

MIGRAINE: HEADACHE AND BEYOND

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ABSTRACT: Migraine is a systemic vascular or endothelial disease. An episode of migraine generally consists of five stages which are namely prodrome, aura, headache, postdrome, normal. Migraine headache results from activation and sensitization of trigeminovascular pain pathway. Migraine and depression share some biological mechanisms, with one migraine increasing the chances of the depression and vice versa. Recently, the role of diet has also been implicated in the migraine pathogenesis. Migraine is also considered to be a triggering factor for fibromyalgia. Thus, migraine prophylaxis can also help in preventing fibromyalgia. The aim of this review is to unravel the pathogenesis of migraine so that a common clinical approach may be offered to all the patients which helps in decrease in frequency of change of episodic migraine to chronic migraine. The review highlights the various aspects of pathophysiology of this debilitating disease.

KEYWORDS: headache, depression, fibromyalgia, CGRP, trigeminovascular, stroke.

INTRODUCTION: Migraine is a very common neurological disorder which usually manifests itself as intense headache with or without aura which may be followed by nausea and/ or vomiting. This impedes oral absorption of available drugs resulting in poor bioavailability. Migraine varies from person to person and is thus difficult to characterize with a number of etiological factors of varying nature. The present review is an attempt to present the treatment guidelines in a concise form, to make them easily understandable.

The word “migraine” is derived from a greek word “hemikrania” that means half-head ^[1, 2]. Migraine is an episodic neurological disorder characterised by intense throbbing pain on one side of head associated with neurological as well as gastrointestinal symptoms. The duration of migraine attack is from 4 to 72 hours ^[3]. Many patients of migraine experience severe and frequent attacks that cause impairment of normal daily function ^[4]. The symptoms includes moderate to severe pain intensity, unilateral pain, nausea/ vomiting, increased sensitivity to light, sound/smells, aggravation by movement thus causing hindrance in routine physical activity ^[5]. It is a major health problem which has great impact not only on patients but society as a whole. According to a study conducted in 2017, global migraine prevalence was reported to be 11.6% while it was 9.7% in North America, 10.1% in Asia, 10.4% in Africa, 11.4% in Europe, and 16.4% in Central and South America. The disease shows female predominance with statistics showing the prevalence as 13.8% among females while only 6.9% among males. Moreover, it varied as per the lifestyle also, with 11.2% among people residing in urban areas, 8.4% among those residing in rural areas ^[6]. The revised International Headache Society provides criteria for seven subtypes of migraine which are classic, common, hemiplegic, chronic, basilar type, abdominal, ophthalmoplegic. Hemiplegic migraine is of two types i.e. sporadic or familial. Migraine attacks are generally triggered by head injuries, even minor in nature ^[7]. Classic migraine includes the focal neurological signs termed as auras. This is also called migraine with aura while “without auras” migraine is known as common migraine ^[7-9]. ^[7]Ophthalmoplegic migraine is relatively uncommon in prevalence and is characterized by the combination of headaches and an oculo-motor nerve palsy ^{10 [10]}. From the natural evolution of migraine, the episodic form leads to chronic migraine. This may happen over several months or years and varies from patient to patient ^{11[11]}. Abdominal migraine includes the very severe, intense periumbilical pain along with other intestinal and extra-intestinal symptoms ^[12]. Migraine that starts in the lower part of the brain, known as the brainstem, is termed as basilar type migraine ^[13].

Stages of migraine

As the nature of migraine differs from person to person, migraine pains are known to follow highly varied patterns ^[14]. Generally speaking, however, migraine patients go through five phases as described in the figure 1. The first phase i.e. the “prodrome” or the warning stage, includes the symptoms such as mood variations, fatigue, unusual hunger or thirst ^[15]. This may continue up to 48 hours. The second stage is known as “aura”. In this stage, headache starts along with symptoms like visual disturbance, pricking sensation, confusion and generally lasts up to an hour ^[16]. The next stage is the main stage which includes symptoms like nausea and vomiting. It may last from four to seventy-two hours. After this, the pain progressively decreases, and this

phase is known as resolution or “postdrome” stage. The last stage may take few days to fully recover ^[17].

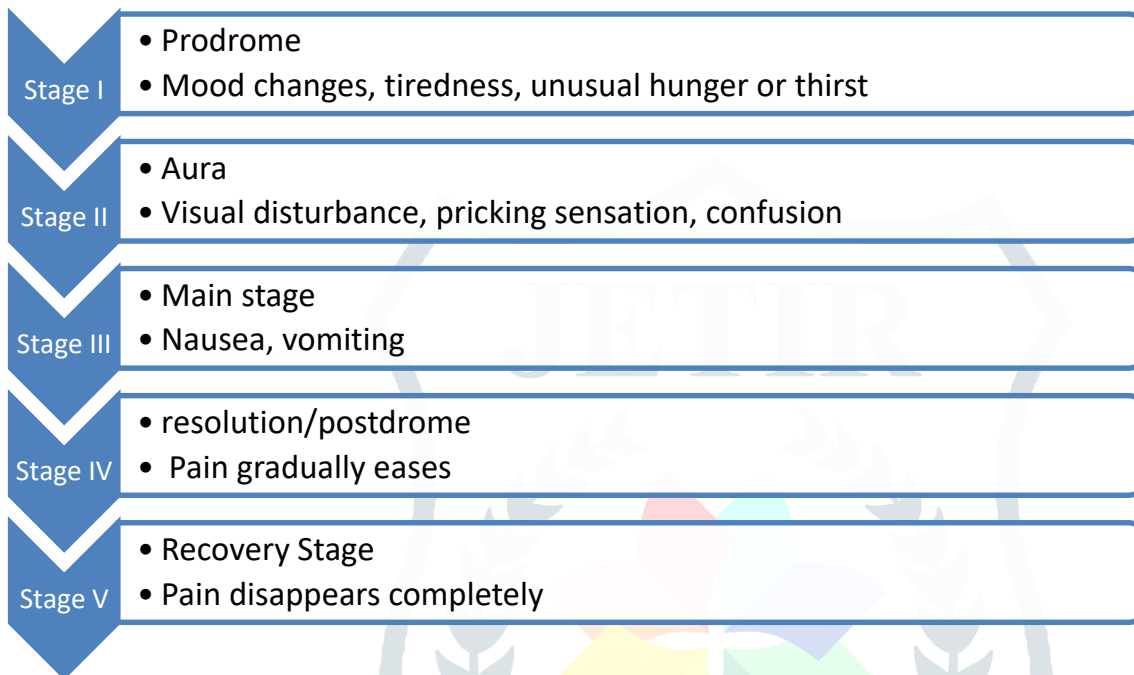


FIG. 1: STAGES OF MIGRAINE ATTACK

Pathogenesis of migraine: Migraine is recognised by a broad sensory processing dysfunction with headache as the main clinical symptom. Symptoms other than headache include nausea, vomiting, photophobia and phonophobia ^[18, 19]. The pathogenesis of migraine is described by two theories i.e. vascular, and central neuronal theory. According to vascular theory, the arteries get dilated in the meninges, resulting in pain. The current concept, however, is that of inflammation which is neurogenic in nature. In this, the activation of trigeminal nerve leads to release of pro-inflammatory peptides that eventually result in neurogenic inflammation of meninges ^[20]. According to neural theory, once the trigeminovascular afferents get activated, the nerve fibres release neuropeptides such as calcitonin gene-related peptide (CGRP), substance P and neurokinin A ^[21] required to promote neurogenic inflammatory response. These, in turn, play a significant role in the sensitization of the sensory afferents, and also the in generation and transmission of pain ^[22]. Due to the shared biological mechanisms, the epidemiological studies indicate a mutually dependent relationship between migraine and depression, with migraine increasing the risk of the depression and vice versa ^[23, 24]. The resulting cortical spreading depression (CSD) has been found to be neurophysiologically correlated to the migraine aura. CSD may be experimentally induced by focal stimulation of the cerebral cortex using a slowly propagating electromagnetic wave which causes both neuronal and glial depolarization ^[25]. In a recent study, ketogenic diet and modified Atkins diet were reported to decrease the CGRP level and thus, suppressing neuro-inflammation ^[26].

High frequency episodic migraine co-occurs with fibromyalgia (FMS) with heightened somatic hypersensitivity towards painful stimuli. Giamberardino *et al.* in 2016 reported that different levels of central sensitization are required in the patient with fibromyalgia and migraine. Migraine is a well-known triggering factor for FMS pain. Thus, migraine prophylaxis can also help in preventing fibromyalgia ^[26].

Diagnosis of migraine: The medical history of patient plays a very important role in diagnosis of migraine. Duration of migraine in children is generally shorter than that in adults. The diagnostic criteria for migraine has clearly been laid down in a screening instrument, known as ID Migraine [19, 27]. Just before or during some headache, less than one third of patients with migraine show preceding neurologic symptoms, known as auras. This is, therefore, diagnosed as “classic migraine”. “Without aura” migraine was formerly called “common migraine” [28] but according to second edition of International Classification of Headache Disorders (ICHD-2), another diagnostic criterion for migraine has been outlined [29]. Migraine is characterised if the patient reports at least one severe headache in a month along with unilateral/ pulsatile pain, either nausea, vomiting, phonophobia, photophobia, visual or sensory aura before headache [30]. Diagnostic criteria of migraine according to IHS guidelines is shown in figure 2.



FIG. 2: DIAGNOSTIC CRITERIA OF MIGRAINE

Strategies for treatment of migraine: Migraine treatment is of three types i.e. acute, preventive and promptive. Acute therapy is recommended for low frequency episodic forms, with a frequency of less than four attacks per month while preventive therapy is used in case of high frequency episodic and chronic forms, with higher than four attacks per month. Promptive treatment, however, is for the time limited and predictable migraine triggers [31].

I. Acute treatment

Acute treatment of migraine is complex because it needs immediate attention from both the patient as well as the health care provider [32]. A number of specific and nonspecific agents continue to be used in acute migraine treatment [33]. The medications used for this type of treatment are listed below.

Nonspecific medication

Simple analgesics: Analgesics like aspirin, paracetamol, or ibuprofen are used as first line of drugs in mild/moderate migraine attacks [34]. Generally, they are taken promptly in combination with an antiemetic agent in the attack.

NSAIDS : Parental non-steroidal anti-inflammatory drug, Ketorolac is generally used for abortive therapy of intense migraines [35]. It exhibits an immediate onset of action with duration of six hours and is generally considered to be very effective. Combination of drugs like isometheptene, acetaminophen, dichlorophenazone (midrin) is also quite effective in the treatment of mild migraine headaches [36].

Antiemetics: In case of migraine complicated by nausea, antiemetics like metoclopramide or domperidone are preferred. These agents give relief from the migraine associated gastric stasis. In adults and adolescents metoclopramide 20 mg is recommended but in children 10 mg domperidone is used [37]. These are given in combination with the analgesics mentioned above.

Opioids: They have proved to have significant effect in acute migraine treatment. But due to their side effects and potential of causing medication overuse headache (MOH), they have limited use [38]. They are less effective than triptans. Moreover, they are contraindicated in pregnancy and heart diseases [39].

Specific treatment

The present treatment for moderate – severe migraine comprises ergot alkaloids and triptans. The medications currently available for treatment of moderate to severe migraine are detailed below:

Ergot alkaloids: These are preferred when the patients do not respond to the opioid analgesics. They exhibit poor absorption when administered orally. Therefore, for effective results, they should be taken in adequate amounts. There should be at least four days gap between two dosage regimens of ergot alkaloids. Even at

normal dosage, it can lead to dependence and tolerance to adverse effects ^[40]. The withdrawal symptoms on discontinuing the drug include nausea, vomiting, vertigo and diarrhoea. Severe peripheral vasoconstriction may arise in case of chronic ergotism which may eventually lead to gangrene in both hands and feet ^[41]. They have a complex mechanism of action. They possess affinity for 5-HT (5- hydroxytryptamine), non- adrenal and dopamine receptors. At lower therapeutic dose, ergotamine act as an agonist for α -adrenoceptor, dopamine D₂ and 5- HT ^[42].

Triptans: Triptans are a part of drugs (tryptamine-based) used as medication in the treatment of acute migraine and cluster headaches. Introduced in 1990 ^[43], triptans are agonists of serotonin 5-HT_{1B/1D} receptors. They effectively relieve the patients from pain, disability, and associated symptoms of migraine ^[44]. Some popular triptans include sumatriptan, naratriptan, rizatriptan, eletriptan, zolmitriptan, frovatriptan, almotriptan, and avitriptan ^[45]. The triptans act by three distinct mechanisms of action, which play role in their antimigraine effects. Primarily they affect the vascular smooth muscles which cause vasoconstriction in the painful distended intracranial extra-cerebral vessels. Secondly, they inhibit the release of vasoactive neuropeptides by trigeminal nerves present inside the intracranial vessels and duramater. They also inhibit nonceptive neurotransmission within the trigeminocervical complex in both brain and spinal cord ^[46]. Hence, the combined mechanisms of action of triptans includes cranial vasoconstriction and inhibition of central and peripheral trigeminal nerve transmission along with altered nociceptive processing ^[47]. In order to develop the most effective migraine treatment, the pharmacokinetic profile of the triptans must be considered. On the basis of the biochemical properties, pharmacokinetic diversity and pharmacokinetic profile of drugs, different patient respond differently to the triptans ^[48], ^[49].

CGRP receptor antagonists: Even the well-established triptans show side effects like dizziness, throat tightness, paresthesia and chest discomfort which may cause some patients to discontinue or change treatment ^[50]. For such patients who do not respond well to the conventional therapies or who are at the risk of cardiovascular diseases, a new class of drugs is being used. CGRP is a neuropeptide having a significant role in the pathophysiology of migraine ^[51]. It is a member of calcitonin family of peptides containing 37 amino acids. It acts as neuromodulator. It is synthesized in cell bodies of trigeminal ganglionic neurons and gets stored in large dense core secretory vesicles ^[52]. Then it is transported axonal to peripheral tissues or to the nerve terminal located in CNS that cause dilation of cerebral and dural blood vessels. It has been established that a significant increase in cardiovascular levels of CGRP is observed in patients during the attack ^[53]. Intravenous infusion of CGRP was also observed to induce migraine. This linkage between CGRP and migraine lead to development of agents that can block the effects of CGRP ^[54]. In migraine, CGRP receptor antagonists act on CGRP receptor antagonists that could block CGRP-induced vasodilatation of meningeal blood vessels and normalize those vessels. On the other hand, CGRP receptor antagonists could also directly inhibit CGRP-mediated pain transmission in the CNS ^[55]. Some of the available CGRP antagonists are MK-0974, MK-1602, MK-3207, BIBN4096BS, BI44370, LY2951742. MK-0974 is also known as “telcagepant”. It was the first orally administered CGRP receptor antagonist. It has limited access to central receptors due to poor penetration across blood brain barrier ^[56]. Unlike triptans it does not cause cerebral or coronary vasoconstriction ^[57]. But it shows liver toxicity because of increased levels of hepatic enzymes. MK-1602 has limited blood brain barrier permeability. It is under clinical evaluation. No data on its efficacy or safety is available yet ^[58]. MK-3207 is more potent than telcagepant. A Study carried out at different doses shows signs of liver toxicity in phase I and II clinical trials ^[59]. BIBN4096, also known as “olcegepant” is one of the first CGRP receptor antagonists which shows clinical effectiveness when given intravenously ^[60]. Specifically, it acts on receptor activity modifying protein (RAMP1) extracellular region and bind to the endogenous ligand CGRP, inhibit its physiological and cellular effects. It has poor bioavailability ^[61]. It exhibits no vasoconstrictive effects like triptans and hence does not show any cardiovascular effects ^[62]. BI44370A is a small molecule CGRP antagonist with good tolerability. It does not show any vasoconstrictive effect like triptans ^[63].

Recently, Lasmitidan, a drug belonging to the class of ditans has been approved for the treatment of acute migraine after a successful trial in 3100 patients.

II. Preventive treatment

Preventive therapy is used to decrease frequency, severity, and duration of migraine. Moreover, preventive treatment improves the results of acute therapy^[64]. It has also been suggested that prevention might slow migraine progression. For the prevention of migraine, non-steroidal anti-inflammatory drugs, antidepressants, antiepileptic drugs, calcium channel antagonists, beta-adrenergic blockers, serotonin (5-hydroxytryptamine) antagonists, and neurotoxins are most commonly used. The number of patients using migraine prophylactic medication has shown a significant increase over time from 42.8% to 49.8%^[65]. Preventive treatment is required when a frequency of four or higher number of debilitating episodes in a month are there or attacks last more than twelve hours or pain-relieving medications aren't effective or a prolonged aura or numbness and weakness are included in signs and symptoms of migraine^[33]. Patient education initiatives related to the preventive theories in reducing the current pain and disability are reported to be quite useful^[30].

Drugs used for preventive treatment of migraine include β –blockers, neuromodulators, serotonin agonists, botox, anti-depressants and calcium channel blockers along with some other unconventional modalities like acupuncture etc.

Beta blockers show their action by decreasing adrenergic tone by presynaptic nor-adrenergic receptor blockade, decreasing nor-epinephrine release, blocking central beta-adrenergic receptors and decreasing the activity at the level of the adrenergic locus^[66]. They reduce the muscle tension, high blood pressure and stress in migraineurs such as propranolol or atenolol. Side effects comprise nightmares, hallucinations, fatigue, cold extremities, stomach upsets and wheezing in asthmatic patients^[67]. Neuromodulators like sodium valproate, topiramate, gabapentin also act as anti-migraine drugs at low doses^[68]. Serotonin (5-HT) agonists like methysergide are also reported to be helpful in the treatment of migraine. The therapy, however, is recommended to be stopped for at least one month in six months due to its side effects^[69]. Pizotifen and methysergide are the most commonly used drugs of this class. These are reported to decrease the intensity and frequency of migraine episodes in about 33% of the patients^[70]. Botox is an injectable drug that can help prevent chronic migraines. Injections are given every 12 weeks. A series of injections are administered in the head and neck area during each treatment. Side effects include neck pain, neck stiffness, and muscle weakness^[71]. Botulinum toxin has been approved for the preventive treatment of chronic migraine by FDA^[72]. Antidepressants may be administered in low doses for prevention of migraine. Among the patients who are not able to sleep well, amitriptyline is the drug of choice^[73]. Low doses of anti-depressants have exhibited good efficacy in lowering the frequency and intensity of migraine^[70]. Flunarizine, a calcium channel blocker has evidence of being very effective in treatment of migraine. The dose is 5-10 mg. Verapamil and cyclandelate are reported to be effective in treating familial hemiplegic migraine^[37].

Alternative treatments for prevention of migraine include:

Acupuncture: In this treatment, a number of thin, sterile, disposable needles are inserted into the skin at particular points. In migraine patients with chronic headaches, treatment involves 10 or more weekly 20-minute sessions^[74].

Biofeedback: It has been reported to be very effective in alleviating migraine. It is a relaxation technique in which certain equipment is monitors a bodily response, such as muscle tension or body temperature. The skill that can be acquired and applied when required to decrease and/or stop migraine^[75].

Massage therapy: As sleep disturbances, depression and anxiety are significantly improved by massage therapy, it was postulated that it may prove to be useful in migraines also. A lot of studies are being conducted to find out the application of massage therapy in preventing migraines^[76].

Cognitive behavioural therapy: Psychotherapeutic intervention alters the attitude towards pain perception and helps in reducing the frequency and severity of migraine^[77]. The combination of pharmacological and the psychotherapeutic treatment has been found to be more effective than drug therapy alone, particularly in long term management^[78].

Herbs, vitamins and minerals: There are numerous herbal treatments that are known to prevent or mitigate migraines. They may contain melatonin and other compounds with regard to their major active ingredient

which are helpful in migraine prevention [79]. *Petasites hybridus*, though effective in migraine is not commonly used because of its long-term toxicity issues [80]. Being an antioxidant and neuroprotective, riboflavin in high doses (upto 50mg) is reported to reduce the migraine attack by 50-60% [81]. Coenzyme Q10 is known to reduce the frequency of migraines [82]. In certain cases where low magnesium levels lead to migraines, use of magnesium supplements have been found to be successful [83].

Relationship between migraine and stroke

Migraine and ischemic stroke both being neurovascular disorders, their mutual dependence is reported to be quite complex [84]. Migraine is a severe neurological disorder that persists throughout life. It starts before 40 yrs and is most common in females than in males [85]. On the other hand stroke is the most common disabling neurologic disease and one of the leading causes of death [86]. The correlation between migraine and ischemic stroke had been observed by retro-specific studies. The risk of stroke is more frequent among patients of migraine with aura [87]. So, migraine is concerned with increased risk of stroke. The most interesting common factor in stroke and migraine is patient foramen ovale (PFO) which plays a pathogenic role in both diseases. To find out this PFO trans-oesophageal echocardiography is conducted [88]. There is a cerebral hyper excitability phenotype associated with migraine which sensitizes the tissue to ischemia [89]. Pharmacotherapeutic agents for the treatment of migraine apparently lead to ischemic stroke. White matter lesions and silent ischemic lesions are known to frequently affect people suffering from long standing migraine. Migraine itself seems to be enhance the risk and should be taken care in the patients at young age itself [90].

DISCUSSION

NSAIDs are first line of drugs for the mild-moderate migraine attacks. Riboflavin, CoenzymeQ10, Magnesium supplements, BOTOX injections have been found to be quite useful for preventing migraine. In patients resistant to analgesics, ergot alkaloids should be administered with caution as it can lead to dependence, tolerance to adverse effects. Triptans are very effective for migraine and cluster headaches but precautions should be taken in patients with cardiovascular risk. Drugs belonging to the classes of triptans and ergot alkaloids exhibit vasoconstrictor effects leading eventually to hypertension, which in turn, enhance the chances of ischemic stroke. Though an increase in the risk of stroke on the use of these medications is not established, overuse of these is anticipated to increase the risk of cerebral and cardiovascular diseases. CGRP antagonists are upcoming antimigraine drugs, which do not show any vasoconstrictive effect like triptans. It is being speculated that CGRP antagonists are better than triptans and ergotamines.

CONFLICT OF INTEREST: Declared none.

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