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Original Research

Association of Dizziness-Related Handicap or Disability with Clinical Features in Patients with Early Parkinson's Disease

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Abstract

Background: Complaining of dizziness is common in patients with Parkinson's disease (PD) even at the early phase of the disease. Therefore, regarding motor or non-motor symptoms, clinical implication of subjective dizziness in early Parkinsonian patients is needed to be explored. **Methods**: Eighty patients diagnosed with early PD (defined by disease duration of five years or less) were retrospectively enrolled for the study. Dizziness handicap inventory (DHI), the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) Functional Level Scale (FLS), and clinical features of parkinsonian motor and non-motor symptoms using representative measurements. **Results**: Through simple and multiple linear regression analyses, we found that both DHI and FLS were significantly and positively correlated with postural instability/gait disorder (PIGD) score but negatively with the Montreal cognitive assessment (MoCA) score. **Conclusions**: We found that subjective dizziness in patients with early PD was related to not only axial symptoms of PIGD, but also global cognitive function of MoCA. Further research is required to confirm our results.

Keywords: dizziness; motor symptom; cognition; Parkinson's disease

1. Introduction

Dizziness is a common complaint among individuals with Parkinson's disease (PD), with a reported prevalence of about 48~68% [1–3]. However, there is no established consensus whether dizziness is a PD-related non-motor symptom (NMS), although one report suggested that dizziness might occur even in early phase in PD [4]. Moreover, the neuropathological basis of dizziness in PD remains to be further elucidated. A few studies reported that orthostatic dizziness (only one type of dizziness) in patients with PD might be related to autonomic dysfunction including orthostatic hypotension [5,6]. However, another study reported that dizziness in patients with PD was not associated with orthostatic hypotension [3]. Likewise, in clinical practice, clinicians often encounter patients with PD showing a mismatch between orthostatic hypotension and dizziness.

Dizziness may significantly impact the quality of life or functional activity [7,8]. Until now, clinical relevance of subjective dizziness has not been fully studied in patients with PD. Therefore, we sought to investigate whether dizziness was associated with well-known clinical features especially in early stages of PD. Two self-reported measurements representing dizziness-related handicap or disability were surveyed to evaluate the severity of subjective dizziness in early PD patients. This is a pilot study to identify the detailed relationship between subjective dizziness and clinical characteristics of patients with early PD.

2. Materials & Methods

2.1 Participants

We reviewed all the medical charts of patients diagnosed with PD, according to the UK Brain Bank criteria [9]. Ninety-six patients presenting with parkinsonism underwent not only brain magnetic resonance imaging (MRI) but also dopamine transporter (DAT) imaging in our movement disorders clinic between 2017 and 2019. Specifically, the inclusion criteria were as follows: (1) subjects with early stages of PD, defined by disease duration of no more than five years, and (2) subjects typically showing a rostrocaudal gradient pattern of the striatal dopaminergic loss on DAT findings [10]. The exclusion criteria were as follows: (1) any subject manifesting atypical clinical features or red-flag signs, indicating Parkinson-plus syndromes or secondary parkinsonism during the follow-ups, (2) any subject manifesting Parkinson-plus syndrome or secondary parkinsonism based on either MRI [11] and DAT findings [10], and (3) any subject with serious medical problems such as poorly controlled diabetes mellitus and cancer, or other neurological problems including dementia. This retrospectively designed research was approved by the Institutional Review Board of our hospital (approval number: 2019-08-018), and individual informed consent was waived because of the study format.

2.2 Clinical Assessments

Clinical demographics including gender, age at registration, disease duration, the level of education, body mass index, and levodopa-equivalent daily dose (LEDD) were

assessed. Subjective dizziness was evaluated in all participants using both the Korean version of dizziness-inventory handicap (DHI) and the Korean version of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) functional level scale (FLS) [2]. Motor symptoms were evaluated through the Unified Parkinson's Disease Rating Scale (UPDRS) part III and the Hoehn and Yahr (HY) stage. Moreover, motor subscores such as postural instability/gait disorder (PIGD) were calculated as described in previous studies [12,13]. The Korean version of the Montreal Cognitive Assessment (MoCA-K) was accessed for global cognitive scale [14]. The Korean version of the Beck Depression Inventory (BDI) [15] and the Korean version of the Beck Anxiety Inventory (BAI) [16] were evaluated for depression and anxiety, respectively. The Parkinson's Disease Fatigue Scale (PFS) was used for fatigue [17]. Finally, the Korean version of the Scale for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT) was surveyed for autonomic symptoms [18].

2.3 Statistics

Simple linear regression analysis and subsequent multiple linear regression analysis was conducted to analyze the relationship between subjective dizziness severity and clinical factors. DHI and AAO-HNS FLS were used as a dependent variable, respectively, while clinical characteristics including demographics, motor symptoms, and non-motor symptoms were used as independent variables. Statistical analyses were carried out using the IBM SPSS statistics 20.0 software (IBM Corp., Armonk, NY, USA) for Windows combined with the Rex version 3.6.3 (URL http://rexsoft.org). $p < 0.05$ was accepted as statistically significant.

3. Results

3.1 Clinical Details of Patients with Early PD

Eighty patients out of 96 with early stages of PD were finally evaluated for the current research. The remaining 16 patients were as follows: 3 were normal pressure hydrocephalus, 3 were vascular parkinsonism, 3 were multiple system atrophy, 2 were drug-induced parkinsonism, 1 was progressive supranuclear palsy, 1 was essential tremor, 1 was dementia with Lewy bodies, and 2 were unspecified parkinsonism. Clinical characteristics including diverse scales for subjective dizziness are exhibited in Table 1. The mean age of all patients was 71.3 years and 57.5% of them were women. The mean duration of PD was 1.9 years. Among antiparkinsonians, 27 patients (33.75%) were taking levodopa, 19 patients (23.75%) were taking dopamine agonist, 9 patients taking monoamine-B inhibitor (11.25%), 11 patients taking amantadine (13.75%), and 4 patients (5%) taking anti-cholinergic agent. Information on other dosing was also examined, and the results were as follows: 26 people (32.50%) took antihypertensive medication and 19 people (23.75%) took diabetes medication.

Table 1. Demographics and clinical characteristics of participants with early Parkinson's disease.

Variable	Patients with early PD (n = 80)
Demographics	
Female, n (%)	46 (57.5%)
Age, yr	71.3 ± 8.4
BMI, kg/m^2	23.6 ± 3.2
Level of education, yr	9.2 ± 5.0
Disease duration, yr	1.9 ± 1.4
LEDD (mg)	149.8 ± 223.2
Subjective dizziness-related scales	
Dizziness handicap inventory	7.6 ± 13.2
AAO-HNS functional level scale	1.6 ± 0.8
Assessment for motor symptoms	
UPDRS-III score (motor)	22.8 ± 12.5
Tremor subscore	2.7 ± 2.2
Rigidity subscore	4.7 ± 2.7
Bradykinesia subscore	10.7 ± 4.4
PIGD subscore	2.8 ± 2.6
HY (Hoehn and Yahr) stage	2.1 ± 0.4
Assessment for non-motor symptoms	
MoCA-K (global cognition)	21.2 ± 5.4
BDI (depression)	9.7 ± 6.6
BAI (anxiety)	5.6 ± 6.0
PFS (fatigue)	40.0 ± 15.5
SCOPA-AUT (dysautonomia)	13.6 ± 7.8

Data are n (%) or mean ± S.D. values.

PD, Parkinson's disease; BMI, body mass index; LEDD, levodopa equivalent daily dose; AAO-HNS, the American Academy of Otolaryngology-Head and Neck Surgery; UPDRS-III, the Unified Parkinson's disease rating scale-part 3; PIGD, postural instability and gait difficulty; MoCA-K, Korean version of Montreal Cognitive Assessment; BDI, Beck depression inventory; BAI, Beck anxiety inventory; PFS, Parkinson's disease fatigue scale; SCOPA-AUT, the Scale for Outcomes in Parkinson's disease-Autonomic.

Fourteen patients (17.5%) were taking BPH medication. In addition, 8 people (10.00%) took antidepressant drugs and 10 people (12.50%) took anti-anxiety drugs. For dizziness-related scales, the mean scores of DHI and AAO-HNS FLS were 7.6 and 1.6, respectively. For motor symptoms, the mean score of Parkinsonian motor symptom using the UPDRS-part III was 22.8 and that of HY stage was 2.1. Individual mean scores of non-motor symptom (NMS) were as follows: Korean version of Montreal Cognitive Assessment (MoCA-K), 21.2; Beck depression inventory (BDI), 9.7; Beck anxiety inventory (BAI), 5.6; Parkinson's disease fatigue scale (PFS), 40.0; and Scale for Outcomes in Parkinson's disease-Autonomic (SCOPA-AUT), 13.6.

3.2 Linear Regression Analysis of DHI in Early PD Patients

Simple linear regression analysis was performed between DHI and demographics, motor, or non-motor symptoms (left panel of Table 2). The results showed that DHI was associated with PIGD, MoCA-K, BDI, BAI, PFS, and

Table 2. Linear regression analysis of dizziness handicap inventory for clinical parameters in patients early Parkinson's disease.

Variable	Univariable			Multivariable		
	β	95% CI	p-value	β	95% CI	p-value
Gender	4.522	–1.402 to 10.445	0.133	–	–	–
Age	0.248	–0.101 to 0.598	0.161	–	–	–
BMI	0.021	–0.906 to 0.948	0.965	–	–	–
Level of education	–0.563	–1.149 to 0.023	0.060	–	–	–
Disease duration	0.540	–1.621 to 2.701	0.620	–	–	–
LEDD	–0.002	–0.016 to 0.011	0.712	–	–	–
UPDRS-III	0.242	–0.098 to 0.581	0.161	–	–	–
Tremor	–0.127	–1.483 to 1.229	0.852	–	–	–
Rigidity	0.347	–0.758 to 1.452	0.534	–	–	–
Bradykinesia	0.507	–0.165 to 1.179	0.137	–	–	–
PIGD	2.077	1.047 to 3.107	<0.001	1.239	0.151 to 2.237	**0.026**
HY stage	1.372	–6.262 to 9.007	0.721	–	–	–
MoCA-K	–0.972	–1.481 to –0.464	<0.001	–0.744	–1.247 to –0.242	**0.004**
BDI	0.489	0.049 to 0.929	0.030	–	–	–
BAI	0.678	0.203 to 1.154	0.006	0.453	–0.002 to 0.909	0.051
PFS	0.220	0.034 to 406	0.021	–	–	–
SCOPA-AUT	0.476	0.110 to 0.842	0.011	–	–	–

Boldface indicates $p < 0.05$ after multiple linear regression analysis.

CI, confidence interval; BMI, body-mass index; LEDD, levodopa equivalent daily dose; UPDRS-III, the Unified Parkinson's disease rating scale-part 3; PIGD, postural instability and gait disorder; HY, Hoehn and Yahr; MoCA-K, Korean version of Montreal Cognitive Assessment; BDI, Beck depression inventory; BAI, Beck anxiety inventory; PFS, Parkinson's disease fatigue scale; SCOPA-AUT, the Scale for Outcomes in Parkinson's disease-Autonomic.

SCOPA-AUT. However, multiple linear regression analysis (right panel of Table 2) revealed that DHI was significantly correlated with PIGD (β = 1.239, p = 0.026) and MoCA-K (β = –0.744, p = 0.004), but not with other factors.

3.3 Linear Regression Analysis of FLS in Early PD Patients

Simple linear regression analysis was performed between AAO-HNS FLS and demographics, motor, or non-motor scales (left panel of Table 3). The results showed that the FLS was significantly correlated with age, education level, PIGD, MoCA-K, and SCOPA-AUT. However, multiple linear regression analysis (right panel of Table 3) showed that FLS was significantly linked to PIGD (β = 0.077, p = 0.020) and MoCA-K (β = –0.043, p = 0.008).

4. Discussion

Dizziness may present in varying manifestations including faintness, light headedness, vertigo, and imbalance [19]. The limitations of vestibular function tests such as caloric tests in the evaluation of the severity of dizziness are as follows: (1) such objective tools reflect neither subjective severity nor the compensatory mechanism of dizziness, and (2) several tests or serial follow-ups are relatively hard due to the costs involved. Further, we focused on the clinical implications of subjective dizziness in patients with PD, rather than on the pathophysiological mechanism of dizziness. Collectively, we used self-reported dizziness questionnaires to evaluate the severity of dizziness and finally selected DHI and AAO-HNS FLS for the survey of movement disorders clinically. DHI is widely used for quantification of dizziness-related handicaps [7,20] and AAO-HNS FLS is known to be simple and a user-friendly vertigo severity scale [21,22].

We initially assume dizziness, as an underestimated symptom of non-motor symptoms (NMNs) in PD, implicated in the neurodegenerative changes of PD, since clinicians including us have occasionally observed that even drug-naïve Parkinsonian patients complain of dizziness. We should also have considered that many drugs, including antiparkinsonian drugs, may cause dizziness as a side effect. Consequently, we designed to enroll eligible patients only with relatively short duration of the disease (disease duration $\leq$5 years) not only to reduce the possible overwhelming effect of medication, but also to identify subjective dizziness as one of PD-related NMNs. Accordingly, we found that dizziness severity was not significantly related to the levodopa equivalent dose in patients with early stage of PD (Tables 2,3). Furthermore, the investigation of various drugs in this retrospective study was limited. Considering the sample size, we examined the association of Parkinson's motor and non-motor symptoms with dizziness scales only. The extent and effect of different drug types and doses on dizziness in patients with PD will require further investigation and research. Besides, subjective dizziness in patients with the early PD might be in part linked with orthostatic hypotension (OH), although the precise as-

Table 3. Linear regression analysis of AAO-HNS functional level scale for clinical parameters in patients early Parkinson's disease.

Variable	Univariable			Multivariable		
	β	95% CI	p-value	β	95% CI	p-value
Gender	0.254	–0.099 to 0.608	0.156	–	–	–
Age	0.020	0.000 to 0.041	0.041	–	–	–
BMI	–0.023	–0.078 to 0.032	0.412	–	–	–
Level of education	–0.037	–0.071 to –0.002	0.040	–	–	–
Disease duration	0.053	–0.075 to 0.182	0.411	–	–	–
LEDD	0.000	–0.001 to 0.001	0.479	–	–	–
UPDRS-III	0.011	–0.009 to 0.031	0.281	–	–	–
Tremor	–0.024	–0.104 to 0.057	0.561	–	–	–
Rigidity	0.004	–0.062 to 0.070	0.905	–	–	–
Bradykinesia	0.019	–0.021 to 0.059	0.352	–	–	–
PIGD	0.105	0.042 to 0.168	0.001	0.077	0.013 to 0.141	**0.020**
HY stage	0.309	–0.141 to 0.760	0.175	–	–	–
MoCA-K	–0.055	–0.086 to –0.024	0.001	–0.043	–0.074 to –0.011	**0.008**
BDI	0.023	–0.003 to 0.050	0.082	–	–	–
BAI	0.018	–0.011 to 0.048	0.219	–	–	–
PFS	0.010	–0.001 to 0.021	0.076	–	–	–
SCOPA-AUT	0.029	0.007 to 0.050	0.011	–	–	–

Boldface indicates $p < 0.05$ after multiple linear regression analysis.

CI, confidence interval; AAO-HNS, the American Academy of Otolaryngology-Head and Neck Surgery; BMI, body-mass index; LEDD, levodopa equivalent daily dose; UPDRS-III, the Unified Parkinson's disease rating scale-part 3; PIGD, postural instability and gait disorder; HY, Hoehn and Yahr; MoCA-K, Korean version of Montreal Cognitive Assessment; BDI, Beck depression inventory; BAI, Beck anxiety inventory; PFS, Parkinson's disease fatigue scale; SCOPA-AUT, the Scale for Outcomes in Parkinson's disease-Autonomic.

sociation between orthostatic hypotension and subjective dizziness in people with Parkinson's disease remains controversial [23,24]. Further research is warranted to address this issue.

Until now, the risk factors for dizziness in Parkinson's patients have been sporadically studied. One study reported that dizziness in patients with PD was associated with not only orthostatic hypotension but also vestibular dysfunction [25]. Another study showed that the presence of dizziness in patients with early PD was related to low global cognitive function [26]. Intriguingly, we revealed that severe dizziness was associated with severe PIGD score. Further, we found that severe dizziness revealed a negative effect on global cognitive function, independent of other NMSs including anxiety, depression, fatigue, and dysautonomia. Studies have shown that PIGD is significantly associated with cognitive impairment or a risk factor of dementia [27,28]. Cholinergic dysfunction and amyloid pathology are implicated as the underlying pathophysiologic mechanisms of the PIGD feature in PD [29,30]. Collectively, it is reasonable to deduce that the possible mechanism of dizziness is linked to cholinergic dysfunction or cerebral amyloidopathy. However, the precise pathophysiologic mechanism of dizziness in PD remains little revealed yet.

The current study has the following limitation. First, due to the retrospective design of the study, a potential selection bias may exist. Second, the global cognitive function evaluated using MoCA-K appears to be relatively crude, suggesting the need for a comprehensive neuropsychological battery to corroborate our findings. Third, we could not investigate the precise etiology of dizziness using vestibular function tests. The dizziness subtype determining the close relationship with PIGD symptom or global cognition was not evaluated. Fourth, the mean duration of disease was very short (1.9 years) yet the MoCA score was relatively low. It was probably estimated that low MoCA scores were associated with old age and low education level in our study population. Nevertheless, this raises the question whether some of the patients may have mild cognitive impairment in dementia with Lewy bodies (DLB). However, classifying such people's diagnoses as PD with mild cognitive impairment (MCI), based on the 1-year rule, seems more reasonable for the current consensus. We supposed that other parkinsonian disorders had not been completely ruled out, although we tried to discriminate PD from other conditions as much as possible. Last, caution is necessary not to generalize our findings, as we only evaluated patients with early stages of PD.

5. Conclusions

In summary, we demonstrated that dizziness was significantly associated with PIGD and global cognitive function in early PD patients. The results provide neuropathological correlates between dizziness, PIGD, and cognitive dysfunction in PD. Dizziness might be a surrogate marker of PIGD and/or a potential risk factor for cognitive decline or dementia in patients with PD. Further follow-up studies are necessary to extend our findings in patients with PD to address this issue.

Abbreviations

PD, Parkinson's disease; DHI, Dizziness Handicap Inventory; MRI, magnetic resonance imaging; DAT, dopamine transporter; UPDRS, Unified Parkinson's Disease Rating Scale; PIGD, postural instability and gait disorder; NMS, non-motor symptom; MoCA-K, Korean version of the Montreal Cognitive Assessment; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; PFD, Parkinson's Disease Fatigue Scale; SCOPA-AUT, Scale for Outcomes in Parkinson's Disease-Autonomic; GI, gastrointestinal; CV, cardiovascular.

Availability of Data and Materials

The data underlying this article will be shared on reasonable request to the corresponding author.

Author Contributions

Conceptualization—KYK; Methodology—KYK; Data curation—JY, ROK, EJL and KYK; Formal analysis—KYK; Funding acquisition—KYK; Investigation—JY, ROK, EJL and KYK; Writing - original draft—KYK; Writing - review & editing—JY, ROK, EJL and KYK; Supervision—KYK. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures were performed in accordance with ethical standards of the institution and/or the national research committee as well as with the 1964 Helsinki Declaration and its subsequent amendments. This study was retrospective and was approved with waiver of individual informed consent by the ethics committee of our Institutional Review Board (IRB No. 2019-08-018).

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Conflict of Interest

The authors declare no conflict of interest.

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