Leading Article

Childhood migraine

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Introduction

Headache is a common problem among children and adolescents. At least one severe episode of headache is reported by 82% by 15 years of age[1]. Often it remains under-recognised as a significant problem by patients, parents, and practitioners. The prevalence of headache among Sri Lankan children is not known. However, in a population based study carried out among 606 school children aged 11-16 years in the Polonnaruwa educational zone, at least one severe episode of headache was experienced by 94% whilst recurrent headaches over a minimum period of three months was reported by 40%[2].

Causes of headache are broadly divided into primary and secondary. Secondary causes are often identifiable by their cause-and-effect association with a specific aetiology. Of the primary headaches, migraine dominates, having the greatest effect on a child's quality of life and causing most disability. It results in absence from school and day care[3] and impaired school performance[4]. It can become a chronic, disabling disorder with a substantial effect on the lives of the patients and their families.

Diagnosis and evaluation of paediatric headache

Diagnosis and classification of childhood headache is based on the International Classification of Headache Disorders (ICHD). This describes key criteria for separation of headaches intrinsic to the nervous system (primary headaches), the more common variety, from headaches directly attributable to another cause (secondary headaches). The latest classification, the third edition (ICHD-3 beta) was published in July 2013[5]. According to this, a headache could belong to one of three main categories: primary headaches, secondary headaches or a group of conditions comprising painful cranial neuropathies, other facial pains and other headaches[5].

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Primary headaches

There are four broad types of primary headaches: migraine, tension type headache (TTH), trigeminal autonomic cephalalgias (TACs) and other primary headache disorders[5]. For the purpose of this article, discussion will be limited to the main type of primary headache, migraine. However, I will briefly describe the other types. *Tension type headache* (TTH) is very common with lifetime prevalence ranging from 30-78%[6]. Although previously thought to be primarily psychogenic, many studies have now shown it to have a neurobiological basis[7,8]. The exact mechanisms of TTH are not known. Peripheral pain mechanisms are most likely to play a role, but central pain mechanisms are also indicated in some[7]. Increased pericranial tenderness recorded by manual palpation is the most significant abnormal finding in patients with TTH[6]. The tenderness is typically present during symptom free periods and is further increased during the actual headache[6]. The *trigeminal autonomic cephalalgias* (TACs) share the clinical features of headache, usually lateralized, with prominent cranial parasympathetic autonomic features which are also lateralized as ipsilateral to the side of headache[5]. Typical migraine aura can be seen rarely, in association with TACs[5]. Cluster headache is the most frequently known syndrome in this group[5]. The fourth group, "*other primary headache disorders*", include a number of primary headache disorders that are clinically heterogeneous. Their pathogenesis is still poorly understood. ICHD-3 has classified 10 different types. A few examples include primary exercise induced headache, primary cough headache and primary external pressure headache.

Migraine

Migraine is the commonest primary headache disorder. In the Global Burden of Disease Survey 2010, it was ranked as the third most prevalent disorder and seventh-highest specific cause of disability worldwide[9]. Recognizing migraine during childhood is often challenging, particularly due to difficulties in recognizing its clinical components. Forty percent of children with migraine were initially

misdiagnosed as 'sinus headache' in a study of paediatric headache from Turkey[10]. Being a clinical diagnosis in its entirety, early recognition and appropriate acute therapies and lifestyle adjustments can affect the disease progression for the lifetime of the individual, prevent long-term discomfort, and enhance quality of life[11].

Epidemiology

Globally, migraine is reported to be the underlying cause for 6 to 20 percent of headaches in childhood and adolescence[12]. There is a slight male preponderance in the younger age group which gradually changes to affect girls more commonly in adolescence[13]. Children of low socioeconomic status are reported to be affected more[4]. Migraine has been studied across different age groups from childhood to adolescence and there is a gradual increase in the numbers with age: 1–3% of 3–7 year-olds, 4–11% of 7–11 year-olds, and 8–23% of teenagers[14]. It is reported to spontaneously remit after puberty in fifty percent[15]. However, if the migraine began during adolescence, it may be more likely to persist throughout adulthood, but with being less frequent and severe over time[16]. The frequency of migraine varies slightly from country to country and region to region. In a study limited to school aged children between 11-16 years in an educational zone in the Polonnaruwa district, prevalence of migraine was 7.75% and it was commoner in girls[2].

Pathophysiology

The pathophysiology of migraine is thought to be based on the interaction between the neural and vascular systems and is considered to be the same in adults and children[17]. This includes the phenomenon of cortical spreading depression (CSD) and trigeminal vascular activation with transmission through the thalamus to higher cortical structures[17]. The process of pathogenesis can be divided into two phases: that related to the underlying basis for the risk of having migraine (genetics and environment) and the biological processes that occur during the attack.

Genetics

There is a contribution from both genetic and environmental factors for the pathogenesis. The balance between these two factors varies between 60-70% contribution from genetic factors and the remaining risk derived from environmental factors[18]. Several genes have been implicated in the pathogenesis. These include mutations in a calcium channel gene, *CACNA1A*[19] and a sodium channel gene, *SCN1A*[20], implicating the role of ion channels in the pathogenesis of migraine. *ATP1A2*, a sodium/potassium pump gene on astrocytes, indicates the connection between neurons and the blood vessels[21]. Several other genes including those that encode serotonin transporters, a potassium channel (KCNN3), methylene tetrahydrofolate reductase (MTHFR), angiotensin-converting enzyme and matrix metalloproteinase have been identified as potential biomarkers for migraine[18]. Identification of these biomarkers suggests a complex interaction between neurotransmitters, channels and metabolism, but need to be further investigated.

Risk factors for recurrence

Suggested risk factors described in the world literature include stress, food items, menstruation, and exercise[22]. These papers do not describe the commonest risk factor that we encounter locally, exposure to sunlight. Hormonal changes may affect the pathophysiology of paediatric migraine similar to that seen in adults[13]. This is seen in menstrual migraine which is related to the change in the sex hormones. As a result, onset of menarche has been shown to be associated with an increased risk of recurrent headache. Certain other biological markers (immunological and inflammatory) are also implicated in paediatric migraine. Recent reviews indicate a potential role of mitochondrial dysfunction in the pathogenesis[23].

Neurophysiological changes

This is the biological process that occurs during a migrainous attack. Apart from the vascular phenomena, which in the past was considered to be the predominant contributor for pathogenesis, several neurophysiological changes have been demonstrated. In adults, these include an altered blink reflex indicating inter-ictal trigeminal sensitization and altered visual and auditory responses. Similar changes in neurophysiological and biological changes are demonstrated in children and adolescents. Some of these are higher latency of P100 visual response and prolongation of N 180 latency in visually evoked potentials as well as alteration of somatosensory responses[18]. These findings indicate that an alteration in the brain sensitivity in patients with migraine, might be responsible for the initiation and propagation of migraine[18]. Some of these are implicated in the pathogenesis of behavioural changes associated with migraine in adolescence. Cortical spreading depression (CSD), a slowly propagated wave of depolarization followed by suppression of brain activity, is a remarkably

complex event that involves dramatic changes in neural and vascular function. CSD results in a brief (30-60 sec) period of propagating depolarization of cortical neurons and glial cells. This is accompanied by a heavy shift and redistribution of ions across the extracellular and intracellular compartments. This has been hypothesized to be the mechanism of migraine aura[17]. In brief, migraine pathophysiology involves an inherited alteration of brain excitability associated with intracranial arterial dilatation resulting in recurrent activation, and sensitization of the trigeminovascular pathway.

Clinical spectrum

There are two main forms of migraine. *Migraine without aura*, previously known as common migraine, is a clinical syndrome characterized by headache with specific features and associated symptoms. Migraine with aura, previously known as classical migraine, is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Distinct from the aura, some patients also experience a premonitory phase. This includes behavioural changes, hyperactivity, hypo-activity, depression, cravings for particular foods, repetitive yawning, fatigue, neck stiffness and/or pain. This may precede the headache by hours or days. Some others experience a headache resolution phase. *Migraine with aura* has been further divided in the new classification into four types according to the aura. These include migraine with typical aura (1.2.1), migraine with brainstem aura, (1.2.2) hemiplegic migraine (1.2.3) and retinal migraine (1.2.4). Other types of migraine (apart from 1.1 and 1.2) include chronic migraine (1.3), complications of migraine (1.4), probable migraine (1.5) and episodic syndromes that may be associated with migraine (1.6)[5]. For ease of understanding, this component of the ICHD-3 classification of migraine is illustrated in figure 1.

1. Migraine
    - 1.1 Migraine without aura
    - 1.2 Migraine with aura
        - 1.2.1 Migraine with typical aura
            - 1.2.1.1 Typical aura with headache
            - 1.2.1.2 Typical aura without headache
        - 1.2.2 Migraine with brainstem aura
        - 1.2.3 Hemiplegic migraine
            - 1.2.3.1 Familial hemiplegic migraine (FHM)
                - 1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
                - 1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
                - 1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
                - 1.2.3.1.4 Familial hemiplegic migraine, other loci
            - 1.2.3.2 Sporadic hemiplegic migraine
        - 1.2.4 Retinal migraine
    - 1.3 Chronic migraine
    - 1.4 Complications of migraine
        - 1.4.1 Status migrainosus
        - 1.4.2 Persistent aura without infarction
        - 1.4.3 Migrainous infarction
        - 1.4.4 Migraine aura-triggered seizure
    - 1.5 Probable migraine
        - 1.5.1 Probable migraine without aura
        - 1.5.2 Probable migraine with aura
    - 1.6 Episodic syndromes that may be associated with migraine
        - 1.6.1 Recurrent gastrointestinal disturbance
            - 1.6.1.1 Cyclical vomiting syndrome
            - 1.6.1.2 Abdominal migraine
        - 1.6.2 Benign paroxysmal vertigo
        - 1.6.3 Benign paroxysmal torticollis

Figure 1: ***Classification of migraine in the ICHD-3***[5]

Migraine without aura

The classical description of this type includes recurrent headache attacks that last between 4-72 hours (in children between 2-72 hours). Headaches are typically unilateral, pulsating in quality, of moderate to severe intensity, aggravated by routine physical activity and may be associated with nausea and/or vomiting with or without photophobia and phonophobia. It is important to note that the duration of the headache includes the period from onset of headache to improvement of symptoms after waking up from sleep, if patient falls asleep during an attack. In order to establish the diagnosis, it is important to fulfill the criteria listed in ICHD-3 which include:

A. At least 5 attacks of headache fulfilling criteria B-D
B. Headache lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache which has at least two of the following four characteristics:
    - Unilateral location
    - Pulsating quality
    - Moderate or severe pain intensity
    - Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache experience at least one of the following
    - Nausea and or vomiting
    - Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

Some important considerations in the diagnosis of migraine in children include a reduced duration of symptoms (minimum of 2 hours) and localization is often bilateral than unilateral (unilateral pain usually emerges in late adolescence or early adult life). The headache localization is usually fronto-temporal. Occipital headaches in children are rare and therefore warrant exclusion of other diagnoses first. In young children, photophobia and phonophobia may be inferred from their behaviour. The attacks may be associated with autonomic features and clinical features of cutaneous allodynia[18].

Migraine with aura

These are recurrent attacks of fully reversible, visual, sensory or other central nervous system symptoms which last a few minutes. These symptoms develop gradually and are usually followed by headache and other associated symptoms of migraine.

Criteria in listed in ICHD-3 include:

A. At least 2 attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
    - Visual
    - Sensory
    - Speech and / or language
    - Motor
    - Brainstem
    - Retinal
C. At least two of the following four characteristics:
    - At least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession
    - Each individual aura symptom lasts 5-60 minutes
    - At least one aura symptom is unilateral
    - The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis and transient ischaemic attack has been excluded.

Other types of migraine described in the ICHD-3 include chronic migraine (1.3), complications of migraine (1.4), probable migraine (1.5) and episodic syndromes that may be associated with migraine (1.6).

Chronic migraine is when headache (migraine or tension headache type) occurs on 15 days or more during a month for more than three months duration. It should have features of migraine headache on at least 8 days per month.

Complications of migraine include status migrainosus (a debilitating migraine headache lasting for more than 72 hours), persistent aura without infarction, migranous infarction and migraine aura with seizure.

Probable migraine is perhaps likely when the migraine-like headache misses one of the features required to fulfill the diagnostic criteria for a subtype of migraine and when it does not fulfill criteria for another diagnosis of a headache disorder.

Episodic syndromes that may be associated with migraine now have been lumped together in the new

classification under 1.6. These were previously known as childhood periodic syndromes. Each of them tends to appear in specific age groups: *benign paroxysmal torticollis* appears in infancy, *benign paroxysmal vertigo* mostly in 2 to 4 year olds, *cyclical vomiting* after 5 years and *abdominal migraine* at a mean age of onset of 7 years[24]. Two other types of migraine variants are *confusional migraine* and *migraine without aura*, both with a later age of onset[25]. These are generally known to occur in children, but cases in adults are also reported[26]. These occur in those who have both migraine with aura and without aura. The affected patients are also reported to have episodes of motion sickness and periodic sleep disorders including sleep walking, sleep talking, night terrors and bruxism.

Cyclical vomiting (recurrent attacks of vomiting of at least four episodes over an hour) and *abdominal migraine* (recurrent attacks of moderate to severe midline abdominal pain) comprise the first group known as recurrent gastrointestinal disturbance (1.6.1). These attacks may be associated with migraine. The second group is *benign paroxysmal vertigo* (1.6.2). This is characterized by recurrent attacks of vertigo without any warning occurring in otherwise healthy children. These attacks resolve spontaneously. Each episode may last between minutes to hours and is associated with autonomic features. Characteristically there is no alteration of conscious status. The third paroxysmal syndrome is *benign paroxysmal torticollis* (1.6.3). This generally occurs in infants or small children. There is sudden head tilt to a side secondary to cervical dystonia often with a rotation and this resolves spontaneously after minutes to days. Although not included in the ICHD-3, some consider *infantile colic* to be an early form of episodic syndrome[27]. The episodic syndromes tend to occur in particular age groups. A progressive overlap of symptoms in the same patient is also documented. Transformation to adult migraine with or without aura is also reported[1].

Treatment

Treatment of migraine is two pronged, acute relief of symptoms and management of chronicity. Acute therapy is aimed at relieving symptoms early. The target of treatment is complete resolution of all symptoms within one to two hours. To achieve optimal outcome, treatment should be commenced as soon as the first symptoms of migraine are experienced[1]. Treatment involves close interaction between parents, patient and the healthcare professionals and involves use of both pharmacologic as well as non-pharmacologic therapies. Prophylactic therapy on the other hand, requires daily therapy over a period of time and is aimed at reducing frequency of attacks and its severity.

Acute treatment

Studies on the acute treatment of migraine in children and adolescents are rare and difficult to design. Since the last review on treatment of childhood migraine in 2003[28] there has not been any further Cochrane reviews on this topic. The Cochrane review in 2013 has been withdrawn. Most of the evidence on treatment of acute migraine is based on a few clinical trials. In the available literature, acute relief of migraine symptoms at the end of two hours is reported in placebo-controlled trials for acetaminophen, ibuprofen and sumatriptan nasal sprays[28-30]. However, in that for acetaminophen, the need for rescue medications was the same for the drug and the placebo[31] but it is widely recognized as good clinical practice that children with migraine should be offered paracetamol unless contraindicated[32]. The role of ibuprofen and triptans for headache relief in children and adolescents is confirmed in another meta-analysis[33]. Study of tryptans has been mainly in children aged 12 to 17 years. This is available in various forms such as nasal spray, chewable tablets and tablets[32]. The use of antiemetics in treating an acute episode of migraine in children has not been effectively evaluated. However, in adult studies, combining pain relief with antiemetics is recommended[34].

Prophylactic treatment

Use of prophylactic medication is targeted at reducing the disease burden by reducing frequency and disability. It is indicated if frequency is more than one or two per week or those with disabling headache [Score $\geq$30 in the Paediatric Migraine Disability Assessment (PedMIDAS)][18]. For use of prophylactic medication for children, the 2003 Cochrane review described two randomized controlled trials (RCTs), each showing benefit for reducing headache frequency when using propranolol[35] and flunarizine[36]. There was no benefit described for trials using other medications such as nimodipine, timolol, papaverine, pizotifen, trazodone, L-5-hydroxytryptophan, clonidine, metoclopramide, and domperidone[28]. However, a subsequent review in 2011 commented that for use of beta-blockade for prophylaxis, the results of RCTs are inconclusive as out of the three trials on propranolol, one showed positive response while other two showed no effect. In this review, the comment on pizotifen as a prophylactic agents indicated that "although pizotifen is almost universally used for paediatric migraine, there is no evidence from well-conducted trials that it

is beneficial"[32]. Use of amitriptyline, topiramate, cyproheptidines, divalproate sodium, leveteracetam, gapapentine, zonisamide, riboflavin has been shown to be effective in open trials[37,38]. Role of botulinum toxin-A in adults is established, but more studies are needed in children[38].

Apart from medical management, many non-pharmacological aspects are crucial for optimal long term management. These include identifying trigger factors and assessing severity of disability, educating child and parent, using headache calendars for assessment of associated symptoms and frequency, reduce emotional mechanisms that provoke stress which may precipitate headache attacks, maintaining healthy rhythm to life with regular meals, good fluid intake, maintain a good BMI, minimize stress and adequate sleep and advice on how to cope with trigger factors etc. behavioural therapy such as biofeedback and relaxation therapy have been identified to be useful[1,38].

References

1. Winner P. Migraine-related symptoms in childhood. *Current Pain and Headache Reports* 2013; **17**(8):339. http://dx.doi.org/10.1007/s11916-013-0339-6

2. Perera KDCTWJ, de Silva U, Agampodi SB. Prevalence of headache among children in Polonnaruwa Educational Zone. Sri Lanka Medical Assiciation Foundation Sessions; 2013 24-25 October; Anuradhapura, Sri Lanka.

3. Fuh JL, Wang SJ, Lu SR, Liao YC, Chen SP, Yang CY. Headache disability among adolescents: a student population-based study. *Headache* 2010; **50**(2):210-8. http://dx.doi.org/10.1111/j.15264610.2009.01531.x

4. Arruda MA, Bigal ME. Migraine and migraine subtypes in preadolescent children: association with school performance. *Neurology* 2012;**79**(18):1881-8. http://dx.doi.org/10.1212/WNL.0b013e318271f812

5. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; **33**(9):629-808.

6. Jensen R. Pathophysiological mechanisms of tension-type headache: a review of epidemiological and experimental studies. *Cephalalgia* 1999; **19**(6):602-21. http://dx.doi.org/10.1046/j.14682982.1999.019006602.x

7. Bendtsen L. Central sensitization in tension-type headache--possible pathophysiological mechanisms. *Cephalalgia* 2000; **20**(5):486-508. http://dx.doi.org/10.1046/j.14682982.2000.00070.x

8. Bendtsen L, Jensen R. Tension-type headache: the most common, but also the most neglected, headache disorder. *Current Opinion in Neurology*. 2006; **19**(3):305-9.

9. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007; **27**(3):193-210. http://dx.doi.org/10.1111/j.14682982.2007.01288.x

10. Senbil N, Gurer YK, Uner C, Barut Y. Sinusitis in children and adolescents with chronic or recurrent headache: a case-control study. *The Journal of Headache and Pain* 2008; **9**(1):33-6. http://dx.doi.org/10.1007/s10194-008-0007-0

11. Arruda MA, Bigal ME. Behavioral and emotional symptoms and primary headaches in children: a population-based study. *Cephalalgia* 2012; **32**(15):1093-100. http://dx.doi.org/10.1177/0333102412454226

12. Lewis DW. Paediatric migraine. *Pediatrics in Review* 2007; **28**(2):43-53. http://dx.doi.org/10.1542/pir.28-2-43

13. Guidetti V, Lucchese F, Bellini B. Is the migrainous female brain different? Some new evidence. *Brain : a Journal of Neurology* 2012; **13**5(Pt 8):2311-3. http://dx.doi.org/10.1093/brain/aws191

14. Gelfand AA. Migraine and childhood periodic syndromes in children and adolescents. *Current Opinion in Neurology* 2013; **26**(3):262-8. http://dx.doi.org/10.1097/WCO.0b013e32836085c7

15. Antonaci F, Voiticovschi-Iosob C, Di Stefano AL, Galli F, Ozge A, Balottin U. The evolution of headache from childhood to adulthood: a review of the literature. *The Journal of Headache and Pain* 2014;**15**:15. http://dx.doi.org/10.1186/1129-2377-15-15

16. Amery WK, Vandenbergh V. What can precipitating factors teach us about the pathogenesis of migraine? *Headache* 1987; **27**(3):146-50. http://dx.doi.org/10.1111/j.15264610.1987.hed2703146.x

17. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. *Brain* 1994; **117** (Pt 1):199-210. http://dx.doi.org/10.1093/brain/117.1.199

18. Hershey AD. Current approaches to the diagnosis and management of paediatric migraine. *The Lancet Neurology* 2010; **9**(2):190-204. http://dx.doi.org/10.1016/S14744422(09)70303-5

19. Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. *Cell* 1996; **87**(3):543-52. http://dx.doi.org/10.1016/S00928674(00)81373-2

20. Dichgans M, Freilinger T, Eckstein G, Babini E, Lorenz-Depiereux B, Biskup S, et al. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. *Lancet* 2005; **366**(9483): 371-7. http://dx.doi.org/10.1016/S01406736(05)66786-4

21. De Fusco M, Marconi R, Silvestri L, Atorino L, Rampoldi L, Morgante L, et al. Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. *Nature Genetics* 2003; **33**(2):192-6. http://dx.doi.org/10.1038/ng1081

22. Neut D, Fily A, Cuvellier JC, Vallee L. The prevalence of triggers in paediatric migraine: a questionnaire study in 102 children and adolescents. *The Journal of Headache and Pain* 2012; **13**(1):61-5. http://dx.doi.org/10.1007/s10194-011-0397-2

23. Sparaco M, Feleppa M, Lipton RB, Rapoport AM, Bigal ME. Mitochondrial dysfunction and migraine: evidence and hypotheses. *Cephalalgia* 2006; **26**(4): 361-72. http://dx.doi.org/10.1111/j.14682982.2005.01059.x

24. Cuvellier JC, Lepine A. [Childhood periodic syndromes]. *Revue neurologique* 2010; **166**(6-7):574-83. http://dx.doi.org/10.1016/j.neurol.2009.10.020

25. Teixeira KC, Montenegro MA, Guerreiro MM. Migraine equivalents in childhood. *Journal of Child Neurology* 2014; **29**(10):1366-9. http://dx.doi.org/10.1177/0883073813504459

26. Mortimer MJ, Kay J, Jaron A. Clinical epidemiology of childhood abdominal migraine in an urban general practice. *Developmental Medicine and Child Neurology* 1993; **35**(3):243-8. http://dx.doi.org/10.1111/j.14698749.1993.tb11629.x

27. Gelfand AA. Childhood migraine is associated with a history of infantile colic. *The Journal of Pediatrics* 2013; **163**(3):922-3. http://dx.doi.org/10.1016/j.jpeds.2013.06.048

28. Victor S, Ryan SW. Drugs for preventing migraine headaches in children. *The Cochrane Database of Systematic Reviews.* 2003 (4): CD002761.

29. Lewis DW, Kellstein D, Dahl G, Burke B, Frank LM, Toor S, et al. Children's ibuprofen suspension for the acute treatment of pediatric migraine. *Headache* 2002; **42**(8): 780-6. http://dx.doi.org/10.1046/j.15264610.2002.02180.x

30. Hamalainen ML, Hoppu K, Valkeila E, Santavuori P. Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo-controlled, crossover study. *Neurology* 1997; **48**(1):103-7. http://dx.doi.org/10.1212/WNL.48.1.103

31. Damen L, Bruijn JK, Verhagen AP, Berger MY, Passchier J, Koes BW. Symptomatic treatment of migraine in children: a systematic review of medication trials. *Pediatrics* 2005;**116**(2):e295-302. http://dx.doi.org/10.1542/peds.2004-2742

32. Barnes NP. Migraine headache in children. Clinical Evidence (Online) 2011;2011. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3275150/

33. Silver S, Gano D, Gerretsen P. Acute treatment of paediatric migraine: a meta-analysis of efficacy. *Journal of Paediatrics and Child Health* 2008; **44**(1-2):3-9.

34. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000; **55**(6):754-62. http://dx.doi.org/10.1212/WNL.55.6.754

35. Ludvigsson J. Propranolol used in prophylaxis of migraine in children. *Acta Neurologica Scandinavica* 1974; **50**(1): 109-15. http://dx.doi.org/10.1111/j.16000404.1974.tb01350.x

36. Sorge F, Marano E. Flunarizine v. placebo in childhood migraine. A double-blind study. *Cephalalgia* 1985; **5 (**Suppl 2):145-8.

37. Termine C, Ozge A, Antonaci F, Natriashvili S, Guidetti V, Wober-Bingol C. Overview of diagnosis and management of paediatric headache. Part II: therapeutic management. *The Journal of Headache and Pain* 2011; **12**(1):25-34. http://dx.doi.org/10.1007/s10194-010-0256-6

38. O'Brien HL, Kabbouche MA, Hershey AD. Treatment of acute migraine in the pediatric population. *Current Treatment Options in Neurology* 2010; **12**(3):178-85. http://dx.doi.org/10.1007/s11940-010-0069-6