Original Article

Diagnosis of primary headache in children younger than 6 years: A clinical challenge

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Abstract
Background: Criteria defined by the International headache Society are commonly used for the diagnosis of the different headache types in both adults and children. However, some authors have stressed some limits of these criteria when applied to preschool age.
Objective: Our study aimed to describe the characteristics of primary headaches in children younger than 6 years and investigate how often the International Classification of Headache Disorders (ICHD) criteria allow a definitive diagnosis.
Methods: This retrospective study analysed the clinical feature of 368 children younger than 6 years with primary headache.
Results: We found that in our patients the percentage of undefined diagnosis was high when either the ICHD-II or the ICHD-III criteria were used. More than 70% of our children showed a duration of their attacks shorter than 1 hour. The absence of photophobia/phonophobia and nausea/vomiting significantly correlate with tension-type headache (TTH) and probable TTH. The number of first-degree relatives with migraine was positively correlated to the diagnosis of migraine in the patients ($p < 0.001$).
Conclusions: Our study showed that the ICHD-III criteria are difficult to use in children younger than 6 years. The problem is not solved by the reduction of the lowest duration limit for the diagnosis of migraine to 1 hour, as was done in the ICHD-II.

Introduction

Headache is the most common neurological symptom in children and adolescents. Epidemiological studies show that recurrent primary headaches of childhood are increasing in prevalence and reducing in age of onset (1). Classification criteria defined by the International Headache Society are the main benchmarks used for the diagnosis of the different headache types in both adults and children. In 1988, the International Headache Society published the first diagnostic criteria for headache disorders (2). Nevertheless, many authors have found them difficult to use in paediatric age due to a poor specificity, compared with the clinical diagnosis as gold standard (3). The second International Classification of Headache Disorders (ICHD-II) focused on an 'evidence-based medicine' approach and partly modified the old criteria

concerning paediatric headaches (4). In particular, some criteria for migraine diagnosis, namely headache duration and unilateral/bilateral location of pain, were adapted to the paediatric population. In the third International Classification of Headache Disorders

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(ICHD-III beta version), the criterion 'duration' for migraine diagnosis in children and adolescents was modified again in a more restrictive direction, shifting from 1–72 hours to 2–72 hours (5).

Primary headaches in very young children are challenging to diagnose, due to the evolution of symptoms in an individual undergoing neurobiological development. Moreover, the symptoms associated with headache, such as photophobia and phonophobia, are rarely mentioned by the young patient, and, as reported in ICHD-III, they can be inferred from children's behaviour. However, an early diagnosis is important to define the prognosis and provide an appropriate treatment (6–9).

Studies investigated the usability of the ICHD criteria in children affected by primary headaches. In a 6-month prospective multicenter study, Curvellier et al. (10) found that the consistency of the investigator's diagnosis with the ICHD criteria was good or excellent. Despite the importance of the mentioned study, the mean age of the sample was 9.8 ± 3.1 years; thus children under 6 years of age were not included. In pre-school children, ICHD criteria for the diagnosis of primary headaches were considered inadequate; the most important limiting factor for diagnosis was the duration of the attack (11).

Our study aimed to: 1) describe the characteristics of primary headaches in children younger than 6 years, and 2) investigate how often the ICHD criteria (4,5) allow us to reach a definitive diagnosis in this population.

Materials and methods

We retrospectively reviewed the charts of patients attending the Headache Clinic of Bambino Gesù Pediatric Hospital in a period from January 2002 to December 2011.

Patients under the age of 6 were selected and those in whom a primary headache was diagnosed were included. In particular, the diagnosis of primary headache was based on the following main elements: 1) all selected children were followed for at least 1 year and no different headache aetiology could be identified in this period, 2) all children had normal neurological examination, including fundus oculi examination, along the entire period considered, 3) all children younger than 5 years had a neuroradiological examination (brain MRI or CT scan), which had to be normal. Other elements for the diagnosis of primary headache were: 1) at least one relative with primary headache (first-degree relatives), and 2) the coexistence or not of the so-called childhood periodic syndromes and related symptoms (cyclical vomiting syndrome, abdominal migraine, benign paroxysmal vertigo, benign paroxysmal torticollis, limb pain and motion sickness) (12).

None of the included children suffered from diseases potentially associated with secondary headache. None of them was assuming anti-migrainous prophylactic treatments at the time of our observations. As for the headache characteristics, we considered: 1) pain location, 2) pain quality, 3) attack frequency, 4) attack intensity (obtained by children's behaviour during the attacks), 5) mean duration of the longest three attacks, 6) associated symptoms (photophobia, phonophobia, nausea and vomiting), 7) worsening due to physical activity, and 8) symptoms or signs of aura. All information was issued from clinical headache diaries, given to the families at the initial visit. The diaries were returned after 2 months, at the time of the clinical control. Regarding attack duration, we told the parents to consider the attack from the beginning of pain to the end, including sleep time when the child referred to headache before going to sleep. Moreover, the attack had to be considered ended when even mild pain disappeared. The end of the attack in the younger children was recognized with the resumption of routine activities. We considered only attacks with spontaneous resolution.

Statistical analysis was conducted by using the dedicated software MYSTAT 12 (v.12.02.). We used a χ^2 test for the correlation analysis and a logistic regression for the regression analysis.

Values of $p < 0.05$ were considered significant.

Results

### Descriptive analysis of headache characteristics and associated symptoms

We identified 526 patients aged < 6 years of 4000 referred to our Headache Centre. Among them, 368 children satisfied the inclusion criteria for the study. In the excluded 158 patients, a diagnosis of secondary headache was either possible or defined. The mean age of our included patients (48.9% boys and 51.1% girls) was 4.4 ± 1.2 years. Pain location, quality, and intensity and attack frequency are shown in Table 1.

As for attack duration, seven groups may be identified: 1) < 10 minutes (108 patients; 29.2%); 2) between 10 and 30 minutes (99 patients; 26.9%); 3) between 30 and 60 minutes (54 patients, 14.6%); 4) between 60 and 90 minutes (11 patients; 2.7%); 5) between 90 and 120 minutes (29 patients; 8.1%); 6) between 120 and 180 minutes (53 patients; 14.6%); 7) > 180 minutes (14 patients; 3.9%) (Figure 1). Interestingly, the majority of patients (260 patients; 70.8%) referred to a duration of < 60 minutes (Figure 1).

Most patients (268; 73%) experienced at least one of the following associated symptoms: photophobia (42.6%), phonophobia (44.1%), vomiting (23.3%) or

Table 1. Headache characteristics in our sample.

Location of pain	Frontal	134/368 pts (36.41%)
	Bilateral	80/368 pts (21.74%)
	Whole head	42/368 pts (11.41%)
	Lateralized	21/368 pts (5.7%)
	Other	91/368 pts (13.26%)
Intensity of pain	Mild	59/368 pts (15.83%)
	Moderate	99/368 pts (27%)
	Severe	210/368 pts (57.14%)
Pain quality	Throbbing	100/368 pts (27.1%)
	Gravative	52/368 pts (14.13%)
	Pressing	70/368 pts (19.02%)
	Other quality	41/368 pts (11.14%)
	Not determined	10/368 pts (28.53%)
Frequency of attacks	Less than 2 per month	111/368 pts (30.32%)
	Between 2 and per month	87/368 pts (23.47%)
	More than 4 per month	128/368 pts (34.74%)
	Daily	42/368 pts (11.29%)
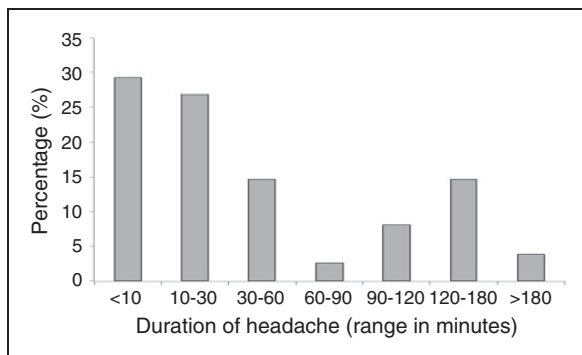
Figure 1. The histogram shows the cumulative percentage of patients with different time ranges of headache attack duration. Notice that in most our patients the headache attack lasted less than 30 minutes.

nausea (22.1%). When photophobia and phonophobia occurred together, we found that throbbing pain was statistically more frequent ($p < 0.001$; Figure 2A). Whereas pain intensity was significantly milder when only one of the two symptoms was present ($p < 0.001$; Figure 2B), both symptoms were associated with pain worsening due to physical activity ($p < 0.01$).

No significant difference between boys and girls regarding headache features was found.

In 290 patients, at least one first-degree relative suffered from primary headache (migraine without aura, Mwo, or tension-type headache, TTH). Mother and father suffered from headache in 175 and 74 children, respectively, whereas 41 patients had both parents with primary headache.

Diagnosis of primary headache according to the ICHD-II and ICHD-III criteria

The diagnosis obtained by using either the ICHD-II or the ICHD-III criteria are shown in Figure 3. According to the ICHD-II criteria (black columns in Figure 3), a high number of patients had a diagnosis of either 'probable migraine' (pMwo) or 'probable TTH' (pTTH). Moreover, 31.6% of patients remained undiagnosed. Approximately the same results were obtained by using the ICHD-III criteria (white columns in Figure 3).

With the aim to identify determinants among the headache characteristics and associated symptoms that allow a correct diagnosis, we performed a multivariate logistic regression analysis. Significant results are displayed in Table 2. We found that associated symptoms were distributed as expected from ICHD-II criteria in 'probable diagnoses'. In other words, the absence of photophobia/phonophobia and nausea/vomiting were significantly not associated with the diagnosis of both Mwo [positive predictive value (PPV) 16%; negative predictive value (NPV) 75%; $p < 0.05$] and pMwo (PPV 23%; NPV 63%; $p < 0.05$), whereas it was significantly associated with the diagnosis of both TTH (PPV 87%; NPV 17%; $p < 0.05$) and pTTH (PPV 95%; NPV 37%; $p < 0.01$). Moreover, pain of mild intensity and pressing quality was significantly associated with the diagnosis of TTH (PPV 96%; NPV 30%; $p < 0.05$) and pTTH (PPV 95%; NPV 37%; $p < 0.05$). The same distribution was found using the ICHD-III criteria (data not shown). All together, these observations confirm that a correct investigation about the associated symptoms and the intensity/quality of pain is useful for a correct diagnosis of primary headache.

The number of first-degree relatives with migraine was positively correlated to the diagnosis of migraine in the patients [$p < 0.001$; 95% confidence interval (CI) 23.20–30.70]. Conversely, a negative correlation was found between relatives with migraine and children with TTH ($p < 0.001$; 95% CI − 36.86 to 24.94).

ICHD criteria revised in our population

Our patients were re-classified after modification of ICHD criteria by excluding the 'headache duration'. It was found that the percentage of diagnosis of both migraine and TTH (Figure 4) increased, compared with both ICHD-III and ICHD-II ($p < 0.001$). The groups of pMwo and pTTH and that of undefined diagnosis decreased ($p < 0.001$). However, the latter group still accounted for 16.1% of cases.

As familiarity for migraine (number of migrainous first-degree relatives) correlated with the diagnosis of migraine, we introduced familiarity as an adjunctive
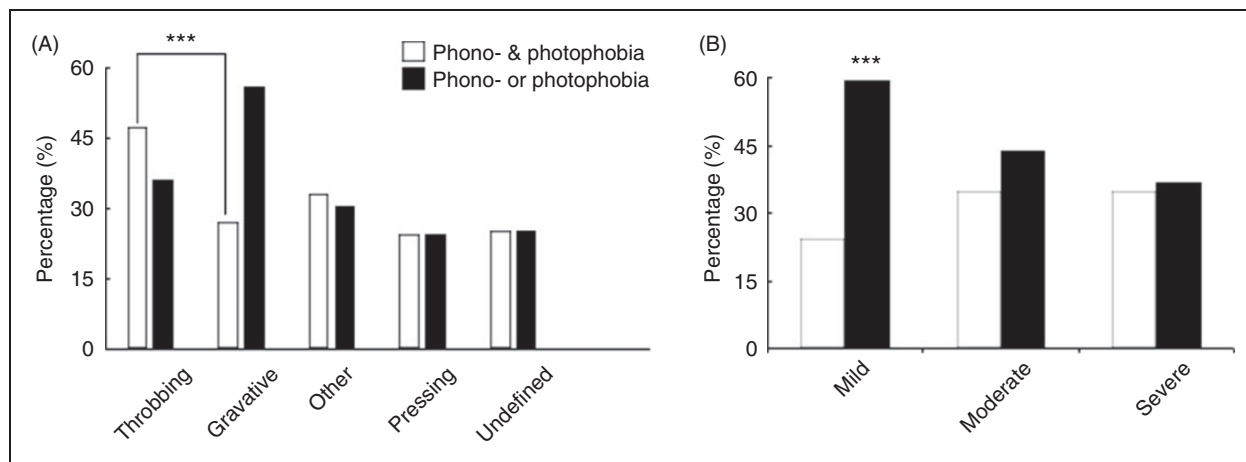
Figure 2. The histograms show the presence of both photophobia and phonophobia (white columns) or only one of them (black columns) in patients with pain of different quality (A) and intensity (B). Notice that the concomitant presence of photophobia and phonophobia is associated with throbbing pain, whereas the patients with mild pain usually show only one of these associated symptoms. ***$p < 0.001$.
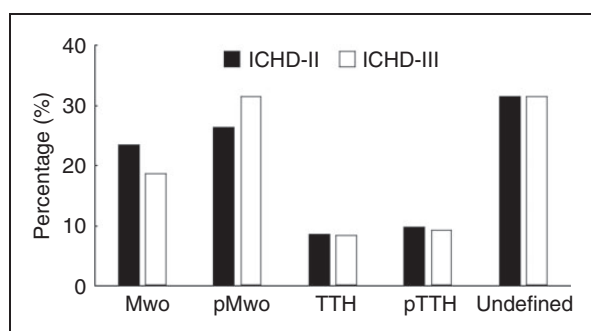

Figure 3. Classification of our patients by using the ICHD-II (black columns) and ICHD-III (white columns) criteria.

criterion. Interestingly, the undefined group further decreased from 16.1% to 8.5% ($p < 0.05$).

Discussion

The main feature of our study is that the current ICHD criteria, in both their second and third versions, can be improved in order to increase the probability of a definitive diagnosis of primary headache in children younger than 6 years. In particular, our findings showed that removing the criterion of 'headache duration' and considering the 'familiarity for migraine' reduced the undefined diagnoses by more than 20% (from 31.6% to 8.5%).

Are ICHD criteria useful for the diagnosis of primary headache in children?

The introduction of the ICHD criteria played a primary role in the diagnosis of several cephalalgic patterns.

This is fundamentally important, as only a correct diagnosis may drive the therapeutic approach (9,13).

Since the initial publication of the first edition of the ICHD criteria in 1988 (2), the indication to consider a time interval of 2 hours as the shortest headache attack duration for the diagnosis of migraine in children has been debated. Several studies showed that the attack duration represents a major limiting factor to reaching a definite diagnosis in children. In a population-based study, around 10% of children with migraine had headache attacks lasting between 1 and 2 hours (14). In 88 children and adolescents, Winner et al. (15) proposed a revisited classification for migraine in paediatric age including the following items: 1) duration – 1–48 hours, 2) location – bifrontal, bitemporal or unilateral, and 3) associated symptoms – including photophobia or phonophobia. Significant improvement in the diagnostic sensitivity of migraine in paediatric population was obtained by applying these specific modifications. A shorter duration of the attacks and the possibility of a bilateral location of pain were the main modifications to previous criteria (15,16). Balottin et al. (17) investigated the clinical features of primary headaches with early onset. They found a large disagreement between the intuitive clinical diagnosis and that based on the ICHD criteria, and attributed it to several factors: 1) the inability of the young patients to describe their own headache features, 2) the failure to meet the criterion of attack duration for migraine and TTH, and 3) the presence of migraine-like symptoms in some patients with a diagnosis of TTH. In a retrospective study of 243 children affected by primary headache, it was found that the attack duration was shorter and the associated symptoms were less intensive in preschool children than in patients older than 6 years (11). The application

Table 2. Determinants associated with the diagnosis of Mwo/pMwo and TTH/pTTH (ICHD-II criteria).

Parameter	Estimate	Standard error	Z	*p*-value	95% Confidence interval Lower	Upper	S; s; PPV; NPV
Mwo							
No photophobia No phonophobia	−1.695	0.574	−2.955	0.003	−2.819	−0.570	S 68%; s 22%; PPV 16%; NPV 75%
No nausea	−2.878	0.850	−3.384	0.001	−4.544	−1.211	S 58%; s 19%; PPV 23%; NPV 63%
No vomiting	−1.720	0.622	−2.766	0.006	−2.939	−0.501	S 66%; s 22%; PPV 25%; NPV 60%
pMwo							
No photophobia No phonophobia	−2.387	0.557	−4.285	0.000	−3.478	−1.295	S 60%; s 19%; PPV 19%; NPV 60%
No nausea	−2.223	0.853	−2.606	0.009	−3.896	−0.551	S 66%; s 21%; PPV 31%; NPV 54%
No vomiting	−1.503	0.607	−2.475	0.013	−2.693	−0.313	S 63%; s 21%; VP 30%; NPV 51%
TTH							
No photophobia No phonophobia	2.927	0.993	2.948	0.003	0.981	4.873	S 81%; s 25%; PPV 87%; NPV 17%
Pressing pain	2.893	1.169	2.474	0.013	0.601	5.185	S 34%; s 91%; PPV 22%; NPV 98%
Mild pain	3.638	1.229	2.961	0.003	1.230	6.046	S 56%; s 91%; PPV 96%; NPV 30%
pTTH							
No photophobia No phonophobia	4.954	1.383	3.581	0.000	2.243	7.665	S 55%; s 92%; PPV 95%; NPV 37%
Mild pain	3.910	1.289	3.032	0.002	1.383	6.437	S 55%; s 92%; PPV 95%; NPV 37%

Results of multinomial logistic regression: Mwo and pMwo correlated negatively (estimate with negative sign) with the absence of phono- and photophobia, nausea and vomiting. TTH and pTTH groups correlated positively with the absence of phono- and photophobia, as well as with pressing pain and mild pain.

Mwo: migraine without aura, pMwo: probable migraine without aura, TTH: tension-type headache, pTTH: probable tension-type headache, S: sensibility, s: specificity, PPV: positive predictive value, NPV: negative predictive value.
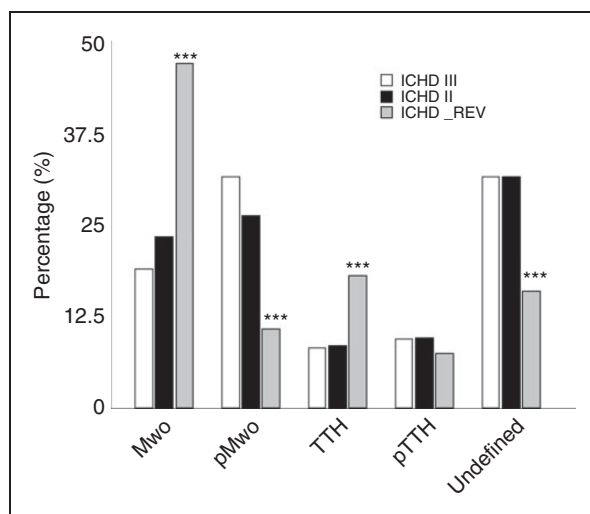

Figure 4. Classification of our patients by using the ICHD-II (black columns), ICHD-III (white columns) and ICHD_REV (grey) criteria. The ICHD_REV criteria are as the ICHD III ones from whom the item 'headache duration' was removed. Notice the increase of migraine without aura (Mwo) and tension-type headache (TTH) diagnoses, together with a reduction of the undefined diagnosis group, with the ICHD_REV criteria. ***$p<0.001$.

of Winner et al.'s revised criteria (15) increased the number of migraine diagnosis in both groups of patients, suggesting that the ICHD criteria may not fully lead to a definite headache diagnosis in juvenile age, especially in preschool children.

In the ICHD-II, published in 2004, the lower limit for migraine attack duration was reduced to 1 hour for children. However, in spite of this modification, several authors considered the ICHD-II unsuitable for a correct diagnosis of primary headache in paediatric age. Balottin et al. (18) studied the clinical evolution in 25 migraine children who had experienced headache before the age of 6. The authors underlined that, using the ICHD-II criteria, a definite diagnosis at time zero was possible only in 9 of 25 patients. In a population of 417 children (2–12 years), the ICHD-II criteria for migraine proved to have high specificity but low sensitivity (19). Another interesting study evaluated the headache characteristics in 260 children by using four different sets of diagnosis: clinical diagnosis, ICHD-I, ICHD-II and ICHD-IIA (Appendix) (20). The expert opinion was considered the gold standard. When ICHD criteria were used, around 70% of patients met the diagnosis, whereas the diagnostic

sensitivity increased to 80.8% if the headache duration was excluded.

The results by Cuvellier et al. (10) were apparently in contrast to the previous ones. Indeed, they showed that the consistency of the investigator's clinical diagnosis and that based on the ICHD-II criteria was good or excellent in their 486 patients. However, the study did not consider children under 6 years of age.

In childhood and adolescence, the achievement of a definitive diagnosis of a primary headache can be hampered also by the phenomenon of transformation of headache type (21). Transformation from migraine to TTH was reported to be 8–32%, and from TTH to migraine, 4–41% (22–25). There are two possible explanations for the changing pattern of childhood headache. First, according to the 'continuum severity theory', primary headache represents a continuum between TTH and migraine. In this model, headache is labelled tension-type when the pain is mild, as common migraine when the pain is more severe and as classic migraine when the pain is associated with neurological symptoms (26). Second, many children may suffer from two or more types of primary headaches, which may start at different ages.

The present study is the first to investigate whether the ICHD-III criteria, in which the shortest attack duration for the diagnosis of migraine was increased again to 2 hours, may be suitable for the diagnosis of primary headache in children younger than 6 years. We found that, in our patients, the percentage of undefined diagnosis was high when either the ICHD-II or the ICHD-III criteria were used. This means that the increase of the minimum attack duration in the ICHD-III, compared with ICHD-II, did not worsen the diagnostic accuracy, which remained inadequate. Indeed, more than 70% of our children showed a duration of their attacks shorter than 1 hour.

Primary headache characteristics in children younger than 6 years

Clinical characteristics of primary headaches may be different in childhood and in adult age. On one hand, this reflects the expression of common pathophysiological mechanisms occurring in a nervous system that is still developing. A child cannot be considered a 'small adult' (27), and many developmental and individual factors may affect the phenotypes of the primary headaches. On the other hand, neurophysiological studies showed that primary headaches in children have peculiar pathophysiological features, which are not found in adult migraineurs and TTH patients (28).

Our very young children with primary headache differed from the adults in pain location. Unilateral headache, typical of adult age, was uncommon (5.7% of cases) and a bilateral frontal pain was reported by most patients. The most interesting difference concerned headache duration, which was shorter than 2 hours, the lowest threshold for the diagnosis of migraine, in more than 75% of cases. Attack duration was even shorter than 30 minutes, the lowest limit for the diagnosis of TTH, in 56.2% of cases. A short duration of the headache attacks seems a major characteristic of paediatric headache and may reflect pathophysiological peculiarities in the mechanisms underlying the attack in children. However, it should be underlined that the problem of determining the duration of the attack in children may be also related to the difficulty in understanding when the attack truly ends. Furthermore, considering the child behaviour (reprisal of the normal activity) can lead to the bias of judging a headache attack ended while the child is still having mild pain. This possibility may have artificially shortened the headache attack duration in some of our youngest children.

Compared with pain duration, other headache features, including associated symptoms, seem to be more useful for a definite diagnosis of primary headache. In our sample, the presence of photophobia and phonophobia was associated with throbbing pain, typical of migraine, while absence of these symptoms was associated with gravative pain of mild intensity, as observed in TTH. Moreover, the regression analysis revealed that symptoms associated with headache were congruent with the diagnosis: that the absence of photophobia and phonophobia correlated negatively with the diagnosis of migraine, and that low intensity pain occurred more frequently in TTH patients than in migraineurs.

An opening question in the diagnostic workup of paediatric headache concerns the difficulty in recognizing symptoms in very young children who cannot communicate or describe them. Therefore, although the diagnostic workup for children suffering from headache is similar to that used for adults, certain peculiarities must be considered. In our daily activity, we also consider non-verbal behaviours, which may indicate migrainous headache: the preference of the child to be in a dark room (photophobia) and/or in a quiet environment (phonophobia), intensity of crying, interference of the pain with daily activities (game, homework, need to stay at bed), suffering face, pale colour of the skin, food refusal and grumbling.

Another important element that may help to reach a definite diagnosis of primary headache in very young children is represented by familiarity for migraine. Indeed, when our patients were re-classified on the basis of ICHD criteria with the exclusion of duration, we had an increase of patients with diagnosis of migraine and TTH. There was a decrease also in the group of undefined diagnosis, however, which kept

including 16% of our patients. Only when the familiarity for migraine was considered did this percentage drop to a more acceptable 8.5%. Genetic epidemiological studies reported that, compared with the general population, first-degree relatives of probands with migraine without aura had a 1.9-fold increased risk of migraine without aura and a 1.4-fold increased risk of migraine with aura (29). Moreover, recent studies showed that having a genetic background of migraine makes a child more susceptible to the condition earlier in life than not having a genetic background (30,31).

Limitations of the study

Our results are issued from a monocentric retrospective study, and thus the proposed criteria need to be confirmed and validated in a perspective multicenter trial. Moreover, the population in study consisted of patients referred to a third-level headache centre and this may result in a biased sample, which may represent the severe end of the clinical spectrum and not the average child with headache. For this reason, we may have missed clinical features of primary headaches present in the general population and not evident in our 'selected' sample.

Conclusions

Our study showed that the ICHD-III criteria are difficult to use in children younger than 6 years. The problem is not solved by the mere reduction of the lowest duration limit for the diagnosis of migraine to 1 hour, as was done in the ICHD-II. Removing the criterion of headache duration allowed us to have a definite diagnosis of primary headache in more than 80% of our children and this value increased to more than 90% if we also considered the familiarity for migraine. Moreover, our findings showed that the associated symptoms, particularly phonophobia and photophobia, can represent useful clinical elements for diagnosing primary headache in preschool children.

Article highlights

- ICHD criteria can be difficult to use in very young children.
- Headache attack duration can be shorter than 30 minutes in children under 6 years.
- Removing the 'headache duration' from the ICHD criteria improves the sensitivity in children under 6 years.
- Familiarity for migraine should be considered among the ICHD criteria for migraine diagnosis.

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