REVIEW ARTICLE

Headache in Children and Adolescents: A Focus on Uncommon Headache Disorders

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Migraine and tension-type headache are common in children and adolescents, but several other headache disorders may pose a great challenge in diagnosis and management to families and attending clinicians. In this review, we highlight several of these disorders, which need appropriate assessment to make the right diagnosis and appropriate investigations where necessary. Timely recognition and implementation of appropriate management strategies can improve the health of children with some disorders, and is vital in achieving improvement in the quality of life.

Keywords: *Migraine, Stabbing headache, Thunderclap headache, Trigeminal autonomic cephalalgia.*

Headache is common in children and adolescents. About 60% of children worldwide report at least 3 attacks of headache per year [1]. Tension-type headache (TTH) and migraine are the most common headache disorders in schoolchildren with a prevalence of 8 and 23%, respectively [2,3]. Despite the high prevalence of headache in children, it continues to be under-diagnosed and undertreated. Many children are managed at home with over-the-counter medications, some children are managed at primary care and only a small proportion of children, with difficult to treat headache disorders, are referred and managed at specialist pediatric services.

Migraine and, to a lesser degree, TTH are well-studied and described in the pediatric literature, but little is written on many others, especially rare primary headache disorders and the uncommon variants and complications of common headache disorders in children and adolescents. Except for migraine, the three editions of the International Classification of Headache Disorders (ICHD-1, ICHD-2 and ICHD-3), provided definitions and criteria for the diagnosis of all headache disorders derived from studies on and experience in adult patients [4-6]. It is conceivable that the clinical presentations of most, if not all, primary headache disorders in children can be different than those in adults [7]. The differences can be due to the inherent nature of the disease itself, neurodevelopmental factors, biopsychosocial influences of the disease, life-style and education, and also children's response to pharmacologic and non-pharmacologic therapies. Therefore, studies on uncommon headache disorders in children and adolescents are badly needed in order to better define the conditions and inform management decisions.

CLASSIFICATION

Headache disorders are classified on the basis of etiology into primary (no other underlying cause), secondary (when headache is a manifestation of another disorder) and undetermined etiology (**Box I**). Headaches are also sub-classified on the basis of frequency of attacks and duration of the headache disorder into episodic (less than 15 days per month) or chronic (attacks occur on at least 15 days per month over at least three consecutive months). Migraine is further sub-classified according to clinical features (different types of migraine) and trigeminal autonomic cephalalgias (TACs) are sub-classified on the basis of attack duration.

ASSESSMENT OF THE CHILD WITH HEADACHE

In the absence of diagnostic tests and biomarkers, the diagnoses of primary headache disorders are based on the clinical features and globally acceptable definitions and diagnostic criteria. A focused and detailed clinical history is essential in assessment of children with headache in order to make a positive diagnosis, and

Box I Classification of Most Common Headache Disorders in Children

Primary headaches
- Migraine
- Tension-type headache
- Trigeminal autonomic cephalalgias
- Others

Secondary headache
- Medication overuse headache
- Posttraumatic headache
- Brain tumors
- Idiopathic intracranial hypertension

Others
- Cranial neuropathies
- Facial neuropathies
- Others

appropriate classification. Making the right diagnosis allows explaining the condition to the child and the family, making a rational decision on investigations if needed, offering the most appropriate treatment options and helps in predicting prognosis. Essential elements of clinical history, general examination and neurological examination are summarized in **Table I** and management workup may follow the steps as shown in **Fig. 1**.

The severity of pain is best assessed by its effects on behavior and activities; severe headache stops all activities during attacks, moderate headache stops some but not all activities, and mild headache dose not interfere with normal daily activities. Absence of symptoms between attacks and complete return to normal self is an important feature of primary headache. Secondary headaches should be suspected and considered if red flags are detected on the clinical history, and physical and neurological examinations (**Box II**).

Table I Clinical Assessment of the Child with Headache

Clinical history	*Examination*
Duration of headache disorder	*Physical examination*
Frequency of attacks	Weight, height
Duration of attacks	Blood pressure
Site of maximum pain	General examination
Quality of pain	Ear, nose and throat
Severity of pain	Sinuses examination
Trigger factors	*Neurological examination*
Aura symptoms	Optic discs
Associated symptoms: loss of appetite, nausea, vomiting, light intolerance, noise intolerance, dizziness	Cranial nerves Motor system: muscle bulk, tone, power, coordination, reflexes
Relieving factors Symptoms between attacks	Cerebellar system: ataxia, nystagmus, intention tremors

The diagnosis of common primary headache disorders such as migraine and tension-type headache can be made confidently on clinical history, normal examination, absent red flags and on the application of the ICHD-3 criteria. Other less common headache disorders may cause difficulties in diagnosis and management and will be the subject for this review.

GENERAL MANAGEMENT STRATEGIES

Exploring and addressing the concerns of patients and their families are the first important steps in successful management. Advice on healthy life style – regular meals, sleep, exercise and rest may reduce impact and improve coping with headache.

For acute treatment, simple analgesics should be used in appropriate dosages and as early as possible after onset of headache. Children should avoid taking painkillers on more than three days per week in order to avoid medication overuse headache (MOH). Triptans can also be given in acute migraine attacks in accordance with local license and regulations and with similar precautions to avoid MOH.

Evidence-based recommendation in the prevention of migraine can be hard to find with conflicting evidence, however treatment with propranolol, topiramate, flunarizine and amitriptyline can be considered on individual basis. Specific treatment for rare headache disorders will be discussed separately.

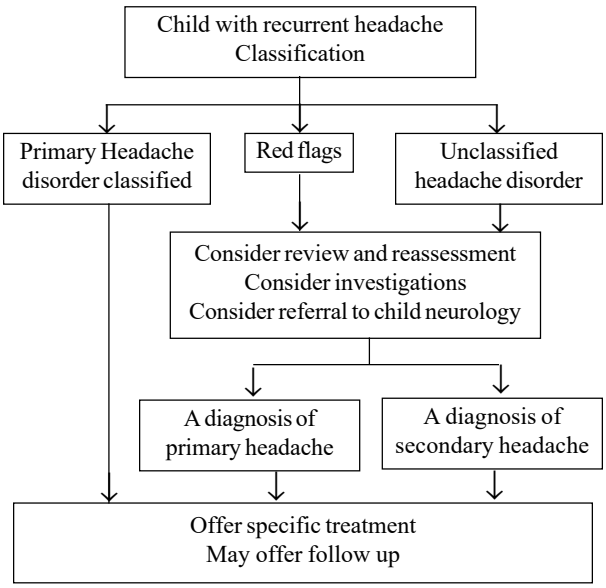

Fig. 1 Headache assessment and classification pathway.

Box II Red Flags and Indications for Investigations

Clinical history
Side locked headache
Acute progressive headache
Vomiting on waking up
Deteriorating vision
Seizures
Personality change
Persisting symptoms between attacks
Physical examination
Hypertension
Faltering growth
Delayed puberty
Neurological examination
Papilledema
New neurological deficit
Ataxia
Nystagmus
New squint

CHRONIC MIGRAINE

Migraine is a common disorder with a prevalence of around 10% in schoolchildren [1], and chronic migraine (CM) is a subtype of migraine. The diagnosis of CM is made when headache occurs on at least 15 days per month on at least 3 consecutive months, of which at least on 8 days per month the headaches are those of migraine [6].

Migraine may present as CM from the onset, but it can also evolve over a period of time in children with episodic migraine. It is estimated that about 2% of adolescents suffer from CM and at least half the patients overuse medication; simple analgesics or anti-migraine drugs such as sumatriptan [8]. CM is more common in girls than boys and more prevalent in adolescents than in younger children. CM has a significant impact on the child's quality of life, school attendance and educational attainment as compared to children with episodic migraine and control healthy children [8].

Management

The management of children with CM can be difficult and, ideally, needs a multidisciplinary approach and a positive contribution from parents and guardians, clinical psychology services, education and school teachers and also from school nurses. Investigations are not necessary except in presence of red flags or new abnormalities on neurological examination. An individual migraine management plan agreed upon by the child, the parents and members of the multi-disciplinary team (MDT) promotes better management of headache at home and at school and may reduce impact on education and quality of life.

Medical management starts with reducing the risk of medication overuse and treatment of MOH when present. Pain killers should, therefore be avoided as they have a limited role. Preventive drugs aim to reduce the frequency and the severity of migraine attacks and to improve the quality of life. Several medications are used but with sometime, a conflicting evidence for their effectiveness. Amitriptyline, with and without cognitive behavioral therapy (CBT), topiramate, flunarizine and botox are commonly offered to patients [9-11]. Greater occipital nerve block and botox injections are possible future management options. Calcitonin-gene related peptide (CGRP) monoclonal antibodies are shown to be successful in migraine prevention in adults, but still awaiting trials and licensing in children.

Prognosis: The prognosis and the long-term course of CM have not been well studied in children, but the impact on quality of life is a consistent feature and studies showed reduced educational attainment and earning power during adult life [12].

HEMIPLEGIC MIGRAINE

Hemiplegic migraine (HM) is a form of migraine with motor aura and depending on presence or absence of other affected family members; it is divided into familial hemiplegic migraine (FHM) or sporadic hemiplegic migraine (SHM). FHM is sub-classified according to the underlying genetic mutation; FHM1 is associated with a mutation on the *CACNA1A* gene, FHM2 on the *ATP1A2* gene, FHM3 on *SCN1A* and FHM (other loci) when no genetic mutation can be found despite the familial occurrence of the disease.

The prevalence of HM is not known, but is considered rare. About 2% of patient seen at a specialist children headache clinic have HM [13]. Girls are more commonly affected than boys and its peak incidence is during adolescence.

The clinical presentation of HM can be distressing to the child, frightening to the family and can pose a dilemma in diagnosis for clinicians. Attacks can be triggered by minor head trauma and followed by complex aura; a combination of visual, sensory, speech and motor symptoms. The headache that follows can be severe and is often associated with intense nausea and vomiting that may lead to confusion and dehydration.

A recent study on a cohort of 46 children with HM showed that children present with fewer non-motor auras than adults and the first attack may be preceded by transient neurological signs and symptoms especially in early childhood [14]. The attacks can last over 1-2 days and children will be, invariably, investigated with

neuroimaging to rule out space occupying lesions, intracranial bleeding or arterial ischemic strokes. Investigation will always be necessary, especially on the first presentation as the diagnosis, as defined by (ICHD-3), can only be made after at least two fully reversible attacks.

Distinguishing HM from stroke can be difficult on clinical features alone as they share many symptoms. Standard MRI of the brain may not be helpful and specialist cerebral perfusion studies using functional MRI and arterial spin labeling (ASL), only available at limited centers, may demonstrate areas of cerebral hypoperfusion soon after onset of symptoms and hyperperfusion 12-14 hours after onset. The changes in perfusion are not limited to the territories of the main cerebral arteries but they are evident across the boundaries suggesting neural rather than vascular basis of this phenomenon [15,16].

Management

Treatment of acute attacks once the diagnosis is established should aim at reassuring the child and parents, providing effective pain relief, hydration and monitoring of symptoms. Simple analgesics (paracetamol 10-20 mg/kg or ibuprofen 7.5-10 mg/kg) are the preferred options. The use of triptans is currently not recommended as all clinical trials excluded children and adults with HM and there is no evidence of their safety in children and adolescents. The exclusion from trials was based on the theoretical risk of triptans exacerbating cerebral vasoconstriction and causing cerebral infarction.

Care should be taken to prevent dehydration by encouraging oral fluids, but intravenous fluids may be necessary. Antiemetic medications such as metoclopramide or ondansetron may also be needed.

Preventative treatment may be necessary if attacks are prolonged, frequent or causes distress to child and parents. Topiramate, amitriptyline and flunarizine in particular are good treatment options.

Prognosis: Counseling of patients should take into account the known natural history of the disease, which is characterized by periods of remissions and relapses. The attacks of HM tend to be frequent and severe during adolescence and also in late adult life with periods of remission in between. A follow up of eight family members for a mean period of ten years showed the disease to be clinically stable [17]. Children with FHM1 due to associated *CACNA1A* gene mutation have an increased risk of progressive ataxia in late adult life and children with FHM3 due to *SCN1A* mutation are at a higher risk for epilepsy.

THUNDERCLAP HEADACHE

Thunderclap headache (TH) is a term given to describe sudden severe headache that reaches its peak intensity within seconds or minutes and persists for hours. TH may become recurrent over several weeks if untreated. TH is a secondary headache in most cases and a diagnosis of primary TH should only be made after full, appropriate and timely investigations including neuroimaging. The prevalence of TH in children and adolescents is not known and it is rare in pediatric clinical practice. Cases reported in children are mostly secondary to sinus venous thrombosis [18].

The clinical features of TH in children are probably similar to those in adults. The clinical picture is usually dominated by the abrupt onset of the headache and its severe intensity described by patients as the most severe headache they have ever experienced, prompting them to seek urgent medical advice and assessment. The headache attacks can be brief, but repetitive. Although the criteria for the diagnosis of TH in ICHD-3 (**Box III**) are that of primary TH, it is always necessary to exclude underlying intracranial vascular disease.

Secondary TH: TH may be the presenting symptoms in patients with several intracranial vascular disorders. The most common causes of TH in children and adolescents are intracerebral haemorrhage, cerebral venous thrombosis, subarachnoid haemorrhage with or without ruptured arterial aneurysms and reversible cerebral vasoconstriction syndrome (RCVS). Secondary TH may not be immediately distinguishable from primary TH and therefore full neurological examination and measurement of arterial blood pressure are mandatory. Prompt recognition and urgent appropriate assessment start at emergency department in order to avoid life-threatening complications [19].

Management

Investigations at presentation should include brain MRI and MR angiography. Other investigations should also include CSF opening pressure, CSF microscopy, culture, protein and glucose (paired with blood glucose) and examination for xanthchromia at appropriate time interval from presentation. MRA may need to be repeated if RCVS is highly suspected, as vasoconstriction may not be apparent in the early stages of the disease.

Box III Criteria for Diagnosis of Thunderclap Headache

A. Severe head pain fulfilling criteria B and C
B. Abrupt onset reaching maximum intensity in <1 min
C. Lasting for ≥5 min
D. Not better accounted for by another ICHD-3 diagnosis.

Treatment aims to relieve symptom while addressing the management requirements of the underlying condition.

CHIARI MALFORMATIONS HEADACHE

Chiari malformation is a congenital anomaly of the posterior cranial fossa characterized by crowding of its contents, a caudal displacement of the cerebellar tonsils and brainstem through the foramen magnum and an associated expansion of the CSF spaces in the cervical and possibly the thoracic spinal canal creating a static or progressive syrinx. Chiari malformation is classified into types 1-4 depending on the degree of malformation, the extent of cerebellar and brainstem herniation into the foramen magnum, cerebellar hypoplasia, syringomyelia, obstruction of CSF flow and presence of an encephalocele.

Chiari malformation type 1 (CM1) is the most common form and it is asymptomatic in the vast majority of cases. In CM1, there is mild to moderate crowding of the posterior fossa and a descent of cerebellar tonsils between 5-10 mm below the foramen magnum with no or a very small syrinx. It is commonly reported as an incidental finding in about 1% of children and young people undergoing brain and spine MRI [20].

Headache due to CM1 is described in the ICHD-3 as brief episodes lasting less than 5 minutes of occipital or suboccipital pain, precipitated by cough or Valsalva maneuver and it remits after successful treatment of CM1 [6]. It is important to keep in mind that children with CM1 may also complain of other types of headache such as migraine and tension-type headache, and they should not be confused with CM1 headache. On rare occasions, children with CM1 may present with other symptoms related to brainstem or cerebellar dysfunction including visual disturbances, dysphonia, dysphagia, sleep apnea, incoordination and sensory disturbances.

The diagnosis of CM1 is usually made on the sagittal MRI of the brain and the cervical spine. The management of children with CM1 is non-surgical in most patients after discussion with a neurosurgeon and a neuroradiologist. Medical management should include appropriate management of the pain symptoms and a follow up imaging over a period of time to confirm the non-progressive nature of the malformation and the size of the syrinx, if present, in particular [21].

Surgery is only recommended for patients with features suggesting brainstem or cerebellar compression, a large or progressive syringomyelia or with a poorly controlled, typical CM1 headache disorder. A single center experience in the surgical treatment of children with CM1 over 25 years showed that children with typical CM1 headache who were treated with foramen magnum decompression (FMD) plus duraplasty achieved a greater improvement in their headache than those treated with FMD alone [22].

PRIMARY STABBING HEADACHE

Primary stabbing headache (PSH) is an uncommon syndrome, also called ice-pick headache, characterized by very short attacks. While ICHD-2 states that pain is confined exclusively to the trigeminal territory, it has been accepted in ICHD-3 to cross beyond the boundaries of the trigeminal nerve and can be unilateral or bilateral in location (**Box IV**). The typical stab lasts a few seconds; however, attacks lasting up to 15 minutes in children and adolescents have been reported [23].

Although the exact prevalence of PHS in the pediatric population is unknown, 4-5% of children referred to headache centers have PSH [23-25]. In an Italian study, 12.4% of children with headache younger than 6 years had PSH [26]. Girls and boys are equally affected, though in adults PSH is more common in females [27]. Other primary headaches; migraine and TTH may coexist with PSH in children [28-30]. Associated symptoms, such as photophobia, phonophobia, nausea, and dizziness, have been described in 20-50% of patients. Absence of autonomic symptoms is the main feature that differentiates PSH from trigeminal autonomic cephalalgias.

The pathophysiology of PSH is unknown, but spontaneous firing of trigeminal fibers or abnormalities of the descending pain control have been suggested as possible mechanisms [27]. The relatively higher prevalence of PSH in younger children suggests that PHS may be a precursor of migraine/TTH [16].

Treatment of PSH in children is often not necessary, unless the stabs are very frequent and interfere with normal activities. Evidence for any medications in the treatment of PSH is lacking, but indomethacin may offer an excellent relief of pain when given in a dose of 25 mg three times per day for 6-8 weeks alongside omeprazole for gastric protection. Melatonin, amitriptyline, propanol, and COX2-inhibitors were effective in adults and may be used in children [27].

Box IV Criteria for the Diagnosis of Primary Stabbing Headache

A. Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B and C
B. Each stab lasts for up to a few seconds
C. Stabs recur with irregular frequency, from one to many per day
D. No cranial autonomic symptoms
E. Not better accounted for by another ICHD-3 diagnosis.

TRIGEMINAL AUTONOMIC CEPHALALGIAS

Trigeminal Autonomic Cephalalgias (TACs) are also uncommon, especially in pediatric age. However, they must be considered even in young children, in order to offer the appropriate treatment. They include cluster headache (CH), Paroxysmal hemicrania (PH), Hemicrania Continua (HC), and Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT) or with cranial autonomic symptoms (SUNA). **Table II** presents the characteristics and the differential diagnosis of these conditions.

Cluster Headache

The prevalence of cluster headache (CH) in the pediatric population is around 0.1% [31]. CH is characterized by severe and sometimes excruciating unilateral pain, mainly in the orbital, supraorbital, and/or temporal region, lasting 15-180 minutes and recurring up to 8 attacks per day. Attacks are often associated with restlessness and/or ipsilateral autonomic symptoms, such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, forehead and facial sweating, miosis, and ptosis. The usual presentation of CH is that of recurrent bouts of headache, each bout consisting of several distinct headache attacks. In episodic CH, the bouts of headache last from 7 days to 1 year, and are separated by headache-free periods without treatment of at least 3 months. In chronic CH, the headache-free period between bouts is shorter than 3 months. It has been recently suggested that the attacks can be shorter and less frequent in children than in adults and restlessness can be more difficult to demonstrate [7,32].

CH is more common in children over 10 years of age, but it has been reported in children younger than 6 years of age [33,34]. Complex genetic factors are probably involved in CH etiology [35,36]. However, it was noted that there is a low prevalence (9%) of CH in the relatives of young patients [34]. Environmental factors such as high exposure to second hand smoking has been suggested as a risk factor for CH development [34,37].

Table II Characteristic Features of Trigeminal Autonomic Cephalalgias

	Cluster headache	*Paroxysmal hemicrania*	*SUNCT*
Female: Male	1:5	1:1	1:1.5
Frequency	1-8/d	1-40/d	Up to 200/d
Attack duration	15-180 min	2-30 min	5-240 sec
Agitations	90%	80%	65%
Autonomic features	Yes	Yes	Yes
Response to indomethacin	No	Yes	No

SUBCT: Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

Treatment: Treatment of acute attacks in children and adolescents consists of administering, as early as possible after onset, either sumatriptan 10 mg or zolmitriptan 5 mg (as nasal spray), which are the only licensed triptans for adolescents 12-18 years of age in Europe as well as high flow 100% oxygen at 12-15 L/min with a rebreathing mask [38].

For the prevention of CH, verapamil is the drug of first-choice in adults. It has been used at the dose of 3-10 mg/kg/d in children and adolescents [38]. However, verapamil can be difficult to manage in pediatric age because of its side effects (effect on length of the PR interval and the negative inotropic effect). Alternative treatments are melatonin (0.1-0.2 mg/kg/d) and topiramate (1-2 mg/kg/d). A short course of steroids like prednisone 2 mg/kg/day is reported to stop the cluster within 5 days [34]. Greater occipital nerve block was shown to be effective in three children [39].

Paroxysmal Hemicrania

Paroxysmal hemicrania (PH) is characterized by short lasting (2-30 min), multiple and unilateral pain attacks, with a typical attack frequency of more than 5 per day. Pain is commonly associated with ipsilateral cranial autonomic symptoms. PH is defined as episodic when attacks last from 7 days to 1 year and are separated by time intervals longer than 3 months. In chronic PH, the attack has to last more than 1 year without interruption or with pain-free intervals shorter than 3 months. In children, PH can be atypical with bilateral pain, attack duration longer than 30 minutes and attack frequency less than 5 per day making it difficult to differentiate from CH [7,40,41].

PH responds well to treatment with indomethacin, making it a good therapeutic first line option in all patients with unilateral short-lasting pain, associated with cranial autonomic symptoms.

Hemicrania Continua

Hemicrania continua (HC) is characterized by continuous unilateral headache with exacerbations of moderate or greater intensity for at least 3 consecutive months. As in PH, cranial autonomic symptoms ipsilateral to pain and/or sense of restlessness are needed for the diagnosis. The response to indomethacin should be complete, but can be variable in some children. Only a few pediatric cases of HC have been published with one patient responding to treatment with Botulinum toxin A [42,43].

Box V Learning Points for Uncommon Pediatric Headache Disorders

Chronic migraine

- Affects 1-2% of adolescents
- Management requires multidisciplinary approach in most patients and realistic targets
- Management aims to revert chromic migraine to episodic migraine
- Emphasis on life style factors and preventive treatment· Avoid medication overuse and address it if present

Hemiplegic migraine

- Diagnosis of HM can only be made after at least 2 fully reversible episodes
- Investigations and neuroimaging will be necessary at first presentation
- Triptans are not recommended for treatment of acute attacks
- Flunarizine may be a good option for the prevention of HM

Thunderclap headache

- TH presents with sudden onset severe headache that reaches its peak within minutes
- Always exclude underlying intracranial cause by appropriate investigations

Chiari malformation 1

- CM1 can be asymptomatic incidental finding in about 1% of people
- Headaches due to CM1 are short, occipital and triggered by Valsalva maneuver. Discuss with a neurologist, a neurosurgeon and a pediatric neuro-radiologist
- Surgical treatment only required in a small proportion of patients

Primary stabbing headache

- Headache due to PSH are very brief and repetitive
- No associated autonomic features
- Excellent response to indomethacin can be expected

Trigeminal autonomic cephalalgias

- Duration of attacks are important in diagnosis, but acknowledge some overlap
- At least one autonomic feature is present
- Agitation and distress are important features
- PH and HC respond to indomethacin in many patients
- Nasal sumatriptan and high flow oxygen are effective acute treatment for CH.

SUNCT and SUNA

These short-lasting neuralgiform attacks, lasting from 1 to 600 sec, involve the trigeminal territory unilaterally. The attacks can be isolated or can recur in series. Pain is associated with conjunctival injection and/or tearing in SUNCT or other cranial autonomic symptoms, such as nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, miosis, and/or ptosis in SUNA. Only four cases of pediatric SUNCT (3 idiopathic and 1 symptomatic) have been described thus far [7].

CONCLUSIONS

Pediatricians are familiar with the diagnosis and treatment of common headache disorders in children and adolescents. Awareness of the different types of atypical or rare headache disorders allows better assessment and a more successful management. Learning points related to these disorders are detailed in **Box V**.

Diagnosis should be based on the recognized clinical criteria of the ICHD. Investigations to exclude serious underlying neurological disorders may be necessary, but should be interpreted with caution, in order to avoid over-diagnosis of incidental findings such as Chiari malformation 1. Chronic migraine can be associated with adverse impact on quality of life and can be difficult to manage. Hemiplegic migraine may pose diagnostic difficulties making investigations necessary including MR angiography, especially at first presentation. Trigeminal autonomic cephalalgias and stabbing headache are relatively rare in children, but with the correct use of diagnostic criteria, management plans with appropriate treatment options and realistic expectations, it is possible to address the patient needs.

Contributors: All authors contributed equally and approved the final manuscript.
Funding: None; *Competing interest*: None stated.

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