

Migraine: A Multifaceted Disorder Involving Neuroinflammation, Environmental Triggers, Treatment Strategies, and Machine Learning-Based Diagnosis

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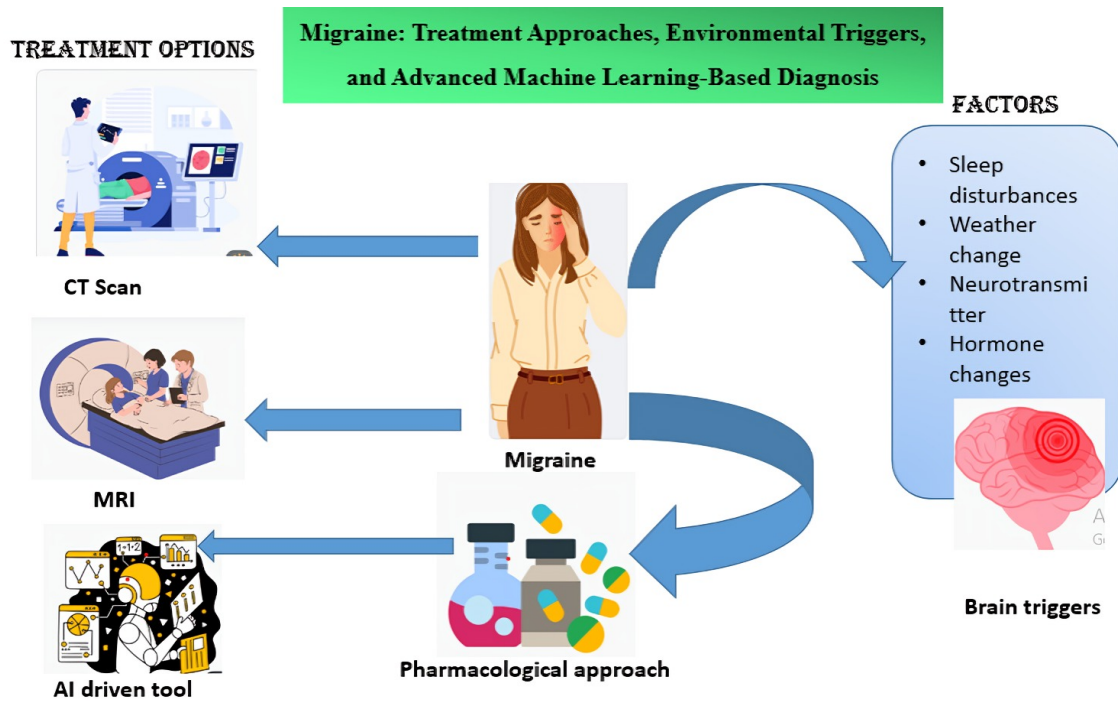
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Migraine is a common neurological condition that may be caused by changes in the weather, stress, trouble sleeping, changing hormones, and not eating for a long time. These causes can affect how the brain works, making the nerves active, changing blood flow, and making the brain more excitable, which can lead to initiation of migraines and how irritating they feel. Identifying underlying environmental factors is important for figuring out how to potentially prevent and manage these health issues. In general, medical strategies like computed tomography (CT) scan and magnetic resonance imaging (MRI) can find out if there are any changes even very small in the brain structure and hence improved the overall diagnosis, but they are not fully accurate in determining migraines. Advanced machine learning and deep learning methods were created to help doctors find out about and treat diseases more accurately and quickly, since the traditional tests are not always perfect. These treatment methods include both treating right away when someone needs it and steps that try to prevent illnesses from happening. Beta-blockers, some seizure medicines, antidepressants, and a new class of medicines like calcitonin gene-related peptide (CGRP) antibodies all help prevent migraines and can be used as a treatment. Chronic medications like triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), and CGRP receptor antagonists can help with the pain patients feel. Furthermore, non-medication methods like talking therapy, changing daily habits, and using electrical devices can help manage migraine. With advanced tools like artificial intelligence (AI) and machine learning, doctors are now able to find out what might be causing migraines in patients in ways that go past just using regular scans. AI-driven tools look at things like medical history, gene information, and scans to help find certain patterns of migraines, guess when an attack might happen, and suggest ways to help manage the condition. These technologies help doctors perform surgery with more precision, find diseases early, come up with better treatment plans, and help patients recover more successfully. As with each passing day, AI is put into more use in healthcare, it will help make migraine research and management better by giving a more accurate and individualized way to care for people with migraines.

Keywords: migraine; headache; neuroinflammation; environmental factors; machine learning-based diagnosis



Graphical Abstract.

Introduction

Headache conditions are one of the most common medical disorders in the world. According to the 2016 Global Burden of Disease survey, migraines are the second most incapacitating health problem globally. Over one billion individuals worldwide are thought to suffer from migraine, out of an estimated three billion who suffer from other headache disorders [1–3]. Cluster headache, tension-type headache (TTH), and other Trigeminal Autonomic Cephalalgias (TAC), a headache brought on by trauma to the head or neck, a headache caused by a cervical or cranial vascular disease. A nonvascular intracranial condition is the cause of the headache. The homeostasis problem is the cause of the headache. Disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures are the cause of headaches or facial pain. Women are more likely than men to suffer from migraines. In Europe and North America, migraines affect 5 to 9% of males and 12% to 25% of women, respectively [1,4]. The current standard for diagnosing headache disorders is the International Classification of Headache Disorders, Third Edition (ICHD-3) [2,5]. Severe migraine is a highly prevalent neurological condition that affects roughly 16% of the population. It is the second most common brain disorder worldwide and results in more impairment than all other neurological conditions combined [6–8]. There are three types of migraines: Aura-producing migraines, Aura-less migraines, and chronic migraines. Aura migraines, which are characterized by the progressive emergence of visual,

speech, and other central nervous system-related symptoms, affect about 25% of people. An hour is the duration of migraine with Aura [9].

The advancement of artificial intelligence (AI), particularly machine learning (ML), is a very advanced technology that has recently advanced rapidly, much like computing and data analysis, allowing programs to operate traditionally in extremely intelligent modes [10]. ML algorithms utilize and process the bulky, complex, and unstructured data in statistical methods to learn from previous experience. Further, machine learning practices are divided into supervised, unsupervised, semi-supervised, and reinforcement learning. Support vector machine (SVM) is a particular form of supervised machine learning (SML) approach that can be used to classify linear and non-linear data. And regression by exploiting the margin in a high-dimensional space between classes [11–14].

The scope of the study was to provide a comprehensive overview of the pathophysiology of migraine with attention to neuroinflammation, environmental factors responsible for migraine, current pharmaceutical and non-pharmaceutical strategies and treatment for migraines, and the emerging role of machine/deep learning in diagnosis and management.

Migraine

Migraine is a frequent neurovascular brain condition marked by repetitive activation of cortical and subcortical brain regions [15]. Common signs include nausea, vom-

iting, with elevated sensitivity to light or sound [16]. Although around one in five women and one in fifteen men suffer from migraine, the actual amount varies [17,18]. Migraine might affect someone for only a few days or for years on end [19,20].

It is not clear if there is a link between migraine and neck pain. The first perspective is that the pain in the neck is caused by the migraine and linked to “central sensitization”, with a higher fear of pain in the neck area. But migraine pain may be worsened by neck pain, which could happen because of peripheral sensitization. Necessary adjustments in the neck region, such as reduced neck strength, may bring on neck discomfort and increase the chance of increased sensitization in the trigeminocervical complex, causing headaches to happen more often [15,21].

Types of Migraine

Migraine With Aura

Aura is experienced by around 1/3 of migraine sufferers [22], perhaps with a single episode or with certain attacks. Aura is described as brief localized neurological signs that typically occur before, however occasionally in addition to, the headache phase of a migraine episode. Aura shows visibly in more than 90% of afflicted people, traditionally as strengthening harmonics. Sensory complaints impact 31% of those afflicted that are often experience mostly unilateral paresthesia (pins and needles and/or numbness), usually developing progressively in the face or arm [23–27].

Migraine Without Aura

Migraine without Aura is distinguished by recurring headache assaults lasting 4 to 72 hours [28]. The event is distinguished by its unilateral localization, pulsing character, mild or intense pain degree, plus intensification by regular physical exertion [29]. Nevertheless, bilateral agony is not rare; demographic figures revealed nearly 40% of migraine sufferers have bilateral pain throughout episodes [30].

Photophobia, hearing problems, nausea, with vomiting seem to be the most prevalent related signs [31,32]. Prodromal indicators might comprise a feeling of loneliness, fidgeting, weariness, as well as an appetite for particular foods before the beginning of pain [33]. Postdrome signs can endure until 48 hours afterwards the headache has resolved, which commonly involve weariness, difficulty concentrating, or even dystonia [34].

Chronic Migraine (CM)

Chronic migraine is considered as ≥ 15 headache days/month for more than 3 months while achieving the ICHD-3 migraine guidelines on ≥ 8 days/month [35,36]. Chronic migraine is not a fixed condition, and relapsing to episodic migraine is not uncommon. Consequently, re-transformation to chronic migraine might emerge in the

prospective [37]. A comparison between those suffering from chronic migraine and those with episodic migraine is necessary to identify genetic variants causing migraine chronification. Grangeon *et al.* (2023) [38] reported that genetic risk factors have been compared chronic migraineurs to healthy controls. However, some other current studies comparing episodic and chronic migraine, genetic variations in the Transient Receptor Potential Cation Channel Subfamily M Member 8 (*TRPM8* gene), the transient receptor potential cation channel subfamily V member 1 (*TRPV1* gene), and Human Leukocyte Antigen (*HLA*) class I alleles have been related to chronic migraine [38–40].

Epidemiology of Migraine

Migraine is a chronic disorder that affects over one billion persons globally, irrespective of culture or socioeconomic status [41]. Migraine is a painful primary headache disease, with a 1-year prevalence of approximately 15% of the general population. Migraine is said to be the second most common neurological disease according to the Global Burden of Disease Study, leading to more disability than every other similar disease together [42]. Almost every age group is affected by migraines, but it is more common in women than in men. The global age-standardized prevalence rate of migraine in 2019 was 10,337.6 per 100,000 males and 17,902.5 per 100,000 females [43,44]. In Pakistan, the prevalence of migraine reported by Herekar *et al.* (2017) [45] was perceived in all age groups (18 to 65), including males and females. The overall ratio of migraine observed was almost 30%, but was more prevalent in females than males, which were 27% and 18%, respectively. Observed results showed that the highest rate for women was 38.4% among females of ages 40–49, while for men, the rate was lower at 20.7% among those of ages 50–59 [45].

Genetics and Inheritance

Genetic components are very strong in migraine, so those with related hereditary migraine suffer three times as much as unaffected family members. While the genetics of migraine are complex, the roles of its specific genes in the disease process are still unclear. This is controlled by a combination of different genes, located throughout the genome, in addition to environmental influences, which modify the way a person is affected by the disease. By understanding the mutations in these genes, scientists can recommend better preventative therapies for migraine patients [46].

Environmental Factors and Clinical Attributes of Migraine

The common biological risk factors involved in the migraine disorder are metabolism, hormonal imbalance, stress genetic influence, stress, sleep disturbance, and fasting [47–53], Table 1 (Ref. [47–56]). The association be-

Table 1. Environmental factors, mechanism and features of migraine.

Serial number	Environmental variables	Mechanism	Migraine features	References
1	Weather alterations	Changes in humidity, temperatures changes, and pressure in the atmosphere	An increase in migraine frequency, intensity to light, Aura and duration.	[54–56]
2	Stress	Triggers cortisol, hypothalamic-pituitary-adrenal (HPA) and other stress hormones to be released, which results in neurotransmitter abnormalities.	Increasing the intensity, duration of time and the incidence of migraine attacks	[47,48]
3	Sleeping disturbance	Circadian rhythm problems that affect melatonin and serotonin levels.		[49,50]
4	Hormonal changes	Hormone estrogen level changes, specifically during menstruation, pregnancy, and menopause.	Increased severe pain, higher sensitivity to triggers, and menstrual migraines	[51,52]
5	Fasting	A drop in blood sugar level that causes hyperexcitability in neurons.	Headaches from hunger, heightened nausea, and severe pain.	[53]

tween migraine and distinct psychological variables, such as the tendency toward perfectionism, neuroticism, repressed aggressiveness, and a gloomy mood, has been observed for more than a century [57,58]. Migraines contributing physiological factors such as stress, anxiety/panic disorders, phobia, obsessive-compulsive disorder (OCD), post-traumatic stress and bipolar disorders, depression and personality are frequently affecting human people [59,60].

Migraine and Weather Changes

Investigation has demonstrated that the relationship between weather and migraine is still controversial. Many people who suffer from migraines have claimed that certain climate conditions might cause migraines. Weather has been reported as a trigger factor by more than half of migraine patients particularly when atmospheric pressure lowers by more than 5 hectopascals (hPa). The suggested mechanism is that during storm fronts, alterations in intracranial pressure or the release of inflammatory mediators may cause vasodilation and meningeal nociceptors to become active. During the transitional seasons of spring and fall, migraine headaches and the resulting impairments frequently reach their height [54,61]. Rainfall and humidity are also considered to play a major role in causing migraines. However, the exact relationship is still unknown. Cloudy and thundery weather may cause migraines, according to several smaller scale research, however, these findings should be interpreted with caution. One of the main causes of migraines has been found to be high temperatures, which may be connected to elevated body temperature. Many studies revealed that certain individuals may experience fewer weather-induced attacks if their behavioral patterns are proactively adjusted in response to anticipated weather changes [54–56].

Migraine and Neuroinflammation

Neuroinflammation, recognized as an essential variable in the pathophysiology of many disorders affecting the brain's nervous system appears as the adaptive reaction brought on by harmful stimuli such infection, damage, and tissue stress. When it comes to migraine, neurogenic neuroinflammation is defined as inflammation that is triggered by neuronal activity in both the central and peripheral regions of the trigeminovascular system. The phrase is frequently used to describe both peripheral nervous system (PNS) structures, including the trigeminal ganglion, and Central Nervous System (CNS) components. With humoral and cellular immunological components, the immune system is separated into two parts: the acquired or adaptive immune system and the more archaic innate immune system [62,63]. The CNS's innate immune system, which comprises astrocytes, trafficking macrophages, and microglia, has been the subject of a flurry of research within the last ten years. Recent advances in our understanding of the interactions between innate immune cells and infiltrating adaptive immune cells (T and B lymphocytes) in the CNS have led to the realization that each of these cell types plays a role in the development of inflammation in the CNS, a highly coordinated immune system response to infectious or non-infectious (sterile) stimuli that is implicated in a number of diseases, including multiple sclerosis, migraine with Aura (MA), and stroke. Depending on the biological circumstances, tissue homeostasis, cell types, and inflammatory components, inflammation in the central nervous system can have both harmful and beneficial consequences [62,64].

Role of Pro-inflammatory Cytokines (TNF- α , IL-1 β , IL-6)

Many investigations, including ones conducted during the attack, during the interictal period, and even after the attack, have been conducted on cytokines and chemokines in

migraine sufferers. During the ictal phase of migraine attacks, there is an increase in interleukin-1 β (IL-1 β), IL-6, IL-8, and tumor necrosis factor- α (TNF- α) [65]. Cytokines have pro- or anti-inflammatory properties and are involved in immune cell mobilization and trigeminal sensitization, which activates the pain pathway. Pro-inflammatory cytokines, including TNF- α and IL-1 β , may rise during or after an occurrence, according to recent studies conducted on migraineurs. Pro-inflammatory cytokines such as IL-1 and IL-6 have been demonstrated in preclinical studies to excite and activate nociceptors in the muscles and meninges [66,67]. Meningeal nociceptors are stimulated by cytokines, and this leads to migraine pain. It has been proposed that increased pro-inflammatory cytokine levels cause changes in anti-inflammatory cytokine levels, and that reestablishing equilibrium during a migraine attack [66,68].

Activation of Glial Cells (Microglia, Astrocytes)

Glial cells, also known as glia or neuroglia, are the most common cells in the neurological system. Glia cells play several roles that are necessary for the proper growth and operation of the nervous system, including preserving the homeostatic environment within it. Furthermore, glia undergoes morphological, transcriptional, and functional alterations in disease; this process has been thoroughly studied in astrocytes (astrogliosis) and microgliosis), underscoring the significant role that glia plays in neurological disorders. Evidence linking the various glial cell types to a variety of clinical diseases, such as neurodevelopmental, neurodegenerative, and neuropsychiatric disorders, as well as various pain problems, is mounting. For example, recent studies suggest that astrocytes play a proactive role in the development and course of epilepsy, most likely because of increased hyperexcitability associated with astrocyte dysfunction. Glial cells are also implicated in the pathophysiology and chronification of pain, according to several studies. In this regard, in neuropathic pain models, microgliosis and astrogliosis follow nerve injury, with microglia playing a greater role in the onset of pain and astrocytes in the transition from acute to chronic pain and in the maintenance of chronic pain [69–71].

Several neurological conditions that depend on glia for their pathogenesis overlap pathways with migraine. Furthermore, it has been noted that migraine is linked to brain hyperexcitability, a feature of epileptic patients that has been connected to astrocyte dysfunction. Chronic pain has been demonstrated to have a significant glial component, and chronic migraine shares several significant characteristics with chronic pain. Moreover, it has been proposed that glial cells are involved in migraine comorbidities such stress and depression [72].

Peripheral Immune Cells in Migraine

Numerous elements contribute to the inflammatory response, such as cytokines and chemokines, which are vital to the central nervous system and secreted in the endothelium and cerebral arteries. After passing through the meninges, the blood arteries that transport immune cells enter the brain and control the movement of immunocytes. In many diseases, including migraine, the development of inflammation can be significantly influenced by the action of mast cells (MCs), which are found in the meninges. It has been revealed that MCs exist in large numbers within the meninges, and their products produce inflammation and may participate in migraine. Moreover, MCs and T cells are activated in migraine and headache, and the expression of inflammatory genes, such as chemokines and Toll-like receptor 2 (*TLR2*), rises, whereas the expression of genes that inhibit inflammation, such as IL-10 and Cerebrospinal fluid (*CSF-1*), falls. Nuclear factor kappa B (*NF- κ B*) failure, chemical inflammatory compound synthesis, and cell adhesion all rise in response to an increase in inflammatory cytokines. Because inflammatory cytokines, TLR, and NF- κ B are involved, reducing the symptoms of inflammation in headaches can have an impact on innate immune response pathways [66,73,74].

Blood-Brain Barrier (BBB) Dysfunction

Harper and colleagues [75] proposed the hypothesis of BBB dysfunction in migraine in 1977. The scientists hypothesized that a breach in the blood-brain barrier allowed substances in the peripheral circulation to enter the CNS and help transmit nociceptive impulses, which in turn cause migraine discomfort [76]. Existing clinical research has shown that there is no correlation between the onset of BBB and primary headache. Matrix Metalloproteinase-9 (*MMP-9*) and Intercellular Adhesion Molecule 1 (*ICAM-1*), which are thought to be typical indicators of BBB abnormalities, are found in migraine patients. It has been observed that an MMP-9 haplotype influences the circulation of MMP-9 levels in migraine-affected women [65,76]. A recent study conducted by Yücel *et al.* [77] found that the migraine attack group had significantly higher levels of claudin-5 and endothelial cell-specific molecule-1 (ESM-1). The vascular endothelium expresses ESM-1, which is controlled by growth factors and a number of cytokines, such as TNF and IL-1. Claudin-5 plays a critical role in maintaining the integrity of cerebrovascular endothelial cells by controlling their permeability. ESM-1 and claudin-5 levels were found to positively correlate with Visual Analog Scale scores. Apart from the correlation between BBB abnormalities and migraine, the findings also point to a connection between BBB disorders and the clinical severity of migraine [65].

According to magnetic resonance imaging (MRI) investigations, BBB permeability did not increase during spontaneous migraine attacks with or without Aura. Additionally, the BBB function during ictal and interictal phases

was unaffected by glyceryl trinitrate-induced dural inflammation, and dihydroergotamine's passage through the BBB was harmful [75,78].

Brain Regions Mainly Abnormal in Migraines

Recent findings from neuroimaging research, such as interictal MRI, indicate that migraine pathophysiology may be linked to both structural and functional alterations in the brain in addition to migraine pain. In both ictal and interictal stages, migraine alters the brain, changing the morphology of the brainstem, cerebellar, and cerebral structures as well as the networks and functions of neurons. Animal research provides data in support of these human study findings. Instead, positron emission tomography (PET) tests during the migraine attack showed lower metabolism in the thalamus, orbitofrontal cortex, anterior cingulate cortex, and ventral striatum, and increased blood flow in the brainstem nuclei and cerebellum. Patients with migraines with Aura shown to have higher gray matter density in dorsolateral pons and periaqueductal gray (PAG). Additionally, gray matter decrease in the frontal, temporal, and parietal lobes, the limbic system, the Anterior Cingulate Cortex (ACC), the brainstem, and the cerebellum was linked to the frequency of migraine attacks and the length of migraine disease in migraineurs [79–81].

Diagnosis of Migraine

Conventional Techniques for Diagnosis of Migraine

The variability of symptoms and the absence of conclusive diagnostic tools make it difficult to diagnose migraines. The primary method for diagnosing migraine is history of migraine [82,83]. However, to rule out other potential headache causes, imaging procedures and blood testing might be carried out. Even though clinical examination can identify a variety of neurological disorders and diseases, confirmation can be confirmed through MRI and computed tomography (CT) neuroimaging. CT studies have been conducted on patients with migraines. These studies have highlighted abnormalities in a certain proportion of migraine cases. White-matter lesions observed in MRI scans have been linked to the clinical characteristics and personal characteristics of migraineurs. The prevalence of white-matter abnormalities is higher in patients with diabetes, hypertension, and heart disease [84].

Machine Learning (ML)

Conventional migraine diagnosis and prediction machines, like CT scans, MRI, and positron emission tomography (PET), are quite costly. Additionally, migraine patients must be advised by extremely skilled medical professionals. In particular, it is monetarily unaffordable for those in developing nations, and there are few resources available for migraine categorization and prediction. For migraine classification and prediction, an automated, accessible, and

reasonably priced method is therefore needed. Thankfully, machine learning algorithms demonstrate cutting-edge performance in tasks like speech recognition, text classification, and several automatic disease classifications and predictions relating to health [85].

Humans reside in the data era, in which anything as a whole is linked to a data stream that things in daily life is converted into digital [86,87]. AI, specifically ML, has grown rapidly in recent decades in the context of data processing and computing, enabling algorithms to function intelligently. ML is widely considered as one of the most prominent contemporary achievements in the fourth industrial revolution since it allows machines to train and develop based on data without being explicitly written [87,88].

Progressive mechanization of traditional production and commercial activities, particularly experimental information interpretation, via the use of emerging sophisticated technologies including machine learning automation. Consequently, machine learning strategies are essential for appropriately understanding such data then developing the related real-world solutions (Fig. 1) [89,90].

AI has been more prevalent in many areas of neurological research in recent years. The study of migraines using ML techniques using MRI data has yielded many significant findings. This approach has been widely used recently for both the classification of migraines and the identification of key brain areas for migraine diagnosis and treatment. Brain resting state MRI data from migraine patients with more than 14 years of disease duration had a classification accuracy of 97%. The migraine brain was best separated from health controls (HCs) by the right middle temporal, posterior insula, middle cingulate, left ventromedial prefrontal, and bilateral amygdala [91,92].

To address the Minimum Wages Act (MwA) classification problem, fewer studies have focused on applying machine learning algorithms based on brain resting-state functional magnetic resonance imaging (fMRI) and structural MRI, which have been used to identify brain networks and regions involved in migraine attacks as well as brain signatures that enable migraine patients to be distinguished from healthy controls [93–95]. ML approaches for migraines include Naive Bayes, Linear Discriminant Analysis (LDA), Logistic Regression (LR), K-nearest neighbors (KNN), Decision Tree (DST), Random Forest (RF), Fuzzy Logic, and Classification and Regression tree (CART) [85].

A SVM is additional popular method in ML that may utilize for classification, regression, or other tasks [96,97]. SVM generates a single hyperplane or a group of hyperplanes in a region with high or infinite dimensions. The hyper-plane—the distance between the closest training data points in any class—achieves a notable differentiation, assuming that the classifier's generalization inaccuracy decreases with increasing range [98]. Although it performs well in high-dimensional fields, its behavior varies based on the kernel, or collection of arithmetic operations. The most

Diagnosis of Migraine by advanced Techniques Machine Learning and Deep learning

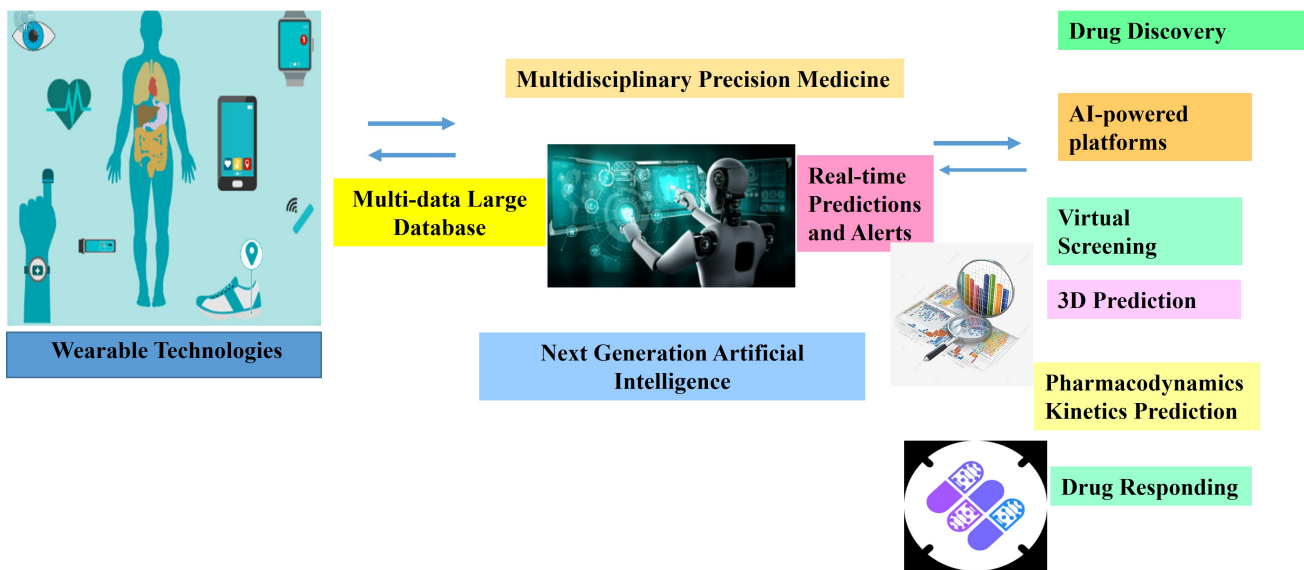


Fig. 1. Influence of deep learning artificial intelligence and its applicability on migraine diagnosis. Support vector machine (SVM) technique. Figure created using Canva (<https://www.canva.com/>) and Microsoft PowerPoint (Microsoft Corporation, Redmond, WA, USA).

widely used kernel properties in SVM classifiers are sigmoid, linear, polynomial, and radial basis functions (RBF) [99,100]. However, once the data set contains extra noise, such as overlapping target classes, SVM performs poorly [101,102].

A promising new path toward more accurate migraine diagnosis has been opened by recent advancements in machine learning. Researchers may now find previously undetectable patterns in data by using device-learning algorithms in time collection analysis. With time series examination, researchers can seek patterns in a patient’s clinical data connected to migraines. SVM and long short-term memory networks (LSTM) are time series analysis tools that look for correlations between a person’s headache patterns over time and their various medical issues. Doctors can identify and treat migraines more successfully by considering lifestyle modifications, environmental factors, and hormone shifts [85].

In addition to time series analysis, system study approaches can be used to identify migraine clusters. Using clustering techniques like k-means, researchers discovered clusters of migraine patients with similar symptoms and indications [103]. Wong *et al.* [104] revealed that algorithms research systems can be used to find trends in time collection records. These models may help in the discovery and examination of migraine-related patterns connected with temporal variations, such as migraine frequency, kind, and duration [104].

Diagnosis of Migraine by Deep Learning

One of the more recent methods in the field of computational medical imaging is deep learning. Using this method, multilevel models with hierarchical representations of the input data are automatically generated, allowing for the extraction of powerful automatic features. In order to enhance diagnostic capabilities and identify the various patterns in patient data that are indicative of an illness, deep learning models are being utilized more and more [105]. Convolutional neural networks (CNNs) model a type of deep learning that has been effectively used for MRI-based disease diagnosis. A study conducted by Li *et al.* [106] to detect Alzheimer’s disease they built a CNN model with two convolutional layers and one fully linked layer. When comparing Alzheimer’s disease (AD) to health controls (HC), they achieved a final recognition rate of up to 92.87% [106].

The diagnosis of migraine depends exclusively on clinical examination, which includes inspection of symptoms and past medical history. Due to the fact that electroencephalography (EEG) is accessible, cheap, and noninvasive, it is the best choice for computer-assisted diagnosis, though imaging procedures like CT and MRI support expert judgment. EEG results are helpful in medical applications, helping with disease treatment and diagnosis. Better EEG-based detection techniques for detecting migraine-related neurological processes have been made possible by devel-

opments in biological signal processing. Our knowledge of migraine pathophysiology is improved by new analysis techniques, especially those based on functional connectivity, which also aid in therapeutic decision-making by providing insights derived from neuroimaging [107,108].

Treatments for Migraine

Recently management and treatments for migraine pain consists of both preventive practices that decrease the frequency of attacks and acute to alleviate symptoms. Acute treatment for migraine and headaches is Gepants (calcitonin gene-related peptide (CGRP) inhibitors), triptans (serotonin agonists), nonsteroidal anti-inflammatory drugs (NSAIDs) (anti-inflammatory medications), ditans (5-hydroxytryptamine (serotonin)-1F (5-HT1F) agonists), and antiemetics are the examples of acute therapy. However, Beta-blockers, antidepressants, antiepileptics, and CGRP monoclonal antibodies are examples of preventive way that calm down neural activity and reduce the intensity of attacks. Non pharmaceutical strategies for Migraine pain control are also used, like cognitive-behavioral therapy, lifestyle changes (diet, sleep hygiene), stress reduction, and neuromodulation techniques (transcranial magnetic stimulation (TMS), vagus nerve stimulation) [53,109–113] (Table 2).

Pharmaceutical Treatments

Nonsteroidal anti-inflammatory medications (NSAIDs) are a diverse group of chemicals with generally similar therapeutic and side effects. The class includes acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen), acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam), anthranilic acids (meclofenamate, mefenamic acid), naphthylalanine (nabumetone), and diaryl heterocyclic compounds (celecoxib, rofecoxib, parecoxib, etoricoxib, and lumiracoxib). NSAIDs are licensed for use as antipyretic, anti-inflammatory, and pain relievers. The primary therapeutic effects of NSAIDs are derived from their capacity to inhibit prostaglandin synthase enzymes known as cyclooxygenases (COXs). COXs exist in two forms: COX1, which is expressed constitutively in most cells, and COX2, which is activated by cytokines, shear stress, and tumor promoters [112,114]. Lasmiditan is a first-in-class ditan that was designed to treat migraines in acute conditions. It activates the 5-hydroxytryptamine (serotonin)-1F (5-HT1F) receptor with great affinity and selectivity. Lasmiditan has a distinct chemical structure based on a pyridinoyl-piperidine scaffold that replaces the indole group found in triptans [115–117].

Beta-blockers are used as the first-line treatment for hypertension. First-line migraine preventive treatments include propranolol, metoprolol, atenolol, and bisoprolol. Although beta-blockers are commonly used in elderly

people, it is unclear if this medicine influences the development of cognitive disorders. One potential mechanism is a reduction in neuronal excitation via antagonism of 5-hydroxytryptamine receptor 1A (5-HT1A) and 5-hydroxytryptamine receptor 2B (5-HT2B) receptors. Beta-blockers are contraindicated in patients with asthma, congestive heart failure, and cardiac dysrhythmia, so alternative drugs for migraine illness prophylaxis are required in these circumstances [113,115,118].

Non-Pharmaceutical Treatment

Non-pharmaceutical strategies are foods or supplements that provide therapeutic or health advantages. The general public's use of them is growing in popularity. Chronic disease patients who want to avoid the problems of long-term prescription medications will find them especially appealing. The use of this type of non-pharmacological therapy is increasing among migraine patients, but it is probably underappreciated. Magnesium, coenzyme Q10 (CoQ10), butterbur root extract (*Petasites hybridus*), feverfew (*Tanacetum parthenium*), riboflavin (vitamin B2), and magnesium are the most widely used nutraceuticals that have demonstrated some benefit in migraine prevention neurostimulation, also known as neuromodulation, is a relatively new and expanding treatment for chronic pain problems such as headache. These approaches use electrical or magnetic stimulation to modify the activity of the brain, cranial, and peripheral nerves, to change pain transmission and perception pathways [119–122].

Innovative and non-invasive neuromodulation are rapidly growing disciplines in migraine research and therapy. Innovative non-invasive neuromodulatory treatments, such as transcranial magnetic stimulation (TMS) and supraorbital nerve stimulation (SNS), with impressive outcomes, have emerged in recent years. Recently, complementary and alternative medicine (CAM) has been identified as a promising treatment option for headache issues. CAM encompasses a variety of health-care approaches and products that are viewed as supplemental or supplementary to traditional treatments and therapies. Furthermore, behavioral techniques can be considered as a supplement to ongoing treatments and frequently result in excellent clinical outcomes. They are not as widely available as nutraceuticals, but they can be obtained in primary and secondary care settings [122–124].

Conclusions

Migraine is a painful neurological disorder characterized by continuous headaches, regularly associated with nausea, sensory disturbances, and cognitive impairments. Recent studies on migraine have pointed out the role of neuroinflammation in its pathophysiology, the contribution of pro-oxidative stress, inflammatory cytokines, and immune system dysregulation. Using these mechanisms has allowed

Table 2. Current treatments for the management of migraine.

Category of treatment	Examples	Action of mechanism	Efficiency
Acute treatments	NSAIDs (Ibuprofen, Naproxen)	Inhibit the cyclooxygenases (COX) enzymes that reduce inflammation as well as pain.	May cause gastrointestinal problems; useful for mild to moderate migraines.
	Gepants (Rimegepant, Ubrogepant)	Antagonists regulate the calcitonin gene-related peptide (CGRP) receptor that prevent pain signals.	Effective for people with vascular risk factors, this tolerated effectively substitute for triptans.
	Triptans (Sumatriptan, Rizatriptan)	Agonists for the 5-HT _{1B/1D} serotonin receptors are substances that narrow blood arteries and block pain pathways.	It works well for moderate to severe migraines, however it shouldn't be used for cardiovascular conditions.
	Ditans (Lasmiditan)	5-hydroxytryptamine (serotonin)-1F (5-HT _{1F}) receptor agonist, which blocks the receptors for trigeminal pain.	Suitable for patients with cardiovascular diseases.
	Anti-emetics (Metoclopramide, Domperidone)	Dopamine antagonists that improve drug absorption and lessen nausea.	Frequently utilized as a supplemental treatment for nausea brought on by migraines.
Preventive treatment	Antidepressants (Amitriptyline, Venlafaxine)	Reduce pain sensitivity by adjusting serotonin and norepinephrine levels.	Essential for adults with co-occurring anxiety or depression.
	Beta-blockers (Propranolol, Metoprolol)	Stabilize vascular tone by reducing sympathetic tone.	It is good for reducing the severity of migraines, but not appropriate for people with asthma.
	Antiepileptics (Topiramate, Valproate)	Inhibits cortical spreading depression and maintain neuronal excitability.	Helpful for chronic migraines but may have adverse effects on cognition.
	CGRP Monoclonal Antibodies (Erenumab, Fremanezumab)	Block CGRP	Excellent for refractory migraines; long acting but very costly.
Non-pharmacological therapies	Behavioral Therapy (CBT, Biofeedback)	Change how pain and stress are perceived.	Reduce the frequency of migraines.
	Lifestyle Modifications (Diet, Sleep Hygiene)	Avoiding stimuli like caffeine, sleep disorders, and dehydration.	Developing treatment that shows promise, particularly in circumstances of drug resistance.

improved treatment approaches that address triggering inflammatory practices in addition to relief from migraine symptoms. The consequences of environmental factors such as stress, sleep disturbances, dietary factors, hormonal changes, and air pollution on migraine symptoms and severity are also associated with migraine symptoms and severity. Lifestyle changes and avoidance of triggers are critical for reducing the frequency and severity of migraine attacks. Obesity management, cessation of alcohol and tobacco use, regular physical activity, enough hydration, and a healthy lifestyle are all easily accessible and cost-effective therapies for any migraine patient. Lifestyle factors, like stress management, dietary changes, improved sleep hygiene, and treatment options, have been found to decrease migraine incidence and intensity significantly. Recent advances in ar-

tificial intelligence and machine learning have transformed migraine diagnosis, enabling sophisticated algorithms to find minute patterns in clinical and imaging data. The AI-driven models increased the accuracy of migraine diagnoses, allowing early diagnosis and facilitating individualized treatment strategies using patient-specific records. However, these innovations show significant possibilities but require more confirmation by significant and large-scale research to ensure clinical application and consistency.

Limitations of the Study

The first drawback of this study is its dependence on existing literature, which may be subject to publication bias or limited by small sample sizes in included studies. Additionally, machine learning models show ensuring real-

world clinical implementation for migraine diagnosis, prognosis (predicting the outcome in future onsets), and treatment predictions (predicting the response to specific therapies) remain at its early stage.

Future Perspectives of the Study

In the future, scientists should examine which environmental factors cause migraines and how to change people's habits to minimize the frequency and severity of attacks. Traditional imaging cannot give precise results, but machines and AI are able to identify details that traditional imaging can't. This technology may allow for earlier diagnosis, specialized treatment for each individual and the ability to monitor things instantly. Moreover, their inclusion in medical treatment must be approved by large-scale studies that guarantee fairness and authenticity in use. It is also important that by merging conventional clinical approaches with developing AI methods and an improved knowledge of environmental causes, future migraine management is likely to become more precise, proactive, and patient-centered.

Availability of Data and Materials

Not applicable.

Author Contributions

MA conceptualized and designed the project. MA, NJ, and MZ contributed to the data acquisition, analysis, and writing of the manuscript. MR supervised the project, interpreted the data, and critically reviewed and revised the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. The Graphical Abstract and Fig. 1 were created using Canva. The authors have no financial or personal relationship with Canva, and the use of this tool does not imply any endorsement.

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