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cording to IHS criteria, between the auras the patients were free of symptoms, there were at least 5 days on which more than two auras occurred, there was at least one period of 5 consecutive days with auras, and the aura status lasted at least 2 weeks.

The cause of migraine aura status is unknown. As there are no qualitative but only quantitative differences with "normal" migraine aura, and because all patients described so far with migraine aura status had had previous attacks of migraine with aura, the cause of normal aura and migraine aura status probably is the same. The observation that one of the patients described here had a daughter with similar complaints suggests that genetic factors play a role in the causation of migraine aura status, as in "normal" migraine.[1]

From the Department of Neurology (Drs. Haan, P. Sluis, Ferrari, and L.H. Sluis), Leiden University Medical Centre; and the Department of Neurology (Dr. Haan), Rijnland Hospital, Leiderdorp, the Netherlands.

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Address correspondence and reprint requests to Dr. J. Haan, Department of Neurology, Rijnland Hospital, PO Box 4220, 2350 CC Leiderdorp, the Netherlands; e-mail: jhaan@rijnland.nl

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K. Stiasny, MD; J.C. Möller, MD; and W.H. Oertel, MD

In 1999, falling asleep at the wheel was reported as a new and worrisome side effect in eight patients with PD treated with nonergot dopamine agonists (DA). Five of these patients reported sudden unexpected "sleep attacks" without preceding fatigue.[1]

Table *Patient characteristics and subjective data*

Patient no.	Age, y/ sex	Duration of RLS, y	Dosage of pramipexole, mg	Adverse events under pramipexol	Efficacy of current RLS treatment	RLS severity compared to before current treatment	ESS points	Daytime fatigue	Dozing off with preceding fatigue (sleep episodes)
1	65/F	43	0.375	None	Satisfied	Much better	11	Daily* (no)	Present‡ (no)
2	60/F	17	0.5	Dry nose*	Markedly satisfied	Very much better	1	—	—
3	61/M	3	0.375	Alertness*	Very satisfied	Very much better	7	—	—
4	73/M	2	0.125	None	Satisfied	Very much better	9	Daily* (no)	Present‡ (no)
5	79/M	20	0.75	None	Very satisfied	Very much better	6	Daily* (no)	Present‡ (no)
6	69/F	10	0.5	Constipation*	Very satisfied	Very much better	5	Daily† (no)	—
7	61/F	11	0.25	None	Very satisfied	Very much better	5	—	—
8	56/M	30	0.375	None	Markedly satisfied	Much better	3	—	—
9	58/M	35	0.375	None	Very satisfied	Very much better	6	—	—
10	54/F	15	0.375	None	Markedly satisfied	Much better	4	3 days* (no)	—
11	55/M	15	0.25	Arrhythmias*	Satisfied (initially)	Much better (initially)	0	—	—
12	56/M	22	0.25	Dry mouth*	Unsatisfied	Moderately worse	3	—	—
13	59/F	21	0.125	None	Satisfied	Much better	6	4 days* (no)	—
14	59/F	35	0.125	None	Markedly satisfied	Moderately better	20	4 days* (no)	—
15	71/F	1	0.375	None	Satisfied	Much better	2	Daily† (yes)	—
16	46/F	6	0.25	None	Markedly satisfied	Much better	4	—	—
17	66/F	6	0.25	None	Very satisfied	Very much better	3	Daily*‡ (no)	—
18	58/F	36	0.375	None	Markedly satisfied	Much better	12	Daily* (no)	Present‡ (no)
19	69/M	8	0.375	None	Unsatisfied	Moderately better	11	14 days†‡ (no)	—
20	69/F	52	0.5	None	Very satisfied	Very much better	9	Daily*‡ (no)	—
21	64/M	20	0.5	None	Markedly satisfied	Much better	0	Daily* (no)	—
22	50/F	35	0.25	None	Very satisfied	Very much better	9	—	—
23	64/F	5	0.375	None	Markedly satisfied	Very much better	11	Daily* (no)	Present‡ (no)
24	68/F	25	0.75	None	Markedly satisfied	Very much better	9	Daily* (no)	—

No patient experienced sudden, unexpected dozing off (sleep attacks). Values in parentheses indicate relationship to drug intake.

* Mild; † moderate.
‡ Daytime nap.

RLS = restless legs syndrome; ESS = Epworth Sleepiness Scale.

Subsequently, more patients who were treated with DA (including ergot DA) for PD have been reported to have similar sleep attacks.[2] Because the nonergot DA pramipexole is successfully used in the treatment of restless legs syndrome (RLS),[3] we investigated its safety with particular regard to sleep attacks in patients with RLS.

Methods. We surveyed all patients in our outpatient clinic who have been treated with pramipexole to control RLS symptoms by a mailed questionnaire. Patients were asked about side effects of pramipexole, occurrence and degree of daytime fatigue, occurrence of unexpected dozing off (sleep attacks), dozing off due to tiredness (sleep episodes) and its relationship to drug intake, and intake of other drugs. Patients who reported dozing off or daytime fatigue were contacted again by telephone. To provide a standardized measurement of the subject's general level of daytime sleepiness we administered the Epworth Sleepiness Scale (ESS).[4] Patients were also asked if they were satisfied with their current RLS medication (7-point scale, very unsatisfied to very satisfied) and how severe their RLS symptoms currently were compared to before pramipexole treatment (7-point scale, very much better to very much worse). Continuous or discrete data were analyzed by descriptive statistics or by frequency tables.

Results. Twenty-four of 31 patients (9 men, 15 women, mean age 62.1 ± 7.6 years, range 46 to 79) with RLS for 19.7 ± 14.1 years (range 1 to 52) participated (77.4%) (table). Twenty-one were on pramipexole monotherapy (67% taking a single evening dose). Additional RLS medication was taken regularly by one patient (levodopa/benserazide 100/25 mg, Patient 13). One patient (no. 15) occasionally took bromazepam 1.5 mg and one (no. 19) occasionally required 100/25 mg levodopa/benserazide to treat RLS symptoms during the day. Additional psychoactive drugs were taken by two other patients (clomipramine 25 mg BID and amitriptyline 15 mg BID, Patient 23; doxepin 100 mg daily, Patient 9). The mean pramipexole dosage was 0.37 ± 0.17 mg (range 0.125 to 0.75). No sudden unexpected sleep attacks occurred in our patients. Eleven patients complained of mild to moderate chronic daytime fatigue. Five of the 11 reported sleep episodes during the day relating to fatigue. Only one patient (no. 15) considered a relationship of sleep episodes to drug intake. Telephone interviews subsequently revealed that these patients referred to regularly taken daytime naps. Concerning the relationship of drug intake to sleep episodes, Patient 15 explained that she became tired in the evening and could easily fall asleep when taking pramipexole. Whereas change of daytime fatigue by pramipexole was not specifically addressed in the questionnaire, all patients confirmed in the telephone interviews that daytime fatigue was not more severe than before treatment—quite the reverse. The mean ESS score was 6.5 ± 4.6 (range 0 to 20), with five patients having a score higher than 10 (11, n = 3; 12, n = 1; 20, n = 1). These patients, however, did not refer to sudden or unexpected onset of sleep. Besides, most patients (n = 22) stated that they were satisfied with pramipexole treatment (markedly satisfied n = 9, very satisfied n = 8).

Discussion. The results of this survey show that sudden unexpected sleep attacks as they have been described in PD patients under treatment with pramipexole did not occur in this limited sample of 24 RLS patients. The PD patients who had sleep attacks had taken pramipexole at an average dose of 2.9 mg/day.[1] Furthermore, somnolence as a side effect of pramipexole has been more frequently observed at higher dosages.[5] Our RLS patients, however, were treated with an average dose of 0.37 mg pramipexole/day. Comparable low doses of pramipexole have been shown to induce sleepiness in rats by the stimulation of presynaptic dopamine autoreceptors,[6] raising the possibility that sleep attacks under pramipexole may also occur during treatment of RLS. This hypothesis has not been supported by our observations, which favor a dose-dependent occurrence of sleep attacks under pramipexole.

Our data, based on a small sample, do not suggest a significant risk of sleep episodes in RLS patients treated with pramipexole. Presence of daytime fatigue or sleepiness in some patients can likely be attributed to the sleep disorder itself rather than to treatment. However, daytime sleepiness in untreated RLS patients has never been evaluated and should be taken into consideration in future treatment trials.

From the Department of Neurology, Center of Nervous Diseases, Philipps University Marburg, Germany.

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Address correspondence and reprint requests to Dr. Karin Stiasny, Department of Neurology, Center of Nervous Diseases, Rudulf-Bultmann-Strasse 8, D-35033 Marburg, Germany; e-mail: stiasny@mailer.uni-marburg.de

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A presenilin-1 mutation (Leu392Pro) in a familial AD kindred with psychiatric symptoms at onset

A. Tedde, PhD; P. Forleo, MD; B. Nacmias, PhD; C. Piccini, MD; L. Bracco, MD; S. Piacentini, MD; and S. Sorbi, MD

Missense mutations in the presenilin genes are implicated in the majority of early-onset familial AD (EOFAD) cases. Presenilin 1 (PS-1) is a multispanning membrane protein composed of 467 amino acids, containing six to nine transmembrane helical domains and a large hydrophilic loop between domains six and seven. To date, more than 50 missense mutations[1] and a splice site mutation in PS-1 have been found to cosegregate with EOFAD. Common phenotypic features of presenilin-1 linked families include onset of memory disturbances before age 50 years, shorter disease duration, and the presence of myoclonus and generalized seizures.

We have performed a clinical and genetic screening in order to search for additional missense presenilin mutations in families with EOFAD, identifying a new family with a previously undescribed missense mutation in exon 11 leading to a Leu to Pro substitution at codon 392. This mutation was not detected in 50 unrelated subjects, indicating that this is not a common polymorphism. The members of this kindred belong to a three-generation family from central Italy (figure). The proband, (III-1), a 38-year-old man, was referred to our clinic with a history of mild memory deficits. His medical history was characterized by the onset of manic symptoms, including reduction of sleep, overactivity, irritability, and weight loss. The patient experienced personal financial troubles for excessive and incoherent expenses. His overactivity forced him to hold several part-time jobs at once and to make further investment plans with friends after midnight, stating that he did not need to sleep further. Impairment of insight was also present. After 3 months, the manic symptoms remitted with a progressive worsening of mood, characterized by lack of interest, loss of social activity, depressed mood, and reduced energy. When he was first observed, the patient was still able to work as a carpenter, but his performance was impaired on all of the administered neuropsychological tests,[2] with a pronounced deficit in episodic memory and space and time disorientation. He was alert and cooperative, with fluent but poor speech and mild impairment of long and complex sentences. His Mini-Mental State Examination (MMSE) score was 15/30, with the majority of points lost on time orientation, calculation, and three-word recall. Physical and neurologic examination was normal. The patient underwent antidepressant and anticholinesterase therapy with mood improvement and moderate weight gain. Over the next 3 years he showed a progressive decline in cognitive functions and in daily living activities. Manic episodes were not observed. At the last follow-up, 6 years after the onset, he is no longer testable or self-sufficient; his speech is repetitive and poor. He presents with episodes of aggressive behavior toward his relatives and alterations of the sleep–wake cycle.

In February 1999, his sister (Patient III-2), a 43-year-old woman, came to our attention because of the presence