

## A REVIEW ON MIGRANE: BEYOND HEADACHE

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**Abstract:** *A migraine is not “just a headache”. It is a neurological condition, which can be very distressing and disabling. Generally it is a one-sided throbbing or pulsating headache that is at least moderately intense and can be aggravated by physical activity. It is quite often associated with nausea and vomiting, as well as increased sensitivity to light, sound and even due to different types of smell. Research is continuing, but at present, we do not know what causes a migraine, there is no clear diagnostic test and, as yet, there is no cure. However, there are many ways to help manage the condition and lessen its impact - ultimately reducing the disruption caused to everyday life. It affects more than 10% of the general population. Regardless of recent progress in drug therapy for preventing and treating migraine remains unsatisfactory for many patients. One problem that slows the development of new therapeutic approaches is the limited understanding of migraine neurobiology. This article reviews current understanding of the mechanisms underlying migraine and approaches to treating it.*

### INTRODUCTION

Headache disorders, characterized by a recurrent headache, are among the most common disorders of the nervous system. A headache itself is a painful and disabling feature of a small number of primary headache disorders, namely migraine, tension-type headache, and cluster headache.<sup>[1]</sup> Not all headaches represent migraines that also mean migraine is not the only condition that can cause severe and debilitating headaches. For example, cluster headaches are very severe headaches that affect one side of the head in a recurrent manner (occurring in a "cluster" over time). The pain is sometimes described as "drilling," and can be worse than migraine pain in some cases. Cluster headaches are less common than a migraine.

Tension headaches are a more common cause of a headache. These occur due to contraction of the muscles of the scalp, face, and neck.<sup>[2]</sup>

Amongst these, the migraine headache is ubiquitous, prevailing, disabling and essentially treatable, but still under-estimated and under-treated.<sup>[3]</sup> Migraines affect around one in 10 people. They are three times more common in females and tend to affect young people who are otherwise healthy. Most people who get migraines will have a family member with the same problem. A migraine is a common neurological disorder that is caused by the stimulation of a mechanism in the brain that leads to release of pain-producing inflammatory substances around the nerves and blood vessels of the head. This disorder usually begins at puberty and mostly affects people aged from 35 to 45 years. Migraine headaches are more common in women, with a ratio of 2:1, due to hormonal factors. (World Health Organization 2016.) Women have more frequent and more severe attacks than men and three times as many women and men are affected. There are differences in migraine prevalence in different countries.<sup>[4]</sup> Ravishankar in his study from an urban headache clinic in India found that 47% of patients

were found to have migraine without aura and only 4% had migraine with aura; Indian data for the incidence of migraine with aura seem to be lower when compared with data from other parts of the world. It is the most frequent cause of a headache in children and adolescents. The study of a migraine in the pediatric population is critical because of its burden on children and their families and the diagnostic and therapeutic difficulties determined by varying phenotype and possible differential diagnosis.<sup>[5]</sup> People with migraines report experiencing symptoms such as nausea, vomiting, unilateral head pain, pulsating or throbbing pain, photophobia, phonophobia, blurring of vision, presence of shimmering lights, circles, other shapes, or colors before the eyes, and the presence of numbness of lips, tongue, fingers, legs before the start of the headache.<sup>[5-8]</sup>

If anyone have two or more of the following symptoms during an attack, it is probable that person is suffering from a migraine. Symptoms includes;

- Intense throbbing headache, often on one side of the head only;
- Nausea and/or vomiting. You may also experience diarrhea;
- Increased sensitivity to light, sound, and/or smells;
- Neurological symptoms that include visual disturbances such as blind spots, distorted vision, flashing lights or zigzag patterns;
- Other common aura symptoms you may experience include: tingling or pins and needles in the limbs, an inability to concentrate, confusion, difficulty in speaking, paralysis or loss of consciousness (in very rare cases).<sup>[9-12]</sup>

These above mentioned symptoms often called 'aura', these can occur before the attack happens lasting from about a few minutes up to an hour. Despite of so many symptom this is usually experienced by about 20 -30% of

people. A migraine with aura was previously known as a classical migraine. The symptoms of a migraine and the way it affect human health can vary from person to person. Migraine attacks may differ in their frequency, duration, and severity, although, normally they last between 4 and 72 hours, and most people are symptom-free between attack.<sup>[13-16]</sup>

#### ETIOLOGY:

The headaches usually are associated with sensitivity to sound, light, and smells. Some people have symptoms of nausea or vomiting. This type of headache often involves only one side of the head, but in some cases, patients may experience pain bilaterally or on both sides.<sup>[17]</sup> The pain of a migraine is often described as throbbing or pounding and it may be made worse with physical exertion. Not all headaches represent migraines, and migraine is not the only condition that can cause severe and debilitating headaches. For example, cluster headaches are very severe headaches that affect one side of the head in a recurrent manner (occurring in a "cluster" over time).<sup>[18]</sup> The pain is sometimes described as "drilling," and can be worse than migraine pain in some cases. Cluster headaches are less common than migraine. Tension headaches are a more common cause of headache. These occur due to contraction of the muscles of the scalp, face, and neck.

#### PATHOPHYSIOLOGY:

It is a neurovascular event that appears in people with a genetically susceptible sensitive nervous system. A migraine is a complex disorder with polygenic inheritance and a strong environmental component. There are many theories that discuss the causes of a migraine.<sup>[19]</sup> The cortical spreading depression (CSD) theory suggests that a migraine is a disease of the brain such as angina is a disease of the heart. Disruption of normal brain functioning is believed to be the underlying cause of the migraine pain and aura. Another theory is the vascular theory which suggests that migraines result from the widening of blood vessels surrounding the brain.<sup>[20-22]</sup> Recent finding postulates that the development of a migraine headache depends on the activation of nociceptive sensory afferent fibers of the ophthalmic division of the trigeminal nerve. In different animal models, including non-human primates, activation of the meningeal trigeminovascular neuropeptides that are released by trigeminal ganglion stimulation produce vasodilation of the meningeal vessels (mainly due to calcitonin gene-related peptide, CGRP), plasma extravasation and mast cell degranulation with a secretion of other proinflammatory substances in the dura (neurogenic inflammation). Trigeminal nerve activation also leads to vasodilation of meningeal blood vessels through activation of a parasympathetic reflex at the level of the superior salivatory nucleus.<sup>[23-26]</sup>

Evidence that activation of the TGVs occurs in humans during a migraine is provided by the increased level of

CGRP that is found in both the external and internal jugular blood during migraine attacks and its return to normal levels after treatment with sumatriptan and subsequent headache relief. The two main open issues in the neurobiology of a migraine headache are, first, the primary cause of a migraine headache—that is, the mechanism of activation of the TGVs and, second, the mechanism of pain generation after activation of the TGVs.<sup>[27-29]</sup> It is now generally recognized that the primary cause of a migraine headache lies in the brain, but its cellular and molecular mechanisms remain largely unknown. While the precise cause of migraines remains unknown, a number of potential migraine triggers (habits or conditions associated with the onset of a migraine) have been identified. Each migraine sufferer has his or her individual triggers. Many migraines in women are triggered by hormonal changes such as those experienced during menstruation and pregnancy. Up to 50% of women can suffer from a migraine related to menstruation. Migraines tend to intensify during puberty and disappear during menopause.<sup>[30]</sup>

Migraines mainly triggered by

- Diet (foods such as cheese, coffee, tea, alcoholic beverages or nuts)
- Strong odors such as perfumes
- Bright lights
- Loud noises
- Changes in the weather
- Stress
- Sleeping more or less than usual
- Certain medications

#### The five stages of an attack

Although not all migraines follow the same pattern, there generally tend to be five phases of a migraine attack:

- a. *The prodrome (warning) stage:* Signs, such as mood changes, tiredness, an unusual hunger or thirst can happen up to 48 hours before an attack.
- b. *The aura:* This part of the attack can last up to an hour and usually precedes the headache. Symptoms may include visual disturbances, pins and needles, confusion etc.
- c. *The main stage of the attack:* A headache will often be present along with other symptoms, such as nausea and / or vomiting and can last between 4 and 72 hours.
- d. *Resolution / postdrome stage:* The pain gradually eases or may disappear, but feelings of lethargy or being 'washed-out' may remain.

e. *Recovery stage:* It can take a few days to fully recover, or for the more lucky ones, recovery can be surprisingly quick.<sup>[31-33]</sup>

#### Subtypes and Subforms of Migraine:

i. *Migraine without aura*

ii. *Migraine with aura*

- Typical aura with migraine headache
- Typical aura with nonmigraine headache
- Typical aura without headache
- Familial hemiplegic migraine
- Sporadic hemiplegic migraine
- Basilar-type migraine

#### Childhood periodic syndromes that are commonly precursors of migraine:

- Cyclical vomiting
- Abdominal migraine
- Benign paroxysmal vertigo of childhood

#### Retinal migraine Complications of migraine:

- Chronic migraine
- Status migrainosus
- Persistent aura without infarction
- Migrainous infarction
- Migraine-triggered seizure

#### Probable migraine:

- Probable migraine without aura
- Probable migraine with aura
- Probable chronic migraine

#### Criteria for Diagnosing Migraine:

i. *Migraine without aura:*

- A. At least five attacks fulfilling criteria B-D
- B. Headache attacks lasting four to 72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
  - a) Unilateral location
  - b) Pulsating quality
  - c) Moderate or severe pain intensity

d) Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D. During headache at least one of the following:

- a. Nausea and/or vomiting
- b. Photophobia and phonophobia

E. Not attributed to another disorder

ii. *Typical aura with migraine headache:*

A. At least two attacks fulfilling criteria B-D

B. Aura consisting of at least one of the following, but no motor weakness:

- a. Fully reversible visual symptoms including positive features (eg, flickering lights, spots, or lines) and/or negative features (ie, loss of vision)
- b. Fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)

c. Fully reversible dysphasic speech disturbance

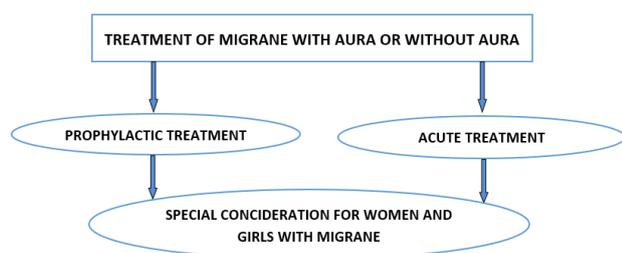
C. At least two of the following:

- a. Homonymous visual symptoms and/or unilateral sensory symptoms
- b. At least one aura symptom developing gradually over  $\geq 5$  minutes and/or different aura symptoms occurring in succession over  $\geq 5$  minutes
- c. Each symptom lasting  $\geq 5$  and  $\leq 60$  minutes

D. Headache fulfilling criteria B-D for migraine without aura begins during the aura or within 60 minutes

E. Not attributed to another disorder

Typical asura without headache is the same as typical aura with migraine headache, except that criterion D is replaced by "Headache does not occur during aura nor follow aura within 60 minutes."<sup>[34-39]</sup>

**TREATMENT:****Fig. 1:** Treatment Flow Chart

With the note of concerning with treatment taking into account about the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life. Offer topiramate or propranolol for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Advise women and girls of child bearing potential that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception if needed. In some case consider amitriptyline for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Do not offer gabapentin for the prophylactic treatment of migraine.<sup>[39]</sup>

If both topiramate and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5–8 weeks according to the person's preference, comorbidities and risk of adverse events. For people who are already having treatment with another form of prophylaxis and whose migraine is well controlled, continue the current treatment as required. Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment. Advise people with migraine that riboflavin (400 mg3 once a day) may be effective in reducing migraine frequency and intensity for some people.<sup>[40]</sup>

**Botulinum toxin type A:**

The following recommendations are from NICE technology appraisal guidance on botulinum toxin type A for the prevention of headaches in adults with chronic migraine.

Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine):

- that has not responded to at least three prior pharmacological prophylaxis therapies and
- whose condition is appropriately managed for medication overuse.

Treatment with botulinum toxin type A that is recommended above should be stopped in people whose condition:

- is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) or
- has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.

People currently receiving botulinum toxin type A that is not recommended above should have the option to continue treatment until they and their clinician consider it appropriate to stop.

NICE has produced information for the public explaining its guidance on botulinum toxin type A to prevent chronic migraine headaches.<sup>[41-49]</sup>

**Interventional procedures:**

NICE has published guidance on the following procedures with special arrangements for clinical governance, consent and audit or research:

- transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine
- transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine
- transcranial magnetic stimulation for treating and preventing migraine
- occipital nerve stimulation for intractable chronic migraine
- percutaneous closure of patent foramen ovale for recurrent migraine.<sup>[47-49]</sup>

**A. ACUTE TREATMENT:**

Offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. For people aged 12–17 years consider a nasal triptan in preference to an oral triptan.<sup>[50-52]</sup>

For people who prefer to take only one drug, consider monotherapy with an oral triptan, NSAID, Aspirin (900 mg) or paracetamol for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events.

When prescribing a triptan, start with the one with the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans.

Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting.<sup>[53]</sup>

Do not offer ergots or opioids for the acute treatment of migraine.

For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated:

- offer a non-oral preparation of metoclopramide or prochlorperazine and
- consider adding a non-oral NSAID or triptan if these have not been tried.<sup>[54-56]</sup>

#### **Interventional procedures:**

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- transcranial magnetic stimulation for treating and preventing migraine.<sup>[57-58]</sup>

#### **B. SPECIAL CONSIDERATION FOR WOMEN AND GIRLS WITH MIGRAINE:**

##### **Menstrual-related migraine:**

For women and girls with predictable menstrual-related migraine that does not respond adequately to standard acute treatment, consider treatment with frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) on the days migraine is expected.<sup>[59]</sup>

##### **Combined hormonal contraceptive use:**

Do not routinely offer combined hormonal contraceptives for contraception to women and girls who have migraine with aura.<sup>[60]</sup>

##### **Treatment of migraine during pregnancy:**

Offer pregnant women paracetamol for the acute treatment of migraine. Consider the use of a triptan or an NSAID after discussing the woman's need for treatment and the risks associated with the use of each medication during pregnancy.<sup>[61-65]</sup>

Seek specialist advice if prophylactic treatment for migraine is needed during pregnancy.

#### **CONCLUSION:**

The recommendations in this review represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian. Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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