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A glance preface and novel approaches for the efficient treatment of a migraine

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ABSTRACT

The reviewing of a migraine mainly aimed to analyze the incessant paroxysmal neurological ailment characterized by moderate to severe head throbbing. The review points out the basic pathophysiology and different types of migraine as well as some of the promising newer antimigraine therapeutic options. The various biomarkers in CSF, as well as blood, are used as standards to diagnose the condition. The triptans released during the 1990s were the initial class of drugs used for acute treatment of migraine. The other conventional therapies offer especially as oral formulations are not exquisitely appropriate for migraineurs having severe nausea and vomiting with reduced gastric absorption. The unmet clinical needs were rapidly advanced, and development of novel drug delivery system ensured better kinetic and dynamic characteristics. The newer drug regimens were more based and targeted on the neurotransmitters directly in involved in the pathophysiology of migraine by utilizing exceptionally confined delivery systems. These include a breath activated the system, transdermal patch, oral inhalers where lower and safer doses of the drug were utilized. Such systems were having improved patient compliance and offered non- invasive route of drug administration that could be suitably substituted by oral medications. The disease disabled the quality of life of patients and also had an abundant effect in the daily activities especially for women. Thus the various nanotechnical approaches are used as novel treatment methods for better and enhanced profiling of drug molecules.

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INTRODUCTION

A migraine is a complex neurological disorder that affects multiple cortical, subcortical and brainstem areas of the brain that regulate the autonomic, cognitive and sensory functions. The word "a migraine" was derived from the Greek word "hemicrania", meaning "half of the head". According to the World Health Organization, globally half to three-quarters of adults aged between 18-65 years is prevalent of current headache disorder (World Health Organization, 2006). The stress of a migraine is consequential due to its widespread temporary disability occurring and is one among the common disorders of CNS which causes a substantial deduction in the daily activity levels. A migraine is a recurrent headache disorder affecting 15% of the population, more commonly in women (19%) than men (11%). Migraine most commonly starts between 15-24 years of age and occur most frequently in 35 - 45 years of age (Steiner, TJ 2003). By the Global Burden of Disease Study 2015, it was the third highest prevalent neurological disability

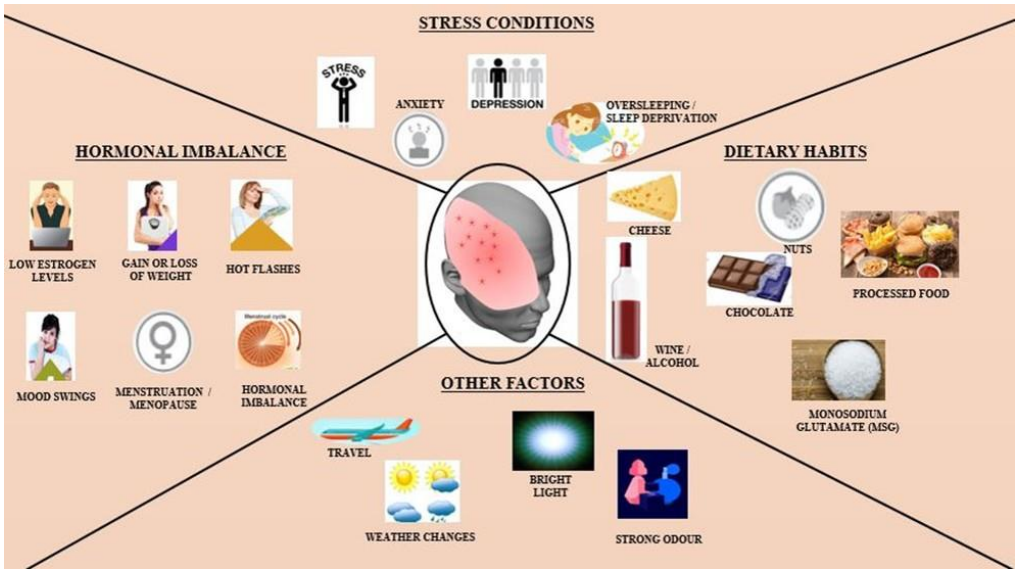

Figure 1: The major trigger factors leading to the advancement of a migraine

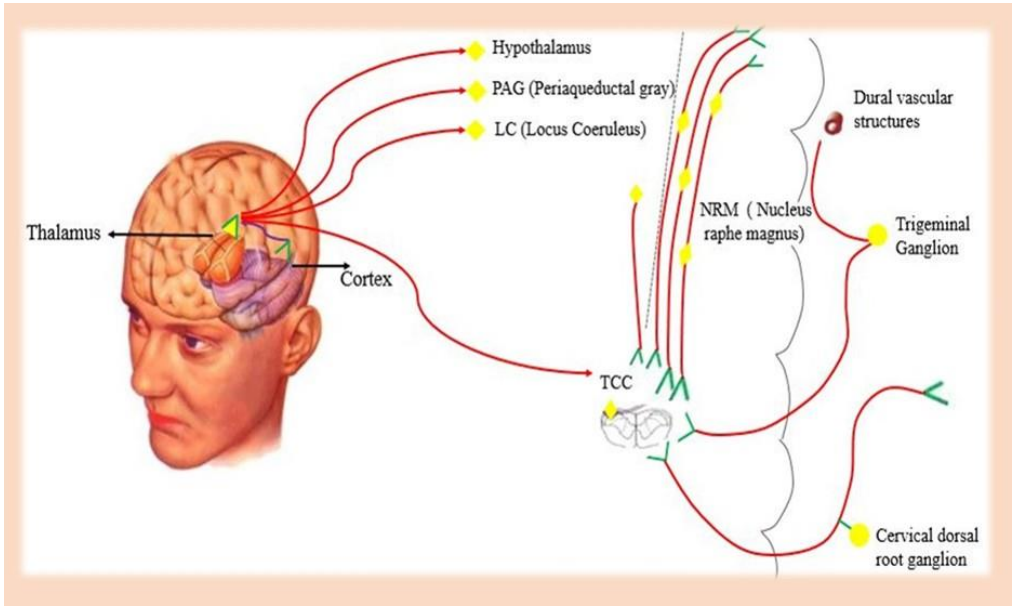

Figure 2: Biochemical transformations occurring during the trigger of a migraine attack

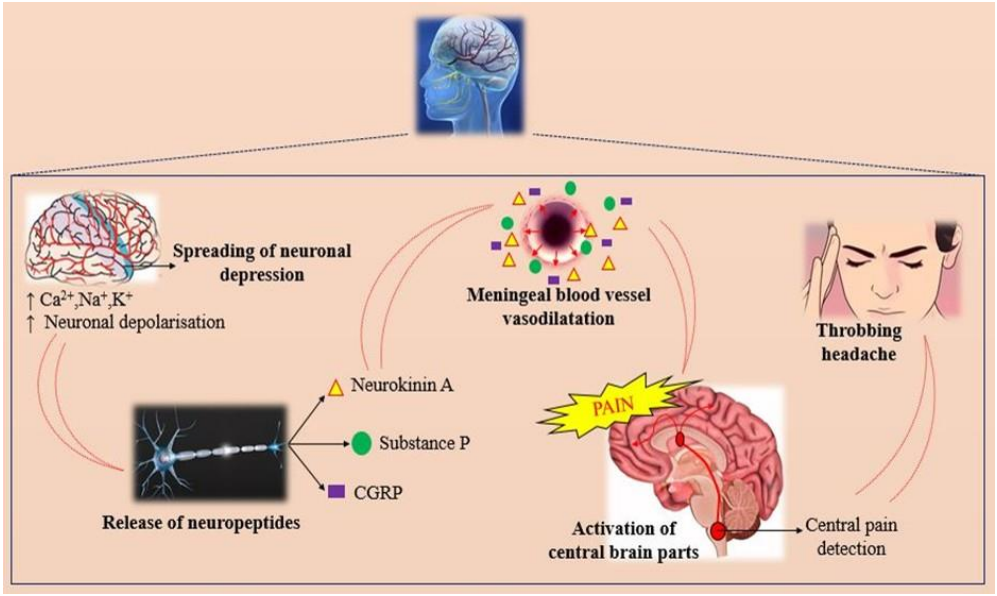

Figure 3: The spreading of cortical depression waves and activation of aura

Table 1: Signs and symptoms of migraine developed at different parts

Sl.No.	Part of symptoms	Signs and Symptoms
1.	Eye	Fluorescent or bright light Pressure at the back of eyes (Symptoms of chronic sinusitis) Ringing noise (Tinnitus) Imbalance (Ataxia) Exposure to wind (Allodynia) Sound sensitive
2.	Ear	Pain around the deep inner ear (Temporomandibular pain) Sensitiveness to smell (Osmophobia)
3.	Nose	Abnormal nasal congestion (Autonomic disorder)
4.	Face	Facial pressure across eye, nose
5.	Mouth	Deep tooth pain Oromandibular disorders
6.	Brain	Sleep deprivation or disorders Loss of cognitive functions Loss of central auditory controls, Temperature control

Table 2: Criteria for the diagnosis of migraine according to IHS

Sl.No.	Criteria for identifying migraine
1.	Migraine without aura A. At least 5 attacks accomplishing the criteria B-D must occur B. A headache lasts for 72 hours (treated or untreated) C. Headache has a minimum of two of the following characteristics i. Unilateral location ii. Pulsating quality iii. Moderate to a severe intensity of pain iv. Aggravation of the condition by or leading t the avoidance o routine physical activity (e.g. Exercise, running) D. During the life period of a headache at least one among below i. Nausea and vomiting ii. Photophobia and phonophobia E. Not attributed to another disorder
2.	Typical aura with a migraine A. At least 5 attacks accomplishing the criteria B-D must occur B. Aura must consist of at least one of follows, but no motor weakness is accompanied i. Completely reversible visual symptoms with positive characters (e.g. Flicking lights, lines, spots) or negative features (e.g. Loss of eyesight) ii. Completely reversible sensory symptoms with positive characters (e.g. Needles, pins) or negative features (e.g. numbness) iii. Completely reversible dysphasic speech disturbance C. At least two of the following criteria must be present i. Homonymous visual symptoms or /and unilateral sensory symptoms ii. At single aura characters developed during ≥5 minutes and varying aura symptoms occurring one by one over ≥25 minutes iii. Every symptom lasts for ≥5 minutes and ≤60 minutes D. Headache with B-D symptoms for migraine without aura begins during the aura or before 60 minutes E. Not attributed to another disorder

worldwide in females and males below the age of 50 years (Lipton, RB 2001). Mainly the pain disturbs one part of the brain but it will also be felt bilaterally in front and back of the head as progress. The effect of a migraine lasts up to 2-72 hours for each individual, which may be accompanied by nausea, vomiting and improved sensitiveness to smell, light and noise (Stewart, WF 1992).

The precise succession of events occurring during a migraine remains ambiguous. Medical profession regards that the intrusion originates in the brain and the nerves branching off from them. Due to the effect of chemical release and neuronal pathways, the bifurcated nerves from the brainstem gets overexcited, causing to bring about dilatation of blood vessels (Karthika, R 2016). The disease develops as a result of hormonal changes, emotional triggers, physical factors, changes in an environment, diet, lifestyle changes and effect of some medications which may induce a migraine, for example sleeping pills (Daniela, P 2003). The major

trigger factors leading to the advancement of a migraine in genetic factors which plays a prominent role in some cases of migraine development are shown in (Figure 1). Population-based studies significantly reported data on both migraines with aura and without aura, which signified that gene related factors are illustrated in both types (Salvatore, S 2009; Gian, CM 2003; Rami, B 2015). Thus multifactorial inheritance characteristics along with environmental components determine the phenotype properties asserted. The genetic etiology of a migraine with the hereditary relationship is seen in specific types like familial hemiplegic migraine where mutations are inherited throughout the generation in an autosomal dominant manner (fablo, 2016). Three genes related to ionic transport and an axonal peptide complex are accountable for the genetic link (Shefrin, S).

While considering some genetic disorders, they can be causes for the development of a migraine especially CADASIL, MELAS and genetic vasculopathies. CADASIL stands for Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (Thomas, NW 2012; Milan, 2012; Cenk, 2010). The disease portrays intermittent migraine attacks with aura, white matter decaying and repeated strokes. Similarly, MELAS is an infrequent, mitochondrial encephalopathy, lactic acidosis and stroke-like incidences affecting the nerves, brain and related muscles (Opherk, C 2009). They are associated with early symptoms like a headache, vomiting, weakness and pain which are lead causes of developing a migraine. Genetic vasculopathies involves attacks at specific target sites of the brain like by cortical spreading depression, endothelial dysfunctioning of vessels and retinal vasculopathy with cerebral leukodystrophy (RVCL) (Pfefferkom, T 2001; Charlotte, LR 2017; Cherubino DL 2012).

Signs and symptoms affecting different parts leading to the development of migraine are listed in Table 1. These develop prior to the occurrence of disease and thus helps in diagnosing the condition much earlier. But the symptoms are more in general so that specificity is less (Amrish, S 2009). Thus it is important to understand the different phases of migraine development and provide suitable treatment according to the severity. The four different phases of migraine are prodrome, aura, headache and postdrome (Amrish, S 2009). Phase 1 postdrome symptoms generate hours or days before the pain is hit and is featured by light and sound sensitivity, lack of appetite, fatigue and depression. Phase 2 defines the aura developing just hours before a headache characterised by the focal neurological phenomenon (Lipton, RB 2001; Peter, JG 2017; Giles, E 2002). The symptoms shown by this phase are more visual related like scintillating scotoma and sensory to motor effects like the feeling of pins on one side of the body. This leads to temporary loss of partial vision since the images visualised will be as flashing lights and symmetrical patterns (Olesen, J 2003). Phase 3 is the headache phase where intense pain is felt either in one or both sides of the head which can last upto three days. There may be a moderate to severe stage of unilateral head throbbing with neck pain which lasts upto several hours (Francis, MV 2016). Parallel symptoms like sweating or pallor, blurred vision and frequent urination may also be encountered. Phase 4 constitute the postdrome symptoms where there will be a sore or tender feeling at the area where migraine was affected (Michael, BR 2011; Grosberg, BM 2005). The patient will have impaired capacity to think logically due to the effects like tiredness, mood changes, general weakness and cognitive difficulties.

Migraine is a frequent chronic impairment of the CNS involved with the neurovascular disease. Thus the diagnosis of migraine depends upon the symptoms shown by the patient during the attack periods (Mark, KW 2015). The disease can be analysed by identifying the medical history, investigations like EEG, MRI and CT of the brain, CSF and blood biomarkers and identifying the migraine triggers (Alan, MR 2011; Samantha, I 2017; Starling, AJ 2015; MacGregor, 2003). Hence early detection of migraine and ideal therapy helps in improving the quality of life of patients. Thus to overcome the limitations of conventional drugs newer therapeutic molecules have been introduced to address the medical care of the disease (Marziniak, M 2005). In the review, at first, we primarily target the basic pathophysiology of migraine and the proposed theories related to the development of migraine, the classification and diagnostic methods (Monteith, TS 2011). Finally, a contrast analysis of conventional and alternative approaches involved in the treatment of migraine using novel nanocarriers are focused.

Migraine: Dominant evolution and pertinent theories

The throbbing pain felt at specific sites of the brain is mainly due to inherited alterations in brain excitation, intracranial arterial dilatation and recurrent activation, sensitization of the trigeminovascular pathway and considerable structural and functional changes occurring in genetically susceptible individuals as shown in Figure 2 (Ramon, C 2017). The disease is attributed to several theories governing the development and prognosis of migraine. The theories include vascular theory, cortical spreading depression, neurovascular theory and neurogenic inflammation pathway.

Vascular theory

Harrold G Wolff explained that the sudden constriction of intracranial blood vessels followed by spontaneous consequent vasodilation induces ischemic attack which is accountable for the activation of peripheral nociceptive vascular nerves culminating in headache pain (Arts, B 2008; Merikangas, KR 2011). The blood vessels present in the meninges covering the brain and continued to the spinal cord gets dilated and initiates such nociceptive signals (Hedvig, B 2009). The attack is stimulated by the release of vasoconstrictors which enhances the headache pain and aura symptoms and vasodilators which aggravate an attack.

Cortical spreading depression

The increased neuronal activity of the brain causes the cellular depolarization resulting in the cortical aura phase leading to a well-defined wave of neuronal excitation. The waves start to spread across the cortex region and thus activates the aura and related pain signals as shown in Figure 3 (Saroj, S 2012). The spreading of a wave throughout the cortical matter occurs at a rate of 2-5mm/min which in turn activates the trigeminal fibres causing the headache pain (Torrent, C 2012). Cellular depolarization caused by the self-propagating wave, spreads through cerebral cortex resulting in depressed neuronal bioelectrical activity and altered brain function, acting as a link to developing migraine aura and headache (Peit, B 2018). In this mechanism, it activates neurons in the trigeminal nucleus caudalis, resulting in inflammatory changes in the pain-sensitive meningeal vascular structures thus producing headache through central and peripheral reflex mechanisms (Charles, AC 2013). In this step, it alters the permeability of the blood-brain barrier (BBB) along with activation and up-regulation of brain matrix metalloproteinase.

Neurovascular theory

The theory is related to the influence of neural and vascular phases in the development of migraine. Due to the neurogenic effects of migraine, there may be secondary alterations in the blood flow to the cerebrum (Jafarian, M 2010; Caolyn, B 2012). This alters the BBB permeability and vascular environment of the cortex.

Neurogenic inflammatory pathway

The changes in the neuronal activity and blood flow results is resulted due to a release of chemicals in the brain to the surrounding tissues. Thus the dysfunctional parts of the brain initiate phases of events that eventually generate the symptoms of migraine (Claus, ME 2017). The extravascular neuronal activity results in the release of chemical substances like CGRP (Calcitonin gene-related peptide), NO (Nitric oxide), neurokinins, substance P, 5-HT etc. These further aggravate the vasodilation inflammatory cascade and protein extravasation leading to the stimulation of trigeminal neuronal complex. The activation and sensitization of trigeminovascular system include the progressive development of cephalic and whole-body cutaneous allodynia during a migraine attack (Bahra, 2001). In addition, other structural and functional alterations which contribute to the development of migraine include the presence of subcortical white mater lesions, thickening of cortical areas involved in processing sensory information and cortical neuroplastic changes induced by cortical spreading depression (Levy, D 2002). The increased excitability of cerebral cortex and abnormal control of pain neurons in the trigeminal nucleus of the brain stem. The three main steps involved in the development of migraine is the activation of the trigeminal vascular system, cortical depression and neuronal sensitisation.

The activation of a trigeminovascular system consists of many pseudounipolar sensory neurons which emerges from the trigeminal ganglion and upper cervical dorsal roots (Benjamin, L 2004; Zhang, X 2011). The aim of these sensory neurons is to reinforce large cerebral vessels, dura matter and large venous sinuses. Most of the anterior structures get stimulated through an ophthalmic division of trigeminal nerve, with a greater contribution of upper cervical roots to the posterior structures (Zhang, X 2010). The projections merge from the upper cervical nerve roots and the trigeminal nerve at the trigeminal nucleus caudalis, which lead to pain in the anterior and posterior regions.

Neuronal sensitisation

It is a process in which there is an increased response of neurons towards nociceptive and non-nociceptive stimulation (Bowyer, SM 2001). Such sensitisation causes decreased thresholds response, expansion of receptive fields, increase in response magnitude and development of spontaneous neuronal activity (Shilpi, P 2004; Alan, MR 2006). Mainly peripheral sensitisation occurs in the primary afferent neurons and central sensitisation occurring at high order neurons of the spinal cord and brain, plays an important role in somatic pain (Campos, F 2013). Some symptoms like allodynia and throbbing pain are related to these sensitisations originated, which alters the normal pathology.

Classes and features of different types of a migraine

The International Headache Society (IHS) has published the International Classification of Headache Disorders (ICHD), where the first category of the neurological syndrome was migraine. Migraine is mainly subdivided into two classes, migraine with aura (MA) and migraine without aura (MO) (Vaccaro, M 2007). Further classes include a chronic migraine, complications of migraine, probable migraine and episodic syndromes that may be associated with migraine.

Migraine without aura: Migraine without aura is a common headache which usually occurs in one side of the head with throbbing or pulsating pain, lasting for 4-72 hours when untreated or treatment fails (Rothrock, JF 2006). The prevalence of the disease in people having migraine is about 70-90% which is characterised by a representation of a headache with certain features with adjuvant symptoms. Some of the symptoms include photophobia, phonophobia, nausea, vomiting, pain, discomfort, pulsing or throbbing pain.

Migraine with aura: Migraine with aura, also known as a classic migraine, evolves along with sensory disturbances called an aura, where symptoms visual aura can be used to detect migraine easily. Some of the symptoms include blind spots, zigzag lines, changes in vision, a feeling of numbness and muscle weakness. People who are having migraine with aura are more prone to develop stroke (Landy, SH 2004). It primarily develops transient focal neurological symptoms before or along with the associated headache. Some of the triggering factors of migraine with aura include stress, bright light, increase or decrease in the duration of sleep etc.

Hemiplegic migraine: In hemiplegic migraine, there occurs paralysis on one side of the body and is also termed as migraine variant. The person might feel speech difficulties, confusion, vision problems and weakness lasting from 1 hour to several days, but the pain gets relived within 24 hours. When an impulse travel from one nerve cell to another, ligand-gated channel gates are opened, resulting in the release of neurotransmitters to the neighbouring cells (IHS, 2013). Any alteration in this mechanism of brain functioning, will alter the proper pathway and thus results in abnormal serotonin release pattern. A hemiplegic migraine is categorised again into a familial hemiplegic migraine and sporadic hemiplegic migraine.

Familial hemiplegic migraine (FHM): Such type of migraine is usually acute, with pulsating pain in one area of the head, convoyed by nausea, vomiting, sensitivity to light and sound. This migraine most often begins at childhood and adolescence stage (Lipton, RB 2001). The most prevalent symptoms related to an aura are flashing light, double vision, blind spots. People having hemiplegic migraine are portrayed by temporary numbness or weakness. Currently, there are three different types of familial hemiplegic migraines that have been identified by researchers, known as FHM1, FHM2 and FHM3 (Chirchjglia, 2016). Treatment differs depending on signs, symptoms and severity of the disease. Some of the drugs used for the treatment of a hemiplegic migraine are verapamil, acetazolamide, lamotrigine etc.

Sporadic hemiplegic migraine: The term sporadic means gene mutations, thus causing the etiology of migraine to be unclear. It has been found out that patients having sporadic symptoms might experience all four typical aura symptoms like visual, sensory, aphasic and motor symptoms among which mostly visual disturbance are seen (Re, G 2007).

Retinal migraine: Such type of migraine is generally occasional and varies distinctly from other types. A retinal migraine is also known as an ophthalmic migraine, visual migraine or ocular migraine. Approximately 1 in 200 people only have a retinal migraine among which women are more effected than men where it specifically affects the vision in one eye only (Vishal, J 2016). Thus it causes temporary blindness or visual problems in one eye, lasting for 1 hour and then returns to normal vision. A retinal migraine originates when there is reduced blood flow to the eye, due to the sudden narrowing of blood vessels, which returns to normal when the blood vessels get relaxed resulting in the disappearance of symptoms and gaining of lost vision (Codeluppi, L 2015). Some factors which prompt the development of retinal migraine are birth control pills, dehydration, smoking, stress, high altitude etc. (Kowacs, PA 2015; Lewinshtein, D 2004). Generally, people with a familial history of migraine and also who are aged 40 years or below with simultaneous disease condition like epilepsy, atherosclerosis are given treatment for a retinal migraine with NSAIDs like ibuprofen, aspirin, beta-blockers, antidepressants, anticonvulsants, calcium channel blockers etc.

Chronic migraine: Generally, chronic migraine attack develops more than once in a month thus called as an episodic migraine. Factors which prompt the development of a chronic migraine are sleep deprivation, hormonal changes, administration of caffeine etc. (Gan, KD 2005). A headache that occurs less than 15 times in a month is called episodic migraine which is a subcategory of a chronic migraine. In a year, nearly 2.5-4.6% people develop an episodic migraine which gradually

changes to chronic migraine (Lantrei, MM 2014). For the treatment of a chronic migraine currently on botulinum toxin A is the only FDA approved drug.

Complications of migraine

Status migrainous: The type of headache lasting for few hours to days or a migraine lasting for more than 72 hours is called status migrainous. Common symptoms of status migrainous are nausea, vomiting, vision changes. Drugs given for status migrainous include dihydroergotamine and sumatriptan which are available as nasal sprays, pills, patch etc. (Turgay, D 2010). But they are not given in case of people who are having blood vessel problems, wherein corticosteroids such as dexamethasone intensol, prednisolone is mainly preferred. Parental preparations are preferred than oral preparations for the treatment due to its prolonged gastric status.

Persistent aura without infraction: According to IHS, persistent aura without infraction is defined as the persistence of a migraine aura for more than a week without radiographic evidence of the infraction. Mainly for this rare condition visual function gets affected. Aura is mainly developed as visual symptoms such as bright spots, flashes of light. They are often bilateral and can last for months or years. The proposed mechanism of persistent aura is sustained rebounding of waves at the cortical spreading depression (Lo, EH 2003). Drugs given for such type of migraine include valproic acid and lamotrigine which act on the cortical spreading depression. The drug furosemide is also an effective therapeutic option.

Migrainous infraction: Migrainous infraction is a rare disease, mostly occurs in the posterior circulation and younger women with a history of migraine aura. There are chances of having an ischaemic stroke in patients with migraine aura. The mechanism behind migrainous infraction related to ischaemic stroke is undefined. Some of the symptoms of visual deficits are mild hemiparesis, aphasia etc. People are having such migraine are instructed to avoid smoking and the use of oral contraceptives, migraine triggering factors and medications which does not promote the migrainous infraction (Maureen, M 2016). Drugs given for the primary treatment of migrainous infraction include antihypertensive medications, statins and anticoagulants.

Migraine aura – triggered seizure: Migraine aura-triggered seizure is also called as migralepsy, where it mainly involves the development of a seizure which is triggered by an attack of migraine with aura. Epileptic seizure develops during or after one hour after a migraine aura attack. The prototypical examples of paroxysmal brain disorders are migraine and epilepsy. Other symptoms include nausea, vomiting followed by impairment or loss of consciousness and involuntary muscle movement.

Probable migraine: Probable migraine is also known as a migrainous disorder. They are divided into two types, probable migraine with an aura and probable migraine without aura (Boyer, N 2014). It is a prevalent migraine which frequently occurs, which mainly depend upon sex, age, health conditions etc.

Episodic syndromes associated with migraine

Cyclic vomiting syndrome (CVS): It is described as episodic attacks of intense nausea and vomiting with cyclic timing of episodes and complete resolution of symptoms between the attacks. CVS mainly begin at childhood where up to 75% of children will have attacks that start between midnight and early morning (Loder, E 2006). Mainly children may experience associated symptoms of lethargy, pallor, retching and abdominal pain about once per month and persist for 2-3 days.

Abdominal migraine: Abdominal migraine mainly affects children aged between 3-12 years old. Girls are likely to be more affected than boys where recurrent pain occurs from 2-72 hours accompanied by anorexia, pallor, nausea or vomiting. The pain of abdominal migraine is severely felt, which interferes with normal daily activities of the patient. For acute treatment of an abdominal migraine, oral medications such as analgesics, triptans, and anti-emetic are effective (Lesk, LJ 2001). Children having abdominal migraine are advised to take regular meals and also to keep a regular sleep schedule, maintain moderate exercise and avoid triggers.

Detection, analysis and interpretation of migraine

The examination of migraine can be typically done by analysing intermittent debilitating headache when compared to normal headache disorders. Migraine can be diagnosed through blood sampling and complete blood count analysis, computerised tomography, magnetic resonance imaging, spinal tap method (Mayeux, R 1998). Computerised tomography of the brain involves a combination of x-rays and computer technologies to produce more detailed axial and horizontal images of the brain. Magnetic resonance imaging provided a combination of large magnets, radio frequencies and a computer to produce detailed images of organs. A spinal tap is a special needle that is placed at the lower back into the spinal canal, around the spinal cord. A small amount of CSF (Cerebrospinal fluid) can be

removed and tested to determine whether there is an infection (Landenson, PW 1996; Riesco, N 2017).

The Headache Classification Subcommittee of the International Headache Society put forward the International Classification of Headache Disorders. The following Table 2 shows the different criteria on the basis of which the disease can be diagnosed.

Biological fluid markers for estimation of migraine severity

Presently the diagnosis of migraine is done in accordance with the criteria classification under the IHS where patients will be grouped according to the symptoms shown. But such identification criteria matter a challenge to doctors basically for diagnosing chronic conditions (Van, DRM 2017). Thus a more reliable and significant method of analysing the disease risk and prediction of forecasting the extent of condition is through the available biomarkers in the body fluids. These biomarkers help in identifying all stages of illness, differentiate subtypes of migraine, identify those who are a risk of developing the complications and monitor its development (Nagata, E 2009). A meta-analysis of migraine biomarkers done by Dongen et al. reveals that commonly detected compounds are CGRP (Calcitonin gene-related peptide), glutamate, homovalinic acid, nerve growth factor, β-endorphin and 5-hydroxyindole acetic acid. From these, the glutamate, nerve growth factor and CGRP concentrations were high in cerebrospinal fluid (CSF) of patients with migraine and β-endorphin levels were found to be low. The increase in the glutamate and CGRP levels may be due to the physiological alterations occurring during the disease condition (Imamura, K 2008; Kulka, M 2008; Keller, J 1991; Emeson, RB 1989). Glutamate comes under the class of excitatory neurotransmitter which is suspected to be released at the time of neuronal excitation of migraine and development of cortical spreading depression. The CGRP mediators are implicated to cause a migraine headache by activating the peripheral meninges nociceptive receptors (Erdling, 2013). The release of CGRP and other neurotransmitters further enhances its effect on the trigeminal vessels of neighbouring fibres. The NGF concentrations become high after induction of hyperalgesia by different inflammatory cascades like mast cell degranulation. Due to the inflammation occurring at central and peripheral areas, NGF along with CGRP expression gets elevated (Ertsey, C 2005). The β-endorphin levels were found to be lower in migraine patients due to their lower analgesic activity (Jain, SK 2003).

The advantage of the study was these changes were found to be seen in blood also except the nerve growth factor thus proving as efficient biomarkers for the diagnosis of migraine.

Yuasa et al. investigated a novel biomarker for migraine which can be used to identify the disease (Luthringer, R 2009). In his study, both migraines with aura and without aura were taken into consideration and which showed that in both groups there were significant levels of apolipoprotein (ApoE). The levels were highly altered in case of migraine with aura, particularly during the free period. During the cortical spreading of depression, various inflammatory mediators including cytokines and others from mast cells are released which sustains the effect of nociception during the migraine attacks. Along with this the endothelial cells and microglial cells are responsible for releasing the nitric oxide (NO) which produces vasodilation. This results in increased blood flow and low vascular resistance which contributes to the pain sensations during migraine attacks. The NO release is linked and regulated by ApoE mediated effect during such inflammatory conditions thus ensuring it as a key molecule for the diagnosis of migraine.

Approaches for drug delivery and treatment of migraine

The current therapeutic options for the treatment of migraine include acute and preventive treatment. Acute treatment aims to treat the fast occurring migraine without recurrence. It aims to stop the initial craving pain occurring on one side of brain and withhold the progression. The preventive treatment helps to decrease the frequency of attack, to enhance the response towards the treatment and improve the overall functioning (Ferrari, 2009). Some non- pharmacological therapies like relaxation classes, behavioural management, nutrition supplements and meditation are used for behavioural therapy of migraine.

The general methods to treat migraine include,

- Avoidance of recognised triggers
- Immediate treatment of acute attacks
- Preventive anti-migraine therapy

Acute migraine treatment: Immediate treatment of acute attack with medication is effective with the drugs available as OTC drugs. Also, specific drugs like triptans, ergot alkaloids, beta-blockers, antidepressants, anti-epileptic drugs, anti-serotonin drugs, calcium channel blockers and anticonvulsants are used [88]. The over the counter (OTC) drugs used for migraine treatment includes paracetamol, metoclopramide and NSAID's like aspirin, diclofenac, ibuprofen, acetaminophen, naproxen, tolfenamic acid and indomethacin.

Table 3: NSAID's and analgesics used for the treatment of an acute migraine

Sl.No	Drug	Dose	Route of administration
1	Phenazone	500-1000 mg	Oral & suppository
2	Metamizole	1000mg	Oral & IV
3	Tolfenamic acid	200 mg	Oral
4	Ibuprofen	200-800 mg	Oral
5	Diclofenac	50-100mg	Oral

Table 4: Currently available triptan medications in different brands

Sl. No.	Drugs	Brand name	Dosage form	Dose(mg)	Side effects
1	Almotriptan	Axert®	Tablet	6.25-12.5mg	Dry mouth, dizziness
2	Eletriptan	Relpax®	Tablet	20-40mg	Nausea, sleepiness
3	Rizatriptan	Maxlt®, Maxlt-MLT®	Orally disintegrating tablets	5-10mg	Warmth, numbness
4	Sumatriptan	Imitrex®	Tablet, Nasal spray injection	Dosage varies on severity	Hot flushing, drowsiness

Table 5: Antiemetics used for antimigraine therapy

Sl.No.	Drug	Dose (mg)	Route of Administration	Notes
1	Metoclopramide	10mg	IV	Sedation
2	Prochlorperazine	20-52mg	IV, IM	Extrapyramidal side effects
3	Ondansetron	4-8mg	IV	Devoid of sedation

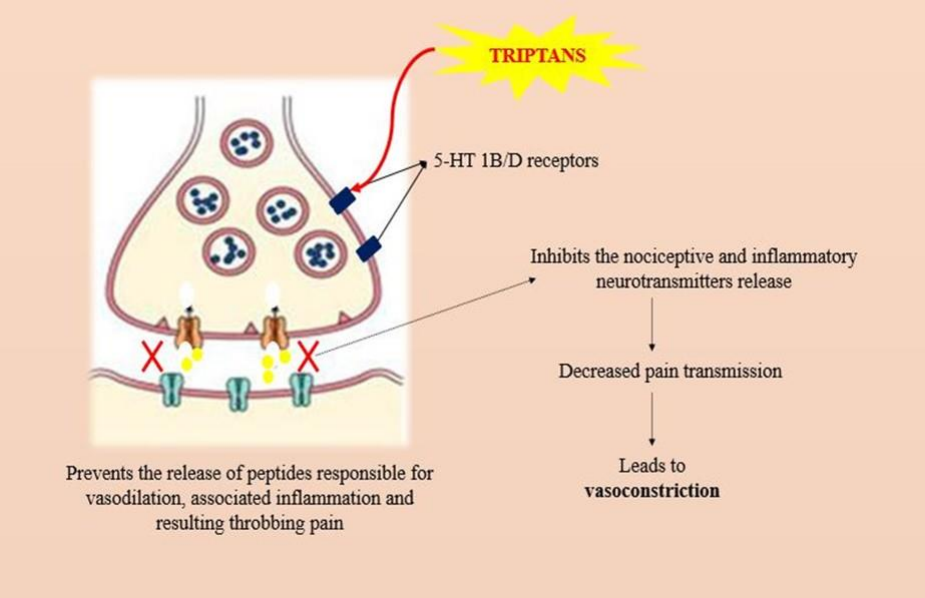

Figure 4: Mechanism of action of triptans

NSAID's: The mechanism of action of NSAID's is that the phospholipid membrane produces arachidonic acid in the presence of phospholipid A2 which results in prostaglandin H2. In the presence of cyclooxygenase during the formation of prostaglandin H2 it simultaneously produces thromboxanes and prostaglandins results in stimulation of migraine (Jhee, SS 2001). So NSAID's inhibits cyclooxygenase resulting decrease synthesis of prostaglandins. The NSAID's offer a nonspecific analgesic effect to the neurogenic inflammation occurring during migraine. They downturn the release of inflammatory proteins, which declines the stimulation of sensory neurons resulting in lowered free radical production and nociceptive activity (Djupesland, PG 2010). This also results in the depression of prostaglandin synthesis and their by controls the inflammatory pain reactions. Some commonly used NSAID's for the treatment of an acute migraine are listed in Table 3.

Combination analgesics like acetaminophen with dichloralphenazone and isometheptene mucate, acetaminophen with caffeine and aspirin are used for the treatment of a mild migraine. The several

classes of drugs which are given for the acute treatment of migraine are as follows,

Triptans

Triptans are selective 5-hydroxytryptamine receptor agonist which is used for the treatment of acute migraine. These classes of drugs are found to be efficient and harmless when administered immediately after the commencement of migraine attack. Thus such acute remedies do not help in the prevention of migrainous attack but necessitate in mitigating the symptoms associated with acute migraine-like pain, nausea and sensitivity to sound and light (Kaniecki, R 2003). These agents are well tolerated, but their responses depend on individuals and are changeable. Based on the mechanism of action of a triptan, two prepositions were put forward. The first preposition suggests that the intracranial blood vessels which include arteriovenous anastomoses undergo constriction by the 5-HT1B receptor. During migraine carotid arteriovenous anastomoses in the head undergo dilatation but its causes are still uncertain. The flow of blood through the carotid artery which constitute about 80% is averted through anastomoses situated in the scalp and the ears. There will be oozing out of blood in the capillaries which ultimately lead to tissue oxygen deficiency and reduced blood flow through cerebrum. An ideal and effective antimigraine drug should be able to divert and reverse the flow of blood through cerebrum. Triptan has the affinity for 5-HT1D and 5-HT1B receptors and not with other 5-HT receptors. The drug does not act on receptors like α1-, α2-, and β- adrenergic, dopamine, cholinergic muscarinic and benzodiazepine receptors. The affinity for the 5-HT1B and 5-HT1D receptors determines the dose of triptan. Secondly, it states that the secretion of proinflammatory neuropeptides on the nerve terminals of perivasculature blocks the 5-HT1D receptor agonists (Wooltorton, E 2006). The migrainous headaches are caused not only because of the cranial vasodilation but also due to neurogenic inflammation which is an inflammatory process. The traction of the perivascular nerve fibres due to the dilatation of arteries leads to the depolarization of fibres as well as releases neuropeptides like substance P and calcitonin gene-related peptide (CGRP) from c and Aδ nerve fibres respectively which in turn causes the generation of action potential which is transmitted to the brain and spinal cord (the main centres of central nervous system) that subsequently leads to artery dilation and activates the pain pathway. From the above prepositions and several other studies conducted, we can draw into a conclusion that triptan has mainly 3 mechanisms of action through which acute attacks of migraine can be controlled. The mechanisms include initiation of vasoconstriction of cranial nerves, blockage of peripheral trigeminal activity, and blockage of trigeminal afferents.

The triptans act by constriction of the extracerebral intracranial vessel and thereby blocks the release of neurotransmitter (vasoactive peptide) that transfers nociceptive instructions to the thalamus. They block the peripheral and central nociceptive ends through 5-HT 1B/1D receptors as shown in Figure 4. The first generation of medication, Sumatriptan is the oldest and the standard gold drug for the treatment of migraine. Second generation triptans like zolmitriptan, eletriptan, rizatriptan were developed to overcome the lower bioavailability profile and showed enhanced kinetic patterns. The triptans are avoided in cases like breastfeeding, chronic liver and kidney failure, heart disease where vasoconstrictive effects will be shown to produce a detrimental effect (Ferrari, MD 2002). The triptan medications currently available in the market are listed in Table 4.

5-HT antagonists

The class of drugs which can block the action of serotonin receptor or 5-hydroxytryptamine (5-HT) are known as serotonin antagonist. Serotonin receptors are a group of G-protein coupled receptors and ligand-gated ion channels in the central and peripheral nervous systems. The serotonin receptor modulates the release of many neurotransmitters, for example, GABA,

glutamate, dopamine, epinephrine and acetylcholine etc. For the treatment of different migraine types, 5-HT antagonists used are non-selective agents, but this drug acts mainly on 5-HT 2A receptors. The 5-HT receptors are responsible for the excitations, which are located at the C-fibre nerves to the PNS and pain modulating sites in CNS. The medication blocks the neural inflammation at the trigeminal nerve and thus reduces the pain (migraine). The 5-HT receptors are of seven types among which 5-HT1 itself is having several classifications like A, B, D, E and F. The trigeminal nerve endings have 5-HT1D/1F receptors, which on antagonism inhibits the release of substance P and Calcitonin Gene Related Peptide (CGRP). The 5-HT®®receptors get stimulated in the cerebral blood vessels which causes vasoconstriction. Similarly, the inhibitory serotonin receptors inhibit the release of other neurotransmitters and vasoactive peptides.

Serotonin reuptake inhibitor

Serotonin reuptake inhibitors (SSRI's) inhibit the reabsorption of serotonin thus results in an increased extracellular level of serotonin in the synaptic cleft. Serotonin acts as a definite neurotransmitter in migraine, and the level of it is controlled in the blood circulation, by giving an intravenous

injection which aborts the migraine attack. But non-selective serotonin produces both beneficial and deleterious effect in the central nervous system and therefore not used as primary therapy (Tepper, SJ 2001).

Ergotamine derivatives: Ergotamine and dihydroergotamine were two classes of drugs which were used as first-line anti-migraine drugs. They have been surpassed in patients by the triptans due to their inferior effectiveness since it has more side effects like coronary vasoconstriction. They are used in combination with antiemetic for the emergency needs and showed lower recurrent headache when compared to triptans. Ergot derivatives along with caffeine combination pills are still used for patients having an inadequate response to triptans (Reuter, U 2006).

Antiemetics: These class of drugs offers nonspecific pharmacological treatment for migraine. They are even used in combination with prompt triptan therapy when a headache continues for more than 2 weeks. IV metoclopramide, prochlorperazine are considered as monotherapy regimens for acute migraine conditions. They are dopamine receptor antagonist thus acts as an effective antiemetic drug. They are used in combination with NSAID's for controlling the vomiting and promote antinausea effect (Lofland, JH 1999). Some antiemetics commonly used for antimigraine therapy are listed in Table 5.

Approach by new FDA approved drugs for migraine

Topamax (100mg) was the first FDA approved drug for prophylactic treatment of migraine in the younger population. Treximet (Sumatriptan and Naproxen sodium 85/500mg) is used in case of a menstrual migraine. Zomig (5mg) is zolmitriptan nasal spray for the acute treatment of migraine in teenagers. Botox® was FDA approved onabotulinumtoxin A used in the treatment of chronic conditions in adults as 12 weeks multiple injection therapy at head and neck.

Improved delivery approaches for the effective treatment of migraine

The major limitation of CNS acting drugs includes their side effects due to the drug, dose as well as the route of administration. Novel methods aim to overcome the problems of the conventional methods of treatment and helps to narrow the wide medication regimens used. They offer better clinical outcome for the patients by improving patient compliance, bypassing of first-pass metabolism and GI degradation and fewer side effects. Thus they offer a great advantage to patients perceiving constant gastric problems like nausea, vomiting, gastric irritation which is seen with migraine pain.

Intranasal drug delivery: The intranasal delivery of anti-migraine drugs is more effective than any other routes such that it bypasses first pass metabolism. There are three main absorption routes for the intranasal route, firstly they get directly into the central nervous system, or to the gastrointestinal tract or directly to the systemic circulation. The intranasal route of drug delivery provides relief within 15 minutes due to its fastest pathway to the brain directly. According to Alan Rapport et al. the intranasal delivery is a non-invasive mode of drug delivery where the main advantage of administering the drug through intranasal route is absorbed directly by the highly vascular mucous membrane which results in rapid delivery of un-metabolised drug to the central nervous system. The route is highly useful and easy to use in case of severe vomiting and nausea patients. Currently, available formulations of intranasal delivery are of zolmitriptan, sumatriptan and dihydroergotamine. Intranasal delivery bypasses drug absorption at gastrointestinal tract, and thus the adverse effects are less when compared to other routes (Srivastava, SS 2004).

The nasal spray of Sumatriptan is used in patients for an acute migraine with/without aura. According to USP, 5mg, 10mg and 20mg doses are available. They bind with the inhibitory 5-HT receptors and produces intracranial blood vessel constriction and thereby depletes the release of the proinflammatory neuropeptide. OptiNoseTM, a breath triggered a nasal drug delivery device which was proven to show enhanced displacement of the drug through the layers of olfactory cells, which provided expeditious systemic absorption. The Phase I clinical studies depicted considerably pervasive amounts of drug reaching the systemic absorption, thus proving better kinetic characteristics than existing Sumatriptan nasal spray (Saxena, PR 1989).

Transdermal route: This route is a non-invasive and innovative route for rapid relief and effective treatment of migraine. According to Michail Vikelis et al., the drug molecules were delivered through a skin patch, where it needs a minimum amount of electrical potential which allowed the faster delivery of ionised medication transdermally into the systemic circulation. The device consists of a thin patch with two shallow wells acting as electrodes, containing the chemicals were non- woven pads are placed on top. The cathode consists of a negatively charged salt solution whereas positively charged Sumatriptan solution is filled in the anode. When a low intense electric potential is applied between two electrodes, due to the effect of electric and magnetic fields it produced movement of ionised drug from anode via skin the layers.

ZelrixTM is an iontophoretic drug delivery system through a transdermal patch using such electric current. Such electric fields developed produces ionised drug particles which bypass the GIT transit and first-pass metabolism and thereby reaches the systemic circulation directly. The kinetic studies performed depicted that the rise in plasma drug concentration was following a uniformity and the option of transdermal drug delivery was efficiently utilized to lower the triptan associated side effects (Rolan, PE 1998). Some other currently arising devices for migraine therapy include transcranial magnetic stimulation and transcranial direct current stimulation which have been used in painful conditions of migraine. These non-invasive methods target the anterior occipital cortex where the primary wave of depolarisation causing hypoperfusion in migraine arises. These are among the promising devices which are now under investigation and can be used as alternatives to existing therapy if proven safe and efficacious (Goadby, PJ 1998).

CONCLUSION

Migraine attack is characterised by an intense headache along with associated disabilities such as nausea, vomiting, sensitiveness to light and alteration in excretion status etc. The disease is one among the most commonly occurring category of headache diseases and thus initial interpretation and instantaneous cure help in developing the overall quality of life the patients. The existing therapies include both specific and nonspecific pharmacological actions. They include the treatment of acute and preventive migraine. The review highlights the basic structure of the disease and the development of new and targeted therapy. The current treatment strategy aims to target the root cause and eliminates the basic proteins itself to achieve the desired therapeutic action so as to prevent the development of an intermittent migraine to chronic stages. The newer novel antimigraine therapies have proven to be widely recognised among the global market for the migraine sufferers with a narrow and effective therapy.

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