

Review on Migraine: Pathophysiology and Treatment

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Abstract Management of migraine headaches should begin with identification and removal, if possible, of factors that consistently provoke migraine attacks. Some of these triggers may include environmental factors such as cigarette smoke, loud noise, and bright or flickering lights; psychological factor including stress, anxiety. A number of medications have been associated with drug-intended migraine. Some of these are cimetidine, cocaine, ethnyl estradiol, fluoxetine, histamine, and hormone replacement therapy. Aspirin is considered the drug of choice in these people. In present time treatment involves the natural therapy, which includes feverfew, turmeric, kava, evening primrose and gymnema. Other herbal remedies are shatavari, brahmi, jatamansi, musta. Acupuncture, Homeopathy, Spinal manipulation also include in natural therapy. This Review provides an up-to-date overview of the classification of migraine, basic mechanisms and risk factors of migraine, and the currently established treatment options.

Keywords: *migraine, ayurveda, herbal, acupuncture, and aromatherapy*

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1. Introduction

Migraine [1] is a chronic disorder affecting approximately 20% people in India. In the past, migraine has been an under diagnosed, misunderstood and mismanaged condition. Fortunately, many advances in migraine management have evolved in recent years.

Migraine is a chronic neurological condition. Migraine refers to a recurrent severe headache [2].

These headaches are often accompanied by nausea, vomiting, sensitivity to light and/or sensitivity to sound [3]. Migraines tend to occur at intervals; there may be days, weeks or months between attacks. Attacks can last between 4 and 72 hours. The term migraine comes from the words "hemicranias", meaning one-sided headache. In most cases the pain occurs only on one side of the head [4].

Headache accounts for 4.4% of all consultations in general practice [5], approximately 5% of all medical admissions to hospital [6] and approximately 20% of neurology outpatient consultations [7,8]. Migraine affects over 20% of people at some point in their lives; epidemiological studies have shown that 4.5% of the population of Western Europe has headache on at least 15 days per month; global studies suggest that approximately 1% of the world's population may have chronic migraine [9]. Chronic migraine imposes a substantial economic burden on society [10]. Migraine is so common that, even though for many people it is no more than an inconvenience, the cumulative burden of the disorder caused it to rank in the top 40 conditions causing worldwide disability according to the World Health Organization's 2012 global burden of disease figures,

above all other neurological disorders other than stroke, meningitis and epilepsy; in the United Kingdom it ranks third behind stroke and the dementias, causing the loss of 230,000 DALYs (Disability-Adjusted Life Years) annually [11].

2. Sign and Symptoms

A migraine is characterized [50] by flashes of light that appear across the field of vision, problems with speech, numbness or dizziness. Migraine pains are typically intense and, at their worst; are debilitating, with weakness, nausea, sweating and vomiting. The senses are heightened and the slightest noise, light or movement unbearable. Usually, the pain is localized or especially intense on one side of the head or over one eye. The person may also suffer from irritability. He or she usually wants to be left alone and out of any direct light [51]. From beginning to end, migraine attacks may last for hours to days.

3. Subtypes of Migraine

The International Classification of Headache Disorders, second edition outlines the following criteria for some of the migraine types: migraine without aura, migraine with aura, and complicated migraine. [12]

A. Migraine without aura

1. At least five attacks fulfilling criteria [13,14,15]
2. Headache attacks lasting 4-72 hours (untreated or successfully treated).
3. Headache has at least two of the following characteristics: unilateral location; pulsating quality;

moderate or severe pain intensity; aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs).

4. During headache at least one of the following: nausea and/or vomiting; photophobia and/or phonophobia.
5. Not attributed to another disorder.

B. Migraine with aura

a. Basilar-type migraine

1. At least two attacks fulfilling criteria [13,14,15].
2. Aura consisting of at least two of the following fully reversible symptoms, but no motor weakness: dysarthria; vertigo; tinnitus; hypacusia; diplopia; visual symptoms simultaneously in both temporal and nasal fields of bilateral eyes; ataxia; diminished level of consciousness; simultaneously bilateral paresthesias.
3. At least one of the following: at least one aura develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes; each aura symptom lasts ≥ 5 minutes to ≤ 60 minutes.
4. Migraine without aura begins during the aura or follows aura within 1 hour.
5. Not attributed to another disorder.

Sporadic hemiplegic migraine

1. At least two attacks fulfilling criteria 2 and 3.
2. Aura consisting of fully reversible motor weakness and at least one of the following: fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (eg, loss of vision); fully reversible sensory symptoms including positive features (eg, pins and needles) and/or negative symptoms (eg, numbness); fully reversible dysphasic speech disturbance.
3. At least two of the following: at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes; each aura symptom lasts ≥ 5 minutes to ≤ 24 hours; migraine without aura begins during the aura or follows onset of aura within 1 hour.
4. No first- or second-degree relative has attacks fulfilling criteria [16].
5. Not attributed to another disorder.

b. Complicated migraine

Chronic migraine [16]

1. Headache ≥ 15 days per month for ≥ 3 months.
2. Occurring in a patient who has at least five attacks of migraine without aura.
3. Headache ≥ 8 days per month for ≥ 3 months: criteria for migraine without aura are met and/or the headache is treated and relieved by triptan(s) or ergot.
4. There is no medication overuse or secondary cause.

4. Pathophysiology of Migraine

Migraine is usually a hereditary disorder, and the genesis of an attack is associated with neuronal activation. The site of initiation of attacks remains debatable. Two current concepts of migraine genesis are via cortical spreading depression (CSD) or a brainstem generator.

CSD is the basis of migraine aura. It consists of cortical neuronal activation, followed by a postictal depression of neuronal firing. CSD can trigger meningeal pain mechanisms through neurogenic inflammation, vasodilatation, and plasma protein extravasation.

As noted, CSD consists of a slow activation of neurons and glia accompanied by hyperemia, implying spreading activation. Precipitating factors include trauma, embolus, chemical exposure, or electrical activity. [17,18]

This initial wave activation is followed by a wave of decreased brain activity and oligemia. The wave of activation and then depression spreads at a rate of 3 mm/minute and occurs in various areas of the brain including the cerebellum, cortex, or hippocampus. CSD further alters the blood-brain barrier by activating brain matrix metalloproteinases, which open the blood-brain barrier and may contribute to migraine pain. [17]

Also related to CSD is the activation of cortical glutamatergic synapses. Subsequent to the initiation of a migraine by either CSD or a brain stem generator, meningeal pain mechanisms commence through trigeminovascular activation. These mechanisms include the release of inflammatory cytokines, neuroinflammatory peptides, and calcitonin gene-related peptide, the latter being responsible for cerebral vasodilatation. The vasodilatation and neurogenic inflammation sensitize trigeminovascular sensory fibers that in turn carry pain signals via the trigeminal ganglion to the trigeminal nucleus caudalis. [19] Activation of these peripheral nociceptors is referred to as peripheral sensitization. Activation of the trigeminal nucleus caudalis and rostral brain structures is referred to as central sensitization. [20]

5. Causes of Migraine [21]

Actual cause of migraine is unknown. There are several theories [22]. It appears that, with the modern imaging techniques; we are making headway in understanding the mechanism of formation of migraine.

Instability of the vascular system:

One of these theories suggests that certain arteries in our brain contract and cause a reduction blood flow to the visual area of our brain. It is suggested that this reduction of blood flow results in the visual and other symptoms that accompany a migraine.

Magnesium Deficiency:

Another theory proposes that nerve cells in the brain begin to lose function which causes a reduction in blood flow, which reduces levels of magnesium, which in turn adds to decreasing nerve cell function and that this dysfunction spreads in a wave like fashion to all affected areas.

Blood platelet disorder:

Blood platelet disorder has also been implicated, with the platelets of migraine sufferers aggregating more readily than normal platelets in response to neurotransmitters such as serotonin and adrenaline, the "stress" hormone [1].

Serotonin:

Many researchers feel that serotonin; an important brain chemical may fuel migraines. Platelets (components of our blood) contain all of the serotonin normally present in blood and after they aggregate, (clump together) serotonin

is released, resulting in a potent constricting effect on the arteries. Eating certain foods, drinking certain beverages, stressing out or sometimes just oversleeping can trigger release of serotonin. Due to this, the blood vessels in head narrowed. As kidney process the serotonin, its blood levels drops; the blood vessels dilate rapidly, pressing on surrounding nerves and causing pain and inflammation. The ache can last for hours or days because the swelling lingers after the blood vessels return to normal.

The nervous system Disorders:

The nervous system itself may also be implicated, as it releases specific neurotransmitters [23], possibly in response to chronic stress.

Food:

Certain foods contain chemicals-amines-that dilate the blood vessels, causing a rebound vasodilatation and may thus precipitate an attack.

Low Blood Sugar or Hypoglycemia:

For most people, low blood sugar caused by fasting or irregular meals often brings on a headache [24]; but it quickly disappears following a meal. But for people prone to migraines, the low blood sugar may start off a chain reaction that a belated meal will not stop.

Estrogen Level Fluctuation in Women:

Women suffer from migraine much more frequently than men. Recent research has pointed to fluctuating levels of estrogen as a factor in their development.

Stress, Anxiety and Excitement [25,26]:

Stress, anxiety, and excitement promote the release of hormones and neurotransmitters, which can provoke a migraine attack. While it may be difficult to avoid stress, it can be alleviated through exercise. One researcher reported that several of his patients became migraine-free after jogging 7 to 9 miles a day, at a speed of seven to nine minutes per mile. Of course jogging is not suitable for everyone, but even moderate exercise can relieve tension and stress.

Other Factors:

Other factors that have been known to precipitate migraines are:

- Changes in routine, such as late rising on a holiday or change of working hours;
- Changes in climate, high winds, loud or high pitched sounds;
- Bright sunlight and bright artificial light, such as fluorescent; and
- Prolonged staring at television, movie, or computer screens.

6. Complementary Therapies

Acupuncture

Acupuncturists suggest that migraine headaches are caused by an imbalance in the body's flow of energy. They use acupuncture [27,28] to reestablish this equilibrium, thereby treating the cause and the pain of migraine. Although acupuncture can ease the pain of an attack, this therapy is best used as a preventive treatment for migraine. Before treating with acupuncture, you need to ascertain the location of the headache. Because the head is traversed by many meridians, the location of the headache determines which meridians are involved. For example:

- Pain in the occipit and nape of the neck indicates blockage in the bladder meridian.
- Pain at the forehead and above the eyes indicates the stomach meridian.
- Pain by the temples and side of the head is related to the gallbladder meridian.
- Pain at the top of the head indicates an imbalance in the liver meridian.

Physiotherapy:

Treatment included relaxation, stretching, ice therapy and teaching control of muscle tension. [29]

Spinal manipulation Aromatherapy:

Aromatherapy, (inhalations, baths, or massages using these essential oils) has been proved to be effective in controlling migraine. It has calming and relaxing effect. Following Oils have been recommended in aromatherapy.

- Anger, worry, hyperactivity: Chamomile
- Sharp, piercing pain, lethargy and despondency: Rosemary, Peppermint
- Mild pain, lethargy: Lemon
- Colds, sinusitis: Eucalyptus
- Hyperactivity, overwork: Sweet marjoram

Deep Breathing:

Rhythmic breathing may reduce pain or accentuate pain. Deep breathing exercises can help to normalize breathing, which will reduce the intensity of pain.

Herbal Medicine:[30]

1. *Feverfew:* Extract of feverfew leaf has been shown to be effective in migraine [31]. A recommended daily dosage of 125 mg of a dried feverfew leaf preparation containing a minimum of 0.2% parthenolide is often prescribed for migraine prevention.

2. *Ginkgo biloba:* Ginkgo biloba increases blood circulation. It has been shown to offer some promise for the management of migraine. The daily dose ranged from 120 to 240 mg may be beneficial in preventing migraine due to its ability to inhibit platelet-activating factor. It can cause minor headaches when initially taken. This effect subsides usually within the first week of use.

3. *Ginger:* Ginger (*Zingiber officinale*) inhibits platelet aggregation. Ginger tea is also effective for a migraine headache in the front of the head. The recommended dose is 500-600 mg every 4 hours for 4 days decreased frequency and intensity of migraines.

4. *Kava:* Kava has a mellowing effect that may be helpful for the treatment of stress-related migraines [32,33]. The recommended dose is equal to 140- 210 mg of kava lactone.

5. *Valerian:* Valerian has traditionally been used for relaxation at bedtime, but may be helpful in reducing the incidence of recurring headaches due to stress. The recommended dose is 300 to 500 mg.

6. *Jamaican dogwood (Piscidia erythrina):* It is used in the form of decoction for migraine accompanied by insomnia or dysmenorrhea.

7. *Black horehound (Ballota nigra):* It is used to relieve symptoms of nausea and vomiting also combined well with meadowsweet and chamomile in infusion.

8. *Damiana, kola, sarsaparilla, and ginseng:* These are recommended when migraine is due to fatigue, lassitude, and general debility.

9. *Fenugreek:* It is used in the form of infusion, steeped 5-15 minutes; recommended dose is 1 cup during the day, hot or cold.

10. Peppermint: It is used in the form of oil, 5-10 drops, 3 times daily; fluid extraction, 1-2 tsp., 3 times daily; infusion, (steeped 5-15 minutes), dose 6 oz., 3 times daily.

11. Rosemary: It is used in the form of infusion, (steeped 5-15 minutes), dose 2 oz., 3 times daily; oil, 1-3 drops, 3 times daily; external: Rub diluted oil (1 part rosemary with 10 parts vegetable oil) on forehead and temples. Also used as a nasal vapor bath.

12. Chamomile: Chamomile tea helps prevent migraines.

13. Lavender: Lavender has antispasmodic and cooling properties. It is used for rubbing on the temples and forehead.

14. Turmeric: Turmeric rhizome has been used for centuries internally as a tonic for the stomach and liver and as a blood purifier, and externally in the treatment and prevention of skin disease and in arthritis complements [34]. The anti-inflammatory strength of turmeric is comparable to steroidal drugs such as indomethacin [35]. Turmeric has been reported to be anti-rheumatic, anti-inflammatory, and antioxidant [36] Many of these pharmacological factors contribute to the supportive use of turmeric in migraine headaches [27].

15. Evening primrose: Evening primrose oil (EPO) is rich in gamma-linoleic acid, which is an omega-6 fatty acid [38,39]. Omega-6 fatty acids reportedly reduce the arachidonic acid cascade and decrease inflammation through inhibiting the formation of inflammatory mediators in this process.

Herbal Teas: [40,41]

Following Herbal Teas are shown to be effective in controlling migraine.

- Marjoram, St. John's wort, fennel or caraway seed tea with 1 tsp. of honey is helpful for relieving symptoms.
- Agrimony, wormwood and centaury are mixed well and Poured boiling water over 1 tsp. of this mix, steeped five minutes and strained.

Bach Flower Remedy/Essence Therapy: [42]

People prone to migraines often have a hard time dealing with anger. Such people may benefit from the Bach remedy Gentian [43], which helps balance out the hopelessness and frustration that can cause migraine.

Nutritional supplementation:

Following nutritional supplements have been proved effective in management of migraine.

1. Magnesium [44,46]
2. Vitamin B233
3. Vitamin D and calcium [47,48]
4. Omega-3 fatty acids and omega-6 fatty acids [49]

7. Conclusion

Daily migraine prevention remains a challenge to clinicians. When deciding on preventive treatment, a care provider should keep in mind the frequency, severity, and disability of migraines. The number of therapies and drug available based upon level of evidence for efficacy, adverse effect profile, and patient co morbidities. In which natural and herbal therapies is the popular and compatible treatment that improves the multiple disorders of migraine at the time to improve adherence.

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