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Osmophobia in migraine classification: A multicentre study in juvenile patients

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Abstract

Aims: This study was planned to investigate the diagnostic utility of osmophobia as criterion for migraine without aura (MO) as proposed in the Appendix (A1.1) of the International Classification of Headache Disorders (ICHD-II, 2004).
Methods: We analysed 1020 patients presenting at 10 Italian juvenile headache centres, 622 affected by migraine (M) and 328 by tension-type headache (TTH); 70 were affected by headache not elsewhere classified (NEC) in ICHD-II. By using a semi-structured questionnaire, the prevalence of osmophobia was 26.9%, significantly higher in M than TTH patients (34.6% vs 14.3%).
Results: Osmophobia was correlated with: (i) family history of M and osmophobia; and (ii) other accompanying symptoms of M. By applying these 'new' criteria, we found an agreement with the current criteria for the diagnosis of migraine without aura (MO) in 96.2% of cases; 54.3% of previously unclassifiable patients received a 'new' diagnosis.
Conclusions: In conclusion, this study demonstrates that this new approach, proposed in the Appendix (A1.1), appears easy to apply and should improve the diagnostic standard of ICHD-II in young patients too.

Keywords

osmophobia, juvenile primary headache, migraine without aura, tension-type headache, International Classification of Headache Disorder 2nd edn

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Introduction

The term osmophobia refers to an unbearable perception of odours that are non-aversive or even pleasurable outside the attacks.

Data regarding the relationship between osmophobia and primary headaches in adult have been accumulating (1–7); despite this, only two preliminary studie. (8,9) have examined the relationship between osmophobia and primary headaches in children, even though migraine (M) represents a significant health problem for the juvenile population (10,11), with a high prevalence in children and adolescents (5–15%) (12) and a strong impact on the quality of life in childhood (13). Studies show an increased interest on the application of the International Classification of Headache Disorders (ICDH-II, 2004) criteria (14) both in adults (15) and in children (16–19).

An accurate analysis of osmophobia occurrence arises from the necessity to give a scientific evidence to a diagnostic criteria for migraine without aura (MO) proposed in the Appendix (A1.1) of the ICDH-II (14), which could improve the diagnostic accuracy in comparison to the current criteria. On this topic, only

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one study attempted to validate these alternative criteria in adults (20), but data in juvenile population are completely lacking.

In the current classification (ICHD-II) (14), accompanying symptoms of phonophobia, photophobia, nausea and vomiting remain an essential part of the differential diagnosis between M and tension-type headache (TTH).

In the Appendix of this classification (A1.1, point D) (14), it was hypothesised that osmophobia could be introduced among the diagnostic criteria of MO. In fact, the proposal is that, in MO, at least two of the following five symptoms must be present – phonophobia, photophobia, nausea, vomiting and osmophobia.

To clarify the role of osmophobia in the differential diagnosis between the main subtypes of primary headache in children, i.e. MO and episodic tension-type headache (ETTH), it is important to simplify the classification criteria and to improve their diagnostic accuracy. Indeed, headache differential diagnosis in childhood is difficult since children are unable to describe their symptoms carefully and, in the juvenile population, headaches appear to be subject to frequent diagnostic changes in the follow-up (21–25).

The aim of this study was to analyse the relationship between osmophobia and primary headaches, both the two major types of primary headaches (M and TTH) and their more relevant subtypes (MO, migraine with aura [MA], chronic migraine [CM], ETTH and chronic tension-type headache [CTTH]) and headache not elsewhere classified (NEC) in juvenile patients, with the following objectives:

1. Verifying the diagnostic usefulness of osmophobia in primary headache to evaluate the applicability of ICHD-II Appendix (14) in juvenile headache sufferers, in particular in the differential diagnosis between MO and ETTH, and in patients with headache NEC.
2. Ascertaining the characteristics of their symptoms in a large sample of juvenile primary headache sufferers.
3. Comparing the characteristics of osmophobic versus non-osmophobic patients.

Subjects and methods

The study was a multicentre survey conducted from January 2005 to February 2008 on 1020 randomised patients admitted to 10 juvenile headache centres in Italy, specialised in the diagnosis and therapy of headache in childhood and adolescence: Padua, Milan (two), Rome, Varese, Ferrara, Perugia, Palermo (two), L'Aquila. Every centre provided a minimum of 30 patients.

Inclusion criteria were: (i) age 4–18 years; (ii) diagnosis of primary headaches (points 1–4 of ICHD-II) including headache NEC (point 14.1 of ICHD-II); (iii) no prophylactic therapy in the last 6 months; (iv) absence of relevant and/or chronic diseases; and (v) adequate cognitive and expressive ability to understand the questionnaire and take part in the interview. Patients with a diagnosis of secondary headaches were excluded.

All the patients were interviewed by using a semi-structured questionnaire, used in a previous study on this topic (9). This questionnaire was sent and explained to all the managers of each centre. For each patient, a specialist in neurology and psychiatry of childhood completed a standardised questionnaire covering: (i) family history for headaches; and (ii) a complete description of the pattern of the headache attacks in the last 6 months.

The 1020 selected patients completed a semistructured questionnaire on osmophobia and its characteristics, applied in our previous study on childhood (9). We asked about the following main characteristics of this disturbance: (i) duration and frequency of osmophobia; (ii) kind of smell (perfumes, food, smoke or other); (iii) possible triggering smell; and (iv) onset of osmophobia in relation to headache history.

The interview and the diagnostic questionnaire for headache were given to patients during the examination and were based on patients' answers, with the help of accompanying parents for children under 10 years of age.

During the visit, an accurate physical and neurological examination was performed. Blood tests or neuro-imaging were used when indicated to rule out a secondary headache.

Statistical analysis

Descriptive statistics were obtained for quantitative (mean ± SD) and qualitative (prevalence, distributions) characteristics on the whole sample, by headache type and osmophobia (presence/absence). The significance of the differences between mean values was evaluated by means of the Student's unpaired *t*-test. The chi-squared test was applied to compare distributions. Age at diagnosis of juvenile primary headache was described by applying the actuarial method for survival analysis. The same analysis was used to compare the age at diagnosis between genders and between headache types (M or TTH). The significance of the difference was evaluated by means of the log-rank test.

To validate the new proposed criteria for MO/ETTH (ICHD-II A1.1, point D) (14), we applied them to the subjects with a diagnosis of MO or ETTH based on the current criteria (ICHD-II). Sensitivity and specificity were evaluated for the new criterion and for each pairs of accompanying symptoms.

All the tests were two-tailed, and the level for significance was set at 0.05. The analyses were performed by means of SAS v.9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Demographic and clinical characteristics

As shown in Table 1, of the 1020 primary headache patients studied, 489 (47.9%) were males and 531 (52.1%) were females; their age ranged between 4.0–17.9 years (mean age ± SD, 11.1 ± 2.8 years). According to the ICHD-II, 622 (61.0%) patients were affected by M, 328 (32.2%) by TTH and 70 (6.8%) by headache NEC. We did not find any patients suffering from cluster headache or other trigeminal autonomic cephalalgias (point 3 of ICHD-II) and other primary headache (point 4 of ICHD-II). No significant difference was found between patients with M or TTH regarding the distribution by gender (in males 49.7% versus 46.6%; $P = 0.18$); however, the subjects with M or NEC were significantly older than patients with TTH ($P = 0.04$).

The diagnosis of M was significantly associated with the anamnestic and clinical characteristics of their form of primary headache. In particular, family history for M and family history for osmophobia were both significantly higher in the diagnosis of M or NEC ($P < 0.0001$ and $P = 0.004$, respectively), while family history for TTH was more prevalent in the diagnosis of TTH ($P < 0.0001$).

The prevalence of the accompanying symptoms (vomiting, nausea, photophobia and phonophobia) and the olfactory stimuli as trigger for crises resulted in a significantly higher burden among the patients with M ($P < 0.0001$ and $P = 0.0005$, respectively).

A second-level diagnosis showed that, among the 622 M patients, 497 had a diagnosis of MO (79.9%), 57 of MA (9.2%) and 68 of CM (10.9%); among the 328 TTH patients, 263 had a diagnosis of ETTH (80.2%) and 65 of CTTH (19.8%).

The age at diagnosis for juvenile headache by gender compared by means of the survival analysis indicated that it was significantly lower for boys than for girls ($P < 0.02$), with an average of 7 years for boys and 8 years for girls, while the difference in age at diagnosis by headache type (M, TTH or NEC) was not significant ($P = 0.10$; data not shown).

Comparison between the current diagnostic criteria (ICHD-II) and the new proposed criteria (ICHD-II A1.1)

In Table 2A, each combination of accompanying symptom, as proposed in the Appendix A 1.1 of ICHD-II (14), were compared with the current diagnostic criteria in the three examined cephalalgic groups (MO, TTH and NEC); in particular, we observed that all the pairs of accompanying symptoms were significantly associated with a MO diagnosis. Points A–C and point E of current criteria for MO and for ETTH were respected in all patients.

Table 1. Characteristics of migraine, tension-type headache and headache not elsewhere classified sufferers

	Total ($n = 1020$) *n* (%)	M ($n = 622$) *n* (%)	TTH ($n = 328$) *n* (%)	NEC ($n = 70$) *n* (%)	*P*-value
Male gender	489 (47.9)	309 (49.7)	153 (46.6)	27 (38.6)	0.18
Age (years) mean (±SD)	11.1 ± 2.8	11.2 ± 2.6	10.8 ± 2.7	11.5 ± 2.8	0.04
Family history for M	580 (56.9)	403 (64.8)	136 (41.5)	41 (58.6)	0.0001
Family history for TTH*	134 (18.1)	60 (13.3)	65 (29.3)	9 (12.9)	0.0001
Family history for osmophobia*	113 (15.2)	80 (17.8)	19 (8.6)	14 (20.0)	0.004
Vomiting	301 (29.5)	293 (47.1)	0 (0)	8 (11.4)	0.0001
Nausea	461 (45.2)	426 (68.5)	12 (3.7)	23 (32.9)	0.0001
Photophobia	613 (60.1)	506 (81.4)	77 (23.4)	30 (42.9)	0.0001
Phonophobia	658 (64.5)	500 (80.4)	115 (35.1)	43 (61.4)	0.0001
Osmophobia	274 (26.9)	215 (34.6)	47 (14.3)	12 (17.1)	0.0001
Olfactory stimulus triggers	131 (12.8)	100 (16.1)	21 (6.4)	10 (14.3)	0.0005

*The characteristics (*n*, % and *P*) refer to a subgroup of 742 patients (patients with M = 450; patients with TTH = 222; patients with NEC = 70).
M, migraine; TTH, tension-type headache; NEC, headache not elsewhere classified.

Table 2A. Comparison between the current and the alternative criteria proposed in the Appendix A1.1 of ICHD-II for diagnosis of migraine without aura*

	Total ($n=830$) *n*	MO ($n=497$) *n*	ETTH ($n=263$) *n*	NEC ($n=70$) *n*	*P*-value
Current criteria for diagnosis of MO (ICHD-II, 2004)					
Vomiting	239	231	0	8	0.0001
Nausea	357	333	1	23	0.0001
Photophobia and phonophobia	408	367	21	20	0.0001
Paired diagnostic criteria proposed for MO in the Appendix A 1.1 (ICHD-II, 2004)					
Osmophobia and photophobia	175	161	9	5	0.0001
Osmophobia and phonophobia	186	161	15	10	0.0001
Osmophobia and nausea	131	127	0	4	0.0001
Osmophobia and vomiting	81	79	0	2	0.0001
Photophobia and phonophobia	408	367	21	20	0.0001
Vomiting and phonophobia	190	184	0	6	0.0001
Vomiting and photophobia	186	182	0	4	0.0001
Nausea and vomiting	196	190	0	6	0.0001
Nausea and phonophobia	276	258	1	17	0.0001
Nausea and photophobia	270	257	1	12	0.0001

*Points A–C and point E of current criteria were respected in all MO and ETTH patients.
MO, migraine without aura; ETTH, episodic tension-type headache; NEC, headache not elsewhere classified.

Table 2B. Comparison between the current and the alternative criteria proposed in the Appendix A1.1 of ICHD-II for diagnosis of migraine without aura*

	Current criteria for diagnosis (ICHD-II, 2004) *n*	Diagnostic criteria proposed in the Appendix (A 1.1 of ICHD-II, 2004) *n*	Agreement of diagnosis *n* (%)
MO	497	555	478/497 (96.2%)
ETTH	263	243	222/263 (84.4%)
NEC	70	32	32/70 (45.7%)
Total	830	830	

*Points A–C and point E of current criteria were respected in all MO and ETTH patients.
MO, migraine without aura; ETTH, episodic tension-type headache; NEC, headache not elsewhere classified.

Table 2B shows a high agreement in the diagnosis of the two main types of primary headache (MO and ETTH) obtained by means of a comparison between the two classification methods (ICHD-II versus A 1.1 of ICHD-II), i.e. 96.2% for MO and 84.4% for TTH.

Moreover, it can be observed that, if the A 1.1 of ICHD-II is used, 54.3% of the 70 NEC patients (38/70 cases) can be correctly classified.

Figure 1A,B shows the second level diagnostic subgroups resulting from the two classifications used and the re-arrangement of the obtained diagnoses; in particular, the application of A 1.1 produces, as a result:

1. An increase in the number of M diagnoses from 622 to 680 (8.5%), 41 of which come from ETTH and 36 from the NEC group (19 MO patients are reclassified as ETTH).
2. A decrease in the number of TTH diagnoses from 328 to 308 (−6.1%), given by the combination of an increase in MO cases (19) and NEC cases (2) and a decrease (41) in the reclassification as MO cases.
3. Out of the 70 NEC cases, 36 can be re-classified as MO and 2 as ETTH, with only 32 remaining NEC cases (45.7%). Among the 36 new MO diagnoses, there was a high percentage of subjects with a family history for M (71.4%)(data not shown).

As regards MA, CM and CTTH, no changes in diagnosis can be observed when comparing the two classification systems.

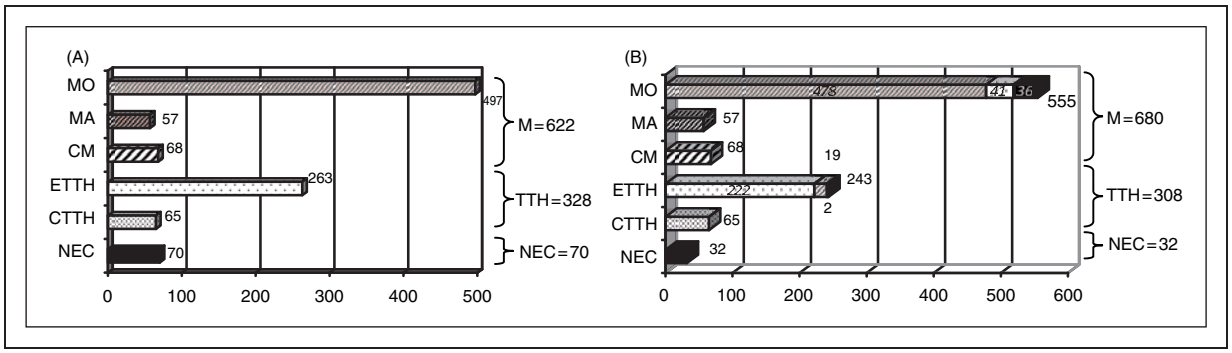

Figure 1. First and second level diagnosis obtained by applying two different classifications: (A) current criteria (ICHD-II,2004) and (B) alternative criteria proposed in the Appendix A1.1 of ICHD-II for the diagnosis of migraine without aura. M, migraine; MO, migraine without aura; MA, migraine with aura; CM, chronic migraine; TTH, tension-type headache; ETTH, episodic tension-type headache; CTTH, chronic tension-type headache; NEC, headache not elsewhere classified.

Characteristics of osmophobia

In our study, 26.9% (274/1020) of patients reported osmophobia during the crisis, with higher values in M, i.e. 34.6% (215/622), than in TTH, i.e. 14.3% (47/328), and in NEC patients, i.e. 17.1% (12/70; $P < 0.0001$). There were no differences in the occurrence of osmophobia either in CM or episodic M (MO and MA; $P = 0.68$) and CTTH and ETTH ($P = 0.36$); by contrast, there were differences in the occurrence of osmophobia between both episodic M (MO and MA) and ETTH ($P < 0.0001$) and CM and CTTH ($P < 0.0001$).

Table 3 shows a comparison between osmophobic and non-osmophobic populations, in total, in M, TTH and NEC patients. Osmophobia was reported in 126 males (25.8% of total males) and 148 females (27.9% of total females) with a difference that is not statistically significant ($P = 0.45$). The subgroup with osmophobia was significantly older than that one without it ($P = 0.0003$) and the prevalence of osmophobia was higher in the older age class ($P = 0.01$). The relationship with the age was not present in M ($P = 0.11$), TTH ($P = 0.31$) or headache NEC ($P = 0.62$) populations, if the three groups were considered separately.

Direct correlation between osmophobia and age was not found for phonophobia ($P = 0.06$), photophobia ($P = 0.10$) and vomiting ($P = 0.44$); while a correlation was present for nausea ($P = 0.02$).

A relationship between osmophobia and the length of headache history was present ($P < 0.005$). Our population can be divided into three groups in relation to the length of headache history: below 2 years, 3–5 years and over 5 years; prevalence of osmophobia increased with this factor (below 2 years, 20.4%; 3–5 years, 28.6%; over 5 years, 32.4%; $P < 0.005$).

The presence of osmophobia was significantly associated with family history for both M ($P = 0.002$) and osmophobia ($P = 0.001$), but not with a family history for TTH. Finally, we observed significant associations with the other accompanying symptoms (vomiting, nausea, photophobia and phonophobia).

Osmophobic features, in relation to diagnosis, are reported in Table 4. This symptom was reported with a high frequency by subjects with osmophobia: 68.6% of patients described osmophobia in more than 30% attacks, and 28.9% in more then 70% of them. The onset of osmophobia was coincidental with the onset of headache in 65.3% of patients. The smell types reported with higher frequency were perfumes (54.5%), followed by food (40.9%) and smoke (30.7%). All the characteristics were not statistically associated with diagnosis and their prevalence was similar in M, TTH and NEC patients; only food odours were more frequently referred by M patients ($P = 0.02$). About this last characteristic, there was a correlation between annoying food odours and nausea or vomiting, both in overall population ($P < 0.001$ for nausea and $P < 0.005$ for vomiting) and in the M group ($P < 0.05$ both for nausea and for vomiting), but not in the TTH group ($P = 0.27$ for nausea; data were not calculated for vomiting because this accompanying symptom is absent in attack of TTH, accordingly with ICHD-II; data not shown).

Olfactory stimuli were reported as attack triggers in 47.8% (131/274) of osmophobic patients.

Discussion

In our study, the prevalence of osmophobia in juvenile primary headaches was 26.9%, higher than in the previous studies in children (20% (8) and 25% (9)), and within the lower range reported in adults (24.7–47.7%) (3–7).

In two previous investigations both in children (8) and in adults (5,7), osmophobia was observed in M but not in TTH cases. In the present study, osmophobia was present not only in migraine patients (34.6%),

Table 3. Characteristics of the patients with or without osmophobia in relation to diagnosis

	Total ($n = 1020$)			M ($n = 622$)			TTH ($n = 328$)			NEC ($n = 70$)		
	O present *n* (%)	O absent *n* (%)	*P*-value	O present *n* (%)	O absent *n* (%)	*P*-value	O present *n* (%)	O absent *n* (%)	*P*-value	O present *n* (%)	O absent *n* (%)	*P*-value
n (%)	274 (26.9)	746 (73.1)	0.0001	215 (34.6)	407 (65.4)	0.0001	47 (14.3)	281 (85.7)	0.0001	12 (17.1)	58 (82.9)	0.001
Male gender	126 (46.0)	363 (48.7)	0.45	97 (45.1)	212 (52,1)	0.10	25 (53.2)	128 (45.6)	0.33	4 (33.3)	23 (39.7)	0.76
Age (years) mean ($\pm$SD)	11.6 ± 2.7	10.9 ± 2.8	0.0003	11.6 ± 2.7	11.0 ± 2.7	0.006	11.6 ± 2.9	10.7 ± 2.9	0.05	11.6 ± 2.6	11.4 ± 2.9	0.89
Age class 1 (4–8 years)	29 (17.8)	134 (82.2)	0.01	22 (25.6)	64 (74.4)	0.11	6 (9.0)	61 (91.0)	0.31	1 (10.0)	9 (90.0)	0.62
Age class 2 (9–13 years)	163 (27.7)	426 (72.3)		128 (34.7)	241 (65.3)		27 (14.8)	155 (85.2)		8 (21.1)	30 (78.9)	
Age class 3 (14–18 years)	82 (30.6)	186 (69.4)		65 (38.9)	102 (61.1)		14 (17.7)	65 (82.3)		3 (13.6)	19 (86.4)	
Family history for M	174 (63.5)	406 (54.4)	0.002	146 (68.5)	257 (64.9)	0.36	21 (46.7)	115 (41.4)	0.50	7 (58.3)	34 (58.6)	0.81
Family history for TTH*	34 (15.2)	100 (18.7)	0.22	21 (9.9)	39 (9.9)	0.99	12 (26.7)	53 (19.1)	0.24	1 (8.3)	8 (13.8)	0.70
Family history for O*	47 (21.0)	63 (11.8)	0.001	41 (23.7)	36 (12.4)	0.0016	3 (7.7)	16 (8.5)	0.87	3 (25.0)	11 (19.0)	0.70
Vomiting	99 (36.1)	202 (27.1)	0.005	97 (45.1)	196 (48.2)	0.470	0 (0)	0 (0)	–	2 (16.7)	6 (10.3)	0.62
Nausea	162 (59.1)	299 (40.1)	0.0001	155 (72.1)	271 (66.6)	0.160	3 (6.4)	9 (3.2)	0.28	4 (33.3)	19 (32.8)	0.97
Photophobia	209 (76.3)	404 (54.2)	0.0001	192 (89.3)	314 (77.1)	0.0002	12 (25.5)	65 (23.1)	0.72	5 (41.7)	25 (43.1)	0.93
Phonophobia	219 (79.9)	439 (58.8)	0.0001	191 (88.8)	309 (75.9)	0.0001	18 (38.3)	97 (34.5)	0.61	10 (83.3)	33 (56.9)	0.11

*These characteristics refer to a subgroup of 760 patients (patients with osmophobia = 224 and without osmophobia = 536; migraineurs with osmophobia = 173 and without osmophobia = 290; tension-type patients with osmophobia = 39 and without osmophobia = 188; headache not elsewhere classifiable sufferers with osmophobia = 12 and without osmophobia = 58).
M, migraine; TTH, tension-type headache; NEC, headache not elsewhere classified; O, osmophobia.

Table 4. Characteristics of osmophobia in the three groups of patients

	Total ($n=274$) *n* (%)	M ($n=215$) *n* (%)	TTH ($n=47$) *n* (%)	NEC ($n=12$) *n* (%)	*P*-value
Frequency*					
Always (>70%)	69 (28.9)	60 (31.8)	5 (12.5)	4 (40.0)	0.70§
Often (30–70%)	95 (39.7)	72 (38.1)	21 (52.5)	2 (20.0)	
Infrequent (10–30%)	37 (15.5)	29 (15.3)	6 (15.0)	2 (20.0)	
Rarely (<10%)	38 (15.9)	28 (14.8)	8 (20.0)	2 (20.0)	
Timing*					
Begins with the headache	156 (65.3)	126 (66.7)	26 (65.0)	4 (40.0)	0.23
Starts later	83 (34.7)	63 (33.3)	14 (35.0)	6 (60.0)	
Smell types					
Perfumes	149 (54.5)	118 (54.9)	26 (55.3)	5 (41.7)	0.66
Food	112 (40.9)	97 (45.1)	13 (27.7)	2 (16.7)	0.02
Smoke	84 (30.7)	67 (31.2)	15 (31.9)	2 (16.7)	0.56
Others	53 (19.3)	36 (16.7)	13 (27.7)	4 (33.3)	0.10
Olfactory triggers	131 (47.8)	100 (46.5)	21 (44.7)	10 (83.3)	0.04

*These characteristics refer to a subgroup of 239 patients (189 M, 40 TTH and 10 NEC).
§Chi-squared test was applied to dicotomised frequency.
M, migraine; TTH, tension-type headache; NEC, headache not elsewhere classified.

but it was reported, although less often (14.3%), also in TTH patients. This result agrees with one study in adult (46% versus 13%) (26) and one in childhood and adolescence (25.1% versus 8.3%) (9).

This large series of patients showed a direct correlation between osmophobia and age ($P<0.001$) which was not apparent in previous studies in juvenile headache conducted in small samples (8,9). Actually, the prevalence of osmophobia was higher in the older age class ($P=0.01$). The age difference in M patients was higher in the 4–8 years age group than in the 9–13 and the 14–18 age groups. This fact was peculiar to osmophobia since it was not observed in phonophobia and photophobia (data not shown). It is important that 4–8-year-old children are able to report osmophobia, even though it is a more sophisticated symptom than photo- and phonophobia. In adults, both osmophobia and the role of odours as a trigger of attacks did not show any particular correlation with age (27). As far as gender is concerned, there are reports of a higher prevalence of osmophobia in adult females (6,7) and of a slight prevalence of osmophobia in males of paediatric age (8). We did not find a significant correlation with gender ($P=0.37$), as shown in our recent study on a juvenile population (9).

Regarding age, we found a significant difference between males and females ($P<0.05$) in the osmophobic group, with a higher prevalence of osmophobia in females in the older class. This feature was not present in M group ($P=0.19$), nor in TTH patients ($P=0.18$) or in NEC patients ($P=0.41$).

The presence of both all the accompanying symptoms ($P<0.0001$) and olfactory trigger ($P=0.0005$) was distinctive of M, even though it was not exclusive for this type of headache; previous studies reported that odours can trigger both M and TTH attacks in both children (28) and adults (29).

The following characteristics could support the value of osmophobia in M diagnosis: (i) family history; and (ii) relationship with the other accompanying symptoms.

Family history of M was prevalent in the osmophobic population ($P=0.002$). Moreover, our overall paediatric sample also had a family history of osmophobia: the presence of osmophobia in one parent had a correlation, not only with the presence of osmophobia with his/her son ($P=0.001$), but also with his/her diagnosis of M ($P=0.004$). If only the M subgroup of patients was considered, family history for M and osmophobia did not show a significant correlation ($P=0.36$) but, as it is well-known in the literature, family history for M is an important characteristic in most M patients (30). Moreover, the high prevalence of family history of M (71.4%) in 36 NEC patients with current criteria and who become MO patients if Appendix 1.1 is applied supports the hypothesis that this 'new' diagnosis could be correct. The correlation with family history for osmophobia and the presence of osmophobia was significant in our M patients ($P<0.005$).

We observed that osmophobia had a greater correlation with all the other accompanying symptoms ($P<0.005$). The correlation with phonophobia ($P<0.0001$) and photophobia ($P=0.0002$) was maintained in M subgroup, but not in TTH patients ($P=0.61$ for phonophobia and $P=0.72$ for photophobia) and in NEC patients ($P=0.11$ for phonophobia

and $P = 0.93$ for photophobia). Indeed, since phonophobia and photophobia could be present also in TTH, the presence of osmophobia could be useful to discriminate when these symptoms are associated with the diagnosis of M, according to a study in adults where osmophobia was demonstrated to be very specific in the diagnosis of M, above all if it was combined with another accompanying symptom (1).

The high frequency of osmophobia during the attacks and its early onset in the headache history confirmed that osmophobia is structurally integrated in the headache history of our young patients, in agreement with the results in children (9) and in adult series (6).

The smell types that were reported with greater frequency were perfumes, followed by food odours and then smoke, in agreement with previous studies both in children (9) and in adults (6). The correlation between the food odour annoying during the attack and nausea or vomiting demonstrated that osmophobia is correlated, above all in M patients, with a complex derangement of processing of sensory stimuli (31,32). An olfactory hypersensitivity seems very specific to this form of headache, since an abnormal activation of olfactory cerebral cortex during M attacks has been observed with positron emission tomography (33).

The high agreement in MO diagnosis (96.2%) is in line with the only study which analysed the validation of A 1.1 proposed in ICHD-II in adults (20): in this study, 98.2% of MO patients were classified as well as using the proposed alternative method.

Conclusions

The criteria proposed in the Appendix 1.1 are an efficacious alternative to the current diagnostic criteria also in children, confirming what was proposed in adults (20). Moreover, it seems easier to apply in the clinical setting also during development, when the anamnesis is more difficult because of the children's limited ability in analysing and describing their symptoms.

A longitudinal perspective study is being carried out on our sample to clarify if osmophobia could be considered as a predictive symptom of M, also in patients at present fulfilling the ICHD-II criteria (14) for diagnosis of TTH.

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