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Case report

Pergolide-associated 'sleep attacks' in a patient with restless legs syndrome

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Abstract

The occurrence of irresistible sleep episodes ('sleep attacks') has been noted in patients with Parkinson's syndrome treated with dopa-agonists. This is the first report of 'sleep attacks' in a patient with restless legs syndrome in whom treatment with pergolide was reduced from 2 to less than 1 mg/day. 'Sleep attacks' were accompanied by a reduced mean sleep latency of 5 min and 20 s (without sleep onset REM periods) on a multiple sleep latency test. 'Sleep attacks' disappeared when pergolide was tapered off and substituted with pramipexol. The appearance of 'sleep attacks' as a 'withdrawal' effect of pergolide is consistent with a wakefulness-promoting action of postsynaptic dopaminergic receptors at higher doses of dopamine agonists. © 2002 Published by Elsevier Science B.V.

Keywords: Sleep attacks; Pergolide; Restless legs syndrome

1. Introduction

Sedation and excessive daytime sleepiness, well known side-effects of treatments with dopa-agonists, can be seen in 10–30% of patients. Over the past 2 years, several publications have drawn attention to the possible occurrence of irresistible sleep episodes ('sleep attacks') in patients with Parkinson's syndrome treated with pramipexol, ropinirole, pergolide, levodopa, and other dopaminergic drugs [1,2]. We report — to our best knowledge — the first observation of a similar side-effect in a patient with restless legs syndrome (RLS) treated with pergolide.

2. Case report

This 69-year-old man has been treated in our Sleep Clinic since 1991 for severe idiopathic RLS, which appeared in the early 1970s. Neurologic examination was always unremarkable. A conventional polysomnography documented the presence of dyskinesias while awake and a few periodic limb movements during sleep (<5/h) while ruling out significant sleep-disordered breathing (apnea–hypopnea-index = 7). In February 1998, the patient was being treated with levodopa (1000 mg/day) and clomethiazol (300 mg/day), and reported severe RLS symptoms. Treatment with pergolide at a dose of 0.05 mg/day was started. Improvement of RLS symptoms led to a discontinuation of levodopa. Over the following months, the patient increased his intake of pergolide (up to 2 mg/day) beyond the suggested doses in order to maintain good control of his RLS symptoms. However, in February 1999, he reported a new increase of the discomfort in his legs. While being treated with pergolide at 2 mg/day and clomethiazol at 300 mg/day, his RLS score (International Restless Legs Syndrome Study Group, Neurology 2001;56(Suppl 3):A4) was 31 (>30: very severe RLS) and his Epworth sleepiness score (ESS) was 8 (<10: normal). Codeine at a dose of 60 mg/day was started and resulted in an improvement of the RLS symptoms (see Fig. 1). In April 1999, with his RLS score at 22 (10–20: moderate RLS) and his ESS at 7, the pergolide dosage was reduced to 1.0 mg/day. He subsequently reported the onset of previously unknown 'sleep attacks', describing episodes — occurring about once daily, often before noon — of an overwhelming sudden sleepiness which lead to voluntary and involuntary naps lasting 10–15 min, and occasionally up to 60 min. The episodes occurred, sometimes without warning, at rest or during moderately intense motor activities, but never during such activities as eating, talking, or walking. He experienced the naps as very deep, non-refreshing sleep unaccompanied by dreams. His wife described his

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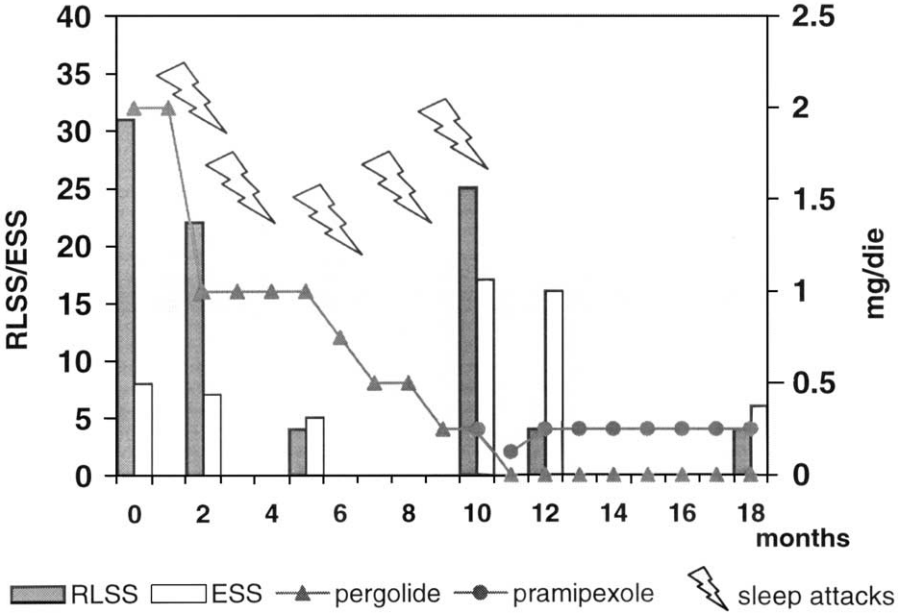

Fig. 1. Course of subjective sleepiness (Epworth Sleepiness Score, ESS) and restless legs symptoms (Restless legs scale score, Neurology 2001;56(Supp 3):A4) in a patient who developed 'sleep attacks' while reducing treatment with pergolide. No 'sleep attacks', conversely, with pramipexole.

sleep as unusually quiet, motionless. The patient could not be aroused and appeared as if 'narcotized'. In July 1999, while taking pergolide at 1.0 mg/day, codeine at 60 mg/day, and clomethiazol at 300 mg/day, the patient reported continuing 'sleep attacks', but good control of his RLS symptoms and decreased daytime sleepiness. His RLS score was 4 (<10: mild RLS) and his ESS was 5. Despite a further progressive dose reduction of pergolide between July and September 1999, the 'sleep attacks' persisted, while his RLS symptoms increased. In December 1999, while on a treatment with pergolide at 0.25 mg/day, codeine at 60 mg/day and clomethiazol at 300 mg/day, his RLS score was 25 and his ESS was 17. An actigraphic recording over 1 week documented regular bedtimes, fragmented night sleep, three daytime sleep episodes lasting several minutes, and an overall reduction of 25% in 'sleep' time. A multiple sleep latency test (MSLT) showed a reduced mean sleep latency of 5 min and 20 s without any sleep onset REM periods (SOREMPs) during the five attempts. The result of the steer clear test was also abnormal at 7% (<2.5%: normal). Following these tests, pergolide was tapered off and treatment with pramipexol at 0.125 mg/day was started. In February 2000, while on pramipexol at 0.25 mg/day, codeine at 60 mg/day and clomethiazol at 300 mg/day, his RLS symptoms were again well under control and his RLS score was 4. The 'sleep attacks' had now disappeared, although his subjective daytime sleepiness had increased slightly (ESS, however, remained almost unchanged at 16). In February 2001, under the same drug combination (with pramipexol increased to 0.75 mg/day), the patient was continuing to enjoy good control of RLS symptoms. In the absence of 'sleep attacks', the daytime sleepiness has also improved, possibly in relation to improved RLS control. His RLS score is 4 and his ESS is 6. The patient does not drive and incurred no accidents or injuries related to his 'sleep attacks'.

3. Discussion

Our observation suggests the following four comments. First, treatment with dopaminergic drugs, including pergolide, may be complicated by 'sleep attacks', not only in patients with Parkinson's disease but also in patients with RLS. After the submission of this communication, we observed the occurrence of 'sleep attacks' in a second RLS patient treated with pramipexol (unpublished). The potential role of concomitant medications in the pathogenesis of these 'sleep attacks' remains open. The sedating effect of codeine, for example, may have had a role in the occurrence of 'sleep attacks' in our patient, although the dosages of codeine remained constant during the observation period. Second, although 'sleep attacks' tend to appear following the start or increased dosage of dopamine agonists (pergolide, pramipexol, ropinirole [1,2]), in our patient, this side-effect appeared during a reduction of pergolide to doses ≤1 mg/day [1]. The appearance of 'sleep attacks' as a 'withdrawal' effect from pergolide is consistent with the presence of both sedating and alerting properties in dopamine agonists. Sedating effects may be related to the involvement of *presynaptic* dopaminergic receptors activated at low doses of dopamine agonists. Conversely, increase of wakefulness could reflect the activation of *postsynaptic* dopaminergic receptors at higher doses of dopamine agonists [3].

Third, 'sleep attacks' and excessive daytime sleepiness (as assessed, for example, by the ESS) are usually present in combination, but can run, as shown in this report, a different course. This dissociation implies the possibility that different pathogenetic mechanisms are implicated in the two phenomena, at least in specific clinical situations or patients. Fourth, 'sleep attacks' in such patients are not necessarily the expression of increased REM sleep pressure. Similar to the findings with our patient, Hauser et al. reported decreased sleep latencies but no SOREMPs in the MSLT of two Parkinson's patients with pramipexol induced 'sleep attacks' [4]. Similarly, episodes of overwhelming ('narcolepsy-like') sleepiness can be observed in patients with idiopathic hypersomnia, also in the absence of SOREMPs and other REM sleep phenomena [5]. In conclusion, our observation draws attention to the possibility of 'sleep attacks' in RLS patients treated with dopaminergic drugs. Considering the relatively high prevalence of excessive daytime sleepiness in RLS patients (ESS of >10 in 24% of cases in one series [6]), these patients should be alerted to this possible side-effect.

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