

## MIGRAINE: AN OVERLOOK AND RECENT ADVANCES IN MANAGEMENT

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### ABSTRACT

Migraine is the most common neurologic disability which considerably affects the social, physical and occupational function of affected person. It is a chronic disease which cannot be cured but can be controlled by various pharmacological and non-pharmacological methods. Because there is considerable interpersonal variation in trigger factors and sensitivity to drug, management of migraine needs personalization. Despite availability of many drugs useful in migraine management, avoidance of trigger factor and coping with non-modifiable factors is of great importance. However many advances have been made in non-pharmacological as well as pharmacological management which had led to the better prevention and treatment of migraine. This review is on migraine overview and recent advances in management.

Migraine is the 2<sup>nd</sup> most common cause of headache and most common headache related cause of disability worldwide. Migraine significantly affects social, physical and occupational function of affected person. It affects 15% of women and 6% of men over 1 year. The prevalence is similar in boys and girls before puberty but in reproductive age group female to male ratio is 3:1 with peak incidence at 35-45 years.<sup>(1,2)</sup>

The sensory sensitivity of migraine is probable due to dysfunction of Monoaminergic sensory control system located in the brainstem and hypothalamus. The role of Calcitonin gene related peptide (CGRP), 5-hydroxytryptamine (5-HT) and dopamine are found related to migraine and this knowledge is being used in the management of migraine. Migraine genes are identified in familial hemiplegic migraine (FHM). Mutation involving Ca<sub>v</sub>2.1 (P/Q) type voltage-gated calcium channel CACNA1A gene are known to cause FHM1.

Approximately 20% individual experiences migraine with Aura. Aura is a sensory, visual or other CNS symptoms followed by headache<sup>(3,4)</sup>.

Premonitory symptoms are usually more common than aura in migraine. Migraine includes different phases- premonitory, headache attack and postdrome phase. Premonitory phase is defined as non-specific symptoms, such as change of mood or appetite or a higher sensitivity. It is considered as warning sign. Postdrome phase is defined as various symptoms, like fatigue, food intolerance, irritability and mood changes, which occur once headache subsides gradually<sup>(5)</sup>.

Migraine attacks may have many triggers factors, which may be several intrinsic and extrinsic factors, and varies in person to person. Exposure of these factors may predict the probability of migraine headache which may start hours after the exposure. Knowledge of trigger factor is very helpful in management of migraine by avoiding them or takes necessary action after exposure. There are many trigger factors diagnosed till date but common are stress, sleep changes, fasting caffeine consumption, anxiety, neck pain, light stimulation, specific odor, loud noise etc.<sup>(6,7,8,9)</sup> Trigger factors are different from risk factors. Risk factors increase the incidence of migraine attack in normal population while trigger factor increases the incidence in patient known to have migraine. Common risk factors are female gender, positive family history of migraine and low socio-economic status.

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### DIAGNOSIS

All headaches in young is not migraine but is often over diagnosed. According to International Classification of Headache Disorders 3<sup>rd</sup> edition (ICHD-III)<sub>10</sub>, migraine in adult is diagnosed on following criteria: repeated attack of headache

lasting 4-72 hour in patient with a normal physical examination, no other reasonable cause of headache and at least 2 (unilateral pain, throbbing pain, aggravation by movement and moderate or severe intensity) plus at least 1 (nausea/vomiting, photophobia and phonophobia).

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Patient with episodes of migraine attack  $\geq 8$  days per month and with at least 15 total days of headache per month are considered as Chronic Migraine. It must be differentiated from Tension Type Headache which is often difficult due to overlapping symptoms. In general, headache with other symptoms are considered as Migraine while headache without other symptoms are considered as Tension Type Headache.

Disability caused by migraine is assessed by Migraine Disability Assessment Score (MIDAS). MIDAS is well validated and easy to use tool and provides grading of migraine. Score of 0-5- Grade I (minimal disability), 6-10- grade II (mild disability), 11-20- grade III (moderate disability) and  $>20$ - grade IV (severe disability).

### **MEDICATION OVERUSE HEADACHE**

Excessive intake of acute medications is a risk factor of Medication Overuse Headache (MOH). It occurs following consumption of simple analgesics or NSAIDs for  $\geq 15$  days per month or consumption of opioid, mixed analgesics, triptans or ergot alkaloids for  $\geq 10$  days per month for  $> 3$  months<sup>(29)</sup>. It can easily be prevented by judicious use of drugs and preferring non-pharmacological methods for prevention and treatment of migraine.

### **MANAGEMENT**

Mild attacks are usually treated with analgesics and antiemetics but moderate to severe cases may require prophylactic treatment including anti-depressant, antiepileptic, Calcium channel blockers, beta blockers and anti-calcitonin gene related peptides (CGRP)<sup>(43,44)</sup>. Despite this migraine is poorly controlled in many patients due to various reasons like some trigger factors cannot be avoided, Medication Overuse Headache (MOH), high economic burden, pregnancy and lactation etc. in such cases non pharmacological methods have shown promising results and are advised alone or with pharmacological agents to all patients of migraine<sup>(3,11)</sup>

### **NON-PHARMACOLOGICAL MANAGEMENT OF MIGRAINE**

Non pharmacological management of migraine provides several benefits to the patients which includes<sup>(3,11)</sup>:

1. Avoiding or reducing the adverse event of medication.
2. Reduces the chance of MOH.
3. Helps individual not willing to take medication.
4. Reduces the economic burden of medication.

5. Helps individual who do not get expected results with medication.
6. Treat migraine during pregnancy and lactation to avoid drug therapy.
7. Treat migraine in individuals where drugs are contraindicated.
8. Increases the efficacy of abortive and preventive treatment.

Different approaches are suggested for migraine management: Behavioral therapy and biofeedback, patient education, relaxation, mindfulness, weight reduction, lifestyle modification, neuromodulation techniques and dietary supplements<sup>(3,12,13)</sup>

Different environmental factors are identified to be associated with migraine attack and vary from person to person. Best recommendation is to rely on patient personal experiences and avoid the trigger factor<sup>(45)</sup>. Maintaining headache diary is helpful in recording attack characteristics, identifying trigger factor, sleep pattern etc. These information helps in making accurate diagnosis, planning best management strategy, predicting future attacks and assessing treatment outcome<sup>(3,7)</sup>. However in many circumstances it is not possible to avoid all triggers. In such cases must be educated and trained to cope with them<sup>(45)</sup>. Migraine is associated with several diseases like depression, anxiety, panic attack, sleep disorders, irritable bowel syndrome, celiac disease etc, and their adequate management are necessary for optimal control<sup>(3)</sup>.

Sleep disturbances are one of the most prevalent trigger factors which include insomnia, too little or prolonged sleep, inappropriate timing etc. however the relationship is bidirectional which means sleep problem triggers headache and headache may cause sleep disturbance. In many, sleep acts as relief factor. Thus good sleep hygiene is important<sup>(14-19)</sup>. Calhoun and Ford recommended following intervention along with the proper management of sleep disorders<sup>(20)</sup>:

1. Scheduling consistent bedtime that allows 8 hour in bed
2. Eliminating watching television, phone, reading and listening music in bed.
3. Using visualization technique to shorten time to sleep onset
4. Consuming dinner  $\geq 4$  hour and fluids  $\geq 2$  hour before bedtime.
5. Discontinuing naps during daytime.

Diet is an important trigger in many patients and shows interpersonal variations. Food diary is helpful in identifying food triggers. Common triggers are alcohol, caffeine, chocolate, red wine etc. diet supplements like riboflavin, CoQ10, magnesium etc are shown to improve brain metabolism and are recommended in migraine patients<sup>(35,38)</sup>. However more research is needed for their efficacy and safety. Following diet modification are recommended along with proper management of GI disorders<sup>(21,22,23)</sup>:

1. Preventing hunger and fasting
2. Having regular and frequent meals (5-6 small meals per day)
3. Avoiding food items known to trigger headache according to food diary.
4. Consuming slow digesting foods and cooked foods.
5. Proper fluid intake and hydration.
6. Consuming low fat diet.

Physical activity can be a trigger factor and can also prevent migraine attack and also improves some comorbid conditions like depression, anxiety, obesity, sleep problems etc<sup>(24)</sup>. Thus regular and moderate exercise, especially aerobics exercise, is advised. Proper warm up exercise is necessary along with proper nutrition and hydration. Exercise must be personalized for duration, intensity and frequency of exercise and must be avoided during headache attack<sup>(25,26,27)</sup>.

Obesity may trigger migraine attack via sympathetic dysregulation adipose tissue function, neurotransmitter related to hypothalamus. It affects more in female, particularly in reproductive age group and may progress to chronic headache. Thus weight reduction, via physical activity and life style modification are promoted in migraine patients and must be targeted to achieve ideal body weight. However caution is needed as underweight may have similar effect like obesity and change in weight is side effect of many medication used in migraine<sup>(3,21)</sup>.

Stress and anxiety has bidirectional effect on migraine patients. They can precipitate headache in migraine patient and headache can cause stress and anxiety. Stress is any stimulus (physical or psychological- internal or external) that starts a biological reaction and results in changing hemostasis to adapt. It is impossible to avoid all stress. Thus patient must be trained to avoid avoidable stress and to cope with unavoidable stress<sup>(28)</sup>. It is also important

to identify and avoid medication associated with migraine according to personal headache diary. Common drugs are- nitrates, theophylline, reserpine, nifedipine and hormonal contraceptives. Estrogen plays a role in pathophysiology of migraine through different mechanism and that is why it is more common in females, decreases during 2<sup>nd</sup> and 3<sup>rd</sup> trimester of pregnancy and increases in premenstrual period, after delivery and menopause. Menstrual related migraine are more severe, longer duration and more disabling<sup>(30,42)</sup>.

Patient education is necessary in migraine as it is a chronic disorder which cannot be cured but can be controlled. To increase effectiveness, patient education must be limited to 4 topic in each session, one must use every day and straight forward language, written supplements can be used, family members must be included and feedback from participants must be asked and major points must be repeated<sup>(34)</sup>.

Acupuncture, a Chinese technique, has been shown effective in both prevention and management of migraine in many studies. They are useful in both episodic and chronic headache. It is safe method and have low rate of side effect. Caution is needed in pregnant women and people with bleeding problems<sup>(39)</sup>.

Behavioral treatment, including relaxation techniques, stress management, cognitive therapy and biofeedback and neuromodulation techniques are found effective in migraine and are being increasingly used in its management<sup>(31,32)</sup>. Thermal biofeedback with relaxation training and electromyographic biofeedback are reported to have Grade A evidence for migraine prevention<sup>(33)</sup>.

Neuromodulation is stimulation of peripheral or central nervous system via electric current or magnetic field and are increasingly used in migraine management. It includes both invasive and non-invasive intervention. Non-invasive techniques include- transcranial magnetic stimulation (tDSC), transcutaneous cranial nerve stimulation like Cefaly, non-invasive vagus nerve stimulation (nVNS), percutaneous mastoid stimulation and non-painful brachial electric stimulation. Invasive techniques include- occipital nerve stimulation, sphenopalatine ganglion stimulation and high cervical cord stimulation<sup>(35,36,37)</sup>. Cefaly and sTMS have level A evidence, tDCS level B and nVNS level C. They are used as alternative or in addition to medication

and are also safe during pregnancy and lactation. Invasive techniques are used when all other approaches are tried and no desired result is achieved<sup>(35,36,37)</sup>.

### ACUTE ATTACK THERAPY

The mainstay of pharmacological therapy is the judicious use of one or more of medication effective in migraine. Drug used in migraine are: NSAIDs, 5-HT<sub>1B/1D</sub> receptor agonist, Dopamine receptor antagonist and 2 new drugs CGRP receptor antagonist and 5-HT<sub>1F</sub> receptor agonists.

### NSAIDS

They are the most commonly used drug for migraine which reduces both severity and duration of a migraine attack. However its effectiveness is less in moderate and severe migraine attacks. US Food and Drug Administration (FDA) has approved combination of Acetaminophene, aspirin and caffeine for mild to moderate case. Dyspepsia and gastrointestinal irritation are the major side effect.

### 5-HT<sub>1B/1D</sub> RECEPTOR AGONISTS

It includes non-selective drugs, like Ergotamine and dihydroergotamine, and selective drugs like sumatriptan (50-100mg), almotriptan (12.5mg), eletriptan (40-80mg), rizatriptan (5-10mg), zalmiptan (2.5mg). Each drug varies slightly in terms of clinical efficacy. Triptans are not much effective as monotherapy and in migraine with aura. They are contraindicated in cardiovascular and cerebrovascular diseases.

They are also available as nasal formulation (dihydroergotamine, zolmitriptan and sumatriptan) and have faster and more effective action. They are useful in patient with absorption problem. Parenteral formulation of Dihydroergotamine and sumatriptan are approved by FDA for rapid relief of attacks<sup>(40,41)</sup>.

### DOPAMINE RECEPTOR ANTAGONIST

Oral as well as parenteral formulation are available ( chlorperazine, prochlorperazine and metoclopramide). They are useful in patients with impaired absorption during migraine as they decreases nausea/vomiting and restore normal gastric motility. They are commonly used in combination with NSAIDs and Triptans<sup>(40,41)</sup>.

### CALCITONINE GENE RELATED PEPTIDE (CGRP) RECEPTOR ANTAGONIST- GEPANTS

Oral gepants are small molecule CGRP receptor antagonists that are effective in acute

treatment of migraine. Two are currently approved by FDA: Rimegepant (75mg) and Ubrogepant (50-100mg). Both render patients pain free at 2 hours and the most bothersome symptoms free (derived by asking patients) at 2 hour. They are extremely well tolerated. Mild nausea is usual side effect<sup>(40,41)</sup>.

### 5-HT<sub>1F</sub> RECEPTOR AGONIST- DITANS

Lasmiditan (50-200 mg), highly selective, oral available, 5-HT<sub>1F</sub> receptor agonist has been approved by FDA for the acute treatment of migraine. They have no vascular effects. Hence can be used in patient with cardiovascular and cerebrovascular diseases where 5-HT<sub>1B/1D</sub> receptor agonists are contraindicated. Major side effect is dizziness and somnolence. Thus patients are advised not to drive for 8hrs after treatment<sup>(40,41)</sup>.

### OTHERS

Oral combination of Acetaminophene, Dichloralphenazone and Isometheptene has been approved by FDA for effective treatment of migraine. Parenteral opioids are modestly effective in acute attack of migraine IV Meperidine (50-100mg) is used in emergency department but has suboptimal effect in recurrent headache as opioid do not treat the underlying mechanism rather alter pain sensation only. Thus opioid use is recommended only to patients with severe headache unresponsive to other pharmacological approach or contraindicated to other therapy<sup>(40,41)</sup>.

### PREVENTIVE TREATMENT FOR MIGRAINE

Preventive treatment is indicated in patients with increasing frequency of migraine attack or in patient with unresponsive or poorly responsive to abortive treatment. Usually they are considered in patients with  $\geq 4$  attack a month as they have considerable side effect and their dose determination are difficult. They are usually started with low dose and then gradually increased. The mechanism of action of these drugs is unclear.

Drugs approved by FDA for this purpose are- Propranolol (40-120 mg), Timolol, Rimegepant(75 mg), Sodium Valproate (400-600mg), Topiramate (25-200mg), Eptinezumab (100-300mg IV every 12 week), Erenumab (70 or 140mg SC monthly), Fremanezumab (225mg SC monthly) and Galcanezumab. Other drugs commonly used for prevention are Amitriptyline (10-75mg), Candesartan (4-24mg), Nortriptyline (25-75mg), Flunazine (5-15mg) and Phenelzine.

The probability of success with any anti migraine drug is approximately 50%. Once effective stabilization is achieved, drug is continued for 6 months and then slowly tapered. Many patients are able to discontinue medication and experiences fewer and milder attacks for long periods. The CGRP monoclonal antibodies and CGRP receptor antagonist has been a landmark in prevention of migraine<sup>(40,41)</sup>.

## CONCLUSION

Migraine is most common neurologic disabling disorder which should be managed adequately and is often difficult to do so. Various pharmacological and non-pharmacological methods have been developed for this. Pharmacologic management is directed for abolishing acute attack by oral or parenteral drug which should be personalized. Preventive medication is considered in patients with chronic migraine or in those with poor or unresponsive to abortive therapy. CGRP receptor antagonist, CGRP monoclonal antibodies and 5-HT<sub>1F</sub> receptor agonist are new advances in this respect. Non-pharmacological management is emerging as more promising approach for migraine as they have many advantages and can be used in patients who are unresponsive, have side effect or contraindicated to drug therapy and also useful in pregnant and lactating woman. Maintaining patient diary has helped in diagnosing migraine accurately, modification of trigger factors. Neuromodulation techniques and biofeedback have been approved by FDA for preventive therapy. However migraine must be differentiated from Tension Type Headache which is often difficult. Medication overuse headache (MOH) must be prevented in patients with migraine

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