

Osmophobia in allodynic migraineurs: cause or consequence of central sensitization?

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Abstract Migraine is a primary headache characterized by recurrent attacks of head pain associated with nausea or vomit, photophobia, phonophobia and osmophobia. The presence of osmophobia during migraine attacks seems to be a very specific complaint. Cutaneous allodynia (CA) is very common in migraineurs, and it is the most evident clinical manifestation of central sensitization, a mechanism involved in migraine chronification. This study was aimed at identifying the possible correlation between osmophobia and CA in migraineurs. 673 migraineurs were studied (492 episodic, 181 chronic). The prevalence of both CA and osmophobia was higher in chronic than in episodic migraineurs. The association between these two symptoms was significant in chronic migraineurs at Chi square test. The highlighted relationship between CA and osmophobia may be interpreted in different ways: central sensitization induced by recurrent pain stimulation may in parallel induce a distortion of both cutaneous sensitivity (CA) and olfaction (osmophobia); alternatively, the recurrent olfactory stimulation in subjects with a hypersensitivity to olfactory stimuli may co-work with repetitive pain stimulation to induce the central sensitization process.

Keywords Migraine · Chronic migraine · Osmophobia · Cutaneous allodynia

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Background

Migraine is a primary headache characterized by recurrent attacks of head pain associated with nausea or vomit, and with hypersensitivity to external stimuli. This cohort of symptoms is the expression of a hyperactive and hypometabolic brain [1] that, episodically, needs to restore a normal energetic level by resting and avoidance of stimulations. Osmophobia seems to be a very specific complaint, although not included in the diagnostic criteria of migraine [2]. Moreover, neuroimaging studies found evidences that olfactory stimulation during a migraine attack increases activity in the rostral part of the pons, a region thought to play a central role in migraine pain [3]. Migraine-associated cutaneous allodynia (CA) is the most evident clinical manifestation of central sensitization that in turn is a process of transformation of the nuclei of the pain matrix, principally induced by recurrent painful stimulations, at least among predisposed subjects [4]. In fact, central sensitization-induced CA may be found in most but not all chronic migraineurs and, on the contrary, it can be observed also in patients with a very low frequency of attacks [5].

Aim of the study

The aim of the study was to identify the possible relationship between osmophobia and CA in migraineurs.

Materials and methods

Population

The study included 673 migraineurs consecutively evaluated at the Headache Center of the L. Sacco Hospital

of Milan during the year 2013. The cohort comprised 101 males and 572 females (mean age 38.4 ± 13.7 years).

Diagnostic criteria

Diagnosis of episodic migraine was made according to the ICHD-II criteria [6]; the diagnosis of chronic migraine was made according to the criteria proposed by Silberstein and Lipton [7].

The presence of CA was assessed by asking the patients a set of standardized questions, already used in previous studies of our group [8]. The patient was asked to give yes/no responses to written questions as follows: (1) Have you experienced abnormal scalp sensitivity or discomfort during headache attacks? (2) If yes, does this abnormal sensitivity or discomfort arise from (a) touching head skin; (b) touching hair; (c) combing hair; (d) brushing hair; (e) wearing glasses; (f) using a hair-band, curlers or ponytail; (g) lying with head resting on the pain side? Patients replying yes to the first question and at least to one of the following options (a–g) were considered to have CA.

Presence of osmophobia was evaluated by asking patients if smells or intense perfumes were avoided during headache attacks and/or were able to induce intense discomfort.

Statistical analysis

The prevalence of osmophobia and of CA was calculated. Chi square test with Bonferroni correction was used to assess the correlation between these two symptoms.

Results

Prevalence of CA

About half of the included patients complained CA during migraine attacks. CA was more prevalent among chronic versus episodic migraineurs (60.8 vs 49.2 % $p = 0.009$ at Chi square test).

Prevalence of osmophobia

Migraine-associated osmophobia was complained by 24.1 % patients from the total sample, with a slightly higher prevalence among chronic versus episodic migraineurs, not significant at Chi square test.

Relationship osmophobia: CA

Among the 161 osmophobic subjects, prevalence of CA was 57.8 %, while among the 508 subjects without

osmophobia, 50.6 % were allodynic, without significant differences ($p = 0.10$).

In the sub-group of chronic migraineurs, the prevalence of CA was higher among osmophobic with respect to non-osmophobic patients (73.9 vs 56.7 %, $p = 0.03$).

No difference was found in terms of prevalence of CA between osmophobic and non-osmophobic patients (51.3 vs 48.4 %, $p = 0.52$) in the episodic migraine sub-group.

The prevalence of CA among all the osmophobic patients was higher in chronic rather than in episodic migraineurs (73.9 vs 51.3 %, respectively, $p = 0.01$). On the other hand, among the 508 non-osmophobic migraineurs, no difference in prevalence of CA was found according to the different diagnostic groups (chronic vs episodic: 56.7 vs 48.4 %, $p = 0.10$) (Table 1).

Duration of migraine history

Duration and mean attack frequency were higher in allodynic patients with respect to non-allodynic ones: 19.5 vs 15.1 years ($p < 0.001$), and 11.2 vs 9.3 days/month, ($p = 0.002$), respectively.

Comparing osmophobic and non-osmophobic migraineurs, history of migraine was longer in osmophobic subjects: 21.1 vs 16.3 years ($p < 0.001$). Mean frequency of attacks was similar in the two groups, without significant differences (10.8 vs 10.1 days/month, $p = \text{NS}$).

Conclusions

We found that osmophobia was associated with a longer history of migraine in a clinical sample with different migraine forms, and that it was related to the presence of CA. These findings suggest that, similar to CA, osmophobia needs time and a history of repeated headache attacks to develop a pattern which suggests a process of hypersensitization.

A previous work on this field seems to support this hypothesis [2]: ictal osmophobia during migraine attacks was found to be related to a broader sensorial hypersensitivity.

On the other hand, the observation that osmophobia, exactly as CA, may also be reported at the onset of a migraine history, and that also people with episodic migraine often report being osmophobic, both during and between acute migraine attacks, may suggest another possible explanation of the observed relationship between osmophobia and allodynia. By this viewpoint, osmophobia may be seen as the expression of a particular hypersensitivity to olfactory stimuli. Among these hypersensitive patients, olfactory stimulations might sensitize pain matrix nuclei, like

Table 1 Correlation of CA and osmophobia in episodic and chronic migraineurs

Osmophobic patients (<i>N</i> = 161)	Chronic migraine (<i>N</i> = 46)	Allodynic	34	73.9 %	<i>p</i> = 0.01
		Non-allodynic	12	26.1 %	
	Episodic migraine (<i>N</i> = 115)	Allodynic	59	51.3 %	
		Non-allodynic	56	48.7 %	
Non-osmophobic patients (<i>N</i> = 508)	Chronic migraine (<i>N</i> = 134)	Allodynic	76	56.7 %	<i>p</i> = 0.10 (NS)
		Non-allodynic	58	43.3 %	
	Episodic migraine (<i>N</i> = 374)	Allodynic	181	48.4 %	
		Non-allodynic	193	51.6 %	

repetitive painful stimulations. Other works, focused on photophobia, put in evidence the possibility that multiple different stimulations, such as the optic one, may converge the neuronal firing on nuclei of the pain pathway reinforcing the sensitisation process [8]: likewise, olfactory stimulation may act in the same way in hypersensitive subjects. The presence of ictal osmophobia also in patients with episodic forms of migraine in which CA is not present seems to reinforce this second physiological explanation. On the contrary, a recent work on episodic migraineurs [9] did not found differences between patients and controls in term of “olfactory identification ability”, apparently in contrast with the hypothesis that the hypersensitivity to olfactory stimulation may contribute to the sensitization process. In fact, this statement is not entirely true: the study was limited to episodic migraineurs and it did not separate osmophobic migraineurs from non-osmophobic neither clinically hyperosmic from non-hyperosmic. It may be possible that these subgroups have a different olfactory identification ability, and consequently a different intensity in the neuronal firing from olfactory structures toward pain matrix nuclei. Furthermore, the same olfactory identification ability may lead to different effects on head pain nuclei of controls, as they do not have a “migraine brain”.

In conclusion, we found a relationship between CA and osmophobia, particularly in patients with chronic migraine. This finding may contribute to the insight in the neuronal abnormalities of the “migraine brain”, and in the mechanisms leading to migraine chronification. The correlation between these peculiar symptoms of migraine may be interpreted in different ways: is osmophobia a cause or consequence of central sensitization in allodynic

migraineurs? The above-discussed hypotheses should be tested in further studies, possibly comparing prospectively the frequency of osmophobia, hyperosmia, and CA, since the onset of a migraine history.

Conflict of interest There is no actual or potential conflict of interest in relation to this article.

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