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ORIGINAL ARTICLE

Excessive daytime sleepiness and its impact on quality of life in de novo Parkinson's disease

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Abstract

Excessive daytime sleepiness (EDS) is one of the most common sleep problems in patients with Parkinson's disease (PD); however, its clinical implications are not clear, especially in early stage, non-medicated PD patients. This study investigated EDS in Korean patients with de novo PD and its impact on quality of life. This cross-sectional study was carried out with 198 PD patients who underwent a structured clinical interview and examination based on common and conventional scales. Motor and nonmotor symptoms were assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) and Non-Motor Symptoms Scale (NMSS). EDS was evaluated with the Epworth Sleepiness Scale (ESS), the nocturnal disabilities and nighttime sleep problems were assessed with Parkinson's Disease Sleep Scale 2nd version, and quality of life was measured with the Parkinson's Disease Quality of Life 39 (PDQ-39). The relationships between ESS score and each scale were investigated. Among the patients studied, 42 patients had EDS defined as ESS > 10. Patients with EDS had a higher motor burden, greater nocturnal disabilities, more severe non-motor symptoms, and lower quality of life than did patients without EDS. Partial correlations revealed that ESS score was related to PDQ-39 summary index, irrespective of age, body mass index, or disease duration. These results show that EDS can have an immense negative impact on quality of life. The causes of EDS are multifactorial, which complicates its treatment. Further investigations are required to determine the safety and efficacy of potential EDS therapies and to develop novel EDS treatments in PD.

Keywords Parkinson's disease · Excessive daytime sleepiness · Health-related quality of life

Introduction

Parkinson's disease (PD) clinical spectrum includes many non-motor features which may even predate the onset of motor symptoms [1, 2]. Various non-motor symptoms (NMS) such as orthostatic intolerance, constipation, mood disturbance, cognitive impairment, pain, and sleep-wake disorders [3] occur in different periods [2]. The significance of these NMS differs regarding their ability to predict PD risk [1, 2] or prognosis in patients already diagnosed with PD [4].

Patient and physician reports of NMS can disagree. Nearly 44% of patient-reported complaints were not documented by physicians in a study [5], and patients do not report some NMS when present [6, 7]. Of the undeclared symptoms, excessive daytime sleepiness (EDS) is one of the most under-recognized, and is only reported to doctors about 50% of the time [6, 7].

In a cross-sectional study, the prevalence of EDS did not differ between untreated PD patients and healthy controls [8]; however, another report suggests otherwise [9]. The prevalence of EDS has been estimated at 11–50% depending on the study design [10, 11]. In two prospective cohorts, frequency of EDS in PD rose and became more persistent with disease duration. This increasing frequency and persistency were observed both in early de novo PD and established PD, regardless of dopaminergic drug use [10, 11].

EDS negatively affects health-related quality of life [4], and its influence becomes prominent as the disease progresses [5]. As stated above, EDS is poorly recognized by both patients and clinicians, and the characteristics of PD with and without EDS have seldom been reported in early or drug-naïve patients. The hypothesis tested in this study was that daytime hypersomnolence may contribute to non-motor

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symptoms, functional status, and health-related quality of life attending early PD. We assessed whether de novo PD patients with EDS have more non-motor symptoms, worse functional status, and worse health–related quality of life.

Methods

One hundred ninety-eight patients with PD from Seoul St. Mary's Hospital, the Catholic University of Korea were enrolled. They visited our movement clinic between Jan. 1, 2015, and Dec. 31, 2017. They were clinically diagnosed according to the criteria of the UK PD Society Brain Bank [12]. Positron emission tomography using ^{18}F-N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane was performed on every patient to support the clinical diagnosis. All enrolled patients had decreased dopamine transporter uptake in the striatum, mainly in the posterior putamen.

Patients received structured clinical interviews and examinations, and clinical information was obtained including age, sex, disease duration, education, body mass index (BMI), history of hypertension, diabetes mellitus, and smoking status.

Motor and non-motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS), modified Hoehn and Yahr (H&Y) stage, and Korean version of Non-Motor Symptoms Scale (NMSS) [13]. EDS was assessed with the Korean version of the Epworth Sleepiness Scale (ESS) [14, 15]. Patients who scored more than 10 on the ESS were categorized as PD with EDS (PD + EDS or EDS group) and 10 or less as PD without EDS (PD−EDS or non-EDS group) [16]. The nocturnal disabilities and nighttime sleep problems were also measured with the Parkinson's Disease Sleep Scale 2nd version (PDSS-2) [17]. Health-related quality of life was measured with the Korean version of the Parkinson's Disease Quality of Life-39 (PDQ-39) [18].

All enrolled patients were PD naïve and did not take any dopaminergic agents. For patients who needed assistance in completing questionnaires, a neurologist or a well-educated rater helped them finish the surveys but did not guide them toward certain answers.

Patients who manifested parkinsonism without an abnormal dopamine transporter scan were excluded. In addition, those who were clinically suspicious of atypical PD such as progressive supranuclear palsy, multiple system atrophy, and dementia with Lewy body were omitted from the study. Patients having a history of restless leg syndrome, sleep apnea, and insomnia, or other medical illness (osteoarthritis, chronic obstructive pulmonary disease, stroke, and heart failure), were also excluded. We excluded patients taking any drugs that could influence sleep-wake cycles.

Statistical analysis

All statistical analyses were executed with the Statistical Package for the Social Sciences, version 24.0 for Mac (SPSS, Inc.; Chicago, IL, USA). The demographic characteristics of 198 PD patients were assessed with descriptive statistics. To compare the EDS and non-EDS groups, independent t tests were used for continuous variables and χ^2 tests for categorical variables. Partial correlations, corrected for confounding effects of age and disease duration, were used to inspect associations between questionnaires. Statistical significance was defined as a two-tailed p value of < 0.05.

Results

Clinical characteristics of enrolled patients are provided in Table 1. A total of 198 patients who met the diagnostic criteria for PD were evaluated. The mean ESS score was 6.5 ± 5.7, and 42 PD patients (21.2%) had EDS with an ESS score > 10. The EDS group had a mean ESS score of 15.6 ± 3.9. The mean age was 69.1 ± 9.7 years, and 95 patients were male (48.0%). A majority of patients had a disease duration less than 1 year. The mean total UPDRS score was 28.0 ± 16.0 points, and H&Y stage was 1.8 ± 0.7.

Clinical demographics including age, sex, disease duration, BMI, and medical history did not differ between PD patients with and without EDS; however, the proportion of diabetes mellitus was mildly higher in PD patients with EDS than it was among PD without EDS group ($p = 0.06$). PD patients with EDS had more severe motor symptoms than did those without EDS, as represented by UPDRS part III and H&Y stage. The EDS group not only performed poorly on motor examinations, but they also had worse mentation, behavior, and mood part score (UPDRS part I; 3.3 ± 2.7 vs. 2.1 ± 2.0, $p = 0.003$) and activities of daily living score (UPDRS part II; 11.0 ± 7.2 vs. 7.7 ± 4.9, $p = 0.001$).

Patients with EDS have greater nocturnal disabilities and poorer sleep qualities which assessed by PDSS-2; they had higher PDSS-2 score than those without EDS (PDSS total score; 17.8 ± 7.1 vs. 12.5 ± 6.8, $p < 0.001$). ESS score was also positively associated with PDSS-2 score (Fig. 1a).

Non-motor features were further investigated (Table 2), and the EDS group had a higher burden from non-motor symptoms (total NMSS score; 117.3 ± 52.4 vs. 62.7 ± 39.2, $p < 0.001$). All patients who had daytime

Table 1 Clinical characteristics

	PD ($n = 198$)	PD–EDS ($n = 156$)	PD + EDS ($n = 42$)	p
Age, years	69.1 ± 9.7	68.4 ± 9.8	71.6 ± 9.0	0.056
Sex, male (%)	95 (48.0%)	72 (46.2%)	23 (54.8%)	0.322
Disease duration, years	0.9 ± 1.4	1.0 ± 1.5	0.7 ± 1.0	0.239
Education, years	10.7 ± 4.6	10.5 ± 4.6	11.1 ± 4.7	0.467
Body mass index,	24.0 ± 3.2	23.8 ± 3.2	24.6 ± 3.5	0.145
Hypertension (%)	94 (47.5%)	72 (46.2%)	22 (52.4%)	0.473
Diabetes mellitus (%)	33 (16.7%)	22 (14.1%)	11 (26.2%)	0.062
Current or ex-smoker (%)	49 (24.7%)	39 (25.0%)	10 (23.8%)	0.874
UPDRS	28.0 ± 16.0	26.2 ± 14.4	34.7 ± 19.8	0.002
UPDRS part I	2.4 ± 2.2	2.1 ± 2.0	3.3 ± 2.7	0.003
UPDRS part II	8.4 ± 5.6	7.7 ± 4.9	11.0 ± 7.2	0.001
UPDRS part III	17.4 ± 10.4	16.3 ± 9.7	21.4 ± 11.8	0.005
Hoehn & Yahr stage	1.8 ± 0.7	1.7 ± 0.7	2.2 ± 0.8	0.001
PDSS-2	13.6 ± 7.2	12.5 ± 6.8	17.8 ± 7.1	< 0.001
Epworth Sleepiness Scale	6.5 ± 5.7	4.1 ± 3.0	15.6 ± 3.9	< 0.001

PD Parkinson's disease, *EDS* exessive daytime sleepiness, *UPDRS* Unified Parkinson's Disease Rating Scale, *PDSS-2* Parkinson's Disease Sleep Scale 2nd version

Values represent the mean with standard deviation or number of subjects (percentage)

Analyses were performed by independent t test for continuous variables and χ^2 test for categorial variables

hypersomnolence had more severe non-motor symptoms in all NMSS subdomains.

In a partial correlation analysis, ESS score was positively related with increasing UPDRS and NMSS scores, even after adjusting for age, body mass index, and disease duration. ESS scores were significantly positively associated with all total and subscores of validated clinimetric scales (Table 3).

EDS was associated with a worse quality of life in general (PDQ-39 summary index; 37.2 ± 16.1 vs. 20.3 ± 12.3, $p < 0.001$) and in every aspect of the questionnaire (Table 4). ESS was positively related to PDQ-39 summary index (Fig. 1b).

Discussion

In this study, 42 newly diagnosed PD patients (21.2%) reported EDS. Patients with EDS had more non-motor symptoms, poorer nighttime behavioral/sleep qualities, worse functional status, and worse health–related quality of life. Early complaints of daytime hypersomnolence were positively associated with motor and non-motor burdens, nocturnal disabilities, and quality of life.

EDS affects up to 50% of PD patients [19], but the prevalence for early and non-medicated PD patients is less than half that [2, 10, 20], which explains the low prevalence in our study. Our study also agrees with other studies evaluating

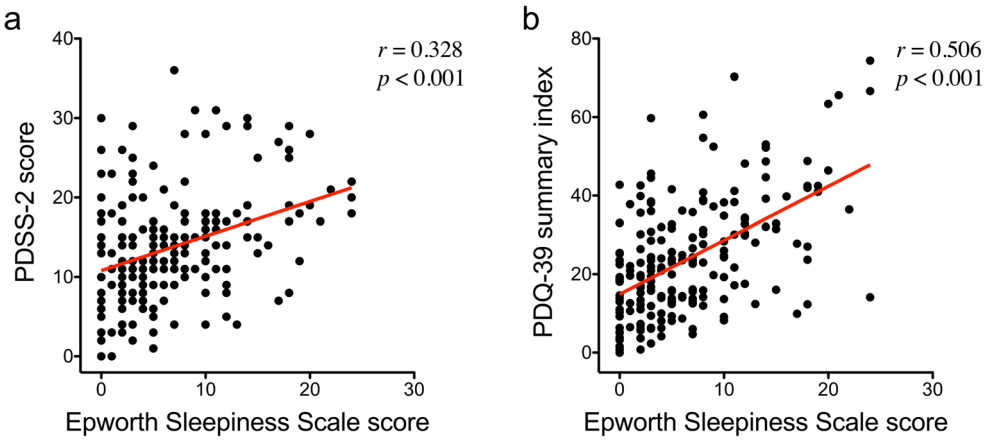

Fig. 1 Partial correlation analysis results. **a** Epworth Sleepiness Scale (ESS) vs. Parkinson's Disease Sleep Scale version 2 (PDSS-2), and **b** ESS vs. Parkinson's Disease Quality of Life-39 (PDQ-39) summary index

Table 2 Comparison of non-motor symptom characteristics between non-EDS vs. EDS groups

	Non-EDS ($n = 156$)	EDS ($n = 42$)	p
Cardiovascular	1.0 ± 2.1	4.8 ± 6.5	< 0.001
Sleep/fatigue	11.4 ± 0.6	22.9 ± 10.4	0.001
Mood	15.8 ± 14.5	30.3 ± 21.1	< 0.001
Perceptional problems	0.6 ± 1.8	1.3 ± 2.4	0.035
Attention/memory	6.4 ± 6.2	13.2 ± 10.0	< 0.001
Gastrointestinal	5.7 ± 5.5	9.4 ± 7.6	0.001
Urinary	12.3 ± 9.4	19.0 ± 9.7	< 0.001
Sexual	2.6 ± 5.0	5.0 ± 7.6	0.019
Miscellaneous	7.1 ± 7.5	11.8 ± 8.8	0.001
Total	62.7 ± 39.2	117.3 ± 52.4	< 0.001

Values represent the mean with standard deviation

Analyses were performed by independent *t* test

EDS in early PD; age, sex, and disease duration did not differ between patients with and without EDS [8, 10, 20].

Numerous studies have shown clinical implications of EDS in PD [9, 21–23], and its characteristics have also been studied in a long-term study [11]. However, only a few studies have assessed EDS in early de novo PD [10, 20]. Those studies found significantly worse non-motor scores in PD + EDS than PD−EDS, but motor correlates did not differ [10, 20]. In the present study, PD with EDS was worse in all motor and non-motor scale domains. The EDS group had a more severe disease status across all UPDRS and NMSS domains. The link between attention/memory domain in NMSS and EDS was also found and this is in line with previous study that emphasized its association between cognitive impairment and EDS [24]. In addition, patients with EDS had greater PDSS-2 score which suggested nocturnal behavioral/sleep disabilities might influence daytime somnolence or vice versa [25]. We speculate the increased non-motor symptoms in the EDS might influence motor function, resulting in more motor impairment [26].

Table 3 Partial correlation analysis results between the ESS score and motor and nonmotor symptom status

	Partial correlation coefficient r (p)
Motor symptom status	
UPDRS part 1	0.243 (0.001)**
UPDRS part 2	0.290 (< 0.001)**
UPDRS part 3	0.263 (0.001)**
UPDRS total	0.286 (< 0.001)**
Non-motor symptom status	
Cardiovascular	0.403 (< 0.001)**
Sleep/fatigue	0.517 (< 0.001)**
Mood	0.329 (< 0.001)**
Perceptional problems	0.189 (0.008)**
Attention/memory	0.415 (< 0.001)**
Gastrointestinal	0.264 (< 0.001)**
Urinary	0.249 (< 0.001)**
Sexual	0.156 (0.029)*
Miscellaneous	0.269 (< 0.001)**
NMSS total	0.493 (< 0.001)**

UPDRS Unified Parkinson's Disease Rating Scale, *NMSS* Non-Motor Symptom Scale

Analyses were performed using the partial correlation coefficients adjusted for age, body mass index, and disease duration

*< 0.05

**< 0.01

Table 4 Comparison of PDQ39 characteristics between non-EDS vs. EDS groups

	Non-EDS ($n = 156$)	EDS ($n = 42$)	p
Mobility	13.6 ± 10.6	23.2 ± 11.0	< 0.001
Activity of daily living	5.3 ± 5.0	8.9 ± 6.1	< 0.001
Emotional well-being	5.0 ± 5.1	10.0 ± 6.8	< 0.001
Stigma	4.0 ± 4.6	5.9 ± 4.7	0.015
Social support	0.7 ± 1.4	1.9 ± 2.4	< 0.001
Cognition	4.2 ± 2.9	8.0 ± 3.0	< 0.001
Communication	0.9 ± 1.7	3.1 ± 3.2	< 0.001
Bodily discomfort	2.5 ± 2.3	3.8 ± 2.4	0.001
PDQ-39 summary index	20.3 ± 12.3	37.2 ± 16.1	< 0.001

Values represent the mean with standard deviation. Analyses were performed by independent *t* test

We also found that EDS was positively associated with health-related quality of life. In previous cohort studies of early PD [10, 20], such associations were not evaluated. Another study looked into the effects of NMS on health-related quality of life in early PD [4], but it did not show an association between EDS and other scales. Our study showed that, irrespective of age and disease duration, EDS relates to worse quality of life in early PD patients. The fact that EDS is present in the early stage of the disease and worsening sleepiness negatively impacts quality of life indicates that EDS should be treated in early PD. Dopamine agonists, a frequent drug for stable, early PD, can induce "sleep attacks" and aggravate somnolence [9, 19]. In clinical practice, such knowledge will help us guide treatment choices and allow physicians to provide appropriate medical advice before prescribing medication.

EDS is thought to be related to disease-specific neurodegeneration [10, 20] and to be the result of extra-nigral pathologic changes [27–29]. The pattern of Lewy body spread was suggested to determine the NMS subtypes and clustered non-motor symptoms [27]. Not only does EDS begin long before motor symptoms onset [2], it also suggests a risk for PD development [21]. Our findings of stronger associations between ESS scores and cardiovascular, sleep/fatigue, and attention/memory domains than with others NMSS domains could be explained by differential pathologic spreads [27]. These

findings agree with a previous study [13], and these findings further substantiate the hypothesis that EDS predicts motor symptoms [2, 21]. These findings suggest that EDS may be related to the arousal system in multiple brain areas. EDS could be a marker of widespread neurodegeneration as PD with EDS had a more severe disease status in our study.

Our study has some limitations. The ESS scores were not substantiated by objective examination such as polysomnography. Had the study included such examination, more comprehensive and analytic insights into the EDS characteristics could have been provided. In addition, many PD patients are elderly, and they frequently have comorbidities such as arthralgia that may affect sleep quality. Although we thoroughly investigated the medical history, for example osteoarthritis, chronic obstructive pulmonary disease, stroke, and heart failure, and controlled the analysis, the etiology of EDS is complex; many clinical conditions were not considered. Especially in the subject of this study, PD patients with EDS had relative higher proportion of diabetes mellitus than those without EDS. In diabetic patients, EDS can be relatively commonly found and EDS has been known to be a novel risk factor for hypoglycemia in patients with diabetes mellitus [30–32].

In summary, EDS occurs in early and drug-naïve PD patients and influences a patient's daily activities and quality of life. These results suggest a possible role of EDS in predicting PD prognosis. Its role needs to be taken into account when treating early PD patients.

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Compliance with ethical standards

The study protocol was approved by the Institutional Review Board at our institution, and all subjects provided written informed consent to participate. All experiments were performed in accordance with relevant guidelines and regulations.

Conflict of interest The authors declare that they have no conflicts of interest.

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