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Various Trigger Factors of Migraine: A Review of Pathophysiology and Mechanism

I Made Oka Adnyana[1], Richard Suherlim[2], I Putu Eka Widyadharma[1]

[1]Staff at Department of Neurology, Udayana University and Sanglah Hospital, Denpasar, Bali, Indonesia.
[2]Neurology Resident, Faculty of Medicine, Udayana University and Sanglah Hospital, Denpasar, Bali, Indonesia

Corresponding Author: Richard Suherlim

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ABSTRACT

Migraine is a high prevalence primary headache. Global epidemiological data from 132 countries in 2016 shows an estimated 1.04 billion people have migraine. Epidemiological data in Bali based on research by Adnyana in 2012 showed 23.7% nursing students had migraines. Although migraine can occur spontaneously, many migraine attacks are triggered by certain trigger factors.

The trigger factors for migraine are various, ranging from foods, hormonal disorders, stress, sleep disorders, and environmental factors. Each of these factors has its own mechanism that contributes to the pathophysiology of migraine. Based on scientific data, some factors have strong supporting evidence regarding their correlation with migraine, but some others are only suggestive and not supported by scientific evidence. Factors that have obvious involvement with migraine are hormonal factors, stress, and sleep. Some types of foods such as chocolate and caffeine have a migraine trigger effect, but they can also treat migraine. It is recommended for patients to be able to identify factors that may trigger headache attacks, so that they can reduce the frequency of attacks in chronic migraine patients.

Keywords: Migraine, Trigger, Mechanism

1. INTRODUCTION

Migraine is a high prevalence primary headache. Migraine is a recurrent headache with an attack duration of 4-72 hours which is characterized by unilateral, pulsating, moderate or severe intensity, aggravated by routine physical activity, associated with nausea, vomiting, photophobia, and phonophobia. Migraine has two main types, namely migraine without aura and migraine with aura [1].

Global epidemiological data from 132 countries in 2016 shows an estimated 1.04 billion people have migraine. Women are more susceptible to migraine than men, with a prevalence of 18.9% and 9.8%, respectively [2]. Epidemiological data in Indonesia obtained from studies in 5 major hospitals found the prevalence of migraine without aura was 10% and migraine with aura was 1.8% [3]. Epidemiological data in Bali based on research by Adnyana in 2012 showed 23.7% nursing students had migraines [4].

The pathophysiology of migraine initiated by cortical spreading depression (CSD) which causes the release of vasoactive neuropeptides such as calcitonin gene-related peptide (CGRP), adenosine triphosphate (ATP), glutamate, hydrogen ions, and nitrous oxide (NO) which stimulates meningeal nociceptors, activating the trigeminovascular pathway, mast cell degranulation, and causes

vasodilation. Impulses from the trigeminovascular will be carried to the trigeminal ganglion, and form the trigeminal cervical complex then transmitted to the thalamus, then to the sensory cortex [5].

Although migraines can occur spontaneously, most migraine attacks are triggered by certain precipitating factors. The trigger factors for migraines are various, ranging from foods, hormonal disorders, stress, sleep disorders, and environmental factors. Identification of trigger factors is crucial in the management of migraine. Avoidance of these factors will improve the outcome of migraine management [6]. This article aims to discuss the mechanism by which each of these trigger factors can influence the pathophysiology of migraine.

2. Trigger Factor

Trigger factors are vital in migraine patients. Based on a study conducted on 200 migraine patients, it was found that all had at least 1 trigger factor, and 95.5% had at least 2 trigger factors. The trigger factors include foods, hormonal disorders, stress, sleep disturbances, and environmental factors [6]. Among those trigger factors, based on research conducted by Sjöstrand et al in 2010, stress is the most common trigger factor for migraines in women aged 22 -36 years [7].

2.1 Food

Foods are important trigger factors for migraines, especially in children and adolescents. According to studies, migraine patients have at least 1 nutritional factor and the most commonly found as a trigger is fasting, followed by chocolate and alcohol [8]. The mechanism by which food triggers migraine attacks relates to the release of serotonin and norepinephrine, vasoconstriction and vasodilation, or directly stimulate the brainstem, cortical neuronal pathways, and trigeminal ganglion [9].

2.1.1 Alcohol

Alcohol is found in many types of drinks, one that commonly causes migraine is wine. In vivo studies have shown that alcohol can cause arterial vasodilation and alcohol consumption has also been shown to be associated with the release of calcitonin-gene-related peptide (CGRP), which is a vasodilator agent and is associated with migraine. In addition to alcohol, there are other ingredients in wine that cause migraines, such as histamine and serotonin. Histamine in wine, especially red wine, causes the release of nitrous oxide (NO) from the endothelium, which causes vasodilation and migraines [10].

Consumption of red wine causes the release of serotonin from platelets, where it was previously known that circulating serotonin is carried and stored by platelets. Serotonin released from platelets stimulate 5-HT2 receptors which will cause migraine through the serotonergic cascade. Changes in serotonin levels play a role in causing headaches through activation of the trigeminovascular pathway [10].

2.1.2 Chocolate

Chocolate is the most common food believed to be the trigger of migraines. However, existing data based on latest researches are still contradictory. There is data that supports chocolate as a trigger factor for migraines, but there are also studies that show chocolate act as a protective factor that reduces migraine attacks [9].

There are several ingredients in chocolate that are associated with migraine attacks. Chocolate contains various types of polyphenols, especially flavonoids with subtypes called flavanols (epicatechin and oligomeric procyanidin) which can stimulate endothelial nitric oxide synthase (eNOS) activity, which results in increased NO production causing vasodilation and migraine. In addition, the cocoa content in chocolate is also thought to have a role in the release of

serotonin, where serotonin is involved in the pathogenesis of migraine. The content of phenylethylamine in cocoa has also been reported as a neurotransmitter that plays a role in migraine. An animal study was found that phenylethylamine significantly increased cerebral blood flow and cerebral oxygen consumption during the first 40 minutes of administration. If continuously given, phenylethylamine will cause cerebral vasoconstriction, causing a pattern of changes in vascular tone as in migraine (Figure 1) [9].

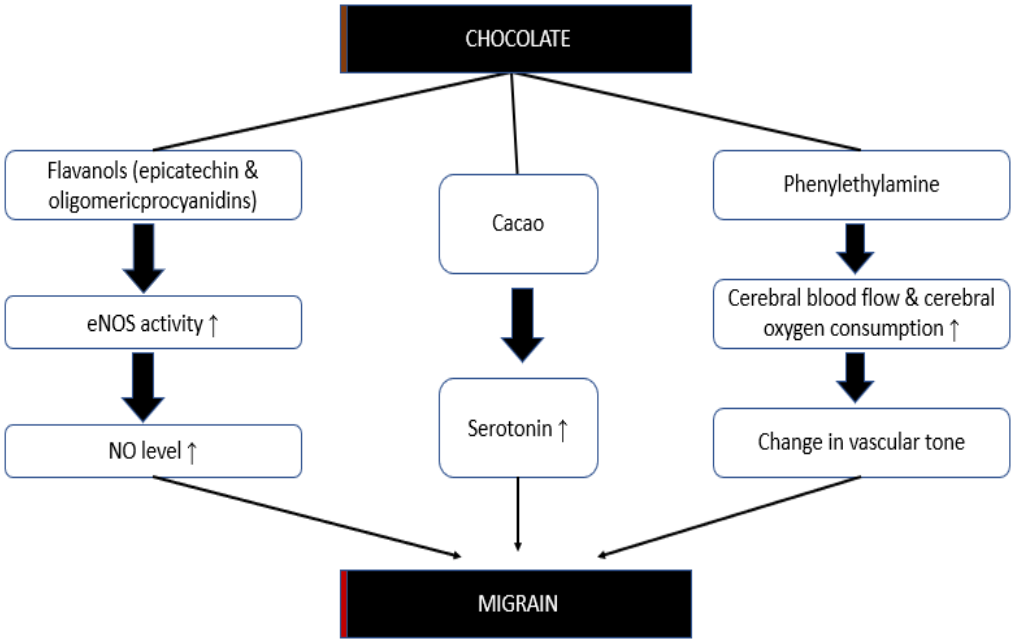

Figure 1. Chocolate triggers migraine mechanism [9]

2.1.3 Cheese

Cheese also often triggers migraine attacks. The content in cheese that is believed to be involved in the pathogenesis of migraine is tyramine [8]. Tyramine is a vasoactive amine that causes cerebral vasoconstriction and then in turn causes cerebral vasodilation leading to migraine attacks [11]. Tyramine can cause changes in vascular activity because tyramine plays a role in the release of norepinephrine in nerve terminals, causing changes in vascular tone [12].

2.1.4 Caffeine

Caffeine is found in various types of beverages that are consumed daily, such as coffee, tea, and soft drinks. Caffeine can function as a migraine treatment agent, but it can also trigger migraine. Caffeine can trigger migraine through excessive consumption and withdrawal process. The prevalence of caffeine as a migraine trigger in the literature ranges from 6.3%–14.5% [13].

There are several mechanisms how caffeine can trigger migraine. The first is that caffeine consumption causes loss of magnesium through the urine due to reduced reabsorption in the renal tubules. Magnesium affects neuromuscular conduction and nerve transmission and has benefits in chronic pain and migraines. Low magnesium level can trigger migraine. Caffeine also induces an acute diuretic effect, causing dehydration, where dehydration is one of the triggers for migraines. Caffeine is an adenosine receptor antagonist. Adenosine when it binds to the adenosine A2A receptor will stimulate NO production which causes vasodilation, whereas when it binds to the A1 receptor it will decrease NO release and cause

vasoconstriction. Caffeine as an antagonist of the A1 adenosine receptor causes vasodilation and triggers headache. Withdrawal of caffeine causes an increase in cerebral blood flow and vasoconstriction that triggers migraine (Figure 2) [13].

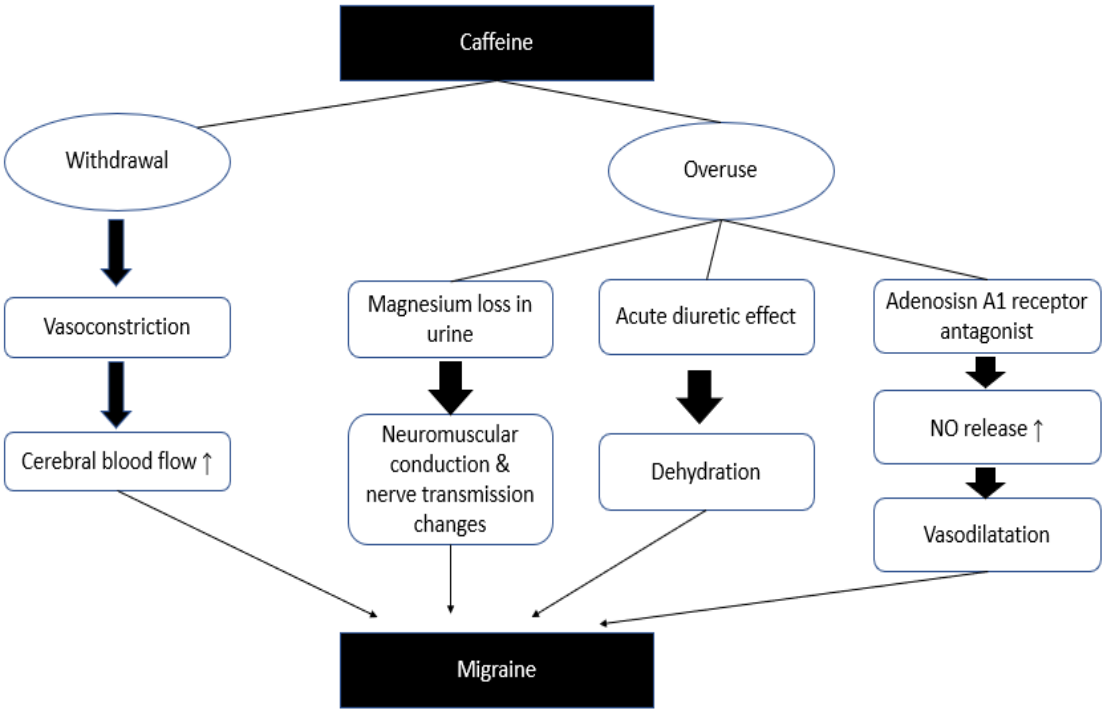

Figure 2. Caffeine triggers migraine mechanism [13]

2.1.5 Aspartame

Aspartame is an artificial sweetener that is 150-200 times sweeter than sucrose. Aspartame consists of phenylalanine and aspartic acid. Aspartame can trigger migraine attacks because phenylalanine competes with L-tryptophan so that it lowers serotonin levels, since L-tryptophan is a precursor of serotonin. Low serotonin causes vasodilation which is thought to cause migraines [14].

2.1.6 Monosodium Glutamate

Monosodium glutamate (MSG) is commonly found in processed foods, but is also found in some natural foods such as meat, tomatoes, cheese, and milk. Consumption of MSG can induce migraine through several mechanisms. MSG cannot cross the blood-brain barrier, the mechanism of MSG inducing headache is through peripheral mechanisms such as vasodilation of dural blood vessels, sensitization of dural sensory nerves, and pericranial muscle afferent fibers [15].

Monosodium glutamate causes dural vasodilation due to an NMDA-dependent increase of NO. Nitric oxide is a very strong vasodilator. Apart from NO, MSG also causes vasodilation by activating dural sensory fibers resulting in the release of CGRP which also causes vasodilation. Animal studies showed that giving 50 mg/kg of MSG to rats caused an increase of 2-3 times glutamate levels in the masseter muscle thereby inducing neuronal release and a 25% decrease in the pain threshold of the masseter muscle afferent fibers. It proved that MSG also can trigger migraine directly apart from vasodilatation process [15].

Increased circulating glutamate levels due to MSG consumption initiates activation of trigeminal afferent fibers coupled with activation of dural blood vessel

mechanoreceptors cause vasodilation. The trigeminal nerve innervation to the pericranial muscles and dura will be combined with impulses from the spinal trigeminal nucleus which will explain the appearance of facial allodynia and muscle tenderness that occurs in patients with migraine [15].

2.1.7 Fasting

Skipping meals and fasting are common triggers for migraines. Hypoglycemia directly and indirectly underlies the mechanism of the headache. In hypoglycemia, the body uses glycogen as a glucose reserve, it also occurs in the central nervous system [16].

Increased sympathetic activity during fasting will accelerate the glycogen degradation process through adrenergic receptors in astrocytes. The decrease in glycogen levels in astrocytes causes the accumulation of extracellular glutamate and potassium which will induce depolarization of a group of neurons and astrocytes and these tissues and trigger the occurrence of CSD. Intense depolarization, accumulation of potassium and glutamate, and CSD will activate the panexin1 neuronal channel. Panexin1 channel opening activates perivascular trigeminal nociceptors via the parenchymal inflammatory cascade. This mechanism is what will eventually cause migraine [16].

2.2 Hormonal Disorder

Epidemiological data show that migraine patients are more common in women. One of the reasons for this may be explained by the presence of more fluctuating hormonal factors. Hormonal changes that often trigger migraines are the pre-menstrual phase and during menstruation. In addition, hormonal changes during pregnancy and childbirth, the use of hormonal contraceptives, and menopause can also affect migraine attacks in women [6].

2.2.1 Menstruation

Menstrual migraine according to International Classification of Headache Disorders (ICHD-3) is a headache that meets the criteria for migraine without aura and occurs between D-2 to D+3 of the menstrual cycle and this pattern repeats in 2 out of 3 menstrual cycles. There are several mechanisms that are thought to explain the emergence of migraines in the female menstrual cycle such as decreased estrogen levels, prostaglandin release, decreased magnesium levels, and decreased inhibitory neurotransmitters in the trigeminal system [17,18].

Among these mechanisms, decreasing estrogen levels has the greatest role. Estrogens are associated with increased serotonin production, decreased absorption, and decreased elimination. Decreasing estrogen levels before the onset of menstruation will also reduce serotonin levels, which can cause migraine. In addition, high estrogen levels have also been shown to be associated with greater pain tolerance in rats. Estrogen binds to intracellular receptors on trigeminal ganglion neurons that regulate the expression of galanin and neuropeptide-Y involved in nociception. So that the decrease in estrogen levels can also cause patients to be more susceptible to pain due to their decreased pain threshold [17].

2.2.2 Pregnancy and Childbirth

During pregnancy, estrogen levels in a woman's body can increase up to 100 times normal levels. Most women with migraine report improvement in symptoms during pregnancy, especially those with menstrual migraines. The improvement in this condition is due to reduced monthly hormonal fluctuations and increased levels of endorphins as natural painkillers [19].

In women with migraines whose condition improves during pregnancy, most will experience migraine attacks soon after giving birth, especially in the first week. This is due

to decreased levels of estrogen and endorphins during the postpartum period [19].

2.2.3 Use of Hormonal Contraceptives

Headache induced by exogenous hormone is headache that appears or worsens within 3 months of hormone administration, and improves or returns to the previous headache pattern within 3 months of hormone discontinuation. Estrogen withdrawal-related headaches occur within 5 days of the last day of estrogen use and resolve within 3 days [20]. Sexual hormones such as estrogen, progesterone, and testosterone can alter the receptor expression of neurotransmitters, as well as modulate the synthesis, release, and transport of neurotransmitters involved in pain and inflammation. Fluctuations in estrogen and progesterone levels due to exogenous hormone administration cause a wide range of effects on the opioid, serotonergic, noradrenergic, beta-adrenergic, dopaminergic, and GABA-ergic systems that will influence the occurrence of migraine [20].

2.2.4 Menopause

Migraine patients who are sensitive to hormonal changes will usually experience a worsening during perimenopause phase due to extreme fluctuations in estrogen levels. The frequency of migraine attacks which are usually only occasionally during peri menstruation becomes irregular during the perimenopausal phase due to fluctuations in estrogen levels which also become more variable. When they have reached the menopause phase, migraines will improve due to reduced hormonal fluctuations [21].

2.3 Stress

Stress is a process of interaction between individuals and their environment where the individual responds to internal or external obstacles. High stress levels have been reported to trigger migraine attacks, especially in chronic migraine patients. Any type of stress be it endogenous stress (such as hormonal changes), exogenous stress (such as light), or psychological stress such as social and economic problems can trigger migraines. Studies show that stress is one of the most common migraine triggers [22].

The biological mechanism of stress that causes migraines can be explained through several pathways. Physiological stress response involving the hypothalamic-pituitary-adrenocortical axis and the sympathetic nervous system. Activation of these two systems explains that stress can change behavior and physiological conditions to cause migraine. An article by Kajal et al in 2017 stated that there is a neural circuit that is responsible for the emergence of the phenomenon of hyperalgesia due to stress. The dorsomedial nucleus of the hypothalamus is a very important component of the central mechanisms that mediate neuroendocrine, cardiovascular, and thermogenic responses to stress. The dorsomedial nucleus of the thalamus also plays a role in stress-induced hyperalgesia via both direct and indirect pathways with the rostral ventromedial medulla (RVM), a region that controls nociception [22].

A study by Sauro et al in 2009 reported that chronic stress that causes hyperalgesia involves activation of N-methyl-D-aspartate (NMDA) receptors and opioid receptors. Chronic stress can also cause migraine through changes in the immune system where pain transmission is facilitated at the neuronal level. Various inflammatory mediators such as tumor necrosis factor alpha (TNF-α), IL-1β, IL-6, and NO act as pain mediators that can increase pain sensitization [22,23].

2.4. Sleep Disorders

Sleep disorders are common risk factor for chronic migraine. Changes in the sleep-wake cycle, such as sleep deprivation is a trigger for migraine. However, the relationship between sleep and migraine is very complex where

patients with migraines can also cause sleep disorder in patients, sleep disorder as migraine symptoms, especially the prodromal phase, and sleep are also thought to reduce symptoms in migraine patients [24,25].

Poor sleep quality can reduce pain threshold, as evidenced in a study in which reduced pain inhibition and increased spontaneous pain were found in subjects who continued to wake up during sleep, even though their overall sleep time was not reduced. The mechanism that explains this is related to the role of serotonin. In the process of sleep, serotonin plays a role in increasing wakefulness and reducing REM sleep. Individuals with high serotonin will have more difficulty sleeping and are also more prone to migraine attacks [24].

Lack of sleep causes increased serotonergic transmission in the brain. In animal studies, sleep-deprived mice have higher serotonin levels in the hippocampus and raphe nucleus with very broad cortical projections. All brain serotonin is produced in the brain stem, specifically in the dorsal raphe nucleus. Signals sent from the dorsal raphe nucleus will go to many areas in the cortex and subcortex including the hypothalamus. Sleep deprivation can also significantly increase the serotonin (5HT-2A) receptor binding potential in various cortical regions. The hypothalamus has an important role in the pathophysiology of migraine because of its role in GABA synthesis. Hypothalamic activity will affect the activity of the spinal trigeminal nucleus which will transmit impulses to the trigeminal cervical complex (TCC) and cause migraines [24,25].

The hypothalamus also has another pathway to cause migraines through its role in producing gonadotropin releasing hormone (GnRH) which will cause the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary and eventually cause the release of estrogen, where as previously discussed, estrogen plays a very important role in the occurrence of migraines [24].

Apart from serotonin, sleep disturbances can also trigger migraines by increasing cortical excitability through mechanisms related to calcium-dependent channels and increased glutamate. In studies conducted on rats, it was found that lack of sleep will cause an increase in glutamate receptors in the hippocampus resulting in an increase in excitability susceptibility in that area. The glutamatergic mechanism is linked to the susceptibility to CSD in sleep-deprived individuals [25].

Sleep deprivation can also increase the susceptibility to CSD by inhibiting the Na+/K+-ATPase pump due to oxidative stress. Lack of sleep will reduce the activity of anti-oxidative enzymes such as peroxide dismutase and glutathione peroxidase which regulate levels of reactive oxygen species (ROS). Lack of sleep also increases lipid peroxidation resulting in higher oxidative stress in the hypothalamus, thalamus, and hippocampus [25].

The high prevalence of sleep disorder in migraine patients is also associated with dysregulation of melatonin secretion. During a migraine attack, plasma melatonin levels decrease. Administering melatonin to migraine patients can reduce pain and prevent attacks. This could be explained because melatonin slows down CSD and attenuates nociceptive impulses in the trigeminovascular system [25].

2.5 Environment

Epidemiological data show that 50%-75% of migraine patients can identify the triggering factors for migraine. Many of them stated that various environmental factors were the trigger for their migraine. Even if a factor is believed to trigger a migraine, it does not always cause a migraine every time the patient is exposed to that factor [26].

2.5.1 Bright Light

Bright light is a trigger for migraine in 26.9% of the migraine population in America. Migraine patients are generally more sensitive to light even when they are not experiencing a headache. Decreased cortical excitability threshold in migraine patients will increase cortical activation susceptibility and facilitate trigeminovascular activation. Migraine patients also have impaired adaptation to light stimulation due to hyperexcitability of the occipital cortex or thalamus [26]. Noseda et al in 2010 stated that the mechanism by which light triggers migraines is by modulating thalamocortical neurons in the dura mater through nonimage-forming retinal pathways. Ultraviolet radiation in sunlight alters CGRP and NO released from intraepidermal sensory nerves in the skin. This condition will cause vasodilation that triggers migraine [27,28].

2.5.2 Smoking and Cigarette Smoke

In a study conducted on a group of medical students, the frequency of migraine attacks in the smoking group was higher than in the non-smokers. There are several mechanisms that can explain the relationship between smoking and migraine, including increased platelet aggregation, NO production, increased monoamine activity in the brain, and genetic factors. In addition to smoking, cigarette smoke has also been identified as a trigger for migraine attacks in more than half of patients. Another study also revealed that the prevalence of cigarette smoke as a migraine trigger reached 29.3% [29,30].

2.5.3 Odor

Migraine patients report odor as a trigger factor in 70% of migraine attacks. Other studies show a figure of 36.5%-43.7% which states that smell as a trigger for migraines. Of the many types of odors, based on research conducted by Sjöstrand et al in 2010, the smell that triggered the most migraines were perfume (86.8%), followed by exhaust fumes (44.7%), and cigarette smoke (42.1%) (Table 1) [7].

Table 1. List of Odors Triggering Migraine [7]

No	Substances	Percentage (%)
1	Perfume	86.8
2	Exhaust fumes	44.7
3	Cigarette smoke	42.1
4	Detergent	26.3
5	Gasoline	28.9
6	Smoke	23.7
7	Vanilla	10.5
8	Fried food	7.9
9	Grilled food	7.9

The mechanism by which odors trigger migraines is still not fully understood. There is a hypothesis which states that smell will trigger the occurrence of CSD processes in the cortex of migraine patients which will initiate the occurrence of pain. In addition, the smell will trigger the activity of the trigeminal nuclear complex (TNC) in the brain stem. Odor will cause disruption of TNC function as a gate of inhibitory signals from central pain modulating neurons in the brain stem so that pain impulses from the trigeminal system and from the cortex will trigger migraine [7].

2.5.4 Hot or Cold Weather

The effect of weather on migraines is still a matter of debate. About 53% of migraine patients believe that weather conditions can trigger a headache attack, although scientific evidence to support this is sparse and inconclusive. Clinical research conducted by Hoffmann et al in 2014 analyzed the effect of specific components of weather on migraine focusing on atmospheric pressure, ambient temperature, and humidity. The result is that only 13% of migraine patients are sensitive to the weather [31,32].

Sudden changes in atmospheric pressure and humidity, hot and dry winds, and geomagnetic activity are thought to accelerate the release of serotonin, which triggers migraines. There is a hypothesis which states that a hot ambient temperature will stimulate thermoreceptors in the skin, which will cause stress in the body and cause migraine attacks, while the cold

temperature mechanism triggers headaches associated with hemodynamic changes [27,31].

There are variations in results in studies of the relationship between temperature and migraine. Research by Tanik et al found that there was no relationship between exposure to hot/cold weather and migraine attacks, while research by Yang et al found that cold weather was the trigger for moderate-severe headaches and hot weather was the trigger for mild headaches. Interpretation of the results of these studies is very difficult because there is very little research on the effects of hot/cold weather on migraine. There are only a few researches on the relationship between weather on migraine, making it difficult to determine the relationship and its pathophysiology [31,32,33].

3. CONCLUSION

Trigger factors are important factors in migraine attacks. There are many things that can trigger migraines, such as foods, hormonal changes, stress, sleep disturbances, and environmental factors. Each of these factors has its own mechanism that contributes to the pathophysiology of migraine.

Based on the search for scientific data, some have strong supporting evidence regarding their correlation with migraine, but some factors are only suggestive and not supported by scientific evidence. Factors that have obvious involvement with migraine are hormonal factors, stress, and sleep. While environmental factors such as weather still do not have strong scientific evidence that supports the trigger for migraine attacks. Some types of foods such as chocolate and caffeine have a migraine trigger effect, but they can also function as migraine therapy.

Declaration by Authors

Ethical Approval: Not Applicable

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