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Study on the relationship between peripheral nerve fiber types and levodopa usage in Parkinson's disease

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Background and purpose – The aim of this study is to comprehensively determine the types of affected fibers in Parkinson's disease (PD) patients by employing nerve conduction studies (NCS), sympathetic skin response (SSR) examinations, and current perception threshold (CPT) testing and to analyze the correlation between levodopa use and nerve involvement.
Methods – This retrospective study included 36 clinically diagnosed PD patients who were recruited between January 2018 and April 2019. All patients underwent NCS, SSR testing, and CPT sensory examinations. Additionally, the PD patients were assessed for disease staging using the Hoehn and Yahr (H-Y) scale.
Results – Fifteen patients were included in the tremor-dominant subtype, ten patients in the rigid-dominant subtype, and eleven patients in the mixed subtype. Eleven patients were using levodopa, while twenty-five patients had never used any anti-Parkinson's medication. Ten patients (28%) showed abnormal sympathetic skin responses (SSR). The CPT examination revealed sensory abnormalities in twenty-four patients (67%), with eighteen patients (75%) experiencing sensory hypersensitivity and six patients (25%) experiencing sensory hypoesthesia. Twelve patients (33%) had normal CPT results. Among the patients with abnormal CPT findings, seven cases (29%) involved large myelinated fiber damage, twenty-two cases (92%) involved small myelinated fiber damage, and nineteen cases (79%) involved unmyelinated fiber damage. The rate of sensory abnormalities was 64% (7/11) in the levodopa group and 68% (17/25) in the non-levodopa group, with no statistically significant difference between the two groups.

A perifériás idegrosttípusok és a levodopahasználat közötti kapcsolat vizsgálata Parkinson-kórban

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Háttér és cél – E vizsgálat célja, hogy átfogóan meghatározza az érintett rostok típusait Parkinson-kóros (PD-) betegeknél idegvezetési vizsgálatok (NCS), szimpatikus bőrválasz- (SSR-) vizsgálatok és áramérzékelési küszöb- (CPT-) tesztek alkalmazásával, valamint hogy elemezze a levodopahasználat és az idegek érintettsége közötti összefüggést.
Módszerek – Ebbe a retrospektív vizsgálatba 36 klinikailag diagnosztizált PD-beteget vontunk be, akiket 2018 januárja és 2019 áprilisa között vizsgáltak klinikánkon. Minden betegnél NCS-, SSR- és CPT szenzoros vizsgálatokat végeztek. A betegeket a Hoehn és Yahr (H-Y) skála segítségével betegségstádiumba sorolták.
Eredmények – Tizenöt beteg tartozott a tremordomináns-altípusba, 10 beteg a rigiditásdomináns-altípusba és 11 beteg a kevert altípusba. Tizenegy beteg használt levodopát, míg 25 beteg soha nem alkalmazott semmilyen PD-ellenes gyógyszert. Tíz betegnél (28%) mutattak ki kóros szimpatikus bőrreakciót (SSR). A CPT-vizsgálat 24 betegnél (67%) mutatott ki szenzoros eltéréseket, közülük 18 betegnél (75%) szenzoros túlérzékenységet, hat betegnél (25%) pedig szenzoros hypoesthesiát. Tizenkét beteg (33%) CPT-eredményei normálisak voltak. A kóros CPT-leletet mutató betegek közül hét esetben (29%) a nagy myelinizált rostok károsodása, 22 esetben (92%) a kis myelinizált rostok károsodása, 19 esetben (79%) pedig a nem myelinizált rostok károsodása fordult elő. A szenzoros eltérések aránya 64% (7/11) volt a levodopacsoportban és 68% (17/25) a nem levodopacsoportban; a két csoport között nem volt statisztikailag szignifikáns különbség.
Következtetés – A kóros CPT-leletek előfordulási gyakorisága a PD-betegeknél

Conclusion – The incidence of abnormal CPT findings in PD patients was higher than that of abnormal SSR responses, suggesting that nerve fiber damage primarily affects small fiber nerves (SFN).

Keywords: Parkinson's disease, peripheral nerves, nerve conduction study, skin sympathetic reflex, current perception threshold

magasabb volt, mint a kóros SSR-válaszoké. Ez arra utal, hogy az idegrostok károsodása elsősorban a kis idegrostokat (SFN) érinti.

Kulcsszavak: Parkinson-kór, perifériás idegek, idegvezetési vizsgálat, szimpatikus bőrreflex, áramérzékelési küszöbérték

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the selective degeneration and death of dopaminergic neurons in the substantia nigra of the midbrain, along with the presence of Lewy bodies[1–3]. These changes lead to a decrease in dopamine levels in the brain, resulting in the classic motor symptoms of PD, such as resting tremors, muscle stiffness, bradykinesia, and postural instability.

In addition to the involvement of the central nervous system, the systemic features of PD have been increasingly recognized in the scientific community. Recent studies have found that peripheral nerve abnormalities are common in PD patients and may contribute to the non-motor symptoms of PD[4]. These non-motor symptoms include but are not limited to sleep disturbances, olfactory dysfunction, depressive mood, and autonomic dysfunction such as constipation and pain, significantly impacting the quality of life of patients. However, the specific mechanisms and implications of peripheral nerve involvement in PD remain unclear, and there is a lack of practical and effective clinical guidelines for diagnosis and disease progression assessment.

Regarding the pathophysiological processes of peripheral nerve involvement in PD, multiple mechanisms have been proposed. Alpha-synuclein (SYCN), a key protein in the pathological process of PD[5], exhibits abnormal aggregation in both the central and peripheral nervous systems of PD patients. Some studies suggest that this protein aggregation may lead to neuronal dysfunction and death by affecting intracellular signaling and cellular transport processes[6]. Additionally, long-term use of levodopa in PD treatment may have direct or indirect effects on the nervous system, but its mechanisms of action are still unclear and subject to debate[7].

In clinical practice, the diagnosis and management of PD primarily focus on improving motor symptoms, while the evaluation of peripheral nerves and their role in disease progression is relatively lacking. Existing literature reports various types of peripheral nerve involvement in PD, including sensory, motor, and autonomic nerve damage. However, these studies often have small sample sizes and yield inconsistent conclusions, failing to establish a consensus. Therefore, further research is needed to clarify the role of peripheral nerves in PD and how their impairments interact with the degenerative processes in the central nervous system. The aim of this study is to comprehensively determine the types of affected fibers in PD patients by employing nerve conduction studies (NCS), sympathetic skin response (SSR) examinations, and current perception threshold (CPT) testing. We analyze the correlation between levodopa use and nerve involvement and explore the potential relationship between these peripheral nerve impairments and the severity of clinical PD.

Materials and methods

Study subjects

The study included 36 clinically diagnosed PD patients from the outpatient and inpatient departments of Aviation General Hospital from January 2018 to April 2019. Inclusion criteria: 1. Clinically diagnosed PD according to MDS criteria[8]. 2. Age between 40 and 80 years. 3. Disease duration between 3 months and 5 years. 4. Willingness and ability to undergo nerve conduction studies (NCS), sympathetic skin response (SSR) examinations, and current perception threshold (CPT) testing. 5. Availability of complete medical history and clinical follow-up data. Exclusion criteria were: 1. Other forms of parkinsonism syndromes, such as multiple system atrophy and vascular parkinsonism, etc[8, 9]; 2. Other neurodegenerative diseases such as Alzheimer's disease[10]; 3. History of peripheral nerve diseases, including but not limited to diabetic neuropathy, vitamin B12 deficiency, etc.; 4. Severe psychiatric disorders such as schizophrenia, major depression, etc., which may interfere with disease assessment and result interpretation; 5. Presence of other diseases that may affect the results of sympathetic skin response (SSR) and current perception threshold (CPT) testing, such as skin lesions, systemic lupus erythematosus, etc.; 6. Current use of anticholinergic drugs

or other medications that affect the functioning of the nervous system; 7. Patients who are not suitable for nerve conduction studies (NCS), such as those with severe burns or amputations of the arms or legs. Finally, a total of 19 females and 17 males were included, with an average age of 67.44±9.86 years. The duration of the disease ranged from 4 months to 6 years, with an average duration of 11.25±8.01 months. The PD of patients included 15 tremor-dominant type, 10 rigidity-dominant type, and 11 mixed type cases. Among the diagnosed patients, 11 were using levodopa, and 25 were not using levodopa. The H-Y staging was performed for the patients. A total of 36 healthy control subjects of the same age group, with an average age of 66.32±8.84 years, were selected from the hospital's medical examination center.

This study met the review criteria set by our ethics committee and was approved by the ethics committee (No. HK2016-03-20). As the study was retrospective in design, the ethics committee exempted the acquisition of informed consent.

Research methods

All patients underwent upper and lower limb nerve conduction studies (NCS), skin sympathetic reflex (SSR) examinations, and current perception threshold (CPT). NCS and SSR Examination nerve conduction studies (NCS) and skin sympathetic reflex (SSR) measurements were performed. NCS included study of motor nerve conduction (NCV) and sensory nerve conduction (SCV) of the median nerve, ulnar nerve, sural nerve, and tibial nerve, as well as measurement of motor terminal latency (ML). The skin sympathetic reflex was stimulated by the bilateral median nerve and bilateral tibial nerve, and the indicators observed were the wave amplitude and latency of SSR.

CPT Evaluation

The patients were seated comfortably in a room with a temperature of 22-24°C, free from external interference. The test was explained to the patients, and the test area was inspected to ensure that there was no recent tissue damage that could affect the test results. The skin temperature was not measured, and no fat was removed. The CPT and corresponding CPT values on the healthy side were measured for the tibial nerve on the affected side. The NEUROMETER CPT sensory nerve quantitative testing instrument from Neurotron, USA, was used for testing. The selective sensory nerve conduction threshold testing program used three different sinusoidal frequency electric stimuli: 2000Hz, 250Hz, and 5Hz, with stimulation intensity ranging from 0.01 mA to 9.99 mA. The selective testing was performed on large myelinated sensory nerve fibers (Aβ), small myelinated sensory nerve fibers (Aδ), and unmyelinated sensory nerve fibers (C fibers). The results were compared with normal values and classified as normal or abnormal. Abnormal results included sensory hyperalgesia and sensory decrease. Aβ fibers, which are responsible for transmitting touch and pressure sensations, typically respond to lower frequencies of electrical currents, such as 5Hz or below. Aδ fibers respond to intermediate frequencies, such as 250Hz, and transmit acute pain and partial temperature sensations. C fibers are sensitive to higher frequencies, like 2000Hz, and have the smallest diameter. These fibers are responsible for transmitting chronic pain and temperature sensations.

Statistical methods

The SPSS 17.0 statistical software was used for analysis. Data were subjected to tests for normality and homogeneity of variance. Normally distributed measurement data were expressed as mean ± standard deviation, and the independent samples t-test was used for two independent samples. Measurement data were analyzed using the χ^2 test (likelihood ratio chi-square test, Fisher's exact test), with $P<0.05$ indicating a statistically significant difference.

Results

The NCS examination of motor and sensory nerves in 36 patients showed no abnormalities, but SSR examination revealed abnormalities in 10 patients, with significantly reduced or absent wave amplitudes. The CPT examination found sensory abnormalities in 24 patients (67%), including 18 cases of sensory hyperalgesia (75%) and 6 cases of sensory decrease (25%), while 12 cases had normal CPT (33%) **(Table 1)**. Abnormalities were found in 7 cases (29%) when stimulated at 2000Hz, in 22 cases (92%) when stimulated at 250Hz, and in 19 cases (79%) when stimulated at 5Hz. The rate of sensory abnormalities in the levodopa group was 64% (7/11), while the rate in the non-levodopa group was 68% (17/25). There was no statistically significant difference in the rate of sensory abnormalities between the two groups **(Table 2)**. The average Hoehn and Yahr (H-Y) staging was 1.63±0.71, with H-Y staging of 1.54±0.54 for patients with no abnormalities, 1.64±0.82 for patients with sensory hyperalgesia, and 1.75±0.76 for patients with sensory decrease, with no statistically significant difference between the groups **(Table 3)**. The NCS, SSR, and CPT results of the control group were all normal.

Discussion

In the pathogenesis of PD, the abnormal aggregation of α-synuclein and the formation of Lewy bodies play crucial roles. There is substantial evidence in the scientific

Table 1. *CPT examination results of PD patients [Cases (%)]*

Group	CPT abnormal types			
	CPT sensory abnormality		Total	
	Sensory hyper-algesia 18 (75%)	Sensory decrease 6 (25%)	24 (67%)	P value
Large myelinated fiber	1	6	7 (29%)	0.006
Small myelinated fiber	17	5	22 (92%)	0.001
Unmyelinated fiber	17	2	19 (79%)	0.419
χ^2 value	13.962			
P value	0.001			

Note: A comparison of the affected fibers in 24 cases of CPT abnormal PD patients was performed using the likelihood ratio chi-square test, X^2=13.962, P=0.001, indicating a statistically significant overall difference among the groups. Pairwise comparisons between groups using Fisher's exact test showed significant differences between large myelinated and small myelinated (P=0.006), large myelinated and unmyelinated (P=0.001), and small myelinated and unmyelinated (P=0.419).

literature supporting the notion that α-synuclein aggregation is not limited to the central nervous system but also involves the peripheral nervous system, which is of significant importance for the development of PD[11]. This study further elucidates the phenomenon of peripheral nerve damage in PD patients from a neurophysiological perspective, with 67% of PD patients exhibiting peripheral nerve impairment, a rate similar to the 70% reported in previous international studies[12]. Our findings are consistent with previous reports of elevated expression patterns of α-synuclein (SNCA) in the peripheral nervous system and skin. Moreover, the damage to the peripheral nervous system is closely associated with physiological changes in the skin, which may have implications for early diagnosis and treatment of PD. This discovery strengthens the link between peripheral nerve damage and PD pathology, suggesting that peripheral nerve impairment may be an early marker of PD development. Therefore, further research should focus on exploring the molecular mechanisms underlying peripheral nerve damage, particularly the role of α-synuclein in peripheral tissues and its comprehensive impact on neural function. Simultaneously, the accumulation of peripheral nerve injury markers, such as α-synuclein in the skin or other peripheral tissues, may provide a basis for the development of non-invasive biomarkers, thereby enabling earlier diagnosis and more accurate monitoring of disease progression in PD. This study provides preliminary neurophysiological evidence for this hypothesis and establishes a foundation for future research directions.

Table 2. *CPT results between levodopa and non-levodopa groups*

Group	CPT result	
	Sensory abnormality	Sensory normal
Levodopa group	7 (64%)	4 (36%)
Non-levodopa group	17 (68%)	8 (32%)
P value	1.000	

Note: Using Fisher's exact test, P=1.000, no statistically significant difference.

Foreign literature reports that the proportion of large fiber lesions in PD is 16.3%[13]. Another study has reported that α-synuclein oligomers and small nerve fiber pathology in the skin are potential biomarkers for PD[14]. The incidence of PD combined with SFN is high[15], and small fiber damage may exist in the early stages of the disease. Our nerve conduction study did not reveal any abnormalities, suggesting that large fiber involvement in PD is rare or mild. Recent years CPT is an effective electrophysiological examination for detecting small fiber lesions. We found that the peripheral nerves of PD patients mainly showed abnormalities when stimulated at 250Hz (excitation of small myelinated fibers) and 5Hz (excitation of unmyelinated fibers), with 92% and 79% affected, respectively. The abnormality rate was significantly lower when stimulated at 2000Hz (excitation of large myelinated fibers), at only 29%. Our study found that patients with sensory abnormalities at 2000Hz also had sensory abnormalities at 250Hz and/or 5Hz, suggesting that the vast majority of PD patients have small fiber damage, with almost no patients have isolated large fiber damage, while the CPT examination at various frequency stimulations was normal in the healthy control group. Therefore, our study suggests that small fiber nerves (small myelinated and unmyelinated) lesions are the main affected fibers in the peripheral nerve lesions of PD, and damage to small fibers nerves may lead to pain or discomfort and/or autonomic dysfunction, suggesting that small fiber lesions are likely one of the pathological mechanisms for the emergence of non-motor symptoms in PD. SSR examination was positive in only 28% of PD patients, while CPT was more sensitive to screen for small fiber lesions.

Regarding the severity of peripheral nerve damage, literature reports that the degree of small fiber nerves in-

Table 3. *H-Y staging and duration results between different CPT groups*

Group	Cases	H-Y Staging	Duration (Months)	t Value/P Value	t Value/P Value
Sensory hyperalgesia	18	1.64 ± 0.82	9.67 ± 3.66	1.627/ 0.118	0.293/0.773
Sensory decrease	6	1.75 ± 0.76	19.50 ± 10.62	–0.124/0.902	0.275/0.785
No abnormality	12	1.54 ± 0.54	9.50 ± 3.53	–1.081/0.195	0.675/0.610

Note: Comparison of duration between sensory hyperalgesia and sensory decrease groups, t=1.627, p=0.118, duration comparison between sensory hyperalgesia and no abnormality groups, t=–0.124, p=0.902, duration comparison between sensory decrease and no abnormality groups, t=–1.081, p=0.195; comparison of H-Y staging between sensory hyperalgesia and sensory decrease groups, t=0.293, p=0.773, H-Y staging comparison between sensory hyperalgesia and no abnormality groups, t=0.275, p=0.785, H-Y staging comparison between sensory decrease and no abnormality groups, t=0.675, p=0.610.

volvement is related to the severity of the disease[16]. The presence of peripheral nerve lesions is related to shorter stride length, slower gait speed, and smaller toe-off angles[2]. We found that approximately 75% of PD patients had a state of sensory hyperalgesia detected by CPT, indicating mild sensory impairment. This may be related to the fact that most of our patients were newly diagnosed and had relatively mild symptoms. However, we believe that sensory hyperalgesia should be the initial state of peripheral nerve involvement in PD, and it is likely a necessary step for every PD patient with peripheral nerve damage. We found no clear correlation between the severity of the disease and the sensory abnormalities detected by CPT.

Some studies have suggested a significant link between levodopa replacement therapy and peripheral nerve fiber neuropathy in patients with PD[17]. However, the exact contribution of levodopa to neuropathy incidence remains uncertain. *Nolano* et al.[18] demonstrated that neuropathy increased with PD severity, even without levodopa exposure. *Rajabally* et al.[19] conducted a study comparing neuropathy prevalence in 33 levodopa-naive and 36 levodopa-exposed PD patients. While they noted an association between neuropathy and cumulative levodopa exposure, they concluded that levodopa's influence was merely contributory, overshadowed by factors like older age and reduced folate levels. In our study, sensory abnormality rates were 64% in the levodopa group and 68% in the non-levodopa group, with no statistically significant difference between the two. However, short time and low dose of levodopa intake were applied in this study. Therefore, whether this effect is attributable to disease duration/severity or to the doses and duration of levodopa ingestion remains unclear.

Our study has certain limitations. Most of the patients included were newly diagnosed PD patients, with a low H-Y staging suggesting mild symptoms. Also, due to limitations in examination conditions, skin nerve biopsy was not performed, and there is no more objective evidence to support our speculation. In the future, we will continue to include early, middle, and late-stage PD patients based on our existing research results, and obtain gold standard diagnosis data through nerve biopsy to further improve the research.

Conclusion

The incidence of abnormal CPT findings in PD patients was higher than that of abnormal SSR responses. This finding contributes to the elucidation of the extent of neuronal fiber type damage in the pathophysiology of PD, providing clues for further research into the etiology and progression of PD.

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