Evaluation of Nociceptive Flexor Reflex Response in Patients with Painful Idiopathic Parkinson's Disease

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Abstract

Aim: We aimed to investigate the utility of trigeminocervical reflex (TCR) and nociceptive flexion reflex (NFR) as objective measures for assessing pain—a common NMS—in patients with PD, targeting both the upper and lower body regions.

Methods: All subjects were further classified into four groups: Group-I: Healthy individuals without PD or pain, Group-II: Individuals without PD but reporting non-specific musculoskeletal pain, Group-III: PD patients without pain, Group-IV: PD patients with pain as a NMS. The clinical assessment of PD was conducted using the Hoehn and Yahr Staging Scale (HYS) and the Unified Parkinson's Disease Rating Scale (UPDR). We divided the human body into upper and lower regions—utilizing the TCR for upper body pain and the NFR for pain around the lumbar and pelvic areas.

Results: The Group-IV had a longer mean disease duration than those in Group-III (8.0±6.6 vs 3.0±3.5 and p=0.121). The mean UPDRS score significantly higher in Group-IV compared to Group-III (42.5±13 vs 27.4±15.3 and p=0.022). The mean VAS score was 7.0±0.7 in Group-II and 6.3±1.3 in Group-IV, with no significant differences in pain localization or VAS scores between the two-groups.

Conclusions: Electrophysiological reflex assessments do not appear to be sufficiently reliable in evaluating pain perception in these patients.

Keywords: *Parkinson's disease; pain; nociceptive flexion reflex*

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease.[1] It affects approximately 2–3% of the population over the age of 65, and its pathophysiological hallmarks include: (i) degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc); (ii) accumulation of α-synuclein aggregates forming Lewy bodies (LBs) within neurons; and (iii) the presence of Lewy neurites (LNs), which are abnormal α-synuclein-containing axonal swellings[2,3] The cardinal clinical features of PD include bradykinesia, rigidity, tremor, and postural instability. In addition to its motor symptoms, PD is frequently accompanied by non-motor symptoms (NMS) such as pain, constipation, depression, anosmia, cognitive impairment, and sleep disturbances.[4] Unlike motor symptoms, NMS are often under-recognized and inadequately treated.[5]

Pain, a relatively underexplored NMS in PD, has received limited attention despite its frequent occurrence. One reason for this may be the high prevalence of pain in the general elderly population, which complicates its attribution to PD. Musculoskeletal deformities and comorbid disorders may further obscure this association. Nevertheless, structures implicated in PD pathophysiology—particularly the basal ganglia, thalamus, and spinal cord—play critical roles in pain processing and perception. Pain is a subjective experience, and its measurement presents a significant challenge.

Although patient-reported outcome measures such as the Visual Analog Scale (VAS) are commonly used, several neurophysiological techniques capable of assessing nociceptive function have been developed. These include electrically or laser-evoked reflexes and potentials[6-10], which are valuable tools in the study of pain perception. Among them, the trigeminocervical reflex (TCR) and the nociceptive flexion reflex (NFR) are particularly notable for evaluating nociceptive responses in cranial and spinal pathways, respectively. We hypothesized that evaluating the TCR and NFR reflexes, which are nociceptive reflexes that assess pain grading in Parkinson's patients, could be useful in monitoring these patients.

In this study, we aimed to investigate the utility of TCR and NFR as objective measures for assessing pain—a common NMS—in patients with PD, targeting both the upper and lower body regions.

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2. Materials and Methods

2.1. Study population

In this prospective study, patients from four different diagnostic groups were screened at the Movement Disorders and General Neurology outpatient clinics of the Department of Neurology, İstanbul University, Faculty of Medicine. PD was diagnosed by the presence of at least one of the following: rigidity with bradykinesia, 4-6 Hz resting tremor, and postural instability not caused by visual, vestibular, cerebellar, or proprioceptive dysfunction. The study population was divided into the following groups: Group I: Healthy individuals without PD and without pain, Group II: Patients without PD who reported non-specific musculoskeletal pain, Group III: Patients diagnosed with PD but without pain complaints, Group IV: Patients diagnosed with PD who reported pain as a NMS. Electrophysiological testing was performed after the entire study population was included in the study. To determine the required sample size, a power analysis was conducted based on data and outcomes from previous studies (with 80% power and $p < 0.05$). The analysis indicated that including approximately 10 individuals per group would be sufficient. Exclusion criteria healthy subjects included individuals under 18 or over 70 years of age, those with thyroid dysfunction, electrolyte imbalance, pregnancy or suspected pregnancy, active malignancy, secondary parkinsonism due to other etiologies, organic disorders that could independently explain pain, other neurological diseases, peripheral neuropathy, or radiculopathy. The study was approved by the local ethics committee of the hospital. Written informed consent was obtained from all participants after they were provided with detailed information regarding the study.

2.2. Demographic and laboratory characteristics of the patients

All participants included in the study underwent a comprehensive medical history assessment and detailed physical examination. For patients with PD, additional clinical evaluations were performed to determine disease duration, the laterality of symptom predominance, pain localization, and whether the assessment was conducted during the “on” or “off” phase of medication response. Pain severity was subjectively evaluated using the VAS, in which patients are asked to rate their pain on a scale from 1 to 10. A score of 10 represents the most severe pain experienced by the patient in their lifetime.[11]

The clinical assessment of PD was conducted using the Hoehn and Yahr Staging Scale (HYS) and the Unified Parkinson's Disease Rating Scale (UPDRS Parts I–III) [12, 13]. The UPDRS evaluates patients across four clinical domains: motor function (92 points), activities of daily living (52 points), mentation and cognition (16 points), and treatment-related complications (23 points), for a total score of 183 points. In this study, participants were assessed using the mental state, activities of daily living, and motor examination sections of the UPDRS, while the complications of therapy section was excluded, resulting in a maximum score of 160 points. To confirm the functional integrity of the brainstem, all participants were initially assessed using blink reflex responses.

2.3. Trigeminocervical reflex application technique

The reflex recordings were performed while the participants were seated comfortably in a chair. Following skin preparation, Ag-AgCl surface recording electrodes filled with conductive paste were bilaterally placed on the posterior neck muscles (m. semispinalis capitis) and trapezius muscles, approximately 2 cm apart near their respective motor points. The ground electrode was positioned over the sternum. For stimulation, monophasic square-wave electrical pulses with a duration of 0.5 ms were delivered to the infraorbital region (IOU) using standard bipolar stimulating electrodes. Participants were instructed to maintain their heads in the midline position and as upright as possible throughout the procedure. The sweep speed was set to 50 ms/division, and the amplitude was initially set to 2 mV, with adjustments made according to the response size. The total sweep duration was 30 ms. Reflex responses elicited by four randomly delivered stimuli were superimposed, and latencies were measured directly from the screen.

2.4. Nociceptive flexion reflex application technique

The reflex recordings were conducted while participants were in the supine position, focusing on the right lower extremity. In patients with unilateral Parkinson’s disease (PD) symptoms, both sides were examined. After skin preparation, Ag-AgCl surface recording electrodes filled with conductive paste were placed approximately 2 cm apart near the motor points of the anterior tibialis (AT) and biceps femoris (BF) muscles. The ground electrode was positioned near the recording electrodes. Electrical stimuli were delivered to the plantar surface of the foot. For this purpose, “train” stimuli consisting of four pulses with a duration of 0.5 ms each were applied using standard bipolar stimulating electrodes.[14]. The sweep speed was set to 50 ms/division, and the amplitude was initially 2 mV, adjusted according to response size. The total sweep duration was set at 30 ms. Reflex responses elicited by four randomly administered stimuli were superimposed, and latency values were measured directly from the screen.

2.5. Statistical analysis

All statistical analyses were performed using SPSS version 15.0 (SPSS for Windows 15.0, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. The Kolmogorov-Smirnov test was used to assess the normality of distribution for continuous variables. For comparisons between two groups, Student’s t-test was applied for normally distributed variables, while the Mann-Whitney U test was used for non-normally distributed variables. For comparisons between two or three-four groups, Student’s t-test or one-way ANOVA was used for normally distributed variables; in the absence of normal distribution, the Mann–Whitney U test or the Kruskal–Wallis one-way ANOVA was applied, respectively. Chi-square (χ^2) test was employed for the analysis of categorical data. A p-value < 0.05 was considered statistically significant for all comparisons.

3. Results

A total of 50 participants were included in this study: 22 patients diagnosed with PD (7 females, 15 males; mean age 64.9 ± 6.3 years) and 28 controls without PD (17 females, 11 males; mean age 56.2 ± 7.9 years). When age and sex distribution were compared between the patient and control groups, PD patients were significantly older and had a higher prevalence of male sex ($p < 0.05$ for both comparisons). All subjects were further classified based on the presence or absence of PD and pain complaints into four groups: Group I: Healthy individuals without PD or pain, Group II: Individuals without PD but reporting non-specific musculoskeletal pain, Group III: PD patients without pain, Group IV: PD patients with pain as a NMS (Table 1). The clinical and neurophysiological parameters were compared across these groups.

3.1. Baseline demographic, clinical and medical treatment data of the study groups

The demographic, clinical, and pharmacological treatment data of the study groups are presented in Table 1. Although numerical differences in age and sex were observed among the groups, these differences were not statistically significant (Table 1).

Table 1

Demographic, clinical and medical treatment data of the study groups

Variables	Group I n=13	Group II n=15	Group III n=9	Group IV n=13	p
Age (year)	57.8 ± 5.9 (51 – 68)	52.8 ± 8.6 (42 – 69)	65.5 ± 5.1 (56 – 74)	64.3 ± 7.3 (53 – 73)	0.234
Gender (Female/Male), n (%)	6 / 7	11 / 4	0 / 9	7 / 6	0.527
Hoehn-Yahr Staging Scale, 1-2-3-4	–	–	1–7–1–0	1– 9– 2–1	0.456
UPDRS, n	–	–	27.4 ± 15.3	42.5 ± 13.0	0.022
Disease duration, n (%)	–	–	3.0 ± 3.5	8.0 ± 6.6	0.121
PH initial side (Right/Left)	–	–	5/ 4	2 / 11	0.411
PH initial symptom tremor, n (%)	–	–	7 (%)	11 (%)	
PH initial symptom bradykinesia, n (%)	–	–	1 ()	2 ()	0.094
PH initial symptom rigidity, n (%)	–	–	1 ()	–	
L-dopa treatment, n (%)	–	–	1	1	0.820
Dopamine agonist + L-Dopa treatment, n (%)	–	–	8	12	
Left upper extremity pain, n (%)	–	4	–	7	
Right upper extremity pain, n (%)	–	7	–	1	0.640
Left lower extremity pain, n (%)	–	3	–	2	
Right lower extremity pain, n (%)	–	1	–	3	
VAS score, n	–	7.0 ± 0.7	–	6.3 ± 1.3	0.456

Group I: *Healthy individuals without Parkinson's disease and pain,* ***Group II:*** *Patients without Parkinson's disease who describe non-specific musculoskeletal pain,* ***Group III:*** *Patients diagnosed with Parkinson's disease and without any accompanying pain,* ***Group IV:*** *Patients diagnosed with Parkinson's disease and without any accompanying pain,* ***UPDRS:*** *The unified Parkinson's disease rating scale,* ***VAS:*** *Visual Analog Scale*

Table 2

Electrophysiological evaluation data of the study groups

Variables	Group I n=13	Group II n=15	Group III n=9	Group IV n=13	p
LOOC RI latency value (msn)	10.4 ± 1.2	9.9 ± 0.9	10.1 ± 0.9	11.1 ± 2.5	0.234
LOOC RII latency value (msn)	34.2 ± 4.1	31.5 ± 4.1	34.2 ± 2.2	34.2 ± 1.4	0.527
ROOC RI latency value (msn)	10.2 ± 0.9	10.3 ± 0.8	10.6 ± 0.7	11.0 ± 1.4	0.456
ROOC RII latency value (msn)	32.1 ± 2.6	29.4 ± 4.0	34.6 ± 7.8	32.7 ± 3.5	0.656
LSC: TCR latency value (LİO) (msn)	49.2 ± 6.7	57.2 ± 12.2	53.5 ± 3.9	49.5 ± 7.3	0.184
RSC: TCR latency value (LİO) (msn)	51.0 ± 8.6	50.6 ± 11.6	53.6 ± 9.2	52.3 ± 5.8	0.718
LTRAP: TCR latency value (LİO) (msn)	46.8 ± 8.3	60.5 ± 17.2	64.0 ± 20.1	70.2 ± 32.2	0.708
RTRAP: TCR latency value (LİO) (msn)	56.7±19.2	54.0 ± 12.2	57.3 ± 12.7	52.8 ± 10.7	0.937
LSC: TCR latency value (RİO) (msn)	54.9 ± 6.8	53.6 ± 12.6	54.6 ± 5.8	52.6 ± 12.5	0.875
RSC: TCR latency value (RİO) (msn)	51.0 ± 5.2	55.8 ± 10.4	57.1 ± 11.4	66.6 ± 19.4	0.073
LTRAP: TCR latency value (RİO) (msn)	49.5 ± 3.5	68.0 ± 17.0	52.9 ± 4.5	113 ± 4.5	0.677
RTRAP: TCR latency value (RİO) (msn)	51.9 ± 7.2	60.8 ± 8.7	54.9 ± 6.5	81.4 ± 40.4	0.331
RAT: NFR latency value (msn)	44.9 ± 5.7	46.0 ± 17.3	39.7 ± 8.3	45.2 ± 13.8	0.431
RIII component: NFR latency value (msn)	131 ± 33	167 ± 43	125 ± 6.8	143 ± 36	0.147
RBF: NFR latency value (msn)	138 ± 48	108 ± 33	105 ± 55	100 ± 42	0.533
Amplitude	1277±580	1185± 1152	1076 ± 631	1683 ± 834	0.729

Group I: *Healthy individuals without Parkinson's disease and without pain,* ***Group II:*** *Patients without Parkinson's disease who report non-specific musculoskeletal pain,* ***Group III:*** *Patients diagnosed with Parkinson's disease who do not report any pain,* ***Group IV:*** *Patients diagnosed with Parkinson's disease who report pain as a non-motor symptom (NMS)* ***Abbreviations: LOOC –*** *Left orbicularis oculi,* ***LSC –*** *Left semispinalis capitis,* ***LTRAP –*** *Left trapezius,* ***NFR –*** *Nociceptive flexion reflex,* ***RAT –*** *Right anterior tibialis,* ***RBF –*** *Right biceps femoris,* ***ROOC –*** *Right orbicularis oculi,* ***RSC*** *– Right semispinalis capitis,* ***RTRAP –*** *Right trapezius,* ***TCR –*** *Trigeminal-cervical reflex*

Table 3

Electrophysiological evaluation data of patients with (Group II+IV) and without (Group I+III) pain

Variables	Group I+III n=22	Group II+IV n=28	p
LSC: TCR latency value (LİO) (msn)	50.7 ± 6.0	54.4 ± 11.2	0.538
RSC: TCR latency value (LİO) (msn)	52.3 ± 8.7	51.3 ± 9.7	0.632
LTRAP: TCR latency value (LİO) (msn)	56.3 ± 17.6	65.1 ± 20.0	0.636
RTRAP: TCR latency value (LİO) (msn)	57.0 ± 14.8	53.7 ± 9.9	0.699
LSC: TCR latency value (RİO) (msn)	54.7 ± 6.2	53.2 ± 12.3	0.070
RSC: TCR latency value (RİO) (msn)	54.5 ± 9.4	59.6 ± 14.7	0.316
LTRAP: TCR latency value (RİO) (msn)	51.9 ± 4.3	77.0 ± 24.9	0.028
RTRAP: TCR latency value (RİO) (msn)	54.0 ± 6.2	69.0 ± 23.9	0.368
RAT: NFR latency value (msn)	53.6 ± 34.0	48.1 ± 19.3	0.510
RIII component: NFR latency value (msn)	126.2 ± 26.9	158.5 ± 39.5	0.018
RBF: NFR latency value (msn)	124.6 ± 51.7	104.7 ± 36.1	0.098
Amplitude	1207 ± 587	1721 ± 830	0.223

Group I: *Healthy individuals without Parkinson's disease and without pain,* ***Group II:*** *Patients without Parkinson's disease who report non-specific musculoskeletal pain,* ***Group III:*** *Patients diagnosed with Parkinson's disease who do not report any pain,* ***Group IV:*** *Patients diagnosed with Parkinson's disease who report pain as a non-motor symptom (NMS)* ***Abbreviations: LOOC –*** *Left orbicularis oculi,* ***LSC –*** *Left semispinalis capitis,* ***LTRAP –*** *Left trapezius,* ***NFR –*** *Nociceptive flexion reflex,* ***RAT –*** *Right anterior tibialis,* ***RBF –*** *Right biceps femoris,* ***ROOC –*** *Right orbicularis oculi,* ***RSC*** *– Right semispinalis capitis,* ***RTRAP –*** *Right trapezius,* ***TCR –*** *Trigeminal-cervical reflex*

Table 4

Electrophysiological evaluation data of patients with (Group III+IV) and without (Group I+II) Parkinson's disease

Variables	Group I+II n=28	Group III+IV n=22	p
LSC: TCR latency value (LİO) (msn)	53.6 ± 10.7	51.3 ± 6.1	0.725
RSC: TCR latency value (LİO) (msn)	50.8 ± 10.3	53.0 ± 7.6	0.144
LTRAP: TCR latency value (LİO) (msn)	54.6 ± 10.3	65.7 ± 21.2	0.281
RTRAP: TCR latency value (LİO) (msn)	57.0 ± 14.8	56.5 ± 11.5	0.534
LSC: TCR latency value (RİO) (msn)	54.7 ± 6.2	53.2 ± 12.3	0.965
RSC: TCR latency value (RİO) (msn)	54.5 ± 9.4	59.6 ± 14.7	0.156
LTRAP: TCR latency value (RİO) (msn)	51.9 ± 4.3	77.0 ± 24.9	0.873
RTRAP: TCR latency value (RİO) (msn)	54.0 ± 6.2	69.0 ± 23.9	0.935
RAT: NFR latency value (msn)	53.5 ± 31.2	46.3 ± 18.6	0.388
RIII component: NFR latency value (msn)	146 ± 42.6	138 ± 27.4	0.592
RBF: NFR latency value (msn)	123 ± 42.6	102 ± 46.5	0.979
Amplitude	1360 ± 657	1353 ± 760	0.206

Group I: *Healthy individuals without Parkinson's disease and without pain,* ***Group II:*** *Patients without Parkinson's disease who report non-specific musculoskeletal pain,* ***Group III:*** *Patients diagnosed with Parkinson's disease who do not report any pain,* ***Group IV:*** *Patients diagnosed with Parkinson's disease who report pain as a non-motor symptom (NMS)* ***Abbreviations: LOOC –*** *Left orbicularis oculi,* ***LSC –*** *Left semispinalis capitis,* ***LTRAP –*** *Left trapezius,* ***NFR –*** *Nociceptive flexion reflex,* ***RAT –*** *Right anterior tibialis,* ***RBF –*** *Right biceps femoris,* ***ROOC –*** *Right orbicularis oculi,* ***RSC*** *– Right semispinalis capitis,* ***RTRAP –*** *Right trapezius,* ***TCR –*** *Trigeminal-cervical reflex*

Patients with PD had been under follow-up and treatment for a period ranging from 1 to 25 years, with a mean disease duration of 6.8 ± 5.7 years across all PD patients. Although patients in Group IV (PD with pain) had a longer mean disease duration than those in Group III (PD without pain), the difference was not statistically significant (Table 1).

The UPDRS scores ranged from 9 to 58 in Group III, while the mean UPDRS score was 42.5 ± 13.0 in Group IV and 27.4 ± 15.3 in Group III, with a significantly higher score in Group IV compared to Group III (Table 1). According to the HYS, 2 patients were classified as stage 1, 16 patients as stage 2, 3 patients as stage 3, and 1 patient as stage 4. The dominant hemibody affected by PD symptoms was the left side in 15 patients and the right side in 7 patients. There were no statistically significant differences between the groups in terms of HYS staging, affected body side at disease onset, or medical treatment regimens (Table 1).

Regarding pain localization in Groups II and IV: Left upper extremity pain was reported by 4 and 7 patients, respectively. Right upper extremity pain by 7 and 1 patients, Left lower extremity pain by 3 and 2 patients, Right lower extremity pain by 1 and 3 patients. Pain presence and intensity were assessed using the VAS in all patients. The mean VAS score was 7.0 ± 0.7 in Group II and 6.3 ± 1.3 in Group IV, with no significant differences in pain localization or VAS scores between the two groups (Table 1).

3.2. Electrophysiological evaluation data of patient groups

When the electrophysiological parameters of the patient groups included in the study were analyzed, no statistically significant differences were observed among the groups in terms of blink reflex latency, TCR latency, and NFR latency values (Table 2). Patients were then re-categorized into two groups as those with pain (Group II + IV) and without pain (Group I + III). The latency values of the blink reflex, TCR, and NFR were compared between these two groups (Table 3). It was found that the latency of the TCR recorded from the left trapezius muscle in response to right infraorbital nerve stimulation, as well as the latency of the RIII component of the NFR elicited by plantar stimulation, were significantly longer in patients with pain compared to those without pain. The remaining reflex latencies did not differ significantly between the groups. In another analysis, patients were grouped according to the presence (Group III + IV) or absence (Group I + II) of Parkinson's disease, and the latency values of the blink reflex, TCR, and NFR were compared between these two groups (Table 4). No statistically significant differences were found for any of the latency parameters between Parkinson's disease and non-Parkinson's disease groups.

4. Discussion

The In our study, we aimed to determine how the presence of pain in patients with PD affects two commonly used reflexes in pain research: TCR and NFR. Specifically, we investigated latency differences and the relationship between reflex parameters and pain localization. We divided the human body into upper and lower regions—utilizing the TCR for upper body pain and the NFR for pain around the lumbar and pelvic areas. TCR was applied to obtain objective data regarding brainstem sensorimotor function, while NFR was used to evaluate polysynaptic reflex impairments associated with neural integration in the lower extremities.

When the clinical and demographic subgroups were evaluated, patients with painful PD had a longer disease duration than those without pain. Moreover, the mean UPDRS score in the painful PD group was significantly higher than in the painless PD group. No statistically significant difference was observed between the painful control and painful PD groups in terms of mean VAS scores.

The classic motor symptoms of PD—resting tremor, bradykinesia, rigidity, and postural instability—are well defined. However, NMS, which affect multiple systems, are equally debilitating. These symptoms negatively impact quality of life and contribute significantly to morbidity. Although the prevalence of pain in PD varies, studies report that 20% to 80% of patients experience pain as a NMS.[15-17] The etiology of pain in PD is multifactorial[18]; both dopaminergic and non-dopaminergic mechanisms in the brain and spinal cord are involved in altered pain perception.[18-20] Our study particularly focused on spinal cord-related pain.

Afferent somatosensory nociceptive inputs are integrated within the spinal cord and followed by efferent motor neuron activation.[6] In PD, abnormalities in the processing of nociceptive inputs lead to a facilitation of NFR responses.[21] In addition, descending inhibitory pathways—normally responsible for NFR suppression—are diminished in PD patients.[21] Since pain is a subjective sensation and difficult to quantify, in addition to subjective scales like the VAS, neurophysiological techniques such as evoked potentials or reflexes induced by electrical or laser stimuli are used for objective pain assessment.[6,22] Among these methods, TCR and NFR are prominent.

Numerous studies have examined ipsilateral lower extremity NFR using electrophysiological methods.[6,22-25] Given the correlation between NFR and pain threshold, NFR has been a valuable tool in human pain research. These investigations have explored the function of various nociceptive pathways at both spinal and supraspinal levels.[6,18-21] Such work has shed light on the role of neurotransmitters in pain modulation and has enhanced our understanding of chronic pain syndromes and disorders of pain perception. NFR comprises two components: RII (tactile) and RIII. The RIII component is nociceptive and correlates with pain threshold.[22] In our study, although the RIII latency in painful idiopathic PD patients was higher than in the other three groups, the difference was not statistically significant. Similarly, RIII amplitude was also higher, though not significantly. However, when only patients with pain were compared to those without pain, RIII latency was found to be significantly prolonged in the painful group. In addition, it has been shown that stimulating the subthalamic nucleus with deep brain stimulation, which is used in cases of PD recently, reduces clinical pain and experimental pain sensitivity by causing a decrease in NFR threshold.[26]

TCR is used in the assessment of upper extremity pain in PD. Compared to lower extremity pain, upper extremity pain in PD has been less studied. TCR consists of short-latency EMG responses recorded from neck and proximal upper limb muscles following electrical stimulation of the supraorbital or infraorbital branches of the trigeminal nerve.[27-30] It is mediated by nociceptive afferents and polysynaptic brainstem circuits converging on upper and lower cervical spinal motor neurons.[27-30] Due to its complex brainstem neural integration, TCR may be valuable in investigating brainstem function in movement disorders. Although limited, recent studies have highlighted the clinical significance of TCR, noting its absence or prolonged latency in idiopathic PD.[31] In our study, TCR latencies were longer in PD patients with pain compared to the other groups (PD without pain, non-PD with pain, and healthy controls); however, the differences were not statistically significant. When comparing only patients with and without pain, the TCR latency recorded from the left trapezius muscle was significantly longer in the painful group.

4.1. Limitations

This study has several important limitations. Firstly, it was conducted at a single center and included a limited number of patients. A multicenter study with a larger patient population would likely yield more meaningful and generalizable results. Secondly, our study included patients with pain in all four extremities; however, in clinical practice, patients with PD more frequently present with lower extremity pain. Therefore, a study specifically focusing on

lower extremity NFR assessment in PD patients might have provided more robust findings. Furthermore, in our study, the VAS and UPDRS scores differed between painful PD patients and painful non-PD patients. If these scores had been more comparable between the two groups, the results would have allowed for more accurate interpretations regarding the electrophysiological correlates of pain in PD. Other limitations of our study include the heterogeneity of pain in PD cases (different types of pain – neuropathic, musculoskeletal, etc. – were evaluated together), the failure to control the effects of medications used in PD patients (e.g., dopamine agonists, analgesics), and the lack of examination of other parameters of NFR such as threshold or amplitude.

5. Conclusion

As observed in our study, previous investigations evaluating TCR and NFR in idiopathic PD have yielded conflicting and inconclusive results. Electrophysiological reflex assessments do not appear to be sufficiently reliable in evaluating pain perception in these patients. It is important to consider that polysynaptic reflex pathways may deteriorate with age, and that response abnormalities observed in older PD patients may therefore fail to reach statistical significance or clinical relevance. Future research should focus not only on fully elucidating the pathophysiology of pain in PD, but also on assessing the effects of both pharmacological and non-pharmacological treatment strategies. In this context, there is a clear need to expand and diversify electrophysiological reflex methodologies in pain evaluation.

Statement of Ethics

The study received approval from the İstanbul University Ethics Committee.(2007-1787)

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. https://tez.yok.gov.tr/UlusalTezMerkezi/TezGoster?key=-Z0vbSUgrhM9fXoGkRe6Q0frHUcPrZR6_SVJUrTliTIbop8WqIRtUsQIxzzXtN2G

Author contributions

All authors contributed equally to the article and read and approved the final manuscript.

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