

Melatonin in the preventive treatment of chronic cluster headache

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Cluster headache is a stereotypic headache disorder marked by short-lasting bouts of severe unilateral head pain and associated autonomic symptoms. Almost pathognomonic of this condition are nocturnal attacks that usually occur during the first random eye movement sleep phase of the evening. Melatonin levels have been found to be decreased in cluster headache patients. A lack of melatonin secretion may predispose the cluster sufferer to nocturnal and, possibly, daytime attacks. Leone et al. demonstrated that melatonin could rapidly alleviate cluster attacks, but only in episodic cluster patients. We report two chronic cluster headache patients who had both daytime and nocturnal attacks that were alleviated with melatonin. □ *Chronic cluster headache, melatonin, preventive treatment*

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Introduction

Cluster headache is characterized by short-lasting unilateral pain attacks, usually located in the orbito-temporal region, with a highly distinctive cyclic recurrence pattern. Its circadian and circannual variation is attributed to a hypothalamic generator (1, 2) in the suprachiasmatic nucleus, known to be the 'biological clock'. Melatonin secretion is regulated by the suprachiasmatic nucleus and is decreased in cluster headache patients (3). Melatonin is effective in the prophylaxis of episodic cluster headache (4) but it has never been reported to be helpful in chronic cluster headache.

We report two patients with chronic cluster headache who became headache-free after melatonin treatment.

Case reports

Case 1

A 38-year-old Caucasian man had a 20-year history of headaches, located in the left temple region, with radiation to the parietal and occipital area. The

headaches lasted 45–60 min and occurred six to seven times per day. The pain was excruciating and was accompanied by ipsilateral tearing, conjunctival injection, nasal congestion, eyelid oedema and ptosis. Photophobia and phonophobia were also present. The patient experienced two to three attacks every evening. His sleep was disrupted, with total sleep time averaging 5 h, with two to three awakenings per night with headache. He consistently developed a headache 1 h after falling asleep. Naps during the day also precipitated a headache. He had never had a headache-free period longer than 14 days since the onset, typically having at least 10 months a year with daily headaches without a remission. MRI of the brain and neurological exam were normal. Failed past preventive drugs included steroid tapers, valproic acid (2000 mg), verapamil (640 mg), and lithium (900 mg). He was on a stable dose of verapamil 640 mg, but was still experiencing six to seven cluster headache attacks per day when melatonin 9 mg was started at bed time. His headaches significantly improved within 2 days of starting melatonin, at which time the patient became headache-free for a period of 6 months. No side-effects were reported, and sleep was no longer disrupted. The patient did not stop the medication.

Case 2

A 40-year-old man with hazel eyes had an 8-year history of excruciating headaches in the right orbital and occipital regions. The headache duration was 2 to 3 hours, three times a day, with one headache always occurring 40 min after falling asleep. The pain was associated with ipsilateral lacrimation, ptosis, nasal congestion and rhinorrhea. Nausea, vomiting, phonophobia and photophobia were not present. The headaches were triggered by alcohol and lack of sleep. MRI of the brain and neurological exam were normal. He had chronic cluster since the beginning, with some headache-free periods, but never for more than 2 weeks. Prednisone tapers usually helped for 1 week. Verapamil 640 mg gave some relief in severity for a short period. Melatonin 9 mg at bedtime as add-on therapy gave immediate pain relief, with both daytime and nocturnal headaches completely abating. No side-effects were reported. The headaches have not recurred since then; the patient has been headache-free for 8 months and does not want to discontinue the medication.

Discussion

It has been suspected that melatonin may be involved in cluster headache genesis, primarily because melatonin is a sensitive marker of endogenous rhythms, which are disrupted in cluster headache (5). It is now well established that the pineal gland is an adaptive organ that maintains and regulates cerebral homeostasis by 'fine tuning' biological rhythms through the mediation of melatonin (6). In 1984 Chazot et al. (7) identified for the first time a decrease in nocturnal melatonin secretion and abolished melatonin rhythm in cluster headache patients. Waldenlind et al. (3) also showed that nocturnal melatonin levels were lower during cluster periods than during cluster remissions. Determining urinary levels of 6-sulphatoxymelatonin throughout the year, Waldenlind et al. (8) found that women had higher melatonin levels than men, Swedes had higher melatonin levels than Italians, and smokers had lower melatonin levels than non-smoking cluster headache patients. Leone et al. (9) observed melatonin and cortisol acrophases significantly correlated in controls but not in cluster headache patients, indicating a chronobiological disorder in cluster headache.

Blau and Engel (10) found that increases in body temperature from exercise, a hot bath or elevated environmental temperature triggered cluster headaches in 75 of 200 cluster headache patients. This finding can be explained by a decrease in melatonin secretion

caused by an increase in temperature (11). Most studies on melatonin have been in episodic cluster headache patients only.

In light of these studies, melatonin supplementation as a cluster headache preventive was studied in a double-blind, placebo-controlled trial by Leone et al. (4). There was a significant decrease in the mean number of cluster headache attacks in the melatonin-treated group compared with placebo. Two patients with chronic cluster headache in the trial did not respond to melatonin therapy. Nagtegaal et al. (12), studying melatonin in delayed sleep phase syndrome, identified a patient with episodic cluster headache in whom both disorders improved after melatonin treatment. There is no report in the literature of chronic cluster headache responsive to melatonin.

We describe two chronic cluster headache patients who responded to melatonin 9 mg at bedtime. The dose used by Leone et al. (4) in the double-blind, placebo-controlled trial was 10 mg; we used 9 mg because 3 mg tablets are available in the United States of America. The improvement could be due to a placebo response, or the patients may have spontaneously entered a remission; however, it is most likely to be due to the therapeutic melatonin effect. Chronic cluster headache can be very difficult to treat and melatonin could be an adjunctive treatment for preventive cluster headache treatment, although a double-blind, placebo-controlled trial is necessary to confirm this assumption. Melatonin not only appears to prevent nocturnal cluster attacks, but daytime attacks as well.

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