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Strategies for Treating Acute Migraines and Identifying Triggers. Literature review

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ABSTRACT
Introduction
Migraine, a prevalent neurological disorder affecting a substantial portion of the global population, poses a significant burden on individuals' overall quality of life. While the exact pathophysiological mechanisms underlying migraine headache attacks remain elusive, the involvement of trigeminal pathway activation is well-documented. A multitude of factors, collectively termed triggers, have been identified as capable of precipitating migraine episodes, ranging from dietary components to environmental stimuli such as bright lights and weather fluctuations. Migraine headaches typically manifest as throbbing pain localized predominantly on one side of the head and are often accompanied by a constellation of additional symptoms including photophobia, phonophobia, and nausea. The management of migraine involves a diverse array of therapeutic modalities tailored to the specific characteristics of the pain experienced. These may include the administration of non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, triptans, and antiemetics, among others. This study endeavors to explore the most prevalent triggers implicated in migraine onset, as well as contemporary treatment strategies, with an emphasis on incorporating the latest research findings and therapeutic advancements in this evolving field.
Aim of the study
This review aims to identify symptoms, triggers of acute migraine and solutions in its treatment process, including latest developments.
Material and method
This article presents the current state of knowledge about acute migraine, triggers and treatment options in various scientific articles. Publications describing acute migraine attacks and treatments including the most recent reports in the field were reviewed using the PubMed platform. The search included the keywords ‘migraine, 'migraine triggers', 'triptans', 'migraine with aura'.
Keywords
migraine; migraine triggers; triptans; migraine with aura

Introduction

Migraine is a frequent, chronic neurological disorder that is estimated to affect 12% of the global population [1]. It is presently ranked as the sixth most incapacitating disorder worldwide, holding the top position among all neurological conditions [2]. The incidence is 40% if one of the patient's parent suffers from migraines and 75% if both parents have migraines. Ailments typically begin in late childhood or early adolescence. Headache attacks tend to peak around the age of 50 and become less frequent as people get older [3]. The ratio of female to male migraine sufferers is 3:1 [4]. Migraine is classified into two categories: episodic migraine (EM) and chronic migraine (CM). Episodic migraine is characterised by having less than 15 headache days per month, while chronic migraine is defined by the incidence of 15 or more days with headache per month for a duration of over three months [5].

Symptoms

Migraine is characterised by paroxysmal symptoms - the most characteristic symptoms are attacks of headache, which patients most often describe as throbbing, localised unilaterally and sensitive to movement and physical activity. Its strength is described by patients as at least moderate or severe.

The average number of attacks (around 70% of the patients) is between one and two attacks per month. During a headache, patients usually need to stay in a quiet and dark room [6]. Migraine attack can last from 4 to 72 hours [7]. The average duration is 24 hours [8].

The headache may be accompanied by additional symptoms such as - hypersensitivity to light (photophobia), sounds (phonophobia) and movement, dizziness, nausea, vomiting, diarrhoea [9].

A migraine attack is often preceded by symptoms that announce an incoming headache. Identifying these symptoms may prove advantageous in averting the initiation of a migraine episode. Among the most common are weakness, drowsiness and difficulty focusing. Other symptoms may also be present, i.e. hypersensitivity to light, nausea, symptoms of mood disorders e.g. irritability, anxiety, frequent yawning, urinary frequency [9,10].

A migraine attack usually consists of three phases - 1. prodromal, 2. headache phase and 3. postdromal [4]. Approximately one third of headache sufferers have a fourth additional phase - called migraine aura. It is a visual, sensory or motor disturbance caused by transient

neurological symptoms that are focally localised [7]. Visual disturbances are the most common symptom of aura [7,11].

- Premonitory phase - preceding the headache, there are non-painful signs that manifest hours or days in advance. The symptoms may encompass tiredness, increased thirst, impaired concentration, heightened frequency of urination or yawning [12].
- Aura – visual, sensory, motor disturbance caused by transient neurological symptoms that are focally localised [7]. Visual disturbances (usually, an enlarging blind spot) are the most common symptom of aura [7,11,12].
- Headache - the stimulation of the trigeminal sensory pathways is responsible for the throbbing pain experienced during a migraine episode [12].
- Postdomal - the predominant symptoms during this period are fatigue, impaired focus, and increased sensitivity to acoustic disturbances [12,13].

Migraine pathophysiology theories

It is unclear what precise phatophysiological process exactly causes migraines. The fundamental characteristic appears to be complex, genetic predisposition coupled with behavioural and environmental circumstances [2]. The current consensus is that the cause of the headache phase in a migraine attack is the activation of the trigeminal pathway. This pathway includes neurons that provide sensory input to the major cerebral arteries and the dura mater. Calcitonin gene-related peptide (CGRP) and other vasoactive neuropeptides are generated by these activated neurons, which also send nociceptive signals to the trigeminal nucleus caudalis. The caudate nucleus transmits signals of pain to specific central regions involved in pain processing, including the cortex, brainstem, thalamus, hypothalamus and basal ganglia. CGRP is linked to migraines by causing inflammation in the dura mater, arterial vasodilation, enhancing neuronal transmission, and influencing the transmission of pain signals in the trigeminal complex. Elevated levels of CGRP have been seen during a migraine attack, although they decrease with therapy and during the intervals between migraines [14,15].

Triggers

There are factors that predict the occurrence of migraine attacks - so-called triggers. It is important to be aware of such factors because patients, by avoiding exposure to triggers, can reduce the number of acute attacks of migraine headaches [16]. The most common triggers for

migraine attacks are consumed foods and alcohol [17]. A study was conducted which showed that one in four people with migraines identified foods as a trigger for a pain attack [18]. The list of these substances is very long, the most commonly mentioned being chocolate, citrus fruits, coffee, nuts, red wine, nitrate-containing foods (eg. bacon, salami), tyramine-containing foods (such as cheddar cheese, beans, rotten meat, smoked fish) and foods that contain monosodium glutamate, which is used as a flavour enhancing agent in a wide variety of processed meals and snacks [17,19]. Also, long periods of fasting can trigger a migraine attack - the direct mechanism for this is hypoglycemia, which is a proven migraine trigger in studies [20,21]. Another known trigger of headache attack is dehydration [21].

Stress is acknowledged to be one of the most important factors triggering a migraine headache attack among patients with this condition. A migraine attack following exposure to severe stress can occur with up to a 3-4 day delay, which may mean that the contribution of stress as a trigger may be understudied [21].

Changes in weather conditions also influence the occurrence of migraine headache in some patients. An association is noted especially between changes in atmospheric pressure, low temperatures, high humidity and certain types of wind [17,19,20]. Hypoxia is another factor that is suspected of triggering the attacks [21]. A study was conducted in which normobaric hypoxia triggered a migraine in six of 14 subjects compared to only two subjects after placebo [22].

Sensitivity to odours is not limited to the pain attack itself - odours, especially strong ones, can also trigger a migraine attack in some people - the most common odours are strong perfumes and cigarette smoke [17]. It has been proven that the average time elapsed from the triggering odour to the onset of the headache is about 10 minutes [23].

Exposure to light, especially intense, bright, flashing light, can also trigger a pain attack in patients with migraine [17,20]. It has been observed that migraine sufferers are more sensitive to the effects of light both during the headache attack and between them. Sunlight exposure is also known to have a triggering potential. Based on studies conducted, it can be seen that the frequency of migraine attacks increased with intensifying daily sunlight exposure [17,24]. Prolonged and persistent exposure to certains forms of noise, such as traffic which can also provoke a migraine attack [19,20].

It is thought that the decreased levels of estrogen in women during the monthly cycle, which occurs before the onset of menstrual bleeding, may act as an initiator of a migraine attack. 6%

of women of reproductive age develop migraine, having a strong association with the menstrual cycle phases [25,26].

Sleep disturbances are also an important factor that can initiate a migraine attack. Problems such as fluctuations in sleep duration (either too little or excessive), poor quality of sleep, insomnia, early waking, are linked to an increased occurrence of attacks [19,20,21].

Nitroglycerin (NTG) is a chemical substance that induces migraine attacks in 60-80% of patients struggling with the condition within 5-6 hours [22]. It is assumed that NTG's activity as a nitric oxide (NO) donor is responsible for triggering migraine headache [27]. Other drugs that can cause acute migraine headache include indomethacin, cimetidine, theophylline, nifedipine, hormonal contraceptives [19].

Awareness of trigger factors is essential among patients managing migraine headaches. Understanding the triggers reduces exposure to triggers themselves, which will translate into less frequent pain attacks. Conscious avoidance of exposure also gives the patient a sense of improved control over headache attacks, which will increase their quality of life. Exposure to trigger can also provide a warning function that will enable the patient to use medication early in a pain attack [21].

Treatment

Fast headache relief, improvement of functional abilities and prevention of recurrence are the primary goals of acute migraine therapy, all while minimising adverse effects [28].

This approach is divided into two categories: acute treatment for alleviating migraine attacks and preventive treatment for decreasing the number, time duration and pain level of migraine attacks [29]. Personalised management of treatment based on the patient's symptoms and preferences is enabled through a range of options, taking into account the effectiveness, unwanted side-effects and cost of medication [30].

The severity of the pain during a migraine attack is an important factor in choosing a treatment. Paracetamol (acetaminophen), aspirin or a non-steroidal anti-inflammatory drugs (NSAIDs) (the best choice is ibuprofen, diclofenac potassium and naproxen sodium) can be used first for mild headaches during a migraine attack [3,29,31]. For people with moderate to severe migraines, triptans or dihydroergotamine are a recommended treatment [3]. Triptans are usually preferred to dihydroergotamine because of the wider choice of dosage forms, tolerability, side-effect profile and better effectiveness [32]. Patients should be strongly

suggested to take their acute treatment drugs as soon as possible after the migraine headache begins (after the pain has started), as this usually makes them more effective [32,33].

It is generally accepted that 3 strategies are used to treat migraine headaches - stratified care, step care across attacks and step care within an attack [30,32]. The preferred approach is stratified care [3].

Stratified care involves selecting medication based on the patient's treatment needs, including intensity of attacks, the occurrence of associated symptoms like vomiting and the level of disability caused by migraine. It is most effective when patients can identify which of their headaches are likely to respond to a non-specific therapy like an NSAID and which require a migraine-specific medication like a triptan [32].

Step care across attacks involves selecting initial medication based on the cost and tolerability profile [30]. The drug should have as few side effects as possible and be suited to the individual patient's financial capabilities [31]. The treatment strategy involves the patient taking an appropriate first medication, such as a non-specific analgesic, for the first few migraine attacks. If this medication fails to reduce symptoms, the patient returns to the doctor and is prescribed another medication, such as a triptan or dihydroergotamine, for future attacks [32].

For the step care within an attack strategy the recommended first-line treatment for migraine is a simple analgesic (eg. acetaminophen) or non-steroidal anti-inflammatory drug (NSAID). If this method proves to be ineffective, the patient should take a rescue medication, such as a triptan, a few hours later [32]. Patients whose attacks develop gradually or whose attacks fluctuate in severity may benefit from this approach [31].

There are a number of rules to consider when trying to treat acute conditions:

1) Patients should take the acute medication at an early stage of an attack - this should be the goal of treatment for most patients. It has been proved that triptans and other acute medications are most effective when taken early in the migraine attack [28,31].

2) To facilitate absorption of the entry drug and improve pain control, the primary drug should be taken with medication that has different mechanisms of action or with antiemetics [28]. Metoclopramide significantly enhances the absorption of other medications and may reduce gastric discomfort during migraine headache [31,34].

3) A suitable medication formulation should be selected based on the characteristics of the patient's migraine headaches [31]. For most people without symptoms of nausea, taking an

oral tablet medication may be a right treatment option. Triptan nasal sprays can be effective for people with stronger nausea and those who may vomit during the attack. For less intense headaches that develop quickly, or when patients prefer a faster effect, there are various oral formulations that may be effective for example, aspirin in effervescent form, diclofenac in powder form, and fast-dissolving oral tablets containing sumatriptan. Injectable formulations may be the most effective for migraine attacks that build up very quickly and are fully developed when the patient wakes up [31].

4) To avoid the potential risk of medication-overuse headache (MOH), patients should be advised to limit their use of simple analgesics to less than 15 days per month and to limit the use of triptans, ergots or combination analgesics to less than 10 days per month [28].

5) A dose of caffeine (≥100 mg) can also be added to a dose of anelgesics - the study found that caffeine combined with aspirin or paracetamol provided pain relief to more people than analgesics alone and reduced the dose of analgesic needed to reduce headache pain by 40% [35,36].

Acetaminophen and non-steroidal anti-inflammatory drugs

Acetaminophen, aspirin and non-steroidal anti-inflammatory drugs are the first choice for the therapy of mild migraine attacks. Recommended single dose of acetaminophen is 1000mg. As first-line treatment in the emergency department in patients intolerant to NSAIDs and aspirin, intravenous acetaminophen 1000 mg is recommended [30,37].

Acetaminophen is less effective compared to NSAIDs [31]. The advantage of acetaminophen is that, as opposed to to aspirin and NSAIDs, it has a lower risk of adverse gastrointestinal effects and has no impact on platelet function [30,31]. To prevent hepatotoxicity, the daily dose of acetaminophen must be limited to 4000 mg [31].

The drug, which is a combination of acetaminophen, aspirin and caffeine has been shown to be highly effective and may be considered as a first-line choice for the management of migraine headaches [30,38].

Ibuprofen is the most often used nonsteroidal anti-inflammatory drug among migraine sufferers. Ibuprofen 400 mg is the recommended dosage, with a daily maximum of 2400 mg [31]. ASA is usually taken at doses of 1000mg (no more than 4000mg per day) [30,31]. Diclofenac potassium is another non-steroidal anti-inflammatory drug which acts fast to relieve migraine headache. The usual dose of diclofenac potassium is 50 mg. The maximum dose is 150 mg per day. Naproxen sodium is also used for relieving migraine headaches.

Standard dosage is 500 milligrammes. The maximum daily dose shouldn't exceed 1375 mg [31].

Triptans

In the treatment of moderate to severe migraine, triptans are an effective initial option.

By stimulating 5-hydroxytryptamine (5-HT1B, 5-HT1D) receptors situated in cranial blood vessels and nerve endings, triptans induce analgesic effects by augmenting 5-HT signalling [31,39]. Triptans are most effective when given early during an headache attack. For those experiencing migraine with aura, research shows that the most effective outcomes are seen by using the triptan medication at the beginning of pain rather than at the beginning of aura [30,31]. It is important to keep in mind that the effectiveness of triptans as a therapy for migraines might be different across patients. It is recommended to try other triptans for another attack if the patient does not respond well to the first one. These alternative triptans can be far more effective [31].

Various 7 triptans are used to treat acute migraines - Sumatriptan, Almotriptan, Zolmitriptan, Eletriptan, Frovatriptan, Rizatriptan and Naratriptan [30]. They are mainly available as oral tablets. Both sumatriptan and zolmitriptan can be delivered in oral and intranasal forms. Sumatriptan can also be administered by subcutaneous injection. Eletriptan has the lowest cardiovascular risk [30,40]. The administration of Sumatriptan as a subcutaneous injection of 6 mg has the most advantageous effect in terms of achieving full pain relief within a two-hour period [40]. It is also a good treatment option for patients who experience nausea and vomiting during a migraine attack and have difficulties with taking oral medication [31].

When used at appropriate dosages, triptans are pharmacologically selective for migraine and have only a few serious side effects. Dizziness, nausea, fatigue, sleepiness, and discomfort in the chest were the most common side effects of triptans for migraine therapy [30]. There are variations in triptan tolerability according to gender, as women appear to experience more side events and headache recurrences when using these medications [2,41].

Triptans are contraindicated in patients with uncontrolled hypertension, cardiovascular disease or cerebrovascular disease due to the vasoconstrictive effect mediated by 5–HT1B [28].

Dihydroergotamine

Published clinical studies and case reports have shown that dihydroergotamine (DHE), when given intravenously, intramuscularly, subcutaneously or intranasally, is highly efficacious and well tolerated for treating migraine headaches [42]. However, it presents a greater frequency of adverse reactions compared to triptans as a result of lower receptor selectivity [30]. In general, nausea is the most frequent negative occurrence observed after using DHE, especially when it is delivered intravenously. That is why intravenous DHE is frequently used together with a preventive antiemetic, typically metoclopramide [42]. DHE shouldn't be used in pregnant women [30].

Antiemetics

In the case of migraine, when severe vomiting and nausea are present, antiemetics are often used. They are often administered parenterally. Antagonists of dopamine, including metoclopramide, prochlorperazine, chlorpromazine, and droperidol, are recommended. All dopamine antagonist drugs have a risk of side effects such as extrapyramidal symptoms, fortunately this occurs rarely. Metoclopramide is the drug that has been most studied in this therapeutic indication [6,30].

Acetaminophen in combination with metoclopramide demonstrated reduction migraine headache more effectively than acetaminophen alone [37].

Opioids

Opioids used to treat migraine are represented by butorphanol, codeine, tramadol and meperidine. This group of drugs is not routinely recommended for the treatment of migraine attacks, due to the high risk of overuse by patients and the possibility of causing respiratory centre depression [37].

Recent developments in acute migraine treatment

The range of medications called triptans has recently been broadened by bringing in ditans, which are serotonin 5HT1F receptor agonists, as well as gepants, which are CGRP receptor antagonists [2]. They can be administered to individuals with cardiovascular disease for whom triptans are not recommended due to contraindications [14].

Ditans

At this time, lasmiditan is the only ditan available to treat a migraine attacks. It is a strong and specific activator of the 5-HT1F receptor, which works in relieving attacks of migraines by inhibiting the electrical activity of neurons in the trigeminal nucleus caudalis [2,43]. In the lasmiditan study, the rate of pain relief after two hours and the absence of the most intolerable migraine symptoms improved significantly in comparison to the placebo group [2]. The use of lasmiditan was frequently linked to mild to severe adverse effects. The major symptoms reported were paresthesias, nausea, dizziness, sleepiness, and feeling fatigued [44]. Regular administration of lasmiditan has the potential to induce medication-overuse headache [45].

Gepants

Gepants are a calcitonin gene-related peptide (CGRP) receptor antagonists that have been created to be used as an acute migraine therapy. Two orally administered substances that FDA has recently approved: rimegepant and ubrogepant as treatment for acute migraine. Early results of trials also indicate the efficacy of the zavegepant nasal spray [2,46]. The study found that administering ubrogepant at dosages of 50 and 100 mg intermittently (one or two doses per attack) resulted in favourable safety and tolerability outcomes. The most frequently observed adverse effects were nausea and dry mouth [45]. Rimegepant has shown effectiveness and acceptability in several clinical studies. An orally disintegrating tablet formulation of rimegepant is offered, potentially providing a quicker onset of action compared to the conventional oral tablet formulation [47]. It exhibited a high level of tolerance when utilised for a duration of up to 1 year. Nausea and urinary tract infection were the most often reported side effect [45,47]. Acute migraines were successfully managed with zavegepant nasal spray in single dosages of 10 or 20 mg. The intranasal route of administration is advantageous for patients who experience nausea or vomiting and are unable to take the medicine orally. Zavegepant had a favourable safety profile [48]. Positive characteristics of gepants involve their capacity to successfully administer multiple dosages of the medication during an attack. These medications provide a minimal risk of inducing migraine headaches as a result of overuse of the drugs [2].

Celecoxib

The newly formulated oral solution of celecoxib, nonsteroidal anti-inflammatory drug (NSAID), has received approval for effectively treating acute migraine headaches.

Administration of celecoxib oral solution in low, intermittent amounts appears to be associated with fewer safety concerns than that of other nonsteroidal anti-inflammatory drugs (NSAIDs). No serious adverse events linked to the medication were recorded in the clinical trials of celecoxib oral solution for the immediate treatment of migraine [49].

REN - Remote electrical neuromodulation

Remote electrical neuromodulation is an innovative therapy for acute migraine that activates the peripheral nerves in the arm to trigger a pain-relieving process. The REN technology is a portable stimulation unit that operates on battery power and may be controlled via a smartphone application. The electrical unit is used for a 45-minute period on the lateral upper arm to stimulate peripheral cutaneous nerves. The FDA has authorised REN for the acute treatment of adult migraines after a randomised controlled clinical study produced favourable results. The frequency of adverse events was minimal, with the most common complaints being of numbness and feeling of warmth on the arm [45,50].

Conclusions

Acute migraine is a neurological disorder that significantly impairs the daily functioning of many people around the world. Trigeminal pathway activation is a known component of migraine headaches, although the precise pathogenesis of these assaults remains unknown. Acute migraine is characterised by a paroxysmal headache, characterised by its pulsating nature and unilateral location. The pain may be associated with other symptoms such as nausea, vomiting, photophobia and phonophobia. There are factors specific to each patient that can initiate a migraine attack, called triggers. The most common ones include specific food groups, exposure to bright, harsh lights, loud noises and stress. Migraines can also be induceded by changes in hormone levels during the menstrual cycle. Medications from a number of groups are used to treat migraine headaches, for example non-steroidal anti-inflammatory drugs (NSAIDs), most commonly used for mild headaches, or triptans. An antiemetic drug such as metoclopramide is often included. It is important to take the medication as soon as possible during the pain phase. New drug groups for the treatment of migraine headache are still in development, such as ditans and gepants. Modern non-pharmacological methods such as remote electrical neuromodulation have also found application in the treatment of this condition. Management of the patient with migraine attacks should include effective analgesic treatment and avoidance of triggers that can evoke

attacks. Therefore, doctor-patient co-operation during the treatment of this condition is important.

Author's contribution

Conceptualization, Zuzanna Kotowicz, Jakub Pabiś; methodology, Zuzanna Kotowicz, Jakub Pabiś and Piotr Podgórski; software, Jakub Pabiś, Piotr Podgórski; check, Miłosz Olszański, Aleksander Bogusz and Anita Król; formal analysis, Oskar Kwiatkowski, Anna Kołodziej and Miłosz Olszański; investigation, Sandra Górecka, Anita Król and Anna Kołodziej; resources, Zuzanna Kotowicz; data curation, Jakub Pabiś, Piotr Podgórski; writing - rough preparation, Zuzanna Kotowicz, Sandra Górecka and Anita Król; writing - review and editing, Zuzanna Kotowicz, Oskar Kwiatkowski and Sandra Górecka; visualization, Jakub Pabiś; supervision, Piotr Podgórski, Anna Kołodziej; project administration, Zuzanna Kotowicz, Miłosz Olszański, Aleksander Bogusz and Oskar Kwiatkowski; receiving funding, Zuzanna Kotowicz

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