MIGRAINE

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ABSTRACT
Migraine is a common disabling condition mostly in adult population and shows female predominance. Unilateral throbbing type moderate to severe intensity headache is a common manifestation of the migraine though it may present with varied presentation. Even though there is rapid advancement in the knowledge of pathophysiology leading to development of novel treatment, evidence based treatment for migraine specially in developing nations is still under-estimated and under-treated. This article reviews the pathophysiology, diagnosis and evidence based approach for management of migraine.

KEYWORDS: Migraine, Clinical Features, Management.

INTRODUCTION
Headache disorders, characterized by recurrent headache, are among the most common disorders of the nervous system. Headache itself is a painful and disabling feature of a small number of primary headache disorders, namely migraine, tension-type headache, and cluster headache.[1] Amongst these, the migraine headache is ubiquitous, prevailing, disabling and essentially treatable, but still under-estimated and under-treated.[2]

Migraine is a common chronic headache disorder characterized by recurrent attacks lasting 4–72 hours, of a pulsating quality, moderate or severe intensity aggravated by routine physical activity and associated with nausea, vomiting, photophobia or phonophobia.[3]

It has been termed the seventh disabler due to its considerable impact on the quality of life (QOL) of patient.[4] It is the most frequent cause of headache in children and adolescents. The study of 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.[5]

PATHOPHYSIOLOGY
1. Vascular and Neurogenic theories
The cause of migraine headache is still not completely understood. Historically, two independent theories, the vascular theory and the neuronal theory, explaining the etiology of migraine headache were proposed. The vascular theory was introduced by Thomas Willis where he recognized that “all pain is an action violated” and argued the pain from headache is caused by vasodilatation of the cerebral and meningeal arteries. The alternative neurogenic theory focuses on the cause of migraine pain and is currently linked to activation of the trigeminovascular system.[6]

2. Cortical Spreading Depression
The alternative and widely accepted theory suggests that cortical spreading depression (CSD), a wave like neuronal hyperactivity followed by an area of cortical depression, accounts for the aura and that the headache depends on activation of the trigeminovascular pain pathway.

In Chronic Migraine (CM), atypical pain processing, central and peripheral sensitization, cortical hyperexcitability, and neurogenic inflammation all have a role to play. Cortical hyperexcitability is thought to be another major factor participating in transformation of EM to CM.[4]

3. CORTICAL HYPEREXCITABILITY IN MIGRAINE
As is the case for many episodic disorders, the trigger for migraine attacks has not been precisely identified. Many clinical factors such as diet, alterations in sleep and stress are known to predispose individuals to attacks. It is particularly intriguing that photic stimulation can trigger both migraine attacks and epileptic seizures. How these factors bring on a migraine attack is not known. However, there is evidence for enhanced cortical responsiveness to diverse stimuli in migraineurs. The techniques that have been used to generate this evidence include psychophysical studies; visual, auditory, and...
somato sensory evoked potentials; magnetoencephalography; and transcranial magnetic stimulation of the motor cortex. In all cases, there is evidence of heightened reactivity between migraine attacks. Results from transcranial magnetic stimulation of the occipital (visual) cortex have been particularly compelling. Most but not all studies have observed that migraineurs have a reduced threshold for induction of phosphenes (the experience of light with non luminous stimulation) compared with controls. This phenomenon appears to be equally present in individuals who experience migraines with and without aura. Thus, a pathologically low threshold for activation of cortical hyper excitability may characterize migraine.\[7\]

TRIGGER FOR MIGRAINE
Mollaoglu M, 2012 conducted study which shows that the most common trigger factors were emotional stress (79%), sleep disturbance (64%) and dietary factors (44%).\[8\] Sleep and stress were significant trigger factors in patients with migraine with aura, whereas environmental factors were important trigger factors in patients with migraine without aura. Stress, sleep and environmental factors were important trigger factors in women and differed significantly from men.

Trigger factors are frequent in migraine patients, and avoidance of such factors may result in a better control of the disorder.\[8\] \[9\]

CLINICAL FEATURES
Women have an 18% risk of having a migraine compared to a 6% chance in men. The higher prevalence in women is typically attributed to hormonal fluctuations especially estrogen. Migraines typically begin during puberty or between the ages of 35 and 45 years.\[9\]

Migraine has two major subtypes: Migraine with aura which is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Some patients also experience a premonitory phase, occurring hours or days before the headache, and a headache resolution phase. Premonitory and resolution symptoms include hyperactivity, hypoactivity, and depression, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain. Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptom such unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity, during headache nausea and/or vomiting or photophobia and phonophobia can occur.\[10\]

DIAGNOSIS
Diagnosis of Migraine can be made through history taking alternatives are rule out with help of orthopedic tests, Cranial nerve examination, Complete blood count, urinalysis and Cranial magnetic resonance imaging was performed if required.\[9\] The International Classification of Headache Disorders defines the migraine by following criteria:\[10\]
A. At least five attacks 1 fulfilling criteria B–D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

TREATMENT
Non Pharmacological treatment
Migraine is the most common type of headache leading patients to consult a physician. For most patients, a combination of non-pharmacologic and pharmacologic interventions should be used to control the headache disorder. Many of the non pharmacologic therapies are based on the theoretic concept of migraine as resulting from neurochemical instability within the brain. These approaches, which are often “biobehaviouristic,” may be complementary or adjunctive to pharmacologic treatment or may provide an alternative to it.

William E.A. et al has developed guideline for the non pharmacologic management of migraine in clinical practice which includes the application of cold or pressure to the head, reduction of activity and of sensory input in a quiet or dark environment and attempts to sleep and are supplemented by the use of pharmacologic therapies when not adequate in isolation. Relaxation therapy, hypnosis, transcutaneous electrical stimulation, acupuncture, and occipital or supraorbital nerve blockade have also been used in the acute situation and are considered. Other specific treatment includes bio-behavioral measures which includes Biofeedback, Relaxation therapy, Cognitive-Behavioral therapy, Psychotherapy, Hypnosis and physical measures such as chiropractic, osteopathy and physiotherapy.\[11\]

A case report by Brette R. et al has made dietary and lifestyle changes as a recommendation for treatment of migraine.\[9\]

Pharmacological treatment
Abortive therapy for migraine
The principles of abortive therapy of migraine headache is to do judicious use of analgesic considering the patient profile, headache intensity, side effects of the agent for the rapid and sustained relief of headache.
5-HT1B/1D receptor agonists

The mechanism of triptans are mediated by 5-HT(1B/1D) receptors and include vasoconstriction of painfully dilated cerebral blood vessels, inhibition of the release of vasoactive neuropeptides by trigeminal nerves, and inhibition of nociceptive neurotransmission. A variety of triptans like sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan are available in market. Amongst the triptan, eletriptan followed by rizatriptan has higher headache response rate and safety profile. It should not be used more than 2-3 times in a week to prevent the emergence of medication overuse headache. They are contraindicated in individual with cerebrovascular disease and cardiovascular disease.

Other analgesics

Paracetamol due to its low cost, wide availability and minimal side effects can be used in migraine as first choice to that patient where NSAIDS are contraindicated or not tolerated. Though the response for paracetamol is better than placebo, still NNT for pain response is lower than other analgesic. It is comparable to the sumatriptan if 10 mg metoclopramide is added to paracetamol. For the management of acute attack of migraine, 1000 mg of aspirin is similar to 50 or 100 mg sumatriptan. Addition of Metaclopromide 10 mg to the aspirin reduces the nausea and vomiting. Side effects of aspirin is lower than the sumatriptan. Ibuprofen 400mg in soluble form is effective of reducing the pain intensity of migraine headache, though complete relief of headache is seen in minority. Oral diclofenac potassium 50 mg is an effective treatment for acute migraine, providing relief from pain and associated symptoms, although only a minority of patients experience pain-free responses. Adverse events are mostly mild and transient and occur at the same rate as with placebo. Naproxen 500 mg alone is clinically not much useful for management of headache of migraine(NNT:11 for pain free response at two hours ). Metoclopromide 20 mg iv is comparable to 6mg SC sumatriptan in emergency setting. Opioids are the one of the alternatives for managing the intensity of migraine headache in emergency setting but due to chance of deteriorating quality of life, concomitant psychiatric co morbidities and development of habituation it’s use is restricted to those only whom the other first line agent are contraindicated. Preventive therapy

Migraine is a chronic disease, bothers a patient a lot hence there is tendency to use the abortive medication frequently which lead to emergence of medication overuse headache and transformation of episodic migraine into chronic migraine. Indication for preventive therapy of migraine:

- More than 2 headaches per month, but fewer than 8 headaches.
- Headaches less frequent but more prolonged (>2 days’ duration) or severe attacks leading to substantial disability.
- Migraines are refractory to abortive treatment measures
- Therapies for acute attacks are intolerable, contraindicated, or overused (>2 per week).
- Migraine with prolonged aura or hemiplegic migraine.

Flunarizine

Flunarizine is a calcium channel antagonist, has moderate action as antihistaminics, serotonin receptor blocking and antidopaminergic. The starting dose is 5mg/day for initial 21 days which is increased to 10mg/day after it. Common side effects noted in flunarizine are drowsiness, depression and weight gain. Beta blockers

Even though Beta blocker like propranolol, atenolol, metoprolol and bisoprolol had shown the efficacy against the migraine headache, most evidences demonstrate maximum efficacy in favor of propranolol. The starting dose of is 20 mg/day. This must be increased slowly since adverse effects can occur prior the prophylactic effects and impair patient compliance. The prophylaxis should be maintained for a minimum of 3 months before efficacy evaluation. The successful prophylactic treatment should be continued for 12 months. Thereafter, discontinuation can be attempted but drug doses should be decreased slowly, in order to avoid tachycardia or hypertension.

Tricyclic antidepressants

Among the tricyclic antidepressant, amitriptyline hydrochloride is the choice of drug for migraine management. The starting dose is 10 mg can be titrated up to 75 mg to achieve the maximal therapeutic effect. Response to these agents of usually within 4 weeks of starting of treatment. Dry mouth, weight gain, postural hypotension, drowsiness and tremor are common side effects of these agent.

Divalporex Sodium

Divalporex sodium reduces the frequency of migraine attacks compared to the placebo (P≤0.05). Starting dose of divalporex Sodium is 500 mg/day can go up to 1500mg/day .nausea, dizziness and tremor are common side effects of it.

Topiramate

Topiramate works by inhibition of glutamatergic excitatory amino acid transmission, inhibition of voltage-gated calcium channels, enhancement of GABA-evoked currents, fast Na+ channel blockade, and carbonic anhydrase inhibition. It reduces the migraine/migrainous headache days (topiramate -6.4 vs placebo -4.7, P=.010). Its starting dose is 25 mg/day which is titrated to 25 mg every week to maximum dose of 100mg/day. Common side effects of topiramate are paresthesia, weight loss, upper respiratory tract infection and fatigue.
Other preventive drug
Calcium channel blocker like cycloclenate, nicardipine ,nifedipine and verapamil had been tried for prevention of migraine headache, no calcium channel blocker was more effective than placebo. Though ACE/ARB, use are postulated for prevention of migraine headache, no clinical trial shows their effectiveness to reduce the frequency of migraine headache by 50%.

Future direction
CGRP receptor antagonists (CGRPRAs) are the novel non-serotonergic, migraine-specific drugs without a vasoconstrictor action hypothesized to be suitable for patients with vascular disease. Serotonin 5HT1F agonists like lasmiditan has shown good efficacy and tolerability as an acute treatment of migraine headache. Glutamate receptor antagonists have shown effectiveness in the acute treatment of migraine without aura. Neurromodulation by occipital nerve stimulation (ONS) with implanted leads was studied as a possible treatment for chronic migraine. In view of the reported preventive effect of sphenopalatine ganglion stimulation in cluster headache, trials are now underway to explore the efficacy of this method as a possible preventive treatment of chronic migraine.

CONCLUSION
Migraine is common cause of headache, early diagnosis and prompt treatment of migraine enhances the quality of life; prevent conversion of episodic migraine to chronic migraine. As there is growing interest in pathophysiology, new armatarium targeting the different pathways are being discovered.

REFERENCES
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