New avenues in treatment of paediatric migraine: a review of the literature

Ann Pakalnis


Background. Headaches are a common problem in paediatric practice. Recurrent headaches can be a significant source of stress for patient and parents, and disruptive regarding school obligations and parental work responsibilities. Most treatment interventions are developed from research data extrapolated from adult studies, with resultant concerns of safety and efficacy when utilizing these therapeutic conclusions in children.

Methods. This paper incorporates current treatment strategies in paediatric migraine utilizing a Medline search of English language studies from January 1988 to December 1999, with a literature search referencing the terms of paediatrics, migraines, headaches, therapy and treatment. Reference sections of the articles were reviewed for pertinent information prior to January 1988. Articles were evaluated systematically to formulate concise terms for diagnosis of paediatric migraine and applicability to clinical treatment studies. Particular emphasis was placed on newer options with relevance in adult treatment such as triptans and anti-epileptic drugs, and their benefit in therapy of paediatric migraine. Non-pharmacological options were also subjected to organized review to determine relevance in treatment of paediatric migraine.

Results. The review of the literature indicates that although migraine in childhood and adolescence appears to be increasing in prevalence, few clinical studies are available, with most current treatment recommendations utilizing data from adult studies.

Conclusion. Further headache treatment studies in the paediatric population are necessary in order to ascertain safety and efficacy of pharmaco-therapeutics in these children. Also, much current interest in treatment in adults with recurrent headaches involves non-pharmacological areas—dietary modification and stress management. Application of these avenues especially warrants further clarification with regard to relevance in paediatric migraine treatment.

Keywords. Paediatric migraine, review of the literature, therapy, treatment.

Introduction

Current information suggests that diagnosis and presentation of migraine differs in paediatric and adult populations. Also, natural history and prognosis are vastly disparate; some studies suggest that response to medication may be different. Migraine in children and adolescents is seen commonly, with prevalence in children aged 15 years and younger ranging from 3.2 to 10.6%, depending on the diagnostic criteria used for migraine and the age of the study sample. This contrasts with prevalence rates ranging from 10 to 25% in the adult US population. Current studies suggest that migraine prevalence in children and adults has increased over the past 30 years. Statistically, one child in nine is affected between the ages of 5 and 15 years. With prevalence rates approximating 10% in school-age children, migraine has significant impact on school attendance and family dynamics involved in caring for a sick child, with loss of job productivity and work attendance in parents.

Many clinical studies have been generated in adults on effective treatment strategies. Migraine is a very common medical problem in the adult population and a notable cause of significant loss in job productivity in the workplace. Little information is available on current clinical treatments and their efficacy and safety when used in children, yet migraine is also very common in this population and has significant socio-economic impact on the
adult population. Also, with better understanding of paediatric migraine, possible changes could be affected in the future to change the natural history of migraine.

This paper focuses on diagnostic criteria, and epidemiology and recent treatment strategies in paediatric migraine, and the application of current adult therapeutic studies for utilization when caring for children and adolescents with migraine.

Methods

A preliminary search of the literature indicated no recent current review of the literature for treatment of paediatric migraine. Medline data were searched from January 1988 to December 1999 with English language publications. Reference sections of articles were reviewed for earlier pertinent work.

Results

Diagnostic criteria and epidemiology of migraine

The diagnosis of migraine has proven more difficult to qualify in children than in adults. In 1988, the International Headache Society (IHS) proposed criteria for diagnosis in adults (Table 1). The revised IHS criteria, modified for paediatric migraine, permit a shorter duration of headache than in adults (15 years and younger with headache duration of 2–72 hours, Table 2). Many children have headaches with migrainous characteristics lasting less that 1 hour, which is a concern regarding IHS criteria. Also, the concept of unilaterality is a consideration. Many authors suggest that this is less common in children, possibly due to differences in pain perception and referred pain in this population. These criteria are controversial, yet at the present time little else is available for reproducible diagnosis, especially when considering need for concise diagnosis with clinical studies. Other associated constitutional symptoms are helpful in making a diagnosis of migraine and may include increased bruxism, tenderness in the occipital and temporal mandibular joint area, and motion sickness. Prevalence rates for migraine with and without aura were estimated in previous studies at 2.8 and 7.8%, respectively. Migraine is slightly more common in boys up to the age of 12 years and then assumes heavy predominance in girls (3:1), approaching adult values probably corresponding to age at menarche. Another associated symptom common in children with migraine was ice cream headaches (93% of migraineurs versus 31% of children without headache).

The natural history of paediatric migraine has seldom been studied. Most information suggests that there is a greater likelihood of a tendency for paediatric migraine to remit in time, at least for several years. This is probably most likely in boys, given the heavy female predominance in adult studies. However, recidivism, especially in older adolescent girls/women, often takes place. Age of onset did not appear to correlate with remission in these studies.

Most childhood migraine studies have pointed to a strong genetic component. Migraine is probably more likely to be a common polygenic mechanism in families when history can be elicited, and studies in monozygotic twins also corroborate a genetic component in childhood migraine. A recent study by Nyholt et al. evaluated families with a rare type of familial hemiplegic migraine and located mutation markers on chromosome 19, which implicates this genetic location for this variant. This

| TABLE 1 Criteria for diagnosis of migraine (International Headache Society) |
|---------------------------------|---------------------------------|
| Migraine without aura           |                                  |
| (A) At least five attacks fulfilling (B) to (D) below |                                  |
| (B) Headache lasting 4–72 h (2–48 h in children) |                                  |
| (C) Headache characterized by at least two of the following: |                                  |
| (1) Unilateral location         |                                  |
| (2) Pulsating quality           |                                  |
| (3) Moderate or severe intensity (inhibits or prohibits daily activities) |                                  |
| (4) Aggravated by climbing stairs or similar routine physical activity |                                  |
| (D) Headache accompanied by at least one of the following: |                                  |
| (1) Nausea or vomiting, or both |                                  |
| (2) Photophobia and phonophobia |                                  |
| Migraine with aura              |                                  |
| (A) At least two attacks fulfilling (B) below |                                  |
| (B) Presence of at least three of the following: |                                  |
| (1) One or more fully reversible aura symptoms indicating focal cerebral cortical dysfunction or brain stem dysfunction, or both |                                  |
| (2) At least one aura symptom develops gradually over more than 4 min or two or more symptoms occur in succession |                                  |
| (3) No aura symptom lasts more than 60 min. When more than one aura symptom is present, accepted duration is proportionally increased |                                  |
| (4) Headache follows aura with a free interval of less than 60 min (it may also begin before or simultaneously with aura). |                                  |

<table>
<thead>
<tr>
<th>TABLE 2 IHS criteria for paediatric migraine without aura</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) At least five attacks fulfilling (B)–(D) below</td>
</tr>
<tr>
<td>(B) Headache attack lasts 2–48 h</td>
</tr>
<tr>
<td>(C) Headaches at least two of the following:</td>
</tr>
<tr>
<td>(1) Unilateral location</td>
</tr>
<tr>
<td>(2) Pulsating quality</td>
</tr>
<tr>
<td>(3) Moderate to severe intensity</td>
</tr>
<tr>
<td>(4) Aggravation by routine physical activity</td>
</tr>
<tr>
<td>(D) During headache, at least one of the following:</td>
</tr>
<tr>
<td>(1) Nausea and/or vomiting</td>
</tr>
<tr>
<td>(2) Photophobia and phonophobia</td>
</tr>
</tbody>
</table>
provides support for genetic heterogeneity of migraine and the need for further study.

**Acute treatment of migraine**

**Analgesics.** Acetaminophen and ibuprofen are widely used for pain relief and antipyresis in children and sold without prescription in many countries. Hamalianen *et al.*\(^{16}\) compared oral ibuprofen with acetaminophen in acute treatment in children. Doses used were acetaminophen 15 mg/kg and ibuprofen 10 mg/kg. Placebo control was used because of the high placebo response rate found in adult migraine (15–70%).\(^{17}\) Eighty-eight children were studied with an age range of 4.0–15.8 years. The results suggested that both were effective and well tolerated, with acetaminophen having slightly less efficacy and ibuprofen producing best overall pain relief. Controlled studies such as these are helpful in treatment of children with migraine and suggest that these over-the-counter medications provide effective and safe pain amelioration. They are a reasonable and economical consideration in first line therapy of childhood and adolescent migraine.

Ergot preparations have also been of benefit anecdotally in paediatric migraines.\(^{18}\) Strict usage guidelines must be employed in order to minimize potential side effects from vasoconstrictive properties; and they are contraindicated with the triptan class of medication or in complicated migraine.

With mild to moderate pain symptomatology, mild analgesics, combination analgesics and non-steroidal anti-inflammatory drugs can be quite effective. An important area of concern often under-recognized in children and adolescents is the possibility of analgesic rebound headache, which is well known in the adult population.\(^{19}\) Typically, following an illness or injury, or more frequently without a precipitating event, the patient starts taking analgesics daily or almost daily without a definite precipitating event. Chronic tension-type headaches make their appearance with an increased frequency of migraine events. Diagnosis is difficult; the headache may persist for years and generally may clear only after the patient refrains from use of all agents containing acetaminophen, non-steriodals, opiates or ergots. Treatment of analgesic rebound headache is also difficult; these headaches can be self-perpetuating with frequent analgesic use. Vasconellos *et al.*\(^{20}\) attempted treatment with low dose amitryptiline in their 46 patient paediatric cohort (mean age 12.1 years) with chronic analgesic rebound headaches. The dose of amitryptiline used was 10 mg, and the average duration of therapy was brief (2.2 months). Most patients significantly improved their headache frequency or their migraine severity with only minimal side effects of sedation.

**Triptans.** Recent research in mechanism of action in migraine involves the trigeminovascular system and activation of vasoactive structures in cranial and dural vessels.\(^{21}\) This causes release of vasoactive neuropeptides. 5-Hydroxytryptamine (serotonin) presynaptic receptors control release of these neuropeptides, and postsynaptic receptors constrict vessel walls. Several lines of research implicate serotonin as a mediator of migraine pain, but to date the specific mechanisms are unknown.\(^{22}\) The triptans are a new class of pharmacological agents, which act as serotonin agonists in affecting reduction in cerebral blood flow and neuropeptide release. They have proven effective in adults for acute therapy of migraine, and recent studies have involved usage in children. Sumatriptan is generally thought to be the reference standard, with several different preparations available, including oral, intranasal and subcutaneous in its earlier release in the USA. Several other triptans are now available with slightly different side effects and pharmacokinetic profiles, including zolmitriptan, naratriptan and rizatriptan\(^{23}\) (Table 3).

<table>
<thead>
<tr>
<th>Name (generic/brand)</th>
<th>Sumatriptan Imitrex©</th>
<th>Rizatriptan Maxalt©</th>
<th>Naratriptan Amerge©</th>
<th>Zolmitriptan Zomig©</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company</td>
<td>Glaxo Wellcome</td>
<td>Merck</td>
<td>Glaxo Wellcome</td>
<td>Zeneca</td>
</tr>
<tr>
<td>Formulations</td>
<td>Injection, nasal spray, tablet</td>
<td>Tablet, orally disintegrating tablet (MLT)</td>
<td>Tablet</td>
<td>Table</td>
</tr>
<tr>
<td>Usual adult dose</td>
<td>50 mg tablet 20 mg nasal spray 6 mg s.c.</td>
<td>10 mg</td>
<td>2.5 mg</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Onset: pain relief at 30 min</td>
<td>10–12% tablet 27% nasal 63% s.c.</td>
<td>20%</td>
<td>8–10%</td>
<td>15–18%</td>
</tr>
<tr>
<td>Efficacy: pain relief at 2 h</td>
<td>50–61% tablet 55–64% nasal 81–82% s.c.</td>
<td>67–77%</td>
<td>48%</td>
<td>62–65%</td>
</tr>
</tbody>
</table>

The source of information is from medication package inserts.
Therapeutic efficacy and assessment of safety of triptans in children have been studied recently only in pre-pubertal children. Hamalianen et al.24 studied oral sumatriptan compared with placebo in 23 children over 8 years old with migraine.24 Oral dosage of sumatriptan was 50 mg for a body surface area of 0.75–1.5 m² and 100 mg for a body surface area >1.5 m². Their placebo-controlled study delineated no significant improvement in pain relief compared with placebo. This contrasts with the efficacy of adult studies (26–31% adults pain free and 50–66% obtained partial relief) compared with this paediatric study (22% pain free and 30% partial relief).25 The authors suggest a different response in children and adults to oral sumatriptan. No significant side effects were reported.

Ueberall and Wenzel26 evaluated intranasal sumatriptan in paediatric patients with migraine. They found significant effectiveness in headache relief compared with placebo, with no significant adverse effects. The intranasal preparation was also easy to administer, and younger children were studied—with 14 children involved, mean age 8.2 years. Adult studies with other triptans (rizatriptan and zolmitriptan) have included adolescents of 12 years of age and older, with no significant adverse events and significant efficacy compared with placebo.15

Sumatriptan is available in several formulations. Rizatriptan is available in a novel preparation—as a wafer that dissolves instantly on the tongue without liquid, which may be preferred in some patients (Table 3). Further studies with other triptans are ongoing in children and adults to determine the safety profile and efficacy in this population compared with the adult studies available. Difficulties are inherent due to IHS classification schema of paediatric migraine and ability to diagnose true migraine concisely and reproducibly versus other types of headaches. Also, the inherently relatively shorter duration of headache in children compared with adults is a notable therapeutic variable in controlled studies.

**Prophylactic treatment of migraine**

In some children, despite non-pharmacological measures, migraine occurs frequently enough and with consistent disability and school absences to consider interval prophylactic treatment. This is an area with few available published controlled studies in children. A guideline for treatment usually is at least three or more migraines per month and with careful concomitant documentation of frequency, duration, side effects and associated factors.18

**Older therapies (β-blockers and antidepressants).** Propranolol and other β-blockers have been used in adults with some efficacy, and some controlled studies have had good results.27 Controlled data in children have shown inconsistent results with mixed success.28 Side effects generally have been mild, including insomnia and weight gain.

Cypriheptadine, an antihistamine, has serotonin-blocking properties and is well tolerated in children. Some problems, including sedation and weight gain, may occur. Earlier studies suggest some efficacy in migraine prophylaxis in children; however, studies have been non-controlled open label studies.29

Tricyclic antidepressants have been used in treatment of analgesic rebound headache in children and adults, and also in chronic daily tension-type headaches in adults with some benefit.20 However, no controlled studies on treatment of migraine in children are available although they currently are frequently used.

**Newer therapies—anti-epileptic drugs.** An area of recent interest has been prophylactic treatment of adult migraine with anti-epileptic drugs. A strong association between epilepsy and migraine has been suspected for many years, with recent information indicating notable co-morbidity.30 This is helpful in devising treatment strategies—using agents helpful for both conditions in patients with migraine and epilepsy. Ottman and Lipton30 studied 1957 adults with epilepsy with 432 patients reporting history of migraine (24%). They reported that the risk of adult migraine in patients with epilepsy is more than twice as high as in those without epilepsy. Andermann and Andermann31 studied prevalence of epilepsy in adults with migraine and reported epilepsy prevalence of 5.9% compared with a corresponding prevalence of epilepsy in the general population of ~0.5%. No controlled paediatric studies currently are available evaluating co-morbidity of epilepsy and migraine or behavioural disorders in migraine. Anecdotally, there does seem to be higher concurrence in children.

Several controlled studies recently have determined the efficacy of divalproex, a commonly used anticonvulsant, in preventing adult migraine.32,33 Divalproex is an inhibitor of γ-aminobutyric acid (GABA) degradation and correspondingly elevates brain GABA levels. The drug was well tolerated, with the most common side effects being somnolence, weight gain and gastrointestinal symptoms. Clinical studies in children and adolescents for migraine are being undertaken at this time. Anti-epileptic drugs such as valproate have a long history of use in paediatric epilepsy, with safety profiles studied thoroughly in children and adolescents.34 Gabapentin,35 topiramate36 and tiagabine37 have been shown to display some effectiveness in treatment of vascular type headache in adults, but controlled adult and paediatric data are not available. Safety profiles have suggested no significant side effects in adults. These agents are generally well tolerated in treatment of paediatric epilepsy.38-40

**Alternative therapies**

Children with migraine have a higher frequency of psychiatric co-morbidity than children with tension headache. Anxiety and depression probably are most common.1
Co-morbid psychiatric problems in 11% of migraineurs versus 2% of children with tension headache have been reported. If stress plays an overall very important role in exacerbating the occurrence of childhood migraine, psychiatric referral in these instances can be ameliorative in reducing headache recurrence.

Another controversial area is applicability of biofeedback and relaxation therapy in children with co-morbid anxiety or significant stressors concurrent with migraine. Fasting and sleep deprivation are also important factors in exacerbating childhood migraine. The importance of taking a complete history from the child and parent is paramount, and the keeping of a thorough headache diary by the family may further elucidate the effects of these variables on migraine frequency and severity. Dietary manipulation in children is difficult to maintain regarding nutritional needs and the inability for thorough vigilance of school-aged children. Dietary provocation of migraine has not been studied thoroughly in children and further investigation is probably warranted.

In older girls, the effects of puberty and sex hormones influence migraine frequency and severity. Ten per cent of women have onset of migraine at menarche, with most of this increase due to menstrually related migraine. This relationship is important to identify early on with thorough history and implementation of a headache diary in order to modify environmental factors and other provoking factors such as fatigue and stress in susceptible adolescent girls. Certain pharmacological treatment options are available in menstrually related migraine including perimenstrual migraine prophylaxis with cyclic oral magnesium supplementation 360 mg/day or treatment with cyclical non-steroidal anti-inflammatory drugs such as naproxen sodium 550 mg b.i.d. for 7 days before the menstrual cycle to 6 days after onset of menstrual flow. Severe migraines may persist despite perimenstrual prophylaxis, and effective pharmacological therapy for acute headaches is necessary.

Further directions
Migraine headaches are common in children and adolescents. They are inherently more difficult to diagnose and classify in children, with associated problems in history taking and pain perception, and inherent differences in manifestation of pediatric and adult migraine. Solidifying IHS diagnostic criteria is a future consideration to simplify diagnosis and assist in the ease of obtaining controlled pediatric studies. Recent current pediatric research studies suggest a notable difference in response to some types of medication, such as sumatriptan, compared with adults, and there is a need for further controlled studies in children.

Recent information suggests that for routine, first time use, over-the-counter analgesics such as ibuprofen and acetaminophen are safe and effective. Frequent usage of analgesics may lead children and adolescents to analgesic rebound headaches as can occur frequently in adults. The new frontier for acute treatment is likely to be development of these triptan agents for use in children, but they need careful study combined with validated diagnostic criteria and doses adapted for children. Non-pharmacological avenues of treatment such as biofeedback, relaxation therapy, and environmental and dietary manipulation should be thoroughly contemplated, and in certain clinical circumstances may prove effective in tempering migraine frequency and severity in children. Physicians treating childhood migraine are tantalized by a new array of treatment options but frustrated by a lack of information regarding doses and efficacy in children.

Prophylactic treatment of migraine in children is least understood and studied. With newer advances in knowledge of co-morbidity with epilepsy, the new frontier for migraine prophylaxis is use of anti-epileptic drugs. Further rigorously performed and carefully designed studies of anti-epileptic drugs in migraine prophylaxis in children are warranted when efficacy has been shown in adult studies. These anticonvulsants have been well studied in children with epilepsy regarding safety and side effects long before their utility in migraine prophylaxis was evaluated in adults. Dosing and related efficacy in children and minimization of toxicity is the next step in migraine therapy. With continued research in pediatric migraine, its frequency, genetics, prognosis and response to treatment, we may even alter the course of adult migraine in the future.

Acknowledgements
This study was sponsored in part by an educational grant from Abbott Laboratories.

References


