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MIGRAINE – UNDERSTANDING ITS EFFECTS AND TREATMENT

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ABSTRACT

Headache disorders, characterized by recurrent headache, are among the most common disorders of the nervous system. Migraine, the second most common cause of headache and indeed neurologic cause of disability in the world and 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. Migraine has multiple phases: premonitory, aura, headache, postdrome, and interictal. The primary cause of a migraine attack is unknown but probably lies within the central nervous system. Migraine can occur due to various triggering factors and can be managed with both pharmacological and non-pharmacological treatment. Migraine attacks are treated with non-steroidal anti-inflammatory drugs (NSAIDS), or triptans. Non-pharmacological treatment includes cognitive behavioural therapy, Complementary Treatments, yoga therapy etc.

KEYWORDS: Migraine, Clinical Features, Management.

INTRODUCTION

MIGRAINE is a common, chronic, incapacitating neurovascular disorder, characterized by attacks of severe headache, autonomic nervous system dysfunction, and in some patients, an aura involving neurologic symptoms.[1,2] Recent advances in basic and applied clinical neuroscience[3] have led to the development of a new class of selective serotonin (5-hydroxytryptamine [5-HT]) receptor agonists that activate 5-HT1B and 5-HT1D (5-HT1B/1D) receptors and are known as the triptans; these agents have changed the lives of

countless patients with migraine. Despite such progress, migraine remains underdiagnosed and the available therapies underused.[4] In this article, we review the current understanding of the epidemiology, pathophysiology, and treatment of migraine.

Migraine is a common chronic headache disorder characterized by repeated attacks lasting 4–72 hours, of a pulsating type, moderate or severe its intensity is aggravated by routine physical activity and associated with nausea, vomiting, photophobia etc.

In 15 percent of patients, migraine attacks are usually preceded or accompanied by transient focal neurologic symptoms, which are usually visual; such patients have migraine with aura (previously known as classic migraine).[5] In a recent large, population-based study, 64 percent of patients with migraine had only migraine without aura, 18 percent had only migraine with aura, and 13 percent had both types of migraine (the remaining 5 percent had aura without headache). Thus, up to 31 percent of patients with migraine have aura on some occasions[6], but clinicians who focused on the presence of aura for the diagnosis of migraine will miss many clinical presentations.
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PATHOPHYSIOLOGY

Migraine is best termed as a primary disorder of the brain.[7] It is a form of neurovascular headache: a disorder in which neural events result in the dilation of blood vessels, which, in turn, results in pain and further nerve activation.[8] Migraine is not caused by a primary vascular event. Migraine attacks are episodic and vary within and among patients. We may best explain this variability by considering the basic biologic problem in migraine to be the dysfunction of an ion channel in the aminergic brain-stem nuclei that normally modulates sensory input and exerts neural influences on cranial vessels.[7]

1) Vascular and Neurogenic theories

The cause of migraine headache is still not completely understood. Historically, two independent theories, the vascular theory and the neural 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 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.[9]

2) Cortical Spreading Depression

The alternative and widely accepted theory suggests that cortical spreading depression (CSD), a wave of 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 hyper excitability, and neurogenic inflammation all have a role to play. Cortical hyper excitability is thought to be another major factor participating in transformation of EM to CM.

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; magneto encephalography; 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.[10]

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%).[11] 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.[11]

Clinical Features

Migraine is characterized by episodes of head pain that is often throbbing and frequently unilateral and may be severe. In migraine without aura (previously known as common migraine), attacks are usually associated with nausea, vomiting, or sensitivity to light, sound, or movement.[12] When untreated, these attacks typically last 4 to 72 hours.[13] A combination of features is required for the diagnosis, but not all features are present in every attack or in every patient.

These symptoms distinguish migraine from tension-type headache, the most common form of primary headache, is characterized by the lack of associated features. Any severe and recurrent headache is most likely to be a form of migraine and to be responsive to ant migraine therapy.[14] In 15 percent of patients, migraine attacks are usually preceded or accompanied by transient focal neurologic symptoms, which are usually visual; such patients have migraine with aura (previously known as classic migraine).[5] In a recent large, population-based study, 64 percent of patients with migraine had only migraine without aura, 18 percent had only migraine with aura, and 13 percent had both types of migraine (the remaining 5 percent had aura without headache). Thus, up to 31 percent of patients with migraine have aura on some occasions,[15] but clinicians who rely on the presence of aura for the diagnosis of migraine will miss many cases. We find it useful to assess the severity and effects of migraine by asking about time lost because of migraine at work or school, in performing household work or chores, or in family, social, and leisure activities. One can ask patients directly about temporary disability, have them keep a diary, or get a quick but accurate estimate with the use of the Migraine Disability Assessment Scale (MIDAS), a well validated five-item questionnaire that is easy to use in practice.[16]

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. The International Classification of Headache Disorders defines the migraine by following criteria.[17]

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.

approaches, which are often “biobehaviouristic,” may be complementary or adjunctive to pharmacologic treatme.

William EA. 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.

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

Pharmacological treatment

Analgesic and Non-steroidal Anti-inflammatory Drugs

In many patients, migraine responds well to simple treatment at the time of an attack. There are several key features of the successful use of such treatments, after the preference of the patient and any contraindications have been taken into consideration. The drug should be taken as soon as the headache component of the attack is recognized.[18] The dose of drug should be adequate; for example, 900 mg of aspirin,[19,20] 1000 mg of acetaminophen,[21] 500 to 1000 mg of naproxen,[22] 400 to 800 mg of ibuprofen,[23] or appropriate doses of a combination of these drugs.[19,20] The administration of antiemetic drugs or drugs that increase gastric motility is likely to facilitate the absorption of the primary drug and thus help to ameliorate the attack.[19,20] Overuse of these drugs should be avoided; for example, intake should be restricted to no more than two to three days a week, and a headache diary should be kept and monitored for any escalation in drug use. It is important to remember that the severity of migraine attacks and their response to treatment may vary; patients may therefore require only one drug for some attacks but several drugs for more bothersome attacks. As a rule, we avoid the use of opiates. These drugs seem to mask the pain without suppressing the pathophysiologic mechanism of the attack, often leaving the patient cognitively impaired. Their use may lead to addiction, and for most patients, they offer no advantages over more migraine-specific therapy.

5-HT$_{1B/1D\ receptor}$ 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.[11] A variety of tripans 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.[21] 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.

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 i.v. is comparable to 6mg SC sumatriptan in emergency setting. Opoids are the one of the alternatives for managing the intensity of migraine headache in emergency setting but due to chance of deterioting quality of life, concomitant psychiatric co morbidities and development of other first line agent are contraindicated.
habituation, it’s use is restricted to those only whom the

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.

Indications for preventive therapy of migraine

• More than 2 headaches per month, but fewer than 8

- More than two 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.

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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, atenelol, metoprolol and bisoprolol had shown the efficacy against the migraine headache, most evidences demonstrate maximum efficacy in favor of propranolol. The staring 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 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 anhydrate 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 cyclendelate, 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 serotoninergic, 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. Neuromodulation 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 spheno palatine 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

1. Lance JW, Goadsby PJ. Mechanism and management of headache. 6th ed. Boston: Butterworth–Heinemann, 1998.
2. Silberstein SD, Lipton RB, Goadsby PJ. Headache in clinical practice. Oxford, England: Isis Medical Media, 1998.
3. Goadsby PJ, Silberstein SD, eds. Headache. Vol. 17 of Blue books of practical neurology. Boston: Butterworth–Heinemann, 1997.
4. Lipton RB, Diamond S, Reed M, Diamond ML, Stewart WF. Migraine diagnosis and treatment: results from the American Migraine Study II. Headache, 2001; 41: 638-45.
5. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia, 1992; 12: 221-8.
6. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology, 1999; 53: 537-42.
7. Goadsby PJ. Pathophysiology of headache. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. Wolff ’s headache and other head pain. 7th ed. Oxford, England: Oxford University Press, 2001: 57-72.
8. May A, Goadsby PJ. The trigeminovascular system in humans: pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. J Cereb Blood Flow Metab, 1999; 19: 115-27.
9. Gasparini CF. et al. Studies on the pathophysiology and genetic basis of migraine. Curr Genomics [Internet], 2013; 14(5): 300–15. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3763681&tool=pmcentrez&rendertype=abstract.+
10. Rogawski MA. Common Pathophysiologic mechanisms in Migraine and Epilepsy. Arch Neurol, 2008; 65(6): 709–14.
11. Mallaoglu M. Trigger factors in migraine patients. J Health Psychol, 2012; 18(7): 984–94.

12. Olesen J, Tfelt-Hansen P, Welch KMA. The headaches. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000.
13. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia, 1998; 8: Suppl 7: 1-96.
14. Lance JW. Headache and face pain. Med J., Aust 2000; 172: 450-5.
15. Tfelt-Hansen P, Olesen J. Effervescent metoclopramide and aspirin (Migravess) versus effervescent aspirin or placebo for migraine attacks: a double-blind study. Cephalalgia, 1984; 4: 107-11.
16. Lipton RB, Baggish JE, Stewart WF, Codispoti JR, Fu M. Efficacy and safety of acetaminophen in the nonprescription treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. Arch Intern Med, 2000; 160: 3486-92.
17. Welch KMA. Naproxen sodium in the treatment of migraine. Cephalalgia, 1986; 6: Suppl 4: 85-92. 66. Kellstein DE, Lipton RB, Geetha R, et al. Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: a randomized, double-blind, placebo-controlled, dose-ranging study. Cephalalgia, 2000; 20: 233-43.
18. Lipton RB, Stewart WF, Ryan RE Jr, Saper J, Silberstein S, Sheftell F. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: three double-blind, randomized, placebo-controlled trials. Arch Neurol, 1998; 55: 210-7.
19. Goldstein J, Hoffman HD, Armellino JJ, et al. Treatment of severe, disabling migraine attacks in an over-the-counter population of migraine sufferers: results from three randomized, placebo-controlled studies of the combination of acetaminophen, aspirin, and caffeine. Cephalalgia, 1999; 19: 684-91.
20. Volans GN. Absorption of effervescent aspirin during migraine. Br Med J., 1974; 4: 265-8.
21. Cottrell J, Mann SG, Hole J. A combination of ibuprofen lysine (IBL) and domperidone maleate (DOM) in the acute treatment of migraine: a double-blind study. Cephalalgia, 2000; 20: 269. abstract.
22. Potter DL, Hart DE, Calder CS, Storey JR. A double-blind, randomized, placebo-controlled, parallel study to determine the efficacy of topiramate in the prophylactic treatment of migraine. Neurology, 2000; 54: Suppl 3: A15. abstract.
23. Graham JR, Suby HI, LeCompte PR, Sadowsky NL. Fibrotic disorders associated with methysergide therapy for headache. N Engl J Med, 1966; 274: 359-68.