OVERVIEW OF MIGRAINE - PATHOLOGY SYMPTOMS AND MANAGEMENT

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ABSTRACT:

Migraine is a paroxysmal neurological disorder with multiphase attacks, disposes to unilateral pain with pulsating quality that comes in attacks and lasts up to 4-48 hours and varies in its frequency, severity and impact. About 11% of global population experiences migraine. Broadly, migraine is of 2 types, Migraine without aura and Migraine with aura. About 80% of migraine sufferers don't experience Aura. It is caused by many environmental triggers, food, and genetics. Vascular theory implicates humoral mediated intracerebral vasoconstriction causes aura followed by an extracerebral vasoconstriction causes headache. It is diagnosed based on International Classification of Headache Disorders(ICHD) guidelines and severity by four- level rating scale and 11- point Visual Rating Scale (VRS). It might be treated with aspirin, acetaminophen, and caffeine as first line therapy. Triptans and dihydroergotamine nasal spray as second and third line therapy respectively. Migraine attacks could be prevented by using prophylactic drugs and by avoiding triggers.

KEY WORDS: Migraine, Brain hypotheses, International Classification of Headache Disorders, Visual Rating Scale, Sumatriptannasal spray.

INTRODUCTION:

Pain is an unpleasant physical sensation which is generally classified in terms of nociceptive and neuropathic pathways. Migraine pain follows a neuropathic pathway in which the pain pathology originates from nervous system. Many neuropathic pain syndromes exist and they are clinicallydifficult to treat,shooting,exaggerated,painful response to eitherAllodyniaor for patients who describe their pain as tingling, burning hyperalgesia[1].Headache disorders are one of the worldwide health concern disorders that affect individuals regardless of ages, races, socioeconomic statuses, and all geographical areas[2].Even though they are common and

sometimes debilitating often accompanies with nausea, photophobia, and sensitivity tosound[3].Migraine is confused with many types of headache disorders like tension-type headache, cluster headache, Medication-overuse headache, trigeminal autonomic cephalalgia etc.Treatment is effective for all types of headaches.

Migraine is a mysterious disorder that accounts for unilateral pain with pulsating quality that comes in attacks and lasts up to 4-48 hours, accompanied by nausea, vomiting, sensitivity to light, sound and flashes of light, vertigo, loose motions, and other symptoms based on phase of migraine[4]. The term migraine is derived from the Latin word *Hemi crania* (Hemi= Half, Crania= Skull) which itself indicates unilateral pain, occurs mostly in migraines than in cluster headaches which affects 1 in 1000 people[5]. The prevalence rate of migraine varies in men and women of western countries i.e. 4 to 9% in men and 11 to 25% in women whereas, Non-Western countries report shows that 1.5 to 6 per 1000 persons in men and3 to 24 per 1000 persons in women. Data on the prevalence of migraine for gender ratio and different age ranges are fairly comparable and close to reality[6].It is estimated that 11% of the global population [7-9] including 3% of Indians [10, 11].

CLASSIFICATION

The migraine classifications are configured by the International Headache Society, and revealed in the International Classification of Headache Disorders (ICHD).ICHD-1 was first published in 1988. Then, ICHD-2 and the current version ICHD-3 were published in 2004 and 2018 [12].The ICHD-3 beta classification involves 6 main subtypes of migraine. They are Migraine without aura, Migraine with aura, chronic migraine, Complications of migraine, Probable migraine andepisodic syndromes that may be associated with migraine[13].

1. Migraine
    1.1. Migraine without aura
    1.2. Migraine with aura
        1.2.1. Migraine with typical aura
            1.2.1.1. Typical aura with headache
            1.2.1.2 .Typical aura without headache
        1.2.2. Migraine with brainstem aura

1.2.3. Hemiplegic migraine

1.2.3.1. Familial hemiplegic migraine (FHM)

1.2.3.1.1. Familial hemiplegic migraine type 1 (FHM1)

1.2.3.1.2. Familial hemiplegic migraine type 2 (FHM2)

1.2.3.1.3. Familial hemiplegic migraine type 3 (FHM3)

1.2.3.1.4. Familial hemiplegic migraine, other loci

1.2.3.2. Sporadic hemiplegic migraine (SHM)

1.2.4. Retinal migraine

1.3. Chronic migraine

1.4. Complications of migraine

1.4.1. Status migrainosus

1.4.2. Persistent aura without infarction

1.4.3.Migrainous infarction

1.4.4. Migraine aura-triggered seizure

1.5. Probable migraine

1.5.1. Probable migraine without aura

1.5.2. Probable migraine with aura

1.6. Episodic syndromes related to migraine

1.6.1. Recurrent gastrointestinal disturbance

1.6.1.1. Cyclical vomiting syndrome

1.6.1.2. Abdominal migraine

1.6.2. Benign paroxysmal vertigo

1.6.3. Benign paroxysmal torticollis

Table 1: Classification of migraine as per ICHD-3 guidelines andtheir symptom's,frequency of attack,and its duration.

Type	Symptoms	Frequency of attack	Duration
Migraine without aura(Common migraine)[14, 15, 16]	Tinglingand numbness spreading over the hand,arm,face,lips,weakness,dysphasia	1 /month	Headache last from 4 to 72 h

Migraine with aura[4,17, 18]	Recurring headache,in tensed head pain, nausea, sensitivity to light and sound.	>12/year	<1 h
Chronic migraine [19, 20]	Severe headache	>15/month	15 days/ month
Complications of migraine [13, 21,22, 23,25]	Migrainous infarction, Migraine-triggered seizures	1-3/month	4-12.5 h
Probable migraine [22, 24]	Poor sleep, Vomiting, Photophobia, Phonophobia	5/year	4 to 72 h
Episodic syndrome [13, 26]	Cyclic vomiting syndrome,abdominal migraine	8/month	4-72h

Based on severity and frequency of attacks, Mild migraine is less than one attack per month of throbbing and it last up to 8 hours. Moderate migraine - When the throbbing headache is more intense, lasts for 6-24 hours, one or more attacks occur per month. Severe migraine patients suffer 2-3 or more attacks per month of severe throbbing headache,lasting 12-48 hours [4]. Other types of migraine include Ophthalmologic Migraine in which neuralgia accompanied by palsy of an ocular cranial nerve during the headache phase and retinal Migraine in which monocular symptoms of retinal vascular involvement during migraine [27].

Etiology: The predisposing factorsof migraines are: i. Migraine is hereditary, if one or both parents with migraine there are 50-75% chances to get in younger generations[28]. Patients with a variation on chromosome 8 between two genes called PGCP(Plasma Glutamate Carboxypeptidase Precursor) and MTDH/AEG-1 that helps control a brain chemical called Glutamate have a significantlygreater risk of developing migraines[29, 30]. ii. Hormonal, Migraine precipitates when hormone levels fall to low and fleed away when hormone levels attain peak[31].iii.In accordance with the National Headache Foundation, foods including all the nuts along withpeanuts, pecans, walnuts, sesame seeds, pumpkin seeds, sesame seeds, walnuts and pecans can trigger headaches. Nuts contain large amount of Tyramine. For people sensitive to Tyramine, peanut butter and other products containing nut oils are also dangerous[32].Many people can't notice foods that trigger migraines, to rectify this American Headache Society advised to keep a food diary and track migraine activity thereby avoid foods that seem to trigger migraines. The most common migraine triggers are capable of generating

oxidative stress, except pericranial pain. Triggers and itsmechanisms determines energy productionrate,membrane protein alterations, that are noxious by the mitochondria, calcium overload, excitotoxicity, neuroinflammation and activation of microglia, and activation of neuronal nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. For some triggers, oxidants also arise as a byproduct of monoamine oxidase or CYP P450 processing, or from uncoupling of nitric oxide synthase[33].

Pathophysiology: Research has revealed that nitric oxide (NO) and calcitonin gene-related peptide (CGRP) do have roles in the pathogenesis of a migraine without aura[34, 35].Several studies have shown that migraines without aura develop in most subjects after the infusion of glyceryltrinitrate which is known to transport NO to tissues [36, 37], but only in patients who are migraine sufferers [38].In spontaneous attacks of migraine without aura[39], nitric oxide synthaseenzymes (NOS) inhibition byL-nitromonomethylarginine (L-NMMA) successfully reduced pain severity (in contrast with a placebo).

The main hypotheses were developed for migraine as follows. i. Vascular theory: This theory implicates humorally mediated intracerebral vasoconstriction causes aura followed by an extracerebral vasoconstriction causing the headacheas givenin the Fig. 1[40].

Role of serotonin in migraine:serotonininvolved in the regulation of pain in the nervous system. Serotonin levels drop during migraine attacks. This may cause trigeminal nerve to release neuropeptides, which travel to the brain through meninges which develop migraine pain. Neurotransmitters like calcitonin gene related peptide (CGRP) play a role in the pain of migraine, including Serotonin syndrome in which too much of serotonin is released by the body and it is a rare, potentially life threatening condition [41].

ii. Brain hypotheses: This phenomenon is linked to cortical spreading depression. A self-propagatingwave of profound neural inhibition progresses slowly over the cortical surface at a rate of about 2mm/min. In an affected area, the ionic balance is badly disturbed, with an extremely high extracellular K+ concentration, and the blood flow is reduced [42].

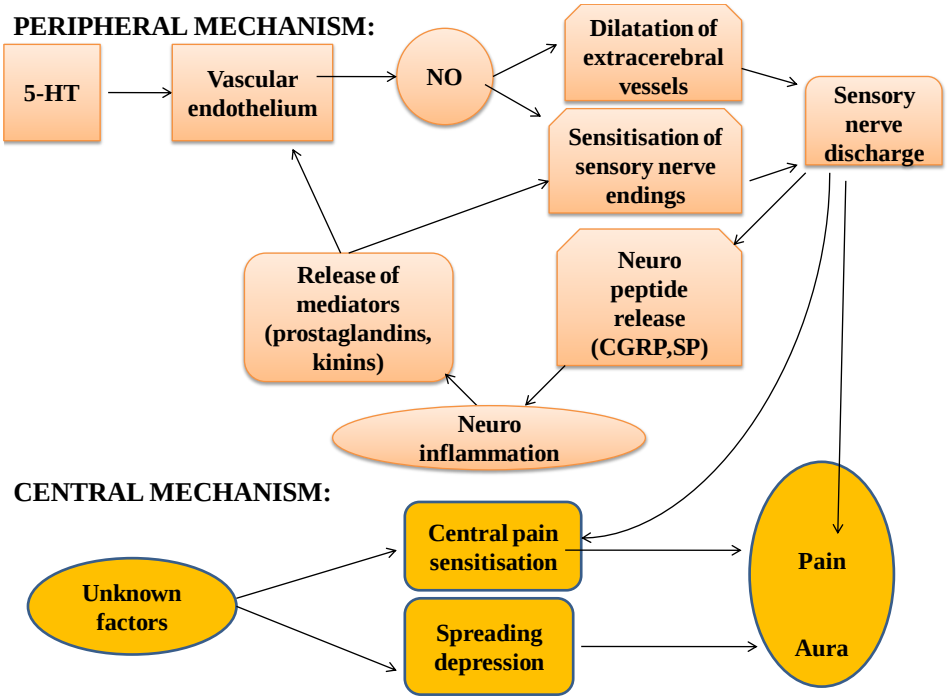

Fig. 1: Pathophysiology of Migraine

iii. Inflammation hypotheses: This theory proposes that activation of trigeminal nerve terminals in meninges and extra cranial vessels is the primary event in a migraine attack. This would cause pain directly and also induce inflammatory changes through the release of neuropeptides and other inflammatory mediators from the sensory nerve terminals (calcitonin gene related peptide) is released into the meningeal circulation during a migraine attack. An antagonist for this peptide is Telcagepant (an investigational drug) which is discontinued because of its liver toxicity, was extremely effective in aborting attacks[43].

Phases of migraine:

A Migraine attack without head ache described as"silent" or "acephalgic" given in Table 2 [44]. A migraine attack can be divided into 4 phases. They are: Premonitory or prodrome phase, Aura phase, headache phase, and post dromal phase [45, 46].

Table 2: Various phases, symptoms and duration of Migraine

Phases	Symptoms	Duration
Prodrome	Yawning, Excitation, Depression, Lethargy, craving	15-20min
Aura	Flashing of lights, Zigzag line,	15-30 min

	Difference in focusing.	
Headache	Anorexia, Nausea, Vomiting, Photophobia, Phonophobia, tinnitus.	4-72hrs
Postdrome	Fatigue, Depression, Severeexhaustion	Few hours (or)up to 2 days

Diagnosis:

Migraine is a condition that is mostly mistaken as other type of headaches. In some cases, it is left undiagnosed, untreated, and lead to complications[47].Diagnosis made through history about medical(including questions about depression, anxiety and sleep disorders), current non headache medications, allergies, family history(especially of headache), social history(including occupation, smoking status, levels of alcohol and caffeine consumption) Other than that ruling out with the help of orthopaedic tests, cranial nerve examination, complete blood count, urinalysis and cranial magnetic resonance imaging was performed if required[17]. Imaging techniques have revealed wide spread changes in brain perfusion. There may be hyperperfusion in some areas and hypo perfusion in other areas suggesting relationship between brain activity and blood flow become disengaged. Such neurovascular uncoupling is a character of cortical spreading depression. The typical constellation of symptoms experienced by migraine sufferers is reflected in the ICHD criteria for the diagnosis of migraine[17].The International Headache Society, developed its criteria for diagnosing migraine in 1988, and the most recent guidelines were published in 2013(ICHDIII).

International Classification of Headache Disorders diagnostic criteria for migraine [43].

(1) At least five attacks per year.

(2) Headache that lasts 4–72 hours, that left untreated or unsuccessfully treated.

(3) Headache has at least two characters among (a) (b) (c) (d): They are (a) Unilateral location, (b) Pulsating quality, (c) Moderate or severe pain intensity, (d) Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs).

(4) During headache at least one of (a) and (b) occurs:(a) Nausea and/or vomiting and (b) Photophobia and phonophobia.

Scales used to test migraine intensity:A categorical, four- level rating scale should be used to rate each headache as absent, mild, moderate, or severe. Intensity alone is not recommended

as a primary outcome measure, but it is important to record a decrease in migraine intensity as an indicator of reduced disability. Subjects should be instructed to record the intensity of each migraine day. An 11- point VRS can be used as an alternative to or in association with the four-level categorial scale. Use of VRS increases likelihood of being able to show a difference in severity[49].A headache that lasts at least 4 hours in a day is defined as a migraine day; that meets ICHD –III criteria.

Treatment: Migraine is biopsychosocial disorders, which involves biological, social and psychological factors, so that it requires comprehensive non pharmacological treatment which is classified into four broad categories [50].They are: I Relaxation training II Temperature biofeedback (for hand warming) combined with relaxation training III Electromyography (EMG) biofeedback (for muscle tension reduction) IV Cognitive behavioral therapy. Use of physical treatment such as acupuncture, cervical manipulation, and mobilizationtherapyas preventive therapy for migraine has also grown in the US[43].

I.Relaxation training: Relaxation training procedure (progressive muscle relaxation) goals to achieve a relaxed state to a patient through a series of muscle exercises and controlled breathing and finally modifies headache-related physiological responses, reduce arousal of the nervous system, and decrease muscular tension[51].

II.Temperature biofeedback (for hand warming) combined with relaxation training. Both Relaxation training and Thermal Biofeedback training consisted of training in progressive muscle relaxation, breathing exercises, and thermal biofeedback. Treatment included the following: (i) the first two sessions comprised relaxation training education regarding the Pathophysiology of head ache and the rationale for relaxation training as a treatment for headache, and training in deep-breathing exercises. (ii) The third and fourth sessions comprised they had previously been taught. Subjects were given homework assignments to practice skills they had learned in treatment twice daily, and were provided with audiotapes of relaxation exercises and portable thermal biofeed- back devices. Home practice sessions were 20 to 30 min each [52].

III.Cognitivebehavioral therapy: Goals to achieve strategies that minimize headache related disability. This helps to recognize patient's unique behavioral risk/trigger factors for headache (often including stress, sleep disruption, and skipping meals) thereby reducing them[53].

Pharmacological treatment: Guidelines from American Academy of Neurology, for treatment of migraine as given inTable 3. They all work best if used them when the migraine is just beginning. Therapy would be started with aspirin/acetaminophen/caffeineor withNSAIDs such as ibuprofen or naproxen.If these drugs fail to relieve headaches, triptans may be used.Dihydroergotamine nasal sprayworks even better as an injection in case of failure of sumatriptan.

Based on severity the migraine can be treated as follows: For mild migraines, Simple analgesics like paracetamol (0.5-1g) or aspirin (300-600mg) taken at the first indication of an attack and repeat the dose 4-6 hourly can prevent development of most mild attacks. Non-steroidal anti-inflammatory drugs and their combinations drugs like ibuprofen(400-800 mg 8 hourly), naproxen(500mg followed by 250mg 8 hourly), diclofenac (50 mg 8 hourly), mephenamic acid (500 mg 8 hourly), indomethacin (50 mg 6-8 hourly) either alone or in combination with paracetamol/codeine/diazepam or another sedative/diphenhydramine or another antihistaminic/caffeine are found more satisfactory by some patients. These drugs are more effective in migraine without aura, but certain patients of migraine with aura also prefer over specific anti migraine drugs like 5-$HT_{1B/1D}$ receptor agonists /ergot alkaloids).Drugs are taken only till the attack passes off. Taken in the prodrome stage they can also abort an attack, but long term treatment on a regular schedule to ward off migraine attack is not advised. Antiemetic gastric stasisoccurs during migraine which delays absorption of oral drugs. So metoclopramide (10mg oral/IM) is frequently used it relieves nausea, vomiting and gastric stasis. When the patient has already vomited, it is better to take the antiemetics by injection. Domperidone (10-20 mg oral) and prochlorperazine (10-25 mg oral/IM).Diphenhydramine or promethazine exert both sedative and antiemetic action.

Moderate migraine: Simple analgesics are usually not effective, but stronger NSAIDs or their combinations are beneficial. The remaining is treated with a specific ant migraine drugs like 5-$HT_{1B/1D}$ receptor agonists/ergot alkaloids). 5-$HT_{1B/1D}$ receptor agonists include Sumatriptan, almotriptan, eletriptan,frovatriptan, naratriptan, Rizatriptan, zolmitriptan. Among them, the triptan, eletriptan followed by Rizatriptan has higher headache response rate and safety profile. They should not be used more than 2-3 times in a week to prevent the emergence of medication overuse headache. They must be avoided in individual with cerebrovascular and cardiovascular diseases.Antiemetics are almost regularly needed. Prophylactic therapy is advised only when attacks are more frequent than 2-3 month.

Severe migraine: Analgesics/NSAIDs and their combinations usually don't afford adequate relief. Specific drugs have to be prescribed along with antiemetics.Triptans cause vasoconstriction of painfully dilated cerebral blood vessel, Inhibition of the release of vasoactive neuropeptides by trigeminal nerves and inhibition of nociceptive neurotransmission[4].

Triptans are the first-line treatment for severe migraines as they are highly effective, with a low risk of side effects. A combination of triptan and NSAID may be more effective than either medication alone.Sumatriptan initial oral dose of is 25-100 mg maximum dose 200 mg and it is safe in pregnancy. Initial nasal dose is 5-20 mgrepeat in 2 hours, maximum dose is 40 mg when it is used during Nausea/vomiting or rapid peak in migraine intensity. Initialsubcutaneous dose is6 mg, may repeat in 1 hour, maximum dose is 12 mg and Used during Nausea/vomiting or rapid peak in migraine intensity. Rizatriptan initialoral dose is 5-10 mg, may repeat in 2 hours, maximum dose is 30 mg Prescribe 5 mg dose with concomitant administration of propranolol. Naratriptan initial oral dose is 1-2.5mgmay repeat in 4 hours, maximum dose is 5 mg. People with ≥ 3day headaches (long half-life) be treated with naratriptan[53].If migraines are often, or if they are very severe, drugs to prevent headaches should be used.The recommended Prophylactic regimen lasts 6 months.

Prophylaxisof migraine: Preventive therapy reduces migraine frequency, severity, and headache-related distress.It can improve quality of life and impedes migraine complications. Preventive therapy is indicated mostly for moderate, severe, debilitating and medication-overuse headaches. The useful strategy to prevent migraines is to identify and manage the environmental, dietary and behavioral triggers.First-line medications established as effective supported clinical evidence include divalproex, topiramate, metoprolol, propranolol, and timolol[54].There's also strong evidence supporting frovatriptan as short-term prevention for menstrual migraines [55]. Medications such as amitriptyline, venlafaxine, atenolol, and nadolol are probably effective but should be second-line therapy [52]. Naratriptan and zolmitriptan may be effective preventives for menstrual migraine [53]. Recently, U.S. Food and Drug Administration approved new drugs that target on calcitonin gene-related peptide pain transmission. However, more studies of long-term effectiveness and adverse effects are needed. The complementary treatments petasites, feverfew, magnesium, and riboflavin are probably effective[54].It may be prudent to discontinue prophylaxis every 6 months to check whether its continuation is needed or not. It is important to avoid the precipitating factors [53].

β-adrenergic blockers: Propanolol is the most commonly used drug and first line medication to prevent migraine used to reduce frequency as well as severity of attacks upto 70% patients. Generally, effect is observed in 4 weeks and is sustained during prolonged therapy. The starting dose is 40 mg BD, which may be increased up to 160 mg if required.The mechanism of action is not clear. That it is due to β adrenergic blockade has been questioned. Some drugs having intrinsic sympathomimetic action and pindolol are not useful and timolol(nonselective) and Other nonselective (timolol) andmetoprolol, atenolol (β1 selective) agents are also effective.

Tricyclic antidepressants: Among many tricyclic compounds, amitryptyline (25-50 mg at bed time) most extensively reduce migraine attacks. They are more effective in many patients but had more side effects than propranolol. It is not known thatitsprophylactic effect and 5-HT uptake blocking property is causally related or not.The antimigraine is independent of antidepressant property, but this class of drugs is better suited for patients who also suffer from depression.

Calcium channel blockers (CCB): Verapamil can reduce migraine attacks, but was judged inferior to propranolol. A relatively weak CCB, flunarizine also inhibits Na+ channels. The convincing proof is lacking for the effectiveness of propranolol. Less documents are available for the intensity and duration of attacks, but frequency of attacks is often reduced. As migraineures experience intracellular Ca2+ overload due to brain hypoxia and other causes, cerebro-selective Ca2+ channel blocker like verapamil may benefit migraine. Side effects are sedation, constipation, dry mouth, hypotension, flushing, weight gain and rarely extrapyramidal symptoms.Anticonvulsants like Valproic acid (400-1200 mg/day) and gabapentin (300-1200 mg/day) have some prophylactic effect in migraine. The newer drug topiramate has recently been approved for migraine prophylaxis. A 50% reduction in the number of attacks in half of the patients was noted in 2 randomized trials. Start with topiramate 25mg OD and gradually increase to 50mg OD or BD. In migraine, the anticonvulsants show lesser effect when compared to β blockers.They were indicated when patients are contraindicated to propranolol.5-HT antagonists show the prophylactic effect of methysergide and cyproheptadine is less impressive than β blockers. They are seldom used now for migraine[4].Triptans and antidepressants known as selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) should be used only in severe migraines, but not in mild attacks. If used in mild attacks, cause serotonin syndrome which cause changes in cognition, behavior and muscle controlsuch as involuntary jerking.

Table 3: Pharmacological and non-pharmacological therapy.

Pharmacological therapy					
Absorptive therapy				Prevent therapy	
Non specific		Specific therapy		Drug	Dose & route
Drug	Dose & route	Drug	Dose & route		
Aspirin	500-650mg Oral	Ergotamine	1-2mg/day Oral	Propanolol	80 mg oral
Paracetamol	500-2000mg Oral	Dihydro ergotamine	0.75-1mg Sc	Flunarizine	10-20mg Oral
Diclofenac	50-100mg Oral/I.M	Sumatriptan	25-300mg Oral(or)sc	Verapamil	120-480mg oral
Naproxen	500-750mg Oral	Rizatriptan	10mg Oral	Amitriptyline	10-20mg Oral
ibuprofen	200-300mg Oral	Ergotamine	1-2mg/day Oral	Fluoxetine	20-60mg oral
Non pharmacological therapy: of triggers, Meditation, Relax training, Psychotherapy, Avoid eating of aged cheese, Yogurt, Bananas, Vinegar, Beans and Peanuts.					
Sleep: Maintain consistent sleep patterns i.e., follow biological clock/circadian rhythms including weekend and holidays.					
Exercise: Daily 20-40 minutes of aerobic exercise can relieve stress.					
Eating: Maintain healthy diet regularly.					
Reduce stress and increase posture: Reduce stress with yoga, meditation and maintain posture that imparts migraine [55].					

On January 27, 2019 US FDA approved Sumatripta nnasal spray for the acute treatment of migraine with or without aura in adults. Its dosage and administration were single dose of 10 mg of nasal spray in one nostril. Maximum dose in a 24-hour period is 30 mg; doses must be separated by at least one hour [56].

Conclusion:

In nervous system, headache is the most frequently occuring disorder.Headache can affect personal, societal burdens of pain, disability, quality of life, and financial cost.Headache has been underrate, under-recognized and under-treated throughout the world. About 59% of females and 71% of males are misdiagnosed and making themselvesis more complicated. So,

early diagnosis and its prevention can improve health status. The progress in the fundamental understanding of migraine may lead to novel, mechanism-based and disease-specific therapeutics of the migraine sufferer.

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