

## MIGRAINE IN CHILDREN AND ADOLESCENTS

Hadi KAZEMI MD <sup>1</sup>,  
Ali GORJI MD <sup>2</sup>

1. Assistant Professor of Pediatric,  
Shahed University, Tehran, Iran  
2. Professor of Neurophysiology,  
Institute für Physiologie I,  
Westfälische Wilhelms-University  
Munster, Munster, Germany

Corresponding Author:  
A. Gorji MD  
Institute für Physiologie  
Universität Münster  
Robert-Koch-Strasse 27a  
D-48149 Munster, Germany  
Tel: +49 251 8355564  
Fax: +49 251 8355551  
E-mail: gorjial@uni-muenster.de

Received: 20-Dec-2010  
Last Revised: 29-Dec-2010  
Accepted: 29-Dec-2010

### Abstract

#### Objective

Headache is a frequent symptom in children and adolescents. Migraine is one of the most common types of primary headache disorders in children that at times can be extremely disabling. Many clinical features of migraine in children differ from that starting in adulthood. This review discusses the epidemiology, clinical features, management, and prognosis of migraine headache in children and adolescents.

**Keywords:** Headache, Pain, Aura phase, Spreading depression.

### Introduction

Although historical references to children's headaches date back to 1000 years (1), the modern era of the headache studies in children and adolescents began a few decades ago. Headaches are very common during childhood and become increasingly frequent during adolescence. Epidemiological studies state that 14-25% of children experience headache episodes (2,3). A headache disorder affects the healthy lifestyle of child and his family and results in significant disability including time lost from school. Among children who experienced migraine, 42% lost school time because of their headaches (4).

The international Headache Society (IHS) (5) diagnostic criteria have been widely accepted for adults, but less so far for children. Many scientists have proposed revisions to the IHS criteria for children and adolescents with migraine (6). Based on the temporal pattern plotted against the severity, headache in children is divided to five patterns: acute, acute recurrent (migraine), chronic progressive (organic), chronic non-progressive (tension-type), and mixed (tension-type and migraine) (7). Acute recurrent headaches are usually migrainous (4). Migraine is a common episodic headache, which is characterized by attacks consisting of various combinations of headache and neurological, gastrointestinal, and autonomic symptoms. Migraine attacks are often precipitated by trigger phenomena. Provocative factors include diet, odors, medication, hunger, illness, anxiety, stress, excessive sleep or lack of sleep, fatigue, menses, and travel (8). Epidemiological studies have shown that 3-7% of the pediatric population suffers from migraine (9). At the age of 7 years, migraine prevalence ranges from 1.2 to 3.2%. Between 7 and 15 years of age, prevalence ranges from 4 to 11% (2,3,10). Migraine prevalence is higher in boys than girls at 3 to 7 years of age. Prevalence is equal in boys and girls aged 7 to 11 years and is higher in girls after age 11 (2). The clinical study of Bille (11,12) on children with

migraine, followed up for more than 40 years, shows that 50% of the patients continuously suffered from migraine attacks throughout their life. Sillanpaa (13) found 22% of remissions in 355 children with migraine followed up for 7 years if the starting age was before 8 years of age and 25% if starting age was after 14. The earlier the migraine attacks begin the more likely is an unfavorable clinical course (9). Children with migraine without aura are usually younger than those with aura (14).

Many clinical characteristics of pediatric migraine differ from that starting in adulthood. Children appear to have fewer attacks per month with shorter duration in their younger age. Their headache attacks seem less severe and more easily controlled. As children mature into adolescents, the numbers as well as the duration of attacks increase and the attacks become more difficult to treat.

A positive family history was recorded in 50 to 90% of migrainous children (9). This positive family history is more commonly recorded in children than in adults (15). However, disagreement exists regarding the mode of inheritance. Some of these families have mitochondrial diseases. Familial hemiplegic migraine has been related to mutations in a brain calcium channel in chromosomes 1 and 19 (16).

### **Migraine with Aura**

Migraine with aura is less prevalent in children and adolescents than migraine without aura. Approximately in 15% to 30% of migrainous children, aura was reported. When aura is present, it can be visual or somatic and may include moving lights, distorted images, colored lights, and fortification spectra. Somatic disturbances such as dysphasia, hemiplegia, and speech disturbances are less frequent. The aura usually lasts 15-30 minutes and may be followed by a bilateral headache or a unilateral cephalalgia contralateral to the aura. The headache is usually severe and throbbing. Migraine with aura is frequently associated with photophobia, phonophobia gastrointestinal symptoms such as nausea, vomiting, and anorexia, abdominal pain and pallor. This type of headache tends to be relieved by sleep (17).

In some cases distortions of somatic perception may precede the migraine attacks, such as the "Alice in wonderland" syndrome. "Alice in wonderland"

syndrome consists of bizarre visual illusions or hallucinations and spatial distortions that precede migraine headaches. Children may describe fluctuations in size and shape of the objects such as metamorphopsia, micropsia, macropsia, or teleopsia before the cephalalgia begins. However, it should be noted that this syndrome has also been reported in acute and persistent Epstein-Barr virus infection (18), coxsackievirus infection (19), frontal lobe epilepsy (20), and drug ingestion such as triazolam (21).

### **Migraine without Aura**

Migraine without aura is the most common type of migraine in children and adolescents. Although aura is absent in this type of headache, many children describe a prodrome prior to the pain attacks. Personality change, irritability, lethargy, and pallor may last from minutes to hours before appearance of headache. This type of headache is frequently associated with abdominal pain and gastrointestinal disturbances. The frequency, duration, and severity of attacks vary and usually occur twice a month. Pain is often resolved during an interval of sleep (22). Complicated migraine refers to migraine attacks associated with transient neurologic disturbances. Most patients recovered spontaneously without any sequelae. It is important to differentiate complicated migraine from serious intracranial diseases. Magnetic resonance imaging, magnetic resonance angiography, and electroencephalography have been suggested to rule out intracranial vascular disorders but not invasive angiography (23). Neuropsychological sequelae are not common and children with migraine headache are not in the risk for impaired cognitive development (24).

### **Basilar Migraine**

Neurologic symptoms referable to disturbance in cortex, brain stem, and cerebellum function accompanied with occipital headache are common among but not restricted to adolescent women. Basilar migraine is known also to occur in children. Basilar migraine episodes begin with total blindness or visual field cuts accompanied or followed by admixtures of dizziness, vertigo ataxia, dysesthesia, dysarthria, tinnitus, and distal or perioral paresthesia. Loss of consciousness may also occur. Neurologic symptoms persist for approximately 30

minutes and are generally followed by a throbbing occipital headache (25). Electroencephalography between or during attacks may reveal occipital spike discharges, which should be differentiated from occipital epilepsy (26). Basilar migraine also should be differentiated from cerebral vascular diseases, demyelinating diseases, and occipital neuralgia.

### **Ophthalmoplegic Migraine**

Ophthalmoplegic migraine is the association of a complete or incomplete third nerve palsy and ipsilateral headache. Appearance of a dilated pupil in a lateral deviated eye may precede, co-exist with, or follow a severe and retroorbital headache. The ophthalmoplegia persists for a variable period of time after relieving of headache. Ophthalmoplegic migraine is very rare in children and adolescents (27). Aneurysms of cerebral arteries should be ruled out.

### **Hemiplegic Migraine**

Hemiplegic migraine is the association of recurrent hemiparesis and headache. Headache always appears contralateral to the hemiparesis. Some patients also described aphasia, meningismus, and visual field defect. Hemiparesis may precede, accompany, or follow the headache. Headache usually disappears before the hemiparesis. Cerebrospinal fluid pleocytosis has been observed in some patients.

In some children, the attacks are familial. At least 3 different genes have been implicated in familial hemiplegic migraine: the CACNA1A calcium subunit gene on chromosome 19p13 in half of the families with FHM, an unknown gene on chromosome 1 in a few families, and at least a third one, as a few families could not be linked to either chromosome 19 or chromosome 1 (28). FHM is an autosomal dominant form of migraine with aura in which the aura is characterized by motor weakness of variable intensity. Symptoms include both typical migraine and severe episodes with prolonged aura, impaired consciousness ranging from confusion to profound coma, fever, and meningismus. Aura can persist for several days to weeks. Some patients also have fixed cerebellar symptoms and signs such as nystagmus and progressive ataxia. Cerebellar ataxia progresses independently of the frequency or severity of hemiplegic

migraine attacks (29,30).

### **Migraine Variants**

Based on IHS classification (5), migraine variants include two clinical entities, benign paroxysmal vertigo and alternating hemiplegia of children. Benign paroxysmal vertigo is common in children. It more commonly affects younger children, who develop sudden unsteadiness and grab everything for stability. Features that are common in migraine, i.e. pallor, nausea, phonophobia, photophobia, and nystagmus, commonly accompany benign paroxysmal vertigo. Migraine is twice as common in first-degree relatives compared to controls. This disorder evolves into migraine in later childhood and adolescence. Antihistamine therapy has been suggested (31,32).

The onset of alternating hemiplegia of children is usually before 18 months of age. Repeated episodes of hemiparesis, monoparesis, or quadriplegia are lasting from a few minutes to several days and accompanied by decreased tone and occasionally involuntary movements. Occurrence of tonic or dystonic attacks, nystagmus, dyspnea and other autonomic phenomena, development of cognitive impairment, and choreoathetotic movement disorder have been reported. Children are normal at the onset of attacks. Over time, more attacks occur and children demonstrate developmental deterioration. Sleep consistently relieves both weakness and associated paroxysmal phenomena. Treatment with the calcium channel blocker flunarizine may be helpful (33).

### **Pathophysiology**

Current concepts regarding the pathogenesis of migraine are based on biochemical studies and techniques that measure cerebral blood flow, as well as biochemical determinants. The pathophysiology of migraine seems to be similar in children and adults. Several studies have been combined to produce the neurovascular hypothesis, which considers migraine an inherited sensitivity of the trigeminal vascular system. Spreading depression (SD), a self-propagating front of depolarization associated by a depression of the neuronal bioelectrical activity for a period of minutes, is proposed to play an important role in induction of aura phase (34). Furthermore, SD seems to be responsible for eliciting of pain and many other accompanied symptoms in migraine (34,35).

### Laboratory Tests

Nine percent of children with migraine have focal epileptiform discharges without any evidence of epilepsy or seizure. This incidence of 9% is higher than the incidence of benign focal epileptiform discharges in the normal population (36). Therefore, the electroencephalogram may help the clinicians to find such an occult epileptiform discharges. Most migraineurs without any symptoms of progressive neurologic disease and with normal neurologic examination do not require any imaging include computed tomography and magnetic resonance imaging. In children suffering from migraine and academic problems psycho-educational tests may be useful.

### Treatment

When a diagnosis of migraine has been made, a treatment plan should be formulated. Migraine treatment divides to pharmacologic and non-pharmacologic therapies. Pharmacologic treatments include symptomatic, abortive, and prophylactic treatments. There is no indication for drug prescription if migraine attacks are infrequent and easily relieved by sleep. For most patients, symptomatic or abortive therapy will suffice. For frequent appearance of migraine episodes, a combination of symptomatic, abortive, and prophylactic therapy will be needed.

The most common type of pharmacologic treatment of childhood migraine is intermittent oral analgesic. Early administration of acetaminophen, ibuprofen, ketorolac, and naproxen sodium at appropriate doses is frequently effective. Combination of abovementioned drugs in some cases is helpful. Narcotics should be avoided during the initial stages. Narcotics and barbiturates are the second drugs of choice if the first agents fail. Once anorexia, vomiting and nausea occur, antiemetics may be helpful. When oral prescription is not possible, medicaments may be administered rectally or by injection.

Abortive substances can be administered orally, rectally, parentally, or intranasally. These agents include ergot preparations, non-steroidal anti-inflammatory drugs (NSAIDs), and triptans. Although ergot preparations are usually useful, due to the risk of nausea and rebound withdrawal headaches in children and adolescents, it should not use more than twice weekly. NSAIDs including flurbiprofen, naproxen, and meclufenamate are

useful for the acute treatment of migraine. The maximal allowable dosage should be administered at the onset of episode. Sumatriptan nasal spray at doses of 10 and 20 mg provided rapid relief in the adolescent migraine population (37,38).

Prophylactic treatment should be considered only when patient has frequent or prolonged attacks. Many substances are advised as preventive agents for migraine attacks in children and adolescents. These include calcium channel blockers such as verapamil and flunarazine,  $\beta$  blockers such as propranolol, NSAIDs such as aspirin and flufenamic acid, tricyclic antidepressants such as amitriptyline, sodium valproate (39), and cyproheptadine. The  $\beta$  blockers are first-line agents for migraine prevention. They also have anxiolytic effects. Calcium channel antagonist flunaraznie has been found to be effective and well-tolerated drug in childhood migraine prophylaxis (40). Sodium valporate, an anticonvulsant agent, suggested to be effective and safe in patients with childhood migraine (39). Non-sedating antidepressant drugs such as desipramine should be administered if patients initiate and maintain sleep easily.

Several non-pharmacologic treatments are suggested to reduce migraine attacks frequency. These include relaxation therapy, sleep hygiene, balanced diet, and appropriate exercise. If stress is a significant triggering agent, relaxation therapy and cognitive training considered beneficial (41,42). It is reported that mean duration and frequency of migraine attacks were significantly reduced by improving sleep hygiene (43). Avoiding foods that precipitate migraine episodes is useful. The education of patients and their parents may be effective.

### Prognosis

Prognosis of migraine in children is favorable. Fifty percent of migraineurs improve within 6 months. Two-thirds of children go into remission for 2 more years through adolescence and early adulthood. However, prognosis for migraineurs with adolescent onset is poor. Sixty percent of these patients report ongoing migraine after 30 years. Once a migraine onset is before 8 years of age, boys are more likely to remit than girls. The remission rate for patients whose onset is between 8 and 14 years of age is 25%, and girls more likely to remit than boys (12,44).



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