



Characterization of adult patients with a diagnosis of migraine and osmophobia: the osmograïne study

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Abstract

Introduction

Osmophobia is associated with a greater intensity of the headache, a more significant presence of affective symptoms, and the appearance of cutaneous allodynia.

Objectives

To determine the sociodemographic and clinical characteristics of patients with episodic and chronic migraine associated with osmophobia.

Methods

A cross-sectional analytical observational study, 100 patients were included.

Results

65% of the patients presented osmophobia, 64.6% of patients with osmophobia had chronic migraine, and 35.4% had episodic migraine without statistically significant differences $p=0.120$. Regarding the clinical characteristics, pulsatile pain was the most frequent in 49%, and severe intensity was present in 81%. Statistically significant relationships were found between osmophobia and photophobia ([95.4 vs 77.1]; $p=0.005$), phonophobia ([96.9 vs 74.3]; $p=0.001$) and allodynia ([75.4 vs 45.7]; $p=0.002$). The that become chronic factors were more frequent in the group with osmophobia, in which an association with the excessive use of analgesics ([43.8% vs. 22.9%]; $p=0.029$) and a history of anxiety and depression ([32.8% vs. 14.3%]; $p=0.045$). In the multivariate model, the variables associated with osmophobia with statistically significant differences were photophobia, allodynia, and botulinum toxin application.

Conclusions

In this first study of osmophobia in migraine in Colombia, osmophobia is a frequent symptom in patients with chronic migraine; it has related to markers of central sensitization; it is also related to that become chronic factors and the use of botulinum toxin. Therefore, it is likely that osmophobia can predict the risk of that factor, causing the disease to become chronic.

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Introduction

Migraine is the most frequent primary headache (1,2); it generates disability and social, interpersonal, work, and academic difficulties (3,4). Among the clinical characteristics, migraine presents associated symptoms such as nausea, vomiting, and hypersensitivity to external stimuli, including photophobia, phonophobia, and osmophobia (5). Osmophobia is defined as intolerance to odors (6), a frequent symptom of migraine. However, it is currently not considered within the criteria for its diagnosis, even though it is a particular symptom, even more so than a migraine. photophobia or phonophobia (7–9). It is also helpful in the differential diagnosis between migraine and other primary headaches and between migraine and secondary headaches (10–12). Additionally, osmophobia is more frequent in patients with chronic vs. episodic migraine (13). This relationship with chronic migraine could be supported by studies indicating that osmophobia is associated with a greater intensity of the headache, a more significant presence of affective symptoms, particularly anxiety (14), as well as the appearance of cutaneous allodynia; considered as a factor that makes migraine chronic (15,16). In Colombia, no studies evaluate the frequency of osmophobia in patients with migraine. This study aimed to determine the association of osmophobia with the sociodemographic and clinical characteristics of patients with episodic and chronic migraine.

Methods

Osmograin was a cross-sectional analytical observational study whose target population was patients diagnosed with episodic migraine and chronic migraine assessed in the specialized headache clinic at Hospital Occidente de Kennedy in Bogotá, Colombia.

Participants

A neurologist performs patients diagnosed with episodic migraine and chronic migraine. The patient's diagnosis followed the ICHD-III (International Headache Classification Criteria), ages between 18 and 60 years; the exclusion criteria were: pregnancy and active infection by the SARS-CoV-2 virus.

For the patients selected from the database of the specialized headache clinic of the West Kennedy Hospital, a random sampling technique uses, and patients with a diagnosis of migraine established in the clinical history take into account. The selected patients had prior informed consent, a survey-type instrument through the free program Google Forms. Sociodemographic variables (age, gender, marital status), clinical variables (frequency of migraine, type of pain, the intensity of pain using the visual analog pain scale, associated symptoms: photophobia, phonophobia, osmophobia, allodynia; excessive use of analgesics) collects defined by ICHD III as habitual use of acetaminophen, ASA,

NSAIDs, for ≥ 15 days/month in a period of >3 months or habitual use of opioids, ergotamines, triptans for ≥ 10 days/month in a period of >3 months; and use of botulinum toxin as a preventive medication). The diagnosis of depression or anxiety in patients who had received a previous medical diagnosis and this work was approved by the Research Ethics Committee of Hospital Occidente de Kennedy under Act No. 12 of 2022.

Sample size

The sample size calculates considering a reported prevalence of osmophobia of 24% (11), 95% confidence, and 80% power; a total of 98 subjects were considered. Epidat 3.1 software (17) uses.

Statistic analysis

The qualitative variables were described in absolute and relative frequencies, and the quantitative variables in measures of central tendency and dispersion following the assumption of normality evaluated by the Shapiro-Wilk test. The squared X² test or Fisher's exact test compares qualitative variables between the group with and without osmophobia. The Student's t or Mann-Whitney U test uses for the quantitative variables according to their distribution. A multivariate logistic regression model to determine the variables associated with the presence of osmophobia. Variables with biological plausibility and p-value <0.25 in the bivariate analysis were included in the model. The model evaluates the area under the curve and the Hosmer-Lemeshow test. All the statistical tests were two-tailed; a p-value <0.05 was considered statistically significant. Stata 16 software was used (18).

Results

A total of 100 participants were included in the study, 35% without osmophobia and 65% with osmophobia (Table 1). The average age of the total population was 39.9 years; the group with osmophobia was 38.8 years younger compared to the group without osmophobia, 41.8 years. Without differences in both groups, the female sex was predominant in the group, and for 95% of the participants, the median age of migraine onset was 17 years. 64.6% of patients with osmophobia had chronic migraine, and 35.4% had episodic migraine without significant differences $p=0.120$. Regarding pain characteristics, pulsatile pain was the most frequent in 49% of the population, and severe intensity was present in 81%. Significant differences were found in the associated symptoms between the groups with and without osmophobia with photophobia ([95.4 vs. 77.1]; $p=0.005$), phonophobia ([96.9 vs 74.3]; $p=0.001$) and allodynia ([75.4 vs 45.7]; $p=0.002$). In the group of patients with osmophobia, excessive use of analgesics was more frequent ([43.8% vs. 22.9%]; $p=0.029$), and a



history of anxiety and depression ([32.8% vs. 14.3%]; $p=0.045$), as well as the application of botulinum toxin ([49.2% vs 17.1%]; $p=0.002$) and were statistically significant.

Table 1. General characteristics of the population

Variables	Total population n=100	Without Osmophobia n=35	With Osmophobia n=65	P
Years old	39,9 ± 11,9	41,8 ± 13,2	38,8 ± 11,3	0,246
Sex (female)	95 (95,0)	33 (94,3)	62 (95,4)	0,810
Civil status				
Married	12 (13)	8 (22,9)	5 (7,7)	
Separate	4 (4,0)	1 (2,9)	3 (4,6)	
Single	55 (55)	16 (45,7)	39 (60)	0,168
Free Union	28 (28)	10 (28,6)	18 (27,7)	
Age at onset of migraine (years)	17 (14 - 22)	18 (14 - 22)	17 (14 - 21)	0,766
Migraine type				
Chronic	59 (59)	17 (48,6)	42 (64,6)	
Episodic	41 (41)	18 (51,4)	23 (35,4)	0,120
Pain type				
Oppressive	23 (23)	9 (25,7)	14 (21,5)	
Pulsatile	49 (49)	17 (48,6)	32 (49,2)	0,872
Stitch	28 (28)	9 (25,7)	19 (29,2)	
Pain intensity				
Mild - Moderate	19 (19)	8 (22,9)	11 (16,9)	
Severe	81 (81)	27 (77,1)	54 (83,1)	0,471
Photophobia	89 (89)	27 (77,1)	62 (95,4)	0,005
Phonophobia	89 (89)	26 (74,3)	63 (96,9)	0,001
Allodynia	65 (65)	16 (45,7)	49 (75,4)	0,002
Use of pain relievers	98 (98)	34 (97,1)	64 (98,5)	0,653
Type of pain relievers				
Acetaminophen	16 (16)	6 (17,1)	10 (15,4)	0,819
NSAIDS	72 (72)	27 (77,1)	45 (69,2)	0,401
Ergotamines	9 (9,0)	3 (8,6)	6 (9,2)	0,912
Triptans	9 (9,0)	3 (8,6)	6 (9,2)	0,912
Opioids	4 (4,0)	0 (0,0)	4 (6,2)	0,134
Excessive use of pain relievers	36 (36,4)	8 (22,9)	28 (43,8)	0,039
Botulinum toxin use	38 (38)	6 (17,1)	32 (49,2)	0,002
History of depression or anxiety	26 (26)	5 (14,3)	21 (32,8)	0,045
History of COVID-19 infection	27 (27)	8 (22,9)	19 (29,2)	0,493

Values as mean and standard deviation, median (p25 – p75), n and (%)

The variables included in the multivariate model (Table 2) were age, sex, chronic migraine, photophobia, allodynia, and use of botulinum toxin. Of these, those associated with the presence of osmophobia were photophobia ([OR 13.888; 95% CI 2.280 - 84.600] $p=0.004$), allodynia ([OR 3.023; 95% CI 1.069 - 8.543] $p=0.037$) and botulinum toxin ([OR 5.543, 95% CI 1.614 - 18.967], $p=0.006$) -Hosmer Lemeshow test $p=0.544$.

Table 2. Multivariate logistic regression model

Multivariate model	OR	CI 95%	P value
Years	0,980	0,943 - 1,019	0,332
Sex	2,222	0,257 - 19,178	0,468
Chronic Migraine	1,215	0,429 - 3,439	0,713
Photophobia	13,888	2,280 - 84,600	0,004
Allodynia	3,023	1,069 - 8,543	0,037
Botulinum toxin	5,534	1,614 - 18,967	0,006

OR: odds ratio, 95% CI: 95% confidence interval, p-value: less than 0.05 statistically significant.



Discussion

In our study, a prevalence of osmophobia of 65% was found in patients diagnosed with migraine. This prevalence was higher compared to studies that have described a prevalence of 33% (19); it was lower than others, reported 84% (20) and similar to that reported by other studies (21). However, it is within the values reported in the scientific literature, with a prevalence ranging from 24 to 95% (11). In addition to the high frequency of osmophobia in migraine, which helps to differentiate it from other primary headaches (22,23), considered by some authors as a specific marker to differentiate migraine from tension-type headache (12) and even a critical value has been described as a characteristic related to chronic migraine compared to episodic migraine (24). The latter may support by functional neuroimaging studies in chronic pain that show changes in the connectivity of the prefrontal cortex, which is involved in the olfactory pathway (25). In this study, osmophobia was more frequent in patients with chronic migraine vs. episodic migraine; However, this relationship was not statistically significant, it is consistent with studies reported so far that describe a relationship between chronic migraine and osmophobia (13,24). Among the results of this study, the presence of osmophobia in patients with migraine had a statistically significant relationship with symptoms such as photophobia, phonophobia, and allodynia, which are part of the most frequent clinical characteristics associated with patients diagnosed with migraine (26). In addition, the relationship between photophobia and allodynia confirms in the multivariate model. Of these, allodynia shows to be a marker of central sensitization (27) which is also related to the duration, severity, and disability of migraine attacks and osmophobia (28); in fact, studies mention that, in those subjects with hypersensitivity to stimuli, for example, olfactory, recurrent olfactory stimulation, as well as recurrent painful stimulation, could induce the central sensitization process (29). That osmophobia should be considered a phenomenon of central sensitization, just like allodynia (13). This central sensitization may explain by several hypotheses, including (a) increased activity in the rostral region of the pons (which has link to migraine attack pain) in response to olfactory stimulation (6), (b) Habituation (a process of decreased sensory perception to a repetitive stimulus involving the anterior insula, middle cingulate cortex, and thalamus) is usually decreased in migraine patients and is involved in the central sensitization process (30,31). Functional imaging studies have shown increased regional cerebral blood flow in the piriform cortex, which plays a vital role in the olfactory habituation process, and this could interpret as a lack of normal habituation in response to permanent environmental olfactory stimulation (32). (c) In migraine, there is the activation of different brain networks, such as the neurologic network (amygdala

and hypothalamus) and thalamic pain control networks (thalamic dysrhythmia), which could generate differences in olfactory and trigeminal processing (33,34). All these theories suggest an increased response to olfactory stimuli or dysfunction of several regions related to pain and smell in patients with migraine (32). That the presence of osmophobia had a statistically significant relationship with symptoms such as anxiety and depression and with the excessive use of analgesics, which are part of the most important modifiable factors that makes migraine become chronic for migraine (35), as well as obtaining a statistically significant difference with the use of botulinum toxin which indicates in the treatment of patients with chronic migraine (36) and this relationship was confirmed in the multivariate model, these findings are consistent with the literature that describes a relationship between osmophobia and anxiety (14) since odors have shown to cause significantly greater activation of the limbic system during migraine attacks (6); In addition, the structure that is most frequently activated is the amygdala, which is related to the pathophysiology of affective disorders and anxiety (37). Within the limitations of our study, we found that it is a cross-sectional study; an objective measure or validated scale for allodynia and depression was not used. Despite this, established diagnostic criteria for depression were taken into account. Headache diaries are not used, although migraine diagnoses in the clinical history according to the ICHD-III criteria. The study was developed after the Covid-19 pandemic, taking into account that active infection by the SARS-CoV-2 virus can cause dysfunction in olfactory processing networks (38), which could interfere with the presence of osmophobia; however, the Patients with active infection not take into account, and history of SARS-CoV-2 infection was not statistically significant. Among the strengths of our study, it describes results that coincide with those described in the literature, a fully complete questionnaire.

Conclusion

This is the first study in Colombia that characterizes patients diagnosed with migraine and osmophobia. Osmophobia has a high prevalence in our population, and it is a symptom that, in addition to being more frequent in patients with chronic migraine, has been related to the presence of factor that makes migraine become chronic (anxiety/depression, excessive use of analgesics) and the use of toxins botulinum. Additionally, osmophobia was associated with markers of central sensitization, such as allodynia, and symptoms, such as photophobia and phonophobia, so that osmophobia could predict the risk of factor that makes migraine chronic. This study could be considered a first step toward a multicenter study that includes a more significant number of patients, which allows for extrapolating the data and confirming hypotheses.



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