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Correlates of Excessive Daytime Sleepiness in De Novo Parkinson's Disease: A Case Control Study

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Abstract

Objective—This study was undertaken to determine the frequency and correlates of excessive daytime sleepiness in de novo, untreated Parkinson's disease (PD) patients compared with the matched healthy controls.

Methods—Data were obtained from the Parkinson's Progression Markers Initiative, an international study of de novo, untreated PD patients and healthy controls. At baseline, participants were assessed with a wide range of motor and nonmotor scales, including the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Excessive daytime sleepiness was assessed based on the Epworth Sleepiness scale (ESS), with a cutoff of 10.

Results—Four hundred twenty-three PD subjects and 196 healthy controls were recruited into the study. Mean ESS (min, max) score was 5.8 (0, 20) for the PD subjects and 5.6 (0, 19) for healthy controls ($P = 0.54$). Sixty-six (15.6%) PD subjects and 24 (12%) healthy controls had ESS of at least 10 ($P = 0.28$). No difference was seen in demographic characteristics, age of onset,

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disease duration, PD subtype, cognitive status, or utilization of sedatives between the PD sleepiness-positive versus the negative group. The sleepiness-positive group had higher MDS-UPDRS Part I and II but not III scores, and higher depression and autonomic dysfunction scores. Sleepiness was associated with a marginal reduction of A-beta ($P = 0.05$) but not alpha-synuclein spinal fluid levels in PD.

Conclusions—This largest case control study demonstrates no difference in prevalence of excessive sleepiness in subjects with de novo untreated PD compared with healthy controls. The only clinical correlates of sleepiness were mood and autonomic dysfunction. Ongoing longitudinal analyses will be essential to further examine clinical and biological correlates of sleepiness in PD and specifically the role of dopaminergic therapy.

Keywords

Parkinson's disease; daytime somnolence; biomarkers

Parkinson's disease (PD) is a progressive neurodegenerative condition associated with a broad scope of motor and nonmotor symptoms (NMS). Excessive daytime sleepiness (EDS) is one of the most common and debilitating manifestations of NMS in PD. The reported prevalence of EDS in the overall PD population is widely variable (16%-74%) and depends on EDS criteria, disease stage, and ascertainment methods, but it is consistently higher than in the general population.[1,2] Respective data on EDS stem largely from studies on patients with advanced PD, whereas hardly any data exist on EDS in early, specifically untreated, PD. The cause of EDS in advanced and treated PD is multifactorial.[3] Disease variables that have been reported to be associated with EDS in PD populations include longer disease duration, older age, older age at PD onset, sex, more severe motor manifestations, nontremor dominant motor phenotype, depression, anxiety, cognitive impairment, and hallucinations.[4-10] In addition, dopaminergic medications have been shown to have a major negative impact on EDS in PD.[4,11-14] The presence of EDS predicts a greater decline over time in motor impairment, cognition, and greater risk of developing dementia.[15] Very limited information is available on EDS in early, specifically untreated, PD.[16-18] Three small studies assessed EDS in de novo PD patients.[16-18] Each of them enrolled fewer than 25 de novo PD patients, and only one had healthy controls (HCs). Excessive daytime sleepiness was defined by Epworth Sleepiness Scale (ESS ≥ 10). All studies came to the same conclusion: that EDS does not seem to be a trait of untreated PD.[16-18] More recent studies assessed EDS as part of the overall NMS by using a validated NMS questionnaire.[19,20] Prevalence of EDS in the cohort of 97 de novo PD subjects was 3.3% and did not change significantly 2 y later with initiation of dopaminergic therapy (4.4%).[20] However, prevalence was substantially higher (28% of 109 subjects) in another de novo cohort compared with 15% of 107 HCs.[19] Thus, uncertainty remains regarding the prevalence and clinicobiological correlates of EDS in de novo PD. That is specifically relevant considering that EDS was shown to be one of the risk factors for development of PD in prospective epidemiological studies and may precede onset of motor manifestations of PD,[4,21] theoretically corresponding to Braak et al.'s data[22] on early involvement of the brainstem sleep wakefulness control system in the disease pathological process.[22] We aimed to

systematically explore prevalence, clinical, and for the first time biological correlates of EDS in a large group of subjects with early untreated PD compared with HCs.

Methods

Participants

Subjects with newly diagnosed untreated PD and matched HCs were enrolled in the Parkinson's Progression Biomarker Initiative (PPMI), a study for which the aims and methods were previously published.[23] At baseline, PD subjects were required to be older than 30 y and 1) have at least two of bradykinesia, rigidity, and resting tremor OR have either an asymmetric resting tremor or asymmetric bradykinesia; 2) have been recently diagnosed (within 2 y); 3) be untreated; and 4) have had a dopamine transporter deficit on the ^{123}I Ioflupane dopamine transporter (DatScan®) imaging. The HCs were matched by age, sex, and education and must have had no significant neurologic dysfunction, no first-degree family member with PD, and a Montreal Cognitive Assessment (MOCA) score greater than 26.

Standard Protocol Approvals, Registrations, and Consents

Each participating PPMI site received approval from an ethical standards committee on human experimentation before study initiation and obtained written informed consent for research from all individuals participating in the study.

Study Design

The PPMI is an observational, international, multi-center (16 US and 5 European sites) study designed to identify PD progression biomarkers. The study was launched in June 2010 and has successfully completed its enrollment goal of 400 PD participants and 200 HCs. The data used for this analysis constitute the analysis of the baseline dataset for the full cohort as obtained from the PPMI database (www.ppmi-info.org, accessed 2014 June 17).

Study Outcomes

Excessive daytime sleepiness was assessed using ESS, a widely used, validated, self-reported, and self-completed instrument[24] that is recommended for screening for EDS in PD.[25] The scale consists of eight questions, each rated on a scale of 0 to 3, with a maximum score of 24; a higher score correlates with a higher degree of EDS. Consistent with the other studies, ESS of 10 or greater was set as a cutoff for EDS.

Other measures included basic demographic variables, Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS),[26] and total and subscale scores. Participants were classified as having tremor-dominant versus non–tremor-dominant subtypes and previously described postural instability and gait disturbance (PIGD), and indeterminate motor subtypes were combined into one group because of concerns regarding the stability of PIGD classification in early PD,[27] Hoehn and Yahr stage as measures of disease severity,[28] Modified Schwab and England Activities of Daily Living Scale,[29] the MOCA for assessment of global cognitive abilities,[30] the 15-item Geriatric Depression Scale,[31] the scale for outcomes for PD–autonomic function,[32] state and trait anxiety scale,[33]

the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease,[34] and rapid eye movement behavior disorder (RBD) questionnaire (RBDSQ).[35] In addition to MOCA, the patients underwent a detailed neuropsychiatric assessment summarized in Table 1. Data on utilization of sedatives and hypnotics were collected based on the FDA classification of the classes of drugs. All subjects underwent DatScan® targeting the dopamine transporter (DAT) that was analyzed according to the imaging technical operations manual (http://ppmi-info.org/). Biological samples included cerebrospinal fluid (CSF) biomarkers (β-amyloid 1-42 [Aβ1-42], total tau [T-tau], tau phosphorylated at threonine 181 [P-tau$_{181}$], and unphosphorylated α-synuclein [α-Syn]) in all participants. The details of sample collection, processing, and biomarker analyses have been previously reported.[36]

Statistical Methods

Prevalence of EDS was established in PD and HC cohorts. Parkinson's disease EDS+ versus EDS− groups were compared against all variables. For between-group comparisons of clinical, demographic, neuropsychological, and imaging variables, *t* tests and χ^2 tests were used. For CSF biomarker variables, a nonparametric rank-based approach was used by performing Mann-Whitney *U* tests.

Effects of these variables on EDS in PD subjects and HCs were also considered in univariate and multivariate logistic models. After adjusting for age and sex, the univariate relationship between EDS and each predictor variable was examined. Any variables that had univariate associations with *P* values less than 0.20 were included in a multivariate model, also adjusting for age and sex. A backward selection approach was used to choose the best model. Variables were removed one at a time until all variables remaining in the model were significant at the 0.10 level. A non-parametric approach was again used for the CSF biomarker variables, with ranks of the biomarkers, rather than raw values, being used as covariates.

To avoid collinearity issues with some of the predictor variables, the following rules were used when fitting the multivariate model: To avoid the issue of correlation between total MDS- UPDRS score and subscale scores, if total MDS-UPDRS score was significant at the 0.20 level in a univariate manner, it was considered in the multivariate model. If not, but any of the subscale scores were significant in a univariate manner, they were considered in the multivariate model. Similarly, to avoid issues of correlation between individual CSF biomarkers with the CSF ratios, if any individual markers were significant, they were considered in the multivariate model. The CSF ratios were only considered in the multivariate model if neither of the individual markers was significant.

Results

Demographic and clinical information for the 423 PD participants and 196 HCs is listed in Table 2. The two groups were well matched by age ($P = 0.55$), sex ($P = 0.77$), race ($P = 0.85$), ethnicity ($P = 0.62$), and education ($P = 0.59$). The mean ESS score in the PD participants was 5.8 (range, 0, 20) and 5.6 (0, 19) in HC ($P = 0.54$). No difference was found in the prevalence of EDS in PD versus HC cohorts; 66 (16%) of PD participants had EDS

versus 24 (12%) HCs ($P = 0.28$). Use of sedatives and hypnotics was no different between the groups (Table 2).

We then compared EDS+ versus EDS− subsets of PD participants. No demographic variables were associated with EDS in PD participants. The only disease characteristics that were associated with EDS were part I (neuropsychiatric assessment) and II (patient-completed experiences of daily living) MDS-UPDRS scores but not part III (motor) (Table 2). The nonmotor disability variables that were associated with EDS were depression ($P < 0.01$), autonomic dysfunction ($P < 0.01$), and anxiety based on state and trait anxiety scale state and trait subscores ($P = 0.04$, $P = 0.03$) (Table 1). Overall, no difference was found in the cognitive performance between PD-EDS+ versus PD-EDS− groups either in MOCA (P p= p=0.59) or in the detailed neuropsychological battery (Table 1).

We analyzed the prevalence of other sleep dysfunction parameters collected in the PPMI and association with ESS (Table 3). Sleep dysfunction was measured by a single item of UPDRS part I (sleep problems, 1.7) and was more common in PD subjects than in HC (P50.02), but no difference was seen between PD-EDS+ and PD-EDS− subjects. As expected, a significant association was seen between EDS as measured by a single item on MDS-UPDRS and ESS ($P < 0.01$), because both are self-reported scales, and between EDS and fatigue ($P < 0.01$). Of note, a significant difference ($P < 0.01$) was found between PD and HCs as reflected on the MDS-UPDRS sleepiness and fatigue scores, although both of them are single-item questions that have not been validated for screening for these conditions. The RBD as measured by RBDSQ was present in 159 (38%) of PD subjects versus 39 (20%) ($P < 0.01$) controls, and the presence of RBD was associated with EDS in PD subjects ($P = 0.01$).

No association of ESS with the degree, distribution, or laterality of presynaptic loss of dopaminergic function as measured by a DATscan was found. The ESS was associated with lower CSF levels of A-Beta and P-Tau/T-Tau and marginally with the higher levels of T-Tau/A-Beta in PD subjects (Table 4). No association was found with the level of α-Syn ($P = 0.19$). In HCs, EDS was associated with a lower ratio T-Tau/A-Beta ($P = 0.03$), but not with other variables. The PD versus HC subjects with EDS had a lower A-Beta ($P = 0.01$) and P-Tau/T-Tau ratio ($P = 0.01$), although the T-Tau/A-Beta difference between the groups was not significant ($P = 0.09$).

After adjusting for age and sex in the univariate model, the same clinical disease characteristics as in Table 1 remained significant (Table 5). In the multivariate model, education became significant, depression and autonomic function remained significant, and anxiety lost significance. The association with RBD remained after adjusting for age and sex, but this became insignificant in the multivariate analysis. In the univariate analysis of biological variables after adjusting for age and sex, all variables that were significant in Table 4 remained significant. In the multivariate analysis A-Beta remained marginally significant ($P = 0.05$). Of note, the ratios T-Tau/A-beta and P-tau/T-Tau were not included in the multivariate analysis, because A-beta and P-tau were already considered in the multivariable model. Because of the correlation between individual biomarkers and their ratios, the univariate associations found in T-Tau/A-beta and P-Tau/T-Tau are likely

explained by the fact that the individual markers A-Beta and P-Tau were at least marginally significant in a univariate manner. When we performed multivariate analysis for the HC group, controlling for the same variables as in PD, education was not significant ($P = 0.17$). Only autonomic dysfunction was significantly associated with EDS ($P = 0.02$), but not other nonmotor variables that carried significance in the PD cohort. In the analysis of the biological variables, only the association with A-Beta was marginally significant ($P = 0.05$).

Discussion

Our study represents the largest observational case-controlled study of EDS in participants with early PD who were not receiving dopaminergic therapy. Our data demonstrate that prevalence of EDS in early untreated PD is no different from that in matched HCs. The prevalence of EDS in HCs was fairly high (12%), although consistent with the other reports in aging populations that used the same ESS cutoff scores.[37] Our results are in accord with previously reported small studies of EDS in early untreated PD,[4,17,18] but they solidify previous data based on the large size of the cohort and the richness of associated clinical and biomarker data. This observation is very important because it points to the fact that EDS, at least in early PD, is driven by factors other than the simple presence of PD-related pathology. These factors can include biological variables of the spread of pathology with the progression of the disease into the reticular activating system and other brainstem structures responsible for alertness as well as clinical variables of the impact of disease progression and specifically dopaminergic medications. This hypothesis will have to be tested in the longitudinal data analysis. Considering that no difference existed in EDS prevalence between PD and HC, we focused analysis of the clinical and DATscan imaging characteristics within the PD cohort as presented in Tables 1 and 3. Substantial data are available on the association of EDS in more advanced stages of PD with demographic (age, sex) and disease characteristics (age of PD onset, disease duration, severity of motor disability, and cognitive status). None of these factors was significant in our cohort, likely because our cohort includes subjects with very early PD and younger age compared with the general PD population. Which of these variables will become significant with longitudinal follow-up remains to be determined. Excessive daytime sleepiness was not associated with the degree of motor disability as measured by MDS-UPDRS Part III, but it was associated with the Part I and II cognitive assessment and experiences of daily living. Such results are not unexpected, because factors other than pure motor dysfunction play a role in functional impairment. Association of EDS with UPDRS part I is expected, because that scale captures a number of sleep-related items.[38] Of note, most of the PD and HC participants with EDS rated it as slight or mild, pointing to the mild degree of EDS-related disability. Severity of EDS could have changed if we had used an ESS cutoff score above 10, but our cutoff was consistent with the other studies in early untreated PD.[17] Excessive daytime sleepiness was not associated with the night sleep impairment, pointing to the fact that EDS is not simply a consequence of a poor night's sleep and is driven by a different mechanism.

Consistent with the data from more advanced PD populations, EDS was associated with depression. This could either reflect a biological substrate for such an association (i.e., early simultaneous involvement of the noradrenergic [locus ceruleus] and serotoninergic [raphe nucleus] structures that are implicated in the control of mood) or could be attributable to

methodological issues (both diagnoses are based on the subject's self-completed questionnaires, and patients with depression may tend to endorse numerous symptoms). Association of EDS with autonomic dysfunction is of interest and to our knowledge has not been systematically explored in early PD. It goes along with Braak et al.'s data[22] on early involvement of the autonomic structures in the progression of PD pathology or alternatively could reflect direct involvement of the autonomic system in the control of alertness via a circadian rhythm mechanism.[39] The latter hypothesis is supported by the fact that autonomic dysfunction was the only clinical variable significantly associated with EDS in HCs.

Our results do not necessarily contradict the data from epidemiological studies that demonstrated EDS as one of the risk factors for development of PD.[21] The association was demonstrated in the cohort of male participants older than age 71; therefore, EDS can be a premotor manifestation only in a subset of PD subjects, similar to RBD presence only in a subset of PD de novo subjects, despite the fact that RBD is a well-established premotor risk factor of PD.[40-42] In addition, because of multiple other risk factors, someone at risk for PD may not be more likely to have EDS. The biological underpinnings of such selectivity remain to be determined.

The novel aspect of this study is the inclusion of biomarkers data. In the multivariate analysis, the only CSF biomarker that was associated with EDS was a marginally lower level of A-Beta ($P = 0.05$). No association was found with α-Syn. The role of amyloidal and Tau biomarkers in PD is not well established, but a number of publications, including pilot PPMI data analysis, reported reduction of levels of CSF Aβ1-42, T-tau, or P-tau in patients with PD with or without dementia compared with HCs.[36,43-46] However, based on the marginal significance and cross-sectional analysis, our data should be considered strictly pilot and hypothesis generating to be further tested in the longitudinal analysis.

One of the study limitations is lack of the objective measures of sleep such as polysomnography; however, the lack of difference in subjective measures of sleep between EDS+ vs EDS− groups supports the validity of our data. Another limitation is that our study might have underestimated prevalence of EDS in the general de novo PD population, because subjects recruited into studies might not be representative of overall PD population. Indeed, a recently published study (The ONSET PD) that assessed EDS as part of the overall NMS burden, using the NMS questionnaire in 109 consecutive de novo PD patients, established a 38% prevalence of EDS in PD versus 15% in HC.[19] Although the studies used different assessment tools and cannot be directly compared, the demographic and baseline disease characteristics were similar, with one important difference of a much higher proportion of participants with PIGD and indeterminate phenotype (87%) in The ONSET PD study versus 29% in our cohort. The PIGD phenotype is known to be associated with axial manifestations and a higher burden of nonmotor disability and could explain the discrepancy. Consistent with that, most of our participants had asymmetric PD onset. Another limitation is the cross-sectional nature of the analysis. Longitudinal data will be essential to confirm and expand our observations and specifically analyze whether biomarkers will correlate with the progression of EDS in both PD and HCs.

In conclusion, no evidence suggests a higher prevalence of EDS in early untreated PD patients enrolled in this large case control observational study. These data can help guide clinicians in counseling de novo PD patients while maintaining vigilance for longitudinal assessment of EDS. The incidence, prevalence, and clinicobiological correlates of EDS with the disease progression, as well as the impact of dopaminergic therapy on EDS, will be established in longitudinal analysis. The association of EDS with a lower level of CSF A-Beta is intriguing but will have to be validated longitudinally.

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References

1. Hobson DE, Lang AE, Martin WR, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. JAMA. 2002; 287:455–463. [PubMed: 11798367]
2. Arnulf I. Excessive daytime sleepiness in parkinsonism. Sleep Med Rev. 2005; 9:185–200. [PubMed: 15893249]
3. Poewe W, Hogl B. Parkinson's disease and sleep. Curr Opin Neurol. 2000; 13:423–426. [PubMed: 10970059]
4. Breen DP, Williams-Gray CH, Mason SL, Foltynie T, Barker RA. Excessive daytime sleepiness and its risk factors in incident Parkinson's disease. J Neurol Neurosurg Psychiatry. 2013; 84:233–234. [PubMed: 23184153]
5. Brodsky MA, Godbold J, Roth T, Olanow CW. Sleepiness in Parkinson's disease: a controlled study. Mov Disord. 2003; 18:668–672. [PubMed: 12784270]
6. Tan EK, Lum SY, Fook-Chong SM, et al. Evaluation of somnolence in Parkinson's disease: comparison with age- and sex-matched controls. Neurology. 2002; 58:465–468. [PubMed: 11839852]
7. Hogl B, Seppi K, Brandauer E, et al. Increased daytime sleepiness in Parkinson's disease: a questionnaire survey. Mov Disord. 2003; 18:319–323. [PubMed: 12621636]
8. Kumar S, Bhatia M, Behari M. Excessive daytime sleepiness in Parkinson's disease as assessed by Epworth Sleepiness Scale (ESS). Sleep Med. 2003; 4:339–342. [PubMed: 14592307]
9. Verbaan D, van Rooden SM, Visser M, Marinus J, van Hilten JJ. Nighttime sleep problems and daytime sleepiness in Parkinson's disease. Mov Disord. 2008; 23:35–41. [PubMed: 17960797]
10. Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? Neurology. 2006; 67:853–858. [PubMed: 16966550]
11. O'Suilleabhain PE, Dewey RB Jr. Contributions of dopaminergic drugs and disease severity to daytime sleepiness in Parkinson disease. Arch Neurology. 2002; 59:986–989.
12. Fabbrini G, Barbanti P, Aurilia C, Pauletti C, Vanacore N, Meco G. Excessive daytime somnolence in Parkinson's disease: follow-up after 1 year of treatment. Neurol Sci. 2003; 24:178–179. [PubMed: 14598075]
13. Valko PO, Waldvogel D, Weller M, Bassetti CL, Held U, Baumann CR. Fatigue and excessive daytime sleepiness in idiopathic Parkinson's disease differently correlate with motor symptoms, depression and dopaminergic treatment. Eur J Neurol. 2010; 17:1428–1436. [PubMed: 20491889]
14. Martinez-Martin P, Falup Pecurariu C, Odin P, et al. Gender-related differences in the burden of nonmotor symptoms in Parkinson's disease. J Neurol. 2012; 259:1639–1647. [PubMed: 22237822]
15. Gjerstad MD, Aarsland D, Larsen JP. Development of daytime somnolence over time in Parkinson's disease. Neurology. 2002; 58:1544–1546. [PubMed: 12034797]
16. Kaynak D, Kiziltan G, Kaynak H, Benbir G, Uysal O. Sleep and sleepiness in patients with Parkinson's disease before and after dopaminergic treatment. Eur J Neurol. 2005; 12:199–207. [PubMed: 15693809]
17. Fabbrini G, Barbanti P, Aurilia C, Vanacore N, Pauletti C, Meco G. Excessive daytime sleepiness in de novo and treated Parkinson's disease. Mov Disord. 2002; 17:1026–1030. [PubMed: 12360553]
18. Buskova J, Klempir J, Majerova V, et al. Sleep disturbances in untreated Parkinson's disease. J Neurol. 2011; 258:2254–2259. [PubMed: 21637949]
19. Pont-Sunyer C, Hotter A, Gaig C, et al. The onset of nonmotor symptoms in Parkinson's disease (The ONSET PD Study). Mov Disord. 2015; 30:229–237. [PubMed: 25449044]
20. Erro R, Picillo M, Vitale C, et al. Nonmotor symptoms in early Parkinson's disease: a 2-year follow-up study on previously untreated patients. J Neurol Neurosurg Psychiatry. 2013; 84:14–17. [PubMed: 22993448]
21. Abbott RD, Ross GW, White LR, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology. 2005; 65:1442–1446. [PubMed: 16275833]

22. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 2004; 318:121–134. [PubMed: 15338272]
23. The Parkinson Progression Marker Initiative (PPMI). Prog Neurobiol. 2011; 95:629–635. [PubMed: 21930184]
24. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991; 14:540–545. [PubMed: 1798888]
25. Hogl B, Arnulf I, Comella C, et al. Scales to assess sleep impairment in Parkinson's disease: critique and recommendations. Mov Disord. 2010; 25:2704–2716. [PubMed: 20931631]
26. Goetz CG. Movement Disorder Society—Unified Parkinson's Disease Rating Scale (MDS-UPDRS): a new scale for the evaluation of Parkinson's disease. Rev Neurol. 2010; 166:1–4. [PubMed: 19910010]
27. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. Mov Disord. 2013; 28:668–670. [PubMed: 23408503]
28. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967; 17:427–442. [PubMed: 6067254]
29. Schwab, RS.; E, A. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham, FJ.; D, I., editors. Third Symposium on Parkinson's Disease. Edinburgh, Scotland: E & S Livingstone; 1969. p. 152-157.
30. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53:695–699. [PubMed: 15817019]
31. Weintraub D, Oehlberg KA, Katz IR, Stern MB. Test characteristics of the 15-item geriatric depression scale and hamilton depression rating scale in Parkinson disease. Am J Geriatr Psychiatry. 2006; 14:169–175. [PubMed: 16473982]
32. Rodriguez-Blazquez C, Forjaz MJ, Frades-Payo B, de Pedro-Cuesta J, Martinez-Martin P. Independent validation of the scales for outcomes in Parkinson's disease–autonomic (SCOPA-AUT). Eur J Neurol. 2010; 17:194–201. [PubMed: 19780808]
33. Kendall PC, Finch AJ Jr, Auerbach SM, Hooke JF, Mikulka PJ. The State-Trait Anxiety Inventory: a systematic evaluation. J Consult Clin Psychol. 1976; 44:406–412. [PubMed: 932270]
34. Weintraub D, Hoops S, Shea JA, et al. Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. Mov Disord. 2009; 24:1461–1467. [PubMed: 19452562]
35. Stiasny-Kolster K, Mayer G, Schafer S, Moller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire: a new diagnostic instrument. Mov Disord. 2007; 22:2386–2393. [PubMed: 17894337]
36. Kang JH, Irwin DJ, Chen-Plotkin AS, et al. Association of cerebro-spinal fluid beta-amyloid 1-42, T-tau, P-tau181, and alpha-synuclein levels with clinical features of drug-naive patients with early Parkinson disease. JAMA Neurol. 2013; 70:1277–1287. [PubMed: 23979011]
37. Vaz Fragoso CA, Van Ness PH, Araujo KL, Iannone LP, Marottoli RA. Sleep disturbances and driving practices of older drivers. J Am Geriatr Soc. 2013; 61:1730–1737. [PubMed: 24001143]
38. Wegelin J, McNamara P, Durso R, Brown A, McLaren D. Correlates of excessive daytime sleepiness in Parkinson's disease. Parkinsonism Rel Disord. 2005; 11:441–448.
39. Buijs RM, Escobar C, Swaab DF. The circadian system and the balance of the autonomic nervous system. Handb Clin Neurol. 2013; 117:173–191. [PubMed: 24095125]
40. Postuma RB, Aarsland D, Barone P, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. Mov Disord. 2012; 27:617–626. [PubMed: 22508280]
41. Postuma RB, Gagnon JF, Vendette M, Charland K, Montplaisir J. REM sleep behaviour disorder in Parkinson's disease is associated with specific motor features. J Neurol Neurosurg Psychiatry. 2008; 79:1117–1121. [PubMed: 18682443]
42. Postuma RB, Gagnon JF, Vendette M, Fantini ML, Massicotte-Marquez J, Montplaisir J. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology. 2009; 72:1296–1300. [PubMed: 19109537]

43. Mollenhauer B, Trenkwalder C, von Ahsen N, et al. Beta-amlyoid 1-42 and tau-protein in cerebrospinal fluid of patients with Parkinson's disease dementia. Dement Geriatr Cogn Disord. 2006; 22:200–208. [PubMed: 16899997]

44. Mollenhauer B, Trautmann E, Taylor P, et al. Total CSF alpha-synuclein is lower in de novo Parkinson patients than in healthy subjects. Neurosci Lett. 2013; 532:44–48. [PubMed: 23149132]

45. Compta Y, Marti MJ, Ibarretxe-Bilbao N, et al. Cerebrospinal tau, phospho-tau, and beta-amyloid and neuropsychological functions in Parkinson's disease. Mov Disord. 2009; 24:2203–2210. [PubMed: 19795497]

46. Shi M, Bradner J, Hancock AM, et al. Cerebrospinal fluid bio-markers for Parkinson disease diagnosis and progression. Ann Neurol. 2011; 69:570–580. [PubMed: 21400565]

Table 1

Non-motor scores

Variable	PD Subjects	PD Subjects	PD Subjects	*P* value
		ESS +	ESS -	(ESS + vs -)
	(n = 423)	(n = 66)	(n = 357)	
MOCA total score				0.59
Mean (SD)	27.1 (2.3)	27.3 (2.7)	27.1 (2.2)	
(Min, max)	(17, 30)	(17, 30)	(17, 30)	
Missing	0	0	0	
HVLT total recall				0.78
Mean (SD)	24.4 (5.0)	24.6 (5.1)	24.4 (5.0)	
(Min, max)	(9, 36)	(13, 35)	(9, 36)	
Missing	1	1	0	
HVLT delayed recall				0.06
Mean (SD)	8.4 (2.5)	8.9 (2.4)	8.3 (2.5)	
(Min, max)	(0, 12)	(0, 12)	(0, 12)	
Missing	1	1	0	
HVLT delayed recognition				0.68
Mean (SD)	11.2 (1.2)	11.2 (1.0)	11.2 (1.3)	
(Min, max)	(0, 12)	(8, 12)	(0, 12)	
Missing	2	2	0	
Letter number sequencing score				0.42
Mean (SD)	10.6 (2.7)	10.3 (2.1)	10.6 (2.7)	
(Min, max)	(2, 20)	(6, 15)	(2, 20)	
Missing	1	1	0	
Symbol Digit Modalities Score				0.11
Mean (SD)	41.2 (9.7)	39.4 (9.8)	41.5 (9.7)	
(Min, max)	(7, 82)	(16, 64)	(7, 82)	
Missing	1	1	0	
Benton Judgment of Line Orientation				0.75
Mean (SD)	12.8 (2.1)	12.7 (2.2)	12.8 (2.1)	
(Min, max)	(5, 15)	(7, 15)	(5, 15)	
Missing	1	1	0	
Semantic fluency				0.81
Mean (SD)	48.7 (11.6)	48.4 (12.0)	48.7 (11.6)	
(Min, max)	(20, 103)	(29, 76)	(20, 103)	
Missing	1	1	0	
GDS total score				<0.01
Mean (SD)	2.3 (2.4)	3.1 (2.9)	2.2 (2.3)	
(Min, max)	(0, 14)	(0, 13)	(0, 14)	
Missing	0	0	0	
SCOPA total score				<0.01

Variable	PD Subjects	PD Subjects	PD Subjects	*P* value
Mean (SD)	9.5 (6.2)	12.3 (6.6)	9.0 (5.9)	
(Min, max)	(0, 39)	(3, 35)	(0, 39)	
Missing	0	0	0	
STAI—State subscore				0.04
Mean (SD)	33.0 (10.2)	35.3 (10.1)	32.5 (10.2)	
(Min, max)	(20, 76)	(20, 60)	(20, 76)	
Missing	1	0	1	
STAI—Trait subscore				0.03
Mean (SD)	32.4 (9.5)	34.7 (10.6)	31.9 (9.2)	
(Min, max)	(20, 63)	(21, 62)	(20, 63)	
Missing	1	0	1	
QUIP				0.12
Mean (SD)	0.3 (0.6)	0.4 (0.7)	0.3 (0.6)	
(Min, max)	(0, 4)	(0, 3)	(0, 4)	
Missing	1	0	1	

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MOCA, Montreal Cognitive Assessment Scale; HVLT, Hopkins Verbal learning test—revised;

GDS-15, 15-item Geriatric Depression Scale;

SCOPA-AUT, the scale for outcomes for PD—autonomic function; STAI, state and trait anxiety scale; QUIP- the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease.

Table 2

Baseline demographics and PD characteristics

Variable	PD Subjects	PD Subjects	PD Subjects	Healthy Controls	*P* Value	*P* Value
		ESS +	ESS -		(PD vs HC)	(ESS + vs -)
	(n = 423)	(n = 66)	(n = 357)	(n = 196)		
ESS					0.54	NA
Mean (SD)	5.8 (3.5)	NA	NA	5.6 (3.4)		
(Min, max)	(0, 20)	NA	NA	(0, 19)		
Missing	0	NA	NA	1		
ESS					0.28	NA
Less than 10	357 (84%)	NA	NA	171 (87%)		
10 or above	66 (16%)	NA	NA	24 (12%)		
Missing	0 (0%)	NA	NA	1 (1%)		
Age					0.33	0.44
Mean (SD)	61.7 (9.7)	62.5 (9.3)	61.5 (9.8)	60.8 (11.2)		
(Min, max)	(33, 85)	(37, 78)	(33, 85)	(31, 84)		
Missing	0	0	0	0		
Age					0.55	0.66
<56 Years	115 (27%)	18 (27%)	97 (27%)	55 (28%)		
56-65 Years	134 (32%)	18 (27%)	116 (32%)	69 (35%)		
>65 Years	174 (41%)	30 (45%)	144 (40%)	72 (37%)		
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Sex					0.77	0.95
Male	277 (65%)	43 (65%)	234 (66%)	126 (64%)		
Female	146 (35%)	23 (35%)	123 (34%)	70 (36%)		
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Education					0.59	0.45
<13 Years	76 (18%)	9 (14%)	67 (19%)	29 (15%)		
13-23 Years	344 (81%)	57 (86%)	287 (80%)	166 (85%)		
>23 Years	3 (1%)	0 (0%)	3 (1%)	1 (1%)		
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)		

Variable	PD Subjects	PD Subjects	PD Subjects	Healthy Controls	*P* Value	*P* Value
Ethnicity					0.62	0.19
Hispanic/Latino	9 (2%)	0 (0%)	9 (3%)	3 (2%)		
Not Hispanic/Latino	414 (98%)	66 (100%)	348 (97%)	193 (98%)		
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Race					0.85	0.61
White	391 (92%)	60 (91%)	331 (93%)	182 (93%)		
Black/African-American	6 (1%)	1 (2%)	5 (1%)	9 (5%)		
Asian	8 (2%)	1 (2%)	7 (2%)	1 (1%)		
Other	18 (4%)	4 (6%)	14 (4%)	4 (2%)		
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Family history of PD					<0.01	0.34
First-degree family members w/PD	55 (13%)	8 (12%)	47 (13%)	0 (0%)		
Other family members w/PD	47 (11%)	11 (17%)	36 (10%)	10 (5%)		
No family members w/PD	320 (76%)	47 (71%)	273 (76%)	186 (95%)		
Missing	1 (0%)	0 (0%)	1 (0%)	0 (0%)		
MDS-UPDRS mean (SD) score & subscores						
MDS-UPDRS total score	32.4 (13.1)	37.8 (14.5)	31.3 (12.6)	4.6 (4.5)	<0.01	<0.01
MDS-UPDRS part I	5.6 (4.1)	7.3 (4.3)	5.3 (3.9)	2.9 (3.0)	<0.01	<0.01
MDS-UPDRS part II	5.9 (4.2)	8.2 (4.9)	5.5 (3.9)	0.5 (1.0)	<0.01	<0.01
MDS-UPDRS part III (motor exam)	20.9 (8.9)	22.3 (8.8)	20.6 (8.9)	1.2 (2.2)	<0.01	0.15
Missing	1	0	1	1		
Hoehn & Yahr					<0.01	0.08
Stage 0	0 (0%)	0 (0%)	0 (0%)	193 (98%)		
Stage 1	186 (44%)	22 (33%)	164 (46%)	2 (1%)		
Stage 2	235 (56%)	43 (65%)	192 (54%)	0 (0%)		
Stage 3-5	2 (0%)	1 (2%)	1 (0%)	0 (0%)		
Missing	0 (0%)	0 (0%)	0 (0%)	1 (1%)		
Modified Schwab & England Activities of Daily Living					NA	0.19
Mean (SD)	93.2 (5.9)	92.3 (6.8)	93.3 (5.7)	NA		
(Min, max)	(70, 100)	(80, 100)	(70, 100)	NA		
Missing	0	0	0	NA		

Variable	PD Subjects	PD Subjects	PD Subjects	Healthy Controls	*P* Value	*P* Value
Duration of disease					NA	0.41
Mean (SD)	6.7 (6.5)	7.3 (6.4)	6.5 (6.5)	NA		
(Min, max)	(0, 36)	(1, 26)	(0, 36)	NA		
Missing	0	0	0	NA		
Age of PD onset					NA	0.38
Mean (SD)	59.6 (10.0)	60.6 (9.6)	59.4 (10.1)	NA		
(Min, max)	(25, 83)	(34, 75)	(25, 83)	NA		
Missing	8	1	7	NA		
TD/non-TD classification					NA	0.09
TD	299 (71%)	41 (62%)	258 (72%)	NA		
PIGD or indeterminate	123 (29%)	25 (38%)	98 (27%)	NA		
Missing	1 (0%)	0 (0%)	1 (0%)	NA		
Side most affected					NA	0.21
Left	180 (43%)	23 (35%)	157 (44%)	NA		
Right	233 (55%)	40 (61%)	193 (54%)	NA		
Symmetric	10 (2%)	3 (5%)	7 (2%)	NA		
Missing	0 (0%)	0 (0%)	0 (0%)	NA		
Utilization of sedatives					0.47	0.33
No sedatives used	369 (87%)	60 (91%)	309 (87%)	175 (89%)		
Sedative(s) used	54 (13%)	6 (9%)	48 (13%)	21 (11%)		
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)		

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Table 3

Associations of EDS with other sleep dysfunction variables

Variable	PD Subjects	PD Subjects ESS +	PD Subjects ESS -	Healthy Controls	*P* Value	*P* Value
	(n = 423)	(n = 66)	(n = 357)	(n = 196)	(PD vs. HC)	(ESS + vs. –)
MDS-UPDRS 1.7 Sleep Problems					0.02	0.60
Normal	198 (47%)	29 (44%)	169 (47%)	111 (57%)		
Slight	125 (30%)	21 (32%)	104 (29%)	52 (27%)		
Mild	62 (15%)	10 (15%)	52 (15%)	19 (10%)		
Moderate	26 (6%)	4 (6%)	22 (6%)	10 (5%)		
Severe	11 (3%)	2 (3%)	9 (3%)	3 (2%)		
Missing	1 (0%)	0 (0%)	1 (0%)	1 (1%)		
MDS-UPDRS 1.8 Daytime Sleepiness					<0.01	<0.01
Normal	213 (50%)	12 (18%)	201 (56%)	128 (65%)		
Slight	123 (29%)	24 (36%)	99 (28%)	49 (25%)		
Mild	84 (20%)	28 (42%)	56 (16%)	18 (9%)		
Moderate	2 (0%)	2 (3%)	0 (0%)	0 (0%)		
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Missing	1 (0%)	0 (0%)	1 (0%)	1 (1%)		
MDS-UPDRS 1.13 Fatigue					<0.01	0.01
Normal	210 (50%)	23 (35%)	187 (52%)	146 (74%)		
Slight	165 (39%)	30 (45%)	135 (38%)	44 (22%)		
Mild	34 (8%)	9 (14%)	25 (7%)	2 (1%)		
Moderate	10 (2%)	3 (5%)	7 (2%)	3 (2%)		
Severe	3 (1%)	1 (2%)	2 (1%)	0 (0%)		
Missing	1 (0%)	0 (0%)	1 (0%)	1 (1%)		
REM Sleep Behavior Disorder					<0.01	0.01
Negative (less than 5)	261 (62%)	31 (47%)	230 (64%)	156 (80%)		
Positive (5 or above)	159 (38%)	34 (52%)	125 (35%)	39 (20%)		
Missing	3 (1%)	1 (2%)	2 (1%)	1 (1%)		

Note: Reported *P* values compare normal vs. non-normal categories.

Table 4

Biologics data

Variable	PD Subjects	Healthy Controls	*P* Value[a]	PD Subjects ESS +	PD Subjects ESS-	*P* Value[a]	Controls ESS +	Controls ESS -	*P* Value[a]
	(n = 423)	(n = 196)	(PD vs. HC)	(n = 66)	(n = 357)	(PD ESS+ vs. −)	(n = 24)	(n = 171)	(HC ESS + vs. −)
A-Beta			0.39			0.02			0.13
Mean	370.56	377.77		345.49	375.09		401.74	374.45	
(Min, max)	(129.20, 796.50)	(88.80, 879.50)		(147.80, 670.00)	(129.20, 796.50)		(292.60, 559.30)	(88.80, 879.50)	
Missing	11	7		3	8		2	5	
T-Tau			<0.01			0.62			0.16
Mean	44.69	52.54		47.45	44.19		47.97	53.13	
(Min, max)	(14.40, 121.00)	(18.40, 223.10)		(15.40, 117.00)	(14.40, 121.00)		(21.50, 117.10)	(18.40, 223.10)	
Missing	15	9		3	12		2	7	
P-Tau			<0.01			0.17			0.84
Mean	15.64	18.27		13.82	15.96		18.21	18.32	
(Min, max)	(4.70, 94.10)	(5.10, 73.30)		(4.70, 42.60)	(5.70, 94.10)		(6.40, 50.00)	(5.10, 73.30)	
Missing	13	7		4	9		2	5	
T-Tau/A-Beta			0.02			0.08			0.03
Mean	0.13	0.16		0.15	0.12		0.11	0.17	
(Min, max)	(0.04, 0.52)	(0.05, 2.12)		(0.06, 0.49)	(0.04, 0.52)		(0.07, 0.21)	(0.05, 2.12)	
Missing	15	9		3	12		2	7	
P-Tau/A-Beta			0.01			0.45			0.72
Mean	0.04	0.06		0.04	0.04		0.04	0.06	
(Min, max)	(0.01, 0.51)	(0.02, 0.66)		(0.02, 0.15)	(0.01, 0.51)		(0.02, 0.10)	(0.02, 0.66)	
Missing	13	7		4	9		2	5	
P-Tau/T-Tau			0.52			0.01			0.19
Mean	0.37	0.37		0.32	0.38		0.42	0.36	
(Min, max)	(0.08, 2.14)	(0.13, 1.40)		(0.08, 1.08)	(0.12, 2.14)		(0.13, 0.79)	(0.14, 1.40)	
Missing	17	9		4	13		2	7	
Alpha-Synuclein			<0.01			0.19			0.31
Mean	1844.68	2204.25		2031.93	1810.88		1959.26	2234.76	
(Min, max)	(332.93, 6694.55)	(592.56, 8608.91)		(665.54, 6694.55)	(332.93, 5174.16)		(829.31, 3948.40)	(592.56, 8608.91)	

Variable	PD Subjects	Healthy Controls	*P* Value[a]	PD Subjects ESS +	PD Subjects ESS-	*P* Value[a]	Controls ESS +	Controls ESS -	*P* Value[a]
Missing	11	7		3	8		2	5	

[a] *P* values from Mann-Whitney *U* tests.

Table 5

Relationship between EDS with baseline demographics, clinical characteristics and biologics in PD subjects

Variable	Univariate *P* Value	# Observations Missing	Multivariate OR (95% CI)	Multivariate *P* Value
Education	0.05	0	1.15 (1.038, 1.267)	0.01
Ethnicity	0.98	0	—	—
Race	0.47	0	—	—
Family history of PD	0.32	1	—	—
MDS-UPDRS total score	<0.001	1	—	NS
MDS-UPDRS Part I score	<0.001	1	—	Not included
MDS-UPDRS Part II score	<.0001	1	—	Not included
MDS-UPDRS Part III score (motor exam)	0.18	0	—	Not included
Hoehn & Yahr	0.06	0	—	NS
Modified Schwab & England ADL	0.18	0	—	NS
Duration of disease	0.45	0	—	—
Age of PD onset	0.88	8	—	—
TD/non-TD classification	0.08	1	—	NS
Side most affected	0.12	0	—	NS
MOCA total score	0.48	0	—	—
GDS total score	0.01	0	1.13 (1.008, 1.260)	0.04
SCOPA-AUT total score	<0.001	0	1.08 (1.028, 1.126)	0.002
STAI—state subscore	0.04	1	—	NS
STAI—trait subscore	0.02	1	—	NS
QUIP total score	0.11	1	—	NS
REM sleep behavior disorder	0.01	3	—	NS
A-Beta	0.02	11	1.00 (0.995, 1.000)	0.05
T-Tau	0.70	15	—	—
P-Tau	0.16	13	—	NS
T-Tau/A-Beta	0.09	15	—	Not included
P-Tau/A-Beta	0.44	13	—	—
P-Tau/T-Tau	0.01	17	—	Not included
Alpha-Synuclein	0.22	11	—	—

Note: All univariate analyses adjust for age and sex. The multivariate analysis forces age and sex into the model.
NS, not significant. Refer to the text for the explanation of the abbreviations and analysis rules
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