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Successful prophylactic treatment of chronic cluster headache with low-dose levomethadone

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Sirs: cluster headache (CH) is a disabling primary headache syndrome. We describe a patient suffering from chronic CH in whom preventive drugs were lacking a sufficient effect. In contrast, former opioid abuse induced complete remission. Therefore, a therapeutic trial with low-dose opioids was initiated. This resulted in prompt and long lasting CH remission.

The patient is a 36-year-old Caucasian salesperson. The headache attacks began at age 16 without being diagnosed as CH initially. The attacks were pulsating, strictly left sided without memorable autonomic symptoms but with a typical duration of 30 minutes and pacing around. Several years later, an increasing attack frequency was one reason for drug abuse. At age 23, after a 2-year period with abuse of a variety of drugs this resulted in intravenous diamorphine abuse. A 3-year period of diamorphine addiction was followed by detoxification and a 3-year period of methadone substitution. During the time of opioid abuse and substitution, the patient remained completely headache free. With cessation of methadone substitution, extremely intense left-sided periorbital pain attacks with ipsilateral lacrimation, rhinorrhea, skin redness, ptosis and miosis reappeared (one to three times daily). Cranial MRI as well as laboratory exams showed no abnormality. The headache was diagnosed as primary CH fulfilling the criteria of the International Headache Society and a variety of therapeutical strategies including a course of corticoids (prednisolone 60 mg/d over 7 days and successive tapering), verapamil up to 720 mg/d, valproate (3 × 600 mg/d), gabapentin (900 mg/d, no further dose increase because of dizziness) and indomethacin (175 mg/d), ergotamine (2 mg/d), lithium (serum levels of 0.6–0.8 mmol/l), topiramate (up to 150 mg/d) and amitriptyline (25 mg/d) and combinations of these medications over months did not lead to sustained effects with the exception of valproate, which was initially partly effective, but discontinued because of excessive weight gain and decreasing efficacy within three months of treatment. At this time (Fig. 1) the patient met the previously proposed selection criteria for deep brain stimulation in intractable chronic cluster headache [1].

The case was discussed at the interdisciplinary pain conference with consultants from the departments of neurology, anesthesiology and psychosomatic medicine. Given the facts that the patient still suffered from severe CH, that opioids previously prevented CH attacks and now a stable social and psychological status was reached, there was agreement to start low dose treatment with levomethadone orally (5 mg/d) once daily in the evening. This led to prompt symptom alleviation and the pa-

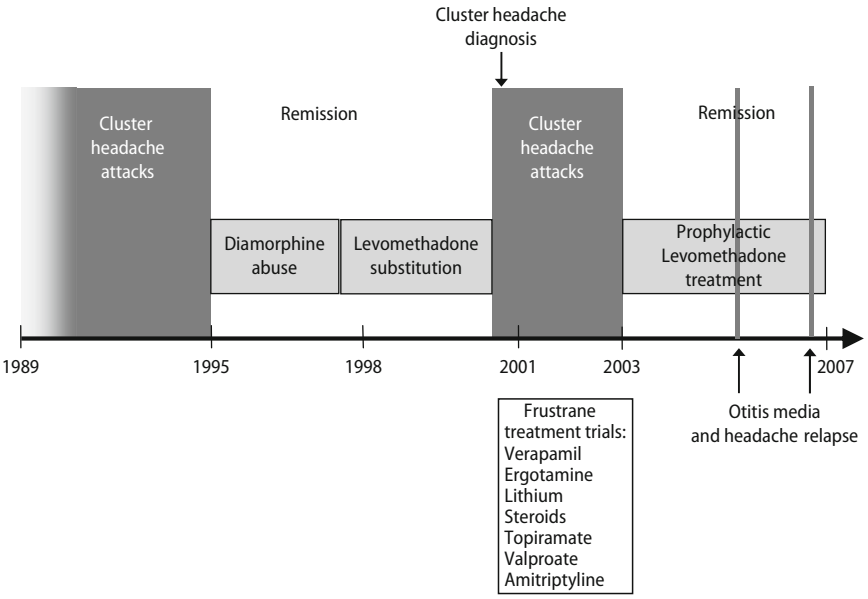

Fig. 1 Relationship between occurrence of cluster headache attacks and opioid application in the patient

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tient reported having started "a whole new life". The CH attacks ceased without dose change until a trial of levomethadone discontinuation six months later. As CH attacks promptly reappeared, levomethadone therapy was restarted. The patient continues to be almost free of CH for now four years. He experienced only two very short relapses coinciding with acute otitis media and disappearing immediately with the healing of the otitis.

To our knowledge, this is the first case of complete CH remission after prophylactic application of opioids. Permanent symptom control was not achieved with the standard treatment. Since a positive relationship between opioid intake and CH symptoms was striking and the patient showed responsible behavior, a trial of low-dose levomethadone was initiated. Levomethadone is the R(-)isomer of racemic methadone, a synthetic mu-opioidergic agonist which has been used to treat pain and opioid addiction for many years [2].

The relationship between opioid administration and CH remission in this case suggests that opioidergic mechanisms might play a stronger role than currently honored. This view is supported by previous observations of altered ß-endorphin secretion [3], reduced circulating levels of opioidergic peptides [4, 5] and changes of the opioidergic receptor availability in the pineal gland in CH patients [6].

It is known that opioids can increase the release of melatonin from the pineal gland and that melatonin levels are decreased in cluster headache patients. A normalization of melatonin levels might therefore be one mechanism by which levomethadone acts in this case.

Our group has previously also shown that with increasing duration of the headache disorder, the opioidergic receptor availability in the hypothalamus decreases [6]. This underlines not only the crucial role of the hypothalamus in the pathogenesis but also the fact that opioidergic mechanisms are involved. Hence, the activation of μ-receptors in the hypothalamus might also contribute to the mechanism of action of levomethadone. Finally, levomethadone has, of course, also an unspecific antinociceptive effect which is mediated via the periaqueductal gray matter.

Conflict of interest The authors declare no conflict of interest.

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