

Migraine headache in children: recent diagnosis and treatment

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Article Review

ABSTRACT

ARTICLE INFO

Keywords:

migraine,
children,
diagnosis and management

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DOI : 10.20885/JKKI.Vol10.Iss2.art11

History:

Received: July 7, 2017

Accepted: February 2, 2018

Online: August 30, 2019

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Migraine headache is one of the most frequent primary headaches that occur in children. It is estimated that 6 million children and adolescent in the United States suffer from migraine. Migraine can affect the quality of life and it can cause a financial and social burden. Migraine is often ignored by not only the parents and teacher but also the doctor. The diagnosis of migraine in children is challenging. Precise diagnosis and management are needed to avoid further impact. In this review, it will be discussed how to diagnose and to establish recent management of migraine in children.

Migraine merupakan salah satu nyeri kepala primer yang paling sering terjadi pada anak-anak. Diperkirakan 6 juta anak-anak dan remaja di Amerika Serikat menderita migraine. Migraine bisa mempengaruhi kualitas hidup dan bisa menyebabkan masalah finansial dan beban sosial. Migraine sering tidak dikenali tidak hanya oleh orangtua tetapi juga dokter. Diagnosis migraine pada anak-anak merupakan hal yang menantang. Ketepatan diagnosis dan manajemen diperlukan untuk menghindari dampak lebih lanjut. Pada review ini akan didiskusikan bagaimana cara mendiagnosis dan menetapkan manajemen migraine pada anak-anak.

INTRODUCTION

Headache is one of the symptoms commonly complained by not only the adult patient but also children patient.^{1,2} Headache also becomes the most referral cases to neurology clinic.² Among the causes of headache, migraine is the most frequent cause as a primary headache. It is estimated that about 6 million children and adolescent in the US have migraine.³ The prevalence increases with age whereby the highest prevalence is during high school as many as 23%. The lowest prevalence is during preschool that is up to 3%. In the elementary age, the prevalence is up to 11%. The prevalence of migraine is also varied in sex. The boys are more frequent than the girls prior to puberty, but they are inversed after puberty.⁴

In a pathophysiology manner, migraine is a neurovascular disorder along with genetic influence. The first degree relative of the patient with migraine has chance to develop migraine 1.9 times compared to general population. One kind of migraine, migraine with aura, can also be affected by genes. It is found that the monozygotic twins have a 34% chance while the dizygotic twins have 12% chance.⁵

Migraine in children, also known as pediatric migraine, is often ignored by the parents, teachers, or even the primary health doctor.² It can cause much impact to the patient. A migraine headache can affect the quality of life and cause financial and social burden.⁶ It can also cause lost school days, social interaction impairment, academic or cognitive impairment,

motor coordination impairment, sleep habit disturbance, and lower physical activity.^{2,7}

Although it has great prevalence and wide range of causes, the diagnosis and treatment are still to be the main problem. Migraine headache is usually unrecognized or attributed as other diagnosis.^{1,8} It is often recognized as a sinus disease or emotional origin.^{1,8} So, it is essential for the clinicians to recognize the disease early and build a treatment plan in order to avoid long term impacts.² In this review, it will be discussed how to diagnose migraine headache in children and to establish a recent treatment plan.

DIAGNOSIS

Migraine is defined as recurrent attacks with at least 5 attacks which last 4-72 hours with at least 2 of the following features: unilateral, throbbing pain sensation, photophobia, phonophobia, moderate to severe intensity, nauseous with or without vomiting, or aggravated by physical activity.⁹ There is two kinds of migraine headache, migraine without aura and migraine with aura.^{5,9,10} Migraine without aura is more common than migraine with aura. Aura is defined as transient neurological symptoms, notably sensory or visual symptoms which occur up to 15% to the patient.¹⁰

The diagnosis of migraine headache in children is based on the International Classification of Headache Disorders (ICHD) 3rd Edition beta version.¹¹ It is still to be the mainstay criterion of the standard diagnosis. The criterion is almost similar to the adult migraine criterion. The clinical features have been explained above. But, there are some diversifications. The pediatric migraine may be bilateral (not unilateral like adult migraine), they can occur in temporal or frontal area, they can last shorter, and the autonomic symptoms like phonophobia or photophobia can be considered by the children's behavior.¹¹

The diagnosis of migraine in children is quite challenging although there is a standard criterion. The children are different from adult both physically and mentally. In the diagnosis

process, it needs careful consideration. If a child comes with a chief complaint of headache, the clinician should take a thorough history and do both general and neurological exam.² All of these processes are aimed to ICHD criterion so that the right diagnosis is built and the precise treatment plan is constructed.

The history-taking of headache include identification of the frequency, duration, severity, location, quality, disability consequences, and the associated symptoms of the headache.^{1,2,5} The histories are taken from not only the children but also their parents. Since the parents know the base condition of their children.² The frequency of the headache should be asked by how many times the headache occurs in a month, considered as episodic or chronic.⁴ If the headache occurs in or less than 14 times a month, it is considered as episodic. If the headache occurs in or more than 15 times a month, it is considered chronic. The duration of the headache may last for 2 to 72 hours.⁵ The location of the pain can be bilateral in children, either in frontal or in temporal region.^{2,3} The location in the occipital region is quite rare. If it happens, the clinicians shall consider other causes like organic factor.⁵

Based on the criterion, the quality of the pain can be throbbing or pulsating pain. Unfortunately, it is difficult to be obtained from the children.⁵ They usually feel difficult to describe the symptoms. In order to assess disability consequences, there is a tool that can be used. It is called as PedMIDAS (Pediatric Migraine Disability Assessment Score).¹ It is a pediatric version of the adult MIDAS. There is also a tool to assess the quality of life of the pediatric migraine patient. It is called as PedsQL (Pediatrics Quality of Life).¹ All of those assessments are important as they can be a sign of deteriorating symptoms or as a sign of response of the treatment.¹ Associated symptoms or also called as classic symptoms are the symptoms that accompany the presence of migraine headache. They are nauseous, vomiting, photophobia (sensitive to light), and phonophobia (sensitive to sound).²

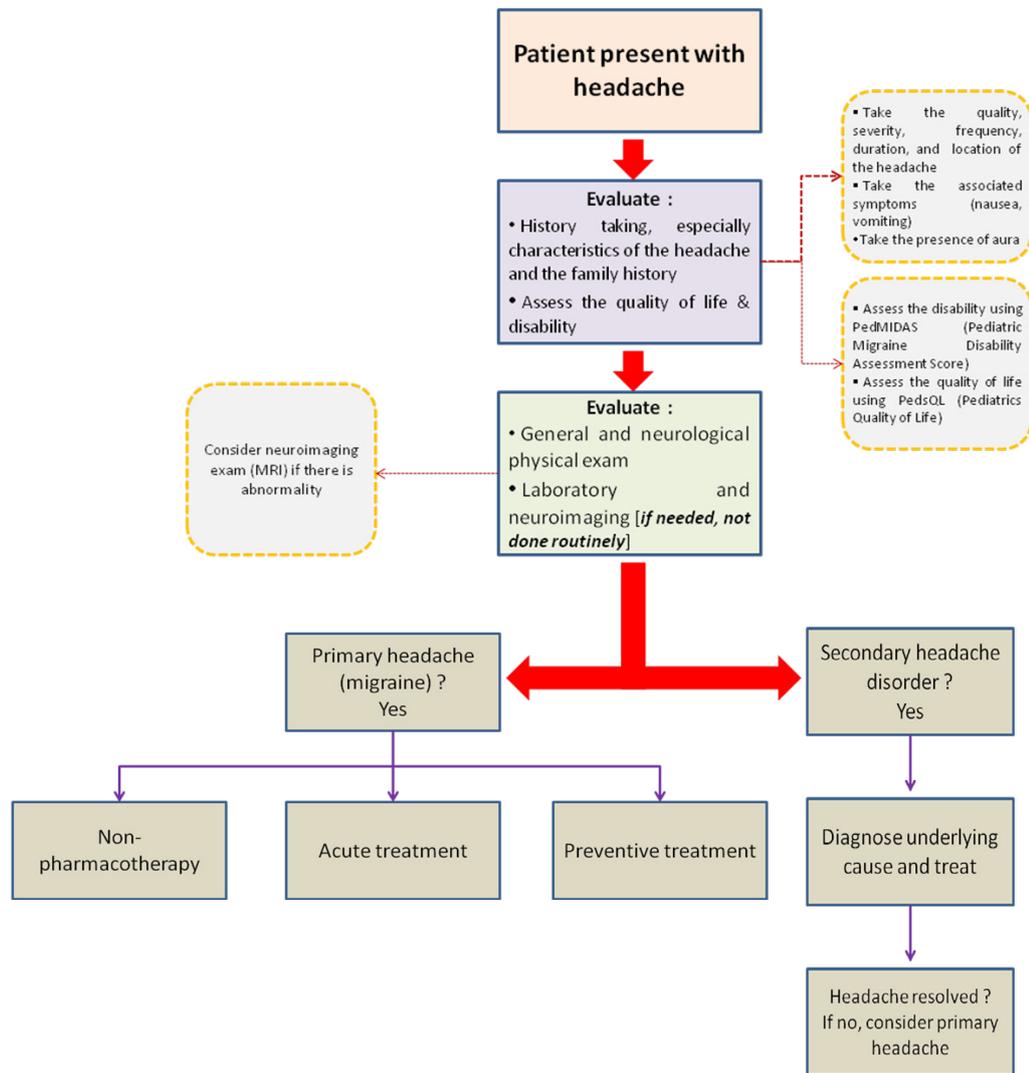


Figure 1. Flow chart of diagnosis and management pediatric migraine headache.¹

It has been explained above that there is migraine with aura and migraine without aura. Migraine with aura is less common than migraine without aura. The aura can be felt as a visual aura or a sensory aura. Visual aura is characterized by a zigzag line near fixation point moving and twinkling laterally. It is called as fortification spectrum. Then, the migraineurs (patient who suffered from migraine) feel blurred vision or sometimes it can be hemianopsia or amaurosis fugax (complete transient unilateral blindness). The sensory aura is characterized by the presence of unilateral paresthesia, hemiparesis, or dysphasia.⁵

The detail and careful history taking should also consider other possible diagnoses, notably the possibility of secondary headache. In primary headache, like migraine headache, there is usually no underlying cause and both general and neurological exam is normal. While in secondary headache, there are found identifiable causes like structural, metabolic, or others.¹² If there is a suspicion of the secondary cause, then the treatment aims directly towards the cause so that the headache is diminished. In history taking, it can also be asked the history of head trauma to the children or the parents as it frequently happens in their age.²

Table 1. Diagnosis criteria of migraine without aura.⁹

- A. At least 5 attacks fulfilling criteria B-D
- B. Headache which lasting 2-72 hours (untreated or unsuccessfully treated)
- C. At least fulfilling 2 of 4 criteria below:
 1. Located unilateral
 2. Pulsating quality
 3. Moderate to severe intensity
 4. Aggravated by or causing avoidance of routine physical activity
- D. During headache, at least fulfilling 1 of this criteria below:
 1. Nausea with/without vomiting
 2. Photophobia and phonophobia
- E. Not better accounted for by another ICHD-3

Table 2. Diagnosis criteria of migraine with aura.⁹

- A. At least 2 attacks fulfilling criteria B and C
- B. Fully reversible symptoms of 1 or more below:
 1. Visual
 2. Sensory
 3. Speech and or language
 4. Motor
 5. Brainstem
 6. Retinal
- C. At least fulfilling 2 of these criteria below:
 1. At least one aura symptom spreads gradually over ≥ 5 minute, and or two or more symptoms occur in succession
 2. The Aura symptom lasts 5-60 minutes
 3. At least one aura symptom is unilateral
 4. The aura is accompanied or followed by headache within 60 minutes
- D. Not better accounted for by another ICHD-3 and transient ischemic attack is excluded

Other secondary causes that have to be ruled out are infections, increased intracranial pressure (ICP), musculoskeletal, and temporomandibular joint. Infections, especially central nervous system infection should be thought by the clinicians. Moreover, if there is a fever in the patients. Increased ICP can be secondary from idiopathic intracranial hypertension. It often causes a long-standing headache. The musculoskeletal is primary from the cervical spine. It can result in headache and perceive as the dermatomal region. The tenderness of the temporomandibular joint can also result in headache.¹³ The children often

feel difficult to open their mouth.

In order to strengthen the diagnosis and exclude other differential diagnoses, the clinician should do further evaluation. The evaluation includes physical examination associated with headache. The exam should include a general exam and neurological exam. The thoroughness of physical examination is essential. The vital sign should not be forgotten. It can identify fever or hypertension. The clinicians should also obtain growth parameters and head circumference measurement. They can identify chronic illness, hydrocephalus, or macrocephaly.¹³ The clinician

should recognize the presence of muscular tightness, cranial bruits, Mueller sign to assess sinus tenderness, and ophthalmic exam including posterior segment exam.¹ A thorough ophthalmic exam is quite critical to exclude papilledema.¹³

Further diagnostic exam like laboratory or neuroimaging can be mulled if there is a sign of secondary headache.¹ Neuroimaging is not done routinely. Unless there is any risk factor or any abnormality during the previous exam

(especially neurological exam) that suggests intracranial pathology. Laboratory studies or lumbar puncture is also not done routinely. If there is a metabolic concern or signs of infection i.e encephalitis or meningitis, they will be considered. Electroencephalography (EEG) is not recommended as routine evaluation.¹³ It is unlikely to be a consideration to distinguish migraine headache from others headache.

Table 3. Primary headache versus Secondary headache.⁹

<u>Primary headache :</u>	<u>Secondary headache:</u>
<ol style="list-style-type: none"> 1. Migraine headache 2. Tension-type headache 3. Cluster headache 4. Other primary headache disorders 	<ol style="list-style-type: none"> 1. Trauma or injury to the head or neck 2. Vascular disorder in cranial or cervical 3. Substance or its withdrawal 4. Infection 5. Disorder of homeostasis

One of the most frequent differential diagnosis is a tension type headache (TTH). It is also the most common of headache in children. The frequency of TTH is about 9,8-18%.¹⁴ In the clinical setting, sometimes it is difficult to differentiate the migraine headache and TTH

as they share the same clinical feature and epidemiological. Some experts say that some migraineurs also have TTH. The current ICHD criterion differentiates among them. ICHD states that migraine and TTH are different syndrome.¹⁴

Table 4. The difference between migraine and tension-type headache.⁹

	MIGRAINE	TENSION -TYPE HEADACHE
Number of attack	≥ 5	≥ 10
Duration of attack	2-72 hours	30 minutes – 7 days
Characteristics		
Location	Unilateral / Bilateral+	Bilateral
Quality of pain	Pulsating	Pressing/Tightening
Intensity	Moderate to severe	Mild to moderate
Aura	May be present	Absent
Aggravated by routine activity	Yes	No
Accompanying symptoms		
Nausea and/or vomiting	Yes	Absent
Photophobia/phonophobia	Both present	Only one possible present
Not attributed to other causes	Yes	Yes

+Location bilateral in children under 15 years old

MANAGEMENT

The first step in the management of pediatric migraine is to reassure the parents. The parents often go to the doctor to look for the cause of their children's headache. They surely worry about the seriousness of the cause. So, reassurance is critical to the parents that the cause of the headaches is not life-threatening or from the brain tumor.⁸

The goals of the long-term management of migraine are:¹⁵

- 1) To reduce the headache frequency, severity, duration, and disability
- 2) To diminish the ineffective, poorly tolerated, or unwanted acute pharmacotherapy
- 3) To improve the quality of life
- 4) To reduce the headache-related distress and psychological symptoms
- 5) To encourage the patients to manage and to control their disease
- 6) To avoid the escalation of the drugs for the acute setting

To attain these goals, the management is divided into three different strategies: non-pharmacological treatment, acute treatment, and preventive treatment.^{8,13}

Non-pharmacological Management

The non-pharmacological treatment remains to be the mainstay treatment in the case of headache.¹³ There are some approaches to this kind of treatment. The approaches are to do regular physical activity, relaxation technique, appropriate sleep hygiene, bio-feedback, self-hypnosis, acupuncture, cognitive therapy or stress management, and limiting caffeine intake.^{8,13} Some approaches give a good result. The behavioural therapy like relaxation technique or biofeedback can give efficacy in the treatment almost 80%.¹³ Besides limiting caffeine intake, there should be restricted consuming cheese, chocolate or citrus fruits that are believed to be the trigger of headache.⁸ Another approach is to make a headache diary. The children and their parents make a collaboration to arrange a diary. It allows them to explore the pattern of the headache and its triggers.¹³ The triggers may

be different from one child to each other. There may be food, stress, tiredness, bright light, etc. There has to be remembered that the child shall be responsible for the diary, not the parents.¹³ An innovative treatment has been proposed by the Italian clinicians using Nintendo Wii Fit Plus™. It is aimed at children who have balance and motor coordination impairment as resulted from migraine without aura.⁷ The device is believed to improve the impairments as it promotes complexity task, cognitive stimulation, as well as motor skills. The study is a preliminary study. There is a positive effect from the device as a rehabilitative device for the children affected by migraine without aura who have visuomotor and balance impairment.⁷ But, further research and long term follow-up are needed. Regardless of all of the treatment, the doctors who involved in this disease do not work by themselves. They need other practitioners like psychologist or physiotherapist as a collaboration to treat the affected patient.

Acute Management

The goal of the management in acute migraine is to abort the pain as fast as possible with minimum side effects. The medicines given to the patients should be used in proper dosage and in short duration.² The clinicians should also consider the potential development of medication overuse headache (MOH).^{1,2,8} MOH will lead to frequent daily headache as a result of long term usage of headache drugs, particularly over the counter (OTC) drugs.⁸

There are some principles to guide in the acute management of headache:

- 1) Take the medicine as soon as possible when the headache begins. It is suggested in 30 minutes⁸
- 2) Take the medicine in precise dose based on body weight^{1,2,8}
- 3) Put the medicine in the place whereby the headache usually attacks, i.e. in the school or home⁸
- 4) Avoid the overuse of the medicine. It was said a maximum of 5 doses per week⁸, no more than 15 headache treatment days per

month¹, no more than 3 days per week.²

There are some medicines used to abort the acute migraine attack. The medicines are OTC drugs like ibuprofen or acetaminophen, triptans, ergot alkaloid, and dopamine antagonist.

Over the Counter (OTC) Drugs

The OTC is non-prescription drugs, mostly analgesics. The drugs are like ibuprofen and acetaminophen. They are possibly the most frequent drugs used by the parents to kill the attack. The children often respond to these drugs. Ibuprofen can be given at dose of 7.5 mg/kg/dose to 10 mg/kg/dose for the treatment of acute headache.^{1,2,8,11,13,16} It has been proven safe and efficacious in two double-blind, placebo-controlled trial.¹³ Its maximum dose is 40 mg/kg/day.¹⁶ The acetaminophen or paracetamol can be given at dose of 10-15 mg/kg/dose.^{2,8,11,13,16} Its maximum dose is 60 mg/kg/day.¹⁶ Some trials have been conducted to compare both of them.

A trial was conducted by Hamalainen et al (1997) showed that Ibuprofen (10 mg/kg liquid suspension) was superior over paracetamol (15 mg/kg liquid suspension) and placebo to generate headache relief 2 hours after the treatment started.² Other trial shows that both ibuprofen and paracetamol has the same outcome.¹³ Both of them are better than the placebo. A trial was conducted by Liza et al (2xxx) showed that ibuprofen was superior over paracetamol in 2 hours primary endpoint only in boys.¹³ In the patient with sensitive to non-steroid anti-inflammatory drugs (NSAIDs), upper gastrointestinal bleeding, renal impairment, bleeding disorder, paracetamol should be reserved as the treatment choice.²

These drugs can be given orally as they are preferred by most of the children. The clinicians should consider if the children have nausea or vomiting. Early treatment with an antiemetic drug may relieve nausea, then the pain killer drugs can be given.¹⁶ The pain killer drugs should be initiated at the onset of the pain or the aura.² It can be repeated in 3-4 hours if the headache persists in the same dose.² The usage of the drugs should be limited to prevent rebound analgesics

headache.¹³ Alternative drugs are naproxen sodium and aspirin. They demonstrate effective, safe, and often prescribe in adult headache. However, aspirin should not be prescribed in children under 15 years old as it can exceed the risk of Reye Syndrome.^{1,2}

Triptans

Triptans are serotonin receptor agonist. Their main action is to activate the serotonin receptor in cerebral and dural vessel walls causing vasoconstriction and inhibition of the trigeminal perivascular nerve terminals.² They are also called as migraine-specific drugs. They are widely used to treat migraine in adult, mainly severe migraine. There are seven triptans in the market and available in various formulations. Triptans are available as an injection (sumatriptan), nasal spray (sumatriptan and zolmitriptan), tablets (sumatriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan, naratriptan, frovatriptan), and dissolving tablets (zolmitriptan, rizatriptan).² All of these drugs are accepted by the FDA to treat migraine in adult.¹⁶ The only drugs approved by the FDA to treat pediatric migraine are sumatriptan, almotriptan and rizatriptan.¹⁶ In clinical practice, if the patients only suffer from mild to moderate headache, it will be wise to take NSAIDs. If the patients suffer moderate to severe headache, it will be muller to take triptans or if the OTC drugs are not responsive.² The triptans should be taken at the onset of a headache to reach maximum effect. The contraindications of the triptans are cerebral or peripheral vascular syndromes, patients who take monoamine oxidase inhibitor, have a pregnancy, have uncontrolled hypertension, have a severe hepatic impairment, and have hemiplegic migraine.²

Sumatriptan is being the most widely studied drug.¹⁶ It has sufficient evidence to use intranasal sumatriptan in acute pediatric migaine.¹⁶ The dose is 10 mg for bodyweight less than 39 kg and 20 mg for bodyweight more than 39 kg. Rizatriptan is used for the children whose age 6 years or above. Its dose is 5 mg for bodyweight less than 39 kg and 10 mg for bodyweight

more than 39 kg.² Various trials have shown its effectiveness and superiority over the placebo. It also decreases the recurrent of the headache and it has minimal side effects. Common side effects are dizziness, somnolence, dry mouth, and nausea. Almotriptan has been approved to be given in the children whose age 12 years or above. It is also superior to placebo and given a dose of 12.5 mg.²

Ergot Alkaloid

The ergot compound is possibly ancient drug for migraine attack. Dihydroergotamine (DHE) is often used to treat acute migraine in adult, notably in emergency management.¹ The mechanism is to cause central vasoconstriction effect as it is a serotonin receptor agonist. Its common side effects are nausea, vomiting, abdominal discomfort, flushed face, muscle cramps, and vasospasm.² The usefulness in children, especially in the inpatient setting, is limited.¹ It can be muller if the attack is intractable or resistant to other drugs. It is advised to give premedication drug to avoid its most common side effect, nausea. The antiemetic drug-like prochlorperazine 0.13-0.15 mg/kg, 30 minutes prior injection of DHE can be given to the patient. The dose of DHE depends on the weight, age, and tolerability, however, its dose range is 0.5–1 mg every 8 h until the pain subsides.²

Dopamine Antagonist

Dopamine antagonist drugs are used to treat associated symptoms like nausea and vomiting. The most common drugs are prochlorperazine maleate and metoclopramide hydrochloride. Studies show that they are effective to minimize nausea and vomiting and the migraine effects. The administration route is preferable via intravenous over others since it is more effective. The clinicians should also consider the side effect of the drugs, mainly the extrapyramidal side effects.¹

Admission

The patients should be admitted if they are in status migrainosus or in severe exacerbation.²

Status migrainosus is an intractable migraine which lasts more than 72 hours and associated with debilitating pain and or associated symptoms.^{9,17} The objective of the admission is to control the headache that has been unresponsive to outpatient therapy.²

Preventive Management

Preventive treatment should be considered if the headache causes an impact on daily or school activity.¹³ The measurement of the disability can use simple scoring like PedMIDAS. Another consideration to give preventive treatment is if the patients have more than three to four headaches in a month.¹ The objectives of the treatment are to reduce the frequency of the headache, to reduce the progression to chronic daily headache, and to reduce the associated pain and disability. There is no guideline for choosing preventive treatment in pediatric migraine. The medications that are frequently used are antidepressants, antiepileptic, and antiserotonergic. It is important to discuss with the family about the treatment plan. The clinicians should tell the parents that it is long-term therapy and it needs time to get the response. The dose has to titrate slowly in order to avoid significant adverse effects. When the effective dose is reached, then it is advised to be sustained for 2-3 month.²

Antidepressants

The tricyclic antidepressant (TCA) is a member of antidepressant that is most widely studied among others.^{1,2} Among the member of TCA, amitriptyline is the most frequent drug used to prevent migraine headache. With the dose of 10-150 mg/day, it has consistent evidence in many trials to prevent a headache in adult.² The efficacy in pediatric has not established yet in randomized controlled trials.² Most of the research is open-labelled and no-placebo controlled. A trial done by Lavenstein showed amitriptyline to be effective in 50-60% of the children. An open-labelled trial done by Hershey et al showed improvement in more than 80% of the children at the dose of 1 mg/kg/day.¹ But

Table 5. Treatment options for acute migraine

Drug	Route	Dose	Level of evidence	Remarks
Paracetamol	Per oral (liquid susp, tab)	10-15 mg/kg/dose	Good evidence supports Class 1, Level B ¹⁹	As alternative if patient is sensitive to NSAID, has upper GI bleeding, renal impairment
Ibuprofen	Per oral (liquid susp, tab)	7,5-10 mg/kg/dose	Strong evidence support Class 1, Level A ¹⁹	Some trials show superiority over paracetamol ^{2,13}
Rizatriptan	Per oral (Tab)	< 39 kg = 5 mg ≥ 39 kg = 19 mg	Insufficient evidence supports Class 4, Level U ¹⁹	For age ≥ 6 years old
Almotriptan	Per oral (Tab)	12,5 mg	Insufficient evidence supports Class 4, Level U ¹⁹	For age ≥ 12 years old
Sumatriptan	Nasal spray	< 39 kg = 10 mg ≥ 39 kg = 20 mg	Strong evidence support Class 1, Level A ¹⁹	For age ≥ 12 years old
Dihydroergotamine (DHE)	Injection (sc, im, iv)	0,5-1 mg	Unknown	Limited evidence. Considered if the attacks is intractable or resistant to other drugs.
Prochlorperazine	Injection (iv)	0,1-0,3 mg/kg	Unknown	For weight > 10 kg. Minimize nausea and vomiting. Consider the extrapyramidal side effect.

it needs to be titrated slowly to reduce the side effects. The titration is by increasing the dose of 0.25 mg/kg/day every 2 weeks over 8-10 weeks.^{1,2} The recent double-blind randomized controlled trial compares amitriptyline (1 mg/kg/day), topiramate (2 mg/kg/day) and placebo and the result is that there are no significant differences in the reduction of the headache frequency and associated disability. The trial precisely warns about the adverse effects of the active drugs.³ The most common adverse effects of amitriptyline are fatigue, dry mouth, sedation, lightheadedness, constipation, and the risk of prolonged QT.¹⁻³ Another member of TCA can be considered as it is less sedative. But, it has the risk of arrhythmia so it needs regular monitoring with EEG.² Serotonin Selective Reuptake Inhibitor (SSRIs) is another member

of the antidepressants drug. It has also been widely studied in adult, but in children, it is still limited.¹

Antiepileptics

The antiepileptic drugs (AED) have been used to prevent migraine attack since 1970.¹⁰ The drug used in that era is carbamazepine. Now, the AEDs have been widely used as they have better effectiveness and tolerability. The drugs that are frequently used in the adult are topiramate, valproic acid, levetiracetam, zonisamide, gabapentin, and pregabalin.^{1,2,10} FDA approved valproic acid and topiramate in adult. In children, topiramate is considered to be used in children down to 12 years old.² The recommended dose is 2 mg/kg/day with slow titration to reach adequate dose.² Many

Table 6. Treatment options for migraine preventive treatment in children

Class	Drug	Route	Dose	Level of evidence	Remarks
Antidepressant	Amitriptyline	Per oral (Tab)	10-150 mg/day	Insufficient evidence support Class II, Level U ¹⁹	Titrate slowly. Watch the side effects.
Antiepileptic	Topiramate	Per oral (Tab)	2-3 mg/kg/day	Insufficient evidence support Class II, Level U ¹⁹	Titrate slowly. Latest evidence fail to show its benefit ³
Antiepileptic	Pregabalin	Per oral (Tab)	50-70 mg/day	Unknown	Promising benefit in a trial. ¹⁰ Need further research.
Antiserotonergic	Cyproheptadine	Per oral (Tab)	0,2-0,4 mg/kg/day	Insufficient evidence support Class II, Level U ¹⁹	No controlled-trial supports
Beta-blocker	Propranolol	Per oral (Tab)	2-4 mg/kg/day	Insufficient evidence support Class II, Level U ¹⁹	Three latest RCTs fail to show its consistency ¹³ . Contraindicated in patient with reactive airway.
Calcium channel blocker	Flunarizine	Per oral (Tab)	5 mg/day	Good evidence supports Class I, Level B ¹⁹	Not available in US. Need further research and long term follow-up.
Nutraceutical	Riboflavin	Per oral (Tab)	50-200 mg/day	Unknown	Limited evidence. Two RCTs show no significant different from placebo.

trials have been demonstrated the superiority of topiramate over placebo and other drugs.^{1,2} One of them is a trial done by Lewis et al with a dose of 100 mg/day, topiramate is superior to placebo. A trial done by Winner et al have also demonstrated the reduction of the headache with a dose of 2 mg/kg.² But, a recent trial done by Powers and colleague shows that topiramate (2 mg/kg/day) fails to demonstrate its effectiveness in over 24 weeks of trial.³ They warn the side effects of topiramate, like paresthesia and weight loss. Another AED, pregabalin, is introduced to be used as pediatric migraine headache prevention. A trial shows that pregabalin (50-70 mg/day) significantly reduces the headache frequency and is comparable toward propranolol.¹⁰ Its common side effects are somnolence, dizziness, and abdominal pain.

Antiserotonergics

Cyproheptadine is the most frequent drug in this group. The supportive evidence is not sufficient enough.¹³ No controlled-trial supports further usage of this drug. A study of small groups in children reported the effectiveness of cyproheptadine. Its dose is 0.2 mg/kg/day to 0.4 mg/kg/day.¹ Its significant side effects are weight gain and sedation.^{1,13}

Beta-blockers

Beta-blocker, particularly propranolol, is long used as prevention treatment of pediatric migraine. The dose is 2-4 mg/kg/day, titrate slowly. But, it is said that three randomized controlled trials fail to show its consistency in therapeutic effects.¹³ Propranolol is contraindicated in children with reactive

airway, diabetes, orthostatic hypotension, and bradycardia.¹³ The adverse effects are hypotension, exercise-induced asthma, and asthma.¹

Calcium channel blockers

Flunarizine is the main drug that often used as a preventive migraine attack. Flunarizine is available in Europe but not available in United States.¹ Its dose is 5 mg/day. A randomized-controlled trial in children showed a beneficial effect of this drug. The headache frequency is reduced in that trial compared with those who received placebo. The applicability of this drug in pediatric migraine prevention needs further research and long-term follow-up. The main side effects are weight gain and sedation.¹³

Riboflavin

In migraine headache, it is believed that mitochondrial dysfunction has played in role in its pathophysiology.¹¹ Riboflavin is a precursor of flavin mononucleotide and flavin adenine dinucleotide.¹⁸ They are involved in the mitochondrial electron transport chain and it has played in role in the Krebs cycle.^{11,18} It was hypothesized that if the patient consumes riboflavin continually, there may improve the mitochondrial brain function.¹¹ Subsequently, there may prevent migraine exacerbation. High dose riboflavin (400 mg/day) shows its good efficacy and tolerability in a trial in adult.¹⁸ The evidence of usage riboflavin in children is limited. Two randomized double-blind placebo-controlled trials done by MacLennan et al and Bruijn et al show no significant difference between riboflavin and placebo.¹¹ These trials use riboflavin with a dose of 200 mg/day and 50 mg/day, respectively. In general, the trials report that riboflavin is safe, well-tolerated, and no serious toxicity.

CONCLUSION

Migraine headache is one of the most common primary headaches in children. It can be debilitating and can cause several

unwanted impacts. The diagnosis of migraine is based on ICHD-III beta version criteria. The construction of diagnosis is primarily made through history taking and physical examination (general and neurological exam). Laboratory and neuroimaging are not done routinely. The clinicians should also consider excluding potential secondary headache and other primary headaches. The principal management is about the reassurance to the parents about the headache. Management encompasses non-medication, acute treatment, and preventive treatment. Ibuprofen is the most recommended drug to abort mild to moderate attack. Paracetamol can be an alternative if ibuprofen is contraindicated. If the patient in status migrainosus or in severe exacerbation, admission will be a consideration. Preventive treatment should be considered if the headache causes an impact on daily or school activity. Many drugs have been proposed as a preventive treatment. But, there are still limited evidence to support the usage of the drugs. Further research should be established.

CONFLICT OF INTEREST

None declare

Acknowledgement

None declare

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