

Osmophobia and Odour-triggered Headaches – Review of the Literature and Main Research Centres

Raimundo Pereira Silva-Néto¹ and Adriana Almeida Soares²

1. Federal University of Piauí, Teresina, Brazil; 2. Center of Neurology and Headache of Piauí, Teresina, Brazil

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There is an important relationship between odours and primary headaches. Patients may present osmophobia during headaches and odours may trigger headache attacks. This review aimed to describe the studies on osmophobia, odour-triggered headache, the main researchers and their research centres. Publications on the relationship between odours and primary headaches were searched in 193 sovereign countries and 48 dependent territories in all continents. We consulted the PubMed database and used the descriptors: “osmophobia in [name of the country or territory]”; “odours and headache in [name of the country or territory]” and “smell and headache in [name of the country or territory]”. A total of 254 articles were found, but only 31 articles were considered relevant and composed this review. Of the 31 articles, 90.3% were cross-sectional studies, 6.5% case reports and 3.2% systematic reviews. All studies were performed on three continents: Europe (45.2%), America (32.2%) and Asia (22.6%). For the purpose of this study, North America and South America have been classed as one continent. No research was developed in Africa or Australia. More than 50.0% of the studies were conducted in Italy and Brazil. Only five authors published 38.7% of the studies. Osmophobia during headache attacks was investigated in 67.7% of studies, and odour-triggered headache in 19.3%. Studies on osmophobia and/or odour-triggered headache were carried out in several countries. They were useful in differentiating between migraine and tension-type headache. This could improve the accuracy of diagnosis of migraine compared to the current criteria.

Keywords

Osmophobia, triggers, odours, primary headaches, migraine

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Corresponding Author: Raimundo Pereira Silva-Néto, Federal University of Piauí, Avenida Frei Serafim, 2280, Centro, Teresina, PI 64001-020, Brazil. E: neurocefaleia@terra.com.br

Several studies have demonstrated the relationship between odours and primary headaches.^{1–31} Generally, we observed a severe intolerance to odours, pleasant or unpleasant, during headache attacks.^{2,4–8,10,11,13–30} However, a limited number of studies showed that odours may trigger headache attacks in some patients, particularly in migraineurs^{1,3,6,7,9,24} and occasionally in cluster headache patients.^{12,18} This intolerance to odours is known as osmophobia, and according to two studies that investigated osmophobia in secondary headaches, it occurred during headache attacks only in the primary headaches.^{32,33} There is no description of osmophobia in secondary headaches yet. Some migraine patients may have osmophobia in the pain-free period.²

Many researchers have confirmed that osmophobia is a symptom associated with migraine.^{2,4–8,10,11,13–30} Despite such research, osmophobia is still not part of the diagnostic criteria for migraine.³⁴ In recent years, these studies were carried out in several countries. It is important to study the relationship between odours and primary headaches because they may improve the diagnostic accuracy of these headaches.^{2,3}

The objective of this study was to review the research on osmophobia in primary headaches and/or odours as a trigger of headache attacks that have been carried out worldwide. To date, there are no review articles on osmophobia, and to the best of our knowledge, this is the first article that reviews the publications on osmophobia and headache worldwide.

Methods

In this review, we researched the relationship between headaches and osmophobia in 193 sovereign countries and 48 dependent territories in all continents. For the purpose of this study, North America and South America have been classed as one continent. In Africa, America, Asia, Europe and Australia, the number of sovereign countries and dependent territories were, respectively: 54 and 4; 35 and 20; 47 and 3; 43 and 10; and 14 and 11.

We consulted the PubMed database and used the following combination of descriptors: “osmophobia in [name of the country or territory]”; “odours and headache in [name of the country or territory]” and “smell and headache in [name of the country or territory]”. For the three descriptors we found, 52, 80 and 122 articles, respectively.

Of the 254 articles found, we excluded those that appeared in more than one descriptor (60 articles) and those that did not have the purpose of researching the relationship between headache and odours (163 articles). After exclusions, 31 articles were considered relevant and composed this review. The origin of the article was defined by the nationality of the first author.

Results

Of the 31 articles, 90.3% (28/31) were cross-sectional studies, 6.5% (2/31) case reports and 3.2% (1/31) systematic review. All studies were performed on three continents: Europe (45.2%), America (32.2%) and Asia (22.6%). No research was developed in Africa or Australia (Table 1).

Research was conducted in many countries, but more than 50.0% (16/31) of the studies were conducted in Italy and Brazil. In relation to the researchers, we found that only five authors published 38.7% (12/31) of these studies (Table 2). The majority of studies investigated the presence of osmophobia. There were 13 comparative studies between migraine and other primary headaches or controls without headache,^{2,3,5,8,13,14,17–20,22,28,31} and 10 that evaluated only migraine patients.^{4,6,7,11,15,16,24,26,29,30} As for odour-triggered headache, there were six studies detected, two comparative studies between migraine and other primary headaches,^{1,3} two with migraine patients,^{7,24} and two case reports.^{9,12} However, there were six other studies where pathophysiological aspects of the association between odours and migraine were studied.^{5,10,21,23,25,27} Frequency of osmophobia during headache attacks in migraine patients ranged from 20.0–95.5%. When studies compared patients with migraine, tension-type headache, and cluster headache, osmophobia predominated in migraine patients. Odour-triggered headache was also more prevalent in migraine patients and ranged from 34.7–90.2% (Tables 2 and 3).

Discussion

While other studies on osmophobia or odour-triggered headache exist, for the purpose of this review we included only those that are indexed in PubMed. Since the 1980s, before the first classification of headache,³⁵ odours were known to trigger migraine attacks and in the pain-free period, some patients remain symptomatic because they present an extreme intolerance to odours.^{36–38} While not having the purpose of researching the relationship between odours and headaches, many studies cited osmophobia as a manifestation associated with headache.^{39–41} We observed that Italy, Brazil and America conducted more research on odours and headaches. In addition, the five authors who have published most of these studies were born in these three countries.^{1–5,7,8,14,15,18–20} We do not have a scientific argument for this fact, but curiously these three countries were pioneers in the study of migraine.

In the 1940s, in America, Harold George Wolff (1898–1962) and John Ruskin Graham (1909–1980) found that ergotamine caused contraction of dilated blood vessels during migraine attacks.^{42–44} In the 1950s, the Brazilian neurologist Edgard Raffaelli Jr (1930–2006) began studies on headaches in Latin America. Currently, Brazilians are the second largest number of members of the International Headache Society, second only to the number of North Americans.⁴⁵ In Italy, in the 1960s, Federigo Sicuteri (1920–2003) demonstrated the role of serotonin in the pathogenesis of migraine attack, therapeutic advances and pathophysiological knowledge.⁴⁶

In this review, we found that relationship between odour and headaches, and osmophobia is common in both adult and paediatric patients with migraine; although, frequency data of osmophobia

Table 1: Distribution of 31 studies on osmophobia or odour-triggered headache according to continent

Continents	Studies	
	n	%
Europe	14	45.2
America*	10	32.2
Asia	7	22.6
Australia	0	0.0
Africa	0	0.0

*For the purposes of this review, North America and South America have been classed as America.

and odour-triggered headache in migraine patients have been heterogeneous, ranging respectively from 20–86% and 34–70%. The methodology used in each study is probably responsible for these variations. Some authors have suggested that osmophobia is very specific in the diagnosis of migraine.^{22,40,41} It has low sensitivity, but high specificity in the differential diagnosis of migraine and tension-type headache, with higher values than the parameters for photophobia or phonophobia.^{8,13} In the International Classification of Headache Disorders, Second Edition (ICHD-2), osmophobia was cited in the appendix as a diagnostic criterion for migraine,⁴⁷ but these data disappeared from the current classification (ICHD-3 β)³⁴ with no explanation. Despite evidences from the literature and constancy in the findings on osmophobia as a useful diagnostic marker, osmophobia is not included among the migraine diagnostic criteria in ICHD-3 β (beta version).³⁴

Migraine patients showed odour-triggered headache attacks even in low concentrations of the odour, and even with odours that are frequently well tolerated by the general population. Among the odours, perfume was the one that most commonly triggered headache, particularly those with floral scent.^{1,13,14,19,26} The trigger mechanism of the headache by odours is still unknown. However, a study by functional magnetic resonance imaging (fMRI) during headache attacks in migraine patients and normal subjects showed increased activity of the limbic system and brainstem in response to olfactory stimulation only in migraine patients. This finding shows the strong relationship between the smell and the trigeminal nociceptive pathway in the pathophysiology of migraine.²¹ There is another hypothesis that the olfactory stimulus excites the locus coeruleus in migraine patients and causes noradrenaline release. Consequently, substance P and calcitonin gene-related peptide (CGRP) are released. These two potent and inflammatory vasodilator substances trigger the painful phenomenon.^{1,2} Recent studies have shown that inhalation of certain odours may cause severe headache attacks through stimulation of transient receptor potential ankyrin 1 (TRPA1), a nonselective cation channel expressed in sensory neurons, and activation of the trigeminovascular system. Consequently, there are nociceptive responses and calcium-dependent release of CGRP from trigeminal nerve terminals in the dura mater. Furthermore, TRPA1 activation may activate dural nociceptors and lead to central sensitization and cutaneous allodynia.^{48,49}

Despite the fact that there have been many previous studies, there is presently no clinical marker for the diagnosis of migraine. Odour as trigger of headache could be a marker and a specific test to be used in patients with headache. In our recent research, we have used a perfume as a test to trigger headache. This test was positive only in migraine patients.³

Table 2: Characteristics of 31 studies published worldwide on osmophobia or odour-triggered headache, according to author and country

Authors	Country of origin	Number of patients	Comments
Silva-Néto et al., 2014 ¹	Brazil	400	Comparative study between patients with migraine and TTH; odour-triggered headache only in migraineurs (70.0%)
Silva-Néto et al., 2014 ²	Brazil	400	Comparative study between patients with migraine and TTH; osmophobia predominated in migraineurs (86.0% versus 6.0%)
Silva-Néto et al., 2017 ³	Brazil	158	Experimental study between patients with migraine and other primary headaches; odour-triggered headache only in migraineurs (34.7%)
Rocha-Filho et al., 2016 ⁴	Brazil	147	A study with migraine patients; osmophobia predominated in migraineurs with anxiety and more years of headache history
Rocha-Filho et al., 2015 ⁵	Brazil	235	Comparative study between migraine patients and TTH; osmophobia predominated in migraineurs (53.0% versus 11.5%), especially in those with more years of headache history
Fornazieri et al., 2016 ⁶	Brazil	113	Cross-sectional study with migraineurs; osmophobia occurred in 95.5%; and odour-triggered headache in 90.2%
Kelman, 2004 ⁷	USA	1,237	A study with migraine patients; osmophobia and taste abnormality occurred in 25% of migraineurs and perfume triggered migraine attacks in almost 50% of these patients
Kelman, 2004 ⁸	USA	727	The study evaluated osmophobia and taste abnormalities in patients with headache and showed that these symptoms are very specific in diagnosing migraine, but very insensitive
Roussos & Hirsch, 2014 ⁹	USA	1	A 32-year-old woman with migraine had a headache attack triggered by garlic and onion aroma associated with osmophobia
Whiting et al., 2015 ¹⁰	USA	50	Comparative study between chronic migraine patients and controls showed that chronic migraine patients do not appear to have a significant change in olfactory acuity during or between migraine attacks but they do appear to be more likely to have abnormal olfactory acuity
Baldacci et al., 2015 ¹¹	Italy	200	A study of consecutive migraineurs; osmophobia during headache attacks was present in 58.0% of them
Benemei et al., 2010 ¹²	Italy	1	A 69-year-old man with cluster headache had a headache attack triggered by the scent given off by a tree
Corletto et al., 2008 ¹³	Italy	275	Comparative study between migraine patients and TTH; osmophobia predominated in migraine patients (25.1% versus 8.3%) and had high specificity (92.0%) in the differential diagnosis between migraine and TTH
De Carlo et al., 2010 ¹⁴	Italy	1,020	Comparative study between migraine patients and TTH; osmophobia predominated in migraine patients (34.6% versus 14.3%) and when it was considered a diagnostic criterion, increased diagnostic accuracy of migraine
De Carlo et al., 2012 ¹⁵	Italy	90	Study of diagnostic variation in young patients with TTH after 3-year follow-up; diagnostic rate of change was significantly higher ($p=0.0002$) in cases with osmophobia (62%)
Lovati et al., 2015 ¹⁶	Italy	673	Study showed that there was a significant association between osmophobia and cutaneous allodynia in chronic migraine patients
Raieli et al., 2005 ¹⁷	Italy	96	Frequency of osmophobia was evaluated in a young population with headaches; osmophobia was present only in migraineurs (20.0%) and absent in other forms of headache
Zanchin et al., 2005 ¹⁸	Italy	775	Comparative study between migraine patients, TTH, cluster headache, and other headaches; osmophobia was present in migraine (42.3%), cluster headache (6.8%), but absent in TTH and other headaches
Zanchin et al., 2007 ¹⁹	Italy	1,005	Comparative study between migraine patients and TTH; osmophobia was present in patients with migraine with and without aura, respectively, 43.9% and 38.5%, and in none with TTH
Zanchin et al., 2016 ²⁰	Italy	14,360	Systematic review compared migraine with TTH and showed predominance of osmophobia in migraineurs, both adults and children; prevalence in adults was 48.5% versus 8.9%; and in children, 23.4% versus 7.9%
Stankewitz & May, 2011 ²¹	Germany	40	Comparative study between migraine patients and controls; migraineurs during headache attack had changes in neuronal processing in response to olfactory stimulation
Porta-Etessam et al., 2009 ²²	Spain	68	Comparative study between migraine patients and TTH; osmophobia during headache attacks was present only in patients with migraine, particularly in migraine without aura
Demarquay et al., 2008 ²³	France	13	Comparative study between migraine patients and controls revealed that during olfactory stimulation, migraineurs showed changes in regional cerebral blood flow
Sjöstrand et al., 2010 ²⁴	Sweden	60	Female migraine patients with headache attacks induced by odour were investigated; in 63.3% of patients, headache was triggered by odours and in 81.7% osmophobia occurred during headache attacks
Park et al., 2015 ²⁵	South Korea	220	Sensory hypersensitivities were examined in migraine patients with suicidality; osmophobia was a critical factor for suicidality
Saisu et al., 2011 ²⁶	Japan	110	An olfactory test conducted to evaluate the association between migraine and smell; osmophobia was found in 63.0% of patients
Ishii et al., 2014 ²⁷	Japan	210	Investigation of gene polymorphisms involved in photophobia and osmophobia in migraineurs
Wang et al., 2012 ²⁸	Taiwan	2,883	Comparative study between migraine patients, TTH and cluster headache; osmophobia was prevalent in migraineurs
Akdal et al., 2015 ²⁹	Turkey	871	A comparative study between migraine patients with both aura and without aura, according to the presence of vertigo or vestibular symptoms; osmophobia was present in migraineurs without aura with vestibular symptoms (46.8% versus 33.2%) and with vertigo (52.4% versus 37.1%)

Table 2: Cont.

Authors	Country of origin	Number of patients	Comments
Baykan et al., 2016 ³⁰	Turkey	5,323	A comparative study between migraine patients with and without allodynia; osmophobia predominated in migraine patients with allodynia (48.9% versus 35.1%)
Kayabaşoğlu et al., 2016 ³¹	Turkey	90	Comparative study between migraine patients and healthy people showed that the olfactory threshold is lower in migraineurs with osmophobia

TTH = tension-type headache.

Table 3: Prevalence of osmophobia during headache attacks in comparative studies of patients with migraine, tension-type headache and cluster headache

Authors	Migraine		TTH		CH		p-value
	n	%	n	%	n	%	
Silva-Néto et al., 2014 ²	172/200	86.0	12/200	6.0	-	-	<0.001
Rocha-Filho et al., 2016 ⁴	78/147	53.1	10/87	11.5	-	-	<0.001
Corletto et al., 2008 ¹³	42/167	25.1	9/108	8.3	-	-	<0.05
De Carlo et al., 2010 ¹⁴	215/622	34.6	47/328	14.3	-	-	<0.001
Zanchin et al., 2005 ¹⁸	241/569	42.3	0/135	0.0	3/44	6.8	<0.001
Zanchin et al., 2007 ¹⁹	347/807	43.0	0/198	0.0	-	-	<0.001
Porta-Etessam et al., 2009 ²²	13/45	28.9	0/23	0.0	-	-	<0.001
Wang et al., 2012 ²⁸	1,125/1,809	62.2	20/138	14.5	45/144	31.3	<0.001

CH = cluster headache; TTH = tension-type headache.

Conclusions

Studies on osmophobia and/or odour-triggered headache were carried out in several countries. They were useful in differentiating

between migraine and tension-type headache. This could improve the accuracy of diagnosis of migraine compared to the current criteria. □

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