Cerebrospinal hypocretin, daytime sleepiness and sleep architecture in Parkinson's disease dementia

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Excessive daytime sleepiness is common in Parkinson’s disease and has been associated with Parkinson’s disease-related dementia. Narcoleptic features have been observed in Parkinson’s disease patients with excessive daytime sleepiness and hypocretin cell loss has been found in the hypothalamus of Parkinson’s disease patients, in association with advanced disease. However, studies on cerebrospinal fluid levels of hypocretin-1 (orexin A) in Parkinson’s disease have been inconclusive. Reports of sleep studies in Parkinson’s disease patients with and without excessive daytime sleepiness have also been disparate, pointing towards a variety of causes underlying excessive daytime sleepiness. In this study, we aimed to measure cerebrospinal fluid hypocretin-1 levels in Parkinson’s disease patients with and without dementia and to study their relationship to dementia and clinical excessive daytime sleepiness, as well as to describe potentially related sleep architecture changes. Twenty-one Parkinson’s disease patients without dementia and 20 Parkinson’s disease patients with dementia, along with 22 control subjects without sleep complaints, were included. Both Epworth sleepiness scale, obtained with the help of the caregivers, and mini-mental state examination were recorded. Lumbar cerebrospinal fluid hypocretin-1 levels were measured in all individuals using a radio-immunoassay technique. Additionally, eight Parkinson’s disease patients without dementia and seven Parkinson’s disease patients with dementia underwent video-polysomnogram and multiple sleep latencies test. Epworth sleepiness scale scores were higher in Parkinson’s disease patients without dementia and Parkinson’s disease patients with dementia than controls ($P < 0.01$) and scores $>10$ were more frequent in Parkinson’s disease patients with dementia than in Parkinson’s disease patients without dementia ($P = 0.04$). Cerebrospinal fluid hypocretin-1 levels were similar among groups (controls $= 321.15 \pm 47.15$ pg/ml; without dementia $= 300.99 \pm 58.68$ pg/ml; with dementia $= 309.94 \pm 65.95$ pg/ml; $P = 0.67$), and unrelated to either Epworth sleepiness scale or mini-mental state examination. Dominant occipital frequency awake was slower in Parkinson’s disease patients with dementia than Parkinson’s disease patients without dementia ($P = 0.05$). Presence of slow dominant occipital frequency and/or loss of normal non-rapid eye movement sleep architecture was more frequent among Parkinson’s disease patients with dementia ($P = 0.029$). Thus, excessive daytime sleepiness is more frequent in Parkinson’s disease patients with dementia than Parkinson’s disease patients without dementia, but lumbar cerebrospinal fluid hypocretin-1 levels were similar in both groups.
Introduction

Excessive daytime sleepiness (EDS) is frequent in Parkinson’s disease and its presence has been associated with longer disease duration and dementia in epidemiological and case-series studies (Gjerstad et al., 2002; Boddy et al., 2007). In addition, EDS is currently part of the proposed criteria for Parkinson’s disease-related dementia as a supporting feature (Emre et al., 2007). However, studies specifically addressing EDS in Parkinson’s disease-related dementia are lacking.

The ultimate cause of EDS in Parkinson’s disease is unknown, although factors such as dopaminergic medications, motor disability or the neurodegenerative process itself have been implicated (Arnulf et al., 2002; Gjerstad et al., 2006). The presence in some Parkinson’s disease patients of narcolepsy-like features, such as daytime rapid eye movement (REM) sleep intrusions associated with visual hallucinations and sleep onset REM periods in the multiple sleep latency test (MSLT), has led some authors to suggest that a mechanism similar to that of narcolepsy might underlie EDS in Parkinson’s disease (Arnulf et al., 2000). However, cerebrospinal fluid (CSF) levels of hypocretin-1, which are typically low in narcolepsy (Nishino et al., 2001), have been normal in all available studies in Parkinson’s disease (Overeem et al., 2002; Baumann et al., 2005; Yasui et al., 2006), except for one using ventricular CSF (Drouot et al., 2003). All of these studies, however, either included a small number of patients or evaluated patients with only mild to moderate disease severity, without much information on EDS or sleep architecture characteristics. In contrast, two recent pathological studies have reported significant hypocretin cell loss in the hypothalamus of Parkinson’s disease patients (Fronczek et al., 2007; Thanickal et al., 2007), with one of them showing a significant association between hypocretin cell loss and disease severity (Fronczek et al., 2007). Hence, the possibility that neurodegeneration of the hypocretin system is related to EDS in advanced disease cannot be excluded.

Other potential contributors to EDS in Parkinson’s disease are night time sleep disorders (Arnulf et al., 2002) or impairment of sleep architecture. Few studies using video-polysomnography (vPSG) have reported altered sleep architecture in Parkinson’s disease (Emser et al., 1988), in association with disease duration rather than disease severity (Diederich et al., 2005), with no mention of its relation with cognitive impairment or dementia.

In this study, we aimed to explore the hypothesis that CSF hypocretin-1 levels are lower in subjects with Parkinson’s disease-related dementia than in Parkinson’s disease patients with no dementia, and to assess their relationship with clinically defined EDS. As a secondary objective, we tried to evaluate the relationship between presence of dementia and EDS and the findings of sleep tests with the secondary hypothesis that a variety of abnormalities in sleep tests may constitute additional factors contributing to EDS in Parkinson’s disease patients.

Methods

Patients

As a part of an ongoing project on biomarkers of dementia in Parkinson’s disease, 46 Parkinson’s disease patients from the Parkinson Disease and Movement Disorders Unit were asked to participate in this study between February 2007 and December 2007. Forty-one agreed. All patients were diagnosed according to United Kingdom Parkinson Disease Society Brain Bank diagnostic criteria (Hughes et al., 1992). At the time of inclusion, 20 of the Parkinson’s disease patients fulfilled the Movement Disorder Society diagnostic criteria for Parkinson’s disease-related dementia as well as the Diagnostic and Statistical Manual of Mental Disorders revised fourth edition criteria for dementia (American Psychiatric Association, 2000; Emre et al., 2007). The control group included 22 subjects admitted for knee surgery with intradural anaesthesia during the recruitment period. These individuals were matched with patients groups for age, and did not suffer from any known psychiatric or neurodegenerative disease.

The study was approved by the Ethical Committee of our institution. All subjects (or their caregiver in the case of patients) gave their informed written consent, according to the Declaration of Helsinki (Br Med J, 1991; 302; 1194), after full explanation of all the procedures.

Procedures

Demographic and clinical variables

Age, gender, years of education and both Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Epworth Sleepiness Scale (ESS) (Johns, 1991) scores were obtained from all study subjects. The interviews were always performed in the presence of the caregivers, whose comments were taken into consideration when answering the ESS, particularly in Parkinson’s disease patients with dementia, but also in Parkinson’s disease patients without dementia. Subjects with an ESS score >10 were considered to have EDS (Johns, 1991).
Years of disease duration, presence of visual hallucinations but not during changes in dosage of anti-parkinsonian drugs or intercurrent illness, motor severity assessed by Part III of the Unified Parkinson Disease Rating Scale (UPDRS-III) (Fahn et al., 1987) in overnight-off condition before the lumbar puncture, and disease stage by means of Hoehn and Yahr classification (1967), were recorded from all Parkinson’s disease patients at their inclusion. Anti-parkinsonian and psychotropic medications were obtained from all subjects, and the equivalent l-dopa dose was calculated as reported elsewhere (Wenzelburger et al., 2002).

Lumbar puncture

All patients and controls underwent lumbar puncture at L3–L4 space using a 22G needle. For Parkinson’s disease patients, the lumbar puncture was performed before the morning dose of the anti-parkinsonian medications.

CSF hypocretin determination

The collected CSF was immediately centrifuged for 10 min at 4000 g and 4°C, and subsequently stored at −80°C in 400 μl aliquots until final analysis. CSF hypocretin-1 levels were determined with commercially available direct radio-immunoassay kit (Phoenix Pharmaceuticals, Belmont, CA, USA) as described elsewhere (Nishino et al., 2001). In order to minimize inter-assay variation, reference samples with internal controls with known hypocretin-1 values were included in each assay and the values were adjusted accordingly, as recommended (Nishino et al., 2005).

Sleep studies

Sixteen of the Parkinson’s disease patients (eight without and eight with dementia) underwent a one-night vPSG, followed by MSLT the following day. Reasons for rejection or exclusion from the sleep studies were: (i) severe physical disability; (ii) nocturnal disorientation and confusion and (iii) caregiver not available to accompany the patient during the vPSG study. One Parkinson’s disease patient with dementia did not tolerate the procedure. The sleep studies were evaluated by investigators unaware of the clinical features.

vPSG was performed with a digital polygraph (Deltamed, Paris, France) including EEG (O1, O2, C3, C4 referred to A1+A2), electrooculogram, surface electromyography from chin, bilateral biceps brachii and bilateral biliialis anterior muscles, electrocardiogram, nasal and oral air flow, thoracic and abdominal effort and oxygen saturation with synchronized audiovisual recording. Visual scoring of sleep stages were according to the American Academy of Sleep Medicine criteria (Iber et al., 2007), except for the fact that frontal derivations were not used and REM sleep was scored even without muscular atonia when the polygraphic features suggested REM sleep behaviour disorder (RBD).

MSLTs were performed according to the standard procedures (Littner et al., 2005) and started 2–3 h after finishing the nocturnal vPSG study with nap times at 9:30, 11:30, 13:30, 15:30 and 17:30 h.

Statistical analysis

An a priori statistical power calculation was carried out for the first hypothesis of this study using nQuery v4.0 software (MTT0-1 method). A sample size of 20 in each group was calculated to have 80% power to detect a difference of -70 pg/ml in CSF hypocretin-1 concentration means, assuming a common standard deviation of 76 pg/ml, with a 0.05 two-sided significance level. The difference in means and the common standard deviation were defined considering CSF hypocretin-1 levels in controls and other neurological diseases from previous studies (Martinez-Rodriguez et al., 2003, 2007) in order to identify clinically relevant rather than marginal differences. As for the second objective of this study, no power calculation was performed since it was an exploratory study of a subset of the original sample.

The statistical analysis was performed using Statistical package for the Social Sciences 15.0 software (SPSS Inc, Chicago, Ill, USA). Chi-square test or Fisher’s exact test was used for comparison between qualitative variables, with data being expressed as percentages or number of cases. Comparison of quantitative variables among all three groups was established by Kruskal–Wallis test followed by Mann–Whitney test for pair-wise comparisons, with data presented as mean ± SD except where otherwise stated. Comparative analyses were performed between the groups of Parkinson’s disease patients with and without dementia, and between Parkinson’s disease subjects with ESS scores >10 and those with scores ≤10, regardless of the dementia classification. Differences in proportion of patients with high ESS between groups were estimated, applying a general linear model with a binomial distribution of the dependent variable, and where the post hoc pair-wise comparisons (control versus Parkinson’s disease patients without dementia; control versus Parkinson’s disease patients without dementia; and Parkinson’s disease patients without dementia versus Parkinson’s disease patients with dementia) were assessed by means of the least significant difference method. The results of this analysis consist of means of estimation of the proportion of patients with high ESS score with the corresponding 95% confidence interval. Spearman’s correlation coefficient between quantitative variables was also calculated.

Level of statistical significance was established at $P \leq 0.05$ (two-tailed). Due to the presence of a priori hypotheses and the exploratory nature of the neurophysiological sleep sub-study, the significant results shown are uncorrected for multiple comparisons (Begg et al., 1996; Perneger, 1998).

Results

Demographic and basic clinical data

The three study groups did not differ in age or gender. Disease duration was not different between Parkinson’s disease patients with or without dementia (mean ± SD: 10.2 ± 4.5 versus 10.15 ± 6.9, respectively). Parkinson’s disease patients with dementia were at a more advanced stage of the disease, as measured by Hoehn and Yahr (1967) staging, despite similar UPDRS-III scores, had more visual hallucinations and were on a lower average equivalent l-dopa dose (Table 1; Supplementary Table 1). There were no significant differences in either demographic or clinical features of the patients who underwent sleep studies and those who did not, except for a smaller proportion of females among the former group (Supplementary Table 2).

Epworth sleepiness scale scores

Both Parkinson’s disease patients with and without dementia had higher ESS scores than controls (Parkinson’s disease patients without dementia = 10.34 ± 5.60; Parkinson’s disease patients with dementia = 13.25 ± 5.00; controls = 5.32 ± 2.73) (global comparison: $P < 0.001$; pair-wise comparisons between...
Parkinson’s disease patients with and without dementia controls: \( P < 0.01 \). ESS scores did not differ between Parkinson’s disease patients with and without dementia \( (P = 0.063) \), despite somewhat higher scores among Parkinson’s disease patients with dementia. Abnormal ESS scores (>10) were significantly more frequent in Parkinson’s disease patients with dementia than those without \( (P = 0.04) \) (Table 1). In order to assess the gradation from less to more sleepiness, according to ESS scores, through the three study groups (controls, Parkinson’s disease patients without and those with dementia), pair-wise comparisons between groups were conducted applying a general linear model for the proportion of subjects with ESS \( \geq 10 \) (this more conservative criterion was used in this case as none of the controls scored >10).

The proportion of subjects with ESS scores \( \geq 10 \) was smaller in the control group than in both groups of Parkinson’s disease patients (with and without dementia) \( (P < 0.001) \), with Parkinson’s disease patients without dementia having a lower proportion groups of Parkinson’s disease patients (with and without dementia) ESS scores \( \geq 10 \) than Parkinson’s disease patients with dementia \( (P = 0.022) \) (Fig. 1; Supplementary Table 3). ESS scores were not significantly related to any other demographic or clinical variables, except for higher scores in patients with visual hallucinations \( (P = 0.047) \). There was no correlation between ESS and any of the quantifiable demographic and clinical variables, except for a weak negative correlation between MMSE and ESS scores in the analysis of all Parkinson’s disease patients \( (r = -0.33; P = 0.053) \; \text{Supplementary Table 4).} \)

When classifying Parkinson’s disease patients as having high or normal ESS scores, those with high scores were significantly older, had more visual hallucinations, scored less on the MMSE and were on a lower equivalent l-dopa dose. However, there were no differences regarding the intake of dopamine agonists between these two ESS-defined groups (Table 2).

ESS scores were not higher among Parkinson’s disease patients taking psychotropic drugs known to be potentially sedative (benzodiazepines, anti-depressants or neuroleptics) \( n = 24 \) versus 17; \( P = 0.45 \). The set of Parkinson’s disease patients who underwent sleep studies and were taking such drugs (two out of eight Parkinson’s disease patients without dementia and five out of seven Parkinson’s disease patients with dementia) did not have the highest ESS scores.

**CSF levels of hypocretin-1**

There were no differences in CSF hypocretin-1 levels among the three groups \( (\text{pg/ml: controls} = 321.15 \pm 47.15; \text{PDND} = 319.60 \pm 50.94; \text{PDD} = 317.60 \pm 52.94; P = 0.47) \)
Parkinson’s disease patients without dementia \(= 300.99 \pm 58.68\); Parkinson’s disease patients with dementia \(= 309.94 \pm 65.95\); \(P = 0.67\) (Fig. 2). There was also no difference when comparing Parkinson’s disease patients with ESS scores >10 with those who scored \(\leq 10\) \((300.60 \pm 57.48\) versus \(309.46 \pm 66.20\), respectively; \(P = 0.49\)), or those with and without visual hallucinations \((304.53 \pm 68.15\) versus \(302.76 \pm 49.90\), respectively; \(P = 0.72\)). There were no significant correlations between CSF hypocretin-1 levels and ESS \((r = -0.02; P = 0.8)\) or MMSE scores \((r = -0.08; P = 0.6)\) in Parkinson’s disease patients. The CSF levels of hypocretin-1 did not differ between the subset of Parkinson’s disease patients with and without dementia who underwent sleep studies and those that did not (in pg/ml: 292.78 \pm 79.48 vs 302.07 \pm 84.97; \(P = 0.45\)).

**vPSG results**

Of the 15, 10 patients studied with vPSG (four Parkinson’s disease patients without dementia: Patients 1, 3, 14, 18; and six with dementia: Patients 6, 7, 10, 16, 18 and 19), sleep could not be scored using standard American Academy of Sleep Medicine criteria, due to an altered non-REM sleep architecture. The abnormalities detected consisted of at least two of the following findings: (i) slow dominant occipital frequency awake that made it difficult to identify the onset of stage-1 non-REM sleep (eight patients); (ii) irregular, continuous or almost continuous, medium-amplitude delta activity during the whole sleep recording (all 10 cases), which did not allow for the different non-REM sleep stages to be distinguished; (iii) persistence during behavioural sleep of a posterior-dominant alpha/theta activity at least 1 Hz slower than the dominant occipital rhythm during wakefulness (eight patients) and (iv) absence of well-defined sleep spindles or K-complexes, the hallmarks of stage N2 (8 and all 10 cases, respectively).

Altered non-REM sleep and/or slow dominant occipital frequency was more frequent in Parkinson’s disease patients with dementia than in those patients without \((P = 0.029)\). Parkinson’s disease patients with dementia had significantly slower dominant occipital frequency than Parkinson’s disease patients without dementia [median: 6 Hz (percentile 25–75: 6–7.5) versus median: 8.3 Hz (percentile 25–75: 7–9.3) Hz; \(P = 0.05\)]. REM sleep was present in all but one of the eight Parkinson’s disease patients without dementia. In five of these patients, RBD was present, three of them with visual hallucinations. Four Parkinson’s disease patients with dementia \((n = 7)\) did not have REM sleep and the other three had RBD. Presence of RBD in these patients was not associated with the presence of visual hallucinations (data not shown).

Parkinson’s disease patients with dementia had shorter total sleep time than those patients without dementia \((240.6 \pm 106.2\) versus \(334.6 \pm 106.6\)); however, this difference was non-significant \((P = 0.18)\). Differences in the number of awakenings longer than \(1\) min \((29.6 \pm 20.1\) versus \(18.6 \pm 10.6\)) or number of arousals per hour of sleep \((26.2 \pm 20.1\) versus \(31.9 \pm 16.7\)) were also not significant \((P = 0.34\) and \(0.3\), respectively).
## Table 3: Findings of vPSG and MSLT recordings in patients with Parkinson’s disease, with and without dementia

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<th>Patient #</th>
<th>S</th>
<th>α-freq</th>
<th>α-θ in S</th>
<th>Sp freq</th>
<th>K</th>
<th>RBD</th>
<th>TST</th>
<th>AW &gt;1</th>
<th>Arousal index</th>
<th>AH</th>
<th>PLMS</th>
<th>MSLT mean lat</th>
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<td>12.0 ± 1.4</td>
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<td>29.6 ± 25.2</td>
<td>26.2 ± 20.1</td>
<td>14.5 ± 17.9</td>
<td>484.5 ± 387.1</td>
<td>14.7 ±</td>
<td>292.78 ±</td>
<td>4.4</td>
<td>79.48</td>
<td></td>
<td></td>
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</tbody>
</table>

S = sleep pattern type (N = normal; P = pathologic); α-freq = dominant occipital frequency (Hz); α-θ in S = persistence of alpha-theta activity during sleep; sp freq = sleep spindles frequency (Hz); K = presence of well-recognizable K-complexes; RBD = presence of REM sleep behaviour disorder; TST = Total sleep time (in minutes); AW >1 = number of awakenings of at least 1 min in duration; AH  = apnoea-hypopnoea index; PLMS = periodic leg movements in sleep index; MSLT mean lat = mean latency at MSLT (seconds); SOREMP = number of Sleep-onset REM Periods; ESS = Epworth sleepiness scale score (out of 24 items); CSF hypocort-1 = levels of CSF hypocretin-1 expressed in pg/ml; + = yes; – = no; RNR = REM sleep episodes not recorded; CNZ = clonazepam; QT = quetiapine; DPZ = donepezil; RVT = rivastigmine; VFX = venlafaxine; APZ = alprazolam; PX = paroxetine. The patient number corresponds to the order of recruitment for the CSF study. All drugs doses expressed in mg. All data expressed as: mean ± SD, median [percentile 25–75], number of cases, or %.
The apnoea–hypopnoea index and the periodic leg movement index were not different between Parkinson’s disease patients with and without dementia (Table 3). None of the quantitative vPSG variables correlated with the ESS scores, except for a mild negative correlation with total sleep time, indicating that the longer the sleep duration at night the lower the sleepiness (r = –0.55; P = 0.041) (Supplementary Table 5). We were not able to associate any of these features with the use of psychotropic drugs (data not shown). We found no correlation between any of the vPSG variables and the ESS.

Multiple sleep latencies test results

There were no differences in mean sleep latency between Parkinson’s disease patients with and without dementia (in seconds: 481.0 ± 361.9 versus 484.5 ± 387.1; P = 0.81) or Parkinson’s disease with ESS <10 versus Parkinson’s disease with ESS >10 (in seconds: 480.50 ± 498.76 versus 484.12 ± 306.15; P = 0.73) (Table 3).

Sleep onset REM periods were observed in two Parkinson’s disease patients without dementia (one with a normal and one with an abnormal sleep pattern) and two Parkinson’s disease patients with dementia (both with abnormal sleep pattern). There was no relation between the apnoea-hypopnoea index or periodic leg movement in sleep index or sleep fragmentation and the MSLT latency.

The mean sleep latency in the MSLTs did not show any correlation with either the ESS scores (Spearman test: r = 0.19; P = 0.54) (Supplementary Table 5) or the CSF hypocretin-1 levels (Spearman test: r = 0.49; P = 0.10). However, in the two patients with the lowest CSF hypocretin levels (Parkinson’s disease without dementia, Patient 14: 115.93 pg/ml; Parkinson’s disease with dementia, Patient 18: 196.75 pg/ml) one had two sleep onset REM periods and the other had the shortest sleep latency (Table 3).

Discussion

In this study, lumbar CSF hypocretin-1 levels were similar in Parkinson’s disease patients and controls and were not associated with the cognitive status, presence of visual hallucinations, ESS scores or vPSG and MSLT results. However, ESS scores were higher in the Parkinson’s disease patients (with and without dementia) than in the control group, and EDS defined as ESS >10 was more frequent in the Parkinson’s disease patients with dementia subgroup. In the subset of patients who underwent sleep studies, Parkinson’s disease patients with dementia showed a slower dominant occipital frequency awake and a more frequent loss of the normal sleep architecture.

In a population-based study, EDS in Parkinson’s disease was related to disease progression and subsequent dementia (Gjerstad et al., 2002). In addition, EDS has recently been included in the clinical diagnostic criteria for Parkinson’s disease patients with dementia (Emre et al., 2007). However, the relative frequency of EDS in Parkinson’s disease patients with and without dementia has seldom been assessed. In one study, where EDS was shown to be more frequent in Parkinson’s disease patients with dementia than in controls or Alzheimer’s disease patients, differences in ESS between Parkinson’s disease patients without and those with dementia were not significant, despite somewhat higher scores in the latter group (Boddy et al., 2007). In other studies, EDS has been linked to disease duration, advanced disease and older age, as well as to cognitive impairment in non-demented Parkinson’s disease patients (Tandberg et al., 1999; Ondo et al., 2001; Arnulf et al., 2002; Gjerstad et al., 2006). Recently, the Sydney Multicenter Study of Parkinson’s disease has shown that after 20 years of follow-up, 83% of the patients have dementia and 70% EDS (Hely et al., 2008). In contrast, other studies have not found any link between EDS and cognition in Parkinson’s disease, probably due to the study design being focused on EDS rather than cognitive impairment (Arnulf et al., 2002; Gjerstad et al., 2006; Shpirer et al., 2006). In our study, both non-demented and demented Parkinson’s disease patients had higher ESS scores than controls, and the number of patients with ESS scores >10 was higher in Parkinson’s disease patients with dementia than those patients without. The weak, borderline significant correlation between MMSE and ESS scores would also be in line with the notion that cognitive impairment and sleepiness are associated in Parkinson’s disease.

We found CSF levels of hypocretin-1 in Parkinson’s disease to be in a similar range to a large and neurologically unimpaired control group, with no significant associations with ESS, MMSE or disease duration. Normal CSF hypocretin levels in our sample agreed with all previous studies assessing lumbar CSF levels of hypocretin-1 (Overeem et al., 2002; Baumann et al., 2005; Yasui et al., 2006). The only two studies showing low CSF hypocretin levels in Parkinson’s disease measured hypocretin-1 in ventricular CSF (Drouot et al., 2003; Fronczek et al., 2007). Therefore, it is possible that lumbar CSF levels of hypocretin-1 may not accurately reflect the hypocretin cell loss shown in pathology studies (Fronczek et al., 2007; Thannickal et al., 2007). Another reason may be that CSF hypocretin-1 levels only drop when hypothalamic hypocretin neurons decrease above 70% (Gerashchenko et al., 2003), whereas the hypocretin cell loss shown to occur in Parkinson’s disease is <70%, even in advanced disease stages (Thannickal et al., 2007). Since a widespread neurodegeneration occurs in advanced Parkinson’s disease, impairment of sleep-related structures other than the hypocretin system may account for EDS in Parkinson’s disease (Arnulf et al., 2002; Baumann et al., 2007; Fronczek et al., 2008 Thannickal et al., 2008).

Normal CSF hypocretin-1 levels, along with the lack of narcoleptic-like findings in MSLT studies, do not support the view that EDS in Parkinson’s disease patients has a narcoleptic basis (Arnulf et al., 2000). However, the two Parkinson’s disease cases with the lowest CSF hypocretin levels, despite being higher than the diagnostic cut-off for narcolepsy (110 pg/ml) (Mignot et al., 2002), had two sleep onset REM periods and the shortest sleep latency, respectively. Therefore, elements of a narcoleptic-like phenotype may occasionally be seen in Parkinson’s disease (Maeda et al., 2006).

The sleep architecture in both REM and non-REM sleep was particularly abnormal in Parkinson’s disease patients with dementia. RBD occurred in all the Parkinson’s disease patients with dementia where REM sleep could be identified. Previous studies
have found that RBD is associated with cognitive impairment in non-demented Parkinson’s disease patients (Vendette et al., 2007). Five of our eight Parkinson’s disease patients without dementia had RBD, and three of them also had visual hallucinations, which have also been linked to progression to dementia in Parkinson’s disease (Ramirez-Ruiz et al., 2007).

Our finding of slower dominant occipital frequency awake in Parkinson’s disease patients with dementia when compared to those without dementia is in agreement with previous awake EEG studies in Parkinson’s disease with dementia and dementia with Lewy bodies, two entities sharing clinical and pathological features (Neufeld et al., 1998; Domitri et al., 1999; Bonanni et al., 2008; Roks et al., 2008). Slowing of the dominant occipital frequency also occurs in Alzheimer’s disease, where a cholinergic deficiency has been implicated in such awake EEG abnormalities (Riekkinen et al., 1991). Since a cholinergic deficiency is also prominent in Parkinson’s disease patients with dementia (Hilker et al., 2005) and treatment with acetylcholinesterase inhibitors increases the EEG frequency awake (Fogelson et al., 2003), cholinergic dysfunction might underlie these abnormalities. Posterior cortical impairment shown in a perfusion SPECT study in Parkinson’s disease patients with dementia could also be linked with slower dominant occipital frequency (Mito et al., 2005).

To date, polysomnographic studies in Parkinson’s disease have shown abnormalities in sleep architecture such as sleep fragmentation, increase of stage 1 sleep and reductions in the REM sleep amount (Emser et al., 1988). However, the pattern of changes in non-REM sleep we have described, and its higher frequency in Parkinson’s disease patients with dementia as compared with those without dementia, have not been reported previously. It is uncertain, however, whether these changes can be explained by the above mentioned cholinergic deficit or not.

The mean sleep latency on the MSLT was not correlated with any vPSG variable, reflecting in part the difficulties in detecting sleep onset with conventional criteria in these patients. Sleepiness measured with the ESS was only negatively associated with the amount of nocturnal sleep in the vPSG. That is, the longer the sleep time at night, the lower the daytime sleepiness, suggesting that advanced Parkinson’s disease patients might be sleep deprived, either by motor problems at night, alerting effects of medications or degeneration of sleep related structures. The lack of association between daytime sleepiness and the apnoea–hypopnoea index suggests that EDS in this group of Parkinson’s disease patients has a complex origin (Arnulf et al., 2002).

Our study did not show a relationship between EDS and higher equivalent L-dopa dose or intake of dopamine agonist (Gjerstad et al., 2006). In fact, we found that both Parkinson’s disease patients with dementia and Parkinson’s disease patients with ESS scores >10, were on lower equivalent L-dopa doses. Even though L-dopa has been associated with improved subjective alertness in Parkinson’s disease (Molloy et al., 2006), we interpreted such lower equivalent L-dopa doses as a consequence of the common clinical practice of reducing anti-parkinsonian medications in patients prone to confusion and hallucinations, such as in patients with dementia, rather than the cause of their EDS.

Since Parkinson’s disease patients with dementia received more hypnotic, anti-depressant and neuroleptic medications than Parkinson’s disease patients without dementia, we cannot exclude that EDS and the above discussed vPSG abnormalities could be related to these medications (Parrino et al., 1996; Bell et al., 2003; Cohrs et al., 2004). We could not find a clear relationship between drug treatment and presence of sleep alterations or EDS. Although quetiapine or paroxetine decrease the amount of REM sleep and could be responsible for the absence of REM sleep in three of the studied Parkinson’s disease patients with dementia (Parrino et al., 1996; Schlosser et al., 1998; Bell et al., 2003; Cohrs et al., 2004; Barbanoj et al., 2005), this feature was also present in patients not taking any of these drugs. Furthermore, benzodiazepines increase, rather than decrease, the number of sleep spindles and thus are unlikely to be responsible for the lack of sleep spindles in Parkinson’s disease patients with dementia (Rye, 2003). Finally, all the pathologic features described above were also found in the only Parkinson’s disease patient with dementia taking no psychotropic medications.

Our study has both strengths and limitations. The strengths are that the patients were classified according to currently accepted criteria for Parkinson’s disease and Parkinson’s disease with dementia. Presence or absence of EDS was not used to select the patients of the study. The control group, consisting of individuals not suffering from any known neurodegenerative disease or serious psychiatric illness, was—to our knowledge—the largest control group included to date in a study of CSF levels of hypocretin-1 in Parkinson’s disease. Moreover, the study was statistically powered to assess differences in CSF hypocretin-1 concentrations between the study groups. As limitations, we have to acknowledge a potential selection bias due to the convenience sample and the referral centre setting. ESS is an auto-administered scale, however, since the caregivers often contributed to completion of the ESS in Parkinson’s disease patients with dementia, they could have mistaken situations frequently associated with advanced Parkinson’s disease (e.g. fluctuating attention) as sleep (Rye, 2003). Conversely, non-demented patients may have also underestimated sleep episodes, although the opinion of their caregiver was also taken into account when discrepancies were detected. Finally, the fact that sleep studies were only available for a subset of Parkinson’s disease patients, and none of the controls, could have led to underpowered analysis for this part of the results. Should this be the case, however, a larger sample might have lent more robustness to our already significant findings of slower dominant occipital frequency and abnormal non-REM sleep. Furthermore, there were no significant clinical differences between patients who underwent sleep studies and those who did not other than gender distribution, which is unlikely to be responsible for the observed vPSG findings. Further studies including larger samples are warranted to eventually replicate such findings.

In conclusion, our study shows that lumbar CSF hypocretin-1 levels in advanced Parkinson’s disease patients with dementia and EDS are normal. Subjective EDS was, however, more frequent in demented than non-demented Parkinson’s disease patients. Thus, causes other than dysfunction of the hypocretin system, such as involvement of other sleep-related structures by the neurodegenerative process might account for EDS in advanced Parkinson’s disease. The loss of normal non-REM and REM sleep architecture.
in the subset of Parkinson’s disease patients with dementia who underwent sleep studies would support this notion.

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Supplementary material

Supplementary material is available at Brain online.

References


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