more

reduced motor and sensory nerve conduction velocities, more increased distal motor latencies and prolonged F-wave-latencies. Characteristic signs of axonal PN consist of a reduction in the amplitudes of compound muscle action potentials and sensory nerve action potentials and only a slight decrease (or near-normal) of conduction velocity [53].

Demyelination typically occurs at numerous locations along a nerve, resulting in variations in the propagation of nerve action potentials, such as a conduction block or a reduced conduction velocity. Abnormal temporal dispersion, also known as slowed conduction velocity in a non-uniform pattern, results in abnormal dispersion of nerve action potential arrival times at the recording site. So, the presence of conduction block and abnormal temporal dispersion could therefore indicate demyelinating injury [54].

It's also crucial to remember that mild axonal damage could develop over time in a PN that is predominantly demyelinating. Although a mixed pattern is also possible, the majority of axonal polyneuropathies can be either motor or sensory dominant [55].

These indicators make the demyelinating pathology has some reduced P300 amplitude and delayed P300 latency [33] and this is consistent with our study although it is not significant. Also, due to the small number of cases in the demyelinating PN subgroup compared to the axonal PN subgroup, this may have led to the results not being significant.

Conclusions

Although patients with PN apparently have normal cognitive function, the results in this study revealed the possibility of subtle cognitive impairment. Cognitive functions are affected in both axonal PN and demyelinating PN, however there were no differences found between the two subgroups. AEPs, particularly P300 can be used easily for early detection of subclinical cognitive impairment before appearance of any neurological manifestations. P300 latencies are more important than amplitudes and may be used alone or in addition to amplitudes in cognitive function assessment.

Abbreviations

AEPs	Auditory evoked potentials
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CNS	Central nervous system
dB SPL	Decibel Sound Pressure Level
DPN	Diabetic PN
ERPs	Event-related potentials
Fpz	Pre frontal midline (high forehead)
Fz	Frontal midline
Hz	Hertz
KΩ	Kilo Ohm
M1	Left Mastoid

M2	Right Mastoid
ms	Millisecond
μV	Microvolt
N	Negative
NCS	Nerve conduction studies
P	Positive
PN	Peripheral neuropathy
SD	Standard deviation

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Authors' contributions

MM, AI and TG conceived and designed the analysis, collected the data, performed the analysis and wrote the paper. TH and SR collected the data.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study is approved by the Scientific Research Ethics Committee on 8th of April 2020 under the number KFSIRB200-2.

Consent for publication

Written informed consent was obtained from the study participants.

Competing interests

The authors have no competing interests to declare.

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