

Accuracy of osmophobia in the differential diagnosis between migraine and tension-type headache



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ABSTRACT

Our objective was to determine the accuracy parameters of osmophobia in the differential diagnosis between migraine and tension-type headache. Migraine or tension-type headache patients, diagnosed according to the criteria of the International Classification of Headache Disorders-II, were interviewed about osmophobia during the crisis and in the period between episodes. We studied 200 migraine patients and 200 tension-type headache patients. During the crisis, osmophobia occurred in 86.0% (172/200) of patients with migraine and 6.0% (12/200) of those with tension-type headache. In migraine, osmophobia was associated with photophobia and phonophobia (57/172, 33.1%) or with nausea, photophobia and phonophobia (92/172, 53.5%) and presented high sensitivity (86.0%, 95% CI 80.2–90.3) and specificity (94.0%, 95% CI 89.5–96.7), with low percentages of false positives (6.5%, 95% CI 3.6–11.4) and negatives (13.0%, 95% CI 8.9–18.4). In the period between attacks, osmophobia was restricted to migraine patients (48/200, 24.0%). The areas under ROC curves were: 0.903 ± 0.017 to osmophobia during crisis; 0.784 ± 0.025 between crises; 0.807 ± 0.023 to photophobia/phonophobia, and 0.885 ± 0.017 to pain developed by odors. Osmophobia may be a specific marker to differentiate migraine from tension-type headache, which suggests its inclusion within the criteria to diagnose migraine.

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1. Introduction

Osmophobia is defined as intolerance to odors and it is associated to primary headaches, particularly to migraine with or without aura [1–7], and it may be present in tension-type headache. The literature of its occurrence in secondary headaches is very scarce [8].

The prevalence of osmophobia during an attack in patients with migraine ranges from 20% to 81.7% [2,4–7,9–11]. However, osmophobia may be present in the absence of pain (period between attacks) [2,3,9,12–15].

Migraine is a chronic neurological disorder with a prevalence of 15.2% in Brazil [16]. It is defined as an abnormal neurovascular reaction that occurs in a genetically vulnerable organism. It externalizes itself clinically by recurrent attacks of headache and associated manifestations, depending on triggering factors [17].

These associated manifestations include nausea or vomiting, photophobia, phonophobia, dizziness and osmophobia [1,2,18,19]. However, only nausea and/or vomiting, photophobia and phonophobia are part

of the diagnostic criteria for migraine. The inclusion of osmophobia as an additional criterion in the appendix of the International Classification of Headache Disorders (ICHD)–2 is proposed [14,19].

In three comparative studies between migraine and tension-type headache conducted with children and adolescents (aged 4 to 18 years) with headache [5,10,12] and in another study with adults [20], osmophobia was more prevalent in migraine patients, in a demonstration that it is a symptom of low sensitivity and high specificity for the differential diagnosis between these two forms of headache. The presence of osmophobia in juvenile patients with tension-type headache has prognostic value, since this form of headache may change to migraine during development [21–23].

The aim of this study was to determine the parameters of accuracy of osmophobia in the differential diagnosis between migraine and tension-type headache.

2. Patients and methods

2.1. Study design and patients

This was a prospective study with comparison of groups. The study population comprised a non-random and convenience sampling, consisting of the first 200 migraine patients and 200 tension-type headache patients (comparison group) treated at a headache clinic in the city

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of Teresina in northeastern Brazil. Data for this study were collected from August to December 2011.

2.2. Inclusion and exclusion criteria

Patients aged between 18 and 60 years, with migraine or tension-type headache, according to the diagnostic criteria of ICHD-II [19], and the presence of headache in the last six months at a frequency less than 15 days per month were included in the study.

In order to obtain consistent and valid data, the study excluded patients without a headache in the last six months, association between migraine and tension-type headache, concomitantly or at different times, the presence of other primary or secondary headaches, the presence of associated diseases or the use of medications that might impair olfaction, and pregnant women.

2.3. Data collection

The patients underwent a thorough standard medical history performed by a headache specialist to record the typical characteristics of their pain over the past six months. They were questioned about osmophobia, both during the headache attack and the period between attacks. Having met the criteria for inclusion and exclusion, patients were invited to participate in the study by signing the informed consent form. There was, then, a structured interview based on a questionnaire to investigate the research objectives. Excluded at this stage were uncooperative patients or those who answered the interview incompletely.

2.4. Statistical analysis

Once the information was organized in the database, the Statistical Package for Social Sciences (SPSS®) version 17.0 for statistical analysis was used. The chi-square test with Yates correction, Fisher's exact test and Mann-Whitney test for differences between averages of unpaired samples were used, assuming a significance level of 0.05. Sensitivity and specificity parameters and positive and negative predictive value were determined.

2.5. Ethical aspects

This study was approved by the Ethics in Research Involving Human Subjects Committee at the State University of Piauí, Brazil, protocol number 049/11 and the National Ethics in Research System, registry number 439715. All patients signed the informed consent form.

3. Results

There were 400 patients averaging 38.6 ± 9.9 in age (95% CI 37.7–39.6) and ranging from 22 to 58 years old, 219 (54.7%) of whom were women, which corresponded to the sex ratio of 0.83:1 male/female.

Two hundred patients (50.0%) were diagnosed with tension-type headache and 200 (50.0%) with migraine, whose distribution differed according to sex and age, as observed in Table 1. Tension-type headache was predominant in men, with a 4.4:1.0 ratio male/female, whereas in migraine this ratio equaled 0.1:1; thus, predominantly female. These differences were significant. Regarding age, tension-type headache was present in patients aged 40.0 ± 10.4 years old, while migraine was diagnosed in younger patients, aged 37.3 ± 9.0 years old, and these differences were significant.

As for symptom differences between tension-type headache and migraine, it was found that, during an attack, migraine patients more often reported osmophobia (172/200, 86.0%), were female (164/172, 95.3%) and reported an association of osmophobia to photophobia and phonophobia (57/172, 33.1%) or to nausea, photophobia and phonophobia (92/172, 53.5%). Patients going through a tension-type headache attack more often did not report osmophobia (188/200,

Table 1

Distribution of sex and age according to diagnosis of 200 patients with migraine and 200 with tension-type headache.

Variables	Diagnostic		P value
	Migraine	TTH	
Sex			<0.001*
Female (n; %)	182 (83.1)	37 (16.9)	
Male (n; %)	18 (9.9)	163 (90.1)	
Age (years)			0.008†
Mean	37.3 (9.0)	40.0 (10.4)	
95% CI	36.0–38.6	38.5–41.4	

Legend: TTH – tension-type headache; CI – confidence interval.

* P value based on the chi-square test.

† P value by the Mann-Whitney test for average difference test between averages of unpaired samples.

94.0%), were male (158/188, 84.0%) and had no other symptoms (164/200, 82.0%) (Table 2).

In the period between attacks, there was a predominance of absence of osmophobia for both migraine patients and patients with tension-type headache, regardless of sex. However, when present, it was restricted to migraine patients (48/200, 24.0%). Odors triggered headache in 140/200 (70.0%) of the migraine patients, including the 48 patients with osmophobia between attacks and 92 patients without it. Both differences reached statistical significance (Table 2).

Table 3 shows the results of sensitivity, specificity, and positive and negative predictive values, as well as false positive and negative values of associations, statistically significant, of osmophobia during attack and between attacks, photophobia/phonophobia, and the triggering of headache by odors with the diagnosis of migraine.

While osmophobia during the attacks and photophobia/phonophobia showed high indicative values of accuracy for diagnosis of migraine, with low percentages of false positives and negatives, osmophobia between episodes and the triggering of headache by odors had low sensitivity and high specificity, from those resulting in high positive predictive values.

In the presence of osmophobia during an attack, the probability of not being migraine was 6.5%, while the probability of being migraine in the absence of osmophobia during the attack was 13.0%. The same reasoning used in relation to osmophobia between attacks made it possible to state that, when present, the probability of not being migraine

Table 2

Distribution of symptoms as diagnosis in 200 patients with migraine and 200 with tension-type headache.

Symptoms	Diagnosis				P value
	Migraine		TTH		
	n	%	n	%	
Osmophobia during attack	172	86.0	12	6.0	<0.001*
Female	164	95.3	7	58.3	
Male	8	4.7	5	41.7	
Osmophobia between attacks	48	24.0	0	0.0	<0.001†
Female	36	75.0	0	0.0	
Male	12	25.0	0	0.0	
Osmophobia associated with other symptoms	172	86.0	12	6.0	<0.001*
Photophobia and phonophobia	57	33.1	0	0.0	
Photophobia or phonophobia	0	0.0	12	100.0	
Nausea, photophobia and phonophobia	92	53.5	0	0.0	
Nausea and/or vomiting	23	13.4	0	0.0	
Odor as a trigger to headaches	140	70.0	0	0.0	<0.001*
Female	134	95.7	0	0.0	
Male	6	4.3	0	0.0	

Legend: TTH – tension-type headache.

* P value based on Fisher's exact test.

† P value by chi-square test.

Table 3
Parameters of the association between symptoms and diagnosis of 200 migraine patients.

Parameters	Osmophobia during the crisis		Osmophobia between attacks		Photophobia/phonophobia		Triggering of pain by odors	
	%	CI 95%	%	CI 95%	%	CI 95%	%	CI 95%
Sensitivity	86.0	80.2–90.3	24.0	18.4–30.6	86.5	80.8–90.8	70.0	63.1–76.2
Specificity	94.0	89.5–96.7	100.0	97.6–100.0	74.0	67.2–79.8	100.0	97.6–100.0
PPV	93.5	88.6–96.4	100.0	90.7–100.0	76.9	70.7–82.1	100.0	96.7–100.0
NPV	87.0	81.6–91.1	56.8	51.4–62.0	84.6	78.2–89.4	76.9	71.2–81.8
FPV	6.5	3.6–11.4	0.0	0.0–9.2	23.1	17.9–29.3	0.0	0.0–3.3
FNV	13.0	8.9–18.4	43.2	38.0–48.5	15.4	10.6–21.8	23.1	18.2–28.8

Legend: PPV – positive predictive value; NPV – negative predictive value; FPV – false positive predictive value; FNV – false negative predictive value; CI – confidence interval.

varied from zero to 9.2%, while the probability of being migraine in the absence of osmophobia between attacks ranged from 38.0% to 48.5% (Table 3).

The triggering of headache by odors showed high specificity, high positive predictive value than that which derived from the low false positive value, differing from the presence of photophobia/phonophobia, which had higher sensitivity than specificity and negative predictive value greater than the positive predictive value (Table 3).

The areas under the ROC curve (Receiver Operating Characteristic) for medical research equated to: 0.903 ± 0.017 for osmophobia during

the attack (Fig. 1A); 0.784 ± 0.025 for osmophobia between attacks (Fig. 1B); 0.807 ± 0.023 for photophobia/phonophobia (Fig. 1C) and 0.885 ± 0.017 for the triggering of pain by odors (Fig. 1D).

4. Discussion

Osmophobia is a frequent complaint from migraine patients [1–7,24,25], as it was demonstrated in this study. Its exact mechanism is unknown; however a recent study shows that the olfactory processing

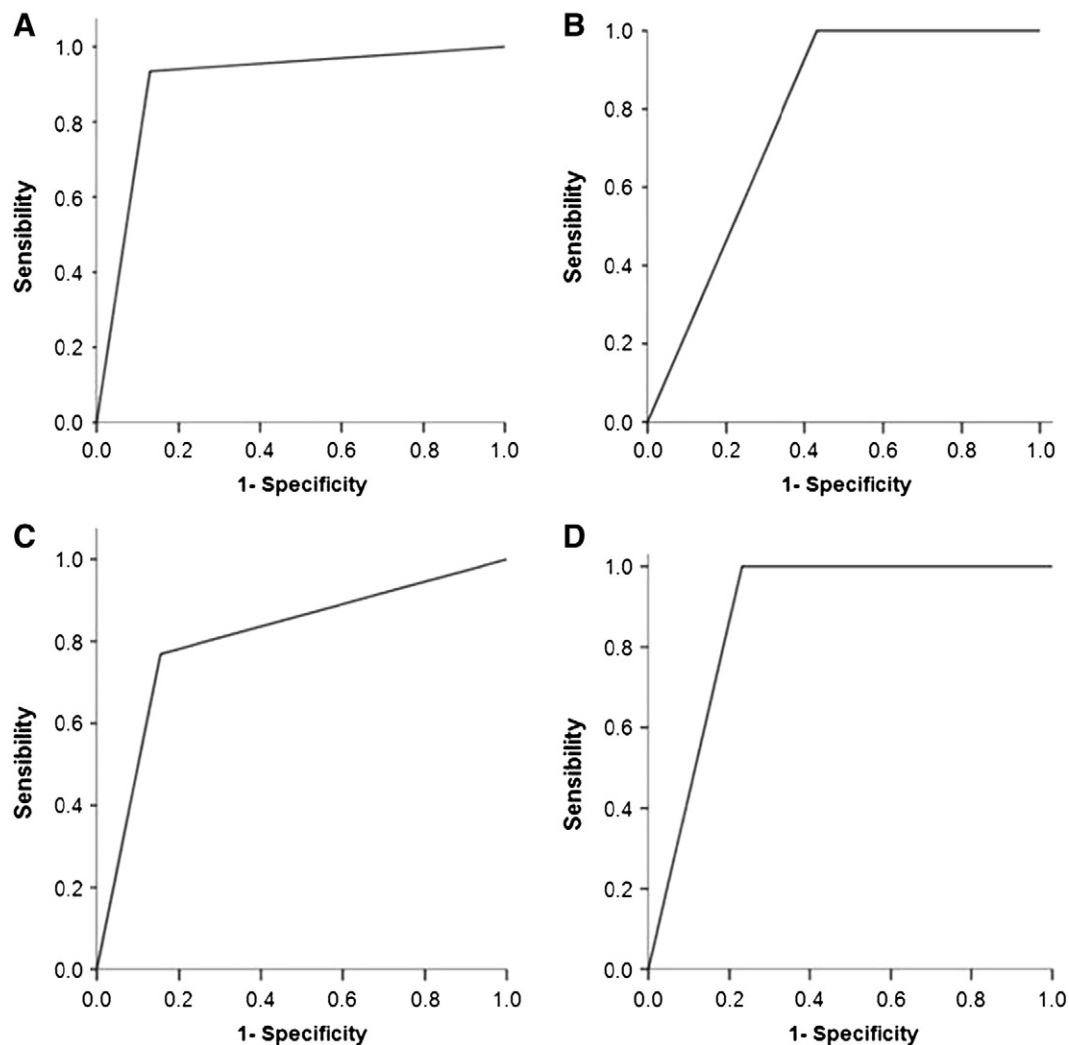


Fig. 1. ROC curves of osmophobia during attack and between attacks, photophobia and phonophobia and headache triggered by odors. Legend: A – osmophobia curve during attack, B – osmophobia curve between attacks, C – photophobia and phonophobia curve, D – curve of occurrence of headache by odors.

is altered during headache attacks in migraine patients, suggesting that there are specific neuronal connections between the olfactory and trigeminal nociceptive system [26], because most odors are bimodal, i.e. active trigeminal and olfactory nerves [27,28]. The trigger mechanism of the headache by odors in patients with tension-type headache is unknown. A study by fMRI during headache attacks in migraine patients and normal subjects showed increased activity of the limbic system and brainstem in response to olfactory stimulation, and only in migraine patients [26].

There is another hypothesis that the olfactory stimulus excites the locus coeruleus in migraine patients and causes norepinephrine release. Consequently, substance P and calcitonin gene-related peptide (CGRP) are released. These two potent and inflammatory vasodilatory substances trigger the painful phenomenon [29].

Up to now, the symptoms included in the diagnosis of migraine are not sufficiently sensitive and specific to be considered pathognomonic, and similarly, osmophobia, although frequent, is not pathognomonic. However osmophobia seems to contribute to the differential diagnosis between migraine and tension-type headache [3].

In this study, when comparing migraine to tension-type headache, it was found that patients with migraine most frequently reported osmophobia in association to photophobia and phonophobia or to nausea, photophobia and phonophobia. Recently, a study with 60 patients with migraine identified the prevalence of the main symptoms associated to headache during the attack equal to 80.0% for nausea, 53.0% for vomiting, 93.0% for phonophobia, 87.0% for photophobia and 81.7% for osmophobia [2].

Several authors suggest that osmophobia is very specific for the diagnosis of migraine [2,26,30–32]. In two studies, osmophobia showed low sensitivity but high specificity in the differential diagnosis between migraine and tension-type headache, greater values than those parameters for photophobia or phonophobia [6,10].

In our study, the specificity of osmophobia for the diagnosis of migraine was higher than the sensitivity, which was also high, corresponding, therefore, to a low percentage of false positives and negatives. Thus, when osmophobia is present during the attack, the diagnosis of migraine is more probable than that of tension-type headache. On the other hand, its absence tends to exclude this diagnosis.

Following the same reasoning, the high value of the area under the ROC curve for osmophobia during the attack showed that osmophobia is a good parameter to separate the patients who have migraine from those who do not [33]. Therefore, its accuracy is high in the diagnosis of migraine.

In our study, osmophobia between attacks was restricted to migraine patients, less sensitive but highly specific. Moreover, all of the patients were associated with the presence of odors triggering attacks.

In a recent study, from the patients who had attacks triggered by odors, 84.0% showed osmophobia between attacks, compared to 13.0% who had no attacks triggered by odors [2].

However, it must be considered that patients with migraine in the period between attacks have changed the threshold for olfactory stimuli [14,15,34], so osmophobia may occur in the absence of pain, in the prevalence of 35.0% [14].

Several studies have shown that osmophobia seems to be a good criterion differential between migraine and tension-type headache. They suggest that if osmophobia occurs consistently in migraine, then it may be part of its diagnostic criteria [3,20]. The triggering of headaches by odors is also a criterion to distinguish these two forms of headache. We found that the odors only trigger headache in migraine patients [35].

5. Conclusions

This study allowed the conclusion that osmophobia seems to be a specific marker to adequately differentiate migraine from tension-type

headache, and it allows the suggestion of its inclusion in the criteria for diagnosing migraine.

Conflict of interest

There is no conflict of interest.

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