

Headaches in children are common, with around 70% of school children experiencing at least one per year and 25% more frequently.¹ They are a cause of considerable morbidity, with school absence and academic underachievement common sequelae in older children. Studies from developed countries indicate that migraine is the most common diagnosis among children with headache who present to a medical practitioner. This article focuses on the diagnosis, epidemiology, differential diagnosis, and management of migraine, and includes a review of the evidence base for currently used treatment.

DIAGNOSIS AND CLASSIFICATION

In 1988 the International Headache Society (IHS) published complex diagnostic criteria for classifying headaches in general.² For young children these criteria were too restrictive, and a recently published revision includes an extensive classification of migraine headache (table 1) as well as more developmentally sensitive criteria for use in children (table 2).³

Diagnostic criteria for children are broader than those for adults, and allow for a broader range of duration and a broader localisation of the pain. In essence, migraine can be defined as a recurrent headache that occurs with or without aura and lasts 1–72 hours. It is usually unilateral, of moderate or severe intensity, pulsating in quality and aggravated by routine physical activity. Nausea, vomiting, phonophobia, and photophobia are common accompanying symptoms (table 2).

EPIDEMIOLOGY AND AETIOLOGY

Migraine affects 3–10% of children,^{1–6} a figure which equates to 50/1000 school age children in the UK and an estimated 7.8 million children in the European Union.⁷ The mean age at onset is 7.2 years for boys and 10.9 years for girls, with 20% of children experiencing their first attack before the age of 5 years.^{8–9} The symptom based definition precludes diagnosis in very young children. The incidence increases steadily with age, affecting girls and boys equally before puberty but girls more commonly thereafter.^{1–5, 10}

The cause of migraine is unknown, and there are few reliable data that have identified risk factors or quantified their effects in children. A family history is common. Proposed precipitants in genetically predisposed children and adolescents include hunger, fasting, menses, exercise, stress (for example, sleep deprivation), and foodstuffs (for example, chocolate).^{10–11} Recently, a link between dominantly inherited migraine with aura and atrial septal defect/patent foramen ovale has been proposed.¹² This is supported by one study of 215 adult patients in which closure of a patent foramen ovale in known migraineurs significantly reduced the frequency of subsequent migraine attacks.¹³

PATHOGENESIS

Migraine is currently thought to be a primary neural process. In the milieu of a hyperexcitable cortex, various stimuli probably produce disturbances in neuronal ion channel activity, resulting in a lowered threshold for external or internal factors to trigger “cortical spreading dysfunction” (CSD). This slowly propagating wave of neuronal depolarisation is most likely responsible for the migraine aura and activation of the trigemino-vascular system.¹⁴ The perception of pain associated with migraine probably begins with activation of trigeminal vascular afferents, which in turn sensitise other peripheral and central afferent circuits to mechanical, thermal, and chemical stimuli. Stimulation of these circuits is painful.¹⁵

An abnormal cerebrovascular response to visual stimuli may also be contributory; when compared with headache-free subjects, migraineurs with aura exhibit a significantly higher cerebral blood flow in response to repetitive visual stimulation.¹⁶ Furthermore, migraineurs significantly lack habituation of this vascular response, suggesting that a reduced adaptation to environmental stimuli (including light) may be part of the pathogenic process.¹⁶

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Table 1 2004 International Headache Society (IHS) classification of migraine³

- ▶ Migraine without aura
- ▶ Migraine with aura
 - typical aura with migraine headache
 - typical aura with non-migraine headache
 - typical aura without headache
 - familial hemiplegic migraine
 - sporadic hemiplegic migraine
 - basilar type migraine
- ▶ Childhood periodic syndromes (commonly migraine precursors)
 - cyclical vomiting
 - abdominal migraine
 - benign paroxysmal vertigo of childhood
- ▶ Retinal migraine
- ▶ Complications of migraine
 - chronic migraine
 - status migraine
 - persistent aura without infarction
 - migrainous infarction
- ▶ Probable migraine

DIFFERENTIAL DIAGNOSIS

A detailed history and meticulous examination is essential in identifying those children that require further investigation. Unless the history is typical of migraine or one of its variants, other causes of headache must be considered (table 3). This initial assessment also provides an insight into the level of patient and family anxiety that might be contributing to symptom perception, facilitating the setting of realistic expectations of management.

Although it is beyond the scope of this article to elaborate on the entire differential diagnosis, a few conditions merit special mention.

Episodic tension-type headaches are usually bilateral, last from 30 minutes to seven days, have a pressing or tightening quality, and are not aggravated by physical activity. Nausea, vomiting, photophobia, and phonophobia are not typical accompaniments.

Cluster headaches are classically severe in nature, unilateral, orbital, supra-orbital, and/or temporal and last 15–180 minutes. Conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis, and eyelid oedema on the side of the headache are all commonly associated.

CHRONIC DAILY HEADACHE

Complex proposed criteria exist for diagnosis of this condition, which may be divided into a number of categories on the basis of specific clinical features and the pattern of headache evolution:

- ▶ *Transformed migraine*—Affected children initially suffer from migraine, but then develop a chronic headache in which isolated migraine attacks may or may not persist.
- ▶ *Chronic tension-type headache*—Episodes occur on average 15 days per month for six months, with the clinical features of episodic tension-type headaches.
- ▶ *New persistent headaches*—Headaches last over four hours per day, more than once per month, with no history of episodic migraine or tension-type headache.
- ▶ *Hemicrania continua*—Characterised by a low level baseline hemicranial headache with superimposed exacerbations of more severe pain. Exacerbations last from minutes to days

Table 2 IHS criteria for paediatric migraine without aura³

- A. At least five attacks fulfilling criteria B–D
- B. Headache attacks lasting 1–72 hours
- C. Headache with at least two of the following features:
 1. Unilateral/bilateral/fronto-temporal location, but not occipital
 2. Pulsating quality
 3. Moderate to severe intensity
 4. Aggravation by/or causing avoidance of routine physical activity
- D. During the headache at least one of the following:
 1. Nausea and/or vomiting
 2. Photophobia and phonophobia
- E. Not attributable to another disorder

and may be associated with ipsilateral autonomic features such as miosis, ptosis, lacrimation, conjunctival injection, and rhinorrhoea; when present, these features tend to be less pronounced than those seen with cluster headache.

- ▶ *Co-morbid/mixed headache*—Affected children have two different headache patterns, which exist independent of each other.

This classification is useful in distinguishing this group of conditions from the other types of migrainous and non-migrainous headache.

Obstructive sleep apnoea may manifest as early morning headaches with accompanying nausea and anorexia, in a child who snores at night with nocturnal arousals and daytime somnolence.

The possibility of environmental exposure to carbon monoxide or non-pharmacological drug use should also be considered when the aetiology of headache is not otherwise obvious.

Clinical findings suggestive of raised intracranial pressure include recent onset headaches worsened by lying down, nocturnal vomiting, altered conscious level, papilloedema, hypertension, and increasing head circumference with/without sun setting. Further pointers to significant intracranial

Table 3 Differential diagnosis of migraine

Organic headache

- ▶ Post-traumatic
- ▶ Infections—for example, otitis media, dental infections, meningitis, sinusitis
- ▶ Post-seizure
- ▶ Pharmacological—for example, analgesics, caffeine, food additives
- ▶ Toxic (substance abuse—for example, marijuana and cocaine, carbon monoxide poisoning)
- ▶ Ophthalmological (refraction errors)
- ▶ Arthritis of the temporo-mandibular joint
- ▶ Vasculitis—for example, systemic lupus erythematosus
- ▶ Hypertension
- ▶ Tumours and other space occupying lesions
- ▶ Raised intracranial pressure—for example, benign intracranial hypertension, hydrocephalus, Chiari malformation
- ▶ Low intracranial pressure (post-lumbar puncture, dural tear)

Vascular headache

- ▶ Cluster headache
- ▶ Intracranial bleed—for example post-traumatic, ruptured arterio-venous malformations, aneurysmal bleeding
- ▶ Venous sinus thrombosis

Non-organic headache

- ▶ Chronic episodic tension-type headache
- ▶ Chronic daily headache
- ▶ Depression

Table 4 Clinical signs suggestive of an alternative diagnosis to migraine include

- ▶ Altered conscious level
- ▶ Inappropriate behaviour (especially if recent onset)
- ▶ Increasing head circumference, sun setting eyes, and prominent scalp veins
- ▶ Papilloedema
- ▶ New or worsening squint
- ▶ Hypertension with or without bradycardia
- ▶ Cranial nerve palsies or motor deficits
- ▶ Cerebellar signs
- ▶ Hepatosplenomegaly

pathology—for example, brain tumours (which account for less than 1% of the lifetime prevalence of headaches¹⁷)—include a change in personality or decline in school performance, and focal neurological signs such as ophthalmoplegia, weakness, ataxia, nystagmus, dysarthria, and hypotonia.

The presence of any of the signs in table 4 suggests an alternative diagnosis.

For the child with longstanding headaches and a normal physical examination, no investigation is required. Routine laboratory studies, lumbar puncture, and electroencephalogram (EEG) are not recommended. It is easy to make the assertion that routine brain computed tomography (CT) or magnetic resonance imaging (MRI) is not indicated; realistically there are individual cases where it is essential to allay extreme levels of anxiety. Such imaging may prove therapeutic, although there remains a risk of detecting an incidental anxiety enhancing (and asymptomatic) abnormality—for example, an Arnold-Chiari malformation.¹⁸

MANAGEMENT

The emphasis in a treatment plan should be on reducing headache frequency, duration, severity, and associated disability, and should be tailored to each individual. Most available literature deals with pharmacological and biobehavioural interventions in the treatment of migraine and its variants.

There is a paucity of controlled data to support the use of any drug in the management of paediatric migraine. This has led to a tendency to extrapolate data from adult trials or to use anecdotal personal experience when considering any drug for use.

Treatment of acute attacks

Paracetamol and ibuprofen

Using simple analgesics (for example, paracetamol, non-steroidal anti-inflammatory drugs) is an appropriate initial therapeutic step, although only limited supportive data are available. Both drugs have been shown to be more effective than placebo in providing reduction of headache pain by two grades ($p < 0.05$)^{19, 20}; in one study¹⁹ ibuprofen (10 mg/kg) was twice as likely as paracetamol (15 mg/kg) to abort migraine within two hours (odds ratio 2.2, 95% confidence interval 1.1 to 4.0). In this study paracetamol was observed to have a faster onset of action than ibuprofen. However, the results of both studies should be interpreted with caution. Both had high dropout rates (17%¹⁹ and 40%,²⁰ respectively) and the first study¹⁹ did not report results before crossover. This is a potential source of bias caused by continued

potential effects after crossover and unequal withdrawals among groups.

Codeine phosphate

There is virtually no published data on the use of codeine phosphate acutely, and the known adverse effects (which include nausea, vomiting, drowsiness, constipation, and a dry mouth) mediate against it for use as a first line agent.

Ergot derivatives

A number of studies have evaluated ergotamine derivatives for use in paediatric practice, but methodological limitations of each make objective conclusions difficult and their use uncommon.^{21, 22} They are contraindicated with the triptan class of drugs and in complicated migraine.

Triptans (5-hydroxytryptamine receptor agonists)

Three randomised controlled trials (RCTs) have demonstrated nasal sumatriptan to be both safe and effective in adolescents with migraine.

The first study ($n = 14$, age 6–14 years) found that 20 mg nasal sumatriptan was more effective than placebo in providing headache relief by two hours ($p = 0.03$).²³

A second RCT ($n = 510$, age 12–17 years) compared 5 mg, 10 mg, and 20 mg sumatriptan nasal spray to placebo. Significant relief was noted at one hour with the 5 mg and 20 mg dose ($p < 0.05$). The 20 mg dose was also more effective than placebo at achieving a pain-free state after two hours and in reducing phonophobia and photophobia ($p < 0.05$). Taste disturbance with sumatriptan was reported by 26% of children.²⁴

A third study ($n = 83$, age 8–17 years) also suggested nasal sumatriptan to be superior to placebo, with significantly more children experiencing some relief of symptoms at two hours ($p = 0.003$). Taste disturbance was again the most commonly reported side effect (29%).²⁵

Oral sumatriptan has not been found to be any more effective than placebo,²⁶ and the subcutaneous formulation has only been evaluated in open label studies.^{27, 28} Limited data exist for other agents in this class (for example, rizatriptan, zolmitriptan), and there are little data currently available to support their use.^{29, 30}

Prophylaxis

In the UK propranolol and pizotifen are widely prescribed as prophylactic agents, though in the absence of convincing RCT derived evidence suggesting a benefit.

Propranolol

Three studies have evaluated the use of propranolol, and each differs in its conclusion; the first suggested a benefit, a second suggested no benefit, and a third concluded that it may actually worsen symptoms.

In a very small double blind crossover RCT of 32 children (aged 7–16 years) with IHS congruent migraine, Ludvigsson demonstrated that propranolol (60–120 mg daily divided in three doses) produced a significant increase in the perception of benefit compared with placebo over a three month period. The reliability of these results is limited because of the small size of this trial, coupled with a 13% dropout rate.³¹

In contrast, Forsythe *et al* showed that propranolol (40–120 mg daily over a 30 week period) actually increased headache duration compared with placebo in 53 children

aged 9–15 years. Again, the reliability of these results is limited because of a 26% dropout rate.³²

Finally, in a trial of 33 children aged 6–12 years Olness compared propranolol (3 mg/kg per day) with placebo for migraine prophylaxis. This RCT found no significant difference between propranolol and placebo when the number of migraine attacks was taken as the primary end point.³³

Pizotifen

Only two trials have evaluated pizotifen for use as prophylaxis, and both have methodological flaws that considerably limit the interpretation of their results.

In a double blind crossover RCT of 47 children aged 7–14 years Gillies³⁴ found no benefit for pizotifen (twice or three times daily dosing, dose range 0.25–0.5 mg per dose) over placebo in reducing the number of attacks, total duration of attacks, duration of the longest attack, or mean duration of attack. This study (1986) predated the IHS diagnostic criteria for migraine, and participants would not all fulfil the current IHS definition for migraine. The reliability of these results is also limited by the fact that 17% of children did not complete the study.

The only other study to have compared pizotifen with placebo was never published in full and so its methodology is not open to scrutiny. In this study Salmon³⁵ evaluated 40 children (aged 6–15 years) with headache, only some of whom had migraine. The results were published only in abstract form and did not include numerical data.

Other prophylactic agents

A number of other agents have been evaluated. Flunarizine has been shown to be more effective than placebo,³⁶ though awaits further study. Nimodipine,³⁷ trazodone,³⁸ L-5-hydroxytryptophan,³⁹ clonidine,⁴¹ and anti-emetics (for example, domperidone, metoclopramide)⁴³ have all been used in small placebo controlled studies, though none were shown to significantly reduce headache frequency or duration. The herbal remedy feverfew (*Tanacetum parthenium L.*), shown in RCTs in adults to be of potential benefit,⁴⁴ is still to be effectively evaluated for use in children, as are phenobarbitone, phenytoin, amitriptyline, carbamazepine, metoprolol, topiramate, piracetam, and cyproheptadine.⁴³

In conclusion, only very limited data on paediatric migraine currently exist to support the use of drugs to relieve acute symptoms or provide prophylaxis. There remains an urgent need for methodologically sound RCTs to determine which agents are therapeutic. Such studies would ideally be large, multicentre, parallel group without crossover, with stringent monitoring of compliance and a low dropout rate. The use of headache frequency as a primary outcome is preferable to headache indices.

Psychological and behavioural therapy

A number of approaches have been evaluated, though few in suitably blinded large RCTs with a low dropout rate.

There are no reliable data on the efficacy of specific dietary exclusion. One small RCT (which pre-dated the IHS criteria for migraine) attempted to investigate the effects of excluding dietary amines in 39 children, but its conclusions are unreliable given that 33% of eligible children were excluded before randomisation.⁴⁵

Though some preliminary evidence is available to suggest that progressive muscle relaxation and self administered stress management programmes are of potential benefit as

prophylaxis, these and other psychological therapies—for example, thermal biofeedback—await more stringent further evaluation.^{46–49}

PROGNOSIS

There are no reliable data regarding the prognosis of paediatric migraine diagnosed by IHS criteria. Spontaneous remission after puberty may occur, and this is supported in part by one 40 year longitudinal study from Sweden (73 children with migraine, mean age onset 6 years).⁵⁰ It found that migraine headaches had ceased before the age of 25 years in 23% of people, although by the age of 50 years more than 50% of people remained affected. This study predated the IHS diagnostic criteria.

CONCLUSIONS

- ▶ Careful consideration of the broad differential diagnosis is important when evaluating a child with headache.
- ▶ Migraine remains a significant source of morbidity in children; despite recent advances an understanding of its pathophysiology remains incomplete.
- ▶ The expectations for the success of treatment should take account of the level to which psychological factors are contributing to symptoms.
- ▶ Ibuprofen and nasal sumatriptan should be considered for the treatment of acute attacks; paracetamol is also probably effective.
- ▶ Limited evidence exists to support the use of any specific prophylactic agent; further evaluation is required in methodologically sound RCTs.

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ARCHIVIST

Primary adrenal insufficiency

Primary adrenal insufficiency (PAI) is uncommon in children. The most common diagnoses are congenital adrenal hyperplasia (CAH) and autoimmune Addison's disease. A series of 103 patients has been described from Montreal (Rebecca Perry and colleagues). *Journal of Clinical Endocrinology and Metabolism* 2005;90:3243–50.

The study included all 55 girls and 48 boys who attended one hospital department with PAI between September 1981 and September 2001. The diagnosis was 21-hydroxylase deficiency CAH for 41 girls and 31 boys (70% of the whole series). Among these, 30 girls and 29 boys had the classic form and 11 girls and two boys had the non-classic form. Of the 59 patients with the classic form 53 had salt-wasting CAH. The average age at diagnosis of the six children with simple virilising CAH was 5.8 years. One patient of each sex had 3- β -hydroxysteroid dehydrogenase deficiency.

Thirteen patients had autoimmune adrenal failure and five of these had a diagnosis of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED). Four of the five had mutations at the *AIRE* locus (the fifth was not tested). Glucocorticoid or mineralocorticoid deficiency was diagnosed at between 5.4 and 13.6 years in patients with APECED and at between 7.8 and 16.3 years in patients with non-APECED autoimmune PAI. Other diagnoses included adrenoleukodystrophy (4 boys), Wolman disease (3), triple A syndrome (1), Zellweger disease (1), X-linked CAH (1), and unexplained PAI (6).

An algorithm for the diagnosis of children with PAI is included in the paper.