REVIEW ARTICLE

Recent Advances in the Treatment of Migraine

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Abstract

This condition causes complicated recurring headaches. It frequently begins with "aura," sensory or visual symptoms. It is typically a headache that comes and goes, often accompanied by specific characteristics such as sensitivity to light and sound. Along with the headache, nausea and vomiting are frequently experienced. The exact etiology of migraine remains still unclear. The most notable causative factor from various studies shows these genes *PRDM16, TRPM8, LRP15,* and *AEG16* have single nucleotide polymorphisms that are the primary genetic causes of migraine. There are multiple theories and postulates to explain the pathogenesis of migraine. Among them, three theories are well known namely vascular theory, neurovascular theory, and cortical spreading depression (CSD). Nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics, which were not created especially to treat migraine, can be used to treat a migraine attack and are considered as the nonspecific treatment of migraine. Recently, antimigraine medication classes have been created, including ditans, gepants, and monoclonal antibodies that bind to calcitonin gene-related peptide (CGRP) or the CGRP receptor. However, in recent years due to advancements in technology and understanding the molecular basis, there are newer targets in migraine treatment such as adenosine receptor agonists, NXN-188, LY2951742, orexin receptor antagonism, TRPV1 antagonism, melatonin, and P2Y purinergic receptors.

Keywords: Antimigraine medication, Migraine, Newer targets, Nonspecific treatment.

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Introduction

Hemikrania, which in Greek means "half of the head," is the root of the word migraine. This condition causes complicated recurring headaches. It frequently begins with "aura," which are sensory or visual symptoms. It is typically a headache that comes and goes, often accompanied by certain characteristics such as sensitivity to light, and sound, or along with the headache, nausea and vomiting are frequently experienced. Migraine is frequently identified by its triggers, sometimes known as activators. The brain of the person with migraine is especially susceptible to environmental likewise sensory input. Women's menstrual cycles cause an increase in this sensitivity in them. A headache can be initiated on or heightened by a variety of triggers, such as glare, strong lights, sounds, or other afferent stimuli such as excitement, hunger, release from tension, physical effort, stormy conditions, or variations in barometric pressure, changes in menstrual hormones, little or excessive sleep, alcohol use, or other chemical stimulation, such as nitrates, are just a few examples. Adjusting a patient's lifestyle as part of management measures can benefit from knowing how susceptible they are to triggers.[1,2]

Definition and Epidemiology

A complicated illness with hereditary influences called migraine is defined by bouts of typical unilateral headaches of moderate and severe grades and frequently accompanied by nausea, light sensitivity, and sound sensitivity. There are three phases to it as follows:

1. Prodrome: Premonitory symptoms linked to activated hypothalamus;
2. Aura: Alterations in brain activity, blood flow, and neurovascular coupling;
3. Headache: Further modifications to the brainstem, thalamus, hypothalamus, and cortical blood flow and function. After a headache has passed, there may still be postdrome symptoms and lingering blood alterations. About 14% of people worldwide have migraines. In India, the prevalence ranges between 16 and 20%. Three times as many women as men are impacted. North America has the highest adjusted prevalence of migraine, followed by South and Central America, Europe, Asia, and Africa. As a rule, migraines run in families. It accounts for 3% of all emergency visits annually and is regularly the fifth most common cause of visits. Puberty is when it starts to become more common, but it does not stop until ages in the range of 35–39 years before it starts to decline as people age, especially after menopause. Men with migraines needed 3.8 days of bed rest annually, compared to 5.6 days for women.[1,3]

Etiology

The exact ethology of migraine remains still unclear. The most notable causative factor from various studies shows these genes, *PRDM16, TRPM8, LRP15,* and *AEG16*, have single nucleotide polymorphisms that are the primary genetic causes of migraine. It has been discovered that mutations in the genes *CACNA1A7,*

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ATP1A28, and *SCN1A9* cause familial hemiplegic migraine. Some autosomal dominant mitochondrial diseases, including mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), have an increased frequency of migraines. Furthermore, hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy (HIHRATL), which is thought to be caused by mutations in the *COL4A1* gene, and retinal vasculopathy with cerebral leukodystrophy (RVCL), which is caused by mutations in the *TREX1* gene, are two genetic vasculopathy diseases that frequently exhibit the symptom of migraine. Nonsyndromic migraines have numerous, poorly understood causes.[1]

Pathophysiology

There are multiple theories and postulates to explain the pathogenesis of migraine. Among them, three theories are well known namely vascular theory, neurovascular theory, and cortical spreading depression (CSD). The perivascular nociceptive neurons are stimulated by cerebral vasoconstriction, which leads to rebound vasodilation, according to the 1950s-era vascular theory. According to the neurovascular theory, migraines are mostly caused by neuronal hyperexcitability in the occipital brain, with consequent changes in cerebral perfusion. In 1944, migraine with aura was explained by Leao by the CSD theory. Cortical spreading depression is a distinct wave of cortical grey matter neuronal excitation that propagates from its source at a rate of 2–6 mm per minute. The first cortical phenomenon, also known as the aura phase, is brought on by this cellular depolarization, which also activates the trigeminal nerve, resulting in the headache phase. The neurochemical basis for CSD is due to potassium or the excitatory neurotransmitter glutamate released from the brain. This neurotransmitter release depolarizes the tissue around it, which in turn causes the release of more neurotransmitters and quickens the depressive state.[4]

Neurotransmitters and Vasoactive Agents

Perivascular nerve activity brings about the release of nitric oxide, neurokinin A, substance P, calcitonin gene-related peptide (CGRP), and other substances that come into contact with the blood vessel wall to cause dilatation, protein extravasation, inflammation, and other physiological changes.[4]

Calcitonin Gene-related Peptide and Migraine

The primary event in a migraine attack, according to Waeber and Moskowitz hypothesis, is stimulation of trigeminal nerve terminals in the meninges and extracranial arteries. Releasing neuropeptides and other inflammatory mediators from the sensory nerve terminals, would both directly elicit pain and trigger inflammatory changes. It is true that one of these peptides CGRP release occurs into the meningeal circulation. During a migraine episode, and both a CGRP-neutralizing monoclonal antibody and an antagonist of this peptide were highly effective in preventing attacks.[5]

Serotonin and Migraine

The receptor known to be most important in the headache pathway is thought to be the serotonin receptor [5-hydroxytryptamine (5-HT)]. Also, 5-hydroxytryptamine-1D (5-HT1D) receptors have been identified by immunohistochemical tests. Smooth muscle cells in meningeal vessels possess 5-HT1B receptors. On the contrary, 5-HT1R receptors are present in trigeminal sensory neurons, which include the solitary tract, the trigeminal nucleus caudalis (TNC), and peripheral projections to the dura; however, both can be found to some degree in both tissues, even in coronary vessels. All of the triptans available today are full agonists of 5-HT1B/D selectively. By preventing the release of peripheral neuropeptides and reducing neurotransmission by targeting second-order trigeminocervical complex neurons, these medications may reduce headaches.[6]

Dopamine and Migraine

Some scholars have suggested that migraines have a dopaminergic foundation. In 1977, Sicuteri proposed that migraine sufferers have a state of dopaminergic hypersensitivity. This hypothesis has recently attracted new interest. Relative dopaminergic activation may be the cause of several migraine headache symptoms, including nausea, vomiting, yawning, irritability, hypotension, and hyperactivity. Dopamine agonists have been used in experiments to demonstrate dopamine receptor hypersensitivity (e.g., apomorphine). Prochlorperazine and other dopamine antagonists totally alleviate almost 75% of acute migraine attacks.[7]

Treatment of Migraine

Nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics, which were not created specially to treat migraine, can be used to treat a migraine attack, and are considered as nonspecific treatment of migraine. Ergotamine was the first and more specific migraine treatment drug developed in 1918, but it had many adverse effects. Hence, more specialized medications have been created over time to treat migraines both acutely and preventatively, such as triptans which has been the industry standard for more than 30 years. Recently, antimigraine medication classes have been created, including ditans, gepants, and monoclonal antibodies that bind to CGRP or the CGRP receptor.[8]

Calcitonin gene-related peptide is an endogenous neuropeptide rich in trigeminovascular system. An increase in intracellular calcium ions brought on by CGRP induces relaxation and concurrent dilating of the arteries. It has been believed that this cranial artery dilatation is an indication that trigeminal nociceptive afferents are activated during migraine episodes. Hence, targeting CGRP is a therapeutic option for prevention of migraine attacks.

The CGRP antagonists such as olcegepant, telcagepant, fremanezumab, erenumab, and galcanezumab inhibit the CSD and suppress CGRP stimulation by preventing endogenous CGRP from binding to its receptors. Olcegepant works similarly well to oral triptans and has fewer adverse effects related to CVS; however, it must be injected intravenously (IV). Telcagepant was found to be potent drug but withdrawn due to hepatotoxicity. Eptinezumab is new drug yet to be approved by the US Food and Drugs Administration (FDA). The humanized monoclonal antibodies include fremanezumab, galcanezumab, and eptinezumab target the ligand of CGRP while CGRP receptor is the target for erenumab. The advantage of the new monoclonal antibodies is that they bypass the liver because the drugs such as fremanezumab, galcanezumab, and erenumab are given subcutaneously while eptinezumab is the first anti-CGRP drug given intravenously. In trials, these drugs were

Table 1: Drugs approved for migraine

Drug name	*FDA approval date*	*Route of administration*	*Mechanism of action*	*Adverse effect*
Erenumab	27 May 2018	Subcutaneous injection	Monoclonal antibody directed against CGRP alpha and beta	Injection site reaction, constipation, cramps, and muscle spasm
Fremanezumab	14 September 2018	Subcutaneous injection		Injection site reaction
Galcanezumab	27 September 2018	Subcutaneous injection		Injection site reaction
Eptinezumab	21 February 2020	IV infusion		Nasopharyngitis, hypersensitivity reaction
Lasmiditan	11 October 2019	Oral tablet	Serotonin receptor agonist selectively binds to the 5-HT1F receptor subtype	Sleeplessness, dizziness, nausea, and vomiting
Ubrogepant	3 December 2019	Oral tablet	Small molecule calcitonin gene-related peptide receptor antagonist	Nausea, somnolence, and dry mouth 2% greater than placebo
Rimegepant	27 February 2020	Oral disintegrated tablet		No serious adverse effect UTI, nausea
Dihydroergotamine mesylate	2 September 2021	Nasal spray	Agonist at the serotonin 5-HT1B, 5-HT1D, and 5-HT1F receptors	Dizziness, headache, nausea, vomiting, flushing, and increased sweating
Atogepant	28 September 2021	Oral tablet	Calcitonin gene-related peptide receptor (CGRPR) antagonist	Nausea, constipation, fatigue/somnolence, and decreased appetite

UTI, urinary tract infection

found to reduce mean monthly headache days significantly when added with preventative therapy.

Lasmiditan

It is 5-HT1F receptor agonist. In preclinical models, it was found to block neurogenic inflammation, decrease cellular oncogene (c-fos) expression and lack vasoconstriction. The primary mechanism of the drug involves inhibition of protein leakage, blockage of secondary trigeminal neuronal activation, and inhibition of glutamate. In trials, it was found to be as effective as sumatriptan with CNS adverse effects.

Tezampanel

It is a competitive antagonist of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainite receptor of ionotropic glutamate receptor family. It is used only through IV route. Dasolampanel is an orally bioavailable analogue of tezampanel.[9,10]

The drugs that are approved for migraine are listed in Table 1.

Nonphrmacological Treatment

Neuromodulation is the most promising new treatment for pharmacologically nonresponsive or intractable chronic migraine, and multiple randomized controlled clinical trials (RCTs) are needed to evaluate long-term safety and effectiveness.

Supraorbital transcutaneous stimulation, transcranial magnetic stimulation, transcranial direct current stimulation, and non-invasive vagus nerve stimulation are examples of noninvasive neurostimulation techniques. Deep brain stimulation, occipital nerve stimulation, sphenopalatine ganglion stimulation, and implanted vagus nerve stimulation are examples of invasive techniques.[9]

New Targets

- Adenosine receptor agonists: GR 79336, GR 190178 inhibit the release of CGRP and having a role in migraine.
- Inhibitor NXN-188: It is a selective neuronal nitric oxide synthase (nNOS) inhibitor and 5-HT1B/5-HT1D receptor agonist and have a role in inhibition of the release of CGRP in animal models.
- Antibody LY2951742: It is a monoclonal antibody to CGRP under trial.
- Orexin receptor antagonism: The rationale of developing orexin receptor antagonism is the prevention of pain in migraine. Filorexant is orexin receptor antagonist used in trials but failed efficacy.
- Ion channel TRPV1 antagonism: Trigeminal nociceptors are stimulated by heat and capsaicin gated channel TRPV1. It is believed that blocking TRPV1 is necessary to prevent migraine attacks from starting because TRPV1 activation results in the release of CGRP from trigeminal nerve terminals and neurogenic inflammation in the meninges; SB-705498 is drug which acts by antagonizing TRPV1 in trials.
- Melatonin: The role of melatonin in decreasing the inhibition of release of CGRP is explored in the treatment of migraine.
- Purinergic receptor P2Y: Purinergic receptors have a role in pain transmission and hence antagonizing the receptors will be the option to treat migraine.[8]

Conclusion

In the recent past, there have been significant developments in the treatment of migraine. New drug development in this field and finding newer targets for migraine could lead to most effective

personalized therapy. All these improvements will inspire us to do clinical research in larger population to improve patient clinical outcome.

Clinical Significance

A frequent and often incapacitating neurological condition known as migraine carries a heavy socioeconomic impact. Ample patient education is essential for effective migraine management; to prevent setting the patient up for disappointment, the disease must be carefully communicated to the patient as soon as it is identified. There are now a wider variety of acute therapies available. Currently, there are two types of abortive migraine therapy as follows: Specific (ergot derivatives and triptans) and nonspecific (analgesics and NSAIDs). Newer classes of drugs such as CGRP receptor antagonists, CGRP monoclonal antibodies, ditans, and AMPA antagonists. Finally, newer targets of migraine undertrial such as orexin, TRPV1 antagonist and melatonin were discussed briefly in this review.

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