

Review

Triggers, Diagnosis and Treatment of Migraine in Primary Care

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Abstract

Migraine remains the second leading cause of disability worldwide. Typically, diagnosis is based on the patient's medical history and clinical examination, and imaging studies are usually unnecessary. Migraine can be classified according to the presence or absence of aura and the frequency of headaches. Migraine can occur episodically or become chronic. Although the exact cause of migraine remains unknown, studies suggest that the trigeminovascular system plays a role in the perception of migraine pain. The most commonly reported migraine triggers include stress, fatigue, fasting, sensory stimuli, hormonal changes, and sleep disturbances. Treatment options include acute, preventive, and non-pharmacological therapies. Recent progress in understanding migraine pathogenesis has led to the development of new mechanism-based medications, expanding the range of available treatments. Tailoring treatment plans to individual patients' clinical characteristics, preferences, and needs is important.

Keywords: migraine, triggers, diagnosis, treatment

Introduction

Neurological disorders are a leading cause of disability worldwide (1). Migraine is a primary headache disorder which affects approximately one billion people worldwide with female predominance (2). According to Global Burden of Disease Study 2016 migraine is the second biggest contributor to disability among neurological disorders (1).

The diagnosis of migraine is based on clinical criteria established by the International Classification of Headache Disorders, 3rd edition [ICHD-3] (3, 4). Clinical features of migraine include recurrent headache attacks of moderate-to-severe pain intensity lasting for 4 to 72 hours. A typical attack of pain is unilateral, pulsating, and is aggravated by physical activity. Patients may also complain of nausea, vomiting, photophobia, and phonophobia. In some cases, migraine is preceded by an aura, which is characterized by reversible focal neurologic symptoms, typically visual or hemisensory disturbances. Chronic migraine is characterized by ≥ 15 headache days per month for >3 months and fulfilment of ICHD-3 criteria for migraine on ≥ 8 days per month (4).

The majority of patients with migraine are handled by primary care physicians. Referral to specialists is only needed in clinically complicated cases (5). Adequate medical history, use of ICHD-3 criteria and exclusion of other causes of headache are essential (5). Diagnostic aids include headache diaries and calendars, as well as screening tools like ID- Migraine questionnaire. In case of the presence of red flags neuroimaging can be implemented to exclude secondary headache causes (6).

Pathogenesis of migraine is not fully understood, but it is considered to involve the trigeminal nerve and its axonal projections to the intracranial vasculature (trigeminovascular system) (7). Numerous clinical studies investigated migraine triggers. The most common triggers include stress, fatigue, fasting, menstrual changes and sensory stimuli (8). Sleep disturbances, caffeine withdrawal, weather changes, physical exercises and light have also been linked to the development of migraine attacks (8-10). It is considered that focusing on

triggers can help patients prevent migraine episodes and encourage them to implement lifestyle changes to reduce the frequency of attacks (11).

Treatment modalities for migraine include acute and preventive medications and a range of non-pharmacological therapies. Acute treatment is aimed at migraine attacks relief and is implemented in stepped care approach (12). Non-steroidal anti-inflammatory drugs are used as first-line therapy followed by triptans. In case of insufficient control of symptoms ditans or gepants can be implemented, however their application is limited (6). In patients who do not achieve control of their symptoms via acute treatment, preventive therapy should be suggested. The range of medications used is wide and includes beta-blockers, antidepressants, anticonvulsants and others (13).

Non-pharmacological therapy is normally complementary to acute and preventive treatments but can also be used instead of them if the medications are contraindicated. Some evidence supports the use of yoga, behavioural therapy, neuromodulatory devices, meditations and accupuncute in migraine management (14, 15). The impact of physiotherapy and dietary interventions remains controversial (16, 17). Patient education and centrivity promote cooperation between the patients and the physician and improve treatment outcomes. Building trustworthy relationship encourages treatment compliance and lowers the risk of complications like medication overuse headache and chronic migraine (18). The purpose of this literature review is to summarize the current understanding of triggers, diagnosis and treatment modalities of migraine in primary care.

Methodology

This study is based on a comprehensive literature search conducted on April 10 2023, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. Articles published in the period between 2018 and 2023 were mostly included. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the

reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about triggers, diagnosis and management of migraine. There were no restrictions on date, language, participant age, or type of publication.

Discussion

Triggers

The exact cause of migraine remains unknown. According to research, the trigeminovascular system is considered as the physical and functional foundation from where nociceptive signals arise and result in the sensation of pain in migraine attacks (7). Events that precede and provoke migraine attacks are referred to as triggers. The most common triggers of migraine include stress, fatigue, fasting, sensory stimuli, hormonal changes and sleep disturbances. Some patients also reported weather changes, physical activity, odours and alcohol to cause headache attacks (8).

Stress is one of the most frequently reported triggers in patients with migraine (9, 19). Studies suggest that the relationship between stress and migraine exists, however the evidence supporting the fact that stress directly influences incidence, chronification, migraine attacks, or increased burden of migraine is still controversial (19). Some patients benefit from stress management-oriented behavioural therapies, suggesting that these techniques should be used as part of management plans depending on patient's preferences (14, 19). In other studies fatigue was a more commonly reported symptom preceding migraine attack, however findings do not support causal relationship between fatigue and headache onset (8). Poor sleep is often reported by patients as a migraine trigger. It is also noted that sleep relieves headaches in some cases. Sleep disturbances are considered to have the same pathophysiological pathways as migraine, which explains their bidirectional relationship (20). Similarly, physical activity has been reported to both trigger migraine attacks and serve as a relatively effective non-pharmacological approach to treat them. This is explained by the fact that regular exercises alter

migraine triggering threshold and lower the frequency of attacks(21).

Dietary triggers are largely discussed in reports nowadays, although the evidence provided is not clear. Fasting proved to be among the best studied and most reliable natural migraine triggers. It is considered to become more common during longer fasts for religious reasons such as Ramadan (22). Caffeine is sometimes used in combination with non-steroid anti-inflammatory drugs (NSAIDs) to treat migraine attacks. It is also cited as a migraine trigger; however, the causal relationship was not established. Caffeine overuse (>200 mg daily) is considered to lead to migraine chronification, whereas sudden caffeine withdrawal may exacerbate migraine attacks (23).

Moreover, hormonal changes during menstrual cycle are the most common migraine trigger in women. Many studies support the correlation between estrogen level and headache attacks. The decrease in estrogen level before menstruation causes the imbalance between pro-migraine factors, such as calcitonin gene-related peptide (CGRP), and anti-migraine factors and provokes migraine (24). Other factors including sensory stimuli, weather, odours and alcohol have insufficient evidence to be considered migraine triggers. They are mostly premonitory symptoms that just mimic triggers (8, 10).

Overall, there is no consensus on practical application of triggers. Some studies suggest that they can be used to forecast migraine attacks and help patients take control of their symptoms (8, 25). On the other hand, some authors state that the role of triggers is overemphasized, except for hormonal changes in menstruation (6).

Diagnosis

The third version of the International Classification of Headache Disorders (ICHD-3) categorizes migraine into three groups: migraine without aura, migraine with aura, and chronic migraine (4). Each type has particular clinical characteristics that are assessed to ensure accurate diagnosis. Recurrent headache attacks lasting 4-72 hours are a typical

feature of migraine without aura. Headache is characterised by pulsating pain of moderate-severe intensity, usually unilaterally localized. Pain is aggravated by physical activity (4). Bilateral pain occurs in around 40% of individuals with migraine (6). The most frequently observed accompanying symptoms include sensitivity to light (photophobia), sensitivity to sound (phonophobia), and feelings of nausea and vomiting. Before the attack prodromal symptoms can include fatigue, low mood, yawning, and cravings for specific foods. After migraine episode patients complain of postdromal symptoms that last up to 48 hours. These include tiredness, concentration difficulties and neck stiffness (26).

Around 30% of patients with migraine experience aura. It may occur inconsistently in some cases. Aura refers to temporary focal neurological symptoms that typically occur before or during the headache phase of a migraine episode. Visual manifestations account for the majority of aura symptoms. Around 31% of patients experience sensory disruptions, which typically involve tingling or numbness that spreads gradually on one side of the face or arm. These symptoms are predominantly unilateral. Less frequently, aura may present with speech difficulties, brainstem symptoms (such as vertigo and difficulty speaking), motor weakness (in hemiplegic migraine), and retinal symptoms (such as recurring visual disturbances in one eye). Aura symptoms may be similar to those of transient ischemic attacks (TIA). Unlike TIA, aura symptoms are characterised gradual (over ≥ 5 min) spread (4). It is important to note that migraine with aura and migraine without aura can coexist in some cases. In such instances, it is necessary to diagnose both conditions. (4).

Around 3% of patients with episodic migraine (EM) develop chronic migraine (CM) within one year (27). Chronic migraine is defined by headache on ≥ 15 days per month for ≥ 3 months, of which at least 8 days/month have migraine headache features (4). Compared to EM, CM is associated with substantial reduction in quality of life and increased disability, resulting in personal and socio-economic burden (28). Studies suggest that patients with CM are underdiagnosed and undertreated, rarely referred to

specialists and, thus, the management is suboptimal (28, 29).

Medical history is the most important part of migraine diagnosis. Meticulous history taking with enables systematic application of the ICHD-3 criteria. To obtain a comprehensive medical history, the following information should be gathered: the age at which the headache started; the frequency and duration of headache episodes; the features of the pain (such as its location, intensity, triggers, and alleviating factors); any accompanying symptoms (such as sensitivity to light and sound, nausea, and vomiting); any aura symptoms experienced (if present); and a record of past usage of preventive and acute medications (6, 12). As heritability of migraine is estimated to be approximately 42% (30), family history is often positive, especially in first-degree relatives. Patients tend to underreport family record; thus, particular attention should be paid to it during examination (6).

Additionally, several diagnostic aids available including questionnaires and screening tools can be used to support the diagnosis (5, 6). Diary information on the pattern and frequency of headache attacks, additional symptoms and use of acute medication can be helpful. Diaries normally are more informative than headache calendars, which include just the frequency of episodes, intensity of headaches, and related events, such as acute and preventive medication use and menstruation. Electronic headache diaries and calendars are important developments that are user-friendly and comprehensive (6). Screening tools can also aid in the diagnosis of migraine. These tools should be utilized in conjunction with a review of the patient's medical history and/or a diagnostic headache journal. The three-item ID-Migraine questionnaire and the five-item Migraine Screen Questionnaire (MS-Q) are validated screening tools that have been translated and tested for use in various languages (5, 6, 28). In cases where the diagnosis is uncertain, a physical examination is necessary, and additional investigations such as neuroimaging, blood tests, or lumbar puncture may be used to confirm or rule out the possibility of secondary causes for the headache (6, 26).

Neuroimaging is not required in patients with migraines who have a normal neurological examination and do not display any atypical features or warning signs. However, it may be advised in certain situations, such as in cases of prolonged or persistent aura, increasing frequency or severity of migraines, changes in clinical features, or if the patient experiences the first or worst migraine. Neuroimaging may also be considered in cases of migraines with unusual manifestations, such as brainstem aura, confusion, or motor symptoms (hemiplegic migraine), as well as in cases of late-life migraine accompaniments, aura without headache, side-locked headache, and post-traumatic headache (26).

Management

Migraine management is based on three approaches: patient centricity and education, pharmacologic and non-pharmacologic treatments. Migraine is a recurrent and episodic disease that is currently incurable but can be controlled. Inadequate treatment of migraine attack has a huge socio-economic impact and may lead to episodic migraine chronification (27).

Non-pharmacologic

The evolution of migraine is connected to lifestyle factors such as sleep, dietary habits, stress, and physical activity (3). Chronic migraine sufferers have less regular sleep, exercise, and meal habits than patients with episodic attacks. Chronic migraine patients also experience higher levels of perceived stress compared to controls (3). The bidirectional relationship between sleep and migraine means that poor sleep routine can increase migraine frequency, and migraine can decrease the quality of sleep (13). Keeping a headache calendar is the initial step to monitor interventions quantitatively (11).

Based on the evidence provided in the referenced studies, there are six important aspects to non-pharmacological treatment for migraine. This includes maintaining daily routines with regular and sufficient periods of night sleep, abundant hydration to avoid dehydration, which is a frequent cause of migraine attacks, regular aerobic exercise to prevent

migraines. Evidence supports the effectiveness of moderate exercise, avoiding stressful situations and fasting, relaxation and mindfulness techniques such as yoga as it has been proven effective in clinical trials as an additional approach for migraine patients (14, 15). Other important aspects include limiting caffeine intake, avoiding aspartame, reviewing the temporo-mandibular joint (TMJ) for dysfunction, considering alternative treatments like magnesium and riboflavin, maintaining proper head posture, and seeking physical therapy for headache symptoms (17).

Pharmacologic

Teaching patients to identify their migraine attacks is crucial for effective acute migraine treatment, as early intervention is essential for attack relief. A stratified approach to treatment should be employed from the start, selecting the appropriate drug based on symptom severity, route of administration, and comorbidity of the patient (13). Acute migraine therapy can be divided into three categories: specific, non-specific, and adjuvant treatments (26). Mild migraine attacks and auras can be effectively managed using non-specific treatments like acetaminophen and NSAIDs such as ibuprofen, diclofenac, and dexketoprofen. For patients who cannot tolerate them, paracetamol (acetaminophen) is a useful first-line option. However, it is generally recommended only in cases of gestational migraine, during adolescence-childhood, and in attacks that do not cause severe disability. In patients who experience nausea or vomiting, adjuvant medications such as dopamine D2 receptor antagonists (antiemetic/neuroleptics) like domperidone, metoclopramide, and chlorpromazine may be necessary. These medications can also aid in the absorption of other treatments. However, the use of these medications should be closely monitored for potential side effects like tardive dyskinesia, extrapyramidal symptoms, sedation, and orthostatic hypotension. Opioids like morphine and barbiturates, codeine, tramadol, and/or caffeine in combination with painkillers should be avoided to prevent headache chronification and the development of medication overuse headache (6).

Specific acute treatments are the drugs of choice for moderate-severe attacks (13). Triptans are a specific class of migraine medications that have been shown to be both safe and effective. However, they are not recommended for patients with uncontrolled hypertension, as well as those with coronary, cerebrovascular, or peripheral vascular disease, due to their vasoconstrictive properties. The most common side effects of triptans include palpitations, neck or chest tightness, dysgeusia, and laryngeal discomfort, and patients should be made aware of these effects before starting treatment. Nevertheless, triptans are generally considered to be safe at the vascular level. There are currently seven different triptans available, and the choice of medication should be tailored to the individual patient based on factors such as the timing and severity of the migraine attack, the presence and timing of nausea or vomiting, levels of disability, and the frequency and pattern of attacks (26).

If a patient does not respond to triptans or cannot use them for any reason after an adequate trial period (consisting of at least three consecutive attacks with no or insufficient therapeutic response), treatment options are currently limited. While ditans or gepants could be considered, they are not readily available. Lasmiditan is currently the only ditan approved for acute migraine treatment, and ubrogepant and rimegepant are the only gepants that have been approved. Although indirect comparisons of data from randomized controlled trials suggest that the efficacy of lasmiditan is similar to that of triptans, its use has been associated with temporary impairment of driving ability, which may discourage widespread adoption. Individuals taking lasmiditan may be unable to self-assess their ability to drive and should avoid operating machinery for at least eight hours after taking the medication (13).

The purpose of preventive treatment is to decrease the frequency, duration, and intensity of migraine episodes, which in turn, makes them more manageable with acute treatment. Ultimately, the goal is to enhance the patient's quality of life by reducing the impact of migraines on their daily functioning. Preventive medications are fundamental in the management of headaches and

should be contemplated for patients who experience frequent headaches (four or more attacks per month or eight or more headache days per month), have not responded to acute medications or have contraindications or side effects to them, or have prolonged auras that are impacting their quality of life despite lifestyle changes and acute migraine treatment. The selection of preventive treatment should be personalized, taking into account factors such as the patient's comorbidities, preferences, lifestyle, age, and gender (28). After evaluating the potential side effects and effectiveness of various options, the physician and patient should select the appropriate medication.

A successful preventive migraine drug reduces the frequency or days of migraine attacks by at least 50% within three months (13). Basic principles of preventive treatment include starting at a low dose and increasing it slowly, maintaining treatment for at least three months, and setting realistic expectations for improvement and adverse effects from treatment. Patients should be warned that treatments can take up to a month and a half to start working, and teratogenic drugs should be avoided in women of childbearing age (6). Oral preventive drugs include antiepileptics, antidepressants, and blood pressure medications.

Topiramate, valproic acid, and gabapentin are some of the anti-convulsant medications that may be effective for preventing migraines. Although there are other options available, the efficacy data for these alternatives has not been well established in migraine patients. Of this group, topiramate is the most frequently prescribed and most effective medication, but it can cause a variety of side effects involving nervous system and gastrointestinal tract. Valproic acid, on the other hand, has more side effects than any of the other options, including weight gain, hair loss, and acne, and should not be used as a first-line treatment option. Ultimately, the choice of medication should be made after careful consideration of the potential side effects and effectiveness, in consultation with the patient (13).

Amitriptyline is the most commonly prescribed antidepressant for the prevention of migraines, but

it can cause weight gain and drowsiness. The dose is gradually increased to a maximum of 1 mg/kg/day. Other antidepressants, such as venlafaxine, may also be used, with treatment starting at 37.5 mg per day and increasing to at least 75 mg per day. Blood pressure should be closely monitored during this treatment, as it may result in an increase in blood pressure. Antidepressants can be employed for migraine prevention even in the absence of underlying depression (18).

Beta-blockers are a frequently utilized class of medications in the preventive treatment of episodic migraines. Propranolol is the most widely used and evidence-based medication. While the available data is limited, lisinopril and candesartan may be effective for preventing episodic migraines and may be an option for individuals with high blood pressure who cannot use beta-blockers. According to available pharmacological evidence, flunarizine, a non-specific calcium channel blocker, is the only effective prophylactic treatment for episodic migraines in this class of medications (6).

In recent years, Erenumab (Aimovig®), Fremanezumab (Ajovy®), Galcanezumab (Emgality®), and Eptinezumab (Vyepiti®) were introduced in the US after demonstrating positive results in clinical trials. These are monoclonal antibodies (mAb) that target Calcitonin Gene-Related Peptide (CGRP) or its receptor, which have a low side effect profile and are effective in preventing migraines. CGRP is the primary chemical that is released from nerve endings in the brain during a migraine attack and is responsible for many of the migraine symptoms. Eptinezumab (Vyepiti®), which also targets the CGRP ligand. Real-world evidence series confirms the good effectiveness and safety profile observed in clinical trials (6).

Conclusion

Migraine is a neurological disorder that is widespread and contributes significantly to the global burden of disease. Even though there are comprehensive diagnostic criteria and a variety of therapeutic options available, the diagnosis and clinical management of migraine continue to be

inadequate worldwide. In the last five years, significant progress has been made in treating migraine, with new mechanism-based therapies that complement standard care. While there are many effective treatment options available, several challenges still need to be overcome. These include a lack of understanding of the biological mechanisms underlying migraine and identifying potential drug targets. Additionally, there is a need for precision medicine strategies that can personalize new therapies to the unique migraine profile of each patient.

Disclosure

Conflict of interest

There is no conflict of interest.

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Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection and final writing of the manuscript.

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