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Understanding Migraine: Insights into Its Mechanisms, Symptoms, Risk factors and Emerging Treatments

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Abstract:

Background: *The complicated neurological condition known as migraine is impacted by genetics and is typified by attacks of mild to acute head pain and a different of concomitant symptoms. The people's everyday activities and quality of life can be greatly impacted by migraine sickness. It is a leading contributor to both productivity loss and disability.*

Findings: *There are two primary forms of migraine: migraine with aura (MA) and migraine without aura (MO). The uncommon monogenic MA subtype known as hemiplegic migraine is brought on by mutations in the three primary genes that encode ion channel and transport proteins: "CACNA1A", "ATP1A2", and "SCN1A". Numerous variables, including genetics, hormones, diet, stress, and sleep patterns, can cause migraines, a frequent, debilitating headache illness. Attacks of migraine typically occur over many hours and intensify with regular exercise. Changes in daily routine and lifestyle can sometimes alleviate this ailment, but other times a doctor's diagnosis and treatment may be required. Together, medical care and lifestyle changes can aid in the disease's eradication.*

Key words: *migraine, migraine with aura, migraine without aura, Hemiplegic migraine, familia Hemiplegic migraine, CACNA1A, ATP1A2 and SCN1A.*

I. Introduction

The complex neurological condition known as migraine is influenced by genetics, therefrom Mild to acute headache attacks and a range of associated symptoms, such as nausea, vomiting, photophobia, phonophobia, and Osmo phobia, are its hallmarks (Stephen Silberstein, 2016). The migraine headache phase may be preceded by a prodrome phase and followed by a postdrome phase. Before or after the headache phase, aura may be present (Ruschel, 2022; de Jesus, 2021). A prevalent, incapacitating main headache condition, migraine is multiphase in nature headache episodes and a variety of accompanying symptoms. A head pain that occurs at least 15 days a month for more than three months is referred to as a chronic migraine (CM) with migraine features occurring at least 8 days per month (Scotton *et al*., 2019).

In western nations, about 2% individuals suffer from CM, which places a significant burden on the individual, their family, and society. According to Lipton *et al*. (2016), Chronification takes place in at least 2.5% of instances that occur in episodes each year, despite the fact that this condition is extremely common and incapacitating, but it is still extensively underdiagnosed and undertreated. A frequent neurological condition

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known as migraine manifests as a persistent headache that lasts 4 to 72 hours and is accompanied by photophobia, nausea, and vomiting, as in affluent nations, 10% of people suffer from migraines, with 6–8% of men and 12–14% of women affected (Evers *et al*., 2009). China participates an identical result the expansion is 9.3%, with 5.0−6.9% in man and 11.5−14.1% in woman (Yu *et al*., 2012). According to a WHO research, migraine is the second most incapacitating neurological condition and the third most common disease worldwide (GBD 2016 Disease & Injury Incidence & Prevalence Collaborators, 2017), it has been found that 51% of migraineurs miss work or school because of excruciating headaches (Lipton *et al*., 2001).

Diagnosis

By examining the patient's symptoms and learning about their family history, migraine headaches can be identified. If the sore head is caused by a sinuses issue and muscle strain, or a acute brain defect, a thorough physical test is necessary. If the headache is unusual, acute, or occurs suddenly, the doctor may perform additional tests to rule out other potential causes (Evans, 2019).

Pathophysiological mechanisms

The precise mechanism backwards migraines is anonymous, but it is thought to be caused by rare vascular phenomena. Typically, migraine headaches start with a variety of prelude sensations, such as nausea, visual aura, loss of vision in a portion of the visual field, and other types of sensory hallucinations. These displays typically appear 30 to 60 minutes before the headache actually starts. Excitation and prolonged mental strain are thought to be the origin of migraines because they induce certain arteries in the head, especially those that supply the brain, to reflexively spasm (Aesar & Aesar, 2025).

The present knowledge of the pathophysiologic mechanisms behind migraine has been greatly aided by neuroimaging. Hypersensitivity of raid producing brain regions may increase susceptibility to raid producing, and the processes of migraine attacks appear to cause raised sensitivity or hyperexcitability of various brain parts, assisting the occurrence of head pain and aura. Recent research has indicated that the brainstem, central dopaminergic system (DA) and hypothalamus (HTH) might be crucially involved in generation of migraine attack (May, 2017). Through regulating the endocrine system, integrating the psyche and soma, coordinating the activity of the sympathetic and parasympathetic nervous systems, governing circadian rhythms, arousal, and participating in nociceptive processing, the HTH plays a variety of roles in preserving homeostasis (Alstadhaug, 2009). Yawning, fatigue, and mood swings during the premonitory period, the assaults' circadian rhythmicity, and the correlation between migraine episodes and cycles of menstruation and hormonal status are some of the clinical characteristics of migraine that suggest HTH involvement (Van Oosterhout *et al*., 2018).

This implies that functional alterations in hypothalamo-brainstem connection might be the actual etiology of migraine episodes. HTH may be a useful biomarker for migraine diagnosis and treatment, since current research also revealed that the greater anteriority portion of hypothalamus seems to be crucial in migraine chronification (Schulte, 2017).

Migraine types

A. Classic migraine or migraine with aura

There are brief neurological signs (auras) before to the headache. The most prevalent auras are visual abnormalities, including hemianopia deficits of the visual field, vasotomy, and larger flashes that radiate outward (Gold, 2022). Observing these signs One-sided throbbing headaches can occur before or during them; headache frequency varies, although 50% of patients do not have headaches more than once per week; and most patients experience headaches for more than two hours but less than a day (Burch *et al*., 2018). Following menopause and throughout the secondly, thirdly and trimesters of gestation, recovery is typical. Classic migraines are characterized by discomfort on one side of the head; however, they can also be bilateral. Therefore, the diagnosis of migraine is not ruled out by bilateral headache. Furthermore, migraine is not ruled out by occipital discomfort, which is typically indicative of tension headaches. Headache is frequently accompanied by nausea, vomiting, photophobia, restlessness, irritability, and osmophobia, or the dread of scent. Vertebrobasilar ischemia

(migraine) is frequently accompanied by Eso motor symptoms, such as lightheadedness, dizziness, ataxia, or altered awareness (Villar-Martinez, &Goadsby,2022). In rare cases, stroke might happen as a result of migraine alone. It is uncommon for migraine to be linked to clear-cut neurological impairments that persist after the headache phase passes. Symptoms, including migraine, may appear without a headache, particularly beyond the age of fifty. These symptoms, which persist for 15 to 60 minutes, include loss of one-sided feeling in speech disorders and visual difficulties with or without hemiparesis (Borończyk *et al*., 2025).

B: Migraine headache without aura (normal)

Migraine headaches are often bilateral around the eyes, more frequently seen in bed, and are characterized by throbbing pain, particularly when severe. In addition to persistent discomfort, symptoms such as nausea, vomiting, and photophobia can be accompanied with contractions of the neck organs (Friedman & Evans, 2017). Tenderness in the scalp frequently appears just after a headache. Untreated headaches continue 27–4 hours, and vomiting can sometimes stop them. Bilateral carotid or superficial temporal artery pressure during a headache is a helpful clinical diagnostic for typical common migraines (Robbins, 2021).

C: Transformed chronic migraine

Over the course of months or years, a periodic migraine can develop into a chronic headache syndrome, causing pain that is nearly constant (Schwedt, 2014). Obesity, the frequency of prior migraines, and caffeine are risk factors for this condition, as chronic migraine headaches can be described differently from tension headaches (Özge *et al*., 2018). Pain relievers, opioids, horgotes, and triptans are all linked to this prevalent subtype of chronic migraine, which is a headache brought on by excessive drug usage that becomes worse when the medicine is stopped. In these situations, stopping the fast-acting medication and beginning the preventative medication at the same time is required (Konstantinos, 2020).

Reasons for Migraine

Migraines have a wide variety of causes. Unfortunately, migraine episodes in migraine sufferers can be caused by a variety of factors. It is more difficult to avoid migraine episodes if the reason is unclear. A variety of variables, including heredity, hormonal changes, food choices, and medical disorders, can trigger migraines (Amiri *et al*., 2022).

1. Genetic variables

Studies on twins and families have shown that a person's vulnerability to migraines is influenced by hereditary variables between 30 and 60%, For those who suffer from monogenic migraine disorders, this is clear such as FHM, wherein the condition may be brought on by pathogenic variation in a just one gene, with almost total penetrance (Polderman *et al*., 2015). Since various methods have been employed to identify and comprehend the role of the genes causing common migraine types including migraine without aura and migraine with aura, as well as monogenic and polygenic migraines, are most likely caused by variations with minimal impact at numerous genetic loci; in other words, these are regarded as polygenic disorders (Grangeon *et al*., 2023).

Familial hemiplegic migraine (FHM), a rare monogenic subtype of MA, was the subject of the first genetic investigations on migraine. Mutations in CACNA1A, ATP1A2, and spinocerebellar ataxia type 6 (SCN1A) genes were found to be implicated in the pathophysiology of FHM types 1, 2, and 3, respectively. Additionally, the "CACNA1A" encodes a subunit of the Cav2.1 (P/Q type) voltage-gated neuronal calcium channel, which is expressed throughout the central nervous system (CNS) (Sutherland *et al*., 2019). Because "ATP1A2 "encodes a subgroup of the sodium potassium pump, the gene has been shown to have 30 mutations that impact the clinical course of migraine, the majority of which have no effect on the disease's progression (Biondo *et al*., 2021). The SCN1A, the last gene linked to FHM, encodes a neuronal voltage-gated sodium channel subunit (Mantegazza & Broccoli, 2019). Ion transporter genes and the neurotransmitter system are important in migraine pathophysiology, according to genetic research in FHM. Since migraine molecular genetic research have examined several polymorphisms potentially linked to MA and/or MO, it is probable that migraine is the polygenic_ oligogenic with a wide genetic frequency (De Vries *et al*.,2009).

The methylenetetrahydrofolate reductase (MTHFR), which is essential for Hcy metabolism. Homocysteine (hcy) conversion to methionine requires MTHFR (Moll & Varga, 2015). Homocysteine is a potentially harmful amino

acid that, when present in excess, remodels Vascular tissue. For example, endothelial dysfunction linked to Hcy may be the cause of migraine onset and maintenance, which lowers oxygen flow to the brain (Cacciapuoti, 2017). with addition to migraine, the most prevalent variant of MTHFR, rs1801133 (C677T), is implicated with heart disease, neural tube abnormalities, stroke, hypertension, glaucoma, and a few other illnesses (F Gasparini *et al.*, 2013).

FHM1 because of CACNA1A mutations: Using Positional cloning and mutation analysis of candidate genes in several familia hemiplegic migraine family pedigrees, CACNA1A on chromosome 19p13 was found to be the first gene implicated in FHM (FHM1) (Freilinger, 2017). It encodes the pore-forming α1 subunit of the neuronal voltage-gated Cav2.1 (P/Q type) channels, which are primarily found in brain and cerebellar neurons and are crucial in regulating the release of neurotransmitters (Grieco *et al.*, 2018). For FHM1, there are around 25 pathogenic mutations in CACNA1A that are hereditary in an autosomal dominant manner. Although" CACNA1A" remove have been observed in familial hemiplegic migraine 1 (FHM1) patients, most of them are missense mutations that are located in important calcium channel functional domains, such as the voltage scout, hole, and hole-lining loops (Labrum *et al*., 2009).

Their gain-of-role impact often result in high Ca inflow, which in turn enhances glutamatergic neurotransmission and causes hyperexcitability in neurons. Apart from FHM1, Episodic ataxia type 2 and Spinocerebellar ataxia type 6 are two more neurological illnesses that can be brought on by heterozygous mutations within CACNA1A (Pereira Mda *et al*., 2016). While spinocerebellar ataxia is distinguished by mature-individual, heavily progressing cerebellar ataxia, dysarthria, and nystagmus, episodic ataxia type 2 is characterized by paroxysmal bouts of ataxia, vertigo, and nausea. Clinical characteristics of the three allelic illnesses may overlap; for example, around 50% of EA2 patients also have migraine, while SCA6 patients frequently experience nausea and episodic headaches (Blumenfeld AE *et al*., 2016).

FHM2 is generated as a consequence of mutations in the ATP1A2 gene: the ATP1A2 gene encodes the-2 subunit of the Na+,K+-ATPase (Leite *et al*., 2020).Whilst CACNA1Amutations in migraine attacks show gain-of-role impact, ATP1A2" mutations product lost-of-role of sodium–potassium ATPases and, in turn, rising K+ levels within the synaptic cleft, thus altering cell membrane sodium gradients in key astrocytic cells and affecting glutamatergic neurotransmission, as well as reducing extracellular potassium clearance (Staehr *et al*., 2025).

The development and start of migraine episodes are facilitated by mutations in ATP1A2, which cause disturbances in ion homeostasis and neuronal excitability. This can happen through a decrease in the sodium/potassium turnover rate, an increase or decrease in potassium clearance, or functional inactivation due to compromised protein stability (Friedrich *et al*., 2016). Since there are over 80 causative variations, heredity is typically autosomal dominant and results in a florid and varied clinical presentation that includes hemiplegic aura and migraine, as well as recurring coma, heat, and hypokalaemic periodic. Since ATP1A2 variations are more frequently seen in people with SHM, they may cause SHM to be mistaken for FHM due to a de novo mutation that can be inherited (Sampedro Castañeda *et al*., 2018). As with FHM1, which is linked to decreased potassium and glutamate clearance, there is clinical evidence of memantine's effectiveness in migraines once again. Modified cortical circuit function and changed electrolyte balance are probably involved (Xu *et al*., 2021).

Mutations in the SCN1A gene, which is found on chromosome 2q24.3, result in FHM3: It encodes the neuronal voltage-gated sodium channel Nav1.1's pore-forming a1 subunit, which controls sodium permeability on GABAergic interneurons. Pure HM or related neurological conditions such as generalized epilepsy tonica-clonic., provoked repeated transient blindness on a regular basis, or juvenile epilepsy can be present in patients with SCN1A mutations (Sutherland *et al*., 2019). Typically, FHM3 mutations are missense. FHM3 mutations (including a folding-defective mutation) cause GABAergic neurons to become hyperexcitable and NaV1.1 channels to acquire function, in contrast to folding-defective epileptogenic NaV1.1 mutants that also displayed loss of function after being rescued (Bechi *et al.*, 2015). One theory for the increased susceptibility to CSD in FHM3 is the rise in extracellular potassium concentration brought on by an increase in GABAergic interneuron firing (Jansen *et al*., 2020). PRRT2 has been proposed as the fourth hemiplegic migraine gene in the search for additional putative HM genes (Ebrahimi-Fakhari *et al*., 2015). Since resect mutations are the most prevalent in

PRRT2-related disorders, a presynaptic transmembrane protein is encoded by it that is involved in the fusion of synaptic vesicles and the control of ca v1.1 in glutamatergic neurons (Sutherland *et al*., 2019).

This gene is linked to pediatric epilepsy/seizure disorders and paroxysmal kinesigenic dyskinesia. PRRT2 variations exhibit a low-penetrance manner of co-segregation since HM has been observed in a small number of carriers of PRRT2 mutations with a "typical PRRT2 phenotype." It is plausible that the PRRT2 gene functions as an illness modifying gene in hemiplegic migraine through a complicated polygenic process (Pelzer *et al*., 2014). Rarely, patients with HM phenomenology have been found to have mutations in the PNKD", SLC2A1", SLC1A3", and SLC4A4" genes. All of these variations may theoretically throw off excitatory-inhibitory balance and cause CSD (Roth *et al*., 2018).

2. Hormonal fluctuations

Migraine: hormones and reproductive factors

The menstrual cycle and migraine: History, physical examination, and diary records may all be used to diagnose monthly migraine. These methods can determine the cyclicity of the menstrual cycle, its duration, the likelihood that the patient is in the menopausal period, and rule out other possible causes of headaches (Chalmer *et al*., 2023). Based on a complicated equal of "neurotransmitters NE, the frequency of migraine episodes changes according to the monthly cycle stages. Given the mechanism underlying migraine attacks and the intricate interactions between synaptic transmitters, migraine attacks are more likely to occur during the menstrual cycle's perimenstrual phase, when estrogen and progesterone levels are lower. Progesterone can alleviate migraine by GABAergic system activation, which inhibits migraine, when estrogen levels are high (mid-luteal phase) (Krause *et al*., 2021).

According to MacGregor (2021), migraines predominantly happen during menstruation for certain patients, and their clinical manifestations are more severe than those of other menstrual cycle phases. Since regulating natural variations in estrogen may be a useful way to avoid menstrual episodes, experts have discouraged hormonal treatments containing estrogens in migraineurs, particularly those with migraine with aura, due to the elevated chance of ischemic stroke and deteriorating of the disease. Numerous studies have also examined the effectiveness of hormonal therapy that aim to reduce Estrogen withdrawal and hormonal changes prior to bleeding during menstruation. In fact, the "perimenstrual window" increased migraine susceptibility, particularly from −2 to +3 days of menstruation, appears to be powerfully linked to removal of hormones (Sacco *et al*., 2018). Apart from hormones, prostaglandins may also participate in the pathophysiology of migraine because they rise in the luteal phase of the menstrual cycle and reach their maximum level 48 hours into the menstrual cycle, which also happens to be the time when menstrual migraines occur the most frequently. contrasted to female with natural blood flow in the vagina, perimenopausal women may have heavier menstrual blood flow and a longer monthly length, which is linked to increased prostaglandin production (Godley *et al*., 2024).

The greater happening of headache during the perimenopausal phase compared to the postmenopausal period may thus be due to these variables. The idea that suppressing hormonal fluctuations may prevent estrogen withdrawal during the tablet-free interval and lower levels of estrogen in the late luteal/early follicular phase is supported by the findings of studies suggesting preventative treatment for menstrual migraine (Ramachandran, 2018). It is possible to administer estradiol (1.5 mg/day percutaneously) five days prior to the anticipated beginning of monthly cycle for seven days. Non-steroidal anti-inflammatory drugs and other medications may also be used, especially for women who experience menstrual migraine and dysmenorrhea (Baldo & Pham, 2020).

3.Nutrition

Although there are several lists of possible food triggers, it is generally acknowledged that migraines are nutrition-sensitive and that certain dietary items can cause headache episodes. Nevertheless, there is still debate in the profession. According to Martin and Vij (2016), the literature has identified the following foods and substances: Monosodium glutamate (MSG), histamine, tyramine, phenylethylamine, nitrites, aspartame, sucralose, gluten, chocolate, citrus fruits, almonds, ice cream, tomatoes, onions, dairy products, and alcoholic

beverages. The amount and time of exposure, among other factors, may influence how a headache sufferer reacts to a particular food trigger (Cairns, 2016).

Certain foods can induce headaches, while others, like caffeine, might create headaches when they stop being consumed. Only some patient subgroups, including those with celiac disease, or those with certain food-related immunological reactions, like those with positive IgG antibodies, may have headaches from certain foods or substances (Biscetti *et al*., 2021).Given that genetic agent also play a part and that some people are more vulnerable to the impact of particular foods, food ingredients, or beverages, patient profiling may be useful in dividing the diverse population of migraineurs. If dietary triggers can be accurately and objectively specific, avoiding them will subsequently prevent migraine in affected individuals (Ebahimzadeh *et al*., 2021).

Although there appear to be conflicting results in the literature, this is the foundation of elimination diet tactics. This contentious result could have resulted from a lack of thorough and controlled research. Furthermore, probiotics have been shown to have a function in altering the gut flora of migraine sufferers, and several complete diets have been developed specifically for migraine sufferers (Dodick, 2018).

However, a multimodal strategy, including Dietary measures, may progress the modality of life for many migraine patients (Lacerenza *et al*., 2015). It's crucial to understand that an intricate non-linear system may be at play here, and that searching for a straightforward reason-and- impact a relationship may be deceptive when examining triggers for food migraines. A different of other stimulates, like as tension, the air, dry, may also trigger the migraine practicability and need to be taken into account as additional inputs into this system is not linear. Establishing a threshold has been suggested since it is difficult to define a connection between diet and migraine (Seng *et al*., 2022).

3. Stress

According to Avijgan (2011), migraine headaches may be brought on by high amounts of mental or physical stress.

5. Modifications in sleeping habits

Migraine headaches may be brought on by changes in sleeping habits, such as getting too much or too little sleep (Ferini-Strambi *et al*., 2019).

Treatment

Treatment can be pharmaceutical (medication) or non-pharmaceutical (non medication).

A. Medication

A variety of medications are particularly made to treat migraine headaches. However, some medications that are intended to treat other conditions can also be used to prevent or relieve migraines. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a good place to start when treating acute migraines, though acetaminophen can be tried if using NSAIDs is contraindicated. Triptans are another option. Acetylsalicylic acid (ASA), diclofenac potassium, naproxen sodium, and ibuprofen (Kirthi *et al*., 2013). Antiemetic drugs are part of the relief. These medications are useful in preventing the nausea and vomiting that typically accompany migraines (Ravisankar *et al*., 2015).

The length, frequency, and intensity of migraine headaches can all be reduced with preventive medicine. While some drugs are given for everyday usage, others are only to be used in response to potential triggers that need to be controlled (Kinderlehrer, 2021) .Among the preventative meds are cardiovascular medications: In addition to being often used to treat high blood pressure and coronary artery disease, beta blockers, such as propranolol, have also been shown to be useful in reducing migraines. Calcium channel blockers: Verapamil in particular, a different family of cardiovascular medications, may also help avoid migraines and alleviate aura symptoms (Fumagalli *et al*., 2020).

Numerous substances are both present and potential targets for pharmacologic therapy and have been linked to the pathophysiology of migraine illness. For instance, pain is reduced when serotonin receptor activation leads in vasoconstriction and peptide inhibition, including calcitonin gene-related peptide (CGRP) (Chiang *et al*., 2024). Furthermore, according to suggested mechanisms such as vasodilatation, effects on central, sensory afferent

stimulation, mast cell degranulation, and the parasympathetic neural system, adenylate cyclase-activating polypeptide in the pituitary "PACAP" is being investigated as a possible treatment (Khan *et al*., 2021).

A. Non-medication treatments

There are several non-pharmacological ways to treat migraines. Among them are: 1. Psychological therapy 2. Massage therapy

1.Psychological treatment

Psychological therapies are a key part of best-practice approaches for managing migraines, and they work best when combined with biomedical and other non-pharmacological interventions. The most evidence supports the effectiveness of cognitive behavioral therapy, relaxation techniques, and biofeedback (Lee *et al*., 2019).

2. Massage therapy

In order to maintain their physical, mental, and spiritual well-being due to extreme drug-tolerance and bad effects, many migraine sufferers have resorted to complementary treatments, despite the availability of conventional medications (Xiao-Yi *et al*., 2016). As a result, a safe and efficient substitute therapy is required. Massage is a type of physical therapy that involves carefully moving particular body regions to relax muscles, ease pain and discomfort, and enhance sleep quality. It is safe, efficient, and convenient (Song & Yu, 2012).

II. Conclusion

Migraine represents a multifactorial and disabling neurological disorder with substantial personal and societal burden. This review highlights the complex interplay between genetic predisposition, hormonal fluctuations—particularly in women—and environmental stressors in shaping the clinical course and therapeutic response of migraine. The significant role of estrogen in modulating migraine activity during different phases of the female reproductive cycle underscores the need for gender-specific approaches in diagnosis and management. Furthermore, despite the emergence of novel pharmacological agents, a considerable proportion of patients remain refractory to current treatments. Therefore, future research should prioritize individualized therapeutic strategies, incorporating hormonal, neurological, and psychosocial dimensions, to enhance long-term outcomes and quality of life for migraine patients.

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