Prevalence of Small Fiber Neuropathy in Idiopathic Parkinson's Disease Patients

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Abstract

Background: Autonomic dysfunction is found to occur in Parkinson' disease. It can be present in the form of peripheral small fiber neuropathy (SFN). Because of inaccessible standard methods, establishing a diagnosis of SFN can be challenging.

Objective: To study the prevalence of SFN in idiopathic Parkinson's disease patients in Vajira Neurological Clinic via the stimulated skin wrinkling test by the eutectic mixture of local anesthetics (SSW-EMLA) method.

Material and Method: Thirty-three idiopathic Parkinson's disease (PD) patients were recruited from the Neurology Clinic. Twenty-two non-Parkinson's patients served as the control. In order to detect SFN, EMLA cream was applied to the tip of digits 2, 3, and 4 and the degree of wrinkling graded. Symptoms were accessed by Symptom Inventory Questionnaire (SFN-SIQ) and determination of the intensity of the neuropathic pain was performed using the Neuropathic Pain Scales (NPSI), and nerve conduction studies (NCS) were performed to excluded large fiber neuropathy.

Results: The prevalence of SFN was 12/33 (36%) in all PD patients, while 24 out of 33 patients in the PD group had symptoms with SFN-SIQ ≥ 5 score. Four out of 24 who had symptoms showed abnormal NCS. Finally, 12 patients showed symptoms with normal NCS and an abnormal SSW-EMLA test among the PD patients. Meanwhile no SFN was detected in the control group. P values 0.003.

Conclusion: Our study showed the higher prevalence of SFN detected by the SSW-EMLA test in PD patients in Vajira Neurology Clinic compared with the non-PD control group.

Keywords: Idiopathic Parkinson's disease, Small fiber neuropathy

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Introduction

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder resulting from abnormal aggregation of alpha-synuclein and the consequences are the degeneration of dopaminergic neurons in substantia nigra. As dopamine decreases, motor symptoms such as bradykinesia, rigidity, tremor, and postural instability can develop.

Several studies have shown clinical and histopathological evidence of small fiber and large fiber neuropathy in PD.[1-10] SFN is an abnormality of thinly myelinated A-delta and unmyelinated C-fiber, and no clear etiology may be an intrinsic feature of the disease or could be treatment-related. Clinical syndrome is characterized by numbness or paresthesia, which is a painful burning or tingling without significant large nerve fiber abnormality.

Establishing a diagnosis of SFN can be challenging because of the special diagnostic tests required for confirmation.[11] Unfortunately, the diagnostic test for the diagnosis of small fiber neuropathy such as Quantitative Sensory Testing (QST), Quantitative Sudomotor Axon Reflex Test, or Intraepidermal Nerve Fiber Density (IENFD) are difficult to access in Thailand.

Stimulated skin wrinkling test by the eutectic mixture of local anesthetics (SSW-EMLA) is the result of the direct stimulation of digital nerve sympathetic fibers by EMLA cream, mediated vasoconstriction with loss of finger pulp volume, overlying skin traction, and wrinkling. SSW-EMLA is another test of small fiber function which is simpler, inexpensive, requires no specialized equipment, and shows similar sensitivity to that of IENFD.

The disability in PD patients mostly occurs from impairment of balance. Dysfunction of small fiber nerves can lead to an inferior quality of life of PD patients.[2] The early recognition of SFN is important because it may help to prevent further disability and maintain good daily functioning of the patient.

We studied the prevalence of small fiber neuropathy in our PD patients in Vajira Neurology Clinic using the SSW-EMLA to evaluate small fiber autonomic dysfunction.

Material and Method

Design: This cross-sectional study was approved by the Ethics Committee of Vajira Hospital and was conducted in the Neurology Division of Vajira Hospital, Bangkok, Thailand. Medical records from the database of the E-phis program were reviewed from January 1, 1992, to March 30, 2020.

Patients: Thirty-three patients (18 males, 15 females) fulfilling the UK Brain Bank criteria for the diagnosis of Parkinson's disease were recruited from the Neurology Clinic. Twenty-two non-Parkinson's patient volunteers form the primary care unit served as the control. Patients with a known history of atypical Parkinson's, diabetes, chronic kidney disease, hepatic failure, cancer, chemotherapy, HIV infection, alcoholism, neuropathy, connective tissue disease, and local anesthetic cream allergy were excluded. All patients had a history of blood test for fasting blood glucose or HbA1c and creatinine within one year. Four patients from the primary care unit were excluded due to impaired fasting blood glucose, leaving 18 patients in the non-Parkinson's patient group and 33 patients in the Parkinson's patient group. All participants gave their written informed consent.

Patient characteristics, past medical history, current medication, and Parkinson's disease and treatment duration details were collected. A

standard physical neurological exam, light touch using cotton, vibration perception on the distal interphalangeal joint of the big toe using a tuning fork 128Hz, proprioception perception by joint position sense test, temperature perception using a cold metal rod, pinprick perception using a toothpick, motor, and deep tendon reflex using a tendon hammer evaluated peripheral neuropathy and the Hoehn & Yahr stage was assessed.

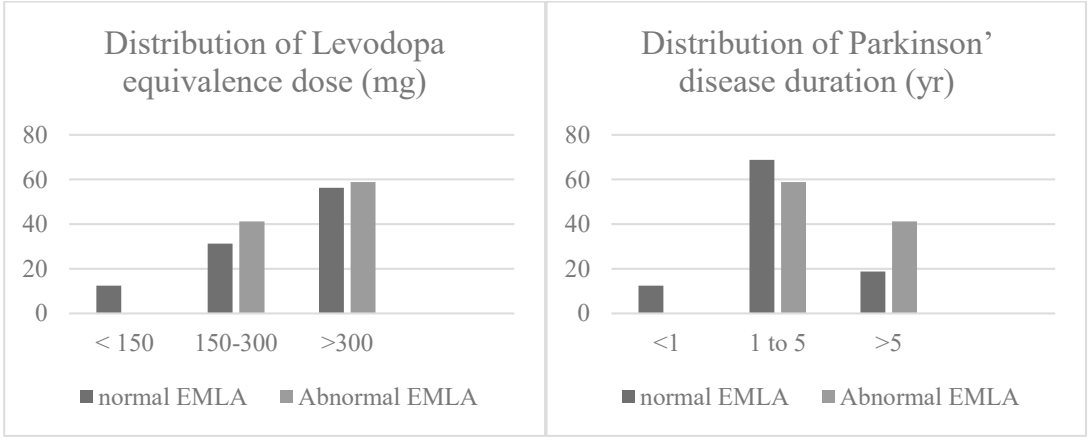


Figure 1: Comparison of the distribution of Levodopa equivalent dose and Parkinson's disease duration in PD patients with normal and abnormal SSW-EMLA tests

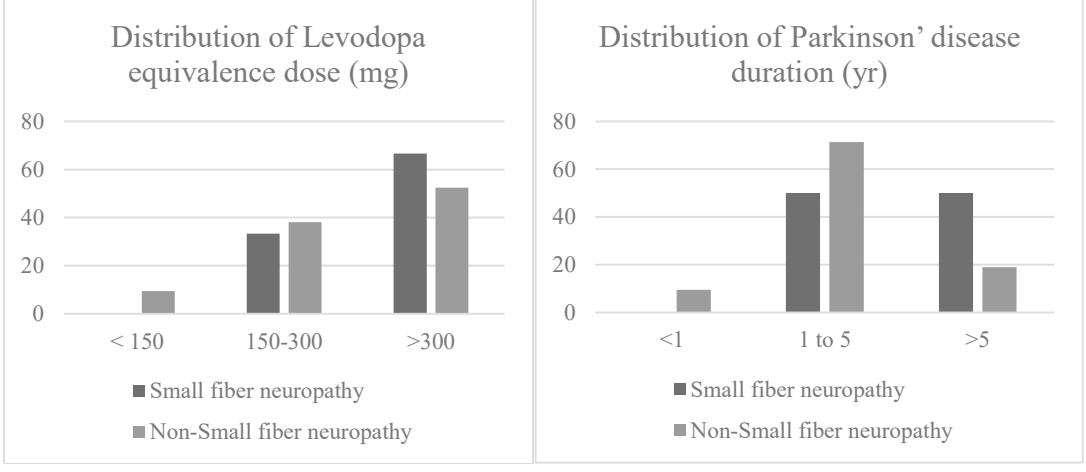


Figure 2: Comparison of the distribution of Levodopa equivalent dose and Parkinson's disease duration in PD patients with SFN and non-SFN

Test Procedures

SFN symptoms were evaluated with the Small-Fiber Neuropathy and Symptom Inventory Questionnaire (SFN-SIQ) and the intensity of the neuropathic pain was determined by the Neuropathic Pain Scales Inventory (NPSI).

SFN-SIQ (Figure 4) represents a potential SFN screening tool and has been used to assess sensory and autonomic symptoms in SFN with a moderate diagnostic value cut-off = 5 (sensitivity 80%, specificity 81.8%).[15]

The NPSI questionnaire (Figure 3) included 12 items: 10 descriptions of the different symptom

components of neuropathic pain (factor 1: burning pain; factor 2: pressing pain; factor 3: paroxysmal pain; factor 4: evoked pain; factor 5: paresthesia or dysesthesia, and 2 items for assessing the duration of spontaneous ongoing and paroxysmal pain.[16]

Nerve conduction studies were performed to address evidence of large fiber neuropathy at both sides of the radial nerves at the anatomical snuffbox and the sural nerves at the mid-calf of both legs with control surface temperature at 32°C by using the Viking application version 21.1.0.195 of Natus ©2013 by attending the neurologist.

Severity of the spontaneous pain

Q1. Does your pain feel like burning?

Q2. Does your pain feel like squeezing?

Q3. Does your pain feel like pressure?

Q4. During the past 24h, your spontaneous pain has been present: permanently / 8 to 12 h / 4 to 7 h / 1 to 3 h / < 1h

Severity of the painful attacks

Q5. Does your pain feel like electric shocks?

Q6. Does your pain feel like stabbing?

Q7. In the past 24 h how many of these pain attacks have you had? >20 / 11 to 20 / 6 to 10 / 1 to 5 / none

Severity of your provoked pains

Q8. Is your pain provoked or increased by brushing on the painful area?

Q9. Is your pain provoked or increased by pressure on the painful area?

Q10. Is your pain provoked or increased by contact with something cold on the painful area?

Severity of abnormal sensations

Q11. Do you feel pins and needles?

Q12. Do you feel tingling?

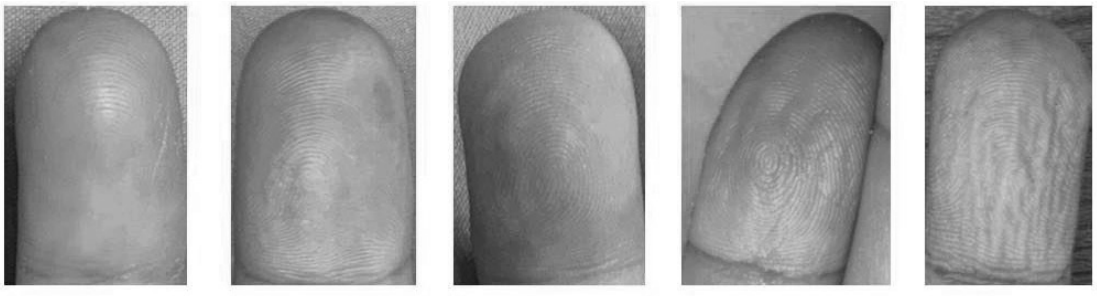
Total intensity score	Sub scores	
1. Q1=	1. Burning (superficial) spontaneous pain:	1. Q1=
2. (Q2+Q3) =	2. Pressing (deep) spontaneous pain:	2. (Q2+Q3)/2=
3. (Q5+Q6) =	3. Paroxysmal pain:	3. (Q5+Q6)/2=
4. (Q8+Q9+Q10) =	4. Evoked pain:	4. (Q8+Q9+Q10)/3=
5. (Q11+Q12) =	5. Paresthesia/Dysesthesia:	5. (Q11+Q12)/2=
(1+2+3+4+5) = /100		

Select “0” if you have not felt such pain, or “10” if you have felt it the worst.

Figure 3: Neuropathic Pain Symptom Inventory (NPSI)

Do you:	never	sometimes	often	always
	0	1	2	3
1. experience changes in sweating patterns (diminished or increased sweating)?				
2. have sudden diarrhea?				
3. have constipation?				
4. have urination problems (incontinence or hesitation)?				
5. have dry eyes?				
6. have a dry mouth?				
7. experience dizziness when standing up from a sitting or lying position?				
8. have palpitations?				
9. have hot flushes?				
10. experience extreme skin sensitivity of the legs?				
11. have a burning feet sensation?				
12. experience sheet intolerance?				
13. experience restless leg?				

Figure 4: Symptoms accessed by Symptom Inventory Questionnaire (SFN-SIQ)



Grade 0 Grade 1 Grade 2 Grade 3 Grade 4

Grade 0	Wrinkling absent
Grade 1	Slight wrinkling and the fingertip are not smooth
Grade 2	Two or fewer lines of wrinkling on each side of the fingertip
Grade 3	Three or fewer lines of wrinkling on each side of the fingertip
Grade 4	Wrinkling completely distorts the pulp of the fingertip

Figure 5: Wrinkling scale (pictures collected from participants in this study) (Front cover page)

The stimulated skin wrinkling test by eutectic mixture of local anesthetics (SSW-EMLA) was performed, in which the distal pulp of both sides of the 2nd, 3rd, and 4th fingers was completely covered with EMLA cream (lidocaine 2.5% and prilocaine 2.5%; AstraZeneca: Cambridge, United Kingdom). This was covered with food grade plastic wrap for 30 minutes with control surface temperature at 32°C. Photographic documentation before-EMLA and after-EMLA was recorded. Wrinkling was graded based on the assessment of the photographic picture by two neurologists blinded to the result of the small nerve fiber testing. The divergence of the results in each patient was reevaluated and discussed by two doctors for final consensus.

Skin wrinkling was defined as abnormal if the total score showed absence or severe impairment of wrinkling (score <9). The grading of wrinkles (Figure 5) was: Grade 0, wrinkling absent; Grade 1, just perceptible wrinkling, finger not smooth; Grade 2, two or fewer lines of superficial wrinkling: Grade 3, three or more lines of deep wrinkling; Grade 4, wrinkling completely distorts fingertip. A total score of ≥ 9 marks for each hand was taken as normal and without evidence of neuropathy.[13,14] Patients cleaned their pulps and were not allowed to ingest coffee or tea before taking the SSW-EMLA test.

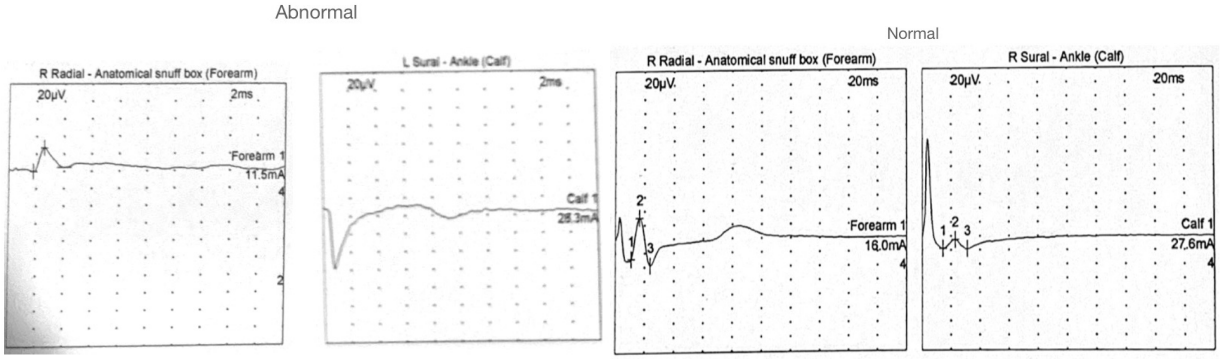


Figure 6: Nerve conduction study (Sensory nerve action potentials, SNAP)

Appendix 1: Electrophysiological data

		control	case	p-value
		Mean ± SD.	Mean ± SD.	
Radial nerve				
Distal latency (msec)	L	2.16 ± 0.31	2.19 ± 0.37	0.753
	R	2.11 ± 0.26	2.15 ± 0.38	0.588
Amplitude (microV)	L	32.2 ± 12.95	25.4 ± 10.22	0.034*
	R	29.85 ± 16.43	27.11 ± 10.56	0.459
Conduction velocity (m/s)	L	58.55 ± 6.57	53.15 ± 7.73	0.010*
	R	60.09 ± 7.24	53.56 ± 6.87	0.001*
Sural nerve				
Distal latency (msec)	L	2.86 ± 0.5	2.99 ± 0.58	0.389
	R	2.54 ± 0.57	2.85 ± 0.54	0.056
Amplitude (microV)	L	13.79 ± 6.43	10.15 ± 4.31	0.018*
	R	18.83 ± 12.21	9.4 ± 3.59	0.002*
Conduction velocity (m/s)	L	55 ± 8.71	47.42 ± 7.18	0.001*
	R	59.14 ± 23.42	47.25 ± 7.26	0.010*
Sural /Radial Ratio	L	0.46 ± 0.22	0.45 ± 0.23	0.835
	R	0.94 ± 1.35	0.4 ± 0.2	0.081

Statistical Analysis

Independent t test or Mann-Whitney U and Chi-square tests were used to compare clinical characteristics data and the results of neurological evaluation between the PD and non-PD groups. Levodopa equivalent dose and disease duration distribution of the PD group between the SFN group and non-SFN groups were compared using the Chi-square test.

Inter-rater agreement used reliability of inter-observation. P-values < 0.05 were considered significant. All statistics were analyzed by SPSS version 26.

Results

Population Characteristics

Thirty-three patients with idiopathic Parkinson's disease in Vajira Neurology Clinic and twenty-two non-Parkinson's disease participants from the primary care clinic were included in the study, while 4 participants were excluded due to impaired fasting blood glucose from the control group. The median ages of the PD group and control group were 66.33 and 57.52 years, respectively. Fifteen (45.5%) were women in PD group and thirteen were women (72.2%) in the control group. The medical conditions of participants were similar except for dyslipidemia, which had higher prevalence in the non-Parkinson's disease group than the PD group (Table 1).

Table 1: Patient characteristics

	Parkinson's disease (n = 33)	Non-Parkinson's disease (n = 18)	P-value
Age (yr.)	66.33 ± 9.02	57.52 ± 6.49	<0.001
Sex			0.066
Female	15 (45.5%)	13 (72.2%)	
Male	18 (54.5%)	5 (27.8%)	
HT	14 (42.4%)	8 (44.4%)	0.889
Dyslipidemia	9 (27.3%)	14 (77.8%)	0.001
BPH	4 (12.1%)	1 (5.6%)	0.451
Old CVA	2 (6.1%)	0 (0%)	0.287
Parkinson' disease duration (yr.)			
<1	2 (6.1%)		
1-5	21 (63.6%)		
>5	10 (30.3%)		
Hoehn and Yahr scale			
I	13 (39%)		
II	8 (24%)		
III	8 (24%)		
IV	4 (12%)		
V	0 (0%)		
Levodopa equivalent dose (mg)	420 (250, 680)		
<150	2 (6.1%)		
150-300	12 (36.4%)		
>300	19 (57.6%)		

In the PD group, 39% had H&Y stage I, 24% had H&Y stage II, and 24% had H&Y stage III. For disease duration, 63.6% had disease duration of 1 to 5 years, 30.3% had disease duration of more than 5 years. Thirty-one PD patients had used a levodopa equivalent dose of at least 150 mg per day. Almost all PD patients had been treated with levodopa for at least 12 months (Table 1).

Table 2: Clinical features and quantitative measures of neuropathy

	Parkinson's disease (n = 33)	Non-Parkinson's disease (n = 18)	P-value
NPSI score			
Burning pain	0.85 ± 2.4	0.39 ± 1.65	0.473
Pressing pain	0.67 ± 1.89	0.17 ± 0.59	0.170
Paroxysmal pain	0.92 ± 1.95	0	0.001
Evoked pain	0.59 ± 1.69	0	0.052
Paresthesia/dysesthesia	1.98 ± 1.89	0.53 ± 0.83	<0.001
Total	0.13 ± 0.2	0.02 ± 0.05	0.005
SFN-SIQ	7 (4, 10)	2.5 (2, 4)	0.001
Sensory nerve conduction test			0.082
Normal	28 (84.8%)	18 (100%)	
Abnormal	5 (15.2%)	0 (0%)	
Skin wrinkling score (before EMLA)			
Left hand	0.5 (0, 3)	0.25 (0, 4)	0.858
Right hand	1 (0, 2)	0 (0, 3)	0.767
Skin wrinkling score (after EMLA)			
Left hand	7.5 (3, 10.5)	10 (1.5, 11.5)	0.559
Right hand	9 (1.5, 10.5)	8.25 (2, 11)	0.851
SSW-EMLA test			0.629
Normal	16 (48.5%)	10 (55.6%)	
Abnormal	17 (51.5%)	8 (44.4%)	

Table 2 shows the clinical characteristics of neuropathy symptoms based on the NPSI score in the PD group. The mean score was 0.85 in burning pain, 0.67 in pressing pain, 0.92 in paroxysmal pain, 0.59 in evoked pain, and 1.98 in paresthesia/dysesthesia pain. The sensory neurological physical exam evaluation showed abnormal pinprick sensation and temperature perception at 48.5% in the PD group and 5.6% in the non-PD group. Five out of 33 in the PD group (15.2%) had large fiber neuropathy on nerve conduction studies (Figure 6 and Appendix1). An abnormal SSW-EMLA test was found at 51.5% (17/33) in the PD group and 44.4% (8/18) in the non-PD group.

Prevalence of Small Fiber Neuropathy

We found that 24 out of 33 patients in the PD group had symptoms with SFN-SIQ ≥ 5 score. Four out of 24 who had symptoms showed abnormal NCS, and one in the PD group was considered to have both small and large fiber neuropathy due to impairment in the vibration test which defined large

fiber neuropathy, and also abnormal results in the SSW-EMLA test. Finally, 12 patients showed symptoms with normal NCS and abnormal SSW-EMLA test in PD patients with inter-rater agreement for two examiners of SSW-EMLA at 0.859 (95%CI 0.742-0.921), indicating a satisfactory level of agreement. Therefore, the prevalence of SFN was (12/33) 36% in all PD patients. We did not find small fiber neuropathy in the control group. P values 0.003.

We analyzed the PD group according to disease duration distribution in short, moderate, and long durations as 1) <1 year (SD); 2) 1-5 years (MD); 3) > 5 years (LD) and levodopa equivalent dose distribution in low, moderate and high dose as 1) <150 mg (LLD), 2) 150-300 mg (MLD); 3) >300 mg (HLD). They showed prevalence of SFN 33.3% in MLD, 66.7% in HLD, 50% in MD, and 50% in LD. However, the prevalence was not significant in comparison with the non-SFN group (Tables 3-4, Figures 1-2).

Table 3: Analysis of Levodopa equivalent dose and Parkinson's disease duration in PD patients with results of SSW-EMLA tests

	SSW-EMLA test		p-value
	Normal (n = 16)	Abnormal (n = 17)	
Levodopa equivalent dose (mg)			
< 150	2 (12.5%)	0 (0%)	0.308
150-300	5 (31.3%)	7 (41.2%)	
>300	9 (56.3%)	10 (58.8%)	
Parkinson' disease duration (yr.)			
<1	2 (12.5%)	0 (0%)	0.164
1-5	11 (68.8%)	10 (58.8%)	
>5	3 (18.8%)	7 (41.2%)	

Table 4: Analysis of Levodopa equivalent dose and Parkinson's disease duration in PD patients with SFN and non-SFN

	Small fiber neuropathy		p-value
	Yes (n=12)	No (n=21)	
Levodopa equivalent dose (mg)			
< 150	0 (0%)	2 (9.5%)	0.482
150-300	4 (33.3%)	8 (38.1%)	
>300	8 (66.7%)	11 (52.4%)	
Parkinson' disease duration (yr.)			
<1	0 (0%)	2 (9.5%)	0.128
1-5	6 (50%)	15 (71.4%)	
>5	6 (50%)	4 (19%)	

Discussion

This cross-sectional study shows the prevalence of small fiber neuropathy in PD patients in our clinic. We used SSW-EMLA, which is a simple and easily accessible test for the detection of small fiber dysfunction. Despite a small sample size, we found the prevalence of small fiber neuropathy (defined by abnormal skin sensation with abnormal SSW-EMLA test without evidence of large fiber neuropathy from nerve conduction study) was around one-third of PD patients, which was significantly higher than the prevalence in the control group and not related to disease duration and the level of levodopa equivalent dose.

The insignificant difference ratio of abnormal SSW-EMLA tests in both PD and non-PD groups may occur firstly because we excluded another suspected cause of SFN by only the history from the patient and the medical record without examining specific blood test results. This may cause various confounding factors to remain. Second, there is a possibility of sympatholytic effects in antihypertensive drug that the patients were taking. Third, increasing age affects the degree of wrinkling through reduced skin elasticity.

This finding is concordant with previous studies, [1,4,9,17] as PD patients had a high prevalence of peripheral neuropathies, especially in small fiber nerves. The pathology of autonomic dysfunction in PD is discussed in multifactorial terms such as the deposition of abnormal phosphorylated alpha-synuclein in the central and peripheral nervous system, and the amount of orally administrated L-dopa subsequently transformed to dopamine which is a regulator of systemic blood pressure through vasodilation and decreased catecholamine release.[9] However, in previous studies, a high prevalence of peripheral autonomic dysfunction was shown in patients in the early disease course and L-dopa exposure was associated with predominant axonal polyneuropathy.[5,7,10] Correlation in our study indicated that the prevalence of SFN is not different in each group of disease duration and levodopa equivalent dose

The limitation of our study is that the small fiber neuropathy assessment was conducted only by SSW-EMLA test, and we are not able to perform additional tests to evaluate sensory and autonomic function of the small fiber nerve because of a lack of availability of equipment in our facilities. We chose the SSW-EMLA test due to its practical usage even in primary care hospitals. Another limitation in our study is the lack of matching ages in the control group due to the difficulty in collecting volunteers during the situation of viral transmission concern in the COVID-19 outbreak.

To further screen for SFN or autonomic dysfunction in PD patients, studies should be designed with more accurate tests such as skin biopsy for IENFD, a larger number of participants, and with specific laboratory tests to rule out other causes of SFN.

Conclusion

Our study presents the higher prevalence of small fiber neuropathy in PD patients in the Vajira Neurology Clinic compared with the non-PD control group. Physicians treating PD patients should be aware of the potential for their autonomic dysfunction and take appropriate evaluation and management measures to maintain quality of life if dysfunction is present.

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