LETTERS

Excessive daytime sleepiness and its risk factors in incident Parkinson's disease

INTRODUCTION

Excessive daytime sleepiness (EDS) can be a feature of various neurodegenerative diseases including Parkinson's disease (PD). EDS puts patients at increased risk of accidents while driving and it is important to identify such patients in order to advise them and others about their individual level of risk and the potential therapeutic options available to them.

The most commonly used method for assessing EDS in the clinic is the Epworth Sleepiness Scale (ESS)—a self-completed questionnaire which scores the tendency to fall asleep during eight everyday situations. The final score ranges from 0–24, with scores greater than 10 generally considered pathological. This questionnaire has been widely used in unselected PD cohorts, with the prevalence of EDS ranging from 3–50%.[1] Although there is a general consensus that dopaminergic medications contribute to EDS in PD,[2] there is less agreement about other risk factors. One possible explanation for these disparities is that heterogeneous PD cohorts were studied at different points in their disease course. Some studies have also suggested that the Catechol O-methyltransferase (*COMT*) val^{158}met polymorphism (which is known to significantly alter enzyme activity) may be associated with EDS.

In this study, we report on the prevalence of EDS and its risk factors in a population-representative incident PD cohort.

PATIENTS AND METHODS

This cohort was recruited between December 2000 and December 2002, when we attempted to collect all newly diagnosed cases of parkinsonism in the country of Cambridgeshire (UK) using multiple sources of case ascertainment to maximise capture rate (CamPaIGN study: Cambridgeshire Parkinson's Incidence from GP to Neurologist).[3] Patients were assessed either at the specialist research clinic within our research centre or the patient's own home.

Following a process of diagnostic revalidation at approximately 3.5 years (mean time from diagnosis of 3.54 years), the cohort comprised 126 patients meeting UK Brain Bank criteria for the diagnosis of PD. Alongside a battery of clinical tests (table 1), the ESS was completed by patients (with guidance from the assessor where necessary). To test for the association between EDS and *COMT* val^{158}met polymorphism, DNA was extracted from peripheral venous blood samples and genotyped using an allelic discrimination TaqMan assay and a HT7900 detector system (Applied Biosystems, Foster City, California, USA).

Surviving patients were also assessed at approximately 5 years (n=101, of whom 90 completed the ESS at a mean time from diagnosis of 5.35 years) and 7 years (n=64, of whom 45 completed the ESS at a mean time from diagnosis of 6.94 years). Four patients taking benzodiazepines were excluded from the analysis at 5 and 7 years due to their effects on daytime arousal.

Table 1 Bivariate comparisons of clinical variables versus ESS score at 3.5 years

Variable	Categories†	n	ESS score	
			Mean	p Value
Sex	Male	67	10.6	0.214
	Female	51	9.6	
Age	<71 years	60	10.4	0.665
	≥71 years	58	10.0	
UPDRS part III‡	<31	60	9.9	0.492
	≥31	58	10.5	
Motor phenotype§	TD	47	8.6	0.003**
	Non-TD	71	11.2	
Levodopa equivalent dose	0–499 mg	54	8.7	0.007**
	500–999 mg	41	11.3	
	≥1000 mg	23	11.4	
Dopamine agonist use	Yes	66	11.3	0.024*
	No	51	9.4	
Mini-mental state examination	<28	47	10.9	0.175
	≥28	71	9.7	
Beck depression inventory¶	<9	54	9.6	0.174
	≥9	62	10.8	
Parkinson's disease questionnaire¶	<45	58	8.8	<0.001***
	≥45	58	11.7	
COMT genotype¶	val/val	28	9.4	0.028*
	val/met	52	9.4	
	met/met	26	12.1	

Student t test (two categories) or analysis of variance (more than two categories) performed since ESS scores followed an approximate normal distribution.
†Non-categorical variables dichotomised at the median, with the exception of levodopa dose which was divided into separate dose ranges.
‡UPDRS part III conducted in the 'on' state.
§Tremor dominant (TD) and non-tremor dominant (non-TD) motor phenotype calculated based on UPDRS tremor, postural instability and gait disturbance subscores.
¶Missing information from two patients.
ESS, Epworth Sleepiness Scale; *COMT*, Catechol O-methyltransferase; UPDRS, Unified Parkinson's Disease Rating Scale.

RESULTS

At 3.5 year follow-up, ESS data was available on 118 out of 126 patients (94%). Mean ESS score±standard deviation was 10.2±4.6. 49% of patients had EDS (ESS>10). Bivariate analyses (Student t test or analysis of variance) found that non-tremor dominant (non-TD) motor phenotype, dopamine agonist use, higher levodopa dose, higher Parkinson's Disease Questionnaire score and *COMT* met/met genotype were associated with higher ESS scores (table 1). Multivariate linear regression confirmed that dopamine agonist use (B coefficient 2.408, p=0.004) and non-TD motor phenotype (B coefficient 2.116, p=0.013) were independent risk factors for higher ESS scores (model F=7.730, R^2=0.187, p<0.001).

The mean ESS score was 11.0±5.1 at 5 years and 10.5±6.2 at 7 years (53% and 44% had EDS respectively). Bearing in mind the smaller numbers studied at these time points, the only factors associated with increased ESS scores on multivariate analysis were a higher Parkinson's Disease Questionnaire score at 7 years (B coefficient 4.027, p=0.045). Patients who did not complete the ESS questionnaire at 5 years and 7 years had significantly higher Unified Parkinson's Disease Rating Scale part III scores and a higher proportion had dementia (defined as mini-mental state examination score less than 24) (all p<0.001) compared with those who did complete the questionnaire.

We found no baseline predictors of 'incident sleepiness' (change in ESS score between 3.5 years and 7 years).

DISCUSSION

We have shown that EDS is a fundamental feature of the PD sleep phenotype, even in early disease. The major strength of our study is the population-representative incident cohort used to determine EDS prevalence.

In PD dementia, Boddy *et al*[4] reported that patients with non-TD motor phenotype had a higher frequency of EDS at baseline (but not at 2 year follow-up). To our

knowledge, only one previous study has looked at motor phenotype in relation to EDS in PD without dementia and this found no significant relationship.[5] Our study found that patients with non-TD motor phenotype were more likely to have increased ESS scores at 3.5 years. Pathological studies indicate that patients with non-TD motor phenotype have more extensive pathology at autopsy,[6] and we propose that loss of wake-promoting neurons in the brainstem may be a fundamental problem in EDS. We also found that patients taking dopamine agonists were more likely to have increased ESS scores. Although the precise mechanisms are not fully understood, activation of D2 and D3 receptors by dopamine agonists is believed to induce sleepiness and this may be a particular problem in PD patients. In our study, there was a trend towards higher ESS scores in patients with the *COMT* met/met genotype (which putatively increases cortical dopamine levels) but this was not significant on multivariate analysis.

Using a structured questionnaire on three separate occasions, Gjerstad *et al*[5] previously found that the prevalence of EDS increased with disease progression (estimated rate of 6% per year), but ESS score was only collected at the final visit in this study. Our data does not support this, although there was a degree of attrition in our daytime sleepiness cohort over time (due to death and, to a lesser extent, non-completion of ESS) which may have led to an underestimation of EDS in later disease.

In conclusion, EDS is common at all stages of PD. We have confirmed the well-recognised observation that EDS is associated with dopamine agonist use, and thus doctors prescribing these drugs should be aware that they might worsen daytime sleepiness. In addition, we have reported for the first time that those patients with non-TD motor phenotype tend to have higher ESS scores, which may relate to more extensive brainstem pathology although this remains to be proven.

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Contributors DPB carried out the analysis and interpretation of the data, and prepared the manuscript. CHWG, SLM and TF carried out patient assessments and edited the manuscript. RAB conceived the study and edited the manuscript. All authors gave final approval for the manuscript to be published.

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REFERENCES

1. **Arnulf I.** Excessive daytime sleepiness in parkinsonism. *Sleep Med Rev* 2005;**9**:185–200.
2. **Homann CN,** Wenzel K, Suppan K, *et al*. Sleep attacks in patients taking dopamine agonists. *BMJ* 2002;**324**:1483–7.
3. **Foltynie T,** Brayne CE, Robbins TW, *et al*. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPalGN study. *Brain* 2004;**127**:550–60.
4. **Boddy F,** Rowan EN, Lett D, *et al*. Subjectively reported sleep quality and excessive daytime somnolence in Parkinson's disease with and without dementia, dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry* 2007;**22**:529–35.
5. **Gjerstad MD,** Alves G, Wentzel-Larsen T, *et al*. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? *Neurology* 2006;**67**:853–8.
6. **Selikhova M,** Williams DR, Kempster PA, *et al*. A clinico-pathological study of subtypes in Parkinson's disease. *Brain* 2009;**132**:2947–57.

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Notes