Medication-overuse headache in patients with cluster headache

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HIGH LIGHT
CME

Medication-overuse headache in patients with cluster headache

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Abstract—*Objective:* Medication-overuse headache (MOH) in cluster headache (CH) patients is incompletely described, perhaps because of the relatively low prevalence of CH. *Methods:* The authors describe a retrospective series of 17 patients (13 men, 4 women) with CH who developed MOH in association with overuse of a wide range of monotherapies or varying combinations of simple analgesics (n = 9), caffeine (n = 1), opioids (n = 10), ergotamine (n = 3), and triptans (n = 14). The series includes both episodic (n = 7) and chronic (n = 10) CH patients. *Results:* A specific triptan-overuse headache diagnosis was made in 3 patients, an opioid-overuse headache diagnosis was made in 1 patient, and an ergotamine-overuse headache diagnosis was made in 1 patient. In approximately half of the patients (n = 8), the MOH phenotype was a bilateral, dull, and featureless daily headache. In the other 9 patients, the MOH was characterized by at least one associated feature, most commonly nausea (n = 6), exacerbation with head movement (n = 5), or throbbing character of the pain (n = 5). The common denominator in 15 patients was a personal or family history, or both, of migraine. The 2 other patients gave a family history of unspecified headaches. Medication withdrawal was attempted and successful in 13 patients. *Conclusions:* Medication-overuse headache is a previously underrecognized and treatable problem associated with cluster headache (CH). CH patients should be carefully monitored, especially those with a personal or family history of migraine.

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Medication-overuse headache (MOH) has been described in association with (episodic) migraine,[1] chronic tension-type headache,[2] hemicrania continua,[3] and new daily persistent headache.[4] It seems that the regular and frequent use of these medications, i.e., several treatment days each week for several months, is important in the development of MOH. The development of MOH has been suggested to occur in cluster headache (CH) in patients with a personal history of migraine.[5] The development of a chronic daily headache (CDH) has been described in 3 patients with CH using subcutaneous (SC) sumatriptan 6 mg within the recommended dosing schedule of a maximum of two injections per day.[6] An increase in CH attack frequency has been described by three authors in patients using long-term treatment with SC sumatriptan.[7-9] Other authors have given accounts of the uneventful overuse of sumatriptan by CH patients,[10-12] and MOH in association with CH is not a widely recognized problem.[13] One of us has previously reported 2 patients with CH who developed ergotamine-induced headache.[14]

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The full spectrum of MOH in CH patients has never been formally described, perhaps because of the comparably low population prevalence of CH of approximately 0.3%.[15] However, given the high attack frequency in CH, these patients may be particularly at risk for development of MOH. A prospective study in migraine patients has indeed shown that a high attack frequency is a predictor of the development of MOH.[16] We report on the development of daily headache associated with medication overuse in 17 patients with CH and propose that it is linked with a shared background of migrainous biology in the majority of patients. The work was reported in preliminary form at the Migraine Trust International Symposium, London, September 2004.[17]

Methods. The study group included individuals attending the National Hospital for Neurology and Neurosurgery, London, United Kingdom (n = 11), and patients attending the Neurology Department at the University of Münster, Münster, Germany (n = 6).

The Ethics Committee of the National Hospital for Neurology and Neurosurgery approved the study. Ethics approval is not required for a retrospective chart review in Germany.

Patients with medication overuse according to the criteria of the International Headache Society[18] were identified from our databases by hand searching our clinical records that contain details of medication use. A standardized questionnaire was used for those patients from the National Hospital for Neurology and Neurosurgery.

Headache classification was consistent with the criteria of the

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Table 1 *Characteristics of cluster headache*

Patient no., sex, age	1, M, 51 y	2, F, 28 y	3, M, 50 y	4, M, 37 y	5, F, 49 y	6, M, 40 y	7, M, 58 y	8, F, 32 y	9, M, 37 y
Source	NHNN	NHNN	NHNN	NHNN	NHNN	NHNN	NHNN	NHNN	NHNN
CH type	ECH	ECH	CCH	CCH	ECH	ECH	CCH	CCH	ECH
Side	Right/Left	Right	Right	Left	Right/Left	Right/Left	Right	Right	Right/Left
Nature	Searing	Excruciating	Searing	Searing	Excruciating	Constant, severe	Pressing, throbbing, sharp	Stabbing, sharp	Boring, burning, stabbing
Lacrimation	✓	✓	✓	✓	✓	✓	✓	✓	✓
Conjunctival injection	✓	✓	✓	✓	x	✓	✓	✓	x
Nasal block	✓	✓	✓	✓	✓	✓	✓	x	x
Rhinorrhea	x	✓	✓	✓	✓	✓	✓	x	✓
Eyelid swelling/ptosis	✓	✓	✓	✓	x	x	✓	✓	✓
Restless	✓	✓	✓	✓	✓	✓	✓	✓	✓
Nausea	x	✓	x	✓	x	x	✓	x	x
Vomiting	x	x	x	✓	x	x	✓	x	x
Photophobia	x	✓	x	✓	x	✓	✓	x	✓
Phonophobia	x	✓	x	✓	x	✓	x	x	✓
Osmophobia	x	✓	x	✓	x	x	x	x	✓
Aura	x	x	x	x	✓	x	✓	x	x

CH = cluster headache; ECH = episodic cluster headache; CCH = chronic cluster headache; NHNN = National Hospital for Neurology and Neurosurgery, London, United Kingdom; UDNM = University Department of Neurology, Münster, Germany.

International Headache Society[18] and was made by one of the authors.

Results. From a total of 430 individuals with CH from the National Hospital for Neurology and Neurosurgery and the University of Münster Neurology Department, 17 individuals also gave a history of CDH associated with medication overuse. The prevalence of MOH among CH patients is therefore approximately 4% in our series. The details of the 17 individual patients are provided in table 1.

Cluster headache characteristics. There were 13 men and 4 women with CH (table 1). The mean age of the patients at presentation to the National Hospital for Neurology and Neurosurgery or University of Münster Neurology Department was 44 years (range 28 to 59 years). Their mean age at onset of CH was 30 years (range 8 to 49 years). Seven patients had episodic and 10 had chronic cluster headache according to the International Classification of Headache Disorders.[18] Two patients (Patients 5 and 7) experienced aura symptoms during CH attacks.[19,20] They had a personal history of migraine (Patient 5) or a family history (Patient 7). CH attacks were sometimes accompanied by gastrointestinal symptoms, such as nausea (5/17) and vomiting (3/17); photophobia (9/17) and phonophobia (6/17) were also common.[20]

Characteristics of daily headache. The most common phenotype (8/17) was a bilateral, dull, and featureless headache (table 2). The headache had unilateral characteristics in only 3 patients. It was throbbing in 5 of 17. The two most common associated features were nausea (6/17) and exacerbation with head movement (5/17). Photophobia (3/17), phonophobia (2/17), and osmophobia (2/7) were less common. Vomiting was present in 1 patient. In at least 5 patients (Patients 2, 3, 9, 10, and 11) the pain exacerbated episodically, with a frequency ranging from five times per week to once per month.

Background headache history. A remarkable 15 of 17 patients had a personal (5/17) or family (11/17) history, or

Table 2 *Characteristics of daily headache*

Patient no.	1	2	3	4	5	6	7	8	9
Laterality	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Unilateral	Bilateral	Unilateral/ Bilateral
Nature	Dull	Mild	Throbbing	Throbbing	Throbbing	Ache	Dull	Ache	Ache
Exacerbation with movement	x	✓	✓	x	✓	x	x	x	x
Nausea	x	x	✓	✓	x	x	✓	x	x
Vomiting	x	x	x	x	x	x	x	x	x
Photophobia	x	x	✓	x	x	x	x	x	x
Phonophobia	x	x	x	x	x	x	x	x	x
Osmophobia	x	x	x	x	x	x	x	x	x
Aura	x	x	x	x	x	x	x	x	x
Past history migraine	x	x	✓	x	✓	x	x	x	x
Family history migraine*	✓	✓	x	x	x	✓	✓	✓	✓

* Family history in parent or sibling, except for Patient 6 (paternal uncle), Patient 8 (maternal grandmother), and Patient 11 (maternal uncle).

Table 1 *Continued*

Patient no., sex, age	10, M, 53 y	11, F, 36 y	12, M, 59 y	13, M, 46 y	14, M, 59 y	15, M, 33 y	16, M, 46	17, M, 40 y
Source	NHNN	NHNN	UDNM	UDNM	UDNM	UDNM	UDNM	UDNM
CH type	CCH	CCH	CCH	ECH	CCH	CCH	CCH	ECH
Side	Right	Right/Left	Right	Left	Right	Right	Left	Right
Nature	Excruciating	Excruciating	Excruciating	Excruciating, stabbing	Excruciating	Excruciating	Excruciating	Excruciating
Lacrimation	✓	✓	✓	✓	✓	✓	✓	✓
Conjunctival injection	✓	✓	✓	✓	✓	✓	✓	✓
Nasal block	✓	x	✓	x	✓	✓	✓	✓
Rhinorrhea	x	✓	✓	x	✓	✓	x	✓
Eyelid swelling/ptosis	x	✓	✓	✓	x	✓	✓	x
Restless	✓	✓	✓	✓	✓	✓	✓	✓
Nausea	x	✓	✓	x	x	x	x	x
Vomiting	x	✓	x	x	x	x	x	x
Photophobia	✓	✓	x	✓	x	✓	x	x
Phonophobia	x	✓	x	x	x	✓	x	x
Osmophobia	x	✓	x	x	x	x	x	x
Aura	x	x	x	x	x	x	x	x

both, of migraine. The family history of migraine was in a parent or sibling, except for 3 patients (Patient 6: paternal uncle; Patient 8: maternal grandmother; Patient 11: maternal uncle). Two more patients gave a family history of unspecified headache in their mother (Patient 4) and both parents (Patient 17). No aura symptoms were described associated with the CDH, even though 2 patients (Patients 3 and 5) had a personal history of migraine with aura. Of the 8 patients with the bilateral, dull, and featureless headache, 6 had a family history of migraine, 1 had a personal history, and 1 had no personal or family history of migraine. Of the 9 other patients who had at least one migrainous feature, 3 gave a personal history of migraine, 1 had a personal and family history, 4 had a family history only, and 1 had no personal or family history of migraine.

Spectrum of medication overuse. The patients used or overused a wide spectrum of drugs (table E-1 on the *Neurology* Web site at www.neurology.org), including simple analgesics (acetylsalicylic acid, paracetamol, and nonsteroidal anti-inflammatory drugs; n = 9), opiates (meperidine/pethidine, codeine, dihydrocodeine, tramadol, dextropropoxyphene, and tilidine; n = 10), ergotamine (n = 3), caffeine (n = 1), triptans (rizatriptan and sumatriptan; n = 14), and diazepam (n = 1). From our retrospective analysis, it is not always clear whether a patient was overusing a particular drug. This is especially relevant to sumatriptan, which was used as an effective acute treatment by most patients. It should be noted that of the 14 patients using triptans, this drug was exclusively related to the development of MOH in 4 of them (sumatriptan in Patients 3, 5, and 12; rizatriptan in Patient 10). The MOH in 3 of these patients (Patients 3, 10, and 12) qualifies as triptan-overuse headache according to the International Headache Society; in the other one (Patient 5), no withdrawal was attempted.[18] The role of sumatriptan in the other 10 patients is not clear; however, in 3 of them (Patients 4, 7, and 15), the headache could qualify as triptan-overuse headache according to the International Headache Society.[18] Otherwise, codeine (6/17), ergotamine (3/17), and acetaminophen (paracetamol) (7/17) stand out as overused drugs. Ergotamine-overuse headache was diagnosed in 1 patient (Patient 14), and opioid-

Table 2 *Continued*

Patient no.	10	11	12	13	14	15	16	17
Laterality	Bilateral	Bilateral/ Unilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral
Nature	Dull, throbbing	Dull, throbbing	Dull	Dull	Dull	Dull	Dull	Dull
Exacerbation with movement	✓	✓	x	x	x	x	x	x
Nausea	✓	✓	x	x	x	✓	x	x
Vomiting	x	✓	x	x	x	x	x	x
Photophobia	✓	✓	x	x	x	x	x	x
Phonophobia	✓	✓	x	x	x	x	x	x
Osmophobia	x	✓	x	x	x	✓	x	x
Aura	x	x	x	x	x	x	x	x
Past history migraine	x	✓	✓	x	x	✓	x	x
Family history migraine*	✓	✓	x	✓	✓	x	✓	x

overuse headache was diagnosed in another (Patient 9). Many patients used multiple drugs (11/17), so a singular MOH association could not be diagnosed. All 17 patients in this series were overusing medication on a daily or near daily basis. Because of the retrospective nature of this study, it is not possible to describe the temporal relationship between the medication overuse and the development of MOH. However, medication withdrawal was attempted, sometimes spontaneously by the patient, and was successful in 13 patients. Strictly speaking, a diagnosis of MOH according to the International Headache Society Criteria can only be made in these 13 patients, because one of the criteria is that the headache must resolve or revert to its previous pattern within 2 months after discontinuation of the overused medication.[18]

The number of patients in this series is too small to compare withdrawal strategies, but it seems that both inpatient and outpatient withdrawal strategies were effective. Less than half of the patients were using effective preventive therapy for their CH. At least 4 patients (Patients 2, 4, 13, and 15) had never received an adequate long-term preventive treatment. From our retrospective data, we note relapses in 2 of our patients (Patients 9 and 13).

Discussion. We describe 17 patients out of a database of 430 patients with episodic and chronic CH, developing MOH associated with a range of monotherapies or varying combinations of drugs. All of these patients had a clear personal or family history of migraine, or regular headache. The data are consistent with the general thesis that migrainous biology confers in some important part the propensity for MOH in a subgroup of patients.[21] If this is true, the general principle is extremely important in advising patients on the treatment of headache.

In a significant number of patients, migrainous features were present during CH attacks, and some had aura, as has been reported.[19,20] Gastrointestinal symptoms, such as nausea and vomiting, during CH attacks have been previously described, as have photophobia and phonophobia.[20,22] In general, when present, photophobia or phonophobia in CH patients is much more often homolateral to the pain than in patients with unilateral migraine.[23]

In this series, the largest group of patients overused multiple analgesics, whereas a specific triptan-overuse headache diagnosis was made in 3 patients, an opioid-overuse headache diagnosis was made in 1 patient, and an ergotamine-overuse headache diagnosis was made in 1 patient. It has been observed in migraine that triptans have the lowest critical monthly intake frequency for inducing MOH, with an average of 18 single doses per month.[24] More than half of our patients were not using adequate preventive therapy, and 4 had never tried a preventive. It is not known whether, similar to migraine, adequate prevention of CH can only be obtained in an individual withdrawn from overused symptomatic medication. Withdrawal may be necessary anyway because of serious health hazards associated with medication overuse, such as analgesic nephropathy,[25] nonsteroidal anti-inflammatory drug gastropathy,[26] or ergotism.[27] Although resolution of headache is required for the International Headache Society diagnosis of MOH, this probably is too stringent, and perhaps for such headache, substantial reduction in frequency or marked alteration of pattern, such as we observed with Patient 7, should be considered as indicating a relationship to a secondary cause. We have recently seen that such a modification is desirable when considering headache related to pituitary tumors.[28] It seems plausible that after a substantial biologic change, return to baseline may take a long time or indeed not occur.

In approximately half of our patients, the MOH was bilateral, dull, and featureless, whereas the headache in the other half had at least one migrainous feature. These data are in line with a previous prospective study in migraine patients showing that approximately 60% developed a tension-type headache phenotype with medication overuse.[24] The development of MOH seems to be most closely related with a personal or family history, or both, of migraine, rather than with the type of medication overused. Assuming the prevalence of migraine among people with CH is similar to that among the general population, although a wide range has been reported, from rare[29] to 65%,[30] one could predict the co-incidence. The population prevalence of migraine is approximately 15%,[31] and the population prevalence of MOH is approximately 1%, most of which are migraine patients.[32,33] From these numbers, it can be derived that the percentage of migraine patients developing MOH is similar to that of CH patients in our series (4%). It seems unlikely that our findings were simply a chance association. Fifteen of the 17 patients had a clear familial history of migraine, whereas the 2 who did not had parents with "headaches." It seems entirely possible, indeed consistent with data from the development program for a migraine screener[34] and recent data on family history and headache severity,[35] that the parents had severe enough headache for their children to notice it perhaps because it was migraine. Previously, we have reported that 26% of a large CH cohort had a history of migraine, and 33% had a family history of migraine.[20] A subgroup of patients taking analgesics for a rheumatologic indication develop daily headache and have a history of migraine,[21] remarkably three times as many taking regular analgesics, have a history of migraine, and do not develop daily headache. Prospective studies show that overuse of analgesics predicts chronic pain in migraine patients[36] and frequent headache.[37] A Chinese study also showed that analgesic overuse and a history of migraine were identifiable risk factors for CDH in the elderly,[38] suggesting that this biologic propensity transcends ethnicity. Taken together, these data suggest that migraine plus some other factor is required for the development of MOH.

From a management point of view, it is important to recognize that CH patients with a previous history

of migraine may be at risk. Subcutaneous sumatriptan and high-flow oxygen are considered to be the most effective abortive treatments for CH. Acute treatments not supported by evidence, such as opiates, combination analgesics, and oral triptans, should be avoided particularly in CH patients with a personal or family history of migraine. Oxygen 100%, administered at 7 to 12 L/minute through a nonrebreathing mask for 15 to 20 minutes, aborts headache in 70% of cases within 15 minutes and is safe, cost-effective, and well tolerated.[39] Subcutaneous sumatriptan renders 74% of patients improved by 15 minutes[40] and should be made available to CH patients up to twice daily. Withdrawal of sumatriptan should only be considered if MOH develops while the patient is receiving the maximal daily recommended dose of subcutaneous sumatriptan. Given the excruciating nature of the pain in CH, however, it may be unethical to withdraw a patient with MOH from sumatriptan in the absence of another effective abortive agent without providing a strategy to control the problem. In this context, and perhaps paradoxically, we find IV dihydroergotamine to be extremely useful in the management of triptan withdrawal in CH. The pain of CH is much worse than that of MOH, and therefore, most patients would rather have the MOH than CH.

Optimization of preventive therapy is another strategy to minimize the risk of development of MOH by reducing the number of CH attacks. If migraine and CH are coexisting, both should be treated.[41] Withdrawal of symptomatic medications was successful in all patients who underwent it in our series. It should be noted that, in contrast to withdrawal in migraine patients with MOH, withdrawal in CH patients with MOH does not seem to be associated with significant changes in the CH frequency-duration-severity, which may contribute to relapses of medication overuse. A prospective study in the CH population is awaited to answer remaining questions, including the mean critical monthly intake frequencies and mean critical monthly dosages of various drugs in susceptible individuals.

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