REVIEW ARTICLES

Migraine management in children - Review of strategies and Recommendations

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Summary:

Headache is a frequent health problem in children and adolescents. It is estimated that headache occurs in around 70% of adolescents and 25% of younger children. This ranks headache and migraine in the top five health problems of childhood. Headache in children is often considered as an excuse to abstain from studies and school; and thus not taken seriously by adults. This article highlights the importance of headache in children and provides evidence based treatment guidelines in this group of patient.

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Introduction

Headache, and more particularly migraine, is a frequent health problem in children and adolescents.[1] It is estimated that headache occurs in around 70% of adolescents and 25% of younger children.[2] The reported prevalence increases from 3% (age 3 to 7 years) to 4 - 11% (age 7 to 11) to 8 - 23% (age 11 to 15+) with the mean age at onset being 7.2 years for boys and 10.9 years for girls.[3,4] This ranks headache in the top five health problems of childhood. Frequent headaches cause a significant impact on performance [5, 6] as well as quality of life,[7, 8] prompting the need for early recognition and treatment. As this group of patients is under supervision of pediatricians since infancy, most of the parents consult them. A few percentage of parents and refractory cases consult neurologist. There are wide variations seen in drug management of pediatric migraine. This review article is aimed to provide all concerned about recent strategies and recommendations recommended by authorities regarding management of pediatric migraine. This can possibly help us to manage this group of patients more efficiently than before.

Diagnosis and classification of Headache

Diagnosis of primary headache disorders of children rests principally on clinical criteria as set forth by the International Headache Society (IHS,1988)[9]. In 2004, the IHS published a modified International Classification of Headache Disorder (ICHD) for primary (e.g. including migraine, with and without aura) and secondary headache disorders (table-1)[10]. For young children, the 1988 IHS criteria were too restrictive, and the second edition ICHD criteria have incorporated more developmentally sensitive criteria.[11,12,13,14,15]

Table-1

IHS Classification of Migraine- 2004

1 Migraine without aura
2 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

3 Childhood periodic syndromes (commonly migraine precursors)
- Cyclical vomiting
- Abdominal migraine
- Benign paroxysmal vertigo of childhood

4 Retinal migraine
5 Complications of migraine
- Chronic migraine
- Status migraine
- Persistent aura without infarction
- Migrainous infarction

6 Probable migraine

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Table-II

IHSS Criteria for Paediatric Migraine without Aura

A. At least five attacks fulfilling criteria (B-D)
B. Headache attacks lasting 1 to 72 hours.
C. Headache with at least 2 of the following 4 features:
   1. Either bilateral or unilateral location (frontal/temporal)
   2. Pulsating quality
   3. Moderate to severe intensity
   4. Aggravated by/or causing avoidance of routine physical activity.
D. At least 1 of the following accompanies headache
   5. Nausea and/or vomiting
   6. Photophobia and Phonophobia
E. Not attributable to another disorder.

Diagnostic criteria for children are broader than those for adults, and allow for a broader range of duration and a broader localization 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, photophobia and phonophobia are common accompanying symptoms.

Aetiopathogenesis

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 included hunger fasting, menses, exercise, stress (for example, sleep deprivation) and food stuff (e.g. chocolate).[16,17]

Recently, a link between dominantly inherited migraine with aura & atrial septal / patent foramen ovale has been proposed.[18] 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.[19]

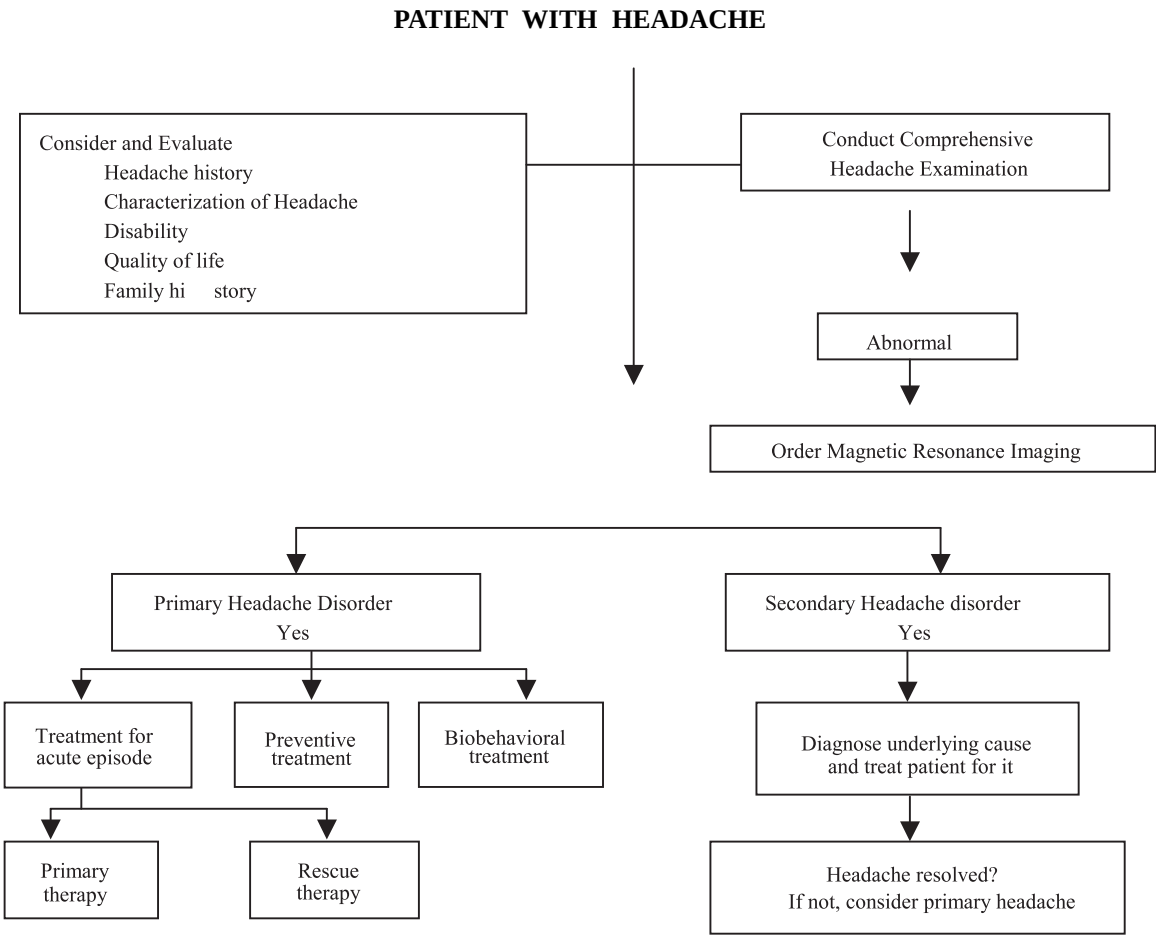
Migraine is currently thought to be a primary process. In the milieu of a hyper-excitable cortex, various stimuli probably produce disturbances in neuronal ion channel activity, resulting in a lowered threshold for external or internal factors to trigger 'cortical spreading dysfunction' (CSD). This slowly propagating wave of neuronal depolarization is most likely responsible for the migraine aura and activation of the trigemino-vascular system.[20] The perception of pain associated with migraine probably begins with activation of trigeminal vascular afferents, which in turn sensitize other peripheral and central afferent circuits to mechanical, thermal, and chemical stimuli. Stimulation of these circuits is painful.[21]

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.[22] 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.[22]

Evaluation

The evaluation of childhood headaches require a complete general health assessment, as well as a neurologic and headache history (figure below). Headache history includes an identification of the frequency, duration, severity and quality of headache components, as well as location on the head, impact of disability and associated symptoms. Guidelines in this evaluation and the use of ancillary tests have been developed.[23]

Headache disability can be assessed with the current PedMIDAS (Paediatric Migraine Disability Assessment Score),[5] a paediatric version of the adult disability instrument MIDAS.[24] Quality of life also can be assessed with Peds QL (Paediatric Quality of life), which has been validated in paediatric migraine populations.[8] Evaluation should comprise a comprehensive headache examination,[26] including recognition of muscular tightness, cranial bruits, the Mueller sign to assess for sinus tenderness, and a detailed ophthalmologic evaluation with observation of the optic disk. If results of the evaluation suggest the presence of a secondary headache, further investigation including laboratory evaluation or neuro-imaging may be necessary.



General Principles of Treatment

General principles of management of adults with migraine headaches have been established by the previously published ANN Practice Parameter. Fundamental goals of long term migraine treatment have been established that include[26] ;1) reduction of headache frequency, severity, duration, and disability; 2) reduction of reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies; 3) improvement in quality of life; 4) avoidance of acute headache medication escalation; 5) education and enablement of patients to manage their disease to enhance personal control of their migraine; and 6) reduction of headache related distress and psychological symptoms.

These general principles of management and fundamental goals of treatment also apply to children and adolescents and once the diagnosis of migraine headache is established a comprehensive treatment program should be implemented. Treatment options include use of: 1) acute or episodic medications; 2) prophylactic or preventive agents; and 3) non-pharmacologic or bio-behavioral interventions.

Modalities selected must be individually tailored to a particular patient's pattern and must also be flexible enough to accommodate a changing frequency.[27] Fundamental to this process is assessment of a patient's degree of disability or headache "burden"; which reflects an individual patient's frequency, duration, intensity, functional disability, quality of life, co-morbidity, and pain tolerance. The extent of medical management should be determined by assessment of the headache burden.

Pharmacologic Treatment

Treatment in children and adolescents can be divided on an acute basis as well as daily to prevent frequent recurring migraine attacks.

Treatment of acute attack of migraine

Recommended general principles for treatment of acute migraine headache as established in the previously published AAN Practice parameter include the following: 1) treat attacks rapidly and consistently without recurrence; 2) restore the patient's ability to function; 3) minimize the use of back-up and rescue medications; 4) optimize self-care and reduce subsequent use of resources; 5) be cost-effective for overall management; and 6) have minimal or no adverse events.[26] A summary of the evidence for treatment of acute attacks of migraine is presented in table-4.

Nonsteriodal anti - inflammatory agents (NSAIDs) and Acetaminophen

Acetaminophen and Ibuprofen are widely used for pain relief and sold without prescription in many countries.[27] Ibuprofen was been the most vigorously studied medication. Two double-blind, placebo-controlled class I trails have shown that Ibuprofen (7.5 to 10mg/kg) in childhood migraine is safe and effective.[28, 29]

One of the study compared Ibuprofen (10mg/kg) to Acetaminophen (15mg/kg) and a placebo.[28] At the 2 hour intent to treat endpoint, Ibuprofen provided alleviation of headache in 56% of treated patients compared to 53% for Acetaminophen and 36% for the placebo group. These differences between Ibuprofen & Acetaminophen were not statistically significant at this point. Complete resolution of headache was found in 60% of Ibuprofen-treated children and 36% of the Acetaminophen group vs. 28% of those who received placebo. This difference is statistically significant. Acetaminophen was observed to have a faster onset of action than Ibuprofen. No statistically significant adverse effects were reported for either drug in these studies.

5 - Hydroxytryptamine receptor agonists (Triptan agents)

Sumatriptan

Recent research in the mechanism of action in migraine involves the trigeminovascular system which causes release of vasoactive neuropeptides. 5 – Hydroxytryptamine (serotonin) presynaptic receptors control release of these neuropeptides, and postsynaptic receptors constrict vessel walls.[30]

Four studies compared Sumatriptan and placebo, including 3-high quality studies. A multicentered, double-blind and placebo-controlled study (age 12 to 17 years) compared 5mg, 10mg, and 20mg Sumatriptan nasal spray to placebo.[31] The 2-hour pain free response showed the 20 mg dose was statistically significant with 46% response rate compared with 25% for placebo (p<. 05). It also produced significant reduction in the migraine associated symptoms by 2 hours (p<. 05) and yielded a reduced headache pain recurrence rate compared with placebo overall.

A double-blind, placebo-controlled, two-way crossover study (class-1) included children aged 8 to 17 years (median 12.4 years). Treatment with Sumatriptan 10 mg (20 to 39 kg) and 20 mg (>40kg) was done with endpoint defined as improvement in headache at 2 hours. The primary endpoint was met in 64% of patients receiving Sumatriptan and in 39% of those receiving matching placebo (p=0.003). Complete pain relief was experienced by 31% of those treated with Sumatriptan and 19% receiving placebo (p=0.14). Secondary endpoints including use of rescue medications and patient preference also favored Sumatriptan (NS).[32]

Subcutaneous Sumatriptan has been studied in two open trials (class IV). The first trial in children 6 to 16 years used the 6 mg dose in children weighing >30 kg and 3 mg in children <30 kg.[33] It was effective in 64% of patients. A second subcutaneous trial in 50 patients aged 6 to 18 years using a dose of 0.06 mg/kg, found an efficacy of 78% with 26% responding within 30 minutes, 46% in 60 minutes, and 6% between 1 to 2 hours.[33] Headache recurrence rate was low as 60% to 90% boys responded, whereas 68% of girls responded.

One class 1 clinical trial including children aged 8.3 to 16.4 years (n=23) taking oral Sumatriptan tablet (50 to 100mg) failed to clearly demonstrate efficacy greater than matched placebo at the primary endpoint of pain relief at 2 hours (p=NS).[34]

Rizatriptan

Studies of Rizatriptan in children are limited. A single class I report (n=296) found no difference compared to placebo in pain relief in children aged 12 to 17 years at the 2-hour primary endpoint (Rizatriptan

66%; placebo 56%; p=0.79). Rizatriptan did demonstrate good tolerability and safety with adverse events being comparable to placebo (3 to 5%).[35]

Zolmitriptan

A class IV open-labeled multicenter trial of oral Zolmitriptan (2.5 to 5mg) in 12 to 17 years old adolescents (n=38) who had 276 migraine attacks found that treatment was well tolerated. Overall improvement in headache symptoms at 2 hours was 88% with 2.5 mg dose and 70% with the 5mg dose.[36] A pain free state was achieved in 66% patients.

Ergot Alkaloids

Limited reports have shown the usefulness of intravenous Dihydroergotamine (DHE) in an inpatient setting to break status migrainous or prolonged migraines in children.[37]

Dopamine antagonist

They were demonstrated to be effective in minimizing the nausea and vomiting, as well as the effects of the migraine.[38] For effectiveness, the IV formulation is superior to all of the formulation, while the oral route being ineffective or of limited effectiveness. An open labeled study in 20 children demonstrated the effectiveness of Prochlorperazine in the emergency department setting, with rehydrating fluids.[39]

Recommendations for the acute treatment of migraine in children and adolescents:

1. Ibuprofen is effective and should be considered for the acute treatment of migraine in children (level A).
2. Acetaminophen is probably effective and should be considered for the acute treatment of migraine in adolescents (level B).
3. Sumatriptan nasal spray is effective and should be considered for the acute treatment of migraine in adolescents (level A).
4. There are no data to support or refute use of any oral triptans in children or adolescents (level C).
5. There are inadequate data to make a judgment on the efficacy of subcutaneous sumatriptan (level-C).

Table-IV

Evidence summary for treatment of acute attacks of migraine

Drug, doses, ages	Class	n	Efficacy		p value	Adverse effects
NSAIDS and nonopiate analgesics			Active %	Placebo, %		
Ibuprofen						
10 mg/kg (4-16y)	I	88	68	37	<0.05	Infrequent
7.5 mg/kg (6-12y)	I	84	76	53	0.006	Infrequent
Acetaminophen						
15 mg/kg (4-16y)	I	88	54	37	<0.05	Infrequent
Triptans						
Sumatriptan						
Nasal 20 mg (6-14y)	I	14	85.7	42.8	0.03	Occasional
5,10,20 mg (12-17y)	I	510	66	53	0.05	
10,20mg (8-17y)	I	83	64	39	0.003	
Oral 50,100 mg(8-16y)	I	23	30	22	NS	Occasional
Subcutaneous						
3, 6 mg (6-16y)	IV	17	64	-	-	Occasional to frequent
0.06 mg/kg (6-18y)	IV	50	78	-	-	
Oral triptans						
Rizatriptan 5 mg (12-17 y)	I	296	66	56	NS	Occasional
Zolmitriptan 2.5 mg						
5 mg (12-17 yrs)	IV	38	85	(2.5 mg) 70(5 mg)	- -	Occasional

Preventive Treatment of migraine

General principles related to the goals of migraine preventive therapies are : i) to reduce frequency, severity and duration of attacks; ii) improved responsiveness to treatment of acute attacks; and iii) to improve function, reduce disability, and improve the patient's quality of life.

Cyproheptadine

One class IV retrospective study on the use of preventive agents for children and adolescents within one child neurology practice found that headache frequency was reduced from a mean baseline of 8.4 headaches/month to 3.7 headaches/month. In 83% of the children receiving Cyproheptadine (n=30) there was an overall favorable decrease in headache frequency and intensity plus acceptability of the agent. Common side effects of Cyproheptadine included sedation and increased appetite.

Antidepressants

Antidepressants have become a mainstay of migraine prophylaxis, although limited controlled data exist in children to validate this convention.

Tricyclic Antidepressants (TCA)

Amitriptyline is the most widely used TCA 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.[41,42, 43] Most of the studies using Amitriptyline in children have been open-label studies; no placebo-controlled studies have been done.

In an open-label study, Hershey et al[44] demonstrated that Amitriptyline at a dose of 1mg/kg/day resulted in a perceived improvement in more than 80% of the children, with a subsequently decreased headache frequency and impact on the children. One class IV retrospective study of the use of preventive agents for children and adolescents within one child neurology practice found that Amitriptyline produced a positive response rate of 89% (n=73). Positive response rate was defined as an overall decrease in headache frequency and intensity plus acceptability of the agent. Headache frequency was reduced from a mean baseline of 11 to 4.1 headaches per month.[40]

Selective Serotonin Reuptake Inhibitors (SSRIs) have been studied in the treatment of headache in adults, but they have not been studied in children. They are not as effective, however, as the TCAs. This is most likely because of nonselective effects of the TCAs, compared with the SSRIs, suggesting that a more global decrease in neurotransmitter reuptake inhibition is needed to manage hypersensitivity of childhood headache disorder.

The serotonin blocking agent Pizotifen was studied in a randomized crossover class I trail (n=47) with two 12-week treatment phases and no washout period between phases.[45] There was no significant difference in either headache frequency or headache duration between the placebo and Pizotifen-treated groups.

Antihypertensive agents

Beta-Blockers

ß-Blockers have long been used for prevention of childhood headaches. [46-47] They have been evaluated in three class II trials with conflicting results. One double blind crossover trial in children aged 7 to 16 years (n=28) using 60 to 120 mg of Propranolol per day found that 71% had complete remission from headache and another 10% experienced a 66% reduction in headache frequency among the Propranolol treated patients ($p<.001$). In the placebo group, 3 / 28 had complete remission and 1 of 28 experienced a 66% improvement.[46] A second trial failed to demonstrate preventive efficacy at doses of 80 to 120 mg/d and, in fact, significantly increased the average duration of headache in the Propranolol group.[48] A third trial compared Propranolol at a dose of 3mg/kg/day vs. self-hypnosis and found no benefit from Propranolol but significant improvement with hypnotherapy.[49]

Clonidine

The alpha-adrenergic agonist Clonidine was assessed in two studies. The first study had two phases. The initial pilot phase (n=50) had an open-label design and 40% of the children experienced extended relief from migraine attacks. The second phase, a follow-up, double blind, cross over design in 43 children, failed to demonstrate significant difference from placebo (class II).[50] The second study compared Clonidine to placebo in parallel-group trail (class II) at doses of 25 to 50 μg for 2 months (n=57).[51] There was no statistically significant difference between the

two groups with 9 of 28 patients in the Clonidine group and 9 of 26 in the placebo group experiencing freedom from headache attacks.

Calcium channel blockers

Calcium channel blockers are thought to exert their effects through selective inhibition of vasoactive substances on cerebrovascular smooth muscle.

Flunarizine

Flunarizine is a calcium channel blocker that has been evaluated in several trials for the prevention of childhood migraine. A double blind, placebo-controlled, crossover trial (class I) using 5 mg / day doses of Flunarizine (n=63) demonstrated significant reduction in headache frequency ($p<.001$) and decreased average headache duration ($p<.81$) compared to the placebo group.[52] A class II trail compared Flunarizine to Propranolol. Headache frequency was decreased in both treatments groups, but no statistically significant difference was detected between the trial agents.[53]

Nimodipine

One controlled, crossover trial including children aged 7 to 18 years (n=37) found inconsistent effects with Nimodipine (10-20mg TID) compared to placebo between the two treatment phases.

Anti convulsants

Considering current views concerning the pathophysiology of migraine involving a primary neuronal initiation and a cortical spreading depression, anti-convulsants have received increasing attention as an alternative therapeutic option.

Divalproex Sodium

One class IV study in 42 children (ages 7 to 16 years) found that over 80% were able to discontinue their abortive medications when treated with Divalproex sodium (15 to 45gm/kg/day.)[55] After 4 months of treatment, 75.8% of patients reported a 50% reduction in headache frequency; 14.2% had a 75% reduction and 14.2% achieved a headache free status. A second study using Divalproex sodium included children aged 9 to 17 years (n=10) with doses between 500 and 1000 mg. Both headache severity and frequency were reduced as compared by visual analog scale. Mean severity was reduced from 6.8 to 0.7 at the end of treatment. Mean headache attacks per month were reduced from 6/month to 0.7/month and mean duration of headache attacks was reduced from 5.5 hours to 1.1 hour following treatment. Side effects including dizziness, drowsiness, and increased appetite were noted but no serious side effects occurred in this small study.[56]

Conclusion

The calcium channel blocker Flunarizine was studied in one class I trail and is probably effective. The evidence is insufficient (class IV) to determine the efficacy of Valproic acid, Cyproheptadine, Amitriptyline, Topiramate and Levetiracetam for prevention of pediatric migraine. There is conflicting class II evidence regarding Propranolol and Trazodone. Clonidine, Pizotifen and Nimodipine were not shown to be more effective than placebo. A recent Cochrane database review of the medical literature also concluded that the calcium channel blocker Flunarizine is the only agent that has been studied in rigorous controlled trials and found to be effective.

Future directions

Standardized criteria for the diagnosis of migraine headaches in children and adolescents are needed in order to facilitate proper diagnosis and for the purpose of providing a case definition that could be used as part of therapeutic clinical trails. Standardized criteria of the response to treatment of migraine in children / adolescents need to be established that are related to the frequency, duration, severity and disability of headache. The safety and efficacy of currently available medications used to treat migraine headaches in adults need to be established in children and adolescents, particularly the dose and range in which these medications are deemed safe and effective to use. It is essential that multi-centered, placebo-controlled clinical trials should be conducted to assess the safety, tolerability, and efficacy of medications used for the acute and preventive treatment of pediatric and adolescent migraine.

Efforts must be made to develop novel and innovative study designs that will address the critical issue of high placebo response rates encountered in clinical trails in children and adolescents, which has proven to be the major impediment to demonstration of

efficacy. It will be important to understand the variations in effects of treatments in relation to age and sex.

References

1. Winner P, Rothner AD, eds. Headache in children and adolescents. Hamilton, ont. BC Decek, imc; 2001.
2. Bille B. Migraine in school children. Acta Paediatrica 1962;51(suppl 136):116-151.
3. Rewast WF, Linet MS, Celentano DD, et al. Age and sex-specific incidence rates of migraine with and without visual aura. Am J Epidemiol 1991;34:1111-1120.
4. Stewart WF, Lipton RB; Celentano DD. Prevalence of migraine headache in United States. JAMA 1992; 267:64-9.
5. Hershey AD, Powers SW, Vokell ALB. PedMIDAS: Development of a questionnaire to assess disability of migraines in children. Neurology 2001; 57:2034-2039.
6. Hershey AD, Powers SW, Vokell ALB. Development of a patient-based grading scale for pedMIDAS. Cephalalgia 2004; 24:844-849.
7. Porwers SW, Patton SR, Hommel KA . Quality of life in childhood migraine: clinical impact and comparison to other chronic illness. Pediatrics 2003; 112:e1-e5.
8. Porwers SW, Patton SR, Hommel KA. Quality of life in paediatirc migraine: characterization of age-related effects using peds QL 4.0. Cephalalgia 2004; 24:120-127.
9. Olesen J. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgia, and facial pain. Cephalalgia 1988; 8(suppl 7):1-96.
10. Olesen J. The International Classification of Headache Disorder. Cephalalgia 2004; 24(Suppl 1):9-160.
11. Mortimer MJ, Kay J. Jaron-A. Epidemiology of headache and childhood migraine in an urban general practice using adhoc, Vahlquist and IHS criteria. Dev Med Child Neurol 1992; 34:1095-1101.
12. Seshia S, Wolstein JR, Adams C. International Headache society criteria and childhood migraine. Dev Med Child Neurol 1994; 36:419-428.
13. Wober-Bingol, Wober C. Karwautz A. Diagnosis of headache in childhood and adolescence: a study of 457 patients. Cephalalgia 1995; 15:13-21.
14. Rossi L, Cortinovis I, Bellettind G. Diagnostic criteria for migraine and psychogenic headache in children. Cephalalgia 1992; 34:515-523.
15. Raieli V, Raimondo D, Gangitano M. The IHS classification criteria for migraine headache in adolescents needs minor modification. Headache 1996; 36:362-366.
16. Amery WK, Vandenbergh V. What can precipitating factors teach us about the pathogenesis of migraine? Headache 1987; 27; 140-50.
17. Blau JN, Thavapalan M. Preventing migraine: a study of precipitating factors. Headache 1988; 28; 481-3.
18. Wilmshurst PT, Pearson MJ. Nightingale S. Inheritance of persistent foramen ovale and atrial septal defects and the relation to familial migraine with aura. Heart 2004; 40:1315-20.
19. Schwermann M, Wiher S, Nedeltechev K. Percutaneous closure of patent foramen ovale reduces the frequency of migraine attacks. Neurology 2004:62:1399-1401.
20. Pietrobon D, Streissnig J. Neurobiology of migraine. Nat Rev 2003; 4:386-98.
21. Burstein R. Yarnitsky D, Goor Arn-yeh I. An association between migraine and cutaneous allodynia. Ann Neurol 2004:614-24.
22. Nedeltchev K, Arnold M, Schwerzmann M. Cerebrovascular response to repetitive visual stimulation in interictal migraine with aura. Cephalalgia 2004; 24,700-706.
23. Lewis DW, Ashwal S, Dahl G. Practice Parameter: evaluation of children and adolescents with recurrent headaches; report of the Quality standards subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2002; 59:490-8.
24. Retwast WF, Lipton RB, Dowson AJ. Development and testing of the migraine disability assessment (MIDAS) questionnaire to assess headache related disability. Neurology 2001; 56(Suppl 6):520-28.
25. Linder SL, Winner P. Pediatric headache. Med Clin North Am 2001; 85:1037-053.
26. Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence based review). Neurology 2005; 55:754-762.
27. Ann Pakalnis. New avenues in treatment of paediatric migraine: a review of the literature. Family Practice 2001;18:101-06
28. Hamalainen ML, Hoppll K, Valkeila E. Ibuprofen or acetaminophen for the acute treatment of migraine in children; a double-blind, randomized, placebo-controlled, crossover study. Neurology 1997; 48; 102-107.
29. Lewis DW, Kellstein D, Burke B. Children's ibuprofen suspension for the acute treatment of paediatric migraine headache. Headache 2002; 42; 780-86.
30. Lance JW. Current concepts of migraine pathogenesis. Neurology 1993; 43:311-15.
31. Winner P. Rothner AD, Saper J. A randomized, double-blind, placebo-controlled study of Sumatriptan nasal spray in the treatment of acute migraine in adolescent. Paediatrics 2000; 106; 789-797.
32. Ahonen K, Hamalainen ML, Rantala H. Nasal sumatriptan is effective in the treatment of migraine attacks in children. Neurology 2004; 62:883-87.

33. MacDonald JT. Treatment of Juvenile migraine with subcutaneous sumatriptan. Headache 1994; 34:581-82.

34. Hamalainen ML, Hoppu K, Santavuori P. Sumatriptans for migraine attacks in children: a randomized placebo-controlled study. Do children with migraine respond to oral sumatriptan differently than adults? Neurology 1997; 48:1100-03.

35. Winne P, Lewis D, Visser WH. Rizatriptan 5 mg for the acute treatment of migraine in adolescents: a randomized, double blind placebo-controlled study. Headache 2002; 42:49-55.

36. Linder SL, Dowson AJ. Zolmitriptan provides effective migraine relief in adolescents. Int J Clin Pract 2000; 54:466-69.

37. Linder SL. Treatment of childhood headache with dihydroergotamine mesylate. Headache 1994; 34:518-80.

38. Jones J, Sklar D. Randomized double -blind trial of intravenous prochlorperazine for the treatment of acute headache. JAMA 1989; 261:1174-76.

39. Kabbouche M, Vockell ALB. Tolerability and effectiveness of prochlorperazine for intractable migraine in children. Paediatrics 2001; 107(4): 662-66.

40. Lewis D, Diamond S, Scott D. Prophylactic treatment of pediatric migraine. Headache 2004; 44:230-37.

41. Couch JR, Ziegler DK, and Hassanein R. Amitriptyline in the prophylaxis of migraine. Effectiveness and relationship of antimigraine and antidepressant effects. Neurology 1976; 36:121-27.

42. Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis. J Neurol Neurosurg Psychiatry. 1973; 30:684-90.

43. Couch JR, Hassanein R. Amitriptyline in migraine prophylaxis. Arch Neurology 1979; 36:695-99.

44. Hershey AD, Powers SW. Effectiveness of amitriptyline in the prophylactic management of childhood headache. Headache 2000; 40:539-49.

45. Gillies D, Sills M, Forsythe I. Pizotifen in childhood migraine. A double-blind placebo controlled trail. Euro Neurol 1986; 52:32-35.

46. Ludvigsson J. Propranolol use in prophylaxis of migraine in children. Acta Neuro Scand 1974:50:109-115.

47. Zeigler DK, Hurwitz A. Propranolol and amitriptyline in prophylaxis of migraine. Arch Neurol 1993:50:825-30.

48. Forsythe WI, Gillies D, Sills MA. Propranolol in the treatment of childhood migraine. Dev Med Child Neurol 1984; 26:737-41.

49. Olness K, MacDonald JT. Uden DL. Comparison of self-hypnosis and propranolol in the treatment of Juvenile classic migraine. Pediatrics 1987; 76:593-97.

50. Sills M, Congdon P, Forsythe I. Clonidine and childhood migraine. Dev Med Child Neurol 1982; 24:837-41.

51. Sillanpaa M. Clonidine prophylaxis of Childhood migraine and other vascular headache. A double blind study of 57 children. Headache 1977; 17:28-31.

52. Sorge F, Desimone R, Marano E. Flunarizine in prophylaxis of childhood migraine. A double blind, placebo-controlled crossover study. Cephalalgia 1988; 8:1-6.

53. Lutschg J, Vassella F. The treatment of Juvenile migraine using flunarizine or propranolol. J Suisse Med 1990; 120:1731-36.

54. Battistella PA, Ruffilli R, Moro R. Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo controlled crossover study. Cephalalgia 1988; 8:16.

55. Caruso JM, Brown Wo. The efficacy of divalprovex sodium in the prophylactic treatment of children with migraine. Headache 2000; 40:672-76.

56. Serdaroglu G, Erhan E, Tekgul. Sodium Valproate prophylaxis in childhood migraine. Headache 2002; 42; 819-822.

57. Victor S, Ryan S. Drugs of preventing migraine headaches in children. Cochrane Database System Reviews 2003; 4:CD002671.