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A new era of Therapeutic Management of Migraine

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ABSTRACT: Migraine is a chronic paroxysmal neurological disorder which is characterized by sudden and severe headache accompanied with symptoms like nausea, vomiting and sensitive to light. The pain of migraine headache is often describes as an intense pulsing or throbbing pain in one area of the head, which lasts for minimum of 4 h to the maximum of 72 h. According to the analysis of WHO, migraine was recorded as top 20 life time disabling conditions. The actual reason for occurrence of migraine is not till date explored but it was concluded that there are some triggering factors that may induce or worse the condition. Medications are suggested to reduce the pain and symptoms but not for permanent cure. Mainly Ergotamine is preferred for the treatment of migraine. Recently new pharmacological treatments are emerged for better improvisation in the treatment and patient compliance. This review study cover the pathophysiology, stages, pharmacological and non-pharmacological treatments along with newly developed treatments.

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INTRODUCTION:

Migraine is a chronic neurological pain that is a sudden and intense headache caused by abnormal processing of sensory output by the peripheral or central nervous system. Around 30 % of the general population are facing the problem of migraine. It is the 2nd most cause of headache characterized by recurrent episodes associated with vomiting, nausea, sensitivity to light, and noise that lasts for hours. It affects all groups of people irrespective of age, sex and social class. About 1/3rd of suffered people have an aura which means a short period of visual disturbances. Migraine is still under diagnosed and untreated. There are many treatment options with medication but as the exact reason for occurrence is not known, permanent cure

therapy is not up to date. Ergotamine is mainly preferred in the treatment of migraine. Now new developments in the treatment of migraine came into light which includes botulinum type A, Rimegepant [1-3].

PATHOPHYSIOLOGY:

Migraine aura is caused by intra cerebral arterial vasoconstriction that is followed by reactive extra cranial vasodilatation and associated with headache. The frequency with which migraine attacks occur may vary from once in a lifetime to almost daily, an indication that the degree of migraine predisposition varies individually.

Migraine genes identified by studying families with familial hemiplegic migraine (FHM) which involves gene mutations CACNAIA of calcium voltage gated (50 %) and SCNIA of Na^+/K^+ ATPase (20 %). Dopaminergic antagonists show effective therapeutic agents against migraine. Pharmacological data support serotonin (5HT) as anti-migraine therapy.

According to platelet hypothesis, it involves abnormal platelet activation with characterization like they do not adhere to each other unless precipitated and certain stimuli (Catecholamines, Thromboxane A2 and ADP). Serotonin enhances sensitivity to pain receptors leading to release of pain producing substances. According to the CNS hypothesis, it is a disturbance with secondary vasomotor changes in CNS. It is initiated in the cerebral cortex and progresses gradually with cerebral depression.

Migraine attacks can be precipitated centrally with physiological stress and fatigue excitation. From the above discussion it is evident that no complete satisfying description of pathological events associated with migraine exists [2-5].

Trigger zones and factors:

Migraine attacks have several trigger zones that are media border of supraciliar arch, close to insertion; medial part of proximal or anterior fibres of temporal muscles; sub occipital area at the level of insertion of thick muscle of neck and medial area of superior trapezius in the neck.

Several factors that are affecting occurrence of migraine are stress, lack or missing meals, foods (Caffeine, alcohol and monosodium glutamate), changing sleep pattern, hormonal factors, over thinking, extreme emotion, obesity and environmental factors (Loud noise, bright light and strong smells) [5,6].

PHASES OF MIGRAINE ATTACKS:

The migraine possesses four stages of attack that are premonitory phase, aura phase, headache and post drone stage [7,8].

Premonitory phase:

Vague premonitory symptoms that begin from 12 to 36 h before the aura. It exhibits yawing, excitation, depression, lethargy and cravings for foods.

Aura phase:

Aura is a warning or signal before onset of headache. Lasts at a wide range of 5 to 60 min. Symptoms include flashing of lights, zigzag lines, difficulty in focussing, difficulty in hearing and partial paralysis. Mainly, 20 % children and young people experience.

Headache:

Headache is generally unilateral and is associated with symptoms like cephalic of abdominal pain, nausea, vomiting, sensitivity to light, sensitivity to sound and tinnitus.

Post drone stage:

It is considered as the final stage of migraine which lasts for hours to days to disappear the feeling of hangover and tiredness.

DIAGNOSIS OF MIGRAINE:

It can be diagnosed based on the frequency and number of attacks and also associated with typical warning signs and symptoms. It is typically manifested by episodes of headache though it is more than normal head pain. Diagnosis is done by investigating family medical history, ECG, CT scan of brain and MRI [9,10].

PAIN MANAGEMENT OF MIGRAINE:

Pain is generally cured by both pharmacological and non-pharmacological factors [11-13].

Non-pharmacological factors:

The methods mentioned above can just prevent the frequency of re-currents of attack, but won't treat it.

Relaxation techniques:

It is the major technique as the common triggers of migraine is stress. Relaxation techniques involve deep breathing and progressive muscle relaxation.

Exercise:

Daily exercise including breathing exercises are recommended. The exercise is proved to be most effective in management of migraine.

Sleep:
Regular intervals of sleep must be maintained as the change in global clock of sleep also triggers migraine.

Acupuncture:
It is one of the modest ways of treating migraine with needles but is managed by specially trained individuals.

Supplements:
Magnesium:
Magnesium has a wide function in our body, fluctuations in levels of magnesium results in triggers of migraine. It is given about 300 to 500 mg/day.

Co-enzyme Q10:
It is a very essential constituent of cells that involves metabolism. The co-enzyme Q10 is mainly used to increase Q10 levels that increase brain metabolism. The co-enzyme Q10 dose is 300 to 600mg/day.

Lifestyle modifications:
Lifestyle impacts the severity and frequency of migraine can be understand and useful for successful prevention of migraine.

PHARMACOLOGICAL TREATMENT:
Pharmacological treatment of migraine includes simple analgesics and NSAIDs for acute to moderate migraine attacks.

Opiate analgesics:
Narcotic analgesic drugs like oxycodone, butorphanol, meperidine, hydromorphone are effective but generally used in treating severe infrequent headache [14].

Antiemetics:
It is useful for combating nausea and vomiting that accompany migraine headache and medication used to treat acute attacks. Examples are ergotamine tartarate and dihydroergotamine (Injectable form is more effective than nasal form) [15].

PROPHYLACTIC TREATMENT:
The β-blockers are widely used drugs for migraine prophylaxis with intrinsic sympathomimetic activity are effective for migraine prophylaxis. These are used with caution in patients with cardiovascular diseases and asthma. They reduce brain cell activities which are involved in migraine. These are generally available in tablet and capsule forms [16]. **A**mitriptyline is an anti-depressant used in migraine prophylaxis it reduces frequency, severity and duration of migraine attacks [17].

Anticonvulsants (valproic acid) 1:1 can reduce frequency of headaches by at least 50 %. Its mechanism is unclear [18].

Calcium channel blockers like verapamil, is a drug of choice for prevention of migraine and considered as a second or third line prophylactic agent. These reduce calcium entry into neurons making them less excitable and block dopamine receptors in the brain [18].

NEW DEVELOPMENTS IN MIGRAINE TREATEMENT:

Botulinum toxin type A:
It inhibits the release of acetylcholine at motor nerve terminals. It is also used in cases of dystopia, lower back pain, and neuropathic pain. Neuro modulation is the other technique emerging forward step in treating acute to moderate migraine [19,20].

Galcanezumab:
It is a human immunoglobulin G for (IgG 4) monoclonal antibody shows its direct action on CGRP receptors and exhibits therapeutic action. This Galcanezumab binds to CGRP receptor and antagonizes CGRP alpha and beta receptor function which are the ideal targets for migraine as it is distributed throughout the nervous system and elevations in these concentration levels are observed during acute and chronic attacks. It is given in recommended dosage form of 240 mg in two consecutive doses of injection of 120 ml each.
Side effects are very less when compared to the other drugs and reported adverse reactions were injection site reactions and hypersensitivity. Plasma time for this drug is about 5 days and galcanezumab undergoes metabolism by degradation into small peptides and amino acids via catabolic pathway [21].

Sumatriptan:
Sumatriptan succinate syringe is a headache medicine which shows its action by narrowing blood vessels around the brain. Reduces the substances that trigger headache pain and other symptoms in the body. This is used to treat the cluster headaches in adults. Its main motto is to reduce or treat the headache but it does not reduce the number of attacks. This is not recommended to the patients with coronary artery disease, blood circulation problems, uncontrollable high blood pressure, and heart attacks. This medicine must not be used by the patients who have used MonoAmine Oxidase inhibitors in the past 14 days [22].

Exceptions:

Sumatriptan can pass into breast milk so do not breastfeed within12 hours after using. It is not approved for use by anyone younger than 18 years old.

Ergotamine is in a group of drugs called ergot alkaloids. This work by narrowing the blood vessels around the brain and effect the blood flow pattern that are associated with certain types of migraine headache and Vitamin A and K and combination of that drug if of ergotamine tartrate and is mainly used for the migraine treatment [22].

EMERGING MEDICATIONS FOR MIGRAINE:

Rimegepant is a drug of new generation for acute migraine was found to eliminate pain and reduce symptoms. The report regarding this drug was issued to the New England Journal of Medicine on July11 2019. It returned with positive results in phase 3 clinical trials and present waiting for the FDA approval. Rimegepant is an orally administered drug which is a calcitonin gene-related peptide receptor antagonist. Prior to this, migraine treatment involves triptan drugs. They act by stimulating serotonin receptors which reduces the inflammation and constrict the blood vessels. Triptans are known to produce intolerable side effects [23,24].

Rimegepant belongs to the class of Gepant. They work by targeting the Calcitonin Gene Related Protein which is mainly responsible for pain caused during migraine attacks. Side effects of these drugs are minimal when compared to the existing drugs they include nausea, urinary tract infections [25,26].

CONCLUSION:

Migraine is a chronic paroxysmal neurological disorder. If diagnosed earlier, we can reduce the intensity and enhance the quality of life. Both pharmacological and non-pharmacological therapy of migraine has a greater impact in reducing the attack. Advanced therapies like Selective Serotonin Reuptake Inhibitors, triptans, Neuro modulation helps in reducing the burden on patients. The main mechanism for occurrence of migraine attack is not known clearly.

Hence awareness of migraine, proper diagnosis and medication will be helpful in reducing the frequently attack and its intensity of attack.

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