



## Recurrence of cluster headache with pramipexole

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### Abstract

*Cluster headache (CH) is among the most painful headache disorders. There is still no unifying pathophysiological hypothesis to explain the trigeminal distribution, the circadian periodicity and the autonomic symptoms of the syndrome. We report the case of a patient with worsening of CH following administration of pramipexole for a restless legs syndrome (RLS). This observation supports the hypothesis that the dopaminergic system may play a role in the genesis or trigger of CH.*

### Case report

A 60 year-old man presented with unpleasant tingling sensations in the legs and a restless sleep with jerks in the legs for several years, which resulted in a significant daytime sleepiness during the last year. A polysomnography performed one year before showed a mild obstructive sleep apnoea syndrome (AHI score of 9.1/hour) and an increase of limb movements index during sleep (score 10.4/hour). The Epworth Sleepiness score was increased to 11/24 and the IRLS score was 21/40. The neurological examination was normal.

We noted that, 7 years ago, the patient suffered from the occurrence of several recurrences of episodic CH, according to the ICHD-II classification, over a 9 months period. Headaches were on the right side and accompanied by ipsilateral lacrimation, conjunctival injection, nasal congestion, rhinorrhea and Claude Bernard-Horner syndrome. They recurred about three times a day. Treatment with pramipexole at an initial dose of 0.18 mg was initiated for the RLS. Three days after initiating pramipexole, the patient experienced a recurrence of the CH. The CH was similar to previous episodes. After a few days, pramipexole was discontinued and the intensity of the CH waned off over 3 days and disappeared completely after a week. Because of the intensity of the CH, the patient refused to repeat

another trial with pramipexole. After a follow-up of 18 months, no spontaneous recurrence of the CH happened.

### Discussion

We report on a patient with several attacks of CH seven years earlier, who experienced a recurrence of the CH shortly after initiating a small dose of pramipexole for a RLS; one week after discontinuing pramipexole, the CH disappeared. The sharp temporal relationship between the course of CH attacks and that of treatment initiation and discontinuation argues against a fortuitous association.

Clinical data concerning the relationship between dopaminergic activity and CH are scarce.

Firstly, the nocturnal melatonin secretion phases are decreased during the acute period of CH, when compared to normal melatonin levels during asymptomatic phases (Waldenlind *et al.*, 1987, Leone *et al.*, 1995).

Thus, since melatonin exert an inhibitory effect on dopamine secretion (Zisapel, 2001), it is not unlikely that dopamine levels may be found increased during the period of CH attacks, suggesting a role of dopamine in the genesis or trigger of CH attacks.

Secondly, a relationship between an antidopaminergic activity and a reduction in CH symptoms has been suggested by an open study using olanzapine, an antagonist of dopamine D2 and serotonin 5-HT<sub>2A</sub> receptors, as an acute treatment of CH (Rozen, 2001). In this study, 4 out of 5 patients showed a marked improvement of CH symptoms. A similar observation has been reported for a schizophrenic patient who presented a complete disappearance of the CH after treatment with clozapine, a dopamine D<sub>4</sub>-D<sub>5</sub> and serotonin HT<sub>1</sub>-2-3-7 antagonist (Datta and Kumar, 2006). In an earlier study with chlorpromazine, a dopamine antagonist, a complete disappearance of symptoms of CH was also noted in 12 of 13 patients (Caviness, Jr. and O'Brien,

1980). These observations suggest that decreasing dopamine level may exert a positive effect on CH attacks, whether acting upon the dopaminergic and/or the serotonergic pathways.

Thirdly, the present observation of a recurrence of CH attacks concomitant with the initiation of the dopamine agonist pramipexole, a non-ergot dopamine agonist with a preferential affinity for the D2 class of receptors and in particular subclass D3, strengthens the hypothesis that an increase in dopamine level may play a role in the trigger of CH. Conversely, Palmieri (Palmieri, 2006) reports a patient with chronic CH in whom the initiation of pramipexole for Parkinson's disease led to a complete disappearance of CH attacks after two months of therapy. Whereas both RLS and Parkinson's disease are hypodopaminergic conditions, the observation of Palmieri is at odd with our own observation and previous report with dopamine antagonists. However, the pathophysiological mechanisms of RLS and Parkinson's disease are different; these differences may explain the seemingly contradictory observations.

Nevertheless, this case provides another piece of evidence for a probable modulating role of the dopaminergic system in the genesis or trigger of CH. Thus, whereas acute CH symptoms may be reduced by dopamine antagonists, our observation supports a trigger role of dopamine agonists on CH attacks.

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