Association of Daytime Sleepiness with COMT Polymorphism in Patients with Parkinson Disease: a Pilot Study

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Study Objectives: To evaluate an association between catechol-O-methyltransferase (COMT) genotype and subjective daytime sleepiness in patients with Parkinson disease.
Design: Structured questionnaire study.
Setting: Tertiary Parkinson disease care center and sleep outpatients' department at the university hospital neurology department.
Participants: All nondemented patients with idiopathic Parkinson disease who had been part of a previous study of D4-receptor polymorphisms in 1997 were eligible to participate. From the original sample of 113 patients, 46 participated in the study, 22 met exclusion criteria, and 43 were not available.
Interventions: Not applicable.
Measurements and Results: In this study, 46 patients were included (27 men, 19 women; 68.4 ± 9.9 years of age; symptomatic disease duration, 12.2 ± 5.2 years; Hoehn and Yahr stage in "on" of 2.6 ± 0.8). Out of the 46 patients, 13 had LL genotype, 22 HL, and 11 HH. The Epworth Sleepiness Scale scores were 9.5 ± 4.8 in LL, 8.5 ± 4.7 in HL, and 6.8 ± 3.1 in HH (mean ± SD) (NS). LL and LH were grouped together. The Epworth Sleepiness Scale score was 11 or more in 40% of the LL+LH group, compared to 9.1% of the HH group (P = .039). The levodopa or dopamine-agonist doses and types did not differ between the LL+LH group versus the HH group.
Conclusions: These preliminary data suggest an association of the L-allele and daytime sleepiness in patients with Parkinson disease.
Key Words: Epworth Sleepiness Scale, COMT, inappropriate sleep composite score, yawning
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INTRODUCTION

EXCESSIVE DAYTIME SLEEPINESS HAS BEEN DOCUMENTED IN UP TO 70% OF PATIENTS WITH PARKINSON DISEASE (PD).[1,2] Underlying causes include altered sleep-wake regulation inherent to the disease and side effects of dopaminergic drugs or other centrally active drugs, as well as comorbidities such as sleep-disordered breathing.[3] Recently, Dauvilliers and coworkers[4] found a strong effect of a functional polymorphism of catechol-O-methyltransferase (COMT) activity on disease severity in narcolepsy.

COMT activity could also contribute to daytime sleepiness in patients with PD due to its involvement in the metabolism of dopamine: The low-activity allele decreases the dopamine turnover and could therefore increase the availability of endogenous or exogenous dopamine at dopaminergic sites[1] related to sleep-wake regulation, whereas the opposite is true for the high-activity allele.

The present pilot study was performed to evaluate whether an association exists between COMT genotype and daytime sleepiness in patients with PD.

Disclosure Statement
No significant financial interest/other relationship to disclose.

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METHODS

Patients

Caucasian patients with a diagnosis of idiopathic PD according to the United Kingdom PD Society Brain Bank criteria were screened for inclusion. They had participated in a genetic study[5] of the D_4-receptor polymorphism at our department in 1997, and DNA samples of 111 patients with PD were available for COMT genotyping. Exclusion criteria were dementia (Mini Mental State Examination scores < 26 or information on significant cognitive impairment provided by caregivers in telephone interviews), drug-induced psychosis, and severe medical comorbidity with a potential impact on the Epworth Sleepiness Scale (ESS).

Study Design

A structured sleep questionnaire, including the ESS[6] and the Inappropriate Sleep Composite Score (ISCS),[7] was applied in all patients available for personal or telephone interviews. The ESS is an 8-item questionnaire in which the probability to fall asleep is assessed for 8 different everyday life situations. The ISCS includes questions 6 and 8 of the ESS and 4 additional questions regarding pathologic aspects of sleepiness, such as falling asleep while conversing (question 6 of the ESS), stopping in traffic while driving (question 8 of the ESS), driving, eating, working, and doing household activities. Each question is rated from 0 to 3.

In addition, patients were questioned about a temporal relationship between subjective sleepiness and dosing of antiparkinsonian drugs and "on" or "off" states, as well as occurrence or worsening of daytime sleepiness after modifications in type or

dose of antiparkinsonian drugs. Severity of PD was assessed by Hoehn and Yahr staging and the motor part of the Unified Parkinson Disease Rating Scale (UPDRS) in "on."

Genomic DNA was extracted by standard procedures from whole blood. COMT genotypes were determined by restriction fragment length polymorphism analysis as described elsewhere.[8] A G to A substitution at codon 158 results in a valine-to-methionine substitution. 158met is associated with a 3- to 4-fold reduction in enzyme activity compared with the 158val. Therefore the 158met allele was called *L allele* (for low activity), and the 158val allele was called *H allele* (high activity).[8]

Statistics

The ESS score was chosen as the main outcome parameter. Results are reported as mean ± SD. Variables with normal and nonnormal distributions were compared by *t*-test and Mann-Whitney-U test, respectively. Categorical variables were compared by the likelihood-ratio test. Although there is no universal acceptance of any specific cutoff score of the ESS to define clinically meaningful daytime sleepiness, most studies have defined a pragmatic score of 10 for this purpose.[9,10] In our study, a cutoff level of > 10 for ESS was selected a priori to differentiate between normal and pathologic daytime sleepiness. SPSS 11.0 for Windows (SPSS, Inc., Chicago, Ill) was used for all statistical analyses. *P* values < .05 were considered to indicate statistical significance.

RESULTS

DNA samples for COMT genotyping were available in 111 out of 113 patients. Forty-three patients with PD were not available for physical examination or telephone interviews (31 had died, 4 refused, 8 were lost at follow-up), and 22 were excluded because of dementia (n = 20) or severe medical comorbidity probably affecting ESS (n = 2).

Forty-six subjects were included in this study. Thirty-one patients could be interviewed personally, whereas 15 could not come to our department and were therefore interviewed by telephone. There was no significant difference in the genotype distribution between participating and nonparticipating patients. The patient group in the final analysis consisted of 27 men and 19 women with a mean age of 68.4 ± 9.9 years and a mean symptomatic PD duration of 12.2 ± 5.2 years. The mean ESS score was 8.35 ± 4.4 and mean ISCS score was 0.54 ± 1.2. Hoehn and Yahr staging was 2.6 ± 0.8 during "on," and the UPDRS motor part performed also during "on" in the 31 patients with personal interviews was 21.6 ± 10.2. Out of the 46 patients, 13 (28.3%) had LL, 22 (47.8%) HL, and 11 (23.9%) HH genotypes. ESS scores were 9.5 ± 4.8 in LL, 8.5 ± 4.7 in HL, and 6.8 ± 3.1 in HH (P = .35 by analysis of variance (see Figure 1). Since both the LL and LH genotype are associated with significant reductions in COMT activity compared to the HH genotype,[11] the frequency of pathologic daytime sleepiness (ESS > 10) was calculated in L-allele carriers (LL and LH genotypes) versus subjects with the HH genotype. Only 1 out of 11 (9.1%) patients with HH alleles had an ESS score > 10, compared to 14 out of 35 (40%) patients who were carriers of at least 1 L allele (P = .039). We observed no significant differences for ISCS scores > 1 between the 2 genotype groups (LL/LH n 4/35 [11.4%] vs. HH n 3/11 [27.3%]). We found no significant frequency difference between the LL + LH versus the HH genotype carriers for the following question items: patient-observed temporal relationship between occurrence of daytime sleepiness and drug ingestion (LL/LH n 4/35 [11.4%] vs. HH n 2/11 [18.2%]), patient-observed temporal relationship between application of drugs and yawning (LL/LH n 7/35 [20.6%] vs. HH n 1/11 [9.1%]), patient-observed temporal relationship between the occurrence of daytime sleepiness and modifications in dopaminergic therapy (including dose and type of dopamine agonist) (LL/LH n 2/35 [5.7%] vs. HH n 2/11 [18.2%]). The use and dose of levodopa (608 ± 283 mg per day vs 630 ± 281 mg per day) as well as the use and type of dopamine agonists did not differ between the 2 groups (Table 1). There was also no significant difference between the Hoehn and Yahr stage or the UPDRS motor score across genotypes.

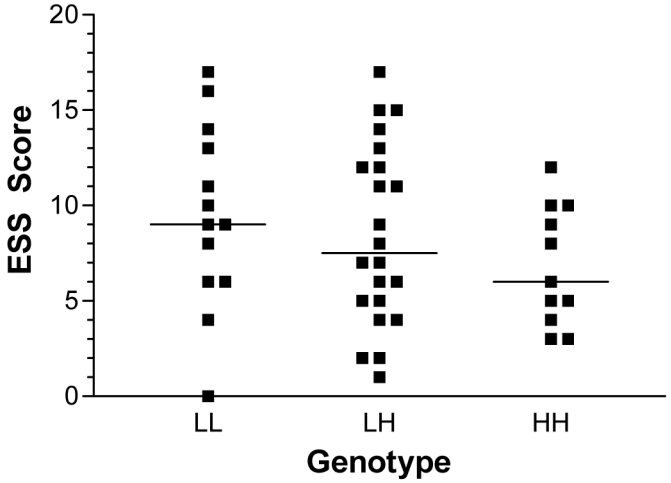

Figure 1—Graphical presentation of distribution of scores from the Epworth Sleepiness Scale (ESS) in the 3 genotypes. Horizontal line represents genotype-specific median value of ESS score.

Table 1—Use and Dose of Antiparkinsonian Drugs in the LL/LH Versus HH COMT Genotype Groups

Antiparkinsonian Drug, Dose	LL and LH (n = 35)	HH (n = 11)	*P*
Levodopa, mean ± SD	608 ± 283	630 ± 281	NS
Levodopa equivalent dose, mean ± SD	166 ± 221	148 ± 133	NS
Pramipexole, n (median)	11 (1 mg)	2 (2 mg)	NA
Pergolide, n (median)	6 (4 mg)	4 (0.5 mg)	NA
Ropinirole, n (median)	6 (5 mg)	3 (20 mg)	NA
Cabergoline, n (dosage)	2 (2, 12 mg)	1 (4 mg)	NA
Entacapone, n (median)	9 (800 mg)	2 (800 mg)	NA
Amantadine, n (median)	13 (300 mg)	5 (400 mg)	NA

LL refers to LL genotype; LH, LH genotype; HH, HH genotype; NA not applicable due to small number.

DISCUSSION

This study suggests that COMT genotype might be associated with daytime sleepiness in patients with PD. An ESS score greater than 10 was 4 times more frequent in subjects carrying the COMT low-activity allele (LL or LH genotypes) than in those with the HH genotype. The important role of dopamine in modulation of sleep and wakefulness states has only recently been investigated in the context of PD.[1] COMT is one of the major enzymes in dopamine metabolism (methyl group transfer from S-adenosylmethionine to dopamine, epinephrine, and norepinephrine), and different activities of this enzyme could potentially result in different rates of turnover of endogenous dopamine or dopamine derived from exogenous sources, such as levodopa, in subjects of different COMT genotypes. The amount of reduction of COMT enzyme activity according to genotype (LL versus HH) ranges from about 60% to 5-fold,[12] according to various studies, while individuals with the LH genotype have intermediate levels.[11,12] We speculate that the mechanism of action of COMT on daytime sleepiness might involve a higher availability of endogenous or exogenous dopamine at sleepiness-related brain structures with dopaminergic binding sites such as the ventral tegmental area or the mesostriatal system.[1] A previous study has shown that sleep induction does not depend on the pathway mediating motor benefit from levodopa.[13]

In patients with narcolepsy, the COMT polymorphism has been reported to be associated with disease severity, frequency of sleep-onset rapid eye movement periods, sleep paralysis,[4] and the response to modafinil.[14] Daytime sleepiness in patients with PD has been said to resemble several aspects of narcolepsy: mean sleep latencies below 5 minutes on the Multiple Sleep Latency Test[15] are common in patients with PD, and the occurrence of sleep-onset rapid eye movement periods has been described in 39% of patients with PD.[16]

It is remarkable that the mean ESS score across the whole sample was 8.35, which is not high for PD patients, in whom pathologic sleepiness frequently occurs. However, the mean ESS score in our sample is similar to recent reports from other Caucasian populations with PD[2,7,17] and may reflect sleep-state misperception in patients with PD. Misperception of sleepiness occurs frequently in sleepy PD patients, 38% of whom were unaware of at least 1 nap during the Multiple Sleep Latency Test.[18] In our study, only subjective measures of daytime sleepiness (ESS, ISCS, questionnaires) were used. Although the ESS has been extensively used in patients with PD,[2,7,10,19] the correlation of ESS and objective polygraphic measures of daytime sleepiness is low.[20]

Besides the ESS score, the study included the ISCS, as proposed by Hobson.[7] No significant difference was found between the genotype groups; in fact, there seemed to be a tendency towards higher ISCS scores in the HH group. However, the ISCS consists of 6 questions (2 of them also form part of the ESS) to capture situations in which falling asleep is extremely inappropriate (eg, while eating or during routine household activities). It may therefore be considered to be an indicator of most severe daytime sleepiness but may be less sensitive to less extreme daytime sleepiness. In a large sample of 638 patients with PD and a mean ESS of 7.0, the median ISCS score was 1.[7] Given the high frequency of zero scores in this scale, its use in comparisons of small groups seems questionable.

The differences in daytime sleepiness between the 2 genotype groups cannot be explained by differences in the medications, since neither the specific dopaminergic drugs (pergolide, pramipexole, ropinirole, cabergoline) nor the respective doses were different in the LL and LH vs. the HH group.

One disadvantage of our study is that the number of subjects was small: from the original sample of 113 patients with PD in 1997, only 46 were available. Additionally, a survival bias cannot be completely ruled out. However, the genotype distribution was not different between our patients and the general population.

One final drawback of our study is the fact that the phenotypic assessment of excessive daytime sleepiness, even apart from its subjective nature, occurred at a single point in time. We do not know if, in PD subgroups with lower or higher disease severity, the relationship between ESS and COMT genotype would be the same.

Due to the small number of patients, these results should be considered preliminary and need replication in future studies, which should also include polysomnography with the Multiple Sleep Latency Test.

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