

Migraine: pathophysiology, evaluation, and management

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Abstract

Migraine is a common long term primary headache disorder characterized by recurrent bouts of moderate to severe headaches. Migraine attacks can be debilitating with significant functional disability. Research has identified key mechanisms and triggers in migraine pathophysiology which has enabled development of promising new targets in migraine management. There are many therapeutic options in the treatment of migraine and the choice of treatment should be geared to the patient needs and co-morbidities.

Key words: migraine, headache, patho-physiology, calcitonin gene related peptide (CGRP), targeted treatment

Introduction

Migraine is a complex long-term headache disorder characterized by bouts of moderate to severe headaches. It is associated with symptoms such as heightened sensitivity to light, increased sensitivity to sound and nausea.¹ The debilitating nature of migraine has significant socio-economic implications. Quantifying the impact of migraine on an individual's quality of life can be challenging. The available data suggest this influence is substantial with approximately 75% of patients experiencing functional disability during an attack of migraine.² Migraine is considered the second major cause of disability after back pain with respect to years of life lived with disability.³

The figures related to migraine prevalence vary across different nations and from study to study. The

estimated average prevalence is close to 12%.⁴ Studies have shown an age standardized migraine prevalence close to 15,000 per 100,000 population in Sri Lanka in 2019.⁵ Females consistently have a higher incidence of migraine than males across all age groups.⁶ Prevalence of migraine increases during puberty and continues to rise until 35-39 years. It decreases later in life particularly after menopause.⁷

There is a strong familial tendency for migraine. If one parent has migraine there is a 40% risk of developing migraines which increase up to 75% when both parents have migraine.⁸ Twin studies indicate that genetic factors may significantly contribute to the risk of developing migraine and the inheritance of migraine may be as high as 65%.^{9,10}

Classification

The headache classification committee of the International Headache Society¹ have classified subtypes of migraine with definitions and their complications which are depicted in Table 1.

Calcitonin gene related peptide (CGRP) and its role in the pathophysiology of migraine

Large unmyelinated nerve fibres arising from the ophthalmic division of trigeminal nerve and the upper cervical nerve roots in the posterior fossa, form a plexus that surrounds large meningeal blood vessels, large venous sinuses, and the dura.¹² Activation of these trigeminal afferents lead to release of pro-inflammatory mediators provoking neurogenic inflammation in the pain sensitive meninges resulting in headaches.

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Table 1. Subtypes of migraine

<i>Subtype</i>	<i>Examples</i>	<i>Description</i>
Migraine without aura		Recurrent headaches of 4 to 72 hours; typically unilateral, pulsating, moderate to severe intensity, aggravated by physical activity, and associated with nausea, photophobia and phonophobia.
Migraine with aura	Migraine with typical aura Migraine with brainstem aura Hemiplegic migraine (Familial and sporadic) Retinal migraine Vestibular migraine	Recurrent reversible attacks, lasting minutes, typically one or more of these unilateral symptoms: visual, sensory, speech and language, motor, brainstem, and retinal, usually followed by headache and migraine symptoms. Vestibular migraine is characterised by acute episodes of vertigo with dizziness and spatial disorientation.
Chronic migraine		Headache on 15 or more days in a month for over three months and has migraine features on at least eight days in a month.
Complications of migraine	Status migrainosus	Debilitating migraine attack that lasts more than 72 hours.
	Persistent aura without infarction	Aura that persists more than one week without evidence of infarction on neuroimaging.
	Migrainous infarction	One or more aura symptoms with brain ischemia on neuroimaging during a typical migraine attack.
	Migraine aura-triggered seizure	Occurs during an attack of migraine with aura, and a seizure is triggered.
Probable migraine		Symptomatic migraine attack that lacks one of the features required to fulfil the criteria for one of the above and does not meet the criteria for another type of headache.
Episodic syndromes that may be associated with migraine	Recurrent gastrointestinal disturbances	Recurrent attacks of abdominal pain, discomfort, nausea, and vomiting that may be associated with migraines
	Benign paroxysmal vertigo	Brief recurrent attacks of vertigo.
	Benign paroxysmal torticollis	Recurrent episodes of head tilt to one side.

A phenomenon called cortical spreading depression of Leão (CSD) is thought to potentially trigger the activation of the trigeminal nerve plexus initiating a cascade of events.¹³ CSD is a propagating wave of neuronal and glial depolarisation in the brain. CSD is thought to cause aura, activate trigeminal afferents, and alter the blood brain barrier permeability.

Neurogenic inflammation following activation of trigeminal afferents lead to release of substance P, Calcitonin gene related peptide (CGRP) and neurokinin A which are all vasoactive peptides.¹² This leads to vasodilatation, oedema, and plasma protein extravasation. Neuropeptide CGRP needs special mention as it is recognized as a critical player in migraine pathophysiology and CGRP targeted therapeutics have been developed based on its role.

CGRP is the most potent vasodilator known in migraine pathophysiology and it increases during spontaneous acute attacks of migraine. CGRP acts both peripherally and centrally to cause migraine. In the periphery, CGRP targets mast cells, blood vessels, glial cells, trigeminal afferents in the meninges, and neural cell bodies and satellite glia in the trigeminal ganglia. In the meninges, CGRP contributes to neurogenic inflammation by triggering the release of neuron-sensitizing agents from mast cells, which in turn leads to increased vasodilation in the dura.

Centrally, CGRP and its receptors are present in multiple pathways and are believed to play a role in migraine pathophysiology. The trigeminal ganglion projects to the trigeminal nucleus caudalis (TNC) where second-order neurons carry the signals to the posterior thalamic area (PTA). Both CGRP and its receptors are present in discrete nuclei of the PTA and are thought to alter the functional connectivity of the PTA with multiple regions in the brain.

In the recent past, different molecules have been developed to block CGRP signalling to treat migraine symptoms. CGRP receptor antagonists "gepants" show high affinity for the CGRP receptor and prevent CGRP binding and signal transduction. Ubrogepant, atogepant and rimegepant are a few examples of gepants. Monoclonal antibodies against CGRP (fremanezumab, galcanezumab, eptinezumab) and against CGRP receptor (erenumab) are emerging treatments against migraine.

Triggers of migraine

Exposure to or withdrawal from several factors contributes as triggers to the development of migraine.¹⁴ Approximately 76% of patients report such triggers.

While some are probable contributors, others are possible or unproven factors.

Stress, hormonal changes (menstruation, ovulation, and pregnancy), skipped meals, weather changes, exposure to lights and alcohol are considered as probable triggers of migraine while excess or insufficient sleep, certain odours (perfumes, colognes, petroleum distillates), neck pain and late sleep may be possible triggers. Smoking, heat, exercise, and sexual activity have not been proven as triggers of migraine. While aspartame (non-saccharide sweetener) is a possible trigger, tyramine and chocolate have unproven potentials to trigger migraine.

Clinical features

Four phases can be recognized in migraine attacks.

The first phase is the premonitory phase which is the transitional phase between asymptomatic interictal phase and the onset of headache. Symptoms originate from activation of hypothalamus¹⁵ and include concentration problems, fatigue, irritability, depression, yawning, lethargy, neck symptoms, light sensitivity, restlessness, difficulties in focusing vision, feeling cold, craving, sound sensitivity, sweating, excess energy, and thirst. Approximately 77% of patients experience premonitory symptoms for up to 24 to 48 hours before headache onset.¹⁵ This is more common in females than males (81 to 64%).¹⁵

The second phase is the aura which typically precedes the onset of headache, but it can present simultaneously with the headache and may even occur without headache. Aura is postulated to be a result of cortical spreading depression (CSD) resulting in changes in cortical function, blood circulation and neuro-vascular integration.¹⁶

Symptoms and at times signs of aura depend on which part of the brain is affected by CSD. They are typically gradual in onset, last less than 60 minutes and are completely reversible. Auras can manifest as positive or negative symptoms. Positive symptoms include bright lines or shapes, scintillating scotoma, tinnitus, noises, allodynia, and paraesthesia while negative symptoms are reduction or loss of vision, visual field defects, hearing, sensation, or motion. Visual aura is the commonest while sensory aura is also common. Language aura characterised by transient dysphasia and motor aura with complete or partial hemiplegia are rare and seen with hemiplegic migraine.

The third phase is the headache phase which results from further changes in blood circulation resulting changes in function of the brainstem, thalamus, hypothalamus, and cortex. This is often unilateral, pulsatile, or throbbing in nature and reaches increasing intensity within the first hours.

Higher intensity migraine attacks can be associated with manifestations of brainstem dysfunction such as nausea, vomiting, photophobia, phonophobia, rhinorrhoea, lachrymation, allodynia, and osmophobia. Headache can last from hours to days at a time. Pain usually resolves with sleep and patients prefer to seek relief in dark places.

The fourth or the final phase is the postdrome where the symptoms caused by persistent changes in the blood circulation after termination of the headache. The symptoms could include exhaustion, dizziness, difficulty in concentration and euphoria. This phase is also characterised by movement-vulnerable pain in the same location as the previous headache.

Diagnosis

Diagnosis of migraine is based on a detailed history and examination followed by fulfilment of

International Classification of headache disorders (ICHD-3) diagnostic criteria¹¹ [supplementary file: page 85].

The differential diagnosis includes other primary headache disorders such as tension type headache, cluster headache, paroxysmal hemicrania or headaches due to secondary headache disorders such as meningitis/encephalitis, giant cell arteritis, cerebral aneurysms and intra cranial/sub arachnoid haemorrhage.

Management of migraine

Management options include acute treatment and prophylactic treatment. Acute treatment aims to stop the progression of the headache. Preventive treatment reduces the frequency, severity, and duration of attacks, improve efficacy of abortive medication during acute attacks, reduces disability and prevents medication overuse headache (Table 2 & 3).

Migraine attacks need to be treated quickly and with a single large dose of medication to stop the progression. A particular concern is gastric stasis that can be seen with migraine which leads to vomiting and unpredicted absorption warranting parenteral treatment.¹⁷

Table 2. Acute treatment of migraine

<i>Drug class</i>	<i>Drug and the dose range</i>	<i>Mechanism of action</i>	<i>Comments</i>
1. non-steroidal anti-inflammatory drugs	Ibuprofen (400 to 600 mg) Naproxen (275 to 825 mg) Diclofenac (50-100 mg) Aspirin (900 to 1000 mg)	Block cyclo-oxygenase enzymes 1 and 2 and reduce prostaglandin synthesis. Inhibition of prostaglandin E2 is effective in relieving headache in migraine.	First line in mild to moderate attacks. All have similar efficacy. If one is not effective, another can be used.
2. Paracetamol	Paracetamol (1000 mg)	Paracetamol may act centrally to inhibit prostaglandin synthesis and to enhance serotonergic pathways.	

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<i>Drug class</i>	<i>Drug and the dose range</i>	<i>Mechanism of action</i>	<i>Comments</i>
3. Triptans	Sumatriptan • S/C 6 mg • Nasal spray- 20-40 mg/ 24 hrs. • Nasal powder 22-44 mg/24 hrs • Oral 50 to 100mg single dose zolmitriptan • Nasal 2.5 to 5mg (single dose) • Oral 2.5 mg as a single dose) Others; eletriptan, rizatriptan, naratriptan, almotriptan, frovatriptans	Serotonin-receptor agonists with high affinity for the post synaptic 5-HT_{1B} in smooth muscle cells of blood vessels, and presynaptic 5-HT_{1D} receptors on trigeminal.	First line in migraine with allodynia. Contraindicated in severe hepatic impairment, prolonged QT interval. Should be avoided in ischaemic heart disease, stroke/TIA, uncontrolled hypertension and used with caution in pregnancy. Patients who do not respond to one triptan may respond to another. Naratriptan and frovatriptan have a slower onset and lower efficacy. All should be used less than 10 days per month to avoid medication overuse headaches. Monitor for serotonin syndrome.
4. Antiemetics	Metoclopramide (10-20 mg), IV/IM/ oral Prochlorperazine 10 mg IV	Metoclopramide antagonizes the D₂ receptor at lower doses and the 5HT-3 receptor at higher doses, providing both antiemetic and migraine relief effects. Prochlorperazine is a dopamine antagonist on D₂ receptor and reduces symptoms of migraine and control nausea and vomiting.	Adjunct to NSAIDs or triptans to decrease nausea and vomiting. Akathisia and dystonic reactions may occur with metoclopramide.
5. Calcitonin-gene-related peptide antagonists (Gepants)	Rimegepant (75 mg as a single dose)	Inhibit CGRP at the CGRP receptor level.	Second-line therapy when triptans are contraindicated, poorly tolerated, or ineffective. Effective in acute migraine but the role in prophylaxis is not clear.
6. Serotonin agonists (Ditans)	Lasmiditan 50-200 mg per 24 hours	Selective serotonin 1F receptor agonist.	Dizziness may require avoidance of driving at least 8 hours after each dose.

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<i>Drug class</i>	<i>Drug and the dose range</i>	<i>Mechanism of action</i>	<i>Comments</i>
7. Ergots	Dihydroergotamine IV, IM, S/C, intranasal use	Like triptans. Potent agonists of 5-HT 1b/1d receptors. Causes constriction of pain-causing intracranial extracerebral blood vessels at the 5-HT _{1B} receptors and inhibition of trigeminal neurotransmission at both peripheral and central 5-HT _{1D} receptors.	Bridge therapy for medication overuse headache and status migrainosus. Significant cerebrovascular, cardiovascular, and peripheral ischemic complications.
8. Dexamethasone	Oral 4 mg twice daily for 4 days.	Acts through prevention of neurogenic inflammation.	Can reduce the recurrence of early headaches but does not provide immediate relief. Effective in status migrainosus.
9. Peripheral nerve blocks	Greater Occipital Nerve (GON) blocks		Useful as a bridging therapy in management of migraine associated with medication overuse headache.

Table 3. Prophylactic treatment of migraine

<i>Drug class</i>	<i>Drug and the dose range</i>	<i>Mechanism of action</i>	<i>Comments</i>
1. Beta-blockers	Metoprolol 25-150 mg Propranolol 80-240 mg Timolol 10-20 mg Other; bisoprolol, atenolol, and nadolol	Beta-1 mediated inhibition of noradrenaline release and tyrosine hydroxylase activity.	Beta-blockers with intrinsic sympathomimetic activity (acebutolol, alprenolol, oxprenolol, and pindolol) have no efficacy for migraine prevention
2. Antidepressants	Amitriptyline 10-150 mg Nortriptyline 25-100 mg Venlafaxine 37.5-150 mg	Mixed serotonin norepinephrine reuptake inhibitor with unclear mechanism of action in migraine.	Preferred in depression or anxiety disorders and insomnia.

(Continued)

<i>Drug class</i>	<i>Drug and the dose range</i>	<i>Mechanism of action</i>	<i>Comments</i>
3. Anticonvulsants	Valproate acid 200-1600 mg Topiramate 25-100mg	Multiple modes of action; blockage of voltage-dependent sodium and calcium channels, reducing glutamate mediated excitatory neurotransmission, enhancing the GABA-A mediated inhibition, carbonic anhydrase inhibition, and decreasing CGRP secretion from trigeminal neurons.	There is a risk of acute glaucoma with topiramate. Both valproate and topiramate have a risk of teratogenicity.
4. Calcium channel blockers	Verapamil 180-480 mg Flunarizine	Reduction of neuronal excitability and interactions with serotonergic systems	Verapamil is considered safe in pregnancy. Flunarizine is not recommended in pregnancy as safety data is lacking.
5. Calcitonin gene-related peptide antagonists	Erenumab S/C 70-140 mg every 4 weeks Galcanezumab S/C 120 mg monthly	Monoclonal antibodies against CGRP	Injection site reactions, hypersensitivity and muscle spasms can occur.
6. Angiotensin receptor blockers	Candesartan 4-16 mg Lisinopril 20 mg	Modulation of vasoreactivity, alteration of sympathetic tone, vasoconstriction and suppression of neurogenic inflammation by deactivating inflammatory nuclear transcription factor NF-kB	Minimal blood pressure lowering effects on normotensive individuals.
7. Onabotulinum toxinA	3-6 monthly injections	Alter the neurotransmitters leading to slow improvement of migraine frequency and severity.	It is recommended only for chronic migraine. This should be administered by a neurologist and is recommended in patients who do not overuse acute treatment, if they failed to respond to at least three oral prophylactic agents.

Nutraceuticals such as Riboflavin, Co-enzyme Q10, Magnesium, feverfew (*Tanacetum parthenium*) and Petasites (extract of the butterbur plant) are being used as complementary medications in prevention. However, this is only supported by low quality evidence.¹⁸

Formulating a management plan for a patient with migraine

Following the clinical diagnosis of migraine, it is essential to determine whether this is episodic migraine or chronic migraine. The latter is defined as having more than 15 days of headache per month with at least 8 of them having migraine features.

Episodic migraine can be managed expectantly with treatment of acute attacks while the chronic migraine and episodic migraine which is difficult to manage will require prophylaxis.

Prophylactic therapy is generally indicated in patients with three or more severe headache days per month causing functional impairment that are not consistently responsive to acute treatments, more than 6-8 headache days per month despite responsiveness to acute treatments, contraindications to acute migraine treatments, particularly disabling symptoms even if infrequent attacks (such as brainstem aura, hemiplegic migraine, syncope), ongoing significant impact to a patient's functioning despite lifestyle modifications, trigger management and use of acute treatments and those at risk of drug overuse headache.¹⁹

Although there are many agents to choose for migraine prophylaxis, Sri Lanka has a limited availability of these medication. Therefore, the choice should be guided by the efficacy, cost of medication, comorbidities of the patient and the characteristics of migraine.

Even though CGRP receptor targeted monoclonal antibodies have the best safety and efficacy profile of all drugs for migraine followed by gepants²¹ neither of these medications are currently available in Sri Lanka.

In a recent meta-analysis in 2023, comparing effectiveness of migraine preventive medication,²¹ topiramate had the highest efficacy in treating migraine after monoclonals and gepants, but with probable high side effect profile compared to placebo. Beta blockers, valproate and amitriptyline had moderate efficacy in preventing migraine. Beta blockers had a good safety profile while both valproate and amitriptyline showed a significant side effect profile than placebo. Oxcar-

bazepine and gabapentin did not show any significant efficacy compared to the placebo while calcium channel blockers showed very uncertain benefits in migraine prevention in the above meta-analysis.²¹ Angiotensin receptor blockers were not included in the study.

Co-morbidities affect the choice of migraine prophylaxis. Hypertensive patient may benefit from calcium channel blockers, beta blockers or angiotensin receptor blockers while patients with co-existing epilepsy will benefit from valproate or topiramate.

Successful treatment is defined as 50% reduction in the number of headache attacks or days, a significant reduction in duration of attacks or an improvement in response to acute therapy. Each treatment needs an adequate trial before considering a switch of treatment. While patient may show some improvement at six to eight weeks, full effect may take up to six months.

Re-evaluation is essential with careful dose titration. Changing treatment can be considered if there is no response in two months.

If headaches are controlled for at least six to twelve months, slow tapering followed by discontinuation can be considered.²²

Non-pharmacological therapy

A meta-analysis by the U.S. Headache Consortium concluded that relaxation training, thermal biofeedback, electromyographic biofeedback, and cognitive behaviour therapy may be considered as treatment options for the prevention of migraine.²³ Behavioural therapy may be combined with preventive drug therapy to achieve additional clinical improvement.²³ According to a 2016 Cochrane review acupuncture added to symptomatic treatment decreased the headache frequency and was at least as effective as prophylactic medication.²⁴

Conclusion

Migraine is a complex headache disorder with significant impact on the quality of life. Advances in migraine research have provided better understanding of the pathophysiology and potential therapeutic targets. CGRP is an effective target for both acute and preventative treatment of migraine, though cost can be a barrier. In the management of migraine, it is crucial to provide personalized care to the patients with empathy and support.

Key points

- Activation of the trigemino-vascular system initiate neurogenic inflammation causing migraine headaches. The activation of the trigeminal nerve afferents is caused by the Cortical Spreading Depression which is the probable cause of the aura.
- Migraine attacks are recurrent and occur through a cascade of events over hours to days.
- A typical attack of migraine progress through a prodrome, an aura, a headache, and the postdrome.
- Treatment of migraine should be individualized based on many factors including frequency and severity of attacks, cost and co-morbidities.

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