Management of migraine in adolescents

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Abstract: Headaches in children and adolescents are still under-diagnosed. 75% of children are affected by primary headache by the age of 15 with 28% fitting the ICHD2 criteria of migraine. Migraine is considered a chronic disorder that can severely impact a child's daily activities, including schooling and socializing. Early recognition and aggressive therapy, with acute and prophylactic treatments, as well as intensive biobehavioral interventions, are essential to control the migraine attacks and reverse the progression into intractable disabling headache.

Keywords: migraine, children, adolescents, headache, biofeedback

Introduction

Primary headache, especially migraine, has been under-diagnosed in children and adolescents. Migraine is not a rare disease in this age group: 10% of children are affected by migraine headaches, and up to 75% of children by the time they are 15 years old report having a significant headache (Bille 1962), which is described as intolerable pain that prevents them from any activity, including going to school or to social events. 28% of these children appear to have migraine (Split and Neuman 1999). This very common disorder has a significant impact on a child's life and school performance, as well their relationship with their family and peers. The impact of this disease can result in school absenteeism and lack of involvement in peer activities, and can have long term socioeconomic and possibly biological consequences. Early recognition and intervention with appropriate treatment is essential to minimize this impact on a child's quality of life, and may be important in preventing long term disability.

Epidemiology

Headaches are very common in childhood. Based on the study of 8993 children between 1957–1961, Bille (1962) found that 40% of children had a significant headache before the age of 7, while 75% had a significant headache before the age of 15. Approximately 4% of these patients between the ages of 7 and 15 were believed to have migraines. In a meta-analysis of childhood headaches examining over 27,000 children, 37%–51% of children by the age of 7 reported a significant headache, while 57%–82% of children reported a significant headache by the age of 15 (Lewis et al 2002a).

Abu-Arafeh and Russell (1994) reported that 10.6% of children had significant headaches consistent with migraine between the ages of 5–15, with an increasing one year prevalence between the ages of 10 and 19. In the meta-analysis of pediatric headache, between 1.2% and 3.2% of children between the ages of 3 and 7 had migraines with a slight male predominance (Lewis et al 2002a). Between the ages of 7 and 11, this increased to between 4 and 11%, with an equal male and female predominance; and between 11 and 15 this increased to 18%–23%, with a female predominance developing. In the 15–19 year old age range, Split and Newman (1999) looked at 2353 children in Lodz, Poland, using the ICHD-I criteria. This study found that 28% of these adolescents had migraines with a female predominance. Of the adolescents with migraine, 19% had migraine without aura and 9% had migraine with aura. Mixed headaches were seen

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in 6.3% had with some tension-type headaches in addition to migraines. There was a strong family history with 81% of the adolescents with migraine with nearly a quarter of the females in this group having a menstrual relationship with their headaches. In addition, status migrainosus was noted in 14.8% of the girls, and 4.7% of the boys (Split and Neuman 1999).

Pathophysiology

The pathophysiology of migraine headache remains undefined. Several theories as to the underlying pathophysiology are being developed. One aspect of migraine that is clear is its genetic nature (Montagna 2004). Twin studies and family studies have demonstrated a high degree of inheritance, reporting a history of migraine as high as 90% in first or second degree relatives. For familial hemiplegic migraine, three genes have been identified as contributing to the disorder in several kindreds: P/Q Calcium channel (CACNA1A), ATPase (ATP1A2), and sodium channel (SCN1A) (Dichgans et al 2005). There has been suggested linkage with some of these genes in familial migraine with aura, yet a consistent gene defect in migraine without aura or migraine with aura has not yet been identified.

The trigeminal neurovascular system's involvement with migraine has been proposed as a unifying theory of migraine. This model has been supported by several imaging studies that have demonstrated involvement of the brainstem near the trigeminal nuclease and the peri-aquaductal gray (Welch et al 1998).

The pathophysiology of tension type headaches (TTH) in children should be similar to that seen in adults. Two theories exist relating migraines and TTH. The continuum model suggests that migraine and TTH are one pathophysiological disorder ranging from mild headaches that appear to be TTH, to the most severe headaches that represent migraines associated with aura (Cady et al 2002). This is contrast to the Spectrum model, which suggests that these are two separate entities, with the migraine patients experiencing a full spectrum of headaches, while TTH patients have headaches limited to the aforementioned mild to moderate pain disorder (Lipton et al 2000a).

With TTH, there may be a secondary muscle contraction component, and some suggestion has been provided that this could enhance a feedback loop, building the TTH (Langemark and Olesen 2000). Recently,the role of central sensitization and other alternative theories have been reviewed (Jensen 1999).

Diagnosis

In order standardize the diagnosis, criteria were developed and were revised at the International Headache Society in Italy, 2003, to better fit the diagnosis of headache in children and adolescents. Previous criteria were lacking sensitivity and specificity in diagnosing childhood headache (ICHD-1) (IHS 1988). The suggestions adopted in the second edition of the ICHD criteria (ICHD-II) (IHS 2004) to make the criteria more sensitive to childhood headache included a shorter duration, lack of some associated symptoms due to the description of difficulties faced by children, as well as the bilateral location of the headache as opposed to the unilateral location in adults. The validity of the ICHD-II has yet to be fully assessed for children. It does appear to be an improvement, although indications are that it remains incomplete in diagnosing primary headache disorders in children (Hershey et al 2005). However, given these limitations, the ICHD-II is the current foundation for the diagnosis and scientific study of headache and migraine. Headaches are divided through the ICHD-1 criteria as primary and secondary.

Primary headaches

Migraine headache

The ICHD-II criteria subdivide migraine into migraine without aura and migraine. In addition, migraine includes migraine variants, such as the periodic syndromes of childhood, and probable migraine, when not all of the features of migraine are met. The ICHD-II also added the category of chronic migraine, defined as frequent headaches – at least 15 times per month for the previous three months – with migraine features that could not be attributed to a secondary cause.

Tension-type headache

Tension-type headaches are generally considered mild, recurrent headaches, and many features are the opposite of migraine. In the past, they have been called muscle contraction headache, idiopathic headache, tension headaches and "stress headache". They can be subdivided into infrequent, frequent, and chronic based on the frequency of the headaches. The headaches themselves are usually described as mild and moderate in severity, diffuse in location, and have a pressing quality. No associated symptoms and no secondary causes are identified.

Impact of migraine

Primary headaches and migraines can have a significant impact on a child's life. The impact of a migraine can be measured by both the loss of ability to participate in activities, as well as the effect on quality of life. In the 1989 National Health Interview Survey, it was found that for adults, there

are three million bedridden days per month in the United States, with 56% of these adults missing at least two days of work per month due to their migraines (Stang and Osterhaus 1993). This same survey evaluated the impact of childhood headaches and found that within a two-week period, 975,000 children had a migraine, resulting in 164,454 missed school days within this two-week period.

Headache can affect all aspects of a child's functioning, leading to negative affective states (eg, anxiety, depression, anger) and increased psychosocial problems (eg, school absences, problematic social interactions). Although the vast majority of children who experience headaches, including those who report recurrent headaches, do not display a diagnosable psychiatric condition, a few of these patients, upon presentation for treatment of headache, are exhibiting symptoms that indicate the presence of a comorbid psychological/psychiatric condition such as an anxiety disorder or depression.

For children who experience frequent headache problems, the relationship between headache and psychiatric symptoms has not been well defined. Although global conclusions about psychopathology in children with headaches have been advanced, the mechanisms underlying these associations remain poorly understood. Specifically, whether psychiatric disorders are a causal factor in the development of headache, whether headache is a causal factor in the development of psychiatric disorders (eg, frequent and severe pain leads to anticipatory anxiety, perceived loss of control, frustration, or other risk factors for psychopathology), or whether a common shared etiological factor may explain both without a causal association between them (eg, biological or neurotransmitter) are unresolved hypotheses. Evolving research is beginning to examine longitudinally the relation between headache and psychopathology in youth, but conclusions pertinent to practice are premature at this time.

Several tools have been developed to evaluate the disability of migraine. In adults this can be addressed with MIDAS (MIgraine Disability ASsessment) (Stewart et al 1999, 2000, 2001; Lipton et al 2001). This tool measures headache-related disability using three domains – work, household work and nonwork or social activities – over a 3-month recall period. MIDAS has been found to be quite useful in assessing disability in adults and has been used in long term studies to demonstrate any change in disability or treatment, as well as the development of new treatment strategies, including the Stratified Care Model (Lipton et al 2000b; Lipton and Silberstein 2001). A simplified scoring system for MIDAS has been developed, with four levels of disability.

For children, however, MIDAS was inadequate, due to the differences in lifestyles of children. Consequently, PedMIDAS was developed (Hershey et al 2001). The PedMIDAS evaluates three similar domains to the adult scale (ie, MIDAS), but the measure was adapted to correspond more with pediatric populations. For instance, on the PedMIDAS the school affect domain was augmented to include three questions assessing days that were fully missed, days that were partially missed, and days where the child remained in school but had diminished functioning due to the migraine. In the home effects domain, only one question was retained from the MIDAS: those days where the child is unable to perform home activities such as chores in the household and homework. Finally, the social effect domain was increased to two questions, with one assessing days where the child was unable to participate in social activities such as interacting with friends and sporting activities, and the other assessing days where the child was only able to participate at 50% of their abilities. The scoring system was based on patient-based disability and had a greater score range than MIDAS due to the child's increased ability to miss out on activities (Hershey et al 2004).

The use of MIDAS for adults and PedMIDAS for children can be highly effective in assessing the disability of migraine and subsequent treatment and outcomes. One recent study found that PedMIDAS was a useful tool in assessing treatment strategies, with an improvement in PedMIDAS scores demonstrated with use of prophylactic medication (Hershey et al 2002).

Quality of life

Assessing health-related quality of life (QoL) is another way to evaluate the impact of a disease. QoL is a multidimensional construct that reflects the impact of disease and treatment on a patient's subjective evaluation of his or her functioning and emotional well-being (Bandell-Hoekstra et al 2000). Initial studies with adults found that headache sufferers evidence reduced mental health functioning, as well as poor physical, social, and role functioning. In one such study assessing QoL in adult patients with migraine headaches in comparison to other chronic diseases, such as hypertension, diabetes, angina and myocardial infarction, it was found that patients with migraines reported a greater impact on their social, mental and pain functioning than patients with other chronic diseases (Osterhaus et al 1994). In addition, the results if this study found that different headache types had a significant impact on the QoL, and that QoL varied according to headache disorders, with cluster headache having a larger impact on

social and pain function when compared to migraine, tension, or mixed headache disorders (Solomon et al 1993).

The assessment of headache-related QoL in children and adolescents is an emerging area of research. Despite the paucity of research on the impact of headache on perceived QoL, the available studies provide compelling evidence that demonstrate the negative impact of headaches on children's QoL. Engstrom (1992) found that, in a sample of 20 headache patients aged 9 to 18 years, children experienced more somatic complaints, lower general well-being, were less communicative, and experienced more physiologic anxiety than matched nonheadache controls. In another study of adolescents, participants with headaches reported worse psychological functioning, more physical symptoms, poorer functional status, and less satisfaction with life and heath than headache free controls (Langeveld et al 1996). Powers and colleagues (2003) found that in their study of 572 pediatric patients between the ages of 5- and 18-years referred to a headache clinic, QoL was adversely affected in all areas of functioning when compared to healthy controls, and the impact on QoL was similar to that of children with juvenile rheumatoid arthritis and cancer. Finally, in a community sample of Swedish adolescents, Fichtel and Larsson (2002) found that adolescents with frequent headache had more functional disability when compared to those who had infrequent headache.

As a result of unpredictable and severe headaches, emotional functioning may suffer as children experience repeated adjustment difficulties. Even in between headache attacks, the QoL of patients with recurrent headaches remains compromised. For example, children and adolescents may worry about whether a headache will start or worsen, fear that peers may not understand, worry about interference with social life and academic life, may experience a loss of control, and feel fed up, frustrated, angry, and worried (Cavallini et al 1995). The ability to perform everyday activities, such as going to school and participating in extracurricular activities, is important for child and adolescent development, and limitations in these areas can have significant negative psychological influences.

Therefore, incorporating reliable and valid pediatric-specific measures of quality of life has important implications for treatment. The assessment of QoL in children is challenging, since measures must account for changes in cognitive and social development, and whether information is more accurate when obtained by child report versus parent report is debatable. The Pediatric Quality of Life Inventory, version 4.0 (PedsQL 4.0) is a valid, developmentally appropriate measure designed to assess pediatric QoL in children between the ages of 2 and 18 years (Varni et al 2001). This brief 23-item questionnaire is a general measure of QoL and has two forms, incorporating both parent and child responses. The PedsQL 4.0 has four age ranges: toddlers (2–4 years), young child (5–7 years), child (8–12 years), and adolescent (13–18 years). The PedsQL asks respondents to indicate how much of a problem each item has been during the past month. The PedsQL 4.0 assesses QoL across four domains including: physical health, emotional, social, and school health. The questionnaire yields a total QoL score and two summary scores: Physical Health Summary Score and Psychosocial Health Summary Score.

When this instrument was compared across ages, it was found to be able to easily detect the impact of childhood headaches on the quality of life of children and adolescents (Powers et al 2004). In one study, a comparison of the QoL of children and adolescents with migraine with norms for healthy children and adolescents demonstrated impaired QoL in all areas of functioning (Powers et al 2003). Cross-sectional comparisons within a migraine sample found differences in functional impairment across age groups, with adolescents (ages 13–18) reporting more impairment in School Functioning than children (ages 8–12) and young children (ages 5–7), and young children reporting more impairment in Social Functioning than children and adolescents. When compared to other disease processes, including rheumatological diseases, oncological diseases, and cardiac diseases, although migraine did not separate out from these diseases, it was found to have a greater significant impact on the quality of life, especially the emotional and school development (Powers et al 2003).

Measures of QoL, such as the PedsQL 4.0, can be effective tools in treatment planning and outcome measurement. In order for evaluation and management of headaches to be most successful, patient perspectives and goals should be accounted for. Thus, it is crucial to understand children's and adolescents' perceptions of the impact of headaches on their daily lives. Treatments that actively involve the patient's perspective typically result in increases in the patient's QoL, which are likely to bring about long term improvements in the overall QoL of the patient's family as well. QoL instruments can be easily incorporated into clinical settings, as well as research protocols, to help inform practice and treatment.

Evaluation

One of the first steps in the evaluation of a child with headache is to identify if it is attributed to a secondary cause.

This is done through a detailed headache history, including the length of time the child has had headaches, the severity of the headaches, the quality of the headache, location of the headache, as well as the impact on the child's quality of life and disability. The headache history also needs to include a detailed review of systems, past medical history, as well as a psychosocial and family history in order to identify warnings. Oftentimes, the parents and patients may have a preconceived determination as to the type of headache that the child has that is incorrect. A recent meta-analysis component of a practice parameter identified that the most sensitive indicator of a need for further assessment is the neurological examination (Lewis et al 2002a). If abnormalities on the neurological examination cannot be explained by medical history, further investigation into the headache etiology is warranted and neuroimaging is most sensitive tool to detect a medically or surgically treatable cause.

Once the detailed history and neurological examination are performed, it is also useful to include a comprehensive headache exam (Linder 2005). This comprehensive headache exam can assist in identifying potential secondary causes, as well as being used to discuss with the family possible misconceptions regarding the etiology of the headache.

Following the detailed history and medical examination, the primary caregiver should be able to determine whether the headaches are primary headaches or secondary headaches. If secondary headaches, it is essential to treat the secondary cause. If the headaches persist after resolution of the secondary cause, a reanalysis as to the etiology of the headaches must be considered.

Once secondary causes have been ruled out, the treatment of primary headaches can begin. In childhood, the most significant primary headache disorders brought to medical attention are migraine. This most commonly includes migraine without aura, probable migraine, migraine with aura, and chronic migraine.

Treatment

The treatment of primary headache disorders in children is threefold. The first component of treatment is acute therapy.

1. Acute therapy is the treatment designed to abort the episodic headache. The goal of this treatment should be quick response, with return to normal activity and without relapse.
2. The second component of treatment is preventative treatment. When a child's headaches are frequent or there is significant disability, preventative treatment must be considered with a goal of minimizing the impact of the headache while reducing the number. Although no defined frequency exists for preventative treatment, typically having more than 2–3 headaches per month warrants treatment. This determination can be augmented by a disability instrument such as PedMIDAS (Hershey et al 2001, 2004).
3. The final component of treatment is biobehavioral therapy. This is a complex treatment that involves normalizing a child's lifestyle, as well as establishing long term healthy goals and promoting proper medication use.

Acute treatment

For the acute treatment of migraine, the National Headache Consortium Guideline recognized in adults that primary treatments can include nonspecific medications, as well as migraine-specific medications (Silberstein and Rosenberg 2000). For children, the nonspecific medications are primarily over-the-counter medications including nonsteroidal anti-inflammatory drugs (NSAIDs; ibuprofen, naproxen sodium, and for older children aspirin), as well as general pain relievers (acetaminophen). Most prescriptive nonspecific medications have either not been evaluated in children, or have not been proven statistically effective. Furthermore, many prescriptive medications contain sedatives or narcotics that may treat the pain, thus not allowing the child to return to normal functioning.

Hämäläinen and colleagues (1997) reported a comparative, double-blinded, placebo-controlled, crossover study of placebo versus ibuprofen versus acetaminophen. Eighty-eight children with a clear diagnosis of migraine participated. These patients treated a migraine headache with either placebo, ibuprofen at a dose of 10 mg/kg, or acetaminophen at a dose of 15 mg/kg. Improvement in pain and pain freedom were assessed. The results of this study indicated that ibuprofen was superior to both placebo and acetaminophen at both the one and two-hour time point, while acetaminophen became superior to placebo at two hours. Lewis and colleagues (2002b) performed a similar study on a group of younger children using a dose of ibuprofen at 7.5 mg/kg versus placebo with a similar outcome, although there was a slight male-to-female difference.

Based on these studies, as well as the tolerability of ibuprofen, it has become a mainstay for the acute treatment of childhood headache and migraines. Proper use of ibuprofen requires the child to learn to identify the onset of the headache in order to initiate rapid treatment, use the proper dose based on their weight and avoid overuse typically limiting it to no more than three times per week.

When NSAIDs are ineffective or not completely effective, migraine specific therapy is oftentimes required. Triptans are 5HT-1B/D agonists, migraine-specific medications. There are currently seven triptans approved for use in the United States in adults, although none have been approved for the use of childhood migraine. This is largely due to study design and a large placebo effect seen in children, whereas the effect of the triptan was comparable to the adult studies. Several studies that were performed, however, did show their effectiveness, including the use of sumatriptan both in tablet and nasal spray form (Linder and Dowson 2000), rizatriptan, and zolmitriptan, both in tablet and nasal spray form.

One of the initial studies in children was subcutaneous sumatriptan at a 0.06 mg/kg dose. The overall effectiveness was 72% at 30 minutes, and 78% at two hours, with a low recurrence rate of 6% (Linder 1995). Injection of medication, however, is often rejected by children and this has limited its use.

Oral sumatriptan has been studied in a double-blinded, placebo control study with 25, 50 and 100 mg tablets (Winner et al 1996). The study' s primary endpoint was at two hours. Headache response and statistical significance was not reached due to a high placebo rate. Sumatriptan was, however, statistically significant over the placebo at 25, 50 and 100 mg at both the 180 and 240 minute mark, with 74% pain relief at the 4 hour mark. Headache recurrence rate remained lower in children than adults at an 18%–28% for sumatriptan, with no significant adverse affects seen.

Sumatriptan nasal spray has been studied in randomized double-blinded placebo control trial in adolescents from 12–17, for a single attack, using 5, 10 and 20 mg doses (Winner et al 2000). At 1 hour, 56% of patients using the 10 or 20 mg dose reported significant headache relief, compared with 41% with placebo. If pain free response is examined, the 20 mg dose was statistically significant with a 46% response rate at 2 hours, compared to 25% for placebo. Associated symptoms were lower in the active medication group with photophobia significantly lower with the 20 mg dose in 2 hours. A recent nasal sumatriptan study using 5 mg, 20 mg and placebo dosing in a one-to-one ratio with 738 adolescents did demonstrate that at 30 minutes a 20 mg dose had a greater headache relief (42% versus 43%, $p = 0.046$). At 1 hour, this increased to 61% for active medicine versus 52% placebo (not significant). By 2 hours response was increased to 68% for sumatriptan versus 58% for placebo ($p = 0.025$). There was also increased sustained release 1 through 24 hours and 2 through 24 hours (Winner et al 2000).

Rizatriptan 5 mg tablets have also been evaluated in the 12–17 age group, with a double-blinded placebo controlled parallel group single attack study (Winner et al 2002). Of 149 adolescents using rizatriptan, compared to 147 using placebo, the response rate at 2 hours for the rizatriptan group was 66%; whereas the placebo affect was 57%. The response of 66% in this study was comparable to the adult studies, although the placebo dose was much greater. Headache free rate at 2 hours was 32% for the rizatriptan group, compared to 28% in the placebo group with no serious adverse effects noted.

Zolmitriptan has also been studied in adolescents age 12–17, using both the 2.5 mg and the 5 mg dose (Peroutka 1997). The response rate was 88% and 70% respectively, with the treatment well tolerated. Nasal zolmitriptan was recently found to be effective, using a unique study design to minimize the placebo response rate. 248 adolescents were studied in a, randomized, double-blind, placebo-controlled, 2 attack crossover trial with a single-blind placebo challenge. Seventy-seven patients responded to the placebo challenge and did not continue in the analysis. Of the remaining 171 patients, zolmitriptan produced significantly higher headache response rates than placebo at 1-hour post-dose (58.1% versus 43.3%; $p < 0.02$), with an onset of action as early as 15 minutes. Zolmitriptan also produced significant pain-free response at 1 hour (27.7% vs. placebo 10.2%, $p < 0.001$) and adolescents experienced a lower incidence of adverse events than usually seen in adults, with no serious adverse events or withdrawals (Peroutka 1997).

Two methods may be used for using triptans (Lipton et al 2000b). One is the rescue therapy or "stepwise treatment within an attack", where the child starts with an NSAID at an appropriate dose at the onset of their headaches. If they recognize that this is not working, a triptan is used as rescue therapy. The alternative method is the "stratified care model." This requires the patient to determine the headache severity at the onset. For a mild or moderate headache, they take their NSAIDs, while for severe headaches, they take their triptans. In this way, the patient stratifies their headaches and the subsequent treatment. This, however, has not been successful in children, as they oftentimes have difficulty recognizing the headache severity at its onset.

Recently, Burstein and Cutrer (2000). identified cutaneous allodynia with central sensitization in adult migraine patients. In patients that do experience allodynia with central sensitization, there is decreased response to medication once the allodynia has been established (Burstein et al 2000; Burstein and Jakubowski 2004). Allodynia can be thought of as extra peripheral sensation or heightening of activity in

sensation beyond the location of the headache or migraine. If a patient is identified as having allodynia, it is important to stress the need for early treatment.

One precaution that must be taken with the use of acute medications is the avoidance of medication overuse. Medication overuse or analgesic rebound headaches are a frequent cause of transformed migraines or chronic daily headaches. It is characterized by inadequate treatment of headache with either a low-dose, or delayed treatment of the attack, resulting in an increasing use of the analgesic or medication over time with decreased effectiveness. When identified, a recovery period free of analgesic use is required. It is imperative to notify the patients of the risk of analgesic overuse headache if any analgesic is used for more then 3 headache per week.

A summary of treatment options can be found in Table 1.

Abortive therapy for migraine in children should focus on aborting an acute attack by controlling the aseptic inflammation at the origin of the vasodilation and the pain. The first line of treatment would be using an appropriate dose of anti-inflammatory medications, such as ibuprofen (10 mg/kg), at onset of the headache in combination with rehydrating fluids. The dose may be repeated once in 3–4 hours for that headache.

Adequate response is defined headache freedom in 1–2 hours, with patient back to baseline. If the headaches are still prolonged and not responding to anti-inflammatory drugs, the use of triptans is warranted. Any triptan can be used as a rescue medication and repeated 2 hours later for the same headache. Triptans have some limitations for the number of headache per month (4–6 per month) they can be used for.

Table 1 Different abortive treatment in children with migraine

Treatment of Migraine	
Abortive	
Reviewed by Igarashi et al 1992, Welch 1993	
♦ Acetaminophen	♦ Ca-channel blockers
♦ NSAIDs	♦ Isometheptene compounds (midrin, midrid)
• Aspirin	♦ Dopamine antagonist (D_2 receptor)
• Ibuprofen	• Metaclopramide
• Other	• Prochlorperazine
♦ 5-HT agonist	
• Triptans $5ht_{1b/1d/1f>1a}$	
• Ergotamine/ dihydroergotamine D_2, adrenergic, 5-HT_1	

They are not yet FDA-approved for use in children. Clinically, they are effective in children, and are frequently used for prolonged headaches.

When a headache does not respond to any of the above therapy, and lasts more than 72 hours, it will be defined as status migrainosus by the ICHD2 criteria and more aggressive therapy is needed to prevent a transformation to chronic headache. The patient at that point should be referred to inpatient therapy starting in th emergency room.

Acute emergency department/inpatient treatment

Available specific treatments for migraine headache in an emergency room setting include the following: antidopaminergic medication such as prochlorperazine and metochlopramide; NSAIDs such as ketorolac; dihydroergotamine (DHE); antiepileptic medications such as sodium valproate; and triptans. When this treatment does not work, a child may need to be admitted to the hospital for the treatment of status migrainous, an exacerbation of chronic severe headache or to check for an analgesic rebound headache. The goal of inpatient treatment is to control a headache that has been unresponsive to other abortive therapy and is disabling to the child.

Dopamine antagonists, including prochlorperazine and metoclopramide, were initially used for the nausea and vomiting effects of migraine headaches (Jones et al 1989). Subsequently, the dopaminergic model of migraine was developed, and these compounds have been re-analyzed for their usefulness in acute therapy (Peroutka 1997). Intravenous (IV) formulation is superior to all of the formulations, with the oral route being ineffective, or showing only limited effectiveness.

Prochloroperazine has been shown to be very effective in aborting an attack in the emergency room when administered intravenously with a load of IV fluids. Results show a 75% improvement with 50% headache freedom at one hour, and a 95% improvement with 60% headache freedom at 3 hours (Kabbouche et al 2001). When comparing prochlorperazine, metochlopramide and placebo in a randomized prospective double blinded placebo controlled study, the response to prochlorperazine was 82% improvement in headache severity, 42% with metoclopramide and 29% with placebo (Coppola et al 1995). The average dose of metoclopramide use is 0.13–0.15 mg/kg, with a maximum dose of 10 mg given intravenously over 15 minutes. These medications are usually well tolerated, but extrapyramidal reactions are more frequent in children compared to the older population, and an acute episode can easily be controlled in the emergency room

with 25–50 mg of diphenhydramine given intravenously. These can often be used to break an acute episode of status migrainosus.

Ketorolac is often used in the emergency department as monotherapy for a migraine attack or in combination with other drugs. In monotherapy, the response to ketorolac is 55.2% improvement (Larkin 1999). When combined with prochlorperazine the response rate increases to 93% (Brousseau et al 2004). Recurrence rate in 24 hours with ketorolac was 30%.

A possible explanation of this high rate of recurrence may be due to the use of ketorolac in patients with an analgesic rebound headache. These patients have been over-using their outpatient abortive treatment, including their NSAIDS. Ketorolac in these cases will only bring a temporary relief.

Ergot alkaloids have a long history of use in the humans, dating back over 400 years. They were first recognized nearly 100 years ago for their usefulness in migraines, with one of the most active forms being dihydroergotamine (DHE-45). Its effect is due to the 5HT1A-1B-1D-1F receptor agonist affinity and central vasoconstriction. It has a greater alpha adrenergic antagonist activity than triptans, and is less vasoconstrictive peripherally. Although it was first to be effective for migraine in 1945 (Horton et al 1945), it fell out of usefulness until Raskin (1986) reported its effectiveness. Subsequently, it has been synthesized and no longer has the complications from the purification, and is used frequently in the inpatient, as well as emergency management of childhood headaches (Linder 1994). Limited reports have shown the usefulness of IV DHE in an inpatient setting to break status migrainosus or prolonged migraines in children, and may have further benefit if premedicated with dopamine antagonists such as promethazine hydrochloride, or metoclopramide hydrochloride. More recently, nasal DHE has been used in adults. The extrapolation of the use in children, however, remains limited.

Single dose dihydroergotamine can be effective in the emergency room department. When compared to the valproate sodium, the response was similar for both at 1, 2, and 4 hours, but DHE showed a better response at 24 hours, with 90% headache free at 24 hours compared to 60% for the valproate (Edwards et al 2001). The effectiveness of these acute emergency department treatments in children and adolescents are limited but the reviews available show an acceptable outcome at 48–72 hours with a recurrence rate of 29%, which include the 6% who need a more prolonged inpatient treatment.

In-patient use of dihydroergotamine include two pediatric protocols that are recommended in children and adolescents. The first one uses more frequent injections, but lower doses to prevent side effects, while the second protocol is more aggressive and uses higher doses for faster response. Before initiation of these protocols, girls who are of child bearing age should be evaluated for any concerns for pregnancy.

Low dose DHE (Larkin 1999)

DHE is administered with metoclopramide (0.2 mg/kg – maximum of 10 mg is given half an hour prior to the administration of the DHE) to prevent gastroenteral side effects. The dose of DHE varies with patient age.

DHE is repeated every 6 hours for a maximum of 16 doses. When headache ceases, an extra dose of DHE is used to prevent recurrence. DHE dose may be increased by 0.05 mg/dose until abdominal discomfort.

High dose DHE protocol (Kabbouche and Linder 2005)

Patients are premedicated with 0.13–0.15 mg/kg of prochlorperazine half an hour prior to the DHE dose. A dose of 0.5–1 mg (depending on age and tolerability) is used every 8 hours until headache freedom. When headache ceases an extra dose is given. After 3 doses, the prochlorperazine is replaced by different antiemetic if significant nausea persists to lessen the risk of extrapyramidal side effects. The response seen to this protocol is a 97% improvement and 77% headache freedom. Response starts being noticeable by dose #5 and can reach its maximum effects after dose 10. Side effects of DHE include nausea, vomiting, abdominal discomfort, flushed face, and increased blood pressure.

This therapy is continued every 8 hours till headache freedom, with a maximum of 20 doses.

There are no placebo controlled studies available, and the only review was a retrospective study reviewing reponse to treatment in children admitted to a pediatric neurology floor for the treatment of status migrainosus ().

Sodium valproate has been introduced in children recently as an abortive treatment for acute attacks, with promising responses. The mechanism in which sodium valproate acutely aborts migraine headaches is not well understood. Sodium valproate is given as a bolus of 15–20 mg per kg push (over 5 minutes). This intravenous administration is to be followed by an oral dose (15–20 mg/day) within four hours after the injection (Mathew et al 2000; Tanen et al 2003). Studies examining the use of other anticonvulsant drugs have been inconclusive and will soon be repeated.

Recently, an inpatient use of sodium valproate has been suggested when DHE is contraindicated or has been

ineffective (Schwart et al 2002). A loading dose of 15 mg per kg is first administered, and then followed with 5 mg/kg every 8 hours till headache freedom, or up to 10 doses, whichever comes first. In adults with chronic daily headaches, this showed an 80% improvement.

The use of sodium valproate is deferred as the second line of treatment for status migrainosus due to the lack of studies reviewing benefits and responses, as well as guidelines and defined protocols. Multiple studies are available on the use of sodium valproate as a preventative medication, but not enough on acute therapy to get the medication to the forefront.

Prophylactic medication

The second component of effective headache treatment is preventative therapy or prophylactic medication. When a headache or migraine becomes highly frequent or disabling, preventative medications need to be considered. The goal of preventative treatment is a reduction of headache frequency and an improvement of headache disability. Prophylactic medication can be largely grouped into antiepileptic medications, antidepressant medications, anti-serotonergic medications, and antihypertensive medications. As with the acute therapy, no prophylactic medication has been approved for the prevention of childhood migraine. Several studies have demonstrated the effectiveness of some of these medications.

In the antiepileptic medications, medications currently being used for the prevention of migraine include divalproate sodium, topiramate, gabapentin, levetiracetam, and zonisamide. For adult migraines, both divalproate sodium and topiramate have been approved for the prevention of adult migraines (Mathew et al 1995; Silberstein 1996).

For divalproate, a study of 31 children, aged 7–16, showed at a dose of 15–45 mg/kg a 76% responsiveness of a greater than 50% reduction in their headache frequency, while 18% had a greater than 75% reduction, and 6% were headache-free (Caruso et al 2000). A study using standardized doses of either 500 or 1000 mg of divalproate in 9–17 year-olds also reported a reduction in severity on the Visual Analog Scale from 6.8 to 0.7, with a decrease in headache frequency from 6 per month to 0.7 per month (Serdaroglu et al 2002).

In a large scale open label study, topiramate demonstrated its effectiveness over placebo (Bandell-Hoekstra et al 2000). In a study of 162 children from age 6–15, using a dose of 2–3 mg/kg/day, with a maximum dose of 200 mg, topiramate resulted in a reduced mean monthly migraine rate over the entire double-blind phase of 2.6 days per month, compared to 2.0 days per month with placebo (Winner et al 2005). Although not statistically significant, the trend was reflective of this ($p = 0.061$). This was due to a large variation in the placebo-response group.

The effective dose for children for both of these medications is not known, but for divalproate sodium a dose of approximately 15–20 mg/kg/day and for topiramate, a dose of 2–4 mg/kg/day appears to be effective. To achieve this dose, however, it must be tapered up slowly, typically increasing the dose in quarter steps over an 8–10 week period. In the case of topiramate, it is especially important to taper the dose slowly, as rapid titration may increase the side effects, especially the cognitive slowing.

Amitriptyline is the most widely used tricyclic antidepressant for headache prevention. Amitriptyline has been used for many decades for its antidepressive properties, and was first recognized in the 1970s as an effective migraine therapy (Gomersall and Stuart 1973; Couch et al 1976; Couch and Hassesnein 1979). Most of the studies in children with amitriptyline have been open label studies, with no placebo-controlled studies.

In a crossover study by Levinstein (1991) comparing amitriptyline with propranolol and cyproheptadine, amitriptyline was found to be effective in 50%–60% of the children. In an open label study, amitriptyline resulted in a perceived improvement in over 80% of the children, with subsequent decrease in their frequency and impact of the child on headaches using a dose of 1 mg/kg/day (Hershey et al 2000). Due to its side effects, especially its somnolence, this must be slowly titrated to this dose, typically over an 8–10 week period, increasing it by 0.25 mg/kg/day every two weeks.

Cyproheptadine, an antihistamine with anti-serotonergic effects, has long been used for the prevention of childhood headaches (Bille et al 1977). In addition, it may also have some calcium channel-blocking properties (Peroutka and Allen 1984). Historic studies have shown the effectiveness in small groups of children with a dosage range of 0.2–0.4 mg/kg/day. It tends to be well tolerated, with the most significant side effect being increased weight gain. Due to the limitations in dosing and the significance of the weight gain, it tends to be limited to the younger children, with less usefulness in teenagers.

Beta blockers have long been used for prevention of childhood headaches (Ludvigsson 1974; Ziegler and Hurwitz 1993). Although one of the original studies did demonstrate effectiveness, follow-up studies have been more controversial. In the recent practice parameter (Lewis et al 2004),

propranolol was found to have a mixed responsiveness when used for childhood headaches. Furthermore, the drop in blood pressure due to beta blockers, as well as exercise-induced asthma and depressive effects, oftentimes limits its usefulness in children. Given the above-mentioned alternatives, other choices may be more beneficial for use in children, whereas the beta blockers may serve a more beneficial use in adults, especially those with high blood pressure.

Calcium channel blockers have been extensively studied in adults for headache prevention. Flunarizine is a calcium channel blocker available in Europe, but not in the United States, and has been demonstrated to be an effective migraine preventive agent (Guidetti et al 1987; Sorge et al 1988). In children in a double-blinded placebo-controlled crossover study, the baseline headache frequency was reduced in the flunarizine-treated compared to placebo. However, it is not currently available in the United States, and the use of other calcium channel blockers may not be as effective and cannot be extrapolated. One childhood study using nimodipine in a double-blinded placebo-controlled crossover study showed no significant difference between the placebo and active drug group (Battistella et al 1990).

Additional prevention medications may include some nonpharmaceutical treatments, including both riboflavin (Schoenen et al 1998; Boehnke et al 2004) and coenzyme Q10 (Rozen et al 2002; Sandor et al 2005). Their effectiveness and usefulness in children yet has to be determined.

One of the keys in the use of prophylactic medications is to slowly titrate the dose to an effective level. This requires an understanding by the parent and patient that it may take several weeks to months before an effective level is achieved, and therefore an effective response. Along with this comes the challenge of identifying a goal dose to achieve, based on the patient's size and weight. Oftentimes failure to respond to the preventative medication is due to inadequate treatment, either due to inadequate time of treatment or inadequate dosing. This can often be based on a patient's and parents' unrealistic expectation about the quickness with which they will respond to their treatment protocol. Educating the patient in the preventative therapy, as with their acute therapy, is essential to the patient's outcome.

It is necessary to emphasise to the patient the need of compliance with their prophylactic therapy. Any lack of compliance will not only increase the risk of side effects and decrease the chance of response, but also increase their risk in worsening their prognosis.

There are no risks of depency or tolerance when preventative medications are used. The main risk is resistance to one drug, and patients will then need to be switched to different therapy.

Rebound headache does not occur with preventative medication, by definition (ICHD2 criteria), rebound headache is an analgesic overuse headache and occurs only when analgesics (acute medications) are used for more then 3 headaches per week.

Biobehavioral treatment

Behavioral interventions provide a treatment option that can enhance, or if necessary, replace pharmacotherapy. The goals of behavioral treatments are to increase the patient's control of their headaches, reduce related disability and affective distress, and limit reliance on poorly tolerated or unwanted medications.

Biobehavioral therapy for childhood headaches is not only essential for headache management, but also to maintain a lifetime response to the headache treatment. Biobehavioral therapy is generally divided into three components: treatment adherence, lifestyle management, and psychological intervention including biofeedback assisted relaxation training.

Treatment adherence

Treatment adherence entails a clear understanding by the patient and parent about the importance of their treatment. Adherence is commonly defined as the "extent to which a patient's behavior coincides with medical or health advice" (Haynes 1979, pp.1–7). This definition delineates a range of patient behaviors (taking medications consistently, keeping clinic appointments, following special diets, making lifestyle changes) and suggests that patients' choice of behaviors may or may not align with medical recommendations. Identified factors related to treatment nonadherence can be placed into one of three categories: (1) regimen characteristics (eg, changes in lifestyle, complexity), (2) disease characteristics (eg, younger age of onset, symptom severity), and (3) patient/family variables (eg, premorbid/comorbid behavioral and emotional problems, family dysfunction) (LaGreca and Schumann 1995).

Because the primary influences on adherence are likely to differ across individuals, psychological or biobehavioral interventions can help identify specific barriers to adherence to the medical plan for individual patients and assist with overcoming these barriers. Therefore, intervention strategies to increase treatment adherence are based on the needs of the patients and their families. Intervention strategies can have an educational focus, providing verbal and written instruction to patients and their parents about the management

of headache symptoms. Educational strategies use factual information about the headaches and regimen requirements to explain the importance of treatment adherence. Intervention strategies can also have a behavioral focus. Behavioral strategies target specific adherent behaviors to help patients incorporate lifestyle changes and medical regimens into their daily schedule. Visual reminders to cue behavior, such as charts for relaxation practice, self-monitoring, and rewards for treatment compliance are often used to help encourage adherent behaviors. Finally, in some cases, interventions may require clinical intervention strategies directed toward modifying behavioral and emotional difficulties displayed by patients and families. Intervention strategies may be used alone or in combination to help patients adhere to medical recommendations.

Lifestyle management

Biobehavioral therapy also involves adjustment of lifestyle habits. Many times, unhealthy lifestyle habits serve as a trigger for childhood headaches. For children, headache triggers often include inadequate nutrition, skipping meals, and altered sleep patterns. Intervention strategies assist patients and families with lifestyle changes by discussing the importance of maintaining healthy lifestyle habits. Specifically, interventions focus on the importance of adequate fluid hydration with limited use of caffeine, place strong emphasis on regular exercise and adequate nutrition, including not skipping meals and eating a balanced diet, and provide recommendations for better sleep hygiene, such as consistent sleep and wake times and development of bedtime rituals.

Lifestyle interventions are focused on the acquisition and maintenance of healthy lifestyle habits. Behavioral therapy is frequently incorporated into treatment to identify and modify target behaviors. Behavioral intervention strategies emphasize maintenance of healthy behavior changes through self-regulatory behaviors, such as self-monitoring, and reinforcement-based procedures, such as contracting, contingency management, and token systems. Emphasis is placed on the notion that these are lifetime goals that will control the impact of migraine and minimize the use of medication, which may result in an overall long term improvement in quality of life, as well as reversing any progressive nature of the disease.

Psychological intervention

A number of behavioral treatments have utility for migraine and tension-type headache. Self-regulation strategies, such as relaxation and biofeedback, as well as cognitive behavior therapies are reported as the most commonly used behavioral treatments for headache (Rains et al 2005). These treatments emphasize patient involvement and personal responsibility, facilitating the use of effective strategies for coping with pain and associated headache symptoms. Active involvement of patients can lead to increased confidence in abilities to prevent and manage headaches (Andrasik 2003), which in turn can lead to less headache-related disability (French et al 2000).

Relaxation skills are used to decrease headache by enabling patients to modify their own headache-related physiological responses and decrease sympathetic arousal (Rains et al 2005). Relaxation therapy teaches a variety of relaxation strategies for reducing tension and stress throughout the body. Techniques commonly employed for headache treatment include: progressive muscle relaxation (PMR) to help children identify and discriminate between tense and relaxed muscle groups, autogenic training or cued relaxation, visualization and guided imagery, diaphragmatic breathing, and mini-relaxation, which focuses on a limited number of muscles in the head, neck, and shoulders. Children are taught techniques over several sessions, often 10 or more. Children are encouraged to practice these techniques daily and incorporate relaxation into daily life situations, particularly when headaches and feelings of stress tend to occur. Relaxation has resulted in generally positive effects with both migraine and tension-type headache (Andrasik and Shwartz 2006).

Biofeedback-assisted relaxation therapy may also be a useful addition to headache treatment (Daly et al 1983; Werder and Sargent 1984; Powers and Spirito 1998; Powers and Hershey 2002). Biofeedback refers to the use of electronic or electromechanical equipment to measure and then feed back information about physiologic functions. Biofeedback is also an ideal tool to assist pediatric patients in understanding and addressing the mind-body connection inherent in headache syndromes.

Biofeedback training involves teaching patients enhanced control over the physiological process. In headache treatment, thermal biofeedback has been used most often for migraine headache and electromyogram (EMG) biofeedback has been used for tension-type headache (Andrasik et al 2002).

Biofeedback may be coupled with relaxation therapy to teach children relaxation strategies for reducing tension and stress throughout the body, to teach controlled breathing techniques, such as diaphragmatic breathing, and to build confidence in self-regulatory pain control. Although biofeedback training for headache may require several sessions, for children and adolescents, single-session biofeedback-assisted

relaxation therapy has been demonstrated to be learned quickly and efficiently.

Beyond its value in providing information to patients about their bodies, biofeedback techniques can provide physiologic data that are helpful to the therapist to evaluate progress or track behavioral responses to certain types of stimuli (eg, mental imagery). Throughout treatment, the therapist may wish to share this data with the patient to help reinforce progress, identify and understand behavioral patterns, and facilitate the process of change.

Another common psychological intervention used in treatment of headaches is cognitive behavioral therapy. Cognitive behavioral therapy is a treatment that targets behaviors, emotions, and cognitions that trigger or aggravate headaches (Rains et al 2005). The goal of cognitive behavior therapy is to help the patient modify overt behavior by altering thoughts, interpretations of events, assumptions, and typical behavior patterns of responding to stressors or events. Applied to headache, cognitive behavioral techniques alert patients to the role of thought processes in stress responses and the relationships between stress, coping, and headaches (Rains et al 2005). Throughout treatment, patients are taught to develop more effective strategies for coping with headache related stress. Cognitive behavioral therapy can be administered in conjunction with relaxation or biofeedback training, during which patients are taught better awareness of their response patterns to a variety of interpersonal triggers.

Efficacy of behavioral interventions

Over the past three decades, behavioral interventions have become standard components of the management of migraine headaches. Meta-analytic literature reviews of behavioral interventions have consistently identified clinically significant reductions in recurrent headache (Penzien et al 2002). Across studies, behavioral interventions have yielded approximately 35%–55% reduction in migraine headache activity from pre- to posttreatment (Penzien et al 2002)

Although researchers have only recently begun to compare standard drug and nondrug treatments for migraine headache among pediatric populations, the available evidence suggests that the level of headache improvement with behavioral interventions may rival those obtained with widely used pharmacologic therapies. The two trials that have compared behavioral interventions and preventative drug therapies for pediatric migraine have each found behavior therapy, but not preventative drug therapy, effective in controlling migraines. One trial (Sartory et al 1998) compared two behavioral treatments (stress management plus relaxation or stress management plus biofeedback) and preventative medication (metropolol, 50 to 100 mg/d). Relaxation lus stress management proved more effective than either biofeedback plus stress management or metropolol alone. An earlier trial (Olness et al 1987) used an incomplete triple crossover design in a placebo-controlled comparison of the effectiveness of relaxation training with self-hypnosis and propranolol (3 mg/kg per day). The average number of migraines observed in the 3-month propranolol and placebo periods did not differ, but significantly fewer migraines were observed in the 3-month relaxation/self-hypnosis periods.

Various behavioral therapies for migraine headache have demonstrated effectiveness in both laboratory and clinical settings, and have become standard components of migraine headache treatment protocols in specialty headache centers and other similar settings. Although all treatments do not work the same for all patients, the integration of behavioral therapies are important to consider in the selection of appropriate, effective treatments for adolescent migraine headache patients.

Disclosure

The authors report no conflicts of interest.

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