CLINICAL AND PATHOPHYSIOLOGICAL PECULIARITIES OF HEADACHE IN CHILDREN AND ADOLESCENTS

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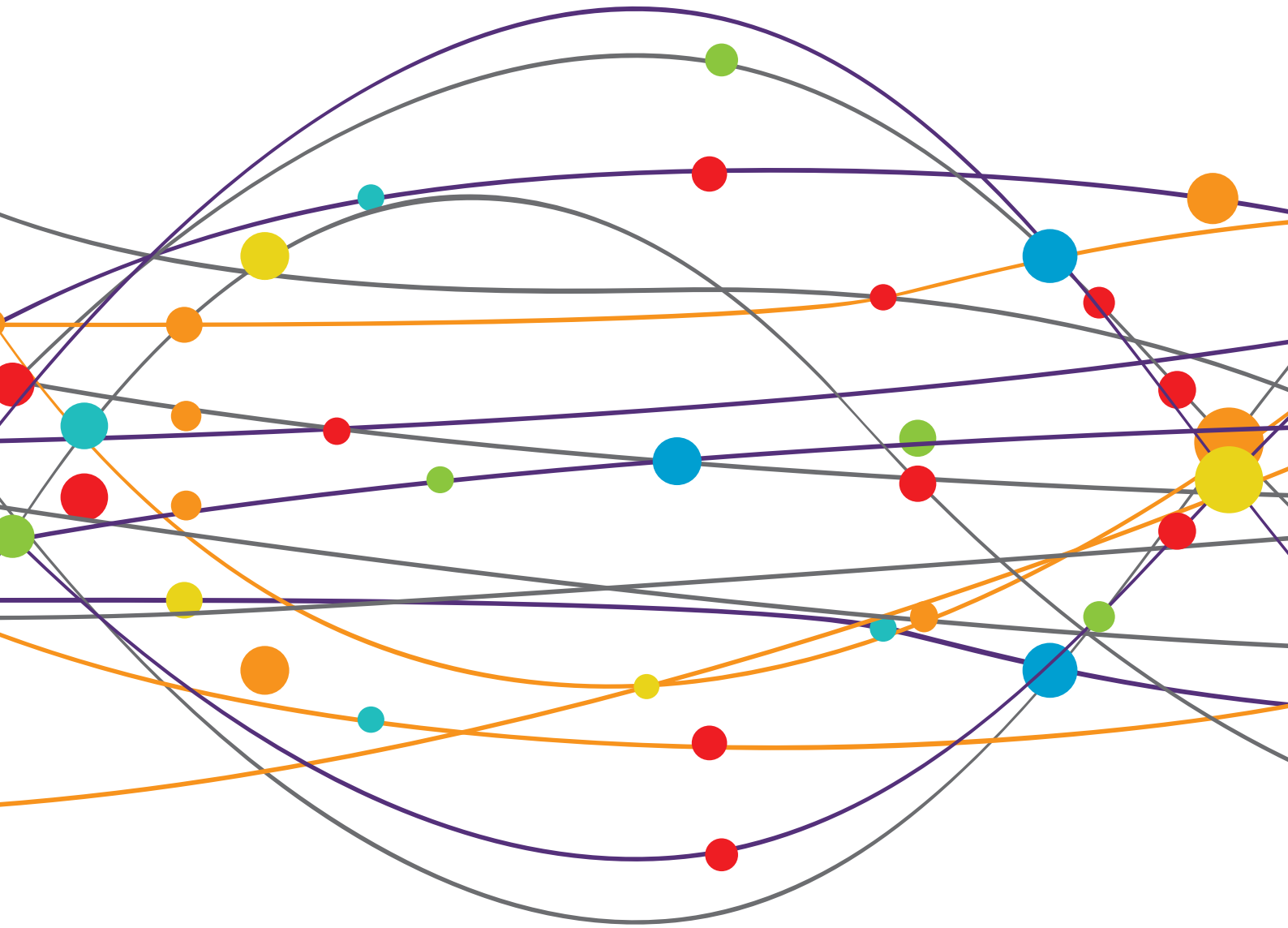

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CLINICAL AND PATHOPHYSIOLOGICAL PECULIARITIES OF HEADACHE IN CHILDREN AND ADOLESCENTS

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EDITORIAL
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Editorial: Clinical and Pathophysiological Peculiarities of Headache in Children and Adolescents

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Editorial on the Research Topic

Clinical and Pathophysiological Peculiarities of Headache in Children and Adolescents

Headache is a very common disorder in adults as well as in children and adolescents. Tension-type headache, migraine, and medication overuse headache are the most prevalent neurological diseases (1) and, therefore, it is not surprising to see a large number of published studies on the clinical characteristics, pathophysiology, and treatment of headache disorders. Despite its high prevalence in children and adolescents and despite being the most common neurological condition for which children are referred for specialist pediatric neurology services, headache continues to be underdiagnosed and undertreated. There are no easy answers for the causes of underdiagnosis and undertreatment of childhood headache. However, it is possible that lack of attention and lack of recognition of the specific peculiarities of the different types of headaches in children may play a major part in this problem. Furthermore, and unfortunately, the international classification of headache disorders in their successive editions do not discuss the pediatric presentation of the different headache disorders except for certain aspects of migraine, giving the erroneous impression that primary and secondary headaches in children are just smaller versions of their counterparts in adult.

In assessing headaches in children, it is important to take into consideration the following major points: Firstly, the clinical, features, presentations, trigger factors, relieving factors, and interpretation of children's behavior during attacks of migraine and tension-type headaches, the most frequent types of primary headaches, can be very different, particularly in young children as compared to adults. Secondly, there is some evidence to suggest that genetic factors, pathophysiological mechanisms, brain development, and maturation of cerebral networks during childhood can influence the presentation of headache disorders in different age groups. Thirdly, children's responses to pharmacological and non-pharmacological treatment of migraine are shown to be different in the pediatric population. The placebo response has been shown to be so powerful in children to make it difficult to interpret the results of clinical trials of acute and preventive treatments (2). Fourthly, common secondary headaches in adults are much less common in children such as cerebrovascular diseases, substance misuse and psychiatric disorders, etc.

The present Research Topic aims to collect clinical observations and experimental evidence highlighting the peculiarities of headaches at this early stage of life. Eleven papers were published as part of the Research Topic and they all made useful contributions in showing how large and varied is the world of pediatric headaches. Most studies discussed issues related to diagnosis and two studies addressed treatment options.

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Looking at the published studies in details, four papers (Moavero et al.; Papetti et al.; Toldo et al.; Parisi et al.) investigated the applicability of the 3rd edition of the International Classification of Headache Disorders (ICHD3). It was shown that, although the ICHD3 is a very useful tool for the diagnosis of headache even in pediatric age, some peculiar clinical characteristics, e.g., the shorter headache attack duration especially in pre-school children, have not been included. Moreover, Toldo et al. underlined the differences in the clinical presentation of hemiplegic migraine between children and adults. On the issue of ictal epileptic headache in children, Parisi et al. suggest that ICHD3 criteria are too vague and, in particular, fail to consider the diagnostic role of the immediate remission of EEG abnormalities and headache after intravenous administration of an anti-epileptic drug.

Cuvellier analyzed prodromic and postdromic symptoms in children and adolescents with migraine. He proposed the interesting hypothesis that these symptoms may shed light on pathophysiological mechanisms that may be specific of the developing brain.

Raucci et al. reviewed the literature concerning the management of headache in the emergency department. This is a clinically relevant issue as life-threatening etiologies of headache exist in any age including children, but fortunately less common than in adulthood. Since the misdiagnosis of these conditions can lead to serious consequences, clear red flags are necessary to improve the safety of young patients and to avoid inappropriate invasive examinations and investigations.

When dealing with pediatric migraine, comorbidities should always be considered. The study by Roccella et al. showed a reduction of arousability and lower NREM sleep instability associated with migraine without aura. This subject deserves further investigation in the future, since it could have important therapeutic implications.

In children and adolescents with migraine, psychiatric comorbidities can have a key role in determining the severity of the disease. Both studies included in the Research Topic (Genizi et al.; Sciruicchio et al.) suggest that personality traits, such as abnormal processing of sensory information and pain catastrophizing, modulate the clinical presentation of migraine and can be fundamental in its chronification.

Although new promising drugs for the treatment of migraine, such as the antiCGRP agents, have been introduced, their use will be limited to adulthood for the next years, since the clinical trials in children and adolescents have just started. The encouraging response to non-invasive stimulation of the brain in the treatment of headache in adults prompted its adoption in pediatric practice, as suggested by Brighina et al. The non-pharmacological interventions for migraine treatment in children, reviewed by Andrasik et al., bear an important role, also in consideration of the side effects associated with the use of preventive drugs, and the limited evidence about their efficacy (2).

In conclusion, we believe that the studies included in this Research Topic highlight eloquently the important differences between adult and childhood headache in its clinical characteristics, diagnostic criteria, pathophysiology and in the treatment approaches. These studies will, hopefully, help in establishing childhood headache as a special entity and not just a "small version of adult headache." Investigating the pathophysiology and the clinical features of children's headaches is mandatory for primary headaches, whose genetic background can be unveiled, with a lower incidence of environmental factors than in adults. Also the treatment of pediatric headaches should not merely mirror that of adult headaches, since pharmacological and non-pharmacological therapies in children and adolescents should take account of the characteristics of the developing brain and the comorbidities typical of this age.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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Clinical Features of Pediatric Idiopathic Intracranial Hypertension and Applicability of New ICHD-3 Criteria

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Idiopathic intracranial hypertension (IIH) is characterized by intracranial pressure >28 cmH_2O in the absence of identifiable causes. Aim of this paper is to describe the clinical phenotype of pediatric IIH and to analyze the applicability of ICHD-3 criteria in comparison to the ICHD-2. We conducted a retrospective analysis of full clinical data of pediatric patients diagnosed with IIH between January 2007 and June 2018. Diagnostic evaluation included neuroimaging (all patients) and ultrasound-based optic nerve sheath diameter measurement (9 patients). Diagnosis of IIH was verified according to both ICHD-2 and ICHD-3 criteria for headache attributed to IIH, to verify the degree of concordance. We identified 41 subjects with suspected IIH; 14 were excluded due a diagnosis of secondary IH or lack of data. We therefore selected 27 subjects (age 4–15 years, mean 11). All patients presented with headache and bilateral papilloedema. Headache was daily in 22% cases, with diffuse gravative pain in 41%. In 4%, pain was exacerbated by cough, stress or tension. The most common presentation symptoms, in addition to headache, were blurred vision or diplopia (70%), vomiting (33%), and dizziness (15%). Twenty patients (74%) were obese. In 6 patients (22%) neuroimaging showed empty sella. Optic nerve sheath distension was detected in 6 out of 9 patients. Regarding the applicability of the ICHD-2 criteria, 18/27 (71%) patients have criterion A; 24/27 (89%) criterion B; 27/27 (100%) criterion C; 27/27 (100%) criterion D. When the ICHD-3 criteria were used, 27/27 (100%) fitted criterion A; 24/27 (89%) criterion B; 27/27 (100%) criterion C; and 27/27 (100%) criterion D. Our study suggests that, as compared with the ICHD-2, the new ICHD-3 criteria for headache attributed to IIH are better satisfied by pediatric patients with IIH. This is mainly due to the fact that qualitative headache characteristics are no longer considered in ICHD-3. Although the risk of under-rating the symptom of headache in IIH should not be disregarded, in pediatric population headache characteristics are usually less defined than in adults and obtaining a precise description of them is often very difficult.

Keywords: pseudotumor cerebri, idiopathic intracranial hypertension, papilloedema, children, adolescents, ICHD-2, ICHD-3

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INTRODUCTION

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri syndrome (PTC), is a rare pediatric neurological disorder (1). It is characterized by increased intracranial pressure (ICP) in the absence of any brain parenchymal lesions, vascular malformations, hydrocephalus, or central nervous system (CNS) infection (2). The diagnosis is usually confirmed by high opening pressure (OP) of cerebrospinal liquid (CSF) (more than 25 cm H_2O), provided there are no secondary causes of intracranial hypertension. In 2013, the opening pressure (OP) for children aged from 1 to 18 years of age was redefined, and the upper limit for a normal OP is actually 28 cm H_2O in the pediatric population (1, 3).

IIH is more frequent in females (females-males ratio 4:1), especially in the reproductive age, with overweight being a significant adjunctive risk factor. Indeed, in fertile age overweight females, the estimated incidence is 12–20 per 100,000 people per year, vs. a general incidence in the adult population of 0.5–2 per 100,000 (4, 5). The exact prevalence of IIH in the pediatric population is not yet well established. Recently, studies from the United Kingdom applying the Friedman criteria revealed an annual incidence of 0.71 per 100,000 (1, 6).

The pathogenesis of IIH is still largely unknown. ICP is determined by the balance between production and absorption of CSF. According to the Monro-Kellie rule, an increase in ICP might be related to increased CSF, expanded brain tissue, or increased blood volume (7). Proposed hypotheses include excess of CSF production, CSF outflow reduction, increase in cerebral blood volume and/or brain water content, obstruction to venous system, endocrinological or metabolic causes, chronic inflammation, and obesity (in pre- and post-pubertal females) (8–15).

The characteristic signs and symptoms of IIH were initially described by Dandy and were later organized into the Modified Dandy Criteria by Smith, combining the lack of other causes of increased ICP (such as neoplasms and cerebral venous sinus thrombosis—CVST), with the presence of the following features: symptoms of increased ICP, papilloedema and raised opening cerebrospinal fluid (CSF) pressure at lumbar puncture (LP) (16) (see **Table 1**). In 2013, revised diagnostic criteria for IIH have been published by Friedman and coworkers, not including symptoms of raised ICP (**Table 2**) (3). According to these revised criteria, IIH can be classified as "definite" (increased OP and either papilloedema or abducens nerve palsy), "probable" (normal CSF pressure in presence of papilloedema), or "suggestive of" (raised CSF pressure plus at least three valid neuroimaging markers of raised ICP, in the absence of papilloedema and abducens nerve palsy) (3).

Headache is the most common presentation symptom of IIH. However, the characteristics of the headache in IIH patients are widely variable and not specific to IIH. Headache is often referred as unusually severe and can be lateralized and throbbing or pulsatile. It can be intermittent or persistent, occurring daily or less frequently, and nausea and vomiting can be present. Headache can be exacerbated by posture changes, and some patients may report relief with non-steroidal anti-inflammatory drugs and/or rest, although drug refractoriness is common. Therefore, in most cases, headache characteristics are similar to migraine and tension-type headache (17). If retrobulbar pain and pain with eye movement or globe compression are present, they can be highly suggestive of IIH (17). Since headache may be the main symptom of changes in ICP, diagnostic criteria for "Headache attributed to IIH" have been published by the Headache Classification Committee of the International Headache Society (IHS) in the second international classification of migraine disorders in 2004 and subsequently modified in 2018 in the third classification (18, 19) (**Tables 3**, **4**). Some patients, especially younger children, might present intracranial hypertension without headache (20). In the absence of headache, the diagnosis is often

TABLE 1 | Modified Dandy Criteria (16).

1. Signs and symptoms of increased intracranial pressure (headaches, nausea, vomiting, transient obscurations of vision, papilledema).
2. No localizing neurologic signs otherwise, with the single exception being unilateral or bilateral VI nerve paresis.
3. CSF can show increased pressure, but no cytologic, or chemical abnormalities otherwise.
4. Normal to small symmetric ventricles must be demonstrated (originally required ventriculography, but now demonstrated by CT).

TABLE 2 | Diagnostic criteria for pseudotumor cerebri syndrome.

1. Required for diagnosis of pseudotumor cerebri syndrome[a]
A. Papilledema
B. Normal neurologic examination except for cranial nerve abnormalities
C. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used
D. Normal CSF composition
E. Elevated lumbar puncture opening pressure [≥250 mm CSF in adults and ≥280 mm CSF in children (250 mm CSF if the child is not sedated and not obese)] in a properly performed lumbar puncture
2. Diagnosis of pseudotumor cerebri syndrome without papilledema
In the absence of papilledema, a diagnosis of pseudotumor cerebri syndrome can be made if B–E from above are satisfied, and in addition the patient has a unilateral or bilateral abducens nerve palsy
In the absence of papilledema or sixth nerve palsy, a diagnosis of pseudotumor cerebri syndrome can be suggested but not made if B–E from above are satisfied, and in addition at least 3 of the following neuroimaging criteria are satisfied:
i. Empty sella
ii. Flattening of the posterior aspect of the globe
iii. Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
iv. Transverse venous sinus stenosis

[a] *A diagnosis of pseudotumor cerebri syndrome is definite if the patient fulfills criteria A–E. The diagnosis is considered probable if criteria A–D are met but the measured CSF pressure is lower than specified for a definite diagnosis.*

TABLE 3 | ICHD-2 criteria for headache attributed to IIH (19).

Headache attributed to IIH
(A) Progressive headache with at least one of the following characteristics and fulfilling criteria C and D:
1. Daily occurrence
2. Diffuse and/or constant (non-pulsating) pain
3. Aggravated by coughing or straining
(B) Intracranial hypertension fulfilling the following criteria:
1. Alert patient with neurological examination that either is normal or demonstrates any of the following abnormalities:
(a) Papilloedema
(b) Enlarged blind spot
(c) Visual field defect (progressive if untreated)
(d) Sixth nerve palsy
2. Increased CSF pressure (200 mm H_2O in the non-obese, 250 mm H_2O in the obese) measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring
3. Normal CSF chemistry (low CSF protein is acceptable) and cellularity
4. Intracranial diseases (including venous sinus thrombosis) ruled out by appropriate investigations
5. No metabolic, toxic or hormonal cause of intracranial hypertension
(C) Headache develops in close temporal relation to increased intracranial pressure
(D) Headache improves after withdrawal of CSF to reduce pressure to 120–170 mm H_2O and resolves within 72 h of persistent normalization of intracranial pressure

TABLE 4 | ICHD-3 criteria for headache attributed to IIH (18).

Headache attributed to IIH
(A) New headache, or a significant worsening of a pre-existing headache, fulfilling criterion C
(B) Both of the following:
1. Idiopathic intracranial hypertension (IIH) has been diagnosed
2. cerebrospinal fluid (CSF) pressure exceeds 250 mm CSF (or 280 mm CSF in obese children)
(C) Either or both of the following:
1. Headache has developed or significantly worsened in temporal relation to IIH, or led to its discovery
2. Headache is accompanied by either or both of following:
a) pulsatile tinnitus
b) papilloedema
(D) Not better accounted for by another ICHD-3 diagnosis

suggested by accidental finding of papilloedema during routine ophthalmologic evaluations.

OBJECTIVE OF THE STUDY

The aim of this study was to analyze the applicability of the new ICHD-3 criteria in comparison to the ICHD-2 criteria in a sample of pediatric patients suffering from headache attributed to IIH.

PATIENTS AND METHODS

We retrospectively analyzed clinical, laboratory, and neuroimaging data of pediatric patients admitted for headache and finally diagnosed with IIH in the Headache Center of Bambino Gesù Children's Hospital between January 2007 and June 2018. Patients with incomplete data for whom a complete verification of diagnosis was not possible were not included in the present study. Also patients with secondary IH have been excluded. Diagnostic evaluation included neuroimaging studies for all patients, and in some cases ultrasound-based optic nerve sheath diameter (ONSD) measurement. All patients/parents/caregivers have been contacted by phone to evaluate whether they suffered from headache before the acute episode, and to understand if clinical characteristics presented some differences.

In all patients diagnosis of IIH was verified both according to ICHD-2 and ICHD-3 criteria for headache attributed to IIH, to verify the degree of concordance.

RESULTS

We identified a total of 41 subjects diagnosed with IIH. Four patients have been excluded due to the identification of possible causes of IH (including cyclosporin therapy and hypoparathyroidism); 10 patients received a clinical diagnosis based on the presence of headache, papilloedema, and obesity, but have been excluded due to lack of data (lumbar puncture not performed or data not available). We therefore selected 27 subjects (15 F, 12 M), ranging between 4 and 15 years of age (mean age 11 years). All patients presented with headache and physical examination revealed the presence of bilateral papilloedema in all of them. Only 3 of them (patients #3, #10, #19) reported a previous history of headache, but in all of them pain characteristics were quite different with more severe symptoms and unsatisfactory response to analgesic treatment. Despite clinical features were highly suggestive for IIH in all patients, in 3 of them the opening pressure of CSF was $<$ 25 cmH_2O thus not satisfying all criteria for the diagnosis of IIH. As for headache characteristics, it was daily in 22% of cases, with diffuse gravative pain in 41% of cases, while throbbing headache was present in 15% of patients. Moreover, in 4% of patients, headache was exacerbated by cough, stress or tension, and in 11% it had a unilateral distribution. The most common presentation symptoms, in addition to headache, were blurred vision or diplopia (70%), vomiting (33%), and dizziness (15%). Twenty patients (74%) were obese (weight centile $\geq$ 90%).

In the majority of patients neuroimaging was normal, while in 6 patients (22%), MRI or CT showed signs of empty sella syndrome. Ultrasound-based ONSD measurement was obtained only in 9 patients, in six of whom an optic nerve sheath distension could be demonstrated. Clinical characteristics of our sample are summarized in **Table 5**.

Regarding the applicability of the ICHD-2 criteria, 18/27 (71%) patients have criterion A; 24/27 (89%) criterion B; 27/27 (100%) criterion C; 27/27 (100%) criterion D. When ICHD-3 criteria were used, 27/27 patients (100%) fitted criterion A; 24/27 (89%) criterion B; 27/27 (100%) criterion C; and 27/27 (100%) criterion D.

TABLE 5 | Clinical characteristics of patients.

N	Age	Headache	Dizziness	Vomiting	Papilloedema	Visual disturbances	Obesity/BMI	Opening pressure	Neuroimaging	ONSD
1	6y10m	y	n	n	y	n	y/30,2	30 cmH_2O	Normal	np
2	11y	y	n	n	y	y	y/31,1	29.9 cmH_2O	Normal	n
3	11y7m	y	n	n	y	y	y/32	40 cmH_2O	Normal	y
4	12y2m	y	y	y	y	y	y/31,6	71 cmH_2O	Normal	y
5	13y	y	n	n	y	y	y/33,2	36 cmH_2O	Normal	y
6	11y	y	n	n	y	y	y/30,9	53 cmH_2O	Normal	np
7	9y	y	y	n	y	y	Y/33	38 cmH_2O	Normal	np
8	15y	y	y	n	y	n	y/32	40 cmH_2O	Normal	np
9	9y	y	n	y	y	y	y/35,2	40.7 cmH_2O	Normal	n
10	10y	y	n	y	y	y	N/22,3	40 cmH_2O	Empty sella	np
11	12y	y	n	n	y	y	n/19	44 cmH_2O	Normal	np
12	14y8m	y	n	y	y	y	n/16,7	65 cmH_2O	Normal	np
13	11y9m	y	n	n	y	n	y/33,4	55.7 cmH_2O	Normal	np
14	11y2m	y	n	y	y	y	y/32,1	89 cmH_2O	Normal	np
15	13y7m	y	n	y	y	y	Y/30,2	47.5 cmH_2O	Normal	np
16	12y	y	n	n	y	y	y/36,3	54 cmH_2O	Normal	np
17	15y4m	y	n	n	y	y	y/37,2	48 cmH_2O	Empty sella	n
18	7y4m	y	n	n	y	y	y/33,3	45 cmH_2O	Empty sella	np
19	11y11m	y	n	n	y	n	y/57,7	29 cmH_2O	Normal	np
20	12y11m	y	n	n	y	y	n/18,9	35 cmH_2O	Normal	y
21	9y3m	y	y	n	y	y	n/19,8	28 cmH_2O	Normal	np
22	4y8m	y	n	y	y	n	n/19	37 cmH_2O	Normal	y
23	9y1m	y	n	y	y	n	y/34,1	36 cmH_2O	Normal	np
24	11y	y	n	n	y	n	n/21,3	50 cmH_2O	Empty sella	np
25	12y	y	n	n	y	n	y/33,6	21 cmH_2O	Normal	y
26	9y9m	y	n	n	y	y	y/35,3	20 cmH_2O	Empty sella	np
27	10y	y	n	y	y	y	y/39	24 cmH_2O	Empty sella	np

y, yes; n, no; np, not performed; ONSD, optic nerve sheath diameter.

DISCUSSION

To the best of our knowledge, this is the first study comparing the applicability of the new ICHD-3 criteria to pediatric headache attributed to IIH. According to the results obtained by our study, the new ICHD-3 criteria seem to be applicable and valid for a higher rate of subjects clinically presenting with symptoms suggestive of IIH. In particular, in our clinical series, the difference was evident in the criterion A, which was fulfilled by all patients when applying ICHD3, but only by 71% when considering the old ICHD2 version. Certainly, this is due to the disappearance of specificity criteria for the headache, which now is no longer required to be daily, diffuse, and/or aggravated by cough or straining. Although this might be considered as a worse reliability and as a risk of under-rating headache as a symptom in IIH (21), it should be underlined that in pediatric population headache characteristics are usually less defined than in adults. Moreover, in younger children obtaining a precise description of headache characteristics could be very difficult. In the ICHD-3, it is only requested that headache must be "new" or show a "significant worsening." This latter expression, according to ICHD-3 specifications, implies at least a double increase in frequency and/or severity of headache. An objective evaluation of a significant worsening was present in all the 3 patients presenting a previous history of migraine, however it could be difficult to be ascertained in younger patients. The ICHD-3 criterion C states that the new or worsened headache leads to the discovery of IIH, thus helping in evaluating the fulfillment of this criterion. Summarizing, the significant change in criterion A with the abolition of precise qualitative characteristics defining headache could help to include a higher rate of pediatric patients presenting with signs and symptoms suggestive of IIH. Another important difference between ICHD versions 2 and 3 is represented by the increase of ICP cut-off in criterion B, keeping a difference between patients with and without obesity. However, in our sample, although limited, this modification did not determine any difference.

A main feature of the ICHD-2 diagnostic criteria was relief from headache after CSF withdrawal, but this was removed in the recently published ICHD-3 criteria. In our series, all patients had an improvement in symptoms after lumbar puncture and CSF withdrawal, but this can be seen also in patients with other types of headache (presenting a sensitivity and specificity of 72 and 77%, respectively).

This criterion has been replaced by the criterion according to which headache should be "no better accounted for by another ICHD-3 diagnosis." This appeared to be a necessary specification since headache secondary to IIH can be really overlapping to chronic migraine or chronic tension-type headache. Indeed, these disorders often coexist with IIH, and in all patients still complaining of headaches after treatment, migraine should be considered in order to use appropriate treatment and prevent unnecessary overtreatment for suspected IIH relapses (22).

ETHICS STATEMENT

This retrospective study received approval by the Local Ethical Board of Bambino Ges Children's Hospital, IRCCS, Rome, Italy.

AUTHOR CONTRIBUTIONS

RM and MV conceived and wrote the paper. MV, GS, LP, BB, and ST collected the data. RM and GS analyzed the data. FV and MV revised the paper.

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REVIEW
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Non-pharmacological Approaches for Headaches in Young Age: An Updated Review

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Headache disorders are common in children and adolescents. Most of the studies on non-pharmacological treatments have however been carried out on adults. In this review we provide information on recent studies examining non-pharmacological approaches for managing headache in children and adolescents. Our search of SCOPUS for primary studies conducted between January 2010 and July 2018 uncovered 11 controlled studies, mostly addressing behavioral approaches, in which a total of 613 patients with a diagnosis of primary headache, and average age 10.2–15.7 years (30–89% females) were recruited. Non-pharmacological treatments were shown to produce sizeable effects on the classical primary endpoint, i.e., headache frequency, with reductions from baseline ranging between 34 and 78%. Among commonly reported secondary endpoints, particularly disability, quality of life, depression and anxiety, marked improvements were noted as well. Taken as a whole, our findings suggest that non-pharmacological treatments constitute a valid option for the prevention of primary headaches in young age. Future research with higher-quality studies is needed. Particular attention needs to be given to studies that randomize patients to condition, blind researchers in charge of evaluating treatment outcomes, routinely include headache frequency as the primary endpoint, include adequate-length follow-up, address changes in biomarkers of disease and other possible mediators of outcome, and that employ predictive models to enhance the level of evidence for these approaches.

Keywords: cognitive-behavioral therapy, biofeedback, mindfulness, transcranial magnetic stimulation, migraine, tension-type headache, disability, depression

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INTRODUCTION

Headache disorders are common in children and adolescents, affecting up to 88% of the pediatric and adolescent population, with chronic headache types impacting up to 6% (1, 2). Headache can result in significant disability, including missed school days and limitations in extracurricular activities, such as social events with peers, family gatherings, and sports. Pharmacological treatment for acute episodes typically include non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, and triptans. As with adults, appropriate administration is needed in order to be effective, with specific attention being given to providing information about the risk for medication overuse headache (3). Among preventive drugs, antiepileptics such as topiramate, are considered as

first-line treatment (4), and several drugs used in the prevention of migraine in adults are commonly prescribed for children (5, 6). Side effects of particular relevance for children and adolescents include weight loss or weight gain, paresthesias, cognitive slowing, and sleepiness. Caution is warranted in adolescent females in particular due to the elevated risk of developing polycystic ovarian syndrome as well as possible teratogenic effects of many of these compounds. Drug treatment, however, is not always needed, and prophylactic treatment is not considered the first line treatment in the vast majority of cases (6, 7). In recent years, attention has been increasingly paid to non-pharmacological treatments of headache disorders, chiefly those that are cognitive, behavioral, or psychophysiological in nature, but with some attention to non-invasive neurostimulation (8–11). Overall, significant benefits, typically ranging from 35 to 50%, have been reported for the above-mentioned treatments with respect to reductions in headache frequency. However, most of the published studies on non-pharmacological treatments have been carried out on adults, and more recent literature reviews have not focused extensively on young headache patients. The aim of the present review is to help fill this gap by providing updated information on more recent investigations of non-pharmacological approaches to the treatment of headache in children and adolescents.

METHODS

Search Strategy

We performed a comprehensive search on SCOPUS covering the period January 2010–July 2018 to identify primary research papers reporting either randomized clinical trials (RCTs) or observational studies that addressed non-pharmacological approaches for headaches disorders in children and adolescents. The following combinations of key-words were searched within the titles, abstracts, or key-words provided:

- headache OR "tension type headache" OR migraine OR "chronic tension type headache" OR "chronic migraine" OR "medication overuse headache."
- young OR adolesc* OR juvenile.
- "cognitive behavio* therapy" OR "acceptance and commitment therapy" OR ACT OR mindfulness OR biofeedback OR "relaxation training" OR "lifestyle modification*" OR "complementary alternative medicine" OR neuromodulation OR neurostimulation OR "single pulse transcranial magnetic stimulation" OR "repetitive transcranial magnetic stimulation" OR "transcutaneous supraorbital nerve stimulation" OR "non-invasive vagal nerve stimulation" OR "caloric vestibular stimulation" OR "sphenopalatine ganglion stimulation" OR "occipital nerve stimulation."
- Our search was limited to original studies, published in English language peer-reviewed journals, and filtered by the following subject areas: Medicine, Neurosciences, Health Profession, Pharmacology, Toxicology and Pharmaceutics, Biochemistry, Genetics and Molecular Biology and Psychology. Finally, we filtered for other key-words clearly not germane to our topic (the detailed search strategy is included in **Supplementary Materials**).

Inclusion and Exclusion Criteria for Articles Selected

We specifically searched for clinical trials and observational studies, either cross-sectional or longitudinal, and excluded reviews, commentaries, letters to the editors, editorials, qualitative studies, case reports and small case series (<10 subjects).

To be included papers needed to provide sufficient information to extract the following: impact of non-pharmacological treatment on headache frequency or other outcomes, such as disability or quality of life, as assessed by patient-reported outcomes measures (PROMs) and/or parent report. Studies further had to focus on the primary headache disorders of migraine or tension-type headache. Studies drawing from populations that included other types of headache disorders (mixed disorders), or wherein the presence of headache was addressed chiefly as a symptom in the context of other general medical conditions were excluded. Finally, studies that included both adolescents and young adults were excluded if the findings were reported in aggregate and it was not possible to disentangle the outcomes for the adolescents or if the average age of the sample suggested that the study was predominantly carried out in a population of adults.

Paper Selection and Data Extraction

Selected abstracts were screened by a single researcher (EG) and, in order to ensure quality and consistency of data extraction, 20% of the abstracts along with the full texts were randomly selected for a second evaluation conducted by another reviewer (AR or ES) who was blind to the initial decision. We determined at the outset if agreement rates were below 70%, each of the double-checked abstract or manuscript would be re-reviewed by the two researchers to arrive at a final decision by consensus (however, as will be seen below, this did not surface as a problem).

Extracted information included the kind of non-pharmacological approach employed, broadly defined in terms of Cognitive Behavioral Therapy (CBT), a mindfulness-based approache, Biofeedback (BFT) treatment, Transcranial Magnetic Stimulation (TMS) and Multimodal treatment. We also recorded the main characteristics of selected studies, which included sample size, percentage of females, mean age, headache frequency at baseline and at follow-up, percent reduction and, when available, clinical significance of outcomes. We converted reported values for headache frequency to conform to a standard, comparable monthly period when authors described it differently (e.g., on a 3-month basis).

RESULTS

The initial search returned 427 records. Following abstract screening and full text assessment, 11 publications were selected for inclusion in this review (12–22). The rate of agreement between reviewers was 99.5% at the abstract check, and 100% at full-text check. **Figure 1** shows the PRISMA flow diagram of our

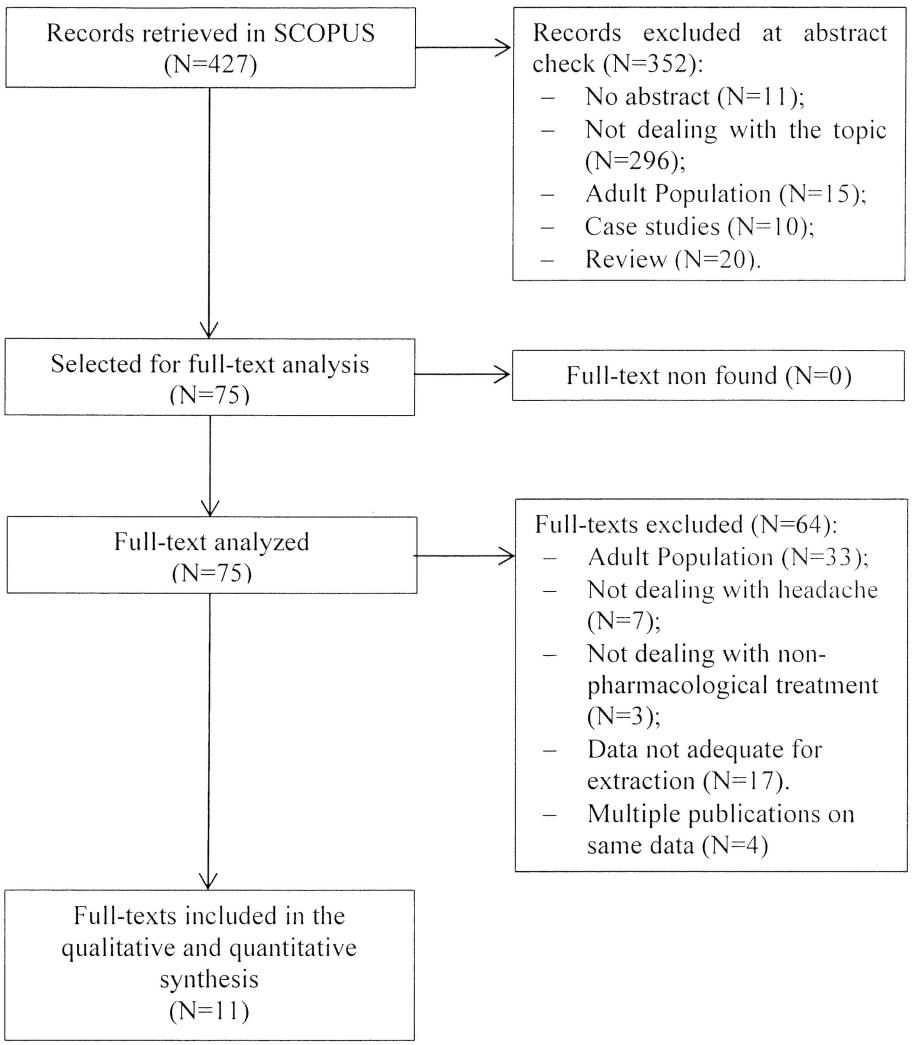

FIGURE 1 | Flowchart of papers' selection.

search process. **Table 1** presents a summary of the main outcome of the publications included in this review.

Across the studies, 613 participants with a diagnosis of primary headache and average age ranging between 10.2 and 15.7 years were recruited. Patients were mostly females, ranging on average between 30 and 88.9%, with one study including females only (20). Six RCTs involved samples of patients with different primary headaches; two studies involved patients with chronic migraine, one with episodic migraine, one with chronic tension type headache, one describing patients only as "chronic headache," and one addressing "recurrent headache."

Five papers consisted of single group studies, while the remaining six were RCTs in which a given non-pharmacologic treatment was compared with either treatment as usual (TAU) (13, 16), headache education (14, 15), education plus amitriptyline (12), amitriptyline or gabapentin (22). The majority of the studies evaluated the effects of CBT (12–16). Three studies included BFB treatment (17–19). The remaining three studies evaluated mindfulness (20), single-pulse TMS (21) and a multimodal treatment (22).

Studies on CBT

Five RCTs assessed CBT, comparing it to education (13, 14), TAU (15, 16) or amitriptyline plus education (12). Two of these studies focused on adolescents experiencing different forms of primary headache (15, 16), whereas the other three trials evaluated CBT in patients with episodic migraine (13), chronic migraine (12) or "chronic headache" (14) alone. In all studies, CBT sessions were delivered weekly, for periods varying between 4 and 12 weeks.

CBT yielded significant reductions in headache frequency that ranged between 35.8 and 71.9% in two studies (12, 15). Although Rapoff and colleagues did not report a statistically significant reduction in headache frequency, the magnitude of improvement was sizeable 47.9%. Two trials did not report on change in headache frequency (14, 16).

TABLE 1 | Main characteristics and main outcomes of the included studies.

ID	Treatment	Control	Headache type	Sample size (% W)	Age	Baseline HA freq—FU freq	% reduction (sig.)	Main results
Powers et al. (12)	CBT + Amitriptyline	Headache education + Amitriptyline	CM	135 (80%)	14.4	21.4–6	−71.9%(**)	CBT determined significant reduction in headache frequency and improvements in migraine-related disability.
Rapoff et al. (13)	CBT	Medical therapy (as prescribed for usual clinical practice)	EM	35 (88%)	10.2	13.7–7.1	−48.2% (ns)	CBT determined improvements in post-intervention headache severity and in 3-months post-intervention QoL.
Hickman et al. (14)	CBT	Headache education	CH	36 (81.2%)	15.1	nr—nr		CBT determined significant improvements in headache disability, anxiety, depression and healthy lifestyle beliefs.
Law et al. (15)	Internet-delivered CBT	Specialized headache treatment (medical, physical, psychological)	Mixed (EM, TTH, both, other)	83 (81.9%)	14.5	24–15.4	−35.8% (**)	CBT determined significant headache reduction and improvements on headache pain intensity, activity limitations, depressive symptoms and parent protective behaviors.
Sharma et al. (16)	CBT	Medical therapy (as prescribed for usual clinical practice)	Mixed (Primary headache)	63 (47.6%)	13.91	nr—nr		CBT determined significant improvements on headache severity, clinician-rated overall anxiety and state and trait anxiety.
Tornoe and Skov (17)	BFB + RT	NA	Mixed (TTH/CTTH)	9 (88.9%)	10.9	19.1–11.1	−41.88% (*)	BFB determined significant headache frequency reduction.
Blume et al. (18)	BFB	NA	Mixed (Primary headache)	132 (69.7%)	13.4	14–8	−42.9% (**)	BFB determined improvements in headache frequency and severity.
Shiri et al. (19)	BFB	NA	Mixed (CTTH, CM)	10 (30%)	13.4	17—nr		BFB significantly improved ratings of pain, daily functioning and quality of life.
Hesse et al. (20)	Mind	NA	Recurrent head	15 (100%)	14.15	4.6—nr		Mindfulness determined improvements in depression symptoms, pain acceptance and in parents-rated physical health-related quality of life.
Irwin et al. (21)	TMS	NA	CM	12 (66.7%)	15	13.3–8.8	−33.8% (*)	TMS determined improvements in headache frequency, acute medication use and headache-related disability.
Prezekop et al. (22)	Multimodal treatment	Medical prophylaxis (Amitriptyline or Gabapentin)	CTTH	83 (80.7%)	15.7	22.3–4.9	−78% (**)	Multimodal treatment determined improvements in headache frequency, pain intensity, general health, pain restriction and number of bilateral tender points.

*Significance was reported as *$p < 0.05$; **$p < 0.001$; ns, not significant; nr, not reported.*

Three of the above-mentioned studies (12–14) reported significant reductions in disability that ranged between 11.8 and 88.1%, as measured by the PedMIDAS. Other studies noted improvements in other secondary outcomes measured by PROMs investigating pain intensity (13, 15), quality of life (13), and parent protective behaviors, which include all parents' responses that, on one hand serve to reinforce pain complaints through increased parental attention and presence and, on the other hand, inappropriately lessen pain complaints by permitting children and adolescent to escape or avoid unwanted responsibilities or roles (15). Furthermore, the two studies that did not report on headache frequency focused their attention on other aspects that are often associated with headache, chiefly symptoms of anxiety and depression. The first of these two studies (14) evaluated the effects of a CBT intervention that focused on improving mental health overall (i.e., decrease perceived stress, anxiety and depression, while strengthening beliefs in ability to manage pain and to engage in a healthier lifestyle) and providing education about identifying and managing headache triggers. This 7-week treatment was compared to an education program of the same duration that focused on potential headache triggers (i.e., lifestyle, environmental, medication, hormonal, and dietary triggers) and headache hygiene measures (i.e., regular sleep and eating habits, moderate exercise, good hydration, and avoidance of caffeine, ethyl alcohol and other drugs). CBT produced significant reductions for symptoms of anxiety (11.3%) and depression (13.9%), as well as improvements with regards to headache disability and healthy lifestyle beliefs, when compared to headache education alone. In the second study, Sharma et al. (16) enrolled adolescents diagnosed as migraine or tension type headache, with comorbid anxiety disorders, who were randomized to either a transdiagnostic group CBT or a TAU control group. The intervention consisted of 12 weekly sessions that focused on identification of shared mechanisms across disorders, psychoeducation about headache and anxiety, cognitive restructuring, and stress management techniques. Adolescents within the CBT group showed significant improvements on headache severity and anxiety as assessed by clinical evaluations and PROMs.

Studies on BFB Treatment

Three single group outcome studies investigated various forms of BFB. The first study (17) included a sample of children with frequent or chronic tension-type headache who underwent 9 sessions of electromyographic biofeedback combined with computer animated relaxation therapy. Between baseline and 3-month follow-up, headache frequency decreased significantly, dropping from 19.1 to 11.1 headache days per month (49.1%). Furthermore, pericranial tenderness was significantly reduced among those who experienced frequent tension-type headache.

The second study, carried out by Blume et al. (18), involved children with different types of primary headaches, who underwent an average of 7 hand warming BFB sessions. Between baseline and the last training session, participants showed a significant reduction of 42.9% in headache frequency (decreasing from 14 to 8 headache/days per month). Median headache intensity also decreased significantly from a value of 6 at baseline to 5 at the final visit on a 10-point scale (16.7%).

Finally, Shiri et al. (19) evaluated the effects of a virtual reality system combined with BFB on a sample of children diagnosed with varied primary headaches. At the beginning of the treatment, participants had their picture taken in various emotional states to which they attached images representing their pain. During the 10 BFB sessions, children were instructed to watch their image and try to relax. Biofeedback yielded significantly improved ratings of pain by 51.9%, daily functioning by 67.4%, and quality of life by 20%. Moreover, the authors reported that most patients seemed to harness their new relaxation skills to relieve headache outside of the laboratory setting.

Mindfulness-Based Intervention

Hesse et al. (20) evaluated a mindfulness-based intervention in a sample composed entirely of female adolescents experiencing "recurrent headaches." All participants underwent eight 2 h weekly mindfulness sessions and were instructed to practice learned techniques at least once per day. The intervention was tailored to address headache and the resultant related distress by teaching the adolescents to become more mindful of breath and sounds, which was supplemented with didactic lessons and group discussions. Due to the small number of adolescents providing headache daily diaries, no formal analyses of improvements for headache frequency and severity were performed. However, improvements were noted with respect to depression symptoms (21.6% lower) and pain acceptance (22.2% lower). Further, while parent-rated questionnaires showed improved physical health-related quality of life (13.4%), reports by the adolescents did not reveal any meaningful decreases in disability over time. Although by no means definitive, this study suggests that mindfulness can be a feasible and acceptable intervention for adolescents with recurrent headaches.

Transcranial Magnetic Stimulation (TMS)

One study investigated the efficacy of single-pulse TMS in adolescents diagnosed with chronic migraine (21). During the 12-week treatment period participants were instructed to apply the device twice daily, administering additional pulses as needed for acute treatment. A significant reduction in headache frequency (33.8%), as assessed by headache diaries, was found when comparing the 28 days prior to treatment (mean of 13.3 days) to the last 28 days of treatment (mean of 8.8 days). Post-treatment data were not provided, so maintenance of effects is unknown. Improvements in headache-related disability as assessed by PedMIDAS were also found, with scores decreasing from 63 ± 46 to 27 ± 27 (57%).

Multimodal Treatment

One study assessed the effects of a multimodal treatment in adolescents with chronic tension type headache (22). The intervention was compared to a group of patients who received a preventative medication, either amitriptyline or gabapentin. The multimodal treatment group was instructed to practice complementary techniques (mindfulness and qi gong) and

received osteopathic manual treatments. At 6-month follow-up, patients showed a 78% decrease in headache frequency that dropped from 22.3 to 4.9 headache days per month. Improvements were also found in secondary outcomes, such as pain intensity (67.2%), general health (67.9%), pain restriction (63%) and number of bilateral tender points (80%).

DISCUSSION

The results of the present literature review showed that various non-pharmacological treatments in populations of young headache patients produced sizeable effects on the primary endpoint, headache frequency, with reductions from baseline ranging between 34 and 78%. These findings are of particular interest as they are comparable to those usually found in trials on pharmacological treatments (23, 24). Moreover, many of the approaches herein reviewed produced meaningful effects on other commonly used patient-reported outcomes as well, particularly with respect to disability, quality of life, and symptoms of depression and anxiety.

The importance of considering non-pharmacological treatments in the array of possible prophylactic treatments in young headache patients lies in several factors. In particular, untoward side effects have not been reported for these procedures when applied with children and adolescents. In the rare instance when such effects have been reported for adults, they are noted to be short-lived and easily overcome (25). This stands in marked contrast to the array of side effects observed in drug prophylaxis, with the most common being sedation or somnolence, dizziness, mood/behavioral changes, constipation, increased appetite, and weight gain (6, 23). Second, in recent years these treatments—particularly behavioral ones—have gained in popularity among adult patients, while conventional pharmacological treatments are being viewed as sometimes ineffective or too expensive (26, 27). It is therefore likely that a similar trend will emerge not only among the parents of child and adolescent patients, but also among the patients themselves. Third, but no less important, non-pharmacological treatments are thought to enable young patients to enhance their abilities to handle pain and cope more effectively with pain episodes absent medications. In the long run, these learned skills may serve to reduce the risk of overusing medication as the adolescents become adults. These mentioned factors—together with the results of the present review—support the idea that non-pharmacological treatments should no longer be considered only as alternative or complementary to pharmacological treatments for headaches. Rather, they merit inclusion in the array of possible first line treatments for headache disorders, in particular among populations of children and adolescents.

Although effects are in general pronounced, mechanisms by which non-pharmacological treatments exert their effects has received only scant attention. Results from the present review suggest that, with regard to CBT and Mindfulness-based treatments in particular, headache improvement may be related in part to concurrent improvements in symptoms of anxiety and depression (14, 15, 20). In fact, available literature suggests that children and adolescents with headache disorders, and migraine in particular, may have higher symptoms of anxiety and depression when compared to healthy counterparts (28–32). We emphasize "suggestive" because of the possibility of false positive responses based on screening tools wherein certain scale items overlap some symptoms of depression, anxiety, and migraine (e.g., mood and energy level changes may incur in both premonitory and post-drome phases of migraine and are core symptoms of anxiety and depression). Taken as a whole, the conclusions of the aforementioned literature reviews indicate that the majority of young patients with headache disorders do not show diagnosable psychiatric comorbidities. However, when present, they deserve attention and appropriate treatments to improve patients' prognoses (29, 30, 33).

Headaches are regarded as bio-behavioral disorders, which means that both dysfunction in several brain areas and behavioral responses to stimuli, such as stress or pain, concur to the maintenance of the disease, which in fact may arise from the complex interaction between biological and psychosocial variables (34). The brain of patients with headache, particularly in migraineurs, is hyper-reactive to prolonged repeated stimuli, and altered inter-ictal information processing is associated with limbic system dysfunction (35). Studies specifically examining cognitive processes related to pain modulation in healthy individuals shed light on core brain regions involved in cognitive interventions, such as the prefrontal cortex, the midcingulate cortex, the thalamus, and the amygdala; i.e., the same brain areas which are involved in the cognitive and affective components of pain (36). However, these have to be taken as hypotheses, since the aforementioned studies are derived from populations of healthy adults. With regard to sTMS, it is proposed that the fluctuating magnetic field delivered by the device may induce electrical currents that disrupt cortical spreading depression (37); i.e., a wave of excitation followed by a wave of inhibition of both neurons and glia, which spreads across the cortical mantle that is purported to be a physiological substrate of migraine with aura (38). It is not associated with side effects, and it is therefore considered a safe treatment for migraine. Among adults, several studies have been carried out on both single-pulse and repetitive TMS (39–42), while the data for pediatric populations is—to the best of our knowledge—confined to the single study included in the present review. Finally, BFB is a bio-behavioral approach through which patients learn to voluntarily modify their bodily reactions via feedback-mediated awareness of physiologic parameters, such as peripheral skin temperature or electromyography (43). It is deemed to act, in part, by reducing cortical excitability and affecting resonance and oscillations of essential feedback loops in the brain (44) induced by modifications of bodily reactions through feedback-mediated awareness of physiologic parameters.

The evidence generated by the present review needs to be tempered somewhat due to certain shortcomings in the available studies, all of which need to be addressed in future research in the field of non-pharmacological treatments for pediatric headache in young patients. Many of the results herein reported have in fact been derived from single group open-label outcome studies, which preclude us from addressing comparative efficacy of these treatments. The inability to implement double-blinding for behavioral treatments remains a contentious issue for some. Although this concern cannot be addressed fully,

rigor can be enhanced by randomizing participants to study and control or comparison groups and blinding those in charge of selecting, assigning, and evaluating treatment outcomes. With studies on non-invasive neurostimulation, sham procedures can be employed to enable double-blinding. Also, headache frequency was not always employed as the primary endpoint, which is specified as critical in all existing trial guidelines. Two studies reported only descriptive baseline information on headache frequency, while two studies did not report frequency at all, thus relying on measures that are traditionally employed as secondary endpoints, such as disability or quality of life. Duration of follow-up is another critical element, as most of the studies reviewed herein that reported data collection beyond the end of treatment did so only for a few months (e.g., around 3–4). This leaves us unable to draw any meaningful conclusions about stability of effects over the long term. Finally, future studies need to examine factors that mediate and/or are associated with positive outcomes. This can be accomplished in a number of ways, such as addressing changes in biomarkers associated with non-pharmacological approaches, based on neuroimaging and biological assays, and developing predictive models. In fact patient selection is of paramount importance in pediatric populations, and thus future studies should encompass a wide spectrum of clinical, psychosocial and biological indicators, in order to identify which are the most relevant patient features that are associated with positive clinical changes.

Our search was confined to SCOPUS because its search engine is noted to be wide ranging and journals within it are indexed from both medical and social science fields. Further, great care was taken to employ quality control measures aimed to reduce the possibility that relevant papers were excluded. Nonetheless, we cannot be certain that all relevant articles were included in our review process. Given our resultant small sample size, overlooking just a few salient articles may have altered our conclusions. Nutraceuticals, another prominent area of non-pharmacological treatments, were not included in the present review because an extensive literature review of this domain was published at the time we launched our search (45). This more recent review confirmed the results of previous current reviews (46, 47); i.e., that few studies exist, most are of low quality, and, consequently, the evidence generated thus far remains sparse.

CONCLUSIONS

Our review on the use of non-pharmacological approaches in young patients with primary headaches showed that these treatments produced sizeable effects on headache frequency, with reductions from baseline ranging between 34 and 78%, which in fact is comparable to that obtained when treating patients with pharmacological compounds. When reported, these treatments led to positive outcomes in various secondary endpoints as well.

Our findings reinforce the conclusions expressed by authors of other recent literature reviews (6, 7). We share the opinion that preventive drug treatment for headache is not always needed in young headache patients, and that the risk of side effects must always be taken into account. Conversely, clinicians should consider non-pharmacological treatments of headache disorders as a first line strategy in children and adolescents with primary headaches.

Future studies, incorporating random assignment, relying on headache frequency as the primary endpoint, employing more extended follow-up periods, and assessing possible mechanisms of treatment, such as changes in relevant biomarkers, would help to shore up the existing data base for the overall value of non-pharmacological treatments for children and adolescents experiencing recurrent headache. Determining factors predictive of outcome merits intensive study as well.

AUTHOR CONTRIBUTIONS

FA, LG, and DD led the initiative and revised the drafted document. ES selected abstracts and revised the drafted document. AR and EG selected abstract, extracted data and drafted the manuscript. All authors approved the final version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.01009/full#supplementary-material

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Features of Primary Chronic Headache in Children and Adolescents and Validity of Ichd 3 Criteria

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Introduction: Chronic headaches are not a rare condition in children and adolescents with negative effects on their quality of life. Our aims were to investigate the clinical features of chronic headache and usefulness of the International Classification of Headache Disorders 3rd edition (ICHD 3) criteria for the diagnosis in a cohort of pediatric patients.

Methods: We retrospectively reviewed the charts of patients attending the Headache Center of Bambino Gesù Children and Insubria University Hospital during the 2010–2016 time interval. Statistical analysis was conducted to study possible correlations between: (a) chronic primary headache (CPH) and demographic data (age and sex), (b) CPH and headache qualitative features, (c) CPH and risk of medication overuse headache (MOH), and (d) CPH and response to prophylactic therapies. Moreover, we compared the diagnosis obtained by ICHD 3 vs. ICHD 2 criteria

Results: We included 377 patients with CPH (66.4% females, 33.6% males, under 18 years of age). CPH was less frequent under 6 years of age (0.8%; $p < 0.05$) and there was no correlation between age/sex and different CPH types. The risk to develop MOH was higher after 15 years of age ($p < 0.05$). When we compared the diagnosis obtained by ICHD 2 and ICHD 3 criteria we found a significant difference for the undefined diagnosis (2.6% vs. 7.9%; $p < 0.05$), while the diagnosis of probable chronic migraine was only possible by using the ICHD2 criteria (11.9% of patients; $p < 0.05$). The main criterion which was not satisfied for a definitive diagnosis was the duration of the attacks less than 2 h (70% of patients younger than 6 years; $p < 0.005$). Amitriptyline and topiramate were the most effective drugs ($p < 0.05$), although no significant difference was found between them ($p > 0.05$).

Conclusion: The ICHD 3 criteria show limitations when applied to children under 6 years of age. The risk of developing MOH increases with age. Although our "real word" study

shows that amitriptyline and topiramate are the most effective drugs regardless of the CPH type, the lack of placebo-controlled data and the limited follow-up results did not allow us to conclude about the drug efficacy.

Keywords: chronic headache, children, chronic migraine, tension-type headache, medication overuse headache, prophylactic therapy

INTRODUCTION

Chronic primary headaches (CPH) are a disabling disorder for children, adolescents, and adults, with a reported prevalence of 2% in adults and 0.78% in adolescents, while the prevalence rises up to 1.75% when including the MOH (1). Nearly 69% of children and adolescents who present to headache specialty clinics have chronic migraine (1). In adolescents and children suffering from this condition, attacks may interfere with the predictability of normal life activities and affect the ability to work, perform routine course and school activities, and maintain functional social relations. CPH determines a huge decrease of the quality of life (1).

Chronic migraine (CM), chronic tension-type headache (CTTH) and new daily persistent headache (NDPH) are classified as CPH in the International Classification of Headache Disorders 3rd edition (ICHD 3). Medication-overuse headache (MOH) is classified among secondary headaches, but it generally affects patients with a pre-existing primary headache. The least common denominator of all these forms of CPH is the persistence of the symptoms for at least 3 months, while the clinical features can vary (2).

CPH may be improved by non-pharmacological treatment, such as lifestyle modifications and complementary therapies (i.e., cognitive behavioral therapy), and/or pharmacological prophylaxis (3).

There are few data concerning the characterization of CPH in the pediatric population, so that most our knowledge emerges from the experience in adulthood. The latest version of the International Classification (ICHD 3) does not include notes for the diagnosis of CPH in pediatric age, although CPH is reported as an increasing condition in children and adolescents with distinct clinical features compared to the adult population (4).

The aims of our "real word" study were: (1) to describe the features of chronic headache in children, and (2) to compare the diagnostic usefulness of ICHD 2 (5) and ICHD 3 criteria. As a secondary aim, we will describe retrospective data of efficacy of the commonly used prophylactic pharmacological therapies.

METHODS

We retrospectively reviewed the charts of patients attending to the tertiary, university-affiliated, pediatric medical Headache Centers of Bambino Gesù Children and Insubria University Hospital. The design of the study is resumed in **Figure 1**. The electronic database of the headache clinics was searched for all children and adolescents up to 18 years of age, diagnosed with CPH during the 2010–2016 time interval. Moreover, in CPH population a history of drug overuse supporting the diagnosis of MOH was looked for. The diagnosis was re-evaluated in all cases by using the ICHD-III criteria (2). The main inclusion criteria was history of headache occurring on 15 or more days/month for more than 3 months. Exclusion criteria were headache types other than CPH and the presence of other internist and/or neurological illness. We considered the following CPH types: CM, CCTH, and NDPH. Data on demographics, headache symptoms, and other clinical headache-related parameters were collected from the medical files of the patients who were found eligible to be included in the study. Electronic medical records included the following information: demographic data (age, sex), familiar medical history including headaches, pregnancy and birth history, past medical history, anthropometrical data (weight and height), general physical exam and neurological exam including fundus oculi. Medical charts included also results of possible neuroimaging exams and the data from headache diary. Headache diary reports the number of the attacks for months, duration of the attacks, qualitative features of pain, presence of associated symptoms (nausea, vomiting, phonophobia, and photophobia), intensity of pain, name of drug for the attack and response to therapy for the attack.

Patients were divided into four age groups: 0–6, 7–10, 11–15, and 15–18 years.

Clinical data, concerning duration, qualitative features of the headache attacks, related symptoms and prophylactic pharmacologic therapies were issued from the first and follow up visits. These data were collected from interviews to children and/or their parents. For very young children headache frequency and symptoms were determined by the child's complaints and the parents' impression from the child's behavior (according to the ICHD-III criteria) (2). In addition, parents were questioned about possible medication overuse of their child. The medical interview was always followed by a complete full physical and neurological examination of the patient.

Statistical analysis was conducted by SPPS version 22.0 and χ^2 test was used to verify possible correlations between: (a) CPH subtypes and population features (age and sex), (b) CPH subtypes and headache qualitative features (nausea, vomiting, phonophobia, and photophobia), (c) predictors of development MOH, and (d) CPH and response to prophylactic therapies (amitriptyline, topiramate, flunarizine, and L-5 hydroxytryptophan). In addition, we performed a comparison between ICHD 2 and ICHD 3 criteria for the diagnosis. A p-value of ≤ 0.05 was considered significant.

Written informed consent was obtained from the parents of the participants in this study. The study was approved by the Ethical Committee of Bambino Gesù Children Hospital.

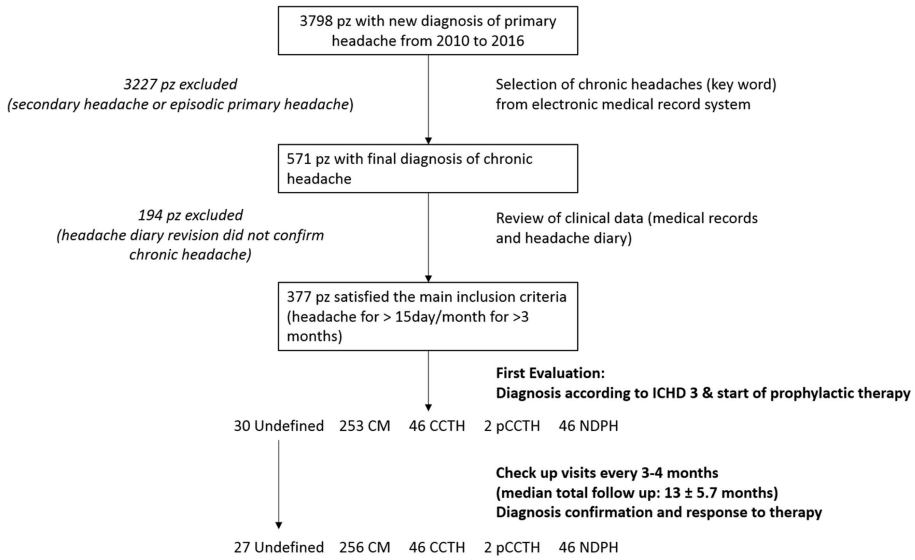

FIGURE 1 | Study methods design.

RESULTS

Descriptive Analysis of Chronic Headache Characteristics and Clinical Correlations

We included 377 patients who experienced chronic headache (66.4% females, 33.6% males; $p > 0.05$). Mean age of selected patients was 10.8 years ± 2.5 standard deviation (SD) (range 3.20–18 years). Pain quality, intensity and frequency of the attacks, and associated symptoms are shown in **Table 1**.

CPH was less frequent under 6 years of age (0.8%; $p < 0.05$), while a significant higher prevalence of CPH was found in females than in males in the age group between 0 and 6 years (23/31 females, 8/31 males) and between 15 and 18 years (41/51 females, 10/51 males) ($p < 0.05$). No significant statistical correlation between age/sex and different CPH types was found. Nausea and vomiting were the two most frequent vegetative symptoms under 10 years of age ($p < 0.05$) while photo/phonophobia were more frequent in patients older than 15 years ($p < 0.05$).

As for attack duration, three groups of patients were identified: (1) attack duration was shorter than 1 h in 122 patients (32.3%), (2) it ranged between 1 and 2 h in 150 patients (39.7%), and (3) it was longer than 2 h in 105 patients (27.8%). When the different age-based groups of patients were considered, a significant different distribution of the attack duration was found. In particular, we found that an attack duration shorter than 2 h was more frequent in the patients between 0 and 6 year (70%) as compared to other groups (39.5% in patients between 7 and 10 years, 24.5% in patients between 11 and 14 years and 13.7% in patients older than 14 years) ($p < 0.05$). As consequence of this phenomenon we detected that the distribution of CH subtypes tends to overlap in the age groups between 7 and 10 years, 11–14 years and above 15 years while in patients younger than 6 years, we have a significant increase in the frequency of probable or undefined diagnoses ($p < 0.05$) (**Figure 2**). The most frequent parameter that did not fill the criteria for a definitive diagnosis in patients under 6 age, was the duration of the attack less than 2 h.

MOH was found in 10.8% of patients and interested only patients with CM and CTTH (**Figure 3**). Ibuprofen was the most frequently overused drug. Excluding the overuse of drugs for the attack, we found that the only clinical factor associated with higher risk to develop MOH was the increasing age (OR 2.2; CI 1.2–4.21; $p < 0.05$) (**Figure 4**).

Comparison Between ICHD 3 and ICHD 2 Criteria

According the last version of ICHD, the most frequent diagnosis was CM (67.1%), followed by CTTH (12.2%), NDPH (12.2%), undefined (7.9%), and probable CCTH (pCCTH, 0.5%). Concomitant history of MOH was detected in 41/337 patients (10.8%), among whom 31 suffered from CM and 10 from CTTH.

When we used the ICHD 2, CM was diagnosed in 60.4% of patients, probable CM (pCM) in 11.9%, CCTH in 9.5%, pCCTH in 3.1%, NDPH in 12.2%, and undefined in 2.6%.

When the diagnoses obtained by ICHD 2 and ICHD 3 were compared, significant differences of frequencies were found for pCM (11.9 vs. 0%; $p < 0.05$) and undefined diagnosis (2.6 vs. 7.9%; $p < 0.05$) (**Figure 5**). When we considered the total of patients who did not receive a conclusive diagnosis (probable and undefined) we found that for ICHD 2 was 17.6% and ICHD 3 was 8.4% ($p > 0.05$).

CPH Subtype Predictors

As we have done in the past for episodic primary headache (6), we used a multivariate logistic regression analysis to identify headache features and associated symptoms correlated with a correct diagnosis. We found that the presence of photophobia/phonophobia and nausea/vomiting were

TABLE 1 | Headache characteristics in our sample.

AGE OF PATIENTS	
0–6 years	31/377 (8.2%)
7–10 years	144/377 (38.2%)
11–14 years	151/377 (40.1%)
15–18 years	51/377 (13.5%)
HEADACHE TYPES (ICHD 3)	
Chronic Migraine (CM)	253/377 (67.1%)
Chronic Tensive Type Headache (CTTH)	46/377 (12.2%)
Probable CTTH	2/377 (0.5%)
New Daily Persistent Headache (NDPH)	46/377 (12.2%)
Medication Overuse Headache (MOH)	41/377 (10.8%)
Undefined	30/377 (7.9%)
PAIN QUALITY	
Throbbing	94/377 (24.9%)
Gravative	113/377 (29.9%)
Pressing	61/377 (16.1%)
Other qualities	109/377(28.9%)
PAIN INTENSITY	
Mild	75/377 (19.8%)
Moderate	132/377 (35%)
Severe	170/377 (45%)
ATTACK DURATION	
Less than 1 h	122/377 (32.3%)
Between 1 and 2 h	150/377 (39.7%)
More than 2 h	105/377 (27.8%)
ASSOCIATED SYMPTOMS	
Photophobia	225/377 (59.6%)
Phonophobia	258/377 (68.4%)
Nausea and/or vomiting	172/377 (45.6%)

significantly associated with the diagnosis of both CM [Odd Ratio (OR) 2.8; confidence interval (CI) 1.76–4.6; positive predictive value (PPV) 81%; $p < 0.05$] and pCM (OR 2.5; CI 1.5–4.1; PPV 78%; $p < 0.05$), whereas it was not associated with the diagnosis of both CCTH (OR 0.17; CI 0.1–0.3; VPP 5%; $p < 0.05$) and pCCTH (OR 0.2; CI 0.1–0.5; VPP 5%; $p < 0.05$).

Prophylactic Therapy

Data concerning the use of prophylactic therapy were issued from 272 patients (72.1%). The drugs used for prophylaxis included 5-hydroxytryptophan, flunarizine, amitriptyline and topiramate. The most frequently used drug was amitriptyline (81.6%), followed by topiramate (21.7%), flunarizine (12%), and 5-hydroxytryptophan (6.9%), while 13.9% of patients needed more than one drug (**Figure 6**). Around half of patients (54%) had a beneficial response (reduction in the frequency of attacks by at least 50%), while 16.5% of patients showed no improvement. However, we could not have follow-up data for 29.5% of patients. Amitriptyline and topiramate were the drugs with higher percentage of efficacy ($p < 0.05$) and no significant difference in efficacy was found between them ($p > 0.05$) (**Figure 7**).

DISCUSSION

CPH represents a growing problem in the pediatric and adolescent age. Our study aimed to fill a lack in the literature regarding CPH description in pediatric age and to verify if the changes made in the third version of ICHD could bring advantages for the diagnosis of CPH in this age group.

The most relevant results of our study were the following:

- ICHD 3 criteria keep presenting limits when applied in pediatric age, especially in children under 6 years of age. The main limit concerns the criterion of the duration of the attack.
- We reported the main correlations between CPH and demographic data and described also the most frequent phenotypes.
- The MOH prevalence in our population was 10.8%, much lower than the in adult patients.
- Amitriptyline and topiramate were the most effective drugs in our CPH patients.

Has ICHD 3 Given an Advantage?

In our CPH population, female sex was prevalent in the age group between 0 and 6 years and between 15 and 18 years (75% female vs. 24% male in 0–6 years; 81 vs. 19% above 15 years;). Our data confirm the findings of studies on both adult and adolescent chronic headaches which showed an higher frequency in females than males (7–11).

Though largely overlapping, ICHD 2 and ICHD 3 show some differences, especially for the non-conclusive diagnoses. These include the so-called "probable diagnoses" (when one of the criteria is not met) and "undefined diagnoses" (when more than one criterion is not met). While the diagnosis of pCM was possible in the ICHD 2, it was abolished in ICHD 3. Patients defined as pCM with the ICHD 2 belong to two categories: those with simultaneous story of MOH and those who did not meet one of the criteria for diagnosis in particular the duration criterion. According to the ICHD 3, the first ones are re-classified as CM, while the second ones as undefined (2, 5).

According to ICHD 2, in patients overusing medications the diagnosis of MOH can be definitely done only if headache improves after overused medication withdrawal. Before being diagnosed definitely, patients with medication overuse were temporarily given a diagnosis of pCM or pCTTH with probable MOH (5). According to ICHD 3, patients meeting the criteria for CM/CTTH and MOH should be coded for both. After drug withdrawal, headache can either revert to an episodic type or remain chronic, and the patient should be re-diagnosed accordingly (2). In our patients, the modification in MOH diagnosis led to a slight increase of CM prevalence from 60.4% (ICHD 2) to 67.1% (ICHD 3).

While CM can be diagnosed with the ICHD 2 whether the patient refers at least 15 days a month of headache with the clinical characteristics of migraine, the ICHD 3 requires that only eight out of 15 episodes must meet the criteria for migraine. Therefore, we should expect an increase in the CM frequency. However, in our patients the CM prevalence did not largely change passing from the second to the third version of the ICHD.

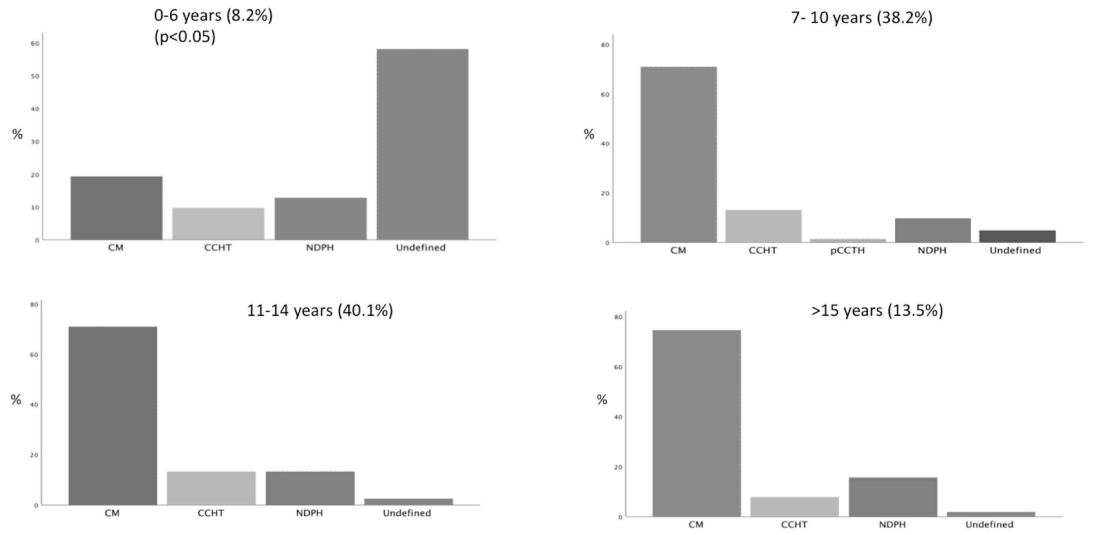

FIGURE 2 | Distributions of headache subtypes (ICHD 3) in relation with age.

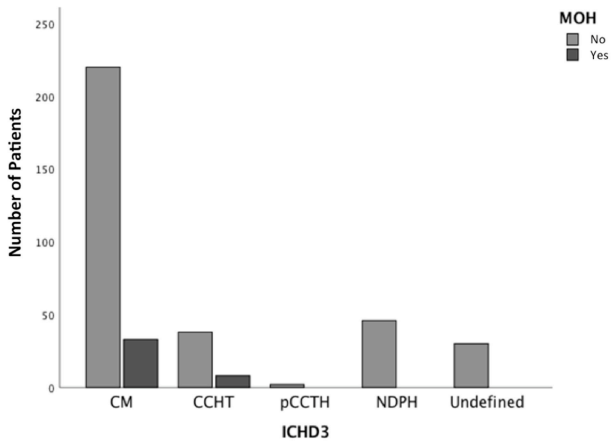

FIGURE 3 | Number of patients with MOH according to headache subtypes.

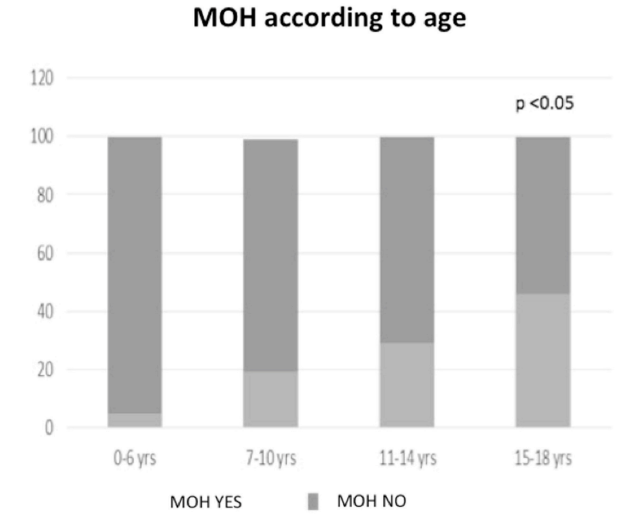

FIGURE 4 | Number of patients with MOH according to patient's age.

This is probably due to the fact that most our chronic patients with undefined diagnosis did not receive such a diagnosis for the qualitative characteristics of their headache, but for the duration of their attacks. Indeed, we found that most children under 6 years of age (70%) could not satisfy the criterion of the attack duration, often suffering from episodes shorter than 2 h. While the most frequent phenotype in patients over 6 years of age was CM, younger patients showed a significant increase in the prevalence of probable or undefined diagnoses. The associated symptoms were useful for a diagnosis of primary headache (6). In particular, the presence of photophobia and phonophobia was associated with diagnosis of migraine, while the absence of these symptoms was a predictor of CTTH. The problem of the duration of the headache attack confirms our previous data showing that very young children can rarely satisfy the ICHD 3 criteria for the diagnosis of episodic migraine and TTH (6, 12).

Taking into account the whole amount of our patients who cannot receive a conclusive diagnosis (probable and undefined), this percentage dropped from 17.5% with the ICHD 2 criteria to 8.5% with the ICHD 3 criteria. This means that, compared to the ICHD 2, the latest ICHD version shows a higher diagnostic power, even if the criteria for children under 6 years of age need a further improvement.

Medication Overuse Headache in Pediatric Age

MOH affects 1–2% of the adult general population and 25–50% of the chronic headache population.

This frequency increased to 30–50% if we consider the cephalalgic patients followed in specialized headache centers

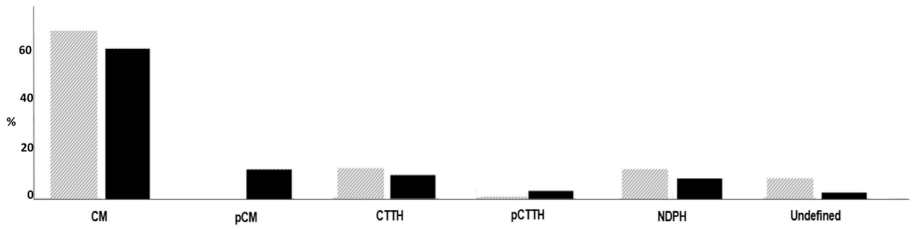

FIGURE 5 | Diagnoses obtained by ICHD 2 (black) and ICHD3 (gray) criteria.

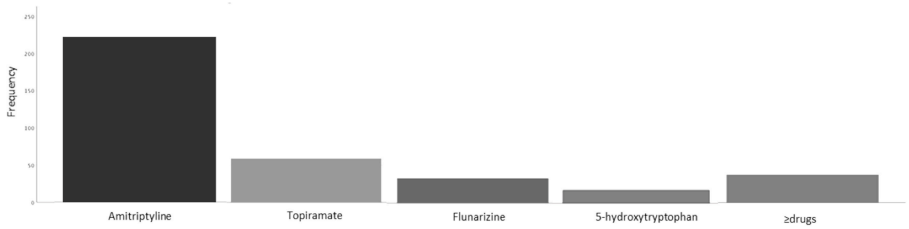

FIGURE 6 | Frequencies of patients that received each drug.

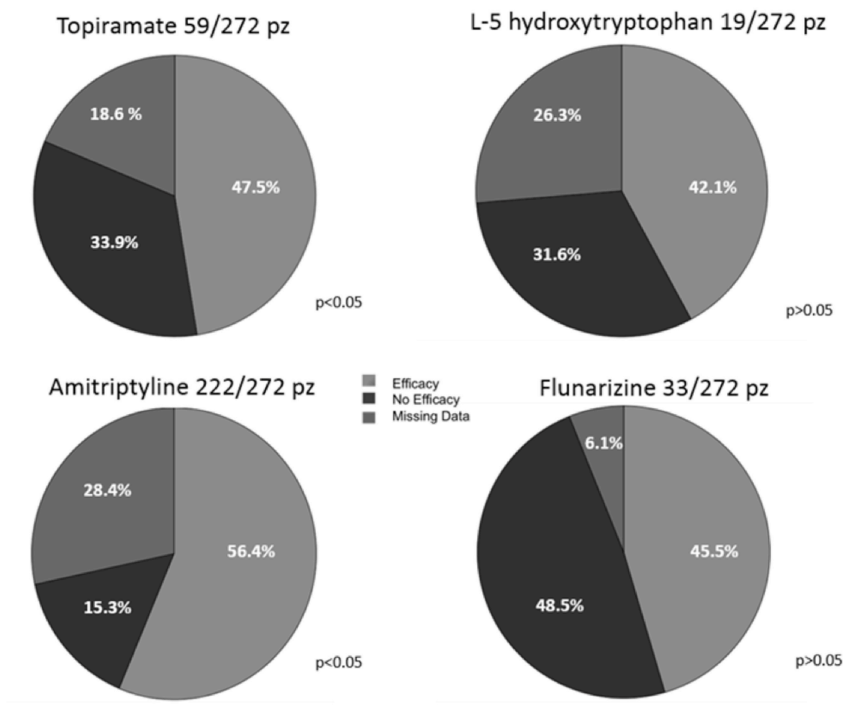

FIGURE 7 | Response to therapy (percentages of patients).

(13). As for pediatric age, population surveys conducted in Taiwan (14) and Norway (15) found that 0.3 and 0.5% of adolescents respectively could receive a diagnosis of MOH. Considering the population of children and adolescents suffering from headache, there are values of MOH prevalence ranging from 2 to 82.5% (16–20). In our sample, the prevalence of MOH, diagnosed according to the ICHD 3 criteria, was 10.8%. The large variability in MOH can be due to several factors, including differences in genetic background, parenting style, and/or a pediatricians "approach to headache treatment (17).

While in adults MOH is more frequent in CM than in CTTH patients (21), in our young patients there was no significant difference. The main risk factor associated with the development of MOH was the age (OR 2.2; CI 1.2–4.21; $p < 0.05$). Indeed, the proportion of patients with MOH was significantly higher in patients over 15 years than in the other age groups ($p < 0.05$). This finding is conceivable, since adolescents can manage the symptomatic drugs by their own while in younger children the drugs are administered under parental control.

Pharmacological Treatment of CPH

There are few trials regarding the efficacy of the pharmacological prophylaxis in young headache patients. Evidence of efficacy for prophylactic treatment of episodic migraine in children and adolescents are available for flunarizine, topiramate, and trazodone (unavailable in the USA), topiramate and trazodone (22). The use of amitriptyline, combined with psychological treatment, in patients with CM is supported by one randomized controlled trial (22, 23). However, clear recommendations for the prophylactic treatment of CPH pediatric patients are currently unavailable.

In our population, the most effective drugs were amitriptyline and topiramate without significant differences between them. Mack et al., (24) investigated the efficacy of amitriptyline in patients with high-frequency headache and found that both headache frequency and intensity significantly improved during treatment. They underlined that also chronic daily headaches or continuous headaches appeared to respond to amitriptyline (24). As for topiramate, its efficacy in the prophylaxis of episodic migraine at high frequency has been reported (22, 23), while there are no recommendations for high frequency TTH or chronic headaches. The good efficacy of topiramate in our population suggests that this drug should be considered also for the CPH treatment.

Unfortunately, since follow-up data were missed for a large proportion of our patients, any consistent conclusion about drug effectiveness cannot be drawn. Drop-out patients are mainly those who did not present to the subsequent control visits. There are 3 main possible reasons for drop-outs: (1) some patients, who had improved, did not return to the control visit, (2) other patients, in whom the treatment had not worked, referred to other centers, and (3) adverse events related to drugs. An emerging literature demonstrates that patients with migraine and other headaches hesitate to adhere to pharmacological regimens (25, 26). The lack of adherence to preventive therapies has significant consequences on disease severity, frequency of the attacks and social economics costs. In children and adolescents, the limit of adherence can be improved not only through an accurate education of the patient and his/her parents, but also increasing the evidence about the diagnosis, management and available therapies.

Limitations of the Study

Our study has some limitations. First, retrospective design of the study can reduce its reliability in the description of the clinical CPH features. However, here we present a picture of pediatric CPH patients referring to third level centers and believe that our data, including those concerning treatment, can be representative also of other similar settings. Second, the findings about the prophylactic treatment are largely affected by the drop-outs and are not placebo controlled. This last point is particularly important, considering the open debate about the efficacy of placebo in children (27–30).

CONCLUSIONS

Literature shows that CPH is a growing phenomenon in the pediatric population. To date, our study includes the most extensive Italian CPH children cohort. We showed that the ICHD3 criteria, though not allowing us to reach a conclusive diagnosis in 8.5% of cases, represented an improvement compared to the ICHD 2 criteria, according to which 17.5% of our patients did not have a definitive diagnosis. The uncertain diagnoses involved 70% of patients under 6 years, being the attack duration, shorter than 2 h, the first cause of uncertainty. MOH prevalence was 10.8% and it was particularly high in patients older than 15 years. Amitriptyline and topiramate proved the most effective drugs, regardless of the headache type.

AUTHOR CONTRIBUTIONS

LP is responsible for the design of the study and the writing of the manuscript, supervision of the patients selection and data collection phase, the statistical analysis, and the interpretation of the results. IS participated in the data collection and writing the manuscript. BaB, RM, ST and FD participated in data collection. CT is responsible for data collection from patients of Insubria University Center. BeB participated in data collection of patients from Insubria University Center. PA carried out the statistical analysis. FV contributed to interpretation of results. MV supervised the patients selection and data collection phase, the statistical analysis, and the interpretation of the results.

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The data of the present study had been presented at 11th European Headache Federation Congress jointly with 31st Congress of the Italian Society for the Study of Headaches Rome, Italy. 01–03 December 2017 (30).

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Pain Catastrophizing in Childhood Migraine: An Observational Study in a Tertiary Headache Center

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Background: Migraine is the most common cause of primary headache in children leading to a decrease in the quality of life. During the last decade, pain catastrophizing construct became a major focus of interest in the study and treatment of pain.

Aim of the study:

1) To evaluate pain catastrophizing in episodic and chronic migraine children and adolescents selected in a tertiary headache Center.
2) To test whether the children's pain catastrophizing might be associated (a) with the frequency of attacks and disability (b) with psychopathological aspects (c) with allodynia and total tenderness score as symptom of central sensitization.
3) To test the best discriminating clinical variables and scores between episodic and chronic migraine, including pain catastrophizing.

Methods: We conducted a cross sectional observational study on consecutive pediatric patients affected by migraine. We selected 190 headache patients who met the diagnostic criteria for Migraine without aura, Migraine with aura and Chronic migraine. We submitted all children to the Child version of the Pain Catastrophizing Scale (PCS-C), and to the disability scale for migraine (PedMIDAS), general quality of life estimated by children (PedsQL) and parents (PedsQL-P), anxiety and depression (SAFA-A; SAFA-D) scales. We also evaluated headache frequency and the presence and severity of allodynia and pericranial tenderness.

Results: No difference was detected in Total Pain Catastrophizing score (PCS-C) between chronic and episodic migraine groups (ANOVA $F = 0.59$, $p = 0.70$); the PedMIDAS, the PedsQL-P for physical functioning and the Total Tenderness Score were discriminant variables between episodic and chronic migraine. The PCS-C was not correlated with migraine related disability as expressed by Ped MIDAS, but it was significantly correlated with general low quality of life, allodynia, pericranial tenderness, anxiety, and depression.

Conclusion: Pain catastrophizing seems a mental characteristic of a clinical phenotype with psychopathological traits and enhanced expression of central sensitization

symptoms. This clinical profile causes general decline in quality of life in the child judgment, with a probable parents' underestimation. In childhood age, it would not be a feature of chronic migraine, but the possibility that it could predict this evolution is consistent and worthy of further prospective evaluation.

Keywords: migraine, children, pain catastrophizing, allodynia, pericranial tenderness, central sensitization

INTRODUCTION

Migraine is the most common cause of primary headache in children leading to a decrease in the quality of life (1).

Chronic migraine affects 0.8–1.8% of adolescents and 0.6% of children and it is a common reason for pediatric patients to seek medical care (2). Consequently, this age group demands special attention. A better understanding of specific pain mechanisms, disease progression, and potential complications in childhood migraine allows the development of more specific and more efficient ways of prevention and therapy. Nowadays, the most important recognized factors associated to chronic migraine are obesity, depression, presence of allodynia, and stressful life events (3).

During the last decade, pain catastrophizing construct became a major focus of interest in the study and treatment of pain. Pain catastrophizing is a negative cognitive-affective response to anticipated or actual pain. More recently, Flink et al. argued that it is a form of negative repetitive thinking, difficult to disengage from, with reduced capacity in problem solving and downregulation of negative affect. It is a complex process involving cognitions, emotions, and behavior, linked to poor outcomes such as higher ratings of pain and disability (4). Pain catastrophizing could be a model to explain the processes of transitions to a chronic state during childhood and adolescence. Describing pain catastrophizing could thus enable to individuate cases with possible negative evolution and multiple psychological and cognitive features. In a validation study of Fear of Pain Questionnaire (FOPQ) in a pediatric headache sample, an association between pain catastrophizing and Fear of Pain emerged (5). Pain catastrophizing is associated with a number of indices of pain sensitivity in experimental settings including healthy pain-free participants and individuals with various chronic pain conditions (6, 7). In particular, one of the most consistent findings was the correlation between pain catastrophizing and heightened pain experience (6, 8). The literature also indicates consistent and generally robust associations between pain catastrophizing and measures of clinical pain severity, pain-related activity interference, disability, depression and quality of life (8, 9).

Thanks to the development of a pediatric version of the Pain Catastrophizing Scale (PCS-C) (10), the interest in pain catastrophizing in the pediatric area is progressively going into increase. Several studies found significant positive associations between PCS-C reports and pain intensity, disability (10, 11), and anxiety ratings (11, 12). The PCS-C items describe different thoughts and feelings that children may experience when they are in pain, using a total score and three subscale scores for rumination, magnification, and helplessness (10). It showed consistency across different children populations. In a German study on children with recurrent pain and specifically headache, pain catastrophizing showed significant association with anxiety, pain severity and disability (13).

In a recent neurophysiological study on children migraine, we observed a correlation between pain catastrophizing and allodynia, which is a symptom of central sensitization (14).

In order to better understand some of the precipitating and aggravating factors of migraine in pediatric patients, the present cross-sectional observational study aimed:

1) To evaluate pain catastrophizing in episodic and chronic migraine children and adolescents selected in a tertiary headache Center.
2) To test whether the children's pain catastrophizing might be associated a) with the frequency of attacks and headache related and general disability b) with psychopathological aspects as anxiety and depression c) with allodynia and total tenderness score as symptom of central sensitization.
3) To test the best discriminating clinical variables and scores between episodic and chronic migraine, including pain catastrophizing.

MATERIALS AND METHODS

Participants

We conducted a cross sectional observational study on consecutive pediatric patients affected by primary headache and referred to the Applied Neurophysiology and Pain Unit of Bari University.

Among the 500 consecutive pediatric patients come for the first time to the Applied Neurophysiology and Pain unit between January 2017 and January 2018, we selected 190 headache patients who met the diagnostic criteria for Migraine without aura, Migraine with aura and Chronic migraine, according to the actual International Classification of Headache Disorders (Headache Classification Committee) (15). Diagnosis was based on history and the headache diaries (see below). Exclusion criteria included the presence of another neurological diagnosis, or psychiatric and medical comorbidities. None of the children was under current use of preventive treatments or other psychotropic medications, at the time of the study.

Data Collection

Upon the first access to the booking desk, the hospital staff gave parents the headache diary and the questionnaire of allodynia in the adult version. All parents and patients were invited to fill the headache and allodynia diary for 3 months, and to present it at their first visit date. We decided to include only patients at their

first access to our Unit, because one exclusion criteria was the use of preventive treatment for migraine, which we generally suggest during the first visit.

Clinical Evaluation

We supposed the frequency of the headache from the diaries. Based on the frequency reported, patients were divided into four categories of frequencies (1–4; 5–9; 10–14; 15–30 days/month).

A team of neurologists and psychologists with experience in headache evaluated the patients and considered the headache and allodynia diaries. One psychologist administered the anxiety and depression scales, the disability scales and pain catastrophizing questionnaires. All children were examined during the not symptomatic phase.

The study was approved by the local Ethic Committee of Bari Policlinico General Hospital. Parents and children were informed about the details of the study procedure and parents signed an informed consent prior to the enrolment, in accordance with the Declaration of Helsinki.

Measures and Procedures

Child Version of the Pain Catastrophizing Scale

The PCS-C is a 13-item self-report measure designed to assess the extent to which children and adolescents experience catastrophic thoughts and feelings when in pain. Items are responded to on a 5-point scale ranging from zero (not at all) to four (extremely). Higher scores indicate more frequent catastrophic pain beliefs (scores range from 0 to 52). The PCS-C assesses three catastrophizing domains: Rumination (i.e., "I cannot keep it out of my mind"), Magnification (i.e., "I am afraid that pain will get worse"), and Helplessness (i.e., "There is nothing I can do to reduce pain"). The original version of measure was adapted from the adult PCS for use with Flemish-speaking children and adolescents. It demonstrated good reliability (total scale a = 0.87, rumination a = 0.73, magnification a = 0.68, helplessness a = 0.79), predictive validity, and invariance across age and sex among Flemish-speaking children and adolescents. The English language version of this measure was validated in a community sample of children (16) and a clinical sample of youth with chronic pain (11). In this study, we used an Italian language version of the PCS-C, translated with the agreement of Geert Crombez, according to the back-translation method (Simeone et al. in preparation). Briefly, the instrument was translated in English by an independent professional native English translator, who had no knowledge of the questionnaire. Only a few discrepancies arose, which the expert panel discussed until a satisfactory version was reached. The total score of this translated version showed high internal consistency (a = 0.9).

Psychiatric Self-Administration Scales for Youths and Adolescents

Psychiatric Self-Administration Scales for Youths and Adolescents (SAFA) (16). The SAFA is an Italian standardized battery which includes six self-report scales for the assessment of a wide range of psychiatric symptoms according to the DSM IV-TR diagnostic criteria. They can be used together or separately with satisfactory psychometric properties (reliability by internal consistency and test–retest; convergent, discriminant, and content validity) (https://www.giuntios.it/catalogo/test/safa). In the present study, we used the anxiety (SAFA A) and depression (SAFA D) scales that includes two or three versions, each tailored for a specific age range. All items rates are on a three-point scale (two = "true," one = "partly true," and zero = "false"). The SAFA-A evaluates generalized, social and separation anxiety and anxiety related to the school. The SAFA-D measures depressed mood, anhedonia, disinterest; irritable mood, feelings of inadequacy, low self-esteem, insecurity, guilt, hopelessness.

Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PQL) and the modules developed for various diseases assess health-related quality of life in healthy children and adolescents, as well as p*e*diatric patients with acute or chronic conditions. They combine into a single system several generic scales and modules for specific diseases (17, 18). In the present study, we used the PQL 4.0 Generic Core Scales, both in the self-report form and in the parent proxy-report form. The PQL 4.0 Generic Core Scales include 23 items self-report form about physical functioning (eight items), emotional functioning (five items), social functioning (five items), school functioning (five items). Child self-report format includes ages 5–7 (young child), 8–12 (child), and 13–18 (adolescent). The instrument instructions ask to score each item, taking into consideration the last month. The choice of answer for each item is on a 5-point Likert scale: zero = never a problem, one = almost never a problem, two = sometimes a problem, three = often a problem, four = almost often a problem). For self-reports by children 5–7 years old, the Likert scale included 3-points (zero = not a problem at all; two = sometimes a problem; four = a great problem), each choice of response being attached to a happy-sad faces scale.

The parent proxy report (PedParQL) also includes ages 2–4 (toddlers), 5–7 (younger children), 8–12 (children), and 13–18 (teens). The two forms, for children and parents, are parallel, providing for an indication of the child's and the parent's perception. The instrument instructions ask how frequently a problem was present during the past 1 month. In the present study, we considered the PedsQL and PedParQL total scores, Physical functioning (PedsQLP, PedParQLP) and Emotional functioning (PedsQLE, PedParQLE) sub scores (18).

Pediatric Migraine Disability Assessment

Pediatric Migraine Disability Assessment Scale (PedMIDAS) is a measure for migraine related disability in children and adolescents. The PedMIDAS is based on the adult MIDAS with developmentally appropriate changes and adjustments for childhood lifestyle. The first three questions are about the impact of headache at school: question 1 asks about school day absences; question 2 asks about partial day absences; and question 3 asks about functioning at 50% or less ability in school. The fourth question assesses the impact due to headache at home and includes inability to perform homework and chores. The final two questions assess disability in social functioning including sports; question 5 asks about complete absence from activities,

while question 6 asks about functioning at 50% or less of their ability. A raw score is obtained by adding the six individual questions (19, 20).

Allodynia Questionnaire

According to previous studies (14, 21), we used the same allodynia questionnaire employed for adults, consisting of the symptom's checklist reported by Lipton et al. (22). We asked mothers to interview their children during migraine attack, in order to help them in filling the allodynia questionnaire for each migraine attack. The allodynia questionnaire is not presently adapted for children, so we suggested the parents to indicate as "not applicable" those questions specific to adults (23). We classified patients as allodynic based on the presence of at least one symptom reported in the questionnaire in over the 50% of the headache episodes. Furthermore, for the allodynia severity, the average number of allodynia symptoms across different attacks was considered.

TABLE 1 | Demographic data of migraine patients.

Diagnosis		age (years)	sex F	M
MA	Mean	13,75	3	5
	SD	2,73		
	N	8		
CM	Mean	11,89	25	19
	SD	2,31		
	N	44		
MO	Mean	10,91	75	52
	SD	2,48		
	N	127		
MA/MO	Mean	12,36	10	1
	SD	2,61		
	N	11		
		ANOVA df 3	chi square df 3	
		$F = 5.2$, $P < 0.002$	6.21 n.s	
		Bonferroni MA VS. MO $P < 0.01$		

MA, Migraine With Aura; MO, Migraine Without Aura; CM, Chronic Migraine; MA/MO, Migraine with aura associated to Migraine without aura.

Total Tenderness Score

We measure the pericranial tenderness, using the scale validated by Langermak and Olesen (24), and employed in childhood headaches (14, 25).

Statistical Analysis

We summarized the quantitative continuous and categorical variables, age and sex, in the main migraine subgroups, and used the ANOVA test and chi square test to compare them among groups.

To satisfy the aim 1), taking into consideration the distribution of cases in the main migraine subgroups, we divided children in episodic and chronic migraine groups (EM and CM), merging the groups including migraine with aura and without aura in a sole group. Data were analyzed by Levene test for equality of variance, which was not significant for any of the considered variables. The Student's *t*-test for non-paired data was used to compare the Total PCS and the sub-items between groups.

To satisfy the aim 2) we applied the Person correlation test and curve estimation using the linear regression test, between PCS-C total and sub-items and main clinical features. Considering the number of correlations, we took into consideration only those exceeding the 0.01 significance level. We also used a one way ANOVA model and the *post-hoc* Bonferroni, to check for total PCS-C and sub-items differences among headache frequencies categories.

To satisfy the aim 3, we run out a step-wise discriminant analysis between chronic and episodic migraine, using the Mahalanobis distance, and *F* value 0.05 and 0.1 respectively as inclusion and exclusion factor.

The variables introduced into analysis were PedMIDAS, TTS, allodynia, SAFA-A, SAFA-D, PQL-ad, PQL-P, and total PCS-S.

RESULTS

Demographic data of selected patients are reported in **Table 1**. The most of patients were diagnosed as episodic migraine without aura –MO. Patients with migraine with aura were older than were patients with migraine without aura. Females prevailed in all but the MA group, though in a not significant

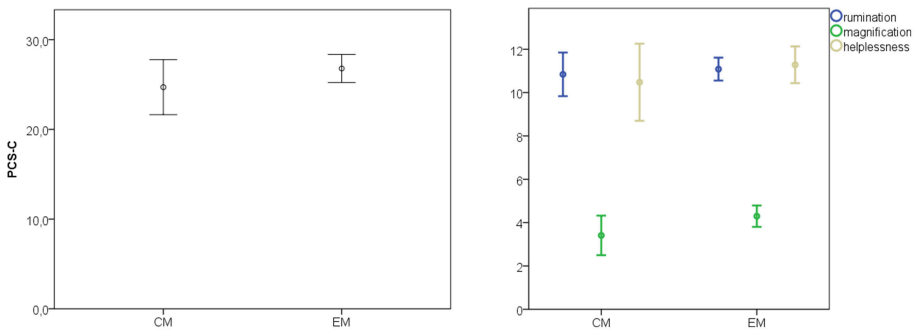

FIGURE 1 | Mean and 95% confidence intervals of total pain catastrophizing test (PCS-C) and main sub-items in the migraine chronic and episodic subgroups. Total PCS-S Student's *t*-test 1.24, $p = 0.2$; rumination, $t = 0.49$, $p = 0.62$; magnification, $t = 1.71$, $p = 0.088$; helplessness $t = 0.36$, $p = 0.33$.

way (**Table 1**). In the Supplementary table, the details of clinical features and PCS-C sub-items in Episodic and Chronic Migraine are reported (**Table 1S**).

Aim 1: Total Pain catastrophizing score was similar between chronic and episodic migraine groups (**Figure 1**).

Aim 2: Total Pain Catastrophizing and sub-items did not correlate with Migraine related disability as expressed by Ped MIDAS, but a significant correlation was present with general low quality of life, both for physical and psychological functioning, as judged by children, allodynia, pericranial tenderness, anxiety, and depression (**Table 2**, **Figure 2**). Some correlations showed a low statistical significance, as for the sub-items Rumination and Magnification and the parents' quality of life scores (**Table 2**, **Figure 2**).

The total PCS-S was similar among the different frequencies groups (ANOVA $F = 0.59$, $p = 0.70$).

Aim 3: The stepwise discriminant analysis allowed selecting the discriminant variables between episodic and chronic migraine, which were the PedMIDAS, the PQL-P for physical functioning and the TTS (**Table 3**). These variables discriminated between episodic and chronic migraine with 73, 2% accuracy.

DISCUSSION

The general impression emerging from the present results is that Pain Catastrophizing seems an important aspect of children with headache, associated with psychopathological features, general reduction of quality of life and central sensitization symptoms. However, it does not distinguish chronic from episodic migraine in children, similarly to anxiety, depression and general disability. Children with frequent migraine differ from episodic ones for those clinical aspects, which seem intrinsic to head pain, as disability linked to migraine, pericranial tenderness and physical functions decline. In the following paragraph, we report the detailed discussion of single points.

Pain Catastrophizing Is Not Associated With Chronic Migraine

The first hypothesis of the study was negative, as this aspect of pain feeling was similar among children with different headache frequencies. More than 20 years ago, Lefebvre et al. studied 252 young subjects to determine the internal reliability of the Coping Strategies Questionnaire. Subjects reporting higher levels of catastrophizing presented with higher levels of pain and higher frequency of both migraine headaches and low back pain (26).

More recent studies in adult migraine, confirmed that pain catastrophizing is associated with more severe and frequent migraine attacks, and that it could be a risk factor for chronic migraine (27–30).

The results of Orr et al study on pediatric migraine (31), confirmed what we observed, that pain catastrophizing was not associated to migraine related disability, but was a negative factor for quality of life.

Structural and functional MRI study, demonstrated that pain catastrophizing as single aspect of migraine, was negatively associated with gray matter volume in areas

TABLE 2 | Pearson correlation test among Pain Catastrophyzing Total Scale (PCS-S) and main sub-items, and clinical features evaluated in 190 migraine patients.

		TTS	ALLODYNIA	PedMIDAS	PEDS-QL	PEDS-QL-PHY	PEDS-QL-PSY	PEDS-QL-P	PEDS-QL-P-PHY	PEDS-QL-P-PSY	SAFAA_TOT	SAFAD_TOT
PCS-S	Pearson correlation	0.210**	0.243**	0.001	−0.380**	−0.0262**	−0.385**	−0.04	0.02	−0.07	0.492**	0.475**
	sig	**<0.0001**	**<0.0001**	0.48	**<0.0001**	**<0.0001**	**<0.0001**	0.32	0.39	0.19	**<0.0001**	**<0.0001**
Rumination	Pearson correlation	0.14	0.170*	−0.07	−0.229**	−0.163*	−0.197**	0.02	0.04	0.02	0.292**	0.259**
	sig	0.05	0.01	0.17	**<0.0001**	0.02	0.01	0.38	0.32	0.40	**<0.0001**	**<0.0001**
Magnification	Pearson correlation	0.181*	0.190**	0.07	−0.384**	−0.229**	−0.448**	−0.177*	−0.11	−0.183**	0.539**	0.516**
	sig	0.01	**<0.0001**	0.16	**<0.0001**	**<0.0001**	**<0.0001**	0.01	0.07	0.01	**<0.0001**	**<0.0001**
Helplessness	Pearson correlation	0.171*	0.230**	0.01	−0.337**	−0.252**	−0.331**	0.01	0.07	−0.04	0.419**	0.425**
	sig	0.01	**<0.0001**	0.43	**<0.0001**	**<0.0001**	**<0.0001**	0.46	0.19	0.28	**<0.0001**	**<0.0001**

*The mean and standard deviations of single items are reported in the **Table 1S**.*

TTS, Total Tenderness Score; PedMIDAS, Pediatric Migraine Disability Scale-MIDAS; PEDS-QL, Pediatric Quality of Life; PEDS-QL-Phy, Physical functioning of PED-QL; PEDS-QL-Psy, Psychological functioning of PED-QL; PEDS-QL-P, Pediatric Quality of Life for Parents; PEDS-QL-P-Phy, Pediatric Quality of Life for Parents Physical functioning; PEDS-QL-P-Psy, Pediatric Quality of Life for Parents Psychological functioning; SAFA-A, Psychiatric Self-Administration Scales for Youths and Adolescents-Amxiety; SAFA-D, Psychiatric Self-Administration Scales for Youths and Adolescents-Depression.

Significant p values are reported in bold.

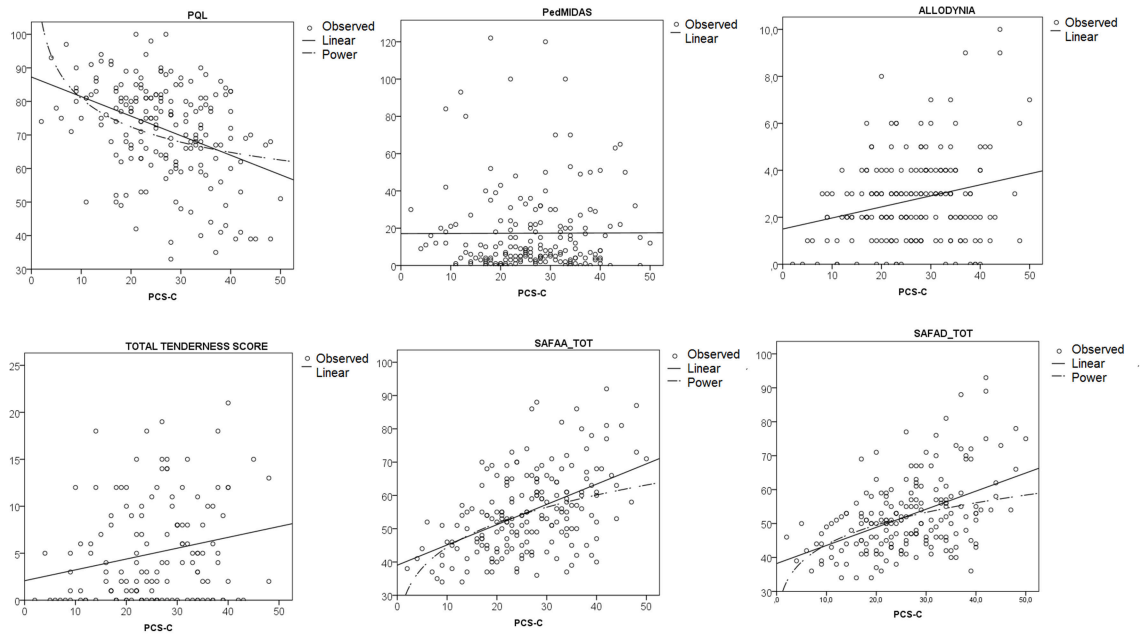

FIGURE 2 | Linear regression analysis curve estimation between Total Pain Catastrophizing Score (PCS-S) and main clinical variables as Quality of Life (PQL), Pediatric MIDAS (PedMIDAS), allodynia, total tenderness score and anxiety, and depression scale (SAFA-A; SAFA-D). Observed cases and linear trends are reported. The power curve is reported in the most significant relationships. ANOVA results, SAFA-A $F = 42.61$, $p < 0.0001$; SAFA-D, $F = 54.8$, $p < 0.0001$; PedMIDAS $F = 0.002$, $p = 0.96$; PQL, $F = 28.31$, $p < 0.0001$; allodynia $F = 2.27$, $p < 0.025$; Total Tenderness Score $F = 2.34$, $p = 0.021$.

TABLE 3 | Discriminant variables between Episodic (EM) and Chronic (CM) childhood migraine.

	Diagnosis	
	EM	**CM**
FISCHER DISCRIMINANT LINEAR FUNCTION		
Ped-MIDAS	0.078	0.107
PQL-P physical fun	0.285	0.255
TTS	0.164	0.266
Constant	−12.943	−11.884

	Diagnosis	**classification**		**Total**
		EM	**CM**	
Cases	EM	120	26	146
	CM	25	19	44
%	EM	82.2	17.8	100.0
	CM	56.8	43.2	100.0

73.2% of cases correclty classified

implicated in processing the sensory, affective, and cognitive aspects of pain in patients, and with disrupted connectivity between default mode, salience, cognitive, visuospatial, and sensorimotor networks (32, 33).

Overall, the exaggerated negative mental disposition toward pain and anticipated pain experience may be an intrinsic feature of migraine patients who could prospectively develop severe migraine.

Correlation Between Pain Catastrophizing and Main Clinical and Psychopathological Variable and Central Sensitization Symptoms

In accord with the similarity of PCS-C values between episodic and chronic migraine, pain catastrophizing did not correlate with disability linked to migraine, but it correlated with general low quality of life. The reason may be in the positive association between this mental set and anxiety and depression levels, which was well-described in adult migraine (27, 29, 30).

This association is also present in children with other forms of chronic pain (34, 35). The increase in pain catastrophizing could thus summarize a clinical phenotype characterized by anxiety, depression and a mental status of hyper-estimation of pain experience, which is causative for poor quality of life. It is conceivable that such clinical phenotype could present with an abnormal function within cognitive and emotional network (32, 33). This cortical network could partly correspond to the so-called salience matrix, which is fundamental in the processing of pain experiences (36), being modified in adult migraine patients (37). In fact, we observed that pain catastrophizing correlated positively with allodynia and pericranial tenderness, which are symptoms of central sensitization. The predisposition to develop central sensitization phenomena was associated with psychopathological factors and pain catastrophizing in adult

patients with muscle skeletal pain (38). At the time of the present evaluation, children sharing this clinical phenotype were not chronic migraneurs, but further prospective studies could clarify if this mental trait could be predictive of chronic evolution. These children, however, presented with a poor quality of life, and low physical and psychological functioning, that could suggest that this clinical phenotype is disabling *per se*, independently from the severity of migraine. Parents seemed not sentient of this frailty, as they generally tended to attribute the reduction of quality of life to migraine severity and perceived the poor quality of life of children with chronic, but not episodic migraine. The tendency to pain amplification, associated to anxiety and depression tracts, could thus be underestimated in parents' consideration, at least as a cause of low quality of life. There was a mild correlation between PCS sub-items, as rumination and magnification, and children quality of life as judged by parents, who probably advise the distress caused by some traits of this mental behavior.

Discriminating Factors Between Chronic and Episodic Migraine

The discriminant analysis confirmed that in our children sample, pain catastrophizing, and associated psychopathological features were not distinguishing factors between episodic and chronic forms, while clinical factors directly associated to migraine, as disability linked to headache frequency, and the general decline in physical functioning in the parents' judgment, distinguished with discrete accuracy episodic from chronic forms. Pericranial tenderness was the other discriminating factor, because persistent muscle pain characterizes chronic migraine in adult and childhood age (14, 39). In previous studies on juvenile cohorts, obesity, depression, presence of allodynia and stressful life events were risk factors for chronic pain (3). Pain catastrophizing could summarize a mental behavior predisposing to evolution into chronic migraine, which seems underestimated in parents consideration and worthy of further evaluation in prospective studies.

Study Limitation

The Italian PCS-C scale has not been presently validated in children, though this study could be considered preliminary to the final publication of the translated version, obtained with the agreement of Geert Crombez, according to the back-translation method [Simeone et al, in preparation; (40)]. The other clinical scales and assessments, as allodynia and pericranial tenderness, were originally applied in adult migraine, and some changes in children and adolescents could exist (14, 22–24). However, all symptoms reported in the classification could appear phenotypically modified in infantile age (41), possibly requiring adjunctive notes and changes to the criteria provided for adult migraine (15).

Another important limit relies in data referring to a selected patients group of a tertiary headache center, and not to general population. The episodic migraine children, who requests for headache specialist's visit, could in some way express a psychological frailty predisposing to chronic evolution, so the generalization of present results to the wider population of children with migraine needs to be confirmed.

CONCLUSIONS

Pain catastrophizing seems a mental characteristic of a clinical phenotype including psychopathological traits and enhanced expression of central sensitization symptoms. This clinical profile causes general decline in quality of life in the child judgment, with a probable parents' underestimation. In childhood age, it would not be a feature of chronic migraine, but the possibility that it could predict this evolution is consistent and worthy of further prospective evaluation.

The utility of this easy evaluation in the clinical setting of children migraine seems highly supported by present results.

AUTHOR CONTRIBUTIONS

MdT: study design and coordination, statistical analysis, manuscript editing. VS: manuscript preparation, clinical data collection. MS: manuscript preparation, psychological assessment. DD: manuscript editing. GL, RB, and MD: clinical data collection, data entry. MF: psychological assessment. RCT: manuscript preparation and editing. All authors read and approved the final manuscript.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00114/full#supplementary-material

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Pediatric vs. Adult Prodrome and Postdrome: A Window on Migraine Pathophysiology?

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Few studies have been conducted on the prodromal and postdromal phases of the migraine attack in children and adolescents. Using a questionnaire, we found that 67% of 103 children and adolescents with migraine reported at least one prodromal symptom, with a mean number per subject of 1.8 (median 2.2). The most frequently reported prodromal symptoms were face changes, fatigue and irritability. In pediatric patients selected as having prodrome, fatigue, mood change and neck stiffness were the most frequently reported prodromal symptoms. Using a different design, Laurell et al. found that 71% of 137 pediatric patients reported at least one prodromal symptom with a mean number per subject of 1.9 ± 2.0. Studying postdrome was fraught with unexpected difficulties as our preliminary research showed. Patients reported 2 groups of symptoms occurring during the resolution phase of the headache: symptoms whose onset was *before* headache cessation and were persisting *after* it, and symptoms whose onset was *after* headache cessation. We referred to the former as persistent symptoms and to the latter as true postdromes. Ninety-one per cent of patients reported persistent symptoms, with a mean of 6.0 and a median of 2, asthenia, pallor, cognitive difficulties, anorexia, somnolence, and nausea being the more frequently reported. True postdromes were reported by 82% of patients, with a mean of 2.6 and a median of 2, thirst, somnolence, visual disturbances, food craving, paraesthesias, and ocular pain being the most frequent reported. Interestingly, several prodromal and postdromal symptoms are also encountered during the aura classic and/or accompany the headache phase. Functional imaging in migraine has showed that the activations in areas such as hypothalamus or brainstem may begin before headache onset and/or persist after headache relief. Thus, one may wonder whether prodromal and postdromal symptoms may indicate the involvement of the limbic system, dopaminergic pathways, the hypothalamus and the brainstem. Differences between children, adolescents and adults might contribute to the understanding of migraine neurobiology.

Keywords: migraine, prodrome, postdrome, child, adolescent, adult, pathophysiology

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INTRODUCTION

Migraine is one of the most debilitating medical conditions, both in adult and pediatric populations (1). In the former it has familial, societal, and work consequences, while it may impede leisure and scholar activities in the latter, with the specific and supplementary issue of school absenteeism (2, 3).

Phenotypical expressions of migraine vary greatly both in the adult and pediatric age range. In both populations, and probably more so in the latter, that migraine headaches are frequently associated with non-headache symptoms has been known for a long time (4). These are ultimately epitomized by episodic syndromes which may be associated with migraine (5). It is meaningful that the historical recognition of these episodic syndromes occurred far earlier in children than in adults.

Symptoms other than headache may occur during the four phases of the attack: the prodrome, the aura, the headache phase, and the postdrome (6). Even in adults, prodrome, and postdrome seem to have been neglected (7, 8). Even fewer studies have been dedicated to them in children and adolescents (7, 8).

This is probably unfortunate as they may provide an insight on migraine pathophysiology, particularly if one takes advantage of the developmental differences in both populations (6, 9). Here we propose to review the available data on the subject, in children, adolescents, and adults as well. We will strive to decipher the possible mechanisms underlying these symptoms and to do so from a developmental perspective.

METHODOLOGICAL ISSUES

Reviewing the available data on the prodrome (PS) and the postdrome (PD) in the pediatric and adult range is fraught with several difficulties, notably methodological, which can be enumerated as follows (10):

1. There are few studies available on the subject:

To our knowledge, only three studies dedicated to the PD in the pediatric population (two included children and adolescents only whereas the third concerned both adults and children (11–13)) are available. Data are even scarcer for PD, as there is only one pediatric study dedicated to them (14).

Even in adults, few studies on the subject have been conducted.

2. Most of these studies are fraught with biases due to methodological differences.

- Definitions for both PS and PD vary from one study to another,
- There are large differences in the populations studied:
  - Children and adolescents vs. both adults and children/adolescents,
  - General population vs. clinic based,
  - Preselected vs. non-preselected patients,
  - Variable sample size,
  - Variable sex ratio,
- Retrospective vs. prospective study,
- Pre-established questionnaire vs. open responses.

The way of collecting data is a major issue. As retrospective data collection leads to recall bias, prospective studies using electronic diary would be more appropriate but difficult to carry out in children and adolescents. Data collection from retrospective studies may also lead to underestimate the actual prevalence of PS or PD in the sample. Questionnaires with a pre-established list are associated with a risk that some patients may discard some symptoms whereas open questionnaires may be fraught with patients being unable to regard some non-specific or poorly specific symptoms as PS or PD symptoms, or mistaking PS for triggers. The issue of cranial autonomic symptoms such as face changes (pallor, flushing, or dark rings under the eyes) is particularly tricky.

Furthermore, some of the difficulties may be heightened in children and adolescents in whom the characterization of such symptoms in children faces difficulties, notably when it comes to history taking, age-related differences in communication, and cognition.

To put it bluntly, there is little comparability between studies… but, in the same time, they contain interesting material that may bring fruitful answers to the issue.

WHAT HAVE WE LEARNED FROM THESE STUDIES?

Generally speaking, PS refers to symptoms preceding the onset of migraine headache whereas PD corresponds to symptoms which begin after headache cessation. PS symptoms are subjective symptoms which develop slowly. They can be categorized as cognitive, behavioral, or physical factors. They characterize the pre-ictal state and should not be confused with the migraine aura, nor with triggers as food craving, for example, may be mistaken as food triggering a headache. Many triggers reported by migraineurs (e.g., sleep deprivation, hunger, or bright light), may in fact represent PS of an already ongoing attack.

The ICHD-3 states that "Prodromal symptoms may begin hours or a day or two before the other symptoms of a migraine attack with aura. They include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light and/or sound, nausea, blurred vision, yawning, and pallor. The term "prodrome," which has replaced "prodrome phase" or "prodromal symptoms," does not include aura" and, later, "Postdromal symptoms, most commonly feeling tired or weary, difficulty with concentration and neck stiffness, may follow resolution of the headache, persisting for up to 48 h" (ICHD-3, p. 21) (4). Further in the glossary, one can read: Prodrome- "A symptomatic phase, lasting up to 48 h, occurring before the onset of pain in migraine without aura or before the aura in migraine with aura. Among the common prodromal symptoms are fatigue, elated or depressed mood, unusual hunger, and cravings for certain foods" (ICHD-3, p. 211) (4). Whereas, the postdrome was not even defined in the glossary of terms in

Abbreviations: MA, migraine with aura; MO, migraine without aura; PD, postdrome; PS, prodrome; PTS, persistent symptoms; TPD, true postdromes.

ICHD-3 beta, it appeared in the ICHD-3 glossary which states: Postdrome: "A symptomatic phase, lasting up to 48 h, following the resolution of pain in migraine attacks with or without aura. Among the common postdromal symptoms are feeling tired or weary, difficulty with concentration and neck stiffness" (ICHD-3, p. 210) (4, 15).

The Migraine Prodrome

Pediatric Studies

We searched for the prevalence of 15 prodromal symptoms using a telephone questionnaire in 103 children and adolescents (<18 years) suffering from migraine (with (MA) and/or without aura (MO), but not chronic migraine) according to the ICHD-II criteria, randomly drawn from a clinic-based database. Each interview concerned the migraine patient and one of his/her parents. The definition of prodrome was the same as in the ICHD-3 glossary (see above). The questionnaire comprised two parts; part 1 addressed migraine characteristics, part 2 listed 15 possible prodromal symptoms selected from the pediatric and adult literature. Patients were educated to distinguish prodromal from aura symptoms. Patients had to answer five questions pertaining to each prodromal symptom reported [see (11) for details and statistical methods]. Written informed consent was waived, as per national guidelines at the time of data collection.

These results have been published elsewhere (11). In short, we included 103 patients. **Table 1** shows main results. Prodrome consisted of one or more, and two or more prodromal symptoms for, respectively, 69 (67%) and 57 (55%) patients (**Figures 1**, **2**). As for frequency, using the following scale: rarely, often, very often, and always when prodromal symptoms occurred, respectively in >0-<1/3 attacks, 1/3–2/3, >2/3-<1 or in each attack, the corresponding distribution was, respectively: 15, 11, 10, and 64% of the 69 subjects who had prodrome. There was no statistically significant link with gender, migraine subtype and mean monthly attack frequency. As for gender, 72% of boys and 65% of girls had prodrome.

The main difference in design in the Karsan study (12), as compared to the other two studies (11, 13) was that patients were preselected as having prodrome by reviewing clinic letters from the initial consultation. The authors argued they wanted to develop "a better understanding of the range of symptoms when they were present." Moreover, included patients (children and adolescents) not only suffered from migraine but also from New Daily Persistent Headache "with migrainous features." Exclusion criteria included typical migraine aura and cranial autonomic symptoms. In this study, prodromal symptoms were defined "as symptoms recognized as occurring prior to the onset of pain and any non-migraine defining features occurring during the pain" with the exclusion of "any cranial autonomic features because of their discrete pathophysiology" (12). Of note, chronic migraine and episodic migraine accounted for 58 and 29% of the diagnoses, respectively. New Daily Persistent Headache with migrainous features (8%) and hemiplegic migraine (5%). Thirty one percent of patients reported a history of infantile colic, which accounted for the most frequent childhood episodic syndrome associated with migraine. The commonest number of reported prodromal symptoms was two. Two or more prodromal symptoms were reported by 85% of patients. Four prodromal symptoms were reported by >30% of patients: fatigue, mood change, yawning, and concentration difficulty.

TABLE 1 | Migraine and demographic properties of patients reporting at least one prodromal symptom ($n = 103$).

	Subgroups	*N* (%)	Number of individuals with at least one prodromal symptom (%)	OR [CI]	*p*-value
Total population		103	69		
Sex	Male	57 (55%)	40 (70%)		
	Female	46 (45%)	29 (63%)	1.4 [0.6–3.1]	0.6
Age (years)	<6	3 (3%) 1 (33%)			
	6–12	41 (40%)	26 (63%)		
	>12	59 (57%)	42 (71%)	1.6 [0.7–3.6]	0.4
Number of migraine attacks per month	<1	29 (28%)	23 (79%)		
	1–2	26 (25%)	15 (58%)		
	3–4	22 (21%)	12 (55%)		
	5–6	13 (13%)	9 (69%)		
	7–8	9 (9%) 7 (77%)			
	9-10	4 (4%) 3 (75%)			
	>10	0 (0%) 0 (0%)		1.5 [0.5–3.9]	0.6
Migraine subtype	MO	11 (11%)	8 (73%)		
	MA	69 (67%)	45 (65%)		
	MO and MA	23 (22%)	16 (70%)	1.4 [0.3–5.9]	0.9

N, number of patients. OR, odd ratio; CI, confidence interval.

Both children and adults were included (mean age 45 ± 17 years [5–96]) in a third study (13). The sample study consisted of patients suffering from migraine seen by neurologists at outpatient headache clinics in six Finnish cities with at least three first-degree relatives with possible migraine. The questionnaire comprised 14 predefined prodromal symptoms. The pediatric sample represented 6.2% (137/2219) of the total sample. Seventy-one of children and adolescents had had at least one prodrome symptom vs. 77% for the whole sample (mean 3.0 ± 2.9). Unfortunately, data pertaining to the pediatric sample were not further detailed by the authors in the article. Considering the whole sample (children and adults), prodromal symptoms were more than twice more frequent in migraine vs. non-migraine patients. Patients with MA had more prodromal symptoms (79%) vs. those with MO (75%; mean, respectively 3.3 vs. 2.7). Interestingly the subgroup with the lesser rate of prodromal symptoms was the typical aura without headache patients (frequency: 41%, mean number of prodromal symptoms:

0.8) whereas patients suffering from hemiplegic migraine had the greater rate of prodromal symptoms (frequency: 93%, mean number of prodromal symptoms: 5; $p < 0.001$). PS was more frequent in females. Females had also a higher number of prodromal symptoms unlike other studies, a tendency that may have been revealed by the large size of the sample. There was an inverse tendency for scintillating scotoma. A limit to the study was that the sample was skewed toward larger hereditary burden and more severe migraine. Moreover, face changes were not included in the list of predefined prodromal symptoms.

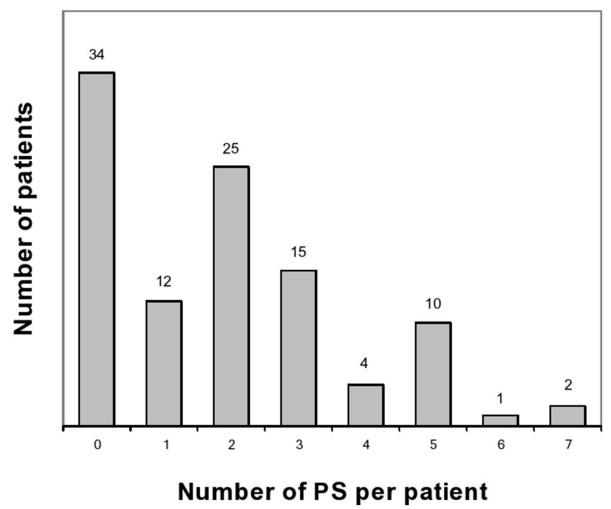

FIGURE 1 | Number of prodromal symptoms per patient. PS, prodromal symptoms.

Comparison to Adult Studies

The proportion of pediatric migraine patients reporting PS was available in two studies only and was comparable: 67% (11) and 71% (13). In the Celeste study which included 398 children and adolescents suffering from primary headache (78.5% with migraine or probable migraine), only 11.8% of patients reported PS (11). These data are difficult to compare to adult studies, in which prevalence vary from 9 to 88% (**Table 2**) (16, 18, 19, 21–24, 26, 27). In population-based adult studies rates range from 12% in patients with MO to 18% in patients with MA (23). The mean number of prodromal symptoms reported per patient varies between 1.8 and 3. A lower figure was reported in the study by Schoonman et al: 3.2 (26). Whereas, PS occurs mainly in the 5–12 years age range, one may suppose that some of younger children may not be able to verbally express a symptom, as Mortimer et al. already noted (29). However, children as young as 18 month have been able to report PS (12). Interestingly, Laurell et al. found that PS rate was age-dependent and were able to estimate that the odds of experiencing PS increased by 1.0% per year (13). Conversely, a source of underdiagnosis (or misdiagnosis) lies in the fact that parents may not regard some symptoms as prodromal symptoms. It is worth underlying

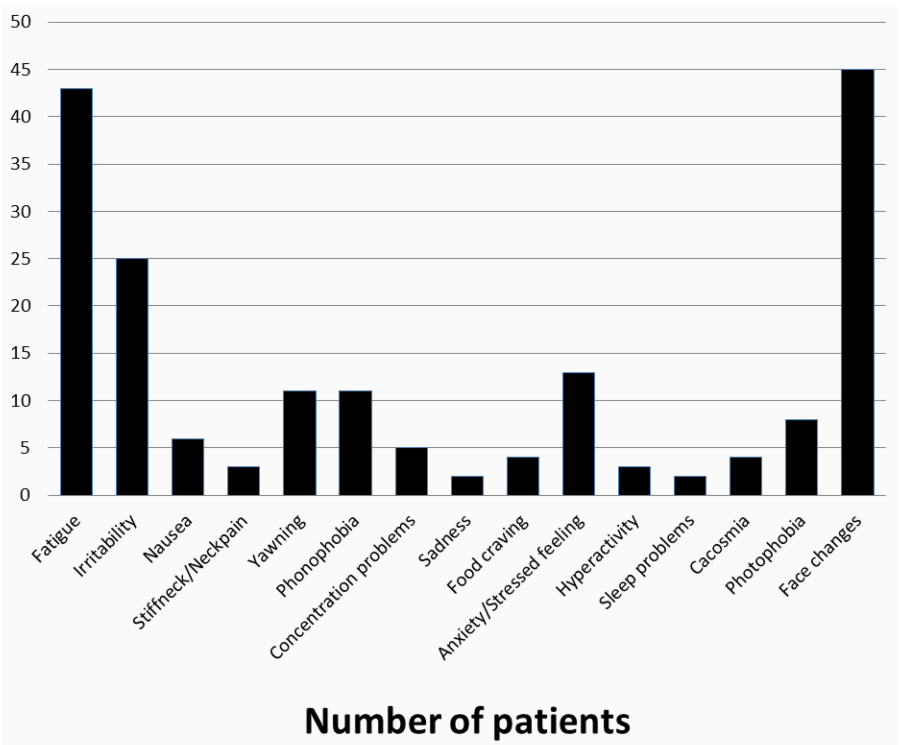

FIGURE 2 | Prevalence of prodromal symptoms.

TABLE 2 | Studies of prodromal symptoms.

References	Type of study	P/R	*N*	Sample	PS symptoms	Comments/other results
Cuvellier et al. (11)	Telephone Questionnaire/ Checklist	R	103	Clinical sample of Children/adolescent with migraine	Face changes (44%), fatigue (42%), irritability (24%)	Frequency of PS trended higher with age but not statistically significant ($p = 0.4$). Differences by gender and migrainesubtype not statistically significant PS reported by 75% aged 12 and older, 68% in 6–12 age range, 33% in those <6.
Karsan et al. (12)	Clinical letter	R	100	Clinical sample with migraine (episodic/chronic, NDPH)	Fatigue (62%), mood change (55%), neck stiffness (33%), and yawning (30%)	Preselected as having PS Infants as young as 18 months reported PS.
Amery et al. (16)	Unstructured recall and checklist	R	149	Population-based sample with migraine	PS–50% of patients with following PS the day before attack: adynamia, pallor, photophobia, phonophobia, hyperesthesia, shivers, taciturn, inactive, intolerant, intellectual disturbance	
Blau (17)	Oral questioning	R	50	Clinical sample	Yawning, tiredness, mood change	Prevalence:34%
Drummond and Lance (18)	Oral questioning	R	530	Clinical sample	Mood change, appetite change, changes of alertness	Prevalence: 30%
Giffin et al. (19)	Electronic diary	P	97	Clinical sample	Tiredness, concentration difficulties, stiff neck, light sensitivity, sound sensitivity	Preselected as having PS
Houtveen and Sorbi (20)	Electronic diary	P	93	Clinical sample	Increase in sensory sensitivity, pain/stiffness, fatigue, negative affect in the 12 h prior to attack	
Kelman (21)	Interview	R	893	Clinical sample with migraine	Fatigue (25.6%); mood change (23.4%); head pain, aching, twitching (5.6%)	No gender difference in frequency
Quintela et al. (22)	Questionnaire	R	100	GP surgery	Anxiety, phonophobia, irritability, low mood, yawning	Prevalence: 84%
Rasmussen and Olesen (23)	Interview & Questionnaire	R	1,000	Population	Low spirit, tiredness, increased activity, depression	Prevalence: 14%
Russell et al. (24)	Face-to-face/telephone interview	R	484	Clinical sample	Increased activity, low spirit, tiredness, depression, particular eating habits, irritability, yawning	Prevalence: 9%
Santoro et al. (25)	Self-report	R	100	Clinical sample with migraine	PS	Thirty-three percent of patients affected by migraine without aura reported PS in at least 50% of attacks. This subset reported a higher average number of trigger factors relative to other patients
Schoonman et al. (26)	Questionnaire	R	461	Clinical sample	Fatigue, phonophobia, yawning	Prevalence: 87%
Waelkens (27)	Questionnaire	P	49	Clinical sample	Irritability, depression, fatigue, hunger, bulimia, yawning	Prevalence: 88%
Wöber et al. (28)	Paper diary	P	327	Population	Muscle tension in the neck, stress, tension, fatigue	

P, prospective; R, retrospective; N, number of patients; NDPH, New Daily Persistent Headache; GP, General Practitioner.

that only an external observer could identify some prodromal symptoms reported by the child (such as face changes in our study), rendering this finding notably dependent from the study design.

In our study we found that face changes were the more frequent prodromal symptoms (44%) reported. Face changes (pallor, shadows under the eyes) seem to be peculiar to children and adolescents, as they have rarely been reported as prodromal symptoms by adults (19, 30). One may suppose that parents are more attentive to their child appearance due to legitimate concern whereas adults in the midst of an attack are not prone to look at themselves in a mirror. This is indeed a study bias easily

missed between self-reporting and reporting by a third party. Inter study comparison precludes further definite conclusions; e.g., Karsan et al. excluded *a priori* cranial autonomic features from their study, pointing out that face changes may be cranial autonomic features, a statement we fully agree with (12).

In the Celeste study, the commonest prodromal symptoms were a feeling of great tiredness, irritability, yawning or sighing, balance disturbance, and mood change (31). The other most frequently reported prodromal symptoms were fatigue [62% (12), 42% (11), mood change (55% (12)], neck stiffness [33% (12)], and irritability [24% (11), 10% (12)]. Fatigue and irritability have been frequently reported in adult studies, with rates of 72% (19), 46.5% (21), and 25.6% (25) for fatigue, and 23.4% (25) for irritability. By contrast, some prodromal symptoms which were reported in adults, such as behavior changes, phonophobia, and gastrointestinal symptoms, were rarely reported in pediatric subjects. One may wonder if these findings represent an age-dependent feature or stem from methodological differences between studies.

As regards the constancy of the association of PS the constancy of PS being associated with the migraine attack, it concerned 64% of patients in our study, a figure higher than those reported in adults. In another study conducted in an outpatient clinic ($n = 460$ adult migraine patients), PS preceded migraine attacks in more than 2/3 of events in 46%; in this subgroup PS was followed by an attack in more than 2/3 of cases in 68% or more of the subjects, which was consistent with other findings reported in adults (26). This raises the issue of the predictability of the imminence of the attack (see below). Another issue is the consistency of PS phenomenology from an attack to the next one. To our knowledge this point has not been studied in pediatric samples but in adults, Quintela et al. showed that PS was reproducible across different migraine attacks (22), which allows self-prediction. Self-prediction is the ability by the migraine patient to assess the probability that he/she will have an attack over a defined time period. It may rely on triggers, PS features, or other considerations. To our knowledge, the question of self-prediction has not been studied in pediatric population.

The prevalence of prodromal symptoms did not differ with gender (11, 12), in contrast with the studies by Schoonman et al. (26) and Laurell et al. (13), where females reported more prodromal symptoms than males. Perhaps, the sex ratio may account for this difference, as there was a majority of women in adult studies, whereas boys were predominant in our study.

The Migraine Postdrome

Pediatric Studies

Our preliminary research on the PD showed that children and adolescents reported two groups of symptoms occurring during the resolution phase of the migraine headache: symptoms that had begun before and went on after migraine headache had subsidized, and symptoms that began strictly after headache cessation. Thus, we decided to embark on their study and instructed both patients and parents to distinguish separately both sets of symptoms, referring to the formers as persistent symptoms (PTS) and to the latters as true postdromal symptoms (TPD). Methods were similar to our study on prodrome [to be included patients, who were randomly selected from my database of headache patients (8), had to be <18 years, to fulfill the ICHD-3 beta criteria for pediatric migraine without typical aura (MO) and/or with aura (MA) at the time of study (i.e., ICHD-3 beta 1.1 and/or 1.2.1), but not chronic migraine, and not be on preventive drugs for migraine or any other medication]. Patients and/or their parents were first informed of the study objective and design. We reviewed with both the phases of migraine, including the concept of PD. We particularly instructed both patient and parents to distinguish separately PTS and TPD. The questionnaire comprised two parts; part 1 addressed migraine characteristics, part 2 listed 31 resolution phase symptoms selected from the adult literature. This list included behavioral, dietary, environmental, infectious, traumatic, hormonal factors, and other symptoms. Patients had to answer five questions pertaining to each postdromal symptom reported (**Supplementary Material**). All patients and their parent(s) provided informed written consent for participation in the study, which was approved by the Ethics Committee of Lille Faculty of Medicine. The results have been published elsewhere [see (14) for details and statistical methods] and we will briefly summarized them. Included patients consisted of 100 children and adolescents (49 boys), with an age range of 4–17 and a mean age of 10.5 years. Migraine subtype distribution (MO, MA, both MO and MA) was, respectively: 66 (66%), 26 (26%), and 8 (8%) patients. Thirty-three (33%), 50 (50%), 7 (7%), 5 (5%), and 5 (5%) patients had a monthly number of attacks of, respectively: <2, 2-<4, 5-<7, 7-<9, and 9-<15. The interviewed parent was mainly the mother (95%). Most patients had either PTS ($N = 80$) or TPD ($N = 82$). Asthenia, cognitive difficulties, pallor, cognitive slowing, anorexia, sleepiness, and nausea were the most frequently cited PTS, by 49, 42, 38, 28, 26, 22, and 22% of patients, respectively (**Figure 3**). The median number of PTS differed according to migraine subtype distribution: 2 [0–10], 3 [0–8], and 3 [0–5] in patients with MO, MA, and both MO and MA, respectively ($p = 0.60$). Thirst, sleepiness, visual disturbances, food craving, paresthesias, and ocular pain were the most frequently cited TPD, by 36, 36, 25, 19, 16, and 16% of patients, respectively (**Figure 3**). The median number of TPD differed significantly according to migraine subtype distribution: 2 [0–11], 3 [0–9], and 1 [0–3] in patients with MO, MA, and both MO and MA, respectively ($p = 0.03$). Onset of TPD occurred <30 min after migraine headache cessation in 95% of patients. **Table 3** presents time data available in the 82 patients/parents capable to specify TPD duration, accounting for 257 TPD.

Several results reach statistical significance: PTS were reported more frequently by boys than girls (94 vs. 67%, $p < 0.001$), mean number of PTS was greater in boys (mean: 3.0 vs. 2.0 for girls, $p = 0.003$). Pooled PTS+TPD lasted less in girls ($p < 0.001$).

Grouping together symptoms which are established prodromal symptoms (sadness, neck pain, food craving, concentration difficulties, asthenia, yawning), aura symptoms (visual disturbances, paresthesias), and classic accompanying symptoms of the headache phase (pallor, nausea, vomiting, abdominal pain, anorexia, irritability, dizziness), we found that they were reported as PTS in 82, 3, and 118 cases and as TPD in 63, 41, and 34 cases, respectively ($p < 0.001$) (**Table 4**).

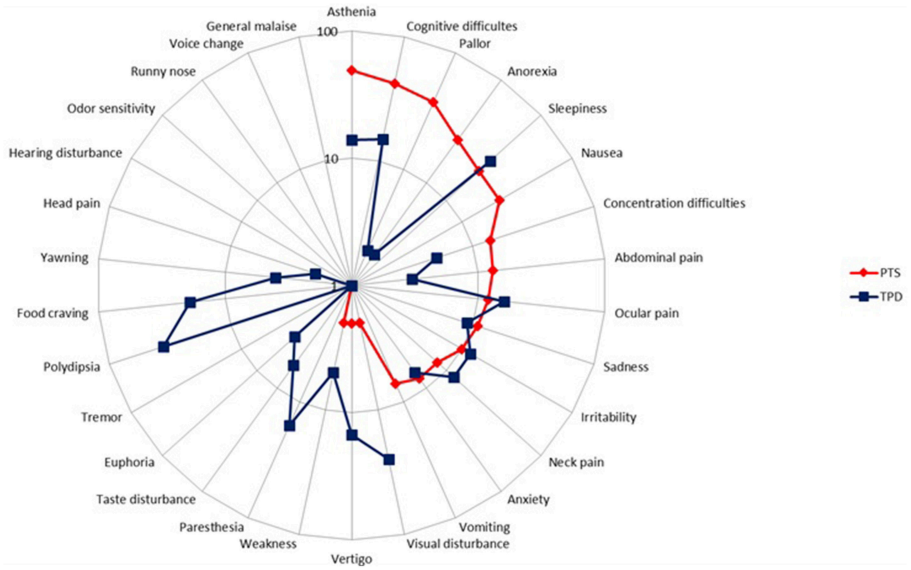

FIGURE 3 | Frequency of persistent symptoms and true postdromes among pediatric migraineurs ($n = 100$). PTS, persistent symptoms; TPD, true postdromes.

TABLE 3 | Frequency and duration of persistent symptoms/true postdromes.

		PTS (*n*, %)	TPD (*n*, %)
DURATION OF PERSISTENT SYMPTOMS/TRUE POSTDROMES			
1	<3 h	100 (34.4%)	185 (72.0%)
2	3 to <6 h	55 (18.9%)	28 (10.9%)
3	6 to <12 h	52 (17.9%)	28 (10.9%)
4	12 to <24 h	83 (28.5%)	11 (4.3%)
5	≥24 h	1 (0.3%)	5 (1.9%)
		291 (100%)	257 (100%)
FREQUENCY OF PERSISTENT SYMPTOMS/POSTDROMES AS A FUNCTION OF MIGRAINE ATTACKS			
1	Always	2 (0.7%)	2 (0.8%)
2	Very often	19 (6.5%)	52 (20.2%)
3	Often	128 (44.0%)	125 (48.6%)
4	Rarely	142 (48.8%)	78 (30.4%)
		291 (100%)	257 (100%)

PTS, Persistent symptoms.
TPD, True postdromal symptoms.

TABLE 4 | Frequency of persistent symptoms/true postdromes as a function of headache phase category.

	Persistent symptoms	True postdromes
Premonitory symptoms[a]	82	63
Aura symptoms[b]	3	41
Accompanying signs[c]	118	34

[a] *Concentration problems, food craving, sadness, stiff neck/neck pain, yawning, asthenia.*
[b] *Visual symptoms, paresthesias.*
[c] *Nausea, pallor, vomiting, abdominal pain, anorexia, irritability, dizziness. ($p < 0.0001$).*

Retrospective character, small sample size, and tertiary unit recruitment were the main limits of our study. One may also underline that some aspects of time and memory were not perfectly handled in the pediatric age group.

Comparison to Adult Studies

From our results we could conclude that children and adolescents with migraine frequently experienced both PD symptoms subtypes. It is also of note that the child falls asleep in as many as 60% of children, which aborts the migraine attack and thus avoids or masks the PD (32). In the absence of another pediatric study, we can but compare our results with adult studies (**Table 5**). However, this is hampered by several difficulties; first, we are unaware of an adult study using the distinction we made between PTS and TPD. Second, PD definition is variable between studies. With these reserves in mind, most adult patients had PD: respectively 94, 68, 80, and 81% in the studies by Blau (33), Kelman (34), Giffin et al. (35), and Quintela et al. (22). The latter was a prospective daily electronic diary study, where the PD was defined as "the time between headache resolution and feeling completely back to normal" (35).

PD duration was longer in adults, with a mean of 18 h (Blau) and 25.2 h (Kelman) (33, 34). Duration of both PTS and TPD was <12 h in most patients (14). In one small study ($n = 34$), the PD lasted between 30 min and 6 h for most symptoms, but some patients could experience PD which lasted up to 4 days for (33). Results were similar in a recent electronic diary study, with 54% of patients having a PD duration <6 h whereas PD duration was >24 h in only 7% of patients (35). TPD phenomenology was notably different from that reported in adult PD. The most commonly PD symptoms reported by adult patients are tiredness, concentration difficulty, and neck stiffness (8). Asthenia, somnolence, phonophobia, photophobia, unhappiness, and yawning (22), head pain, cognitive difficulties, "hangover," gastrointestinal symptoms, mood change, and

TABLE 5 | Postdrome adult studies.

References	Type of study	P/R	*N*	Sample	Postdrome symptoms	Duration	Prevalence
Blau (33)	Interview	R	50	Clinical sample	Mood variations, muscular weakness, abnormal appetite, yawning, tiredness, and changes in fluid balance.	1 h–4 d	94%
Giffin (19)	Electronic diary study	P	120	Clinical sample	Tiredness or weariness (88%), difficulty with concentration (56%) and stiff neck (42%).	≥24 h in 93%	81%
Kelman (34)	Structured interview	R	827	Clinical sample	Tiredness (71.8%), head pain (33.1%), cognitive difficulties (11.7%), "hangover" (10.7%)	56% < 12 h, 32% 12 ≤ 24 h, 12% > 24 h	68%
Quintela (22)	Interview	R	100	GP clinical sample	Asthenia (55%), tiredness (46%), somnolence (29%), concentration difficulties (28%)		80%
Giffin (35)	Electronic diary study	P	120	Clinical sample	Tiredness or weariness (88%), difficulty with concentration (56%), and stiff neck (42%).	≥24 h in 93%	85%

P, prospective; R, retrospective; N, number of patients; GP, general practitioner.

weakness (34), nausea, physical weakness (36), tiredness (22, 34, 35), concentration difficulties (34, 36) have also been reported. In our study PTS were more frequent in patients with MA only compared to MO only and both MO and MA, as in some adult studies (22, 34).

SO WHAT?

Children, adolescents, and adults suffering from migraine do have PS and PD frequently. Bearing in mind the great heterogeneity between studies, prodromal symptoms are roughly the same in the three age ranges, with the notable exception of face changes which seem to be a pediatric peculiarity, but so far they have been reported in our study only. As to PD, it is difficult to draw definite conclusions with only one study but let us notice that whereas temporal characteristics of PTS/TPD shared some similarities, with the obvious exception of time lag, as expected due to the definitions employed, the nature of TPD and PTS showed differences, as shown in **Table 3**.

Some authors of adult studies have attempted to group PS and PD symptoms according to general categories such as cognitive or sleep-related, migraine-like and sensory sensitivities, and other homeostatic symptoms. The same approach can be made in the pediatric population.

It is remarkable that some PS and PD symptoms share similarities, if not identities. Karsan and Goadsby have proposed to group PS starting simultaneously with pain, or occurring during the pain itself under the umbrella term "premonitory-like" as they "have observed that they can start simultaneously with pain, or occur during the pain itself" (37). Some PTS and TPD reported in our study dedicated to the PD in children and adolescents are clearly reminiscent of PS symptoms (14). Several adult studies dedicated to the PD of a migraine attack led to comparable conclusions (34, 35, 38). This suggests that PS and PD may have pathophysiological similarities and be generated by the activation of shared neural networks.

Possible Window on Migraine Pathophysiology and Developmental Differences

Neuronal Networks Into Play

Understanding the factors associated with headache beginning and cessation might provide insights into the mechanisms of attack initiation and termination, and perhaps shed light on the issue of why there being different subtypes of migraine (39–41). The hypothesis of (a) possible migraine generator(s) has gained credit over the last years and one may raise the issue whether PS reflect the early activation of them while PD in the same way would indicate that some of these networks would still be ongoing once the headache has ceased. The chronology of this process may indeed prove more interesting; in other words, does the sequence progression of PS and PD reflect the successive activation of generators? And what degree of dependency do they share? Once activated, are they able to withdraw from their counterparts and to which degree?

The brainstem seems a good candidate in the generation of some prodromal symptoms, such as yawning, mood changes, irritability, hyperactivity, and sleep disturbances. Other prodromal symptoms point to the hypothalamus (thirst, food craving, sleep disturbances, pissing, and neck stiffness). Some of the former prodromal symptoms reflect dopaminergic hypersensitivity and are mediated by nitric oxide pathways (42).

Del Zompo et al. have shown that alterations in dopaminergic neurotransmission can modulate clinical susceptibility to migraine, at least in some migraine patients, and dopamine can play a key role in activating the biochemical cascade leading to the PS, and ultimately in the migraine attack (43). Vasopressin and the orexins are alternative candidates, through their connections with the limbic system. Some authors (30) hypothesized that many prodromal symptoms might share a common biological basis related to the headache phase (some brainstem nuclei, which regulate the amount of pain as well as other sensory inputs, may be disinhibited, thus disrupting their associated motor and autonomic activities). As a result, it would be necessary that a critical physiological threshold be reached to induce the full-blown migraine headache (19). Other prodromal symptoms (emotional change, fatigue, and concentration difficulties) may reflect the involvement of the limbic system, whereas other brainstem nuclei brain structures outside of pain pathways may, for instance, account for nausea. Furthermore, hypothalamic-brainstem connections may account for fatigue and sleep and wakefulness disturbance may also arise from hypothalamic-brainstem connections (44).

Blau saw in the PD the converse process of the PS. He additionally proposed that it might reflect a slow decline in migraine processes and that the diversity of PD symptoms could be accounted for by an involvement of the whole brain (38), notably the frontal lobes and the hypothalamus. Thus, the multitude of symptoms reported by patients in the PD could be explained by a diffuse cortical and subcortical involvement. Bose et al. have proposed that the PD might be explained by widespread vasoconstriction mediated by an alpha2-adrenoreceptor mechanism mediated by activation of brainstem nuclei. As one of the major neuromodulatory structures of the brainstem implicated in the regulation of cortical function and the modulation of responses to afferent traffic, the locus coeruleus might play a pivotal role in this process (8). An alternative hypothesis involves cortical spreading depression. As persistent hypoperfusion following cortical spreading depression has been demonstrated (45), Bose et al. proposed that this hypoperfusion shown during the migraine attack might be related to cortical spreading depression (8).

Functional Imaging Studies

Several functional imaging studies performed in adults have provided some support to the previous assertions. As regards PS, one study by Maniyar et al. using positron emission tomography, has showed that several brain areas were activated before headache. These included subcortical (posterior hypothalamus, ventral tegmental area, periaqueductal gray matter, dorsal pons, putamen, caudate nucleus, and the pulvinar nucleus of the thalamus) but also cortical areas (occipital cortex, frontal, prefrontal, temporal, parietal cortex, anterior cingulate, and posterior cingulate) (46). These findings outlined the early involvement of the hypothalamus and brainstem (especially dorsal rostral pons and periaqueductal gray matter) in the mediation of the migraine attack. The same team conducted a second positron emission tomography study which showed that patients who experienced nausea during the PS showed activation in rostral dorsal medulla and periaqueductal gray, which was absent in patients without nausea (47). Using a similar design, Maniyar et al. assigned the origin of photophobia to the visual cortex during the premonitory phase of migraine in the absence of headache (48). With a completely different design, investigating a single patient daily over a whole month, Schulte and May found hypothalamic activation within the 24 h before headache onset as compared with the interictal state (49).

Less functional imaging study has been dedicated to the PD. Using arterial spin labeling MRI, Bose et al. have shown that cerebral perfusion was diffusely reduced during postdrome (50). The authors concluded that their results might be explained by the participation of several brain areas, both in the cortex and the brainstem, namely "the superior frontal gyrus, medial frontal gyrus, middle frontal gyrus, putamen, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, posterior cingulate, anterior cingulate, thalamus, hypothalamus, and midbrain" (8). Alternatively, other functional imaging studies have shown that the activations in areas such as hypothalamus (51) or brainstem may persist after headache relief by sumatriptan (52), lending support to the hypothesis that some neural networks remain active when the headache has stopped.

For evident ethical grounds reasons, such studies are lacking in children and adolescents. This is all the more regrettable as the localization of prodromal and postdromal symptoms is harder to assess in a pediatric brain. It would be interesting to know whether adult findings can be transposable in children and adolescents, moreover in an age dependent fashion, in view of changes in brain development and maturation. Such studies would be invaluable in young children who are unable of identifying "subtle" symptoms due to their cognitive developmental level.

Temporal Meltdown?

Perhaps, one may imagine that some prodromal symptoms start before headache onset, go on during the headache phase, more or less masked with relative success by the headache and accompanying symptoms, and reappear at the forefront after headache cessation under the mask of the PD. In short, everything would happen as if the classical temporal relationship between PS, aura and headache had been challenged. In this view, symptoms occurring during the PD (both PTS and/or TPD) would have made a "temporal mistake" and would not have followed the expected pattern. Examining the classic temporal relationship between aura and headache, Viana et al. have recently shown that aura occurred after resolution of the headache phase in 9% of their patients (53). In my experience, the upheaval of the classic sequential order is also very common in children and adolescents. One may suppose that just like aura may occur during the headache phase or follow it, the same might hold true for PD (19). Hence the question: are PTS/TPD an extension or a recurrence of the aura symptoms, which would eventually be masked by the headache phase, or are there similar mechanisms between aura and PTS/TPD? One may wonder whether hypothalamic activation may occur in phases, reflecting upset temporal patterns of symptoms. Similar mechanisms might be at work for prodromal symptoms, possibly

through connections between the trigeminovascular system and the midbrain and the amygdala. This would also explain why patients are more prone to have PS if they suffer from MA.

A Developmental Explanation Attempt

Goadsby stated that "migraine is a disorder for life, from the more unsettled child with colic, to the late-life migrainous accompaniments" (54). And below: "Perhaps this explains why the disease has the same flavor all through life but runs at different temperatures" (54). Let us remember that PS symptoms have been reported in infants as young as 18 months (12).

One is tempted to link changes in migraine symptomatology with developmental features associated to brain maturation. In this perspective, how can we account for differences in PS and PD between adults, children and adolescents? First of all, it is more difficult to infer the pediatric cerebral localization of symptoms; all the more because to analyze symptoms phenomenology in children and adolescents may prove more difficult and because an age-dependent precise description is lacking so far. It is noteworthy that the well-known modification of migraine pain location, evolving from bilateral in children and adolescents to unilateral in adults, has not been explained so far (55). As Chakravarty et al. pointed: "It can only be postulated that this may be the result of differences in degree of brain maturation comprising myelination, new synapse formation and synaptic reorganization." One may infer similar hypotheses explaining the pediatric peculiarities of PS and PD (55).

Data drawn from the study of a periodic syndrome such as abdominal migraine may be more in line with the issue under examination. Abdominal migraine is a childhood disorder which evolves to more usual migraine subtypes as the child gets older. Symptoms consist of abdominal pain, pallor, nausea, and vomiting, but usually not headache. Gastroparesis often accompanies attacks, the cause of which has not really been investigated, to our knowledge. Besides gastroparesis, other symptoms include abdominal pain, nausea, and vomiting. A dysfunction of the autonomic nervous system and the maturation of the autonomic nervous system with age may account for this transformation and the persistence of a core of similar symptoms. One could speculate that these changes might be explained by a modulatory influence on (a) common network(s), the latter changing with age due to maturational changes (and/or perhaps, due to targets changes). Triggering factors such as stress or excitement suggest the involvement of aminergic systems, such as locus coeruleus, in this process. In this way, migraine attacks would be initiated through dysautonomia. That the influence of sleep is more important in children and adolescents than in adults may be another hint. Sleep alterations constitute an important trigger of migraine attacks and many migraine attacks terminate with the child falling asleep and awakening pain-free (32). These data may be accounted for by corresponding changes in autonomic tone as the child ages. However, up to now, the longitudinal maturational evolution of the autonomic nervous system has not been determined (56).

Another candidate is the serotoninergic network. Serotonin plays a vital role as a neurotransmitter in adult brain. It appears earlier in development than other monoamine transmitter systems and its turnover rate is higher in the immature mammalian brain than at any other. It is also involved in the regulation of brain development, intervening in particular notably in the processes of long-term potentiation and synaptic plasticity. An additional issue is how neural circuits change during before and with puberty. Remembering that migraine often starts in adolescence, or attacks frequency is influenced by puberty, there is further need to investigate the potential effects of sex hormones (57). It should not be forgotten that the mechanisms underlying this activation of the three most important neuroendocrine axes involved in puberty (that is the hypothalamic-pituitary-gonadal axis, the hypothalamic-pituitary-adrenal axis, and the growth hormone-insulin like growth factor axis) are only partly understood. Complex interrelations between stimulatory (leptin, glutamate, serotonin, galanine, dopamine, norepinephrine) or inhibitory (neuropeptin Y, melatonin, GABA) factors are at play to control the timing of puberty onset. Among the modulator substances, adrenal hormones exert key roles in the regulation and trophicity of cell survival, differentiation, maturation, and synaptogenesis of the central nervous system (58).

It would be interesting to test these hypotheses with functional sequential and longitudinal imaging, but as previously said, this is actually unavailable. However, we dispose of both cross-sectional and longitudinal studies dedicated to event-related potentials. The measurement of event-related potentials to sensory stimuli (e.g., visual) and slow cortical potentials suggests altered maturation of cortical information processing (59, 60) in children with migraine.

Taking account of established comorbidities of migraine, such as attention deficit disorder, anxiety, depression, and immunological disorders may suggest supplementary hints. Attention enhancement with age reflects the increasing frontal influence of connectivity modifications in many brain regions. One of the most critical adjustments in adolescence is an increase in brain dopamine, particularly in the "reward" pathway that involves the ventral tegmental area, the nucleus accumbens, and connections through the limbic system and eventually the frontal cortex (61–63). Mood change may be associated with cingulate gyrus activation, perhaps with the involvement of some of its limbic connections (46, 64). Limbic structures mature more rapidly than prefrontal and frontal cortex (61). Of note in a developmental perspective is the role of the anterior cingulate cortex. Located in the frontal lobe which is known to mature belatedly in adolescence, it is involved in the emotional processing of pain. Development of frontal regions appears to occur more rapidly from early adolescence to middle adolescence (ages 12 to 17) than from childhood to early adolescence (ages 9 to 12). The prefrontal cortex contains neurons that influence the parasympathetic or sympathetic motor neurons; it also contains different neurons that project to diverse body compartments, suggesting links with the autonomic nervous system. Since the hypothalamus is connected in different ways to systems which modulate pain and also to the spinal trigeminal nuclei, the influence of these maturational changes may perhaps affect less the successive involvement of specific neural networks with aging, but, instead, the evolving

changes in functional connectivity between neural networks as the child grows older which matters (65). Whereas, brain maturation may affect migraine symptoms phenomenology as time goes, conversely, migraine may influence the development of the brain.

Finally, it is noteworthy to note that several immunological changes have been identified to be altered or associated with migraine in children and adults (66), including increased levels of calcitonin gene-related peptide (67), decreased levels of coenzyme Q 10 (68), and hormonal changes (69–72). These may constitute fruitful ways of research.

Whereas, the underlying basis for "hyperexcitability" (better accounted for as a brain tendency to over-respond) in migraine is unclear, genetic factors are also at play. Several susceptibility gene variants have been identified. It is of interest that, among these genes, some may regulate synaptic development and plasticity, such as ASTN2 and FHL5 (73, 74).

POSSIBLE IMPLICATIONS

Understanding mechanisms and networks at play before attack onset may ultimately lead to new, more targeted and more efficacious therapeutic strategies. PS may constitute an ideal window for early treatment. Even in adults, data which support this statement are scarce but the efficacy in migraine prevention of naratriptan and dopamine antagonists is suggested by nonrandomized trials (75, 76). It should be interesting to undertake placebo-controlled, randomized trials to ascertain this hypothesis. Similarly, domperidone, a dopamine antagonist, may block a migraine attack, provided it is taken at least 6 h before the putative attack (77, 78). The fact that children and adolescents experience shorter migraine attacks as compared to adults makes this issue eminently sensitive. Developing new molecules which, given during the PS, could ultimately prevent pain onset, would represent a major breakthrough. However, to our knowledge, such studies are unavailable so far in children and adolescents.

It has been shown, in adult migraine sufferers, that nitroglycerin and pituitary adenylate-cyclase activating protein could induce postdromal symptoms, which are similar to those experienced during spontaneous attacks (42, 79). In the wake of the recent interest for pituitary adenylate-cyclase activating protein, researchers have designed molecules that target the PAC1 receptor. This may represent a new therapeutic avenue for migraine, as may also the understanding of neurobiological mechanisms that underlie PD.

CONCLUSION

Clinicians should be alert to both PS and PD and learn to recognize them (and differentiate them from triggers) in order to better evaluate the whole burden of the migraine attack, but also reliably predict the impending onset of the attack. Similarly, one should educate parents to be attentive to and recognize early PS symptoms which are, for part, noticeable, which is all the more interesting in non-verbal patients such as young children. At the same time, new research seems necessary to better characterize both PS and PD symptoms with rigorous, prospective methods, ideally using electronic diary systems. This may allow a better estimation of the population prevalence of PS and PD in different age ranges. The reproducibility of these symptoms across serial attacks should also be studied as well as their probability at predicting an impending headache attack.

Finally, these studies should be more oriented in a developmental perspective. The answers to the following questions appear crucial: are there distinct PS and PD as a function of different age range (infancy, childhood, and adolescence vs. adults)? Are there distinct subgroups of patients which could be categorized according to their specific PS and/or PD phenomenology? How do these symptoms evolve with age? How are PS and PD related in these patients? Thinking at new ways to circumvent current hindrances in conducting functional brain imaging studies in the younger pediatric populations would certainly lead to further advances. Maybe the answer to these questions would help to decipher the complex interrelations between PS, aura, headache, and PD, and design new therapeutic strategies, in an age-dependent fashion, with the ultimate goal of reducing morbidity, negative impact on academic performance, and school absenteeism. This is all the more urgently needed in children where the therapeutic armentorium is reduced in comparison with adults. This is unbelievably an interesting and exciting area for future migraine research!

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00199/full#supplementary-material

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Non-invasive Brain Stimulation in Pediatric Migraine: A Perspective From Evidence in Adult Migraine

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Pediatric migraine remains still a challenge for the headache specialists as concerns both diagnostic and therapeutic aspects. The less ability of children to describe the exact features of their migraines and the lack of reliable biomarker for migraine contribute to complicate the diagnostic process. Therefore, there's need for new effective tools for supporting diagnostic and therapeutic approach in children with migraine. Recently, promising results have been obtained in adult headache by means of application of neurostimulation techniques both for investigating pathophysiological mechanisms and also for therapeutical applications. Non-invasive brain stimulation (NIBS) techniques like transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) indeed proved to be generally safe and showing also some evidence of efficacy particularly for the symptomatic treatment. On such basis, in the last years increasing interest is rising in scientific pediatric community to evaluate the potential of such approaches for treatment pediatric headaches, particularly in migraine, even if the evidence provided is still very poor. Here we present a perspective for application of TMS and tDCS technique in children migraine principally based on evidence coming by studies in adults.

Keywords: transcranial magnetic stimulation, transcranial direct current stimulation, non-invasive brain stimulation, pediatric migraine, therapeutics

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INTRODUCTION

Pediatric migraine remains a challenge for headache specialists, as concerns both diagnostic and therapeutic aspects. The low ability of children to describe the exact features of their migraines and the lack of reliable biomarkers complicate the diagnostic process, while symptomatic and prophylactic treatments are limited due to placebo effect and the parents' fear of pharmacological side effects (1–3). Therefore, there is a need for new effective tools for supplementing the existing diagnostic and therapeutic approaches in children with migraine.

Recently, promising results have been obtained in adult headache by applying neurostimulation techniques for investigation of pathophysiological mechanisms as well as for identification of potential clinical biomarkers, and last, but not least, of possible better-tolerated therapeutic alternatives (4). On such basis, over the last few years, the scientific pediatric community has become increasingly interested in evaluating these methods with respect to the therapeutic approach to pediatric headaches, particularly migraine.

Non-invasive brain stimulation (NIBS) techniques are defined as neurophysiological approaches for transcranial application of electrical currents or magnetic fields that are able to modulate brain activity, and are employed for investigating pathophysiology and also as diagnostic and therapeutic tools in many neuropsychiatric diseases (4). The first reported application of neurostimulation dates back to the first century AD, when Scribonius Largus relieved pain using the black torpedo, a bioelectric fish, delivering an electrical pulse to the painful area (5). Subsequently, from nineteenth century onward, new electrical generators were utilized; since then, the application of electric stimulation of the vagal nerve has been used, at first, for treatment of refractory epilepsy, and later, also in different pain states (4). Other NIBS techniques have also been experimented with for treatment of pain and other neuropsychiatric diseases in adults, but in the field of pediatric headache, only some anecdotal reports are available. The majority of these reports are principally aimed at exploration of safety issues associated with the techniques (6–9).

Neuromodulation can modify the activity of several brain networks by modulating neuronal excitability, and excitatory or inhibitory effects, depending on different stimulation parameters (polarity, duration, or frequency of stimuli) (4). The NIBS techniques have the relevant advantage of inducing brain changes by non-invasive stimulation, which does not require intervention for application of permanent leads, is painless and optimally tolerated, and can be employed in awake subjects at rest or during execution of different tasks. These techniques function through transcranial application of magnetic or electric currents (transcranial magnetic [TMS] and electrical stimulation [tES], respectively).

In TMS, weak but rapid electric currents are elicited in the brain regions through fast variation of magnetic field (4), which activates cortical neurons, triggering them to discharge; TMS can be delivered in a single pulse, double pulse, or trains of repeated pulses (repetitive TMS [rTMS]). The first modality has been principally employed to study brain physiology and for diagnosis of diseases of the motor system and pathways, but has also found therapeutic application in symptomatic treatment of migraine with aura attack (10).

Double-pulse TMS has found application in investigation of cortical facilitation and inhibition owing to the ability of paired stimulation to selectively modulate cortical inhibitory or facilitatory circuits depending on the interval between the pulses (11, 12). Further, rTMS can induce lasting effects determining prolonged neuroexcitability-related changes that remain beyond stimulation, suggesting the potential for therapeutic use in neuropsychiatric diseases with abnormal (increased or decreased) cortical excitability, especially for long-term treatment (13). Generally, high-frequency stimulation increases cortical excitability while low-frequency decreases it; however, several modifications of stimulation parameters allow flexibility in the brain responses obtained, depending further on different diseases (4, 9).

Conversely, tES functions through application of direct or alternating weak currents (0.5–2 mA), delivered via electrodes attached to the scalp. The initial, and yet most frequent, approach is based on application of direct currents (transcranial direct current stimulation [tDCS]); tDCS acts by modulating neuronal excitability. Contrary to TMS, tDCS is not able to induce direct neural activation but affects excitability through polarization. Anodic currents induce depolarization, increasing excitability and the probability of spontaneous firing, while an opposite inhibitory effect is induced by cathodal stimulation through neuronal hyperpolarization (13). Further, tDCS is able to induce long-lasting neuroplastic effects that have been found to be critically dependent on glutamate-NMDA neuro-transmission and represents the physiological basis for therapeutic application (4, 13).

Here we present a perspective about the potential of NBS techniques in children migraine based on data about safety, coming from studies on other disease in children, and on evidence about efficacy by TMS and tES studies in adult migraineurs.

SAFETY OF TMS AND tDCS IN THE PEDIATRIC POPULATION

The safety of NIBS techniques has been mainly studied in the adult population, and there are only a few reports on their use in the pediatric population (6–9). These pediatric studies investigated mainly single-pulse or paired-pulse TMS protocols that are not of therapeutic interest. A recent report examined in detail the issue of safety of TMS and tDCS in children through an extensive review of the articles published till 2014; based on an electronic search, 48 studies were found and evaluated, including a population of more than 500 children, and adolescents aged 2.5–17.8 years (9). The NIBS methods were used in several disorders (autism, epilepsy, depression, etc.). In nine studies, patients underwent only a single stimulation session while in the others, designed for therapeutic purposes, more stimulation sessions were applied; the frequency and number of stimulation sessions varied across reports, ranging from repeated daily to weekly sessions. In these studies, TMS was the most commonly applied NIBS technique, with different parameters of stimulation on referred thresholds as control, globally reporting only 1.2% important negative side effects (seizure and syncope). Minor side effects were headache, scalp discomfort, fatigue, neck stiffness, etc. Headache is a more frequent side effect (11.5%), although it is temporary and usually does not need any therapy. Sixteen studies were found to have used tDCS, accounting for more than 190 subjects, and the methodology varied considerably for range of intensity, session duration, and session number. Serious side effects were not reported, while mild side effects (redness, tingling, itching sensation, etc.) were reported in cumulative analysis, with the frequency ranging from 1.5 to 11.5%; they were transitory and no medical treatments were needed. The authors' conclusion was that TMS and tDCS are safe (1% serious adverse effect); however, considering that the majority of the data obtained using these methods originate from adult studies, it is necessary to follow some precautions, such as not including subjects with alcohol consumption, epileptogenic medication intake, recent cranial trauma, or history of seizures. Further, the

authors suggested searching for possible history of syncope in order to minimize the risks. The fact that headache was the more common mild side effect suggests the contraction of the muscles near the stimulation site as a possible cause. Headache, always mild and brief, was also reported in the sham groups (i.e., placebo stimulation), suggesting non-specific effects.

The tDCS appears to present fewer side effects, especially those related to the site of stimulation, and local symptoms are principally observed in the adult population, whereas no skin lesion is reported in children. In the adult population, repeated tDCS sessions did not appear to increase side effects (14); however, the lack of studies with prolonged repetition over time does not allow clear conclusions to be drawn regarding long-term safety of tDCS in these populations, even if studies on animal models suggest safety of long-term use (15).

Our actual conclusion on the safety of using TMS and tDCS in the pediatric population are limited by the low sample size (∼500 subjects), variability in the stimulation parameters that does not allow correlation between specific parameters and side effects, few long-term studies, the fact that many studies are performed on other outcomes and not specifically to evaluate the safety via appropriate questionnaires or follow-up, the lack of correlation with structural, neurophysiological, and general data (MRI, different neurophysiological alterations, or blood test results).

DIAGNOSTIC AND THERAPEUTIC USE OF TMS AND tDCS IN THE PEDIATRIC MIGRAINOUS POPULATION

Several cortical and subcortical areas are involved in the pathogenesis of pain and migraine; a central role is played by the trigeminocervical complex, which has sensitive afferents and connections with the autonomic nervous system, as well as other subcortical and cortical centers. The trigemino-vascular system and trigemino-autonomic reflexes are believed to be involved in the main mechanism of migraine pain through multiple vasoactive peptides (calcitonin gene-related peptide, substance P, vasoactive intestinal peptide, pituitary adenylate cyclase-activating peptide, etc.) (16). Cortical and subcortical areas (the occipital and associative cortices, hypothalamus, periaqueductal gray, and locus coeruleus) are believed to activate, inhibit, or modulate the trigeminocervical complex (17). Peripheral and central sensitization mechanisms are invoked as causes of signs and symptoms of migraine attack and chronicization (18). On these bases, it is reasonable that each of the aforementioned nodes could represent a target of putative non-pharmacological strategies.

Visual aura has been extensively investigated as a marker of cortical dysfunction. The TMS has been used to analyze cortical excitability through the phosphene thresholds in migraineurs and controls (19–21). A single pulse applied to the visual cortex can induce an artificial percept or "phosphene," which may be enhanced by adding a conditioning stimulus. The evoked phosphenes increase depending on the stimulation intensity, allowing establishment of the "phosphene threshold" of a subject. The phosphene threshold may also be modulated by TMS stimuli applied to the associated cortical area. Phosphene-induction using TMS allows assessment of the occipital cortex excitability in subjects with and without migraine. In the adult population, data suggest the existence of primary visual cortex hyperexcitability, especially in migraine with aura (21). These studies are limited by variability of stimulation parameters in absence of uniformly adopted protocol for measuring phosphenes; however, response to TMS seems to be a very promising biomarker for migraine. Recently, anodal tDCS application to the temporal pole has been shown to enhance interictal excitability of the visual cortex in migraineurs, restoring normal habituations, underlining the role of the temporal pole in visual processing (22).

Evidently, in the pediatric population, the data are few and sparse, and show lower phosphene thresholds in interictal migraineurs vs. controls, with changing excitability levels 1–2 days before migraine attacks, reflecting the relation of fluctuating excitability to the migraine cycle (23). To date, to our knowledge, only one pivotal study (24) in adolescents affected by migraine has explored the therapeutic use of rTMS as a preventive treatment, showing reduction in the number of headache days, use of abortive drugs, and MIgraine Disability Assessment score, and safe use and few side effects. However, the study has several limitations, such as an open-label design and small sample population.

The matter, however, is worth investigating further because NIBS showed promise in the treatment of pain and migraine in adults. High-frequency magnetic stimulation of the motor cortex indeed showed level A evidence of effectiveness against neuropathic pain (13). A large randomized study on a population migraineurs with visual aura using single-pulse stimulation for acute attacks showed significantly greater improvement following real stimulation, compared with sham stimulation, at 2 and 24 h with regard to the following outcome measures: pain relief, nausea, and phono- and photo-phobia, in the absence of side effects (10). The limitations of the study were mainly the sample population exhibiting only migraine with visual aura; moderate gain on sham effect (17%), lower than that reported using traditional therapeutic drugs such as triptans (25); and the difficulty in achieving a true blind effect with this method. The results from the ESPOUSE Study (26) (observational post-marketing study) support the possible therapeutic effect of TMS as a preventive agent against adult migraine, with low-to-mild side effects and no serious adverse effects. Recently, the US Food and Drug Administration has authorized the use of single-pulse TMS for abortive therapeutic purposes (27).

In chronic migraine, the available results on rTMS prophylactic therapy are contradictory, with the few published studies having small sample populations, lack of consensus regarding brain targets, variation in stimulation parameters, and issues related to the utilized masks, causing difficulties in their comparison and establishment of clear conclusions regarding the effectiveness of TMS against chronic migraine (28–30). However, the generally reported lack of side effects and the potential of this method make its use promising in the pediatric population, where the parents' fear of side effects is an important limitation on the use of pharmacological drugs (31).

tDCS IN PAIN AND MIGRAINE

To our knowledge, studies using tDCS in the treatment of pediatric migraine and pain have not yet been published. However, observing the increasing number of instances of tDCS use in adult pain and considering the data from its use in other pediatric disorders, we can hypothesize the effective application of this technique in pediatric pain. Evidence regarding the effect of tDCS on adult patients with migraine is still inconclusive; however, two studies applying cathodal currents over the primary visual cortex showed a significant amelioration of the symptoms compared with the baseline, pretreatment condition with respect to duration, intensity, and severity of attacks, even though only the intensity changed significantly compared with placebo sham stimulation (32, 33). No severe adverse effects were reported, with good tolerability. In a meta-analysis, Luedtke et al. (34) concluded that clinical data does not support the use of tDCS in the treatment of pain and migraine. However, the authors advise designing studies with larger sample populations using shared protocols on stimulation parameters and stimulation sites to better evaluate the effectiveness of this method, which is promising due to its low cost, easy applicability, non-invasiveness, and lack of serious adverse effects. These aspects are even more relevant in the context of the pediatric population, where tolerability, and non-invasiveness are critical characteristics for its consideration for therapeutic treatment.

POTENTIAL STRATEGIES FOR TMS AND tDCS APPLICATION IN PEDIATRIC PAIN AND MIGRAINE, AND CONCLUSIONS

The Cochrane reviews do not provide clear conclusions regarding the effectiveness of TMS and tDCS against adult chronic pain, although small benefits appear to have been observed. However, the authors point out many biases and important heterogeneities of these studies (30).

At the moment, it is not possible to establish useful guidelines on the use of TMS and tDCS in the treatment of pediatric migraine and, in general, for pediatric pain treatment. However, adult studies as well as preliminary pediatric reports show that the application of these techniques is safe, with few side effects, potentially low costs, and easy applicability. Furthermore, in adults, for some serious painful disorders, such as chronic regional pain syndrome, level A evidence has been obtained regarding the pain-relieving effects of these techniques. Preliminary reports, principally in adults but also in the pediatric population, suggest that migraine may represent an effective therapeutic target. Moreover, NBS of cortical areas as DLPFC, that has been explored in migraine, was found to be effective for treatment of other conditions, that are comorbid with disease, sharing also a stimulation target employed for migraine treatment, like DLPFC. Among these disorders, in addition to the role played by the psychiatric diseases, of particular importance is obesity which also favors the chronification of migraine (35, 36). Due to the large prevalence of the disease and the disability associated with it, and also considering the parents' relevant fears and concerns regarding pharmacological therapies, especially for continuing preventive treatment, pediatric migraine appears to be an optimal candidate for future studies on therapeutic NIBS. Therefore, this topic is worth exploring further through rigorous, opportunely suited randomized controlled trials with uniform diagnostic protocols, and stimulation parameters to reveal the real therapeutic potential of NIBS techniques against pediatric migraine.

AUTHOR CONTRIBUTIONS

FB and VR study conception. LM, GS, DP, FD, and LR data collection. FB, VR, FV, and GG data analysis. FB, VR, and SM manuscript writing. FB, VR, SM, FV, and GG manuscript revision.

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Sensory Processing Difficulties Correlate With Disease Severity and Quality of Life Among Children With Migraine

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Introduction: Headaches are common among children and about 80% of children reporting them. Migraine and tension type headaches are the most common primary headaches in children and the prevalence of migraine is about 8%. Accompanying sensory symptoms are common before, during and after migraine attacks. They may be a part of a wider symptom constellation called sensory processing disorder or difficulties (SPD). This includes both hyper or hypo sensitivity to sensations. However, the literature regarding sensory processing symptoms of children and youth with headaches as well as its interaction with child's emotional aspects and quality of life is scarce.

Materials and Methods: One hundred and thirty-four children between the ages of 8 and 12 participated in this study. Fifty-four children (22 boys and 32 girls) with episodic migraine were prospectively recruited from pediatric neurological clinics during the years 2014–2017. The control group included 80 healthy children. Both groups completed a health and demographic questionnaire, headache assessment including Ped-MIDAS, Short Sensory Profile, State-Trait Anxiety Inventory (STAI) for children, and the Pediatric Quality of Life Inventory.

Results: Children with migraine showed significantly higher prevalence of sensory processing difficulties and lower quality of life compared to healthy controls. Among children with migraine, sensory processing difficulties significantly correlated with lower quality of life. Headache-related disability and sensory processing difficulties predicted quality of life.

Conclusion: The possible relationship between migraine and sensory processing disorder or difficulties stresses the need to screen for sensory processing difficulties among children with migraine and when found—refer to their impacts on children's daily function and quality of life.

Keywords: sensory processing, quality of life, children, headache, migraine

INTRODUCTION

Headache is one of the leading chronic conditions of childhood (1) and the most common pain complaint when seeking medical advice (2–4), with evidence for increased incidence of primary headaches in children and adolescents in the last 50 years (5, 6). Headaches begin to emerge during the early years of life, but the disorder usually becomes more evident and frequent from the impact of school life, with a peak around 7 years old (7). The prevalence of migraine increases from 3% in the preschool years to 4–11% by the elementary school years, and up to 8–23% during the high school years. The mean age of onset for migraine is 7 years for boys and 11 years for girls (8, 9).

Children who suffer from chronic headaches were found to have more somatic complaints such as abdominal pain and disordered sleep (4, 10), which can also explain why headaches correlate with a significant reduction in quality of life (11, 12). Aromaa et al. (13) investigated pain experience among children with headaches and found they seemed to play more carefully, compared to their family members, because they were afraid of getting hurt. They also found that increased general pain sensitivity proved to characterize children with headache and their parents (13). Migraine in particularly is associated with increased hypersensitivity to various sensory stimuli: visual, auditory, odor, and somatosensory both before aura and during the headache attack (14).

Sensory processing disorder or difficulties (SPD) is a term used to describe difficulties in processing and modulating sensory information in order to respond appropriately to the situation (15). SPD may result in hyper- or hyposensitivity to sensory input. Individuals who are more sensitive to sensory information than others (16) often perceive sensory events as noxious and stressful (17). They are hyperaroused, and more likely to have depression, anxiety disorders as well as social phobia (18) and avoidant personality disorder (19–21). Dunn's model for sensory processing may provide a possible explanation for the relationship between sensory processing abilities and the behavioral output. Dunn's model outlines the relationship between a person's central neurological thresholds and behavioral response (22, 23). Among individuals with hyposensitivity, the central mechanisms of habituation support high thresholds. On the other hand, among individuals with low thresholds, the neurons trigger more easily and thus, cause more frequent reactions to stimuli from the environment resulting in hypersensitivity (23).

Nevertheless, the knowledge about the ability of children with migraine to process sensory input is limited. Since sensory processing abilities have a direct impact on daily function (24) and quality of life (25), by exploring the prevalence of SPD among children with migraine and their impacts on children's quality of life, intervention programs may be more efficient. Hence, the aims of this study were: (1) Compare sensory processing abilities between children with migraine and healthy controls (2) Compare the quality of life between children with migraine and healthy controls (3) Examine the correlations between sensory processing, migraine characteristics and severity and quality of life among children with migraine (4) Examine the contribution of headache-related disability and sensory processing to the prediction of quality of life among children with migraine.

It was hypothesized that children with migraine will have more difficulties to process sensory information and lower quality of life as compared to healthy controls; that sensory processing would correlate with enhanced migraine pain and with lower quality of life and that Sensory processing difficulties and headache-related disability will significantly predict quality of life.

MATERIALS AND METHODS

Participants

According to G-Power software (26), to identify an effect size of 0.25, with $p = 0.05$ and power of 0.80, a total sample of 92 participants is recommended. Each group should include 46 participants. One hundred and thirty-four children between the ages of 8 and 12 years participated in this study. Sixty children with episodic migraine were prospectively recruited from the following outpatient pediatric neurology clinics: (1)The pediatric neurology clinics at the Bnai- Zion Medical Center, (2) the pediatric neurology clinics at the Schneider Children's Medical Center, Petach Tikva, and (3) the pediatric neurology clinics at the Meuhedet Medical Services in the city of Haifa, during the years 2014–2017. Out of 60 children: 57 agreed to participate in the study and 54 (22 boys and 32 girls) completed the questionnaires. The control group included 80 healthy children, 37 boys and 43 girls, who did not have any significant illnesses; did not have positive neurological findings or developmental disorders. **Table 1** summarizes the study and control groups' demographic information (**Table 1**).

METHODS

Medical Assessment

A prospective medical history including a thorough headache history and physical and neurological assessment by a pediatric neurologist, were performed on all children during the visit at the pediatric neurology clinic. All children met the diagnostic criteria for migraine, according to the International Classification of Headache Disorders, 3rd edition (ICHD-3 beta) (27). Allodynia was not formally assessed.

PedMIDAS

Headache related disability was evaluates by the PedMIDAS questionnaire. It was developed to assess migraine disability in pediatric and adolescent patients and has been tested and validated for ages 4–18 (28).

The Short Sensory Profile (SSP) (26)

This parent report evaluates children's sensory processing patterns, as expressed in all sensory modalities and in daily living situations (for example: "will only eat certain tastes"; "reacts emotionally or aggressively to touch"). The Parent scores their child's response to sensory stimuli on a 5 point Likert scale, where 1 represents "always" and 5 "never." Seven subtests are scored: tactile sensitivity, taste/smell sensitivity, sensitivity to

TABLE 1 | Participants' health and demographic information.

		Children with migraine ($n = 54$)	Healthy controls ($n = 80$)
Age range		7–12	7.5–11
Mean age ± SD		10.06 ± 1.53	9.33 ± 1.14
Gender - *n* (%)	Boys	22 (40.7%)	37 (46.3%)
	Girls	32 (59.3%)	43 (53.7%)
MIDAS level (%)	No functional impairments	36.7%	
	Minimal functional impairments	30%	
	Moderate functional impairments	16.7%	
	Severe functional impairments	16.7%	
VAS (range, mean ± SD)	6–10, 8.33 ± 1.43		
Headache frequency (%)			
Once a week	43.8		
Twice a month	40.7		
Twice a year	15.5		
Mean ± SD of headache frequency (per month)	2.51 ± 0.84		
Median of headache frequency (per month)	2		
Duration of episodic migraine (%)			
1 h	26		
2 h and more	62		
12–24 h	10		
More than 1 day	2		

SD, standard deviation.

movement, visual/auditory sensitivity and auditory filtering, as well as a total score, which ranges from 38 to 190. Higher scores (155–190) reflect typical/normal performance. A score between 142 and 154 reflects a probable difference in performance while a score between 38 and 141 reflects a definite difference in performance (29, 30).

The Pediatric Quality of Life Inventory (PedsQL) (31)

We used Version 4.0—child's report, which profiles children's Health-Related Quality of Life (HRQoL) in four dimensions: (1) Physical Functioning (eight items), (2) Emotional Functioning (five items), (3) Social Functioning (five items), and (4) School Functioning (five items). A higher order dimension of the Psychosocial Health dimension encompasses emotional and social functioning. The child marks the frequency of problems which occurred in the past 1 month on a five-point Likert scale (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are then transformed into a 0–100-point scale (0 = 100; 1 = 75; 2 = 50; 3 = 25; 4 = 0) to present the HRQoL percentage. A higher percentage indicates a better HRQoL.

PROCEDURE

After receiving ethical approval from the Bnai Zion Medical Center Ethics Review Board, children from the study group were recruited during their visit at the neurology clinics as described above. All patients' parents signed an informed consent to participate in the study. The headache history was taken and the neurological examination was performed during the visit. After the diagnosis of migraine was made according to ICHD-3 beta (27), including the PedMIDAS questionnaire, the children's parents were asked to complete the Short Sensory Profile and the Pediatric Quality of Life Inventories. Children from the control group were recruited after their parents answered the advertisements calling to participate in the study by contacting the study conductor, and after having met the inclusion criteria. The controls were evaluated in their homes.

DATA ANALYSIS

Normality tests were applied and most dependent variables showed abnormal distribution. Hence, Mann–Whitney test was used to examine if significant differences existed between both groups in SSP and PedsQL scores. Chi square analysis examined whether significant differences existed between groups in the percentage of children found in each of the SSP performance ranges (typical performance; probable difference in performance and definite difference in performance). Among children with migraine, Spearman correlation examined the correlations between sensory processing patterns, migraine characteristics/related disability and quality of life. Stepwise linear regression was examined to identify the relative contribution of MIDAS and SSP scores to the prediction of HRQoL. The level of significance was adjusted for multiple testing for all analyses using Bonferroni correction.

RESULTS

Comparing the Sensory Processing Abilities Between Children With Migraine and Healthy Controls

Children with migraine had lower scores (greater sensory processing difficulties) than healthy controls in SSP total scores and in all SSP subtests. This difference was significant only in regards to taste/smell sensitivity (**Table 2**).

Based on Chi square analysis, significantly higher percentage of children with migraine was found in the definite difference performance range in the taste/smell sensitivity and in the SSP total score (**Table 3**), representing sensory processing difficulties expressed in hypersensitivity.

TABLE 2 | Comparing the Short Sensory Profile scores between children with Migraine and healthy controls using Mann–Whitney test.

	Children with migraine ($n = 54$)			Healthy controls ($n = 80$)			
SSP subtest	**Median**	**Mean ± SD**	**Range**	**Median**	**Mean ± SD**	**Range**	***Z***
Tactile sensitivity	32	31.13 ± 3.35	21–35	33	32.58 ± 2.36	23–35	−2.66
Taste/smell sensitivity	17	16.12 ± 3.86	5–20	19	18.32 ± 2.07	9–20	−3.45***
Movement sensitivity	14	13.31 ± 2.34	5–15	15	14.03 ± 1.63	7–15	−1.97
Under responsive/seek	31	29.98 ± 4.88	17–35	32	31.21 ± 3.41	22–35	−0.91
Auditory filtering	25.5	24.84 ± 4.48	13–30	26	25.73 ± 3.41	10–30	−0.73
Low energy/weak	29	27.27 ± 3.66	5–25	30	28.37 ± 2.35	20–30	−1.92
Visual/auditory sensitivity	23	21.89 ± 3.81	5.00	25	23.82 ± 1.84	16–25	−2.53
Total	169.5	164.58 ± 19.94	102–190	175	174.11 ± 9.35	156–190	3.29

*The level of significance was adjusted to $p \leq 0.006$. ***$p \leq 0.001$; SD, standard deviation. Lower scores indicate worse sensory processing.*

TABLE 3 | Comparing differences between groups in the percentage of children found in each of the SSP performance range using Chi square analysis.

	Typical performance		Probable difference		Definite difference		
SSP subtest	**Migraine**	**controls**	**Migraine**	**controls**	**Migraine**	**controls**	χ^2
Tactile sensitivity	36	64	61.5	38.5	71.4	28.6	6.15
Taste/smell sensitivity	33	67	81.8	18.2	87.5	12.5	17.81***
Movement sensitivity	35.2	64.8	55.6	44.4	63.6	36.4	5.35
Underresponsive/seek	35.8	64.2	50	50	77.8	22.2	6.81
Auditory filtering	35.8	64.2	50	50	70	30	5.24
Low energy/weak	36.1	63.9	60	40	54.5	45.5	4.13
Visual/auditory sensitivity	35.8	64.2	85.7	14.3	100	0	12.97
Total SSP	32.8	67.2	100	0	100	0	25.02***

*The level of significance was adjusted to $p \leq 0.006$. ***$p \leq 0.001$.*

Comparing the HRQoL Between Children With Migraine and Healthy Controls

Children with migraine reported lower Health-Related Quality of Life than healthy controls. However, this difference was significant only in the physical domain (**Table 4**).

The Correlations Between Sensory Processing, Migraine Characteristics/Related Disability, and Quality of Life Among the Study Group

After performing Bonferronni correction, ($p \leq 0.004$), no significant correlations were between sensory processing and migraine characteristics/related disability. However, lower physical HRQOL significantly correlated with greater movement sensitivity and lower energy. Lower emotional HRQOL significantly correlated with greater tactile sensitivity, visual/auditory sensitivity. Lower emotional and school HRQOL significantly correlated with more extreme sensory processing patterns as represented by the total SSP score. Most correlations were found between psychosocial HRQOL and SSP scores: lower psychosocial HRQOL significantly correlated with greater sensitivity to taste/smell, movement, auditory filtering, low energy, with more extreme sensory processing patterns represented by the total SSP score. **Table 5** summarizes the correlations.

Predicting the Quality of Life Children With Migraine by Their Measure Headache-Related Disability (PedMIDAS Score) and Sensory Processing

After adjusting the level of significance to $p \leq 0.01$, stepwise linear regression analysis revealed that emotional HRQOL was significantly predicted by tactile sensitivity. accounting for 22% of the variance [$F_{(1,28)} = 8.29$; $B = 2.86$; SE $B = 0.99$; $\beta = 0.47$, $p \leq 0.01$]. Social HRQOL was significantly predicted by PedMIDAS score, accounting for 25% of the variance [$F_{(1,28)} = 9.71$; $B = -0.32$; SE $B = 0.11$; $\beta = -0.51$, $p \leq 0.01$].

DISCUSSION

The main outcomes of the present study found that sensory processing difficulties are prevalent among children with migraine and that their quality of life is predicted by both headache-related disability and sensory processing difficulties.

A connection between migraine and sensory processing difficulties is not surprising. Patients with migraine tend to have enhanced perception of various sensory stimuli including

TABLE 4 | Comparing the HRQoL between children with Migraine and healthy controls using Mann–Whitney test.

	Children with migraine ($n = 54$)		Healthy controls ($n = 80$)		
	Median	**Mean ± SD**	**Median**	**Mean ± SD**	***Z***
Physical HRQOL	84.37	81.97 ± 13.44	90.62	89.08 ± 11.37	−3.25***
Emotional HRQOL	70	69.91 ± 18.56	75	74.31 ± 15.44	−1.21
Social HRQOL	95	88.21 ± 13.85	95	90.06 ± 13.44	−0.77
School HRQOL	75	74.23 ± 16.09	80	79.81 ± 14.32	−1.86
Psychosocial HRQoL	78.33	77.31 ± 12.85	81.66	81.39 ± 10.01	−1.64
Total HRQoL	81.33	78.26 ± 12.13	83.18	82.93 ± 9.47	−2.01

*The level of significance was adjusted to $p \leq 0.008$. ***$p \leq 0.001$; SD, standard deviation. Higher scores indicate better HRQoL.*

TABLE 5 | The correlations between sensory processing patterns and quality of life among children with Migraine using Spearman correlation test.

	Physical HRQOL	**Emotional HRQOL**	**Social HRQOL**	**School HRQOL**	**Psychosocial HRQOL**	**Total**
Tactile sensitivity	0.34	0.43***	0.11	0.19	0.37	0.39
Taste/smell sensitivity	0.42	0.41	0.24	0.324	0.47***	0.48***
Movement sensitivity	0.49***	0.42	0.23	0.362	0.49***	0.54***
Under responsive/seek	0.28	0.38	0.17	0.293	0.39	0.42
Auditory filtering	0.31	0.44	0.34	0.426	0.54***	0.55***
Low energy/weak	0.53***	0.31	0.38	0.424	0.46***	0.54***
Visual/auditory sensitivity	0.16	0.44***	0.11	0.320	0.42	0.41
Total	0.45***	0.55***	0.31	0.44***	0.61***	0.63***

*The level of significance was adjusted to $p \leq 0.004$. ***$p \leq 0.001$.*

sound, somatosensory stimuli (14) odors (32, 33), and increased sensitivity to light during and between migraine attacks (34). According to some reports, smells and flashing lights are triggers of migraine attacks. These symptoms correlate with the findings that have atypical symmetry and amplitude of the initial negative and positive cortical responses to visual stimuli (35) and different high frequency oscillations of the somatosensory evoked potential compared to controls (36). Another finding, irrespective of the stimulus modality, is an impairment of habituation in interictal migraineurs as compared to healthy controls (37). Enhanced sensory sensitivity and habituation difficulties among patients with migraine were also observed in studies that applied quantitative sensory testing (QST) (38) noting that patients with migraine may have greater reactivity to pain. The meta analysis performed by Nahman-Averbuch et al. (39) revealed that patients with migraine present lower heat and pressure pain thresholds, higher pain ratings to cold suprathreshold stimuli for combined and nonlocal areas, and higher pain ratings to electrical suprathreshold stimuli for nonlocal areas, than healthy controls. All these findings raise the hypothesis that migraineurs might have basal abnormalities in sensory processing and integration. Tyll and Noseda both (40, 41) suggested that sensory hypersensitivity may result from activation of subcortical brain regions that receive convergent inputs and then project broadly to various cortical brain regions involved in integrating multiple sensory modalities such as visual, auditory, and olfactory. Mainero et al. (42) demonstrated that patients with migraine have stronger connectivity between the ventrolateral periaqueductal gray (PAG) and other brain areas that are involved in nociceptive and somatosensory processing. Recently it has been proposed (34, 43) that both the aura and the migraine attack, may represent a form of hypersensitivity due to sensory processing difficulties.

The present study used the Short Sensory Profile in order to measure sensory processing abilities, as reflected in children's daily life. In the present study, a relatively high percentage of children with migraine were found to score in the "definite difference" range on most SSP scales.

The other main outcome of the present study was that children with migraine had lower quality of life in various domains as compared to healthy controls. This is supported by previous reports. For example, Powers (11, 12) found that migraine may reduce children's QoL, and this impact may differ by age group: teens reported lower school functioning than older and younger children and younger children reported lower social functioning than older children and teens (11). Physical complaints as well as mental problems can adversely affect a patient's quality of life (QOL) (44, 45). This may be reflected directly by children's self-reports, as found in our study.

The present study is the first, to our knowledge, to find a correlation between the reduction in social quality

of life in children with migraine and the PedMIDAS score. Nevertheless, this study not only supports the relationship between migraine influence and children's HRQoL, but it brings innovative information about the involvement and contribution of sensory processing difficulties to the prediction of children's HRQoL. This prediction together with the result according to which greater sensory processing difficulties correlated with lower quality of life in the physical as well as in the psychosocial and school domains, emphasizes the relevance of screening for sensory processing difficulties among children with migraine and refer to their impacts on child's daily life in intervention programs.

Moreover, based on previous reports highlighting the correlations between sensory processing difficulties, emotional status and hyperarousability (that frequently characterize individuals with migraine), intervention programs should consider the commonality of anxiety disorders, depressive disorders and other forms of psychopathology in children, and adolescence with migraine (4, 46–48) with respect to sensory processing difficulties and to quality of life. By referring to these interactions in research and practice, we may better understand other factors, such as SPD, that may be associated with higher levels of somatic and emotional complaints in children that lead to poorer school attendance, school refusal, and poorer academic performance (49, 50). Thus, by applying this broad perspective screen for SPD, early intervention may be provided, focusing on providing coping strategies to deal with the sensory difficulties and optimize function. By that, clinicians may reduce the negative consequences of migraine and related difficulties in terms of social, academic and personal adjustment (51, 52), and elevate children's HRQoL.

LIMITATIONS

Our study has a few limitations. This study was conducted in tertiary pediatric clinics, and not on a sample of healthy children (like a school-based study). According to Berkson's principal (53), people who seek medical care are more likely to have more than one medical problem. Therefore, the relationship between two diseases should not be studied in such a population. In addition, in this study we did not formally assess allodynia.

CONCLUSIONS

Sensory processing difficulties may characterize children with migraine and reduce their quality of life. Hence, sensory processing difficulties should be screened and treated when relevant, with respect to their impacts on children's daily function and quality of life. The implication of these findings as regards the treatment of migraine in children needs further study.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of name of guidelines, Bnai Zion IRB number bnz 21-14 with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Bnai Zion IRB number bnz 21-14.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Ictal Epileptic Headache: When Terminology Is Not a Moot Question

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The relationship between headache and epilepsy is complex and despite the nature of this association is not yet clear. In the last few years, it has been progressively introduced the concept of the "ictal epileptic headache" that was included in the recently revised International Classification of Headaches Disorders 3rd edition (ICHD-3-revised). The diagnostic criteria for ictal epileptic headache (IEH) suggested in 2012 were quite restrictive thus leading to the underestimation of this phenomenon. However, these criteria have not yet been included into the ICHD-3 revision published in 2018, thus creating confusion among both, physicians and experts in this field. Here, we highlight the importance to strictly apply the original IEH criteria explaining the reasons through the analysis of the clinical, historical, epidemiological and pathophysiological characteristics of the IEH itself. In addition, we discuss the issues related to the neurophysiopathological link between headache and epilepsy as well as to the classification of these epileptic events as "autonomic seizure."

Keywords: ictal epileptic headache, hemicrania epileptica, epilepsy, migraine, tension-type headache, EEG, autonomic seizures, panayiotopoulos syndrome

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HEADACHE, EPILEPSY, AND "ICTAL EPILEPTIC HEADACHE"

Headache and epilepsy are characterized by transient attacks of altered brain function. The links between headache and epilepsy are complex and in the last century there have been several attempts to improve the classification, the clinical characterization, and the physiopathology of this association (1, 2).

In the 20th century, Sir W. R. Gowers, first suggested that "migraine is in the borderland of epilepsy" (2), sharing some pathophysiological mechanisms, presenting themselves as dysfunctions of neurotransmitters and ion channels. Indeed, these two conditions are common, often co-morbid, with headache attacks in epilepsy, temporally related as pre-ictal, ictal, post-ictal, or inter-ictal events. In addition, they can present with either visual, cognitive, sensorial and motor signs/symptoms (1, 2). Furthermore, the concept of "headache" as "an epileptic headache" that "…may even be the only clinical manifestation of idiopathic epilepsy" dates back from a long time ago. Already in the pre-EEG era, Gowers stated that "…in extremely rare instances one affection may develop while the other goes on," (2). Nowadays, the availability of digital EEG recordings allow us to state that chronic headache itself may occasionally represent an epilepsy condition and that

often headache can represent the only ictal epileptic phenomenon (i.e., ictal epileptic headache, IEH) (3–6).

The first description of IEH dates to the 1950s (7–10) but the term migralepsy was coined 10 years later by Lennox and Lennox (11) and become strongly rooted in the epileptological culture, hindering the verification and awareness among experts of the possible complete overlap of an epileptic seizure and a cephalalgic event. In fact, following the introduction of the migralepsy concept, an increasing number of ictal headaches have been described (12–15) and it has been hypothesized that the migralepsy sequence may not exist at all and that the initial part of the "migralepsy" may merely be an "ictal headache" followed by other ictal autonomic, sensory, motor or psychic signs/symptoms, being thus classified in fact as "hemicrania epileptica" (16).

Although the revised International Classification of Headaches Disorders 3rd edition (ICHD-3) now includes the term "ictal epileptic headache" (17), it does not take into account the original clinical criteria (3). Indeed, since the first demonstration (13) of the immediate remission of EEG abnormalities and of the headache after the administration of intravenous anti-epileptic drug, over than 30 cases of IEH have been reported (3–6, 12–16, 18–34). These papers suggest that a diagnosis of IEH is possible when all the following criteria occur (3): (a) headache lasting minutes, hours, or days, headache that is ipsilateral or contralateral (if the headache is not generalized) with epileptiform EEG discharges (if the anomalies are localized); (b) variable EEG abnormalities may be observed without a specific EEG or clinical headache pattern required; (c) headache and EEG abnormalities immediately resolved after antiepileptic drugs intravenous administration (**Table 1**).

However, these criteria have not been fully taken into account into the recent revised ICHD-3 (17), thus creating confusion. However, we feel that even if the concomitant appearance of the EEG epileptiform discharges with headache is the mainstay criteria for the diagnosis of IEH, the prompt response to antiepileptic treatment is still crucial to confirm the clinical suspicion (34).

Coci and Riedel recently described two patients, with chronic headache unresponsive to analgesics therapy and disappeared after oral antiepileptic therapy (24). An ictal EEG recording in these adolescents during a headache attack revealed diffuse spike-wave and poly-spikes, and spontaneous drug withdrawal resulted in a recurrence of the headache, which resolved again on anticonvulsant therapy. These authors classified these cases as "probable IEH" due to the lack of clinical-EEG demonstration of the resolution of both the headache and EEG anomalies, after the administration of intravenous anticonvulsant therapy. Therefore, although an EEG recording may not be routinely recommended in children with headache, it should be performed promptly in patients with prolonged headache that do not respond to anti-migraine therapy (35–39), particularly in children with epilepsy that also express other types of seizures (34). Nevertheless, the use of clear-cut IEH criteria (3) will facilitate communication among clinicians and researchers, avoiding misdiagnoses, incorrect therapies, and eventually reducing health costs (40–52).

CORTICAL DYSEXCITABILITY AND CORTICAL SPREADING DEPRESSION: THE GENETIC AND NEUROPHYSIOPATHOLOGICAL LINKS BETWEEN HEADACHE AND EPILEPSY

Several data support the view that increased neocortical excitability is the leading mechanism underlying headache and epilepsy (53). Taking into account that in migraine, during the "spreading depression," hypo- and hyper-excitation occur, both (sequentially), as rebound phenomena, it could be suggested the term "dys-excitability" to better describe these physiopathologic events, rather than generically "hyperexcitability" (5, 6, 50, 54–57). Cortical Spreading Depression (CSD), that many Authors believe to be the most likely pathophysiological link between headache and epilepsy (5, 6, 36, 39, 40, 58, 59), is a slowly propagating wave of strong neuronal depolarization which induces fleeting (but intense) spike activity, followed by a neural suppression, lasting for minutes. The depolarization proceeds simultaneously with an increased regional cerebral blood flow, while the phase of reduced neural activity is associated with a decrease in brain perfusion. CSD starts the trigeminovascular system, provoking the release of many inflammatory molecules and neurotransmitters, responsible for the pain characterizing the headache phase (50, 60). Both, basic and clinical neurosciences findings, are in favor of "CSD" and "epileptic focus" as phenomenons able to facilitate reciprocally each other, although with different effectiveness and efficiency. The achievement of a minimum threshold necessary to start depolarization is the key to both phenomenas, but, the required threshold is presumed to be lower for CSD than for an epileptic discharge, the onset of both facilitating each other, anyway. This may explain why it is far more likely to observe an epileptic subject who also presents a peri-ictal headache than a cephalalgic patient who presents epilepsy (36, 40, 43, 50, 53, 57, 60). The two phenomena (CSD and epileptic seizure) possibly being triggered by more than one pathway converging upon the same destination: depolarization/dysexcitability (36, 40, 48, 50, 61).

The etiology could be environmental or individual (due genetic causes or not), originating a flow of ions that provokes CSD through neuronal and glial cytoplasmic bridges, rather than through interstitial ways as conversely occurs in the spreading of epileptic seizures (5, 50, 55, 56, 62).

Both migraine and epilepsy have an important genetic component, with strong evidence pointing to a shared genetic basis between headache and epilepsy emerging from clinical/EEG and genetic studies on Familial Hemiplegic Migraine (FHM) (63–69). Recent data suggest shared genetic substrates and phenotypic-genotypic correlations with mutations in some ion transporter genes, including CACNA1A, ATP1A2, and SCN1A (69–73). Other genetic findings pointing to a link between migraine and epilepsy have been published (74, 75). In addition, glutamate metabolism (76), serotonin metabolism (77), dopamine

TABLE 1 | Proposed original criteria for Ictal Epileptic Headache (IEH) [reproduce from Parisi et al. (3), with permission].

Diagnostic criteria A–D must all be fulfilled in IEH
A. Headache* lasting minutes, hours, or days
B. Headache that is ipsilateral or contralateral to lateralized ictal epileptiform EEG discharges (if EEG discharges are lateralized)
B. Evidence of epileptiform (focal **, lateralized or generalized) discharges on scalp EEG concomitantly with headache; different types of EEG anomalies may be observed (generalized spike-and-wave or polyspike-and-wave, focal or generalized rhythmic activity or focal sub-continuous spikes or theta activity that may be intermingled with sharp waves) with or without photoparoxysmal responses (PPRs)
D. Headache and EEG abnormalities resolves immediately (within few minutes) after i.v. antiepileptic drugs administration

*A specific headache pattern is not required (Migraine With or Without Aura, or Tension-type headache are all accepted). **Any localization (frontal, temporal, parietal, occipital) is accepted.

metabolism (78), and ion channel (sodium, potassium, and chloride) function might be impaired in both epilepsy and migraine (69, 79).

IN MOST CASES IEH IS PROBABLY AN "AUTONOMIC SEIZURE"

To clarify why headache could be the sole ictal epileptic manifestation, we (3, 5, 6, 34) previously hypothesized that an autonomic seizure remains purely autonomic if ictal neuronal activation of non-autonomic cortical areas does not achieve the symptomatogenic threshold (80). Accordingly, we suggested that IEH should be considered an autonomic form of epilepsy, like Panayiotopoulos syndrome, and, thus, people with long-lasting IEH attacks may even fulfill the criteria for autonomic status epilepticus (81). Although it is difficult to explain the reasons for which IEH remains an isolated manifestation lasting up to several hours or even days (13), one can speculate that the threshold for ictal autonomic manifestations could be lower from that required for motor-sensory areas, as observed for autonomic seizures in pediatric age (e.g., Panayiotopoulos syndrome).

In addition, while the presence of epileptiform abnormalities usually confirm the diagnosis of epilepsy, in IEH patients the lack of clear epileptic spike-and-wave activity does not rule out the diagnosis of epilepsy. The same diagnostic difficulties arise for patients with a deep epileptic focus arising, for example, from the orbito-mesial frontal zone (82). In such cases, ictal epileptic EEG activity may be recorded exclusively by means of deep stereo-EEG recording, even, sometimes, purely by chance (83).

Another crucial point is the lack of a clear, repetitive EEG headache-associated pattern, owing to the fact that the ictal EEG recording is usually not associated with specific EEG picture. Indeed, different EEG patterns have been recorded during headache-like complaints in both symptomatic and idiopathic IEH cases (18, 20, 28–34).

Moreover, when EEG abnormalities are recorded, no specific cortical correlations emerge (e.g., focal frontal, parietal, temporal, occipital and primary or secondary generalized), as reported (confirming, thus, our hypothesis) for autonomic manifestations in Panayiotopoulos syndrome.

Accordingly, we may interpret a headache as the sole expression of an epileptic seizure, supporting thus the autonomic nature of the IEH, at least in the most of the cases.

FURTHER NEUROPHYSIOPATHOLOGICAL REFLECTIONS ON THE POSSIBLE LINK BETWEEN AUTONOMIC AND HEADACHE PATHWAYS

To understand the complexity of the pathways and networks involved in the onset and transmission of "primary headache" from the periphery (intracranial vessels) within the central nervous system until all potentially involved brain areas, you have to sum up the main stages of such nociceptive structures, fibers, pathways and such neuro-vascular structures. This careful examination can make evident why is so difficult, at moment, to classify the "Ictal Epileptic Headache" as "sensory" or "autonomic" seizure to propose a precise classification in the new Epilepsy classifications (84).

The cephalalgic attack originates as consequence of the activation of nociceptors innervating pial, arachnoid, and dural blood vessels, as well as large cortical arteries and sinuses. These structures are activated by mechanical, electrical or chemical stimulation (pro-inflammatory molecules, blood or infection), causing a painful perception similar to migraine and its most commonly associated symptoms/signs (nausea, throbbing pain, photophobia, and phonophobia).

The intracranial vessels and the meninges are innervated by unmyelinated fibers (C fibers) or thin little myelinated fibers (Ad fiber), which convey nociceptive sensitivity; these axonal terminations contain vasoactive neuropeptides such as substance P (SP) and the peptide related to the calcitonin gene (CGRP). They, originating from the trigeminal ganglion, reach the dura through the ophthalmic branch of the trigeminal nerve (V1) and, to a lesser extent, through the maxillary (V2) and mandibular branches (V3).

The dura is also innervated by neurons located in the ganglia of the upper cervical dorsal root. For decades, a possible vascular origin of headache pain has been debated. At present, the results of the various studies are conflicting and inconclusive, suggesting that vascular changes would not have a primary role, or at least, may not have a unique and predominant role in the pathophysiology of headache (85–87).

The mechanisms that explain the efficacy of the Vagus Nerve Stimulation (VNS) in the treatment of migraine and cluster headaches are not yet clear; probably, it is realized through a modulation of the intracranial trigeminal-vascular nociceptive transmission. Most of the fibers of the vagus nerve includes sensory afferents that terminate bilaterally in the nucleus tractus

solitarius (NTS), before projecting into other nuclei, including the locus coeruleus (LC), the nucleus of the dorsal raphe (DRN), parabrachial nucleus, and PVN. It has been shown for the first time that VNS inhibits nociceptive activation of trigeminal-cervical neurons in preclinical models of acute dural-intracranial (migraine-like) and trigeminal-autonomic (cluster) pain (87).

The insula and other part of so-called Limbic System (part of frontal, temporal, and parietal regions which receive projections from autonomic networks), have a role in various processes including goal-directed cognition, conscious awareness, autonomic regulation, enteroception, and somatosensation. There are complex behaviors in migraine (conscious awareness and error detection), which are less investigated of other well-known, such as autonomic and somatosensory alterations during the clinical attacks. The insula processes and relays afferent inputs from brain areas involved in these functions, to areas involved in higher cortical function, such as frontal, temporal, and parietal regions. Insula role could be to decode the signals of altered internal milieu in migraine (along with other chronic pain conditions), taking into account the insula role in translating and integrating of multiple informations into complex behaviors (88).

It is also important to remember that, the activation of lateral and ventrolateral periacqueduttal gray (PAG) neurons by direct ascending lamina I e II projections (where make connection the afferent fibers C amyelinic which comes from cerebral vessels, as proposed for trigemino-vascular theory to explain physiopathology of migraine), produces non-selective, non-specific headache pain relief, cardiovascular reactions (decrease in blood pressure), homeostatic reactions (temperature changes), and defensive reactions (immobility, arousal, avoidance behavior, and vocalization), as well as a more general emotional state of fear and anxiety (89). Since the PAG undoubtedly projects a more dense fiber connections to the rostral ventromedial medulla (RVM), but minimally to the spinal and medullary dorsal horn, RVM neurons constitute a direct link for descending modulation through bilateral projections to all levels of spinal and medullary dorsal horns. These functional and anatomical studies are consistent with a broader modulatory role of the PAG–RVM circuit and suggest an "*absence of specificity*" for headache.

CONCLUSIONS

IEH does not have a specific clinical picture of headache/migraine (migraine without aura or tension-type headache or aspecific headache patterns, have all been reported), and it can last from seconds to days, with evidence of synchronous ictal epileptiform EEG anomalies; different EEG patterns may be observed, with or without a photoparoxysmal response (see **Table 1**). In fact, in particular, the ictal EEG recording in most patients does not yield a particular EEG pattern or specific cortical topographic correlations (focal frontal, parietal, temporal, occipital, and focal with primary or secondary generalization, have all been reported). EEG recording is not recommended routinely in children with headache but should be considered promptly in case of prolonged migraine/headache not responsive to antimigraine drugs. If the main IEH criterion (EEG-clinical response to antiepileptic intravenous administration) is not satisfied, we can just pose a "probable IEH" diagnosis. The concept of migralepsy is potentially confusing and should not be used to describe the sequence of visual aura-seizure and an ictal EEG recording is mandatory in these patients to exclude an "hemicrania epileptica" (16).

AUTHOR CONTRIBUTIONS

PP, MP, and PS formulated original idea and the design of the review and wrote the first draft of the manuscript. ND, UR, VB, and MV approved the design and final version of the manuscript. All authors reviewed, approved, and agreed to be accountable for all aspects of the work.

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REVIEW
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Management of Childhood Headache in the Emergency Department. Review of the Literature

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Headache is the third cause of visits to pediatric emergency departments (ED). According to a systematic review, headaches in children evaluated in the ED are primarily due to benign conditions that tend to be self-limiting or resolve with appropriate pharmacological treatment. The more frequent causes of non-traumatic headache in the ED include primitive headaches (21.8–66.3%) and benign secondary headaches (35.4–63.2%), whereas potentially life-threatening (LT) secondary headaches are less frequent (2–15.3%). Worrying conditions include brain tumors, central nervous system infections, dysfunction of ventriculo-peritoneal shunts, hydrocephalus, idiopathic intracranial hypertension, and intracranial hemorrhage. In the emergency setting, the main goal is to intercept potentially LT conditions that require immediate medical attention. The initial assessment begins with an in-depth, appropriate history followed by a complete, oriented physical and neurological examination. The literature describes the following red flags requiring further investigation (for example neuroimaging) for recognition of LT conditions: abnormal neurological examination; atypical presentation of headaches: subjective vertigo, intractable vomiting or headaches that wake the child from sleep; recent and progressive severe headache (<6 months); age of the child <6 years; no family history for migraine or primary headache; occipital headache; change of headache; new headache in an immunocompromised child; first or worst headache; symptoms and signs of systemic disease; headaches associated with changes in mental status or focal neurological disorders. In evaluating a child or adolescent who is being treated for headache, physicians should consider using appropriate diagnostic tests. Diagnostic tests are varied, and include routine laboratory analysis, cerebral spinal fluid examination, electroencephalography, and computerized tomography or magnetic resonance neuroimaging. The management of headache in the ED depends on the patient's general conditions and the presumable cause of the headache. There are few randomized, controlled trials on pharmacological treatment of headache in the pediatric population. Only ibuprofen and sumatriptan are significantly more effective than placebo in determining headache relief.

Keywords: headache, migraine, emergency, child, life threatening condition, secondary headache, diagnosis, neuroimaging

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INTRODUCTION

Headache is a frequent complaint in pediatric population, even more frequent than adults. There has been a substantial increase in the incidence of childhood migraine and headache over the last 30 years. This increase is alarming and likely reflects children's lifestyles (1). Diagnosis and treatment can be challenging due to its varying presentation, etiology, and triggers. Secondary headaches manifest differently in children than in adults and the degree of brain maturation could be the cause of this difference (2, 3). Headache disorders are the main cause of absence from school, affecting negatively school performance (4), as well as other daily activities (5). Headaches are common, incapacitating, and often stress inducing for pediatric patients and parents alike. The individual and social costs of pediatric headache disorders are due to the high incidence, frequency, and lifetime prevalence of these conditions (6).

The incidence of headache is variable according with age (3–8% of children aged 3 years, 19.5% of children aged 5, and 37–51.5% of children aged 7) (7–9). Frequency is higher in males before puberty and in females after puberty (10). Another important consideration is that 35% of children with headache present to an emergency department (ED) at least once a year for any reason, compared with 17% of the general pediatric population (11). Children suffering from headaches also have a higher rate of hospitalization for any reason (5.1% per year) compared to children without headaches (1.7% per year) (12). Non-traumatic headaches represent 0.7% (13) to 2.6% (11) of visits in a pediatric ED. The hospital admission rate for headache ranges from 8 (12) to 29% (14) in studies carried out in patients accessing the ED. Headache is unusual as an isolated complaint and is most often associated with other symptoms such as fever, sore throat, neck pain, and vomiting (15). The most common recurrent headache in childhood is migraine, while tension headaches prevail in adolescence (16). Males are more frequently affected at preschool age, while incidence is higher in females in junior-high school age (17, 18). Differential diagnosis of pediatric headache in the ED includes a variety of benign causes and viral infections, sinusitis, migraine, and post-traumatic headaches are the most common diagnoses (2). Burton et al. (13) reported viral infections, sinusitis and pharyngitis in over 60% of pediatric patients presenting to the ED for headache. Secondary life-threatening (LT) causes of headache can be associated with high mortality and morbidity and health personnel should be aware of the differential diagnoses. Headache in the ED is mainly due to benign conditions that tend to be self-limiting or resolve after appropriate treatment. The most common causes of non-traumatic headache in the ED are secondary benign headaches (35.4–63.2%) and primary headaches (21.8–66.3%) and while secondary LT headaches are less frequent (2–15.3%; **Table 1**) (11, 13, 18–26). Conditions to worry about include brain tumors, central nervous system infections, ventriculo-peritoneal shunt malfunction, hydrocephalus, idiopathic intracranial hypertension and intracranial hemorrhage (**Table 2**) (3, 13, 27).

The following work aims to suggest useful elements for the ED pediatrician in the management of headaches in children. In particular, the identification of factors associated with LT secondary headache (red flags), the identification of causes of LT headaches and the rational use of laboratory tests and diagnostic imaging are discussed.

Headache Classification

The International Headache Society (IHS) (28) publishes a standardized classification scheme that provides diagnostic criteria for headaches in general and its most recent update was released in 2018 (**Table 3**).

PRIMARY HEADACHE

Migrane Without Aura

Primary headache accounts for 21.8–66.3% of headaches in children and migraine is the most frequent type. Migraine is a recurrent headache disorder that manifests with attacks lasting 4–72 h (28) (**Tables 4**, **5**). In children up to 5 years of age, a shorter duration period for the attacks has been suggested (29). The pain is typically unilateral, pulsating, of moderate or severe intensity, aggravated by physical activity and associated with nausea and/or photophobia and phonophobia (28).

The prevalence ranges from 3.2 to 14.5%. Family history is often positive for headache with a frequency of 60–77.5% (3). As already observed by other authors we believe that the time span of headache attacks in children should be changed to 30 min or longer. This could result in a greater number of children being diagnosed with migraine, in particular those younger in age (3, 30). In children, pain is more frequently frontal (60.9%), whereas it is ocular (53.17%) followed by temporal (38.67%) in adults (31). Pain is usually described by children as throbbing or pounding, while it is frequently pulsating in adults (32). It is common practice that when the episodes are specific for duration and characteristics, the diagnosis of migraine can be made before five episodes. In the new revision of the ICHD-3 (28) five episodes of headache are still necessary for diagnosing migraine. In an emergency setting this seems to be limitation and some authors (30) have proposed reducing the number of episodes needed for diagnosing migraine.

The typical headache pattern and associated symptoms make it possible to differentiate migraine without aura from other forms of primary and secondary headache.

In the case of headache with features highly suggestive of migraine, a completely negative neurological examination and the absence of so-called "red flags" suggest that the patient can be sent to a specialized Headache Center. In an observational study, other authors report a reduction in ED access for recurrent headache in those patients for whom indication was given to contact a specialized Headache Center within 10 days from ED discharge (22).

Migrane With Aura

Migraine with aura is characterized by transitory focal neurological symptoms that generally appear before or sometimes together with the cephalalgic pain. A prodromal phase may be present in some patients, which occurs hours or days before the onset of headache/or a post-dromal phase that appears after the resolution of the headache. Symptoms

TABLE 1 | Etiology of headache in Emergency Department: comparison of the published studies.

	Burton LJ (11)	Kan L (19)	Lewis DW (20)	Leon-Diaz A (21)	Conicella E (14)	Scagni P (22)	Lateef TM (23)	Hsiao HJ (24)	Massano D[a] (11)	Rossi R (25)
Years of publication	1997	2000	2000	2004	2008	2008	2009	2014	2014	2018
Years of Recruitment	1993	1996	1996	2002–2003	2004	2003–2004	2003–2006	2008	2009–2012	2011–2015
Number of patients	696	130	150	185	432	526	364	409	101	1,833
Patients Age(years) (mean–ag.e years)	2–18	<18 (9.3)	<IS (9)	2–15	2–17 (8.9)	0–16 (8.8)	2–5	2.6–17.8 (9.2)	6–18	<18 (9.68)
Percentage (%) of ED visits	1.3	0.7	ne	0.57	0.8	1.0	ne	0.9	2.63	0.9
Primary headaches	21.8	10	18	24.3	24.5	56.7	15.7	27.6	66.3	62.1
Secondary benign headaches	63.2	63.2	59.6	60.5	35.4	38	72.3	65.6	33%	32.9
Secondary life-threatening headaches	5.6	15.3	14.9	4.3	4.1	4	7.9	6.8	9.9	1.3
Brain Tumors %	ne	1.5	2.6	2.5	0.69	0.36	0.2%	0.97	1.9	0.38
Unclassified	13	11.5	7	10.8	36	1.3	5	5	ne	7.8

ED, Emergency Department; ne, not expressed; [a]Only patients with focal neurological signs at admission to ED.

include hyperactivity, hypoactivity, depression, cravings for certain foods, repetitive yawning, fatigue and stiffness, and/or neck pain (28). Visual and sensory auras are the more common symptoms (87.1%) in pediatric population as well as in adults. Migraine with aura is most common in adolescents compared to younger children (3), but this may be due to the inability of young children to describe their symptoms clearly (33).

Migraine with brainstem aura is a particular kind of migraine in which symptoms of aura originate unequivocally from the trunk-encephalic region and/or reflect the simultaneous involvement of both hemispheres, in the absence of motor deficits (28). The symptoms of aura of this particular form of migraine are immediately traceable to the brain stem in the absence of an ischemic etiology. This condition consists of completely reversible words/language, sensory or visual auras with retinal symptoms or lasting engines, by definition, from 5 to 60 min. A cephalalgic pain may accompany the aura within 1 h. The most common symptoms are nausea and vomiting (30–50%), ataxia (43–50%), bilateral visual symptoms, or altered consciousness. In these cases, posterior fossa circulatory insufficiency (vertebral dissection or thrombosis), transient ischemic attack, posterior fossa vascular, and congenital structural abnormalities may need to be excluded by MRI (34). The difference between migraine with brainstem aura and migraine with typical aura is the origin of the symptoms. In the first case the brainstem or bilateral occipital hemispheres are involved, while migraine with typical aura is mainly restricted to a unilateral hemisphere.

Hemiplegic migraine (HM) is a type of migraine with aura and motor weakness. For diagnosis, fully reversible motor weakness is associated with constant aura symptoms, consisting in visual, sensory, and/or speech/language disorders (28). However, more than 70% of patients have baseline symptoms with prolonged hemiplegia, confusion, coma, fever, or seizures. In this case it is imperative to exclude an acute ischemic process by performing brain MRI with DWI sequences.

It is mandatory in the ED setting to exclude those secondary headache disorders than can mimic migraine and are potentially life threatening (35, 36), by investigating for red flags (**Table 6**). Furthermore, it is essential to know the characteristics of the primary forms of migraine in order to avoid unnecessary, expensive, and potentially dangerous investigations (for example neuroradiological imaging). Nevertheless, it is clear that whenever there is suspicion for secondary headache, migraine should be a diagnosis of exclusion. Migraine is also the more common cause of brain attack (stroke-like) symptoms in children accessed to the ED, accounting for 11–29% of cases (37). Some warning signs can significantly raise the suspicion of a secondary form due to stroke or other vasculopathies: rapid onset of headache, presence of focal neurological signs and/or symptoms and altered consciousness. In these cases it is necessary to carry out neuroimaging studies. This is particularly relevant for a thunderclap headache (more frequent in adults), which warrants rigorous evaluation to exclude a secondary cause. Any headache with a very rapid onset reaching peak intensity in <1 min is, by definition, a headache of thunderclap onset and can be a symptom of a subarachnoid hemorrhage, hemorrhagic stroke, reversible cerebral vasoconstriction syndrome, venous sinus thrombosis, or even pituitary apoplexy (38). The more gradual onset of neurological symptoms in migraineurs, usually >5 min, is attributed to the cortical spreading depression of Leao, consisting of depolarization followed by hyperpolarization, at a speed of 3–5 mm per min, across the cerebral cortex (39). Furthermore, hemiparesis is an infrequent form of migraine aura, with a frequency of <10% and seldomly presents without other symptoms. In sporadic hemiplegic migraine, motor symptoms develop gradually over minutes, affecting more often the arm than the leg (while sparing the face). They can be bilateral and are primarily associated with headache (40). Another useful element is that children with arterial ischemic stroke (AIS) are older than those with migraine, and considered at risk (red flag) up to 8 years

TABLE 2 | Life-threatening causes of headache in children.

Hypertension
Coarctation of aorta
Central nervous system infections
Ventriculo-peritoneal shunt malfunction or infection
Venous sinus thrombosis
Ischaemic Stroke
Reversible cerebral vasoconstriction syndrome (RCVS)
Cervical artery dissection
Hemorrhage Brain tumor Hydrocephalus
Brain malformation (Chiari type I, Dandy Walker)
Idiopathic intracranial hypertension
Carbon monoxide poisoning

TABLE 3 | ICHD-3 revised Headache Classification (28).

Primary headache
Migraine (with or without aura)
Tension-type headache
Trigeminal autonomic cephalalgias
Other primary headache disorders
Secondary headache
Headache attributed to trauma or injury to the head and/or neck
Headache attributed to cranial and/or cervical vascular disorder
Headache attributed to non-vascular intracranial disorder
Headache attributed to a substance or its withdrawal
Headache attributed to infection
Headache attributed to disorder of homeostasis
Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure
Headache attributed to psychiatric disorder
Painful cranial neuropathies, other facial pain, and other headaches
Painful lesions of the cranial nerves and other facial pain
Other headache disorders.

TABLE 4 | ICHD-3 diagnostic criteria for migraine without aura (28).

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4–72 h (when untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

TABLE 5 | ICHD-3 diagnostic criteria for migraine with aura (28).

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal
C. At least three of the following six characteristics:
1. At least one aura symptom spreads gradually over $\geq$ 5 min
2. Two or more aura symptoms occur in succession
3. Each individual aura symptoms lasts 5–60 min
4. At least one aura symptom is unilateral
5. At least one aura symptom is positive
6. The aura is accompanied, or followed within 60 min, by headache
D. Not better accounted for by another ICHD-3 diagnosis.

of age (40). In fact, migraine with aura is uncommon in children <8 years of age and has a prevalence of 3–4% between age 3–7 years, compared to 23–31% in teenagers (11, 41). Odds of AIS are significantly increased in the case of sudden onset of the following symptoms: weakness, seizures, speech disturbance, ataxia, signs of face, inability to walk, dysarthria, dysphasia, and altered consciousness. Significant features associated with decreased odds of AIS include older age, vomiting, visual or sensory aura, other symptoms, and absent focal signs on assessment (40). Hypersensitivity conditions such as photophobia, phonophobia, or osmophobia are often seen only with migraine. Visual aura, in the form of positive signs such as zigzag lines or spreading scintillating scotoma, is by far the most common, unilateral sensory disturbance. Dysphasia may occur either at the same time or sequentially. Sometimes aura may occur without headache and must be differentiated from stroke in which negative signs with visual defects are present. Furthermore, a migrainous aura typically develops within a few minutes and migrates from one area to another (36, 42, 43).

Episodic Syndromes That May be Associated With Migraine

The "childhood periodic syndromes" were renamed by the ICHD-3 as the "episodic syndromes that may be associated with migraine" (44) and include four main conditions: two recurrent gastrointestinal disorders: cyclic vomiting syndrome and abdominal migraine; benign paroxysmal vertigo; benign paroxysmal torticollis. Common features of these disorders are: complete well-being between episodes, stereotypy of episodes, familiarity for migraine or headache (2). Patients with this group of disorders can present with migraine (with or without aura) or are likely to develop them. These patients may also have motion sickness or periodic sleep disorders (28). Episodic syndromes can be difficult to recognize and treat. These patients often undergo intensive diagnostic workup, including neuroimaging, and frequently require access to ED as well as hospital admissions.

Recurrent gastrointestinal disorders are defined as episodes of recurrent abdominal pain and/or discomfort, nausea, and/or vomiting, which occur rarely, chronically or at foreseeable intervals. These conditions can be associated with migraine (28). An acute presentation could be confused with an acute abdomen or an intracranial mass, though a detailed history and physical examination should rule them out. A more subtle presentation could suggest a systemic disease that may take time to evolve (44).

Cyclic vomiting syndrome is defined as episodes of intense nausea and vomiting, usually stereotypical, with predictable timing of the episodes. Attacks may be associated with pallor and lethargy. A typical element is the complete resolution of

TABLE 6 | Warning signs in children with headache (red flags).

Red flags
Changes in mood or personality over days or weeks
Related to severe vomiting, especially in early morning
Worsening of pain with cough or Valsalva maneuver
Altered conscious state
Papilledema
Focal neurologic deficit or meningismus
Seizures or fever
High-risk population (patients with sickle cell anemia., malignancy, recent head trauma, ventricular-peritoneal shunt, others)
Pain that wakes the c.hild from sleep or occurs on waking
Change of the character of headache in patients diagnosed with primary headache
Poor general condition
Increased head circumference
Cranial nerve palsies
Abnormal ocular movements, squint, pathologic pupillary responses
Visual field defects
Ataxia, gait abnormalities, impaired coordination
Sudden onset of headache (first or worst ever)
Increase in severity or characteristics of the headache
Occipital headache*
Age < 5 years*

*Modified by Roser et al. (36); *relative red flags.*

symptoms between attacks. Nausea and vomiting occur at least four times per hour and the attacks last for 1 h, up to 10 days and occur 1 week apart (28). Symptoms can be so intense as to require ED management (45) and hospitalization for intravenous rehydration (44). The diagnosis is generally delayed and these patients often undergo multiple hospitalizations and invasive diagnostic tests. The differential diagnosis is made with acute abdominal disease, intracranial disorders, or systemic diseases such as metabolic-endocrinological conditions. It is difficult to establish the exact prevalence of cyclic vomiting syndrome because it is often misdiagnosed or unrecognized.

Abdominal migraine is an idiopathic condition, which is found mainly in subjects aged between 3 and 10 years of age, characterized by recurrent attacks of moderate to severe midline or poorly localized abdominal pain. The attacks are associated with vasomotor symptoms, nausea and vomiting, pallor and anorexia, lasting 2–72 h and there is a complete resolution between the episodes. Cephalalgic phase is typically not present during the attacks (28). The abdominal pain is often described as dull or just sore, not colicky, and interferes with daily activities in 72% of patients (46). The history and physical examination must exclude other medical conditions (gastrointestinal or urogenital diseases and central nervous system disorders). A careful history regarding headache must be taken and a diagnosis of migraine without aura should be considered if headache is present during attacks (28). Significant indicators for diagnosis are the absence of recurrent head pain, especially on initial presentation, and vomiting episodes that are less severe compared to cyclical vomiting syndrome (46). The abdominal pain resolves in 61% of patients, but 70% develop migraine with or without aura (47). Migraine therapies have been reported effective in treating abdominal migraine (48).

Benign paroxysmal infantile vertigo (BPV) is a disorder characterized by brief recurrent attacks of vertigo in otherwise healthy children. The vertigo is maximum at the onset of the attack and resolves spontaneously after a few minutes or a few hours without loss of consciousness. Nystagmus, ataxia, pallor, and vomiting may be associated symptoms (44). Between the attacks neurological examination, audiometric examination, and vestibular tests are normal. Posterior fossa tumors, epilepsy and vestibular disorders must be excluded (28). BPV has a prevalence of 2.6% in children. Onset is typically between 1 and 5 years of age and it is generally self-limiting within 10–12 years (49). BPV is the most frequent cause of vertigo in children aged 2 to 6 years and has a prevalence of about 2.6% in children from 5 to 15 years of age. In particular BPV account for 6.3% of the children who come to the emergency room for vertigo (50).

Benign paroxysmal torticollis (BPT) is a disorder characterized by recurrent episodes of head tilt to one side, with or without slight rotation, which resolve spontaneously after a few minutes to 30 days (28). The child's head can be positioned neutrally during attacks, although it is possible to find resistance during movement. This condition occurs in infants and young children with onset in the first year of life (44). Nausea, irritability, vomiting, pallor, drowsiness, eye abnormalities, dystonia, and nystagmus may be associated. Ataxia is seen more frequently associated in older children (28). Attacks occur from once a week to once every 5 months (44). Neurological examination is normal between the attacks. Differential diagnosis includes gastro-esophageal reflux, idiopathic torsion dystonia, and complex partial seizures, but special concern goes to the posterior fossa and cranio-cervical junction where congenital or acquired lesions may determine stiff neck (28). BPT management is essentially reassurance and supportive care (44).

Tension-Type Headache

Tension-type headaches (TTH) are common in children with a prevalence of 5–25% in children and adolescents and an average onset age of ∼7 years (26). The pain usually arises in the afternoon hours while the child attends school and the child often continues to practice his favorite activities despite severe or constant headaches (2). The average frequency of the attacks is about two per month and the duration about 2 h per single episode. In children TTH can be triggered by psychosocial stressors and anxiety; comorbidities frequently present are mood disorders, prevailing if the headache pain is chronic. It is not rare for the characteristics of tension headaches to change from pre-school age to adolescence. For this reason the so-called red flags must prompt further investigations on the tension-type headache. In particular, neuroimaging must always be sought in order to exclude life-threatening headaches. Often the symptoms of TTH can overlap with those of migraine and a migraine may transform over time to a tension type of episodic headache. Unlike migraine, TTH is not associated with photophobia, phonophobia or nausea, nor aggravated by physical activity. Furthermore, the pain is generally mild or moderate and not pulsating (28).

Trigeminal Autonomic Cephalalgias

Trigeminal autonomic cephalalgias (TACs) are represented by various forms of headache syndromes such as: cluster headache (CH), paroxysmal hemicranias (PH), short-lasting unilateral neuralgiform headache attacks with conjunctival tearing and injection (SUNCT), and short-lasting unilateral headache attacks with cranial autonomic symptoms (SUNA) (28). The hallmark of these headache syndromes is the presence of unilateral, autonomic manifestations during the headache episode (3).

CH is a rare condition in children (from 0.03 to 0.1% of pediatric headaches) with a male preponderance (2.5:1). Only 5–10% of CH develop in childhood with a peak of onset in adolescence (mean age 11–14 years). A familiarity for CH is present in about 10% of pediatric cases compared to 25% for migraine (3). The clinical characteristics of pediatric onset CH, like in adults, are severe typically unilateral attacks of pain which are orbital, temporal, or in contiguous areas, lasting 15–180 min and which occur from one to eight times a day. Pain is associated with ispsilateral conjunctival injection on the same side as headache, watery eyes, nasal congestion, rhinorrhea, sweating, miosis, ptosis and/or palpebral oedema, and agitation (28). Tearing of the eye homolateral to the cephalalgia is the more frequent symptom of pediatric CH, followed by conjunctival injection and nasal secretion (3).

TACs share the clinical hallmarks of unilateral headache with prominent, ipsilateral, cranial parasympathetic autonomic features.

Recurrent Painful Ophthalmoplegic Neuropathy

The previous and inappropriate nomenclature of this condition was "ophthalmoplegic migraine." This terminology has been rejected, as this condition is not migraine, but rather a recurrent and painful neuropathy. It is a rare condition that occurs in 0.7/million people, in which headache is associated with partial or complete, unilateral paralysis of the oculomotor nerves. Clinically, it presents with repeated attacks of headache that have the characteristics of migraine, but are associated with loss of function of one or more oculomotor nerves (in most cases paresis of the third cranial nerve), in the absence of demonstrable brain lesions on neuroimaging (28). When the third cranial nerve is involved, the pupil is rarely spared, unlike what happens in the case of ischemic paralysis. This condition is found more in children than in adults and should be considered in the differential diagnosis of third nerve palsy in pediatrics (34). However, this disorder is rare and onset usually occurs before the age of 10. Injuries of the parasellar region or the upper orbital fissure and aneurysms of intracranial vessels should be excluded with appropriate neuroimaging studies. In some cases, MRI shows a capillation of gadolinium in the intracisternal portion of the affected cranial nerve, suggesting a recurrent demyelinating neuropathy (3), which may sometimes determine permanent cranial nerve deficit (51).

Particular Forms "Sub Judice" Classified at Present in Appendix Section in ICHD-3 Revised

Infantile colic, alternating hemiplegic migraine, and vestibular migraine represent three additional forms that may be listed among "Episodic Syndromes" possibly associated with migraine (section 1.6 point in ICHD-3 revised) (28). Nevertheless, these conditions do not present sufficient evidence to be classified in this group (1.6) and require further studies.

Infantile colic affects one infant out of five and is defined as an episode of irritability, agitation, or inconsolable crying without a specific, apparent cause in an infant without stunted growth. Generally, the episodes last three or more hours a day for at least 3 days a week. Given the recent evidence of a possible association between migraine and infantile colic, the latter is now part of the "Episodic syndromes that can be associated with migraine" included in the appendix section of ICHD-3 (28).

Alternating hemiplegia of infancy (AHC) (or alternating hemiplegia of childhood) is a rare neurodevelopmental disease characterized by recurrent episodes of hemiplegia and paroxysmal disorders associated with persistent developmental delay and mental retardation. The incidence is about 1/100.000 newborns. AHC is classified by the ICHD-3 as an episodic syndrome that may be associated with migraine. The main features are recurrent episodes of intermittent hemiplegia, often migratory, and alternating associated with other neurological features such as dystonia, choreoathetosis, and developmental delay (44), lasting from a few minutes to a few days, with unilateral or bilateral onset. These episodic symptoms disappear immediately with sleep, but reappear after waking up with longer attacks. The diagnosis is primarily clinical and the initial signs are hemiplegia and dystonia in the first six months of life. Paroxysmal movements of the ocular globes appear in the first three months. An exclusion diagnosis is made on the basis of absence of epileptiform changes on EEG during the episodes.

Migraine-related syndromes [such as BPV and *vestibular migraine* (VM)] are the most common cause of episodic vertigo in children (52). In 35–60% of cases are associated with headache that can precede, follow or occur simultaneously with vestibular symptoms. The diagnostic criteria for VM proposed by Neuhauser (53), initially based on clinical and epidemiological observations of adult patients, have recently been validated (28). The clinician should arrive early to a reasonable diagnosis to start treatment early. This approach also minimizes parents' and children's anxiety, reduces interruption of leisure time and school activities, and prevents the development of VM.

Two other headache conditions are well-known to pediatricians, also in the emergency setting, as possible "variant forms of migraine": Alice in Wonderland Syndrome and acute confusional migraine.

The *Alice in Wonderland Syndrome* (AWS) is a rare disorder first described by Todd and historically attributed to Lewis Carroll, author of the novel Alice in Wonderland. It seems that Carroll suffered from migraine and described in his famous story the symptoms that he himself presented. This syndrome of altered bodily perceptions consists of variations

in dimensions and shape and distorted body images. Patients often narrate grotesque visual illusions, spatial distortions, micropsy, macropsy, metamorphopsia, and teleopsia (44). These experiences can precede or accompany a headache or occur without headaches. EBV infection appears to be the most common cause of AWS in children, unlike in adults where it occurs in conjunction with migraine episodes (54). It can also present in different disorders including epilepsy, drug intoxication, fever delirium, brain injury, schizophrenia, and hypnagogic states (44). Increasing scientific evidence of the relationship between migraine and AWS, means that in many patients it was considered an aura or equivalent migraine, particularly in children (54).

Acute confusional migraine (ACM) is a rare condition and the data reported is scarce. ACM is characterized by the onset of an acute confusional state which manifests itself in the form of agitation, memory impairment, disorientation, increased vigilance, dysarthria, or perceptive disorder. It occurs predominantly in late childhood and adolescence (50% of cases) and there is often a positive family history for migraine. The headache can appear before, during or after the confusional state, lasting a few minutes to a few hours. Resolution within 24 h and often associated with retrograde amnesia. Encephalitis, convulsions, strokes, vasculitis of the central nervous system, metabolic encephalopathy, toxic ingestion, and other causes of acute confusion must be excluded. During the disorder, the EEG can detect a generalized slowdown and sometimes an intermittent frontal rhythmic delta activity (44).

SECONDARY HEADACHES

According to the ICHD-3, a new headache of recent onset that presents with another disorder recognized as capable of prompting it, is always diagnosed as secondary.

Secondary headaches in the pediatric population are more frequently due to non-LT diseases such as upper respiratory tract infections, sinusitis, and systemic infections. In a minority of patients, headache is secondary to serious LT intracranial disorders such as brain tumors, hydrocephalus, idiopathic intracranial hypertension, brain abscess/meningitis, aneurysm and vascular malformation, intoxication, and ventriculo-peritoneal shunt malfunction. LT causes of headache are found in patients whose clinical history and physical examination reveal so-called "red flags" (36, 55) (**Table 6**).

Thunderclap headache is a severe and acute headache that reaches its maximum peak intensity in about a minute and lasts about 5 min. This form of headache can be associated with a considerable number of potentially LT disorders (28) so it is essential to carry out imaging tests to exclude them.

Headaches due to increased intracranial pressure are associated with pain that wakes the patient at night and pain early in the morning (55). However, 25% of children with episodes of primary headache wake up at night. In these cases the pain usually starts before the child goes to sleep. The importance of a good and detailed history should always be stressed, together with a careful and oriented physical examination, fundamental in identifying these cases.

The role of the ED physician is to identify the causes of headache that require rapid intervention. Failure to do so may have devastating consequences for children.

Thunderclap Headache

Thunderclap headache (TCH) is an acute onset headache that quickly reaches its maximum intensity level in a minute and lasts about 5 min (56). This type of headache in adults is described as "the worst headache ever had." In children, it represents a medical urgency since this form of acute onset headache is mainly associated with LT causes for which rapid diagnosis and prompt treatment are essential (57).

Various conditions can be associated with TCH including: leaking intracranial aneurysm; cervical arterial dissection; venous sinus thrombosis; reversible cerebral vasoconstriction syndrome; pituitary apoplexy; posterior reversible encephalopathy; hypertensive crisis; spontaneous intracranial hypotension. Very rarely, TCH may represent a primary form but a diagnosis can be made only after other etiologies have been excluded by appropriate investigations such as computed tomography (CT) angiography (CTA), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), magnetic resonance venography, and cerebrospinal fluid evaluation (38).

Cervical artery dissection in children occurs with a TCH in 25% of cases (58). Laceration of the vascular wall determines extravasation of blood within the vessel wall which occludes the distal portion of the vessel involved. For this reason, classic dissection of carotid or vertebral vessels in children presents with acute onset headache associated with neck pain and/or tenderness and ipsilateral supraorbital, auricular, or mandibular pain (57). Focal neurological deficits may be other presenting symptoms. In these cases it is therefore mandatory to perform diagnostic imaging and proceed with the appropriate treatment.

Venous sinus thrombosis begins with headache in more than 75% of cases in childhood (59). The headache is mainly severe with a chronic, progressive pattern that worsens over days or weeks. However, about 10% of children present an "explosive headache" onset triggered by coughing, sneezing and/or change in position (57). Other symptoms associated are vomiting, diplopia and papilledema, and convulsions. Dehydration is a predisposing factor in patients with infectious conditions or pre-existing brain lesions (58). For the diagnosis it is mandatory to perform a CT scan with contrast medium in an emergency setting though the gold standard remains MRI if available in the ED.

The *reversible cerebral vasoconstriction syndrome* (RCVS) is a clinical condition of transient dysregulation of the cerebral vascular tone. An acute and transient malfunction in control of the intracranial vascular tone causes narrowing and micro-dilatation of a cerebral area, characterized by a mainly favorable outcome (60, 61). RCSV may be primitive or a complication of other clinical conditions such as cerebral infarctions, intracranial hemorrhages or cerebral edema. The classic clinical manifestation is the sudden onset of recurrent headaches that are brief, but extremely painful and associated with an altered level of

consciousness and/or focal neurological symptoms. In these case the physician must use diagnostic imaging (MRI, angiography) (57). RCVS treatment is the elimination of possible triggering factors, together with symptomatic measures.

Spontaneous *intracranial hemorrhage (ICH) and ischemic stroke* are rare causes of headache in children. Although an acute TCH is the classic presenting symptom of ICH, most children who have ICH or ischemic stroke have additional signs or symptoms by the time they present to a medical facility. ICH should be considered in patients who have an acute onset of severe headache, particularly if the patient has an abnormal neurologic examination or a disorder that places him or her at risk for hemorrhage (62).

Infection

Infections of the central nervous system must always be suspected in case of a patient with headache, systemic symptoms (in particular fever) and altered consciousness (38, 62). Photophobia and neck stiffness are frequent symptoms in children with meningitis. Hypotension or the presence of hemorrhagic skin lesions (petechiae and/or ecchymosis) are also considered red flags for central nervous system infections and warrant immediate lumbar puncture with cerebrospinal fluid examination (60). In children with fever, localized headache and focal neurological deficits, a brain abscess should be considered especially if there is a recent history of otitis media, mastoiditis, endocarditis or immunosuppression (57). In encephalitis (viral, bacterial, and/or autoimmune) the distinctive sign is headache in association with a variety of psychiatric and behavioral symptoms such as hallucinations and psychosis, convulsions, memory dysfunction with short-term memory loss, language disorders and altered level of consciousness (2).

Intracranial Masses

Brain tumors are rare in children with an incidence of 5 per 100,000 between 0 and 19 years of age (2), and delayed diagnosis can affect negatively morbidity and mortality. The characteristics of headaches due to brain tumors are generally linked to the position, size, and rate of growth of the mass. Prevalence of brain tumor in pediatric patients accessing the ED varies from 0.4 to 3% in relation to the studies examined (**Table 1**). In most cases it is a chronic and progressive headache with frequent nocturnal awakenings or a morning headache with or without vomiting. Exacerbation of the headache with Valsalva, cough, and change of position occurs in a minority of patients. Patients are often unable to give a specific location of the pain. However, supratentorial tumors affecting the structures innervated by the ophthalmic branch of the trigeminal nerve can sometimes produce a frontotemporal headache, whereas posterior fossa tumors that compress the glossopharyngeal and vagus nerve may cause occipital-nuchal pain (2). In a study on 393 pediatric patients diagnosed with a brain tumor in the ED, emerged that the posterior fossa was the site of tumor in 48.3% of cases, supratentorial in 21.8%, brainstem in 16.1%, and central in 13.8% (63). This same study underlined that the mean onset of any symptom was 86.3 days and for headaches was 104.5 days before the diagnosis was made in the ED. Symptoms or signs reported were headache (66.7%), hydrocephalus (58.6%), nausea/vomiting (49.4%), gait disturbance (42.5%), vision problems (20.7%), seizure (17.2%), change in behavior/academic performance (17.2%), cranial nerve deficits (16.1%), altered mental status (16.1%), back/neck pain (16.1%), papilledema (12.6%), facial asymmetry (10.3%), sensory deficits (8%), focal motor weakness (6.9%), cranial nerve deficit (6.9%), ptosis (5.7%), macrocephaly (4.6%), asymptomatic (3.4%), and anisocoria (1.1%) (63). Headache and vomiting are the most common and early symptoms in children with brain tumors. However, symptoms or visual signs and behavioral changes are often present. Abnormalities in neurological examination are reported in most of the children. Symptoms of intracranial hypertension suggest the need for a neurological clinical examination and an ophthalmological assessment. Among children and young adults with an intracranial tumor, non-localizing features such as headache, vomiting, lethargy, drowsiness, failure to thrive, parental concern, and features of raised ICP were far more common than specific features, such as focal neurological deficits, prior to diagnosis. In all age groups, cranial nerve II, III, IV, or VI dysfunction was also common. Many of these symptoms occurred with increasing frequency with tumor progression. Signs of raised ICP become the most common group of presenting features in the final month before diagnosis (64, 65).

Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (IIH) or pseudotumor cerebri is a condition characterized by increased intracranial pressure (>28 cmH_2O) in the absence of clinical or radiological evidence of an intracranial lesion recognized as capable of causing it. In these patients ophthalmic assessment shows bilateral papilledema while neuroimaging is found to be within normal limits. Neuroimaging findings more easily associated with the diagnosis of IIH include empty turcic saddle, distention of the perioptic subarachnoid space, compression of the posterior sclerae, cupping of optic disks and distension of the optic nerve sheaths, and transverse cerebral venous sinus stenosis. Normal physical chemical examination of cerebrospinal fluid (CSF) with high opening pressure confirms the diagnosis of IIH (28, 66). For diagnostic purposes, CSF should be measured in the absence of treatment to lower intracranial pressure. IIH occurs in obese adolescent females (28). Visual acuity loss is reported in 6–22% of children and visual field loss occurs in up to 91% at clinical onset. In our experience it is useful to evaluate serum electrolytes in patients with suspected IIH as this condition can be associated with underlying hypocalcemia. The role of neuroimaging and ultrasound-based optic nerve sheath diameter measurement has significantly changed the evaluation of IHH patients.

EVALUATION OF HEADACHE IN ED: *HOW TO DIAGNOSE HEADACHE*

History

History and physical examination are extremely important in the evaluation of children who present headaches. They are reliable indicators of headaches secondary to life-treathening conditions. An accurate history is crucial for a correct diagnosis, so it is important to ask the right questions to both the child and the parents. The emergency physician should ask

about headache description (onset, duration, quality, and pain severity), triggers and exacerbating factors (stress, sleep pattern changes), alleviating factors (**Table 7**), and specifically search for warning signs (**Table 6**). Background information must be investigated, such as drug use, systemic disease (sickle cell disease, immunodeficiency, malignancy, pregnancy, neurocutaneous syndrome, or congenital heart disease), associated symptoms, trauma, and family history.

A systematic review (36) proposed to distinguish between "high risk red flags" and "relatively red flags" (**Table 6**) which are outlined in detail in this review. Any high risk red flag should suggest performing neuroimaging. In the case of relatively red flags, a more restrained approach can be appropriate on the individual setting (36). Household and family dynamics, psychosocial stress factors, and school performance should also be evaluated because they can be precipitating factors in children and adolescents. A HEADSS (home, education, alcohol, drugs, smoking, sex) screen should be performed in all adolescent patients (16).

Lewis et al. (55) suggested classifying headaches into four temporal patterns (acute, recurrent acute, chronic progressive, chronic non-progressive; **Table 8**). Acute headaches which evolve suddenly can be considered suggestive of organic disease and must be evaluated very carefully. Fever during upper respiratory tract infection and sinusitis are the most frequent causes of sudden onset of pediatric headache (1). The acute-recurrent pattern of episodic headache, separated by symptom-free intervals, occurs in migraine, tension-type headache, cluster headache, neuralgias, and epileptic variants (55). Migraine episodes occur more frequently as acute recurrent headaches with chronic pain episodes. If ICHD-3 criteria for a primary headache disorder are met, no further investigations are necessary (36). Chronic progressive headaches are particularly concerning because they are generally associated with conditions characterized by gradual increase in intracranial pressure (brain tumor, hydrocephalus, IIH, brain abscess, aneurysm, and vascular malformations, intoxication) (1, 36). The chronic non-progressive and mixed patterns usually fall within the spectrum of chronic daily headache with or without superimposed migraine or analgesic abuse (55). Headache on awakening or sleep interruption due to headache have been commonly regarded as a potential sign of raised intracranial pressure and, therefore, significant underlying pathology, but this issue is debated and warrants further investigation. Medina et al. (67) found persistent headache that wakes a child repeatedly from sleep or occurs immediately on awakening, with no family history of migraine, to be the strongest predictor of intracranial lesions that require neuroimaging. Nevertheless, a recent study of Ahmed et al. (68) reported that neuroimaging among 4% of patients with headache sleep interruption or on awakening revealed intracranial abnormalities that were unlikely to have caused the awakening and none of them required prompt intervention. The authors concluded that awakening or sleep interruption due to headache among clinically well and neurologically normal pediatric patients was most likely to be caused by primary headaches, particularly migraine or tension type headaches, and this needs to be more widely recognized in order to avoid unnecessary brain imaging.

TABLE 7 | Key questions in taking the clinical history in a child with headache.

Acute headache	Tinte of onset
	Duration
	Localization
	Quality
	Intensity
	Premonitory symptoms
	Aura
	Associated vegetative symptoms
	Impairment of daily routine
	Ameliorating factors
	Aggravating factors
	Triggering factors
	Factors possibly associated to onset
	Efficacy of medications taken
Additional features inrecurrent headache	Number of headache types
	Frequency
	Sequence of typical episode
	Impairment of quality of life

Modified by Ozge et al. (1) and Papetti et al. (35).

TABLE 8 | Causes of headache by temporal pattern.

Acute headache	**Acute recurrent headache**
Upper respiratory tract infection, with or without fever	Migraine
Acute sinusitis	Tension-type headache
Pharyngitis	Cluster headache
Meningitis (viral or bacterial)	Seizures
Migraine (first attack)	Hypertension
Post-ictal headache	Hyperthyroidism
Hypertension	Pheochromocytoma
Substance abuse (e.g., cocaine)	Medication-induced headache
Medication (e.g., methylphenidate, oral contraceptives, steroids)	MELAS
Intoxicants (e.g., lead, carbon monoxide)	
Ventriculoperitioneal shunt malfunction	
Brain tumor	
Hydrocephalus	
Subarachnoid hemorrhage	
Intracranial hemorrhage	
Venous sinus thrombosis	
Chronic progressive headache	**Chronic non-progressive headache**
Brain tumor	Chronic migraine
Hydrocephalus (obstructive or communicating)	Chronic tension-type headaches(analgesic overuse)
Pseudotumor cerebri	Post-concussive syndrome
Brain abscess	Temporomandibular joint syndrome
Hematoma (chronic subdural hematoma)	Cluster headache
Aneurysm and vascular malformations	
Medications (e.g., birth control pills, tetracycline, vitamin A)	
Intoxication (lead poisoning)	

Adapted by Lewis et al. (55) and Papetti et al. (35).

Physical Examination

The general physical examination is of extreme importance and must be conducted in a complete manner. The first step is to assess the patient's severity of pain, which may be indicative of a more serious underlying condition (14, 16), further to investigate the clinical features of children presenting to a pediatric ED with headache as the chief complaint and report in their observational study that all patients with LT secondary headache can present very intense pain. One must investigate for important clues leading to the correct diagnosis (skin rash, petechiae, stiff neck, organomegaly). Altered vital signs (in particular body temperature and blood pressure) are suspect for serious conditions (69). When evaluating of a child with headache it is mandatory to perform a complete neurological examination aimed at identifying signs of intracranial lesion. Particular attention must be paid to the level of consciousness, meningeal signs, visual disturbances, focal neurological deficits, disorders of gait and coordination, speech and hearing disorders, and localized altered sensitivity of the scalp or any area of the body. In younger patients, it may be useful to evaluate the head circumference. The head and neck should be inspected and palpated, investigating for visual signs (i.e., unequal pupils) and sinus tenderness. The skin should be searched for possible signs of a neurocutaneous syndrome, in particular neurofibromatosis and tuberous sclerosis, which could be indicative of intracranial neoplasms (70). In addition, a psychiatric evaluation of children and parents should be performed when needed. In the majority of patients with primary headache disorders, general physical and neurological examination are both normal (1).

Red flags (**Table 6**) at physical examination should include headache with signs of systemic disorders (skin rash, petechiae, stiff neck, organomegaly), focal neurological signs, symptoms of disease (other than typical aura), and papilledema (35, 36).

Occipital headache is considered a risk factor for serious secondary headache, but it is currently under debate whether to consider it an absolute or relative red flag. Some authors (14, 55) aimed to identify clinical clues for headaches associated with serious LT intracranial disorders. They agreed that occipital location and the inability of the child to describe the quality of his pain are risk factors that require further investigation. In contrast, Genizi et al. (33) in a retrospective study of 314 pediatric patients with headache (39 patients with occipital headache), reported that etiology of occipital headaches does not differ from other sites, suggesting that occipital headaches should not be evaluated differently from other headaches.

Diagnosting Testing

The few children that need further evaluation should have the work-up guided by the underlying cause suspected. Diagnostic tests are varied; they include routine laboratory analysis, CSF examination, and neuroimaging with CT or MRI. Routine neuroimaging is not indicated and guidelines recommend that it be performed in children presenting with an abnormal neurological examination and a history of CNS disease (71).

Fundoscopic Examination

Ophthalmologist consultation is frequently requested by the emergency room physician to rule out papilledema (optic disc swelling) in patients with headache (72). Papilledema can be a sign of increased intracranial pressure and is believed to develop from hours to weeks after the onset of the headache. A meta-analysis of about 400 pediatric patients with brain tumors reported the presence of papilledema in only 13% of patients (73). Segev-Becker et al. (74) analyzed 479 children with headache in the ED to investigate for papilledema. Only six children (3.5%) had papilledema (four IIH, one meningococcal meningitis, and one patient was lost to follow-up). Furthermore, medulloblastoma was diagnosed in one of the patients with normal funduscopic examination. The authors point out that it is not useful to evaluate routinely the ocular fundus in the emergency room, especially if the onset of symptoms is <24 h (74). However, we believe that fundus examination should always be included in the neurological evaluation of a child with headache even though it does not always exclude dangerous secondary conditions.

Neuroimaging

Assessment and diagnosis of headaches can be very difficult for pediatricians and neuroimaging (CT or MRI) is often required as part of the investigations (70). CT is the first neuroimaging performed in the ED in patients with suspect secondary headache because it is a fast and easily performed test. Modern CT machines used in pediatrics have developed low-dose radiation systems therefore representing the first-instance examination in an emergency setting. MRI provides superior quality images but is more expensive and children under 6 years of age may need sedation or anesthesia to perform it (24, 70).

Studies on the utilization of neuroimaging in the ED show that the frequency of pathological findings that lead to significant variation in management are rare, about 1.2% of neurologically normal patients (75). Neuroimaging techniques should be reserved for children with a suspicious clinical history, abnormal findings on neurological examination or other symptoms suggestive of intracranial space-occupying lesions (76). Therefore, before deciding on neuroimaging, it is essential to have complete information regarding age at onset of headache, type of onset (abrupt or gradual), frequency, severity, presence of an aura, as well as perform a thorough clinical and neurological assessment. In ED, the headache characterization is mandatory in order to identify patients who would benefit from neuroimaging. At the same time it is essential to identify children who can do without neuroradiological investigations to avoid subjecting them to useless and potentially harmful procedures (70). A headache that appears during or after treatment of otitis media or sinusitis may indicate the possible intracranial spread of the infection. In the literature intracranial complications are reported in about 3% of patients with sinusitis being represented by epidural and subdural empyema, followed by brain abscess (77). In the subdural empyema the patient is usually febrile with associated neurological symptoms such as altered state of consciousness, focal neurological deficits, and signs of meningeal irritation (77, 78). Sinus thrombosis is a possible complication of otitis media and mastoiditis (77). In infants and toddler, signs of intracranial mass include the presence of an increase in head circumference, prominent scalp veins, and disjunction of cranial sutures. In older children the most

frequent disorders are represented by headache or diplopia. Signs of brainstem herniation are bradycardia, arterial hypertension, and abnormal in inspirations; these features should require prompt urgent neuroimaging (23). Red flags are the basis of existing guidelines and recommendations regarding the use of neuroimaging (**Table 6**). However, there is no clear consensus on which findings should be used for decision making, resulting in a large number of findings proposed to be concerning enough to warrant urgent imaging. Tzse et al. (76) enrolled 224 patients of which 197 (87.9%) had at least one red flag in their history, including headache waking from sleep (34.8%), headache present upon or soon after waking (39.7%), or headaches increasing in frequency, duration, and severity (40, 33.1, and 46.3%). The prevalence of urgent intracranial abnormalities was 1%. Abnormal neurological exam, extreme pain intensity of presenting headache, severe vomiting especially early in the morning, and positional symptoms were independently associated with emergency neuroimaging. These data suggest that many children with headache receive unnecessary neuroimaging due to the high prevalence of non-specific red flag findings (76). The yield of neuroimaging in pediatric headache with normal neurological examination is low. However, in patients with positive neurological signs or symptoms the likelihood of positive neuroimaging findings is high (79). In fact, the presence of ataxia, focal crises, dysfunction of the cranial nerves, nystagmus, and abnormal reflexes are indications to perform neuroimaging. Symptoms of increased intracranial pressure such as papilledema, increased head circumference (in the youngest), vomiting, mood or behavior changes, and altered mental status are further indications.

We must keep in mind that children under age 5 years still represent a further challenge in the emergency setting for the pediatrician or neurologist. In this age group it would seem that headache may be the only symptom. Nevertheless, a study examining 364 children (between 2 and 5 years of age) with headache demonstrated that diagnostic yield of CT scans is low for children who present no worrying history and a normal neurological examination (23). A previous analysis of data regarding more than 3,000 children with brain tumors showed that 98% had one of the following five signs: papilledema, ataxia, hemiparesis, abnormal eye movements, or depressed reflexes (80). In the case of abnormal neurological examination or suspicious clinical history, imaging should be performed. MRI is preferable, but CT without contrast agent, because of its accessibility and rapidity, is acceptable as a routine protocol in ED (23). Proper neuroimaging of children with headache is very specific to the headache type. The choice of the most correct sequences, CTA or if we use MRI (i.e., MRA, T2-weighted gradient-echo, diffusion-weighted sequences, and post-gadolinium-enhanced sequences), is fundamental to perform the most appropriate path to arrive at an etiological diagnosis by maximizing the capacity of the imaging technique with the minimum risk of the child [see ACR Appropriateness Criteria Headache Child for more detailed information ref. (81)]. In emergency setting some centers prefer the use of CTA over MRA so we would suggest considering both (one or the other) when vascular imaging is indicated.

Laboratory Tests, Lumbar Puncture, EEG, and Neurophysiological Examinations

Laboratory tests are rarely useful in the evaluation of headaches (69). They can be useful just to demonstrate that the most frequent type of secondary headache in children admitted to the ED is related to upper respiratory tract infections. Lumbar puncture (LP) is not routinely recommended in the assessment of headaches in children. This procedure should be performed in children with suspected intracranial infection, subarachnoid hemorrhage or IIH (72).

EEG and neurophysiological examinations (including evoked cortical potentials) are not routinely used in the diagnosis of children with headache in the ED (71). In particular, EEG is not necessary for distinguishing a primary headache disorder in children from secondary headache due to head and neck structural disease, or those due to a psychogenic cause (55). Its' use is limited to "migraine-triggered seizures" (migralepsy concept) (20, 82) and to the rare cases of "Ictal Epileptic Headache" [see the criteria by Parisi et al. (83)]. Recently, the "migralepsy concept" has been seriously questioned, in favor of the concept of "Hemicrania Epileptica," which is an ictal epileptic headache followed and/or associated with other motor, sensory, and autonomic signs/symptoms (84).

TREATMENT

Appropriate advice and treatment requires consideration of a wide differential diagnosis between primary and secondary headaches, as well as the different types of primary headache. In the ED general measures include stabilization of the airway, breathing, and circulation in critical patients. In patients in good general condition, the treatment should include placing the child in a quiet, dark room where he can rest since sleep is often the most effective treatment. Diagnosis and therapeutic decisions are often complicated by comorbidities, and different primary headaches can co-exist. Being familiar with general pediatrics, and pediatric headache disorders in particular allows for better advice and better treatment options for the patients (85). The three major domains of headache treatment in a pediatric ED include lifestyle changes, abortive therapy and complementary therapies (62).

Non-drug Treatments and Advice

Children will often naturally seek out dark, quiet area when they have a headache and this should be encouraged. They should also be encouraged to take frequent, small sips of water to remain hydrated. If they are in a place where they can fall asleep, sleep may be useful in terminating a migraine attack.

A variety of physical, complementary, and lifestyle interventions are available and summarized by the SMART acronym (get sufficient and appropriate Sleep; regular healthy Meals; appropriate Activity neither excessive nor deficient; consider methods of Relaxion; recognize, and avoid Trigger); though mostly with poor empirical evidence of efficacy (85). Excess caffeine, aspartame, monosodium glutamate, nitrite, alcohol, and chocolate can cause headaches. Therefore, we advise not to exceed with these substances though the role of exclusion diets in infantile migraine is still not demonstrated.

Acute Treatment

Treatments for migraine include symptom relief of acute attacks (**Table 9**). Usually the therapies aim to eliminate head pain and reduce the associated symptoms, such as nausea, phonophobia, and photophobia. Since acute medications are most effective when taken while pain is still mild, which tends to be early in an attack, families and adolescents should work out strategies to ensure that the medications are available and on hand (86). During acute head pain or exacerbation of chronic headache, nausea, and/or vomiting may make oral administration of medications difficult (85). Vomiting can sometimes be a very important part of a migraine attack in young children. In these cases, it is a priority to start intravenous (IV) rehydration and to administer antiemetic drugs (**Table 10**). When it is impossible to administer drugs by mouth, IV administration should be considered in the pediatric ED.

Oral analgesics such as paracetamol (10–15 mg per kg) and ibuprofen (10 mg per kg) are the mainstay of acute therapy for headache in pediatrics (6). Often the child or adolescent has already taken analgesics without apparent benefit, so one should check that the drug has been taken with the correct dosage and give indications for repeat administration.

Other drugs such as ergot derivatives (e.g., dihydroergotamine) and triptans (serotonin 1b/1d receptor agonists) have demonstrated efficacy in adults. Many of these medications have now been studied in children and adolescents and some have been approved for use in the pediatric age group. Four kinds of triptan are labeled by the US Food and Drug Administration for acute migraine in adolescents 12–17 years of age: almotriptan (oral), zolmitriptan (nasal spray), rizatriptan (oral), and sumatriptan/naproxen (oral); and one medication, rizatriptan (melt), is labeled for use in children 6 years and older.

A recent Cochrane (87) examined 27 randomized controlled pediatric trials of drugs compared to placebo to assess the efficacy in providing pain relief 2 h after acute headache treatment. Based on a systematic review, ibuprofen seems more effective, making it an excellent choice for the treatment of head pain; paracetamol has not been shown to be effective in providing headache relief. In a small cross-over study, predominantly in children, oral paracetamol was not superior to placebo or ibuprofen (88). Triptans were more effective than placebo in determining pain relief in 3 studies involving children and 21 studies involving adolescents and no significant difference was observed between the subgroups of triptans (including almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan). No difference was found between oral and intranasal administration of triptans in terms of efficacy, though the oral form is better tolerated (86). No patient in the studies analyzed reported serious side effects after administration of triptans. Side effects, usually mild, included fatigue, dizziness, asthenia, dry mouth, and nausea or vomiting with oral preparations, and taste disturbance, nasal symptoms, and nausea with intranasal preparations. The combination of sumatriptan with naproxen sodium was also more effective than placebo in producing pain relief in a study in adolescents (86).

Children with long-lasting migraine or status migrainosus may need ED treatment, if home therapy has failed and symptoms remain debilitating.

Dopamine receptor antagonists (chlorpromazine, prochlorperazine, promethazine, metoclopramide) are possible therapeutic options in the acute treatment of pediatric headache for their ability to control both pain and nausea/vomiting, always considering that the possible side effects include appearance of extrapyramidal reactions and sedation (89). Acute treatment of head pain via saline infusion, with intravenous ketorolac (0.5 mg/kg with a maximum dose of 30 mg) and prochlorperazine (0.15 mg/kg with a maximum dose of 10 mg), given intravenously, proved effective with a reduction of pain within 60 min in 55% of patients treated (90). A recent study comparing the effectiveness of three commonly used parenteral dopamine antagonists (prochlorperazine, metoclopramide, and promethazine) to abort pediatric migraine, found that promethazine was significantly associated with higher odds of treatment failure leading to opioid administration and poor pain control. The authors recommend using prochlorperazine or metoclopramide instead of promethazine for pediatric ED migraine treatment (91).

Dihydroergotamine (DHE) has shown efficacy and good tolerability in the treatment of pediatric migraine. The drug is usually administered in a hospital setting at both a high (0.5–1.0 mg/kg every 8 h) and a low dose (0.1–0.2 mg/kg every 8 h) (92), but there are still few studies in the pediatric population (93–95).

The usefulness of IV DHE in pediatric migraine has been suggested by two small retrospective studies of a total of 62 children and adolescents admitted to hospital for refractory migraine or status migrainosus (93, 94). Pain-free status upon discharge was reported in 74.4% of patients following repeat administration of DHE (0.1–0.5 mg per dose; on average 5–7 doses per patient). Nevertheless, these studies were weakened by prior treatment of the subjects with dopamine agonists. A recent study on treatment of 145 patients with pediatric refractory headache (only 28 with status migrainosus) showed that most responded to intravenous therapy with DHE, but complete resolution was more easily achieved in children with status migrainosus (96). However, only seven patients had headache duration of less than a week and it is likely that some cases reported as status migrainosus were actually worsened chronic migraine.

There is a lack of evidence regarding the use of *bolus IV fluids,* despite the fact that many protocols in the ED include this treatment. Only one single blinded randomized controlled trial is present in literature with patients divided into two groups: A (no medication given in combination with IV fluid 10 mL/Kg) and B (medication may be given simultaneously) (97). The authors conclude that the overall decrease in pain, measured with VAS scale, with IV fluid was small and no statistically clinical difference was found. Treatment with IV fluid hydration did not significantly influence headache relief at 30 min in children or adolescents with migraine in the ED. However, a clinically meaningful response was observed in 17.8% while recurrence of headache after ED discharge was 33%.

Sodium valproate IV could represent a treatment option for acute migraine, as suggested by two small retrospective studies on 31 and 12 adolescents (98, 99). Only the second study (99) was carried out in the emergency setting and

TABLE 9 | Abortive therapies for pediatric migraine.

Drug	Usual Dosage
Ibuprofen	10 mg/kg every 6–8 h Age > 12 y to adult: 400–600 mg every 6 h Max: 2,400 mg/day
Naproxen sodium	5-7 mg,kg every 8–12 h Age > 13 y to adult: 250–500 mg every 8 h Max: 1,250 mg/day
Acetaminophen	10–15 mg/kg every 4–6 h Age > 13y to adult: 650–1,000 mg every 6-8 h Max: 3,000 mg/day
Rizatriptan	Children< 40 kg: 5 mg PO once Children> 40 Kg: 10 mg PO once Max: 30 mg/day (propranolol will increase serum concentration of rizatriptan)
Zolmitriptan	Nasal Children > 12 y: 2.5–5 mg IN once Max: 10 mg/day Oral (tablet or ODT) Max: 10 mg/day
Sumatriptan	Nasal Age 4–6 y: 5 mg Age7–11 y: 10 mg Age > l2 y:20 mg Subcutaneous Child: 0.06 mg/kg, age > 12 y: 6 mg Oral Child: 1 mg/kg, max 50 mg/day
Almotriptan	Age > 12 y:6.25–12.5 mg PO, may repeat once in 2 h Max: 25 mg/day
Sumatriptan/naproxen	Age 12–17 y: 1 tablet 10 mg sumatriptan/60 mg naproxen, max dose 85 mg sumatriptan/500 mg naproxen

IN, Intranasal; Max, Maximum; ODT, Orally disintegrating tablet; PO, oral.

TABLE 10 | Antinausea/vomiting medication options in pediatric migraine.

Drug	Dose	Toxicity
Prochlorperazine	Oral Child: 10–13 kg: 2.5 mg every 12–24 h Child: 13–18 kg: 2.5 mg every 8–12 h, max 10 mg/day Child: 18–40 kg: 2.5 mg every 8 h, or 5 mg every 12 h Intravenous Child: 0.1–0.15 mg/kg/dose	Sedation Dystonic reaction
Promethazine	Oral or Rectal Child: 0.25–1 mg every 4–6 h	Sedation Dystonic reaction
Ondansetron	Oral 4–8 mg every 8 h <15 kg: 0.2 mg/Kg 15–30 kg: 4 mg >30 kg: 4–8 mg	Sedation Dystonic reaction

pain reduction was 39.8% with time to maximum relief of 63 ± 31 min at a dose of 100 mg. Three adolescents required a second dose of 500 mg that was infused over 14 ± 6 min, determining a 57% reduction in pain intensity from baseline.

Opioid medications are explicitly discouraged for primary headache disorders because they may potentiate migraine pathophysiology at the molecular level by blunting the response to targeted abortive therapies, converting episodic to chronic headache (100, 101). In fact, the American Academy of Neurology published a statement recommending against the use of opioids for primary headache (102). The increased use of opioid analgesics to treat pain has been concurrent with the rising rate of prescription opioid abuse and related morbidity and mortality, especially in adolescents (103, 104). Nevertheless, opioids were prescribed for pediatric pain, including headache, particularly in the ED setting (103–106). However, in a very recent study it emerged that opioid prescribing rates for pediatric headache were low compared to adults, with a decreasing temporal trend. Nonetheless, ED prescribing rates were 4-fold higher than ambulatory care settings, though pediatricians, also in the ED, prescribed opioids less frequently. This was especially true for children seen in a pediatric hospital compared to a generalist hospital (107) or tertiary care vs. community based ED (106). Opioids are not part of the American Academy of Neurology practice parameter for pediatric pharmacological treatment of headache (71). At present they do not have a scientific evidence of efficacy in the pediatric population and

they seem to be associated with an increase in hospitalization time (108).

Treating Medication Overuse Headache

Sporadically you can observe in pediatric EDs an acute attack in adolescents affected by medication overuse headache (MOH). These patients, who previously had episodic tension-type headache, migraine without aura or migraine with aura, develop a chronic headache(≥15 days a month for ≥3 months) while taking the following drugs, alone or in combination:

- triptans, ergot alkaloids, opiates or combination analgesics for ≥10 days a month;
- paracetamol, aspirin, or any non-steroidal anti-inflammatory drug for ≥15 days a month. MOH typically presents when a bad patch of migraine with or without aura has transformed into a chronic daily headache, including chronic migraine (85).

The suspect medication must be withdrawn abruptly and advice given on alternative treatments including, in some cases, prophylactic medication. Complete remission after withdrawal is no longer a diagnostic criteria (109).

CONCLUSION

Most of the pediatric headaches in the ED are secondary benign headaches related to acute upper respiratory tract infections or a primary headache syndrome. Nevertheless, we must be able to detect the associated signs and symptoms of secondary headache; both the more frequent, non-LT conditions and the less frequent, severe conditions (i.e., brain tumors or other intracerebral space

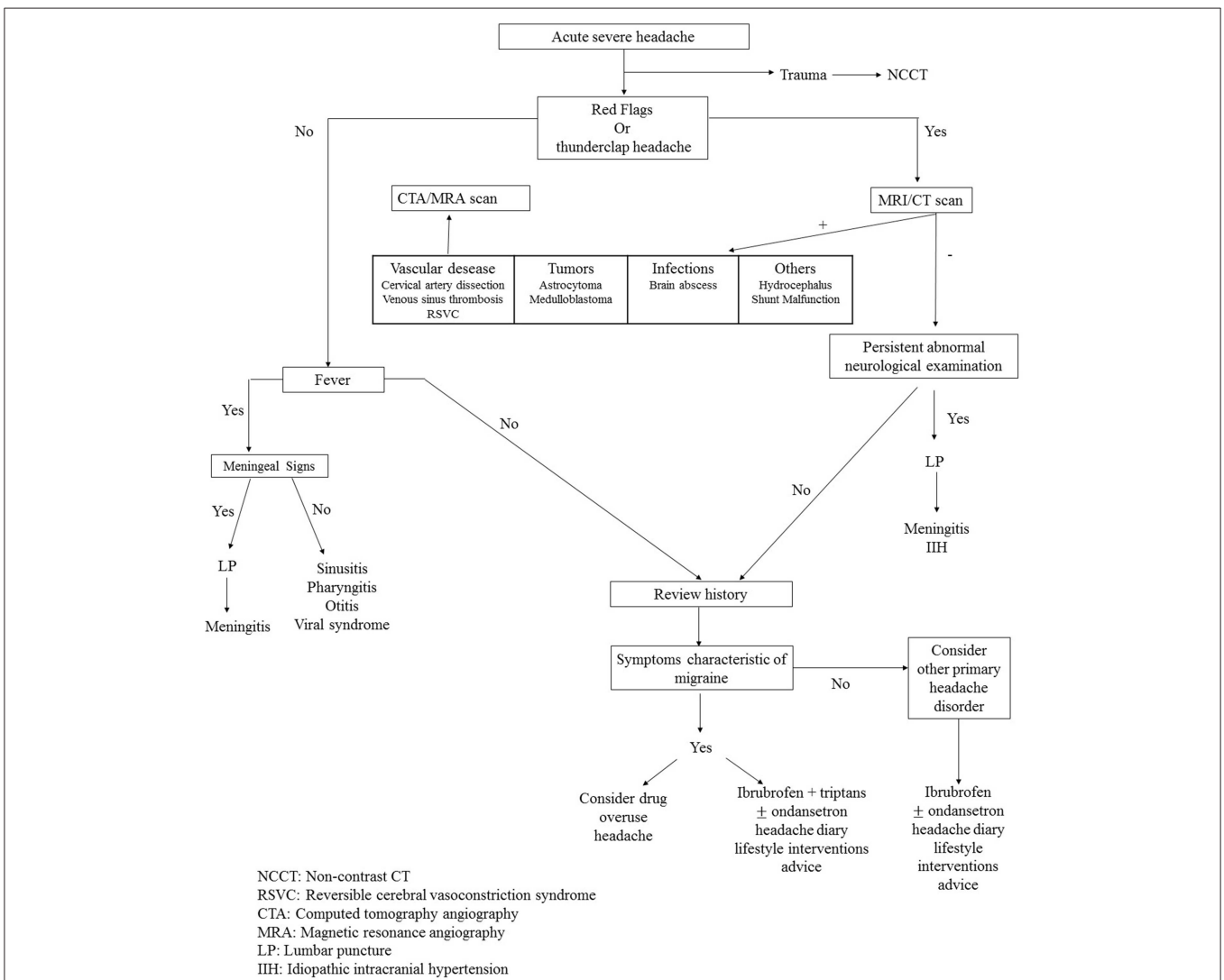

FIGURE 1 | Clinical pathway of pediatric patient with headache in emergency setting. NCCT, Non-contrast CT; RSVC, Reversible cerebral vasoconstriction syndrome; CTA, Computed tomography angiography; MRA, Magnetic resonance angiography; LP, Lumbar puncture; IIH, Idiopathic intracranial hypertension.

occupying lesions). A stepwise approach to pediatric headaches is essential to avoid missing secondary headaches and to promptly make the correct diagnosis. A complete history is paramount, including features of the headache and its characteristics, family and social history, and risk factors for systemic illness, as well as the symptoms or factors associated with the headache. A detailed physical and neurological examination, with attention to abnormalities that could be associated with a secondary cause of headache, is important for the subsequent diagnostic workup. Fundoscopic evaluation, in our opinion, should be part of the neurological examination of these patients and could be extremely useful in identifying doubtful cases. One must always search for red flags, distinguishing "high risk red flags" and "relatively red flags." Any "high risk red flag" should prompt neuroimaging while, in the case of "relatively red flags," a more restrained approach can be appropriate in the individual setting. Neuroimaging and other tests must be performed for positive findings on neurological evaluation or if there is concern for a secondary cause of headache in the history or physical examination. LP should be performed in case of suspected meningitis and it is diagnostic in the case of IIH. If ICHD-3 criteria for primary headache are not fulfilled, further investigations may be necessary. In patients with headache it is essential to treat the acute episode immediately according to evidence based medicine. When migraine is suspected, the administration of NSAIDs and triptans should be considered. In case of nausea and vomiting, antiemetic drugs and IV rehydration should be administered. Indications on lifestyle changes and a diary of headaches are useful in these patients. New symptoms and reactions to treatment should prompt review of the initial plan and appropriate changes.

In conclusion, we propose a clinical pathway for pediatric patients with headache in an emergency setting (**Figure 1**) that can guide the ED pediatrician in clinical practice.

AUTHOR CONTRIBUTIONS

UR, ND, and PP formulated the original idea and the design of the review and wrote the first draft of the manuscript. CO, MP, MV, and AR approved the design of the study. All authors reviewed, approved, and agreed to be accountable for all aspects of the work.

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NREM Sleep Instability in Pediatric Migraine Without Aura

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Children with migraine headaches appear to have a range of sleep disturbances. The aim of the present study was to assess the NREM sleep instability in a population of school-aged individuals affected by migraine without aura (MoA). Thirty-three children with MoA (20 males, 13 females, mean age 10.45 ± 2.06 years) underwent to overnight Polysomnographic (PSG) recordings and Cyclic Alternating Pattern (CAP) analyses accordingly with international criteria. MoA group showed a reduction in sleep duration parameters (TIB, SPT, TST; $p \leq 0.001$ for all) and in arousal index during REM sleep and an increase in awakenings per hour (AWK/h) vs. Controls (C) ($p = 0.008$). In particular, MoA children showed a reduced CAP rate% ($p \leq 0.001$), CAP rate% in S1 ($p \leq 0.001$) and CAP rate% in SWS ($p = 0.004$) vs. C. Moreover, A phases distribution were characterized by a reduction in slow wave components (total number CAP A1%, CAP A1 index) ($p \leq 0.001$) and an increase of fast components representation (total number of CAP A2% and CAP A3%) ($p < 0.001$) in MoA vs. C. Moreover, MoA children showed an increased A1 and A2 mean duration ($p \leq 0.001$). Our findings show a reduction of arousability in MoA group and lower NREM lower sleep instability associated with MoA in children.

Keywords: migraine without aura (MoA), NREM sleep instability, cyclic alternating pattern (CAP) analysis, sleep macrostructure, full overnight polysomnography

INTRODUCTION

Sleep and headache are widely related from a clinical point of view. The biological relationship between sleep and pain processing is not fully understood yet. Presently, a unique hypothesis about the mutual inter-relationship between sleep and primary headaches cannot be presented. In this picture, we can assume that various mechanisms may be responsible for the different clinical features observed in association with headache and sleep (1). However, the connection

between sleep disorders and primary headaches is clinically relevant since both conditions tend to establish mutual interrelationships that influence each other (2–4). In this context, the clinical observation raises questions regarding the pathogenesis of these disorders, involving pivotal cerebral structures (i.e., thalamus, hypothalamus, and some brainstem nuclei) and specific neurochemical pathways both in pain perception and sleep regulation.

The hypothalamus is crucial in both headache pathogenesis and sleep-wake cycle regulation because of its connection with the anti-nociceptive system [i.e., medulla oblongata, serotoninergic raphe nucleus, noradrenergic locus coeruleus, and periaqueductal gray matter (PAG)] the stimulation mediated by orexin on ventro-lateral part of PAG, and the inhibition on the anti-nociceptive activity in the caudal trigeminal nucleus (5–7).

In childhood, the most frequent primary headaches could be considered the migraine without aura (MoA) and tension-type headache with a prevalence of 2–17 and 0.9–24%, respectively (8, 9). Children with migraine headaches appear to have more frequent sleep troubles consisting in insufficient sleep, maternal co-sleeping, longer sleep latency, more bedtime resistance, shorter sleep duration, daytime sleepiness, night awakenings, sleep anxiety, parasomnias, and sleep-disordered breathing compared to children from a normative community sample (10).

To date, a limited number of polysomnographic studies carried out on patients with migraine, with no conclusive association about any peculiar characteristics of sleep architecture, although migraine attacks seem to be linked to REM stages and associated with a large amount of deep sleep (11). Moreover, Goder et al. (12) reported that migraine attacks were preceded by a significant decrease in arousals number, REM density, and in beta power band in the slow wave sleep, and by a decrease in alpha power during the first REM period. However, Vendrame et al. evidenced a high prevalence of sleep fragmentation (i.e., sleep disordered breathing, high rate of awakenings) in children with mild or severe migraine with an increasing related to the severity of symptoms (13, 14). In a PSG study Karthik et al. showed significantly lower sleep efficiency, prolonged sleep onset latency, lesser stage 4 and NREM sleep, and a greater number of total awakenings in migraineurs compared to the controls (15). In 2016, Nayak et al. showed a decreased REM arousability as well as a decreased overall CAP rate and CAP cycling in adult patients with migraine as compared to controls (16). In this perspective, we have hypothesized that the sleep parameters (such as macrostructure and microstructure) could be different in children affected by MoA respect of typical developing healthy comparisons (control subjects [C]). Therefore, the aim of the present study was to assess the NREM sleep instability in a population of school- aged individuals affected by MoA vs. C.

MATERIALS AND METHODS

Study Population

Thirty-three children affected by migraine without aura (MoA) (20 males, 13 females, mean age 10.4 ± 2.0 years) underwent to an overnight PSG recording, after one adaptation night to avoid the first-night effect in the Sleep Laboratory of Child and Adolescent Neuropsychiatry at the Università degli Studi della Campania "Luigi Vanvitelli", Campania Region, Italy. The diagnosis of migraine was made according to international criteria (17). None of those recruited children had taken prophylactic medication or neither any other regular medication for at least the 2 weeks prior to neither recruitment nor migraine attacks for 48 h at least before the study began.

Following recruitment, to verify the headache characteristics monthly headache frequency and mean headache duration was assessed from daily headache diaries kept by all the children. The headache intensity was assessed on a visual analog (VAS) scale. Exclusion criteria were neurological (i.e., epilepsy, neuromuscular disorders) or psychiatric symptoms (Attention Deficit Hyperactivity Disorder, anxiety, depression, behavior problems), mental retardation (IQ $\leq$70), borderline intellectual functioning (IQ ranging from 71 to 84), and referred signs suggestive for the presence of sleep-related breathing disorders (i.e., habitual snoring, nocturnal apneas), for periodic limb movement disorder (i.e., nocturnal hyperkinesias) and recurrent parasomnias (>3 episodes per week).

In order to compare the data from MoA children with a control group, 52 healthy children (C) (29 males, 23 females, mean age 9.9 ± 2.4 years) were enrolled from the Campania and Sicily regions schools. The subjects of both groups were recruited from the same urban area, were all of Caucasian origin and had middle socioeconomic status.

The investigation was carried out in accordance with the principles of the Declaration of Helsinki (18). All adult subjects provided written informed consent and a parent or guardian of any child participant provided written informed consent on their behalf. All procedures were performed in accordance with International guidelines and were approved by Scientific Committee of University of Palermo (n° 2015-001160-19).

Polysomnographic Evaluation (PSG)

Full overnight PSG recordings were performed according to international criteria (19–21), started at the subject's usual bedtime and continued until spontaneous morning awakening. The PSG scoring was visually analyzed by means of Hypnolab 1.2 sleep software analysis (SWS Soft, Italy) and the following conventional sleep parameters were evaluated:

1) Time in bed (TIB);
2) Sleep period time (SPT);
3) Total sleep time (TST);
4) Sleep latency (SL);
5) First REM latency (FRL);
6) Number of stage shifts/hour (SS/h); Number of awakenings/hour (AWN/h);
7) Sleep efficiency (SE%);
8) Percentage of SPT spent in wakefulness after sleep onset (WASO%);
9) Percentage of SPT spent in sleep stages 1 (N1%), 2 (N2%), slow-wave sleep (N3%), and REM sleep (REM%).

Moreover, the Arousal Index during the REM sleep was calculated.

About respiratory parameters, central, obstructive and hypopnea events were counted according to the standard criteria (22) considering as abnormal an Apnea/Hypopnea index (AHI) >1 (23). Moreover, periodic limb movements (PLMs) events were identified (24) and a PLMI≥5 was considered abnormal.

Cyclic Alternating Pattern (CAP) Analysis

CAP was scored following the standard criteria defined by Terzano et al. (25). CAP A phases have been subdivided into a 3-stage hierarchy of arousal strength: A1 is defined as the A phase with synchronized EEG patterns (intermittent alpha rhythm in stage 1 and sequences of K complexes or delta bursts in the other NREM stages) associated with mild or trivial polygraphic variations; A2 is defined as the A phase with desynchronized EEG patterns preceded by or mixed with slow high-voltage waves (K complexes with alpha and beta activities, K alpha, and arousals with slow-wave synchronization) linked to a moderate increase of muscle tone and/or cardiorespiratory rate; and A3 as the A phase with desynchronized EEG patterns alone (transient activation phases or arousals) or exceeding two thirds of the phase A length and coupled with a remarkable enhancement of muscle tone and/or cardiorespiratory rate (25).

The following CAP parameters were measured:

- CAP time (temporal sum of all CAP sequences) in NREM sleep;
- The CAP rate (percentage of total NREM sleep time occupied by CAP sequences);
- The number and duration of CAP cycles; the number and duration of CAP sequences;
- The number, duration, and percentage of A phases (including the phase A subtypes);
- A1 index (number of A1 phases per hour of NREM sleep);
- A2 index (number of A2 phases per hour of NREM sleep);
- A3 index (number of A3 phases per hour of NREM sleep);
- and the number and duration of B phases.

Statistical Analysis

The comparisons between sleep architecture and CAP parameters, obtained in MoA children and typically developing children (C), were carried out by the Mann–Whitney *U* test. Bonferroni correction was applied. *P*-values <0.01 were considered statistically significant. STATISTICA (data analysis software system), version 6, StatSoft, Inc. (2001) was used for all statistical tests.

RESULTS

The two groups (MoA and C) were matched for age, sex, and z-score Body Mass Index (z- BMI) (**Table 1**). The migraine characteristics such as frequency, intensity and duration of attacks were showed in **Table 1**. None of the children with migraine in our series were affected by a migraine attack during the sleep study.

As for the macrostructural findings, MoA group showed significant reduction in sleep duration parameters (TIB, SPT, TST; $p \leq 0.001$ for all) and a significant increase in awakenings per hours (AWK/h) vs. C ($p = 0.008$; **Table 2**). Moreover, the Arousal Index during REM sleep was lower in MoA vs. C children ($p < 0.001$; **Table 2**).

TABLE 1 | The comparison between migraine without aura (MoA) and typically developing children (Control) groups in age, sex distribution, and *z*-score Body Mass Index (z-BMI).

	MoA (*N* = 33)	Control (*N* = 52)	*p*
Age	10.45 ± 2.06	9.98 ± 2.42	0.355
Sex (M/F)	20/13	29/23	0.830
z-BMI	0.43 ± 0.51	0.59 ± 0.41	0.115
Frequency (attacks/month)	9.18 ± 2.84	–	–
Duration (h)	6.39 ± 2.56	–	–
Intensity (VAS)	7.45 ± 2.39	–	–

The frequency, duration, and intensity (assessed with Visuo-analogic Scale, VAS) of migraine attacks were described for MoA group. The t-Test and the Chi-square test, when appropriated, were applied. p values <0.05 were considered statistically significant.

As for the NREM sleep analysis, MoA children showed a reducing in CAP rate% ($p \leq 0.001$), CAP rate% in N1 ($p \leq 0.001$) and in CAP rate% in SWS ($p = 0.004$) vs. C. Moreover, the A phases distribution were characterized by significant reduction in slow wave components (Total number CAP A1%, CAP A1 index) ($p \leq 0.001$) and an increasing in fast components representation (Total number of CAP A2% and CAP A3%) in comparison to C. MoA children show also an increased A1 and A2 mean duration ($p \leq 0.001$; **Table 3**) in comparison to the healthy control group (C).

DISCUSSION

Several reports in the medical literature suggest the existence of a correlation and/or comorbidity between sleep disorders and headache linked to putative common pathophysiological substrates. In general, it has well-known that specific headache disorders, like paroxysmal hemicrania, cluster headache, and hypnic headache may be related to the rapid eye movement sleep (REM) or to obstructive sleep apnea syndrome (OSAS) (4). The details of the relationship mutual relationship between headache and sleep regulation are not still clearly understood, but it is known that sleep may be related to the occurrence of some headache syndromes while headache could cause or sustain various degrees of sleep disturbance (i.e., parasomnias, sleep disordered breathing, sleep-wake transition disorders). To date, in pediatric populations few studies seem to indicate a suggestive association between headaches and sleep disturbances, including primary snoring, obstructive sleep apnea, and NREM parasomnias although these data are mainly derived from questionnaire-based studies (8, 26–30).

On the other hand, clinical, and experimental data indicate that the thalamus may be considered as the key structure for migraine pathophysiology. EEG studies have shown that interictal migraine have low thalamo/thalamocortical

TABLE 2 | Polysomnographic sleep macrostructure findings in MoA and normal control group.

	MoA control				Mann-Whitney *U*-Test	
	N = 33		*N* = 52			
	Mean	Std.Dev.	Mean	Std.Dev.	*U*	*p**
TIB-min	473.697	46.459	588.933	88.132	185.0000	0.000
SPT-min	446.076	47.033	557.462	83.305	186.0000	0.000
TST-min	397.712	70.858	529.356	78.345	159.0000	0.000
SOL-min	15.470	13.070	21.288	17.928	658.5000	NS
FRL-min	143.727	58.193	124.423	50.707	695.0000	NS
SS-h	9.242	2.700	8.756	3.490	787.5000	NS
AWN-h	4.088	2.615	2.137	1.826	472.5000	0.008
SE%	83.888	12.056	90.058	5.205	647.5000	NS
WASO%	11.058	11.485	4.910	4.303	620.5000	NS
N1%	2.333	2.266	2.800	3.543	843.0000	NS
N2%	36.200	9.286	43.269	24.558	667.0000	NS
N3%	34.015	10.684	31.194	9.466	759.0000	NS
REM%	16.361	7.217	21.200	5.338	526.0000	NS
AHI	0.561	0.240	0.658	0.211	649.0000	NS
ODI	0.592	0.174	0.587	0.148	834.5000	NS
PLM%	2.970	1.088	2.748	0.889	769.5000	NS
REM arousal index	6.606	2.164	13.269	2.657	44.5000	0.000

*Differences evaluated with the Mann-Whitney-U test, among children affected by migraine without aura (MoA) and control group in the following parameters: TIB, Time in bed (in minutes); SPT, Sleep period time (in minutes); TST, Total sleep time (in minutes); SOL, Sleep onset latency (in minutes); SS/h, Stage shifts per hour; AWN/h, Awakenings per hour; SE%, Sleep efficiency percentage; WASO% percentage, Wakefulness after sleep onset percentage; S1 and S2%, Sleep stages N1 and N2 percentages; N3%, Slow-wave sleep percentage; REM%, Rapid eye movement sleep percentage; AHI, Apnea/Hypopnea Index; ODI, Oxygen Desaturation Index; PLM, Periodic Limb Movements; R arousal Index (REM arousal index). NS means not significant. p values <0.01 were considered as significant. *Bonferroni-corrected value.*

TABLE 3 | The mean differences, evaluated with the Mann-Whitney-*U* test, among children affected by migraine without aura (MoA) and control group in the following parameters: CAP refers to cyclic alternating pattern; CAP rate (percentage of total NREM sleep time occupied by CAP sequences); percentage and duration of each A phase subtype; A1 index (number of phases A1 per hour of NREM sleep, and of N1, N2, and N3 sleep stage); A2 index (number of phases A2 per hour of NREM sleep, and of N1, N2, and N3 sleep stage); A3 index (number of phases A3 per hour of NREM sleep, and of N1, N2, and N3 sleep stage); duration of B phases; number and duration of CAP sequences.

	MoA		Control		Mann-Whitney *U*-Test	
	N = 33		*N* = 52			
	Mean	Std.Dev.	Mean	Std.Dev.	*U*	*p**
CAP_Rate%	26.539	12.506	34.346	6.496	423.0000	0.001
CAP_Rate%N1	5.817	18.501	19.877	18.025	256.0000	0.000
CAP_Rate%N2	21.197	11.414	28.288	10.519	521.5000	NS
CAP_Rate%N3	35.785	18.298	47.548	7.043	452.0000	0.004
Tot_num_A1%	47.224	21.804	79.233	11.871	135.5000	0.000
Tot_num_A2%	36.612	19.302	13.087	12.124	154.0000	0.000
Tot_num_A3%	16.594	9.725	7.683	3.236	287.0000	0.000
A1_mean_dur	13.600	4.463	5.312	1.632	39.0000	0.000
A2_mean_dur	18.079	6.269	8.923	2.632	259.5000	0.000
A3_mean_dur	13.342	3.714	15.981	6.598	684.5000	NS
A1_index	14.776	9.607	40.779	10.005	50.0000	0.000
A2_index	11.521	10.327	7.063	6.324	607.5000	NS
A3_index	4.288	3.811	3.535	2.943	739.0000	NS
B_mean_dur	22.715	4.412	22.237	4.066	784.0000	NS
Cycle_mean_dur	38.024	6.347	28.673	4.881	245.0000	0.000
Seq_mean_dur	211.852	82.054	202.685	50.890	806.0000	NS
Num_of_seq	23.939	6.413	39.981	9.407	107.5000	0.000

p values <0.01 were considered as significant.
NS means not significant.
**Bonferroni-corrected value.*

transmission associated with low brainstem activation (31). In this picture, we could explain the low arousal index during REM sleep reported in children affected by MoA respect of healthy controls.

Moreover, some reports have showed that children affected by migraine may exhibit disrupted sleep architecture, such as abnormalities in total sleep time (TST) and sleep latency (SOL) compared with healthy control subjects (30). Conversely, the previous PSG study by Vendrame et al. (13) showed an important alteration/disruption in sleep in children affected by migraine and chronic migraine linked to the presence of sleep-disordered breathing, shortened TST, and high SOL, even if no healthy controls were used for comparisons.

About these alterations in TST and SOL, the Authors suggested that because some children may find relief from migraine attacks with daytime naps (or the sleep could be useful to stop the attacks), the attacks occurred during the daytime may impact the normal sleep-wake cycle (32). The severity and frequency of headache attacks may negatively affect sleep architecture provoking sleep disruptions and REM sleep percentages, as confirmed in adult subjects with migraine (33). Moreover, in adults, the reduction in REM sleep and number of arousals during REM was reported during the night preceding the migraine (34), and in this perspective a shorter sleep latency during the night before a migraine attack was observed also in children, suggesting a sort of decreasing in cortical activation the night before the onset of headache (35, 36).

Our findings seem to partially confirm some of the results reported previously such as the reduction in TST and SPT, but not in SOL and stages percentages, which in our sample, were not significantly different from healthy controls. As for the sleep disruption, our results seem to confirm the observation that children with migraine tend to show a higher rate of awakenings per hour respect of controls.

As for the NREM sleep instability analysis, the main finding of our study was the reduction in CAP rate percentage and also in N1 and N3. In our population, the CAP A1 representation was reduced in the total number and index, but with a prolonged duration than controls, and the CAP A2 and CAP A3 higher in the total number, and the CAP A2 with a longer duration in MoA vs. C. Our results are substantially in line with the data found in the study conducted in 2016 by Nayak et al. (16) on a sample of adults with MoA. In their findings the overall CAP rate, the number

of CAP cycles and phase B duration was lower among migraineurs while the total phase A and phase 1 duration were increased.

Moreover, our findings confirm the reduction in CAP rate evidenced by Della Marca et al. in adults with frequent MoA (37). From this point of view, the reduction in oscillatory components during sleep in our sample could be reflecting a general hypoactivity of the arousal systems. Each of these systems has ascending projections to the cortex (which stimulate cortical activation and induce fast EEG activity) and descending projections to the spinal cord (which stimulate motor activation and induce high EMG activity) (38) and are located within the brainstem, the thalamus, the hypothalamus, and the basal forebrain (39). These areas could be considered actually as the generators of the migraine attacks (40, 41).

In our sample the CAP reduction involved prevalently the A1 phases subtypes, less so the high-frequency EEG arousals. One main role of CAP A1 fluctuations is to buffer the effect of perturbations occurring during NREM sleep (37). It can therefore be speculated that the reduction of CAP expresses a reduced efficacy of such mechanisms of processing of incoming inputs during sleep in migraine. Finally, we have to consider that to the best our knowledge, this is the first attempt to evaluate NREM instability and CAP parameters in children affected by migraine without aura compared with a control group.

In conclusion, the reduction of arousability and lower NREM sleep instability seem to be associated with MoA in children. These findings may have clinical implications. However, further studies are needed for a better comprehension of the pathophysiological mechanisms underlying the link between migraine and NREM sleep and to investigate possible consequent clinical implications and preventive treatments.

ETHICS STATEMENT

The investigation was carried out in accordance with the principles of the Declaration of Helsinki (18). The Departmental Ethics Committee approved the study. Ethics committee protocol and approval was not considered as necessary, because the evaluation done is part of the clinical routine normally performed for children and adolescents in our Unit referred for migraine without aura.

AUTHOR CONTRIBUTIONS

MR, RM, FO, DS, FP, IB, GM, DI, and MC: substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MR, RM, FO, DS, FP, IB, GM, BG, ME, FS, GD, CL, MS, VR, PM, DI, and MC: drafting the work or revising it critically for important intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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First Attack and Clinical Presentation of Hemiplegic Migraine in Pediatric Age: A Multicenter Retrospective Study and Literature Review

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Background: Data on clinical presentation of Hemiplegic Migraine (HM) are quite limited in the literature, particularly in the pediatric age. The aim of the present study is to describe in detail the phenotypic features at onset and during the first years of disease of sporadic (SHM) and familial (FHM) pediatric hemiplegic migraine and to review the pertinent literature.

Results: Retrospective study of a cohort of children and adolescents diagnosed with hemiplegic migraine, recruited from 11 Italian specialized Juvenile Headache Centers. Forty-six cases (24 females) were collected and divided in two subgroups: 32 SHM (16 females), 14 FHM (8 females). Mean age at onset was 10.5 ± 3.8 y (range: 2–16 y). Mean duration of motor aura was 3.5 h (range: 5 min−48 h). SHM cases experienced more prolonged attacks than FHM cases, with significantly longer duration of both motor aura and of total HM attack. Sensory (65%) and basilar-type auras (63%) were frequently associated to the motor aura, without significant differences between SHM and FHM. At follow-up (mean duration 4.4 years) the mean frequency of attacks was 2.2 per year in the first year after disease onset, higher in FHM than in SHM cases (3.9 vs. 1.5 per year, respectively). A literature review retrieved seven studies, all but one were based on mixed adults and children cohorts.

Conclusions: This study represents the first Italian pediatric series of HM ever reported, including both FHM and SHM patients. Our cohort highlights that in the pediatric HM has

an heterogeneous clinical onset. Children present fewer non-motor auras as compared to adults and in some cases the first attack is preceded by transient neurological signs and symptoms in early childhood. In SHM cases, attacks were less frequent but more severe and prolonged, while FHM patients had less intense but more frequent attacks and a longer phase of active disease. Differently from previous studies, the majority of our cases, even with early onset and severe attacks, had a favorable clinical evolution.

Keywords: hemiplegic migraine, FHM, SHM, children, adolescents

BACKGROUND

Hemiplegic migraine (HM) is a rare form of migraine with aura characterized by transient motor weakness or hemiparesis (motor aura), associated with other non-motor aura symptoms (visual, sensory, aphasic, or basilar-type/brainstem symptoms) accompanied by headache, nausea, vomiting, photophobia, or phonophobia, as occurs in migraine (1). The presence of motor deficits represents the peculiarity of HM compared to other forms of migraine with aura and its diagnostic criteria have been recently revised (ICHD-III, 2018) (2). HM can be sporadic (SHM) or familial (FHM) with autosomal dominant inheritance (1). Three genes have been classically associated with the disease: *CACNA1A, ATP1A2*, and *SCN1A* (1). HM can also be part of the phenotypic manifestations associated with *PRRT2* gene mutations, but *PRRT2* most likely acts as a disease-modifying gene within the context of complex polygenic rather than autosomal dominant disease (3).

The onset of disease is typically in the second decade of life, but it can occur in people aged 1–45 (1). Most of the series available in literature include both pediatric and adult HM cases (4–7) and in these works the pediatric data cannot be extrapolated; series reporting exclusively pediatric cases are very limited (8).

Information on first hemiplegic attack, trigger factors, associated symptoms, duration, and frequency of the attacks and time courses of the disease are lacking, especially in pediatric cases.

AIM OF THE STUDY

The present study describes a large multicenter Italian pediatric cohort of HM in order to refine the clinical phenotype at disease onset and the disease course in children and adolescents affected by HM, through in-depth analysis of personal data and literature review.

Abbreviations: ATP1A2, ATPase Na+/K+ transporting subunit alpha 2; CACNA1A, calcium voltage-gated channel subunit alpha1 A; CT, computed tomography; FHM, familial hemiplegic migraine; HM, Hemiplegic migraine; ICHD-III, International Classification of Headache Disorders, third edition; MRI, magnetic resonance imaging; PRRT2, proline rich transmembrane protein 2; SCN1A, sodium voltage-gated channel alpha subunit 1; SHM, sporadic hemiplegic migraine.

METHODS

Subjects

This was a retrospective study of a cohort of all children and adolescents diagnosed with HM according to the ICHD-III criteria (2), recruited from 11 Italian specialized Juvenile Headache Centers.

The study included all children and adolescents meeting the following entry criteria:

(1) diagnosis of HM (according to the ICHD-III criteria) (2);
(2) onset of HM before 16 years of age.

The Headache Centers shared clinical criteria and methods related to the study. All the physicians who took part to the study have a consolidated clinical experience in the diagnosis of HM according to the ICHD-III criteria (2) and in its management.

An *ad-hoc* clinical report form was fulfilled for each patient, based on clinical documentation (such as emergency care records, neurological examination records at first visit and during follow-up).

Cases with uncertain diagnosis or incomplete clinical data were excluded.

Clinical Data

The following clinical data we collected: demographic data, family history for headache or epilepsy, information on first HM attack (including trigger factors, prodromal phase, duration and types of aura, associated signs and symptoms, features and duration of headache, time to complete recovery), personal history for other types of headache or epilepsy, neurological examination in the acute phase and during follow-up, instrumental investigations, genetic tests, symptomatic, and preventive pharmacological therapies of HM.

In our study "total duration of the attack" refers to the duration of the aura symptoms and the headache phase, while "total recovery" represents the time needed to fully return to the condition before the attack onset.

Patients were divided into two subgroups based on the HM family history (SHM or FHM). Clinical data were collected in a database by the leading Center (Padua). The patients' records were handed with respect of confidentiality, and the study protocol was approved by the Institutional Review Board of the Department of Woman's and Child's Health of Padua. The study was conducted according to good clinical practice recommendations of the local Ethics Committee.

Literature Review

For this update we searched the Pubmed database from the first available paper up to date 1st September 2018. The following search keys were applied: "hemiplegic migraine," "FHM," "SHM," or "HM series."

The filter was set to English publications.

Three authors (FB, IT, VM) screened all abstracts and full texts available and searched manually for relevant articles. Within the available articles, we searched for adult and pediatric series of HM cases describing clinical and genetic features of patients. Works based on at least 10 cases of HM were selected.

The following exclusion criteria were applied: (1) series formed by <10 patients; (2) series in which clinical features of patients were not available; (3) studies which described clinical and genetic features of one or few (<5) families with FHM.

Genetic and clinical data acquired from each study were reported in **Tables F1–F3**, **S1–S3**, **M1–M3**. FHM series (**Tables F1–F3**), SHM series (**Tables S1–S3**), and mixed (FHM+SHM) series (**Tables M1–M3**) were treated separately.

From each study we searched and reported the following data if available: gender, age of HM onset, clinical features of HM attacks at onset and during follow-up (trigger factors, duration of motor aura, characteristics of non-motor aura), frequency and severity of HM attacks and other associated neurological manifestations, genetic tests.

Statistical Analysis

Data collected were analyzed through simple descriptive, bivariate and multivariate analysis. Quantitative variables were summarized by performing continuous descriptive analysis: mean, median, standard deviation, minimum value, and maximum value. If the variables were not normally distributed, location was analyzed by calculating median, first quartile, third quartile. Categorical variables were described by means of absolute and relative frequencies. Where applicable, Chi square test and Fisher exact test were applied to prove a statistical significance of the difference between the frequencies, while the significance of the difference between mean values was evaluated by one-way analysis of variance. Simple and multivariate logistic regression models were applied to assess efficacy and tolerability of the pharmacological and non-pharmacological therapies in relation to type of headache, gender, and age.

In all the tests performed, the level of significance was set at 0.05. The statistical analysis was performed by means of SAS versions 9.13 (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS

General Characteristics of the Study Population

The most relevant general clinical data have been summarized in **Table 1** considering the entire population and patients divided in the two subgroups (SHM and FHM).

The study population included 46 patients (females $n = 24$, 52%) with pediatric HM. 32/46 (70%) cases were diagnosed as SHM (females $n = 16$, 50%), and 14/46 (32%) cases were diagnosed as FHM (females $n = 8$, 57%). The mean age at first HM attack was similar in both subgroups (SHM 10.7 ± 3.7 y, range 2–16 y vs. FHM 10.2 ± 4.2 y, range 4–15 y; $p =$ n.s). 10/46 (22%) cases had the first HM attack before age 6 (SHM 6/32, 19% vs. FHM 4/14, 29%; $p = 0.46$) (**Table 1**).

Concerning the personal history for other types of migraine, migraine with non-motor aura prevailed in SHM than in FMH cases (SHM 5/32, 16% vs. FHM 0/14, 0%) while migraine without aura was less frequent in SHM than in FHM cases (SHM 8/32, 25% vs. FHM 5/14, 36%). The personal history for febrile convulsive seizures was similar among the two groups (SHM 4/32, 13% vs. FHM 1/14, 7%). One FHM case had a past history of benign myoclonic epilepsy. One SHM patient had a neurological disorder prior to the onset of HM attacks (congenital cerebellar ataxia with bilateral atrophy); this patient, previously described (7), carried a missense mutation c.4013C>T of *CACNA1A* gene.

A higher proportion of SHM patients had a positive family history for migraine (SHM 50% vs. FHM 33%; $p = 0.33$), while a positive family history for epilepsy was more common in FHM cases (SHM 6% vs. FHM 20%; $p = 0.23$) (**Table 1**).

Genetic tests for HM were performed overall in 24/46 (52%) cases (**Table 1**). Molecular analysis of *CACNA1A*, performed overall in 15/46 cases, revealed a pathogenic mutation in 5/13 (38%) SHM and in 0/2 (0%) FHM patients. The *ATP1A2* analysis, performed in 13/46 cases, was positive in 4/7 (57%) SHM and in 5/6 (83%) FHM patients. Mutation in the *SCN1A* gene was found in one SHM case, while mutation in the *PRRT2* gene was found in one FHM case (**Table 1**).

The First HM Attack

The features of the first HM attack of all patients have been summarized in **Table 2**.

Trigger Factors

21/46 (46%) patients reported at least one trigger factor at the first HM attack (SHM 44% vs. FHM 50%) (**Table 2**). Emotional stress was the most common trigger factor, reported overall by 43% of patients, without significant differences between SHM and FHM subgroups. Head trauma (SHM 21% vs. FHM 29%) and intense physical effort (SHM 21% vs. FHM 14%) were the other major trigger factors. Fever, viral infections or excessive use of video games were reported in some cases (**Table 2**).

Non-motor Auras

40/46 (87%) cases experienced at least one non-motor aura associated to the motor deficit in the first HM attack, without significant differences between SHM and FHM subgroups; different types of non-motor aura were more frequently reported by FHM than SHM patients (**Table 2**).

Sensory aura was the most frequent type of non-motor aura (65%), followed by basilar-type/brainstem (63%), and visual (35%) auras. All these three aura types prevailed in FHM patients. On the other side, aphasic aura was slightly more common in the SHM subgroup (11% vs. FHM 8%) (**Table 2**).

Duration of HM Attack

The mean duration of motor aura was significantly longer in SHM subgroup (4.8 h vs. FHM 27.7 min; $p < 0.01$) as well as

TABLE 1 | Characteristics of the study population.

Population characteristics		TOT (*N* = 46)	SHM (*N* = 32)	FHM (*N* = 14)	*p*
Sex, F: M (%)		24 (52%): 22 (48%)	16 (50%): 16 (50%)	8 (57%): 6 (43%)	–
Age at onset y, mean ± SD (range)		10.5 ± 3.8 (2–16)	10.7 ± 3.7 (2–16)	10.2 y ± 4.2 (4–15)	–
	≤6 y	10 (22%)	6 (19%)	4 (29%)	0.46*
	7–12 y	18 (39%)	13 (41%)	5 (36%)	–
	13–18 y	18 (39%)	13 (41%)	5 (36%)	–
Genetics					
CACNA1A	(*n* = 15)	5/15 (33%)	5/13 (38%)	0/2f (0%)	0.52*
ATP1A2	(*n* = 13)	9/13 (69%)	4/7 (57%)	2/3f (5/6) (66%)	–
SCN1A	(*n* = 1)	1/1 (100%)	1/1 (100%)	–	–
PRRT2	(*n* = 2)	1/2 (50%)	0/1 (0)	1/1f (100%)	–
Family history		7/46 (15%)	2/32 (6%)	2/10f (4/14) (20%)	0.23*
Epilepsy					
Migraine°		21/46 (46%)	16/32 (50%)	3/10f (5/14) (33%)	0.30*
Other neurological manifestations					
Tension-type headache		7/46 (15%)	3/32 (9%)	4/14 (29%)	0.54*
Migraine with typical aura		5/46 (11%)	5/32 (16%)	0/14 (0%)	0.30*
Migraine without aura		13/46 (28%)	8/32 (25%)	5/14 (36%)	0.49*
Febrile seizures		5/46 (11%)	4/32 (13%)	1/14 (7%)	–
Epilepsy		2/46 (4%)	1/32 (3%)	1/14 (7%)	0.52*
Cerebellar ataxia		1/46 (2%)	1/32 (3%)	0/14 (0%)	0.23*
Intellectual disability		4/35 (11%)	3/23 (13%)	1/12 (8%)	–

*F, females; M, males; f, families: as it concerned genetic data and family history we considered families instead of single patients in FHM subgroups; SD, standard deviation; y, year; –, p > 0.99; °migraine with non-motor aura or without aura; *significance level obtained by Fisher exact test.*

the mean headache duration (17 h vs. FHM 5.6 h; $p = 0.02$). The mean total duration of the HM attack was over three times longer in SHM than FHM patients (19.6 h vs. 6 h, respectively; $p < 0.01$) (**Table 2**).

Associated Signs and Symptoms

29/46 (63%) patients presented other signs and symptoms associated with the HM attack, more commonly in SHM (23/32, 72%) than FHM patients (6/14, 43%; $p = 0.06$). Vigilance loss (SHM 26% vs. FHM 66%) and drowsiness (SHM 22% vs. FHM 33%) tended to prevail in FHM patients, but without significant differences probably due to sampling number. Irritability associated to episodes of psychomotor agitation and fever were reported only by SHM patients (39 and 30%, respectively) (**Table 2**).

Prolonged Attack

3/34 (9%) patients had a prolonged HM attack lasting at least 72 h as well as a prolonged motor aura (longer than 6 h) and they were all SHM. Two patients had prolonged aphasia (longer than 6 h) and they all were FHM (**Table 2**).

Follow-Up

The most interesting data obtained at follow-up have been summarized in **Table 3**.

Mean duration of follow-up was 4.4 years in the overall population and was longer in FHM patients (7.6 y vs. SHM 3 y; $p = 0.04$).

In the first year after disease onset, the mean number of HM attacks was 1.5 in SHM patients, and 3.9 in FHM patients ($p = 0.14$) (**Table 3**). Since the second year of disease, mean frequency of attacks was 1–2 every year without significant differences within the two subgroups (SHM 17% vs. FHM 21%; $p = 0.99$). At last follow-up, freedom from attacks in the previous 3 years was reported in 9/19 (47%) SHM patients and in 4/12 (33%) FHM cases (p = n.s.).

Similar to the first HM attack, even during the follow-up prolonged attacks were experienced only by SHM patients (3/32, 9% vs. FHM 0/14, 0%; $p = 0.54$) (**Table 3**).

Neurologic examination at follow-up was abnormal in 3 SHM (2/3 clumsiness, 1/3 hemiparesis), and in 2 FHM patients (1/2 cerebellar ataxia, 1/2 clumsiness).

Cognitive and neuropsychological evaluation was available for 35 patients (23/32 SHM and 12/14 FHM). Among the 23 SHM patients tested, three had mild intellectual disability, one expressive language disorder, one praxis difficulties, and one dyslexia. Among the 12 FHM patients tested the following problems were detected: moderate intellectual disability (1/12), praxis difficulties (1/12), and low sustained attention (1/12).

Preventive drugs (in particular flunarizine and topiramate) were used overall by 9/46 (20%) patients (SHM 5/32, 16% vs. FHM 4/14, 28%).

All patients underwent neuroimaging testing during acute or post-acute phase (CT or MRI); 6 out of 46 cases (13%) showed cortical unilateral (or partial) cytotoxic edema. Two *CACNA1A* mutated patients showed cerebellar atrophy signs (1/2

TABLE 2 | Features of the first HM attack in the study population.

First HM attack		TOT (*N* = 46)	SHM (*N* = 32)	FHM (*N* = 14)	*p*
Trigger factors *at least one trigger*		21/46 (46%)	14/32 (44%)	7/14 (50%)	–
Emotional stress		9/21 (43%)	6/14 (43%)	3/7 (43%)	
Head trauma		5/21 (24%)	3/14 (21%)	2/7 (29%)	
Physical effort		4/21 (19%)	3/14 (21%)	1/7 (14%)	
Fever		1/21 (5%)	1/14 (7%)	0/7 (0%)	
Others		2/21 (10%)	1/14 (8%, videogames)	1/7 (14%, viral infection)	
Type of non-motor aura					
At least one type		40/46 (87%)	28/32 (88%)	12/14 (86%)	–
Visual		14/40 (35%)	8/28 (29%)	6/12 (50%)	0.30*
Sensory		26/40 (65%)	16/28 (57%)	10/12 (83%)	0.16*
Aphasic		4/40 (10%)	3/28 (11%)	1/12 (8%)	–
Basilar-type (dysarthria, vertigo, etc.)		25/40 (63%)	16/28 (57%)	9/12 (75%)	0.48*
Number of type simultaneously	0	6/46 (13%)	4/32 (13%)	2/14 (14%)	–
	1	17/46 (37%)	15/32 (47%)	2/14 (14%)	**0.05***
	2	17/46 (37%)	11/32 (34%)	6/14 (43%)	0.74*
	3	6/46 (13%)	2/32 (6%)	4/14 (29%)	0.06*
Duration of motor aura, m or h, mean ± SD (range)		3.5 h ± 8.7 h (5 m–48 h)	4.8 h ± 10.1 h (5 m–48 h)	27.7 m ± 22.7 m (5 m–90 m)	**0.001****
Duration of headache, m or h, mean ± SD (range)		13.7 h ± 17 h (10 m–48 h)	17.0 h ± 18.3 h (20 m–48 h)	5.6 h ± 9.2 h (10 m–24 h)	**0.02****
Total duration of HM attack°, m or h, mean ± SD (range)		15.8 h ± 18.9 h (30 m–48 h)	19.6 h ± 20.5 h (40 m–48 h)	6 h ± 8.9 h (30 m–24 h)	**0.007****
Signs and symptoms associated					
At least one sign or symptom		29/46(63%)	23/32 (72%)	6/14 (43%)	0.06
Irritability-agitation		9/29 (31%)	9/23 (39%)	0/6 (0%)	0.14*
Drowsiness		7/29 (24%)	5/23 (22%)	2/6 (33%)	0.61*
Vigilance loss		10/29 (34%)	6/23 (26%)	4/6 (66%)	0.14*
Fever		7/29 (24%)	7/23 (30%)	0/6 (0%)	0.29*
Seizures		1/29 (3%)	1/23 (4%)	0/6 (0%)	–
Others		3/29 (10%)	3/23 (13%: vomiting, amnesia)	0/6 (0%)	–
Number of signs/symptoms simultaneously	0	17/46 (37%)	9/32 (28%)	8/14 (57%)	0.06*
	1	21/46 (46%)	15/32 (47%)	6/14 (43%)	–
	>2	8/46 (17%)	8/32 (25%)	0/14 (0%)	0.08*
Prolonged attack					
Total recovery°° >72 h		3/34 (9%)	3/25 (12%)	0/9 (0%)	0.55*
Hemiplegia >6 h		3/38 (8%)	3/26 (12%)	0/12 (0%)	0.54*
Aphasia >6 h		2/38 (5%)	0/26 (0%)	2/12 (17%)	0.09*

*m, minutes, h, hours; *significance level obtained by Fisher exact test; **significance level obtained by Wilcoxon rank sum non-parametric test; –, p > 0.99; °total duration of HM attack refers to the duration of the aura symptoms and the headache phase; °°total recovery represents the time needed to fully return to the condition before the attack onset.*

pancerebellar atrophy with clinical signs of congenital ataxia, 1/2 hypoplasia of superior vermis folia with no clinical signs). Electroencephalogram showed asymmetrical slow-wave activity in 19/29 patients (66%), during or soon after HM attacks.

Literature Review

A review of the literature retrieved seven studies (3–9) investigating HM series and addressing clinical characteristics (3–9), correlation with genetics (6–11) and features of the HM attacks (4–7). The most interesting results have been summarized in **Tables F1–F3** (FHM series), **S1–S3** (SHM series), **M1–M3** (mixed FHM and SHM series). Any additional selection criteria or clarification about data collection or analysis, concerning each study included in the review, has been highlighted in each table.

All studies but one were based on mixed adults and children cohorts, without a systematic stratification of results by age. The study by Riant et al. (8) reported a cohort of children and adolescents with SHM.

We underline that in all previous studies information about the features of HM attack refers to the "typical HM attack" among the pool of HM attacks experienced by each patient during his/her entire lifespan, while our study provides information specifically on the first HM attack.

TABLE 3 | Characteristics of the study population during follow-up.

Follow-up			TOT (*N* = 44)	SHM (*N* = 30)	FHM (*N* = 14)	*p*
Age at follow-up y, mean ± SD (range)			14.9 ± 6.7 (6–47)	13.9 ± 4.3 (6–27)	17.3 ± 10.5 (6–47)	0.16
Duration of follow-up y, mean ± SD (range)			4.4 ± 2.4 (2–38)	3.0 ± 1.6 (2–15)	7.6 ± 4.6 (3–38)	**0.04**
Frequency of HM attacks (n/y)						
	First year		2.2 ± 5.3	1.5 ± 4.5	3.9 ± 6.7	0.14**
	Later years	No	20/44 (46%)	16/30 (53%)	4/14 (29%)	0.19*
		<1/y	10/44 (23%)	5/30 (17%)	5/14 (38%)	0.25*
		1/y	6/44 (14%)	4/30 (13%)	2/14 (14%)	–
		>1/y	8/44 (18%)	5/30 (17%)	3/14 (21%)	0.70*
Prolonged HM attacks						
	Total recovery° >72 h		3/46 (7%)	3/32 (9%)	0/14 (0%)	0.54*
	Hemiplegia >6 h		7/46 (15%)	6/32 (19%)	1/14 (7%)	0.41*
	Aphasia >6 h		2/46 (4%)	1/32 (3%)	1/14 (7%)	0.52*
Alterations revealed by clinical investigations						
	Acute cytotoxic cortical edema (MRI)		6/46 (7%)	5/32 (10%)	1/14 (0%)	–
	Cerebellar atrophy (MRI)		2/46 (2%)	2/32 (3%)	0/14 (0%)	–
	Slow-wave activity (EEG)		19/29 (66%)	16/23 (70%)	3/6 (50%)	0.88*

*y, years; SD, standard deviation; n/y, number per year; h, hours; *significance level obtained by Fisher exact test; **significance level obtained by Wilcoxon rank sum non-parametric test; –, p > 0.99; °total recovery represents the time needed to fully return to the condition before the attack onset.*

DISCUSSION

The present study, focused on the clinical presentation of HM in an Italian pediatric cohort, shows a certain heterogeneity of the disease onset. Furthermore, both at the onset and during the follow-up, phenotypic differences emerged between the sporadic and the familial form. Moreover, differently from previous literature data, the neurological outcome was favorable in the majority of patients, even in those with early disease onset and severe HM attacks.

Finally, our literature review shows that previous works have not analyzed in detail the clinical onset of HM so far. In the present study, we described for the first time the clinical features of the first HM attack in a series of both SHM and FHM pediatric patients.

SHM vs. FHM

First Attack

At onset, SHM patients tend to have less non-motor auras and more associated signs and symptoms (agitation, drowsiness, alteration of awareness, fever etc.) than FHM patients, which otherwise tend to simultaneously exhibit several non-motor auras but fewer associated symptoms.

Literature dealing with HM is still debating whether awareness impairment should be considered part of the brainstem aura symptoms (3–5) or an associated symptom of the HM attack (6). In our study, we decided to consider this symptom separately in order to give greater emphasis to it and because its duration could exceed the temporal criteria (5–60 min) typical of non-motor auras' symptoms.

Prolonged attack lasting more than 72 h were documented in 32% of SHM cases by Riant et al. (8), while this figure corresponds only to 9% of our SHM cases. However, our SHM patients (particularly those with mutation of one disease genes), had longer duration of hemiplegic attack, motor aura, and headache compared to FHM patients.

In the literature, studies comparing clinical features of SHM with those of FHM are lacking, because SHM and FHM series (based on adults or both adults and children) have been described so far only separately. However, in these studies (see **Tables F2**, **S2**), a prolonged duration of motor aura has been reported in SHM cases (5), rather than in FHM cases (4).

In two FHM studies, head trauma was a trigger factor in 25% (6) and 9% (4) of cases, respectively; data on other trigger factors were not reported (**Table S2**). Riant et al. (8) described 25 SHM pediatric patients reporting the number of HM attacks and their trigger factors during the first years of the disease since onset. In this study, the major trigger factor was head trauma (24%) similarly to our SHM patients (21%). In our cohort a significant proportion of patients (46%) had at least one trigger factor, emotional stress being the most common (43%), reported by Riant et al. only in 8% of cases (8). The occurrence rate and features of trigger factors preceding the first HM attack did not significantly differ between our SHM and FHM patients.

Follow-Up

The frequency of hemiplegic attacks ranges from 3 to 4 attacks per year to daily attacks; some patients can experience only one or few episodes in lifetime (1). In our cohort, we found that in the first year of disease the mean frequency of attacks was

higher in FHM patients. SHM patients, despite having longer and more severe attacks compared to FHM, tended to have a lower frequency of episodes, especially during the first years after disease onset. On the other hand, the "active phase" of the disease was longer in our FHM cases. However, as far as concerns duration and frequency of attacks, the distribution of values was not normal in the two subgroups, supporting the idea of a wide clinical heterogeneity of the disease both in SHM and FHM cases.

Prolonged attacks can also occur during disease evolution. Indeed we previously reported the case of a girl with SHM, carrying a missense mutation of *ATP1A2,* who presented at age 8 a severe HM attack lasting 6 weeks; in this case the disease begun very early, at age 2 (12).

Children vs. Adults

In about one sixth of patients (15%), early transient neurological symptoms (i.e., prolonged aphasia during fever, isolated seizures, transient hemiparesis, prolonged clumsiness after minor head trauma) occurred between age 1 and 4 and preceded, even for a long time, the very first episode of HM. These symptoms may be interpreted as isolated auras without a cephalalgic phase or may correspond to the actual disease onset, which is misunderstood because of the child's difficulty in communicating the symptoms. In any case, these findings support the idea that HM can start very early in childhood with non-specific paroxysmal motor or non-motor manifestations. These paroxysmal manifestations should be further investigated, especially in cases with family history for HM.

In our cohort the F:M ratio was about 1, similarly to what reported by Riant et al. (8) in SHM pediatric patients (1.3), while in adults the ratio was much more higher (2.5–6) (4, 7) (**Tables F1**, **M1**). It is noteworthy that in adult series this ratio seems to be inversely related to the frequency of the monogenic HM form; in fact the F:M ratio was higher (6:1) in the Hiekkala's series (7) where only 4% of patients had a disease-associated mutation, whereas in the Thomsen's (4) FHM series with a greater frequency of HM monogenic forms, the ratio was 2.5 (**Table F1**).

It is therefore possible that in the polygenic forms of HM the role of hormones is preponderant, as occurs in the common forms of migraine (13), while in the monogenic forms of HM the role of genetics exceeds that of hormones. Studies on larger populations are necessary to obtain conclusive data.

In our cohort, the prevalence of non-motor auras (visual, sensitive, and aphasic) was remarkably lower than that reported in adults (4–7) (**Tables S2**, **F2**, **M2**). These differences might depend on data collection bias, incomplete recall of the aura at first HM attack in adults, children's inability to describe all the aura symptoms, and on actual change of aura characteristics with age.

In the previous HM series, data on neurological and neuropsychological profile were quite heterogeneous and biased by the study selection criteria and the genetic characteristics of the study population (3–9). In fact, progressive cerebellar ataxia and epilepsy were more frequent in patients with a disease-associated mutation (6, 8) (**Tables F3**, **S3**, **M3**). This figure has been recently confirmed by Pelzer et al. (3).

Among 25 SHM pediatric patients, all carrying a disease-associated mutation, Riant et al. (8) documented a high prevalence of neurological manifestations (epilepsy, ataxia, mental retardation), thus delineating a severe neurological profile in patients with pediatric onset of monogenic HM. However, these patients were recruited from the genetic laboratory, therefore this cohort could not be considered representative of the natural history of pediatric HM due to selection bias and small sample size.

Our cohort, including both patients with and without disease-associated mutation, shows that pediatric HM is associated with cognitive and/or neurological manifestations only in a minority of cases and that the overall neurological outcome is favorable. In fact, during follow-up, none of our patients developed cerebellar signs. Even SHM cases with early disease onset and severe attacks had a favorable clinical evolution.

Limitations of the present study include: (a) the retrospective data collection might have hampered the phenotypic characterization. The recruitment in Centers with a high experience and a multidisciplinary approach should have decreased the underestimation of correct diagnosis and clinical data; (b) the limited number of cases in the two subgroups (SHM and FHM) has failed to achieve, in some analyzes, statistical significance, however the disease is rare and this represents the larger Italian HM population ever reported; (c) genetic analysis was performed overall in half of cases and it is not possible to infer more information about genotype-phenotype correlations, although a maximal effort was made to collect samples to complete genetic analysis.

In conclusion, to the best of our knowledge, this study represents the first Italian pediatric series of HM ever reported, including both FHM and SHM patients.

Our cohort highlights that in the pediatric HM has a heterogeneous clinical onset.

Children present fewer non-motor auras as compared to adults and, in some cases, the first attack is preceded by transient neurological signs and symptoms in early childhood. The overall neurological outcome is favorable in the majority of cases.

A better understanding of the phenotype and natural history of the HM may help identifying prognostic factors, contribute to the genotype-phenotype correlations and guide genetic analysis.

Further multicenter studies on pediatric patient populations are needed in order to evaluate the characteristics of the disease at this age. Finally, studies focused on the neuropsychological profile of these patients are warranted.

ETHICS STATEMENT

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

AUTHOR CONTRIBUTIONS

IT: study concept and design, analysis and interpretation of data, and drafting of the manuscript. FB and VM: acquisition of data, material support, and drafting of the manuscript. EP: statistical analysis and interpretation of data. MV, DP, ET, FMo, GF, RF, MC, CL, SR, FMa, CT, GD: acquisition of clinical data. MN: drafting of the manuscript and English language advice. SS: study supervision. PB: critical revision of the manuscript for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01079/full#supplementary-material

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