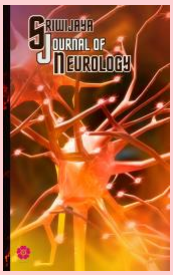

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Pathophysiology of Primary Headache Syndrome: A Narrative Literature Review

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A B S T R A C T

Primary headache syndrome is a chronic recurrent type not associated with structural abnormalities or systemic disease and includes migraine, cluster, paroxysmal hemicrania, and tension headaches. This literature review aimed to describe the types of primary headaches and their pathophysiology. Migraine is an episodic neurological disorder characterized by headaches that last 4 to 72 hours. This disorder is diagnosed when two of the following features occur: unilateral headache, throbbing pain, the pain worsening with activity, moderate or severe pain intensity, and at least one of the following: nausea and/or vomiting, or photophobia and phonophobia. Cluster headaches are one of a group of rare disorders known as trigeminal autonomic cephalgia. Tension-type headache (TTH) is the most common type of recurring headache. It's not a vascular headache or a migraine. The mean age of onset is during the second decade of life. Usually mild to moderate bilateral headaches with a feeling of tight bands or pressure around the head.

1. Introduction

Headache is a common neurological disorder and is usually a benign symptom. However, it can be associated with serious illnesses, such as brain tumors, meningitis, giant cell arteritis, and cerebrovascular disease (secondary headache). Primary headache syndrome is a chronic recurrent type not associated with structural abnormalities or systemic disease and includes migraine, cluster, paroxysmal hemicrania, and tension headaches (Table 1).[1-5] This literature review aimed to describe the types of primary headaches and their pathophysiology.

Migraine

Migraine is an episodic neurological disorder characterized by headaches that last 4 to 72 hours. This disorder is diagnosed when two of the following features occur: unilateral headache, throbbing pain, pain that worsens with activity, moderate or severe pain intensity, and at least one of the following: nausea and/or vomiting, or photophobia and phonophobia. Migraines are broadly classified as (1) migraine with aura with visual, sensory, or motor symptoms; and characteristics more general, (2) migraine without aura (most common), and (3) chronic migraine.

Table 1. Characteristics of common headaches.

	Migraine		Cluster headache/ hemicranial paroxysmal	Tension-type headache
	Without aura	With aura (25%-30%)		
Age of onset	Childhood, adolescence, or young adulthood	Childhood, adolescence, or young adulthood	Young Adult, Middle age	Young Adult, Middle age
Gender	Higher on women	Higher in women	Man	Not specific
Family history of headaches	Yes	Yes	No	Yes
Onset and evolution	Slow to fast	Slow to fast	Fast	Slow to fast
Time of onset of symptoms	Episodic	Episodic	Cluster	Episodic, maybe to be constant
Quality	Usually throbbing	Usually throbbing	Still	Still
Location	Variable, unilateral to bilateral	Variable, unilateral to bilateral,	Orbits, chin, cheeks	Varies
Related features	Prodromal, vomiting	Auras: visual disturbances, sensory, language, and motor Prodromal, vomiting	Lacrimation, rhinorrhea, Horner's syndrome	No

Migraines occur in about 18% of women, 6% of men, and about 10% of children in the United States. It is more common in those aged 25 to 55 years. There is often a family history of migraines. In susceptible women, migraines most often occur before and during menstruation and decrease during pregnancy and menopause. Stopping the estrogen and progesterone cycles can trigger migraine attacks.

Migraines are caused by a combination of several genetic and environmental factors. People with migraines have an increased risk of epilepsy, depression, anxiety disorders, cardiovascular disease, and ischemic stroke. Migraines can be triggered by triggers. Individuals with migraines tend to have a genetically determined threshold for triggers. Triggers can include endogenous factors (e.g., altered sleep patterns [being tired or sleeping too much], missed meals, fatigue, changes in weather, stress or relaxation due to stress, hormonal changes [such as menstrual periods], stimulus excessive afferents [bright light, strong odors], and chemicals [alcohol or nitrates]).

The pathophysiological basis for migraine is complex and unclear. There is no identifiable pathology, but there are associated changes in brain metabolism and blood flow. The current theory includes neurological, vascular, hormonal, and neurotransmitter components. A Migraine aura is associated with cortical spreading depression (CSD). CSD is a spontaneous self-propagating wave of glial and neuronal depolarization resulting in hyperactivity that begins in the occipital region and spreads throughout the cortex. CSD begins the headache phase with discharge neurotransmitters which activate the trigeminal vascular system (afferent projections from cranial nerve V), stimulate dural vascular vasodilation, activate inflammation, sensitize peripheral and central pain receptors (hypersensitivity to pain), and activate brainstem and forebrain areas that modulate pain. The release of inflammatory mediators with sterile meningeal inflammation and vascular edema may be important components of migraine pain. Vasodilation of blood vessels is not enough to explain migraine pain. Calcitonin gene-related peptide (CGRP) release by the trigeminal vascular system is associated with migraine pain. The mechanism is unclear, but CGRP antagonists prevent headaches. The concentration of glutamate (an

excitatory neurotransmitter) increases, and the concentration of 5-hydroxytryptamine (5-HT, serotonin) decreases. 5-HT causes vasoconstriction and antagonizes CGRP. Consequently, 5-HT(1B/1D) receptor agonists (i.e., triptans) and CGRP receptors and glutamate receptor antagonists have been used for the treatment of acute migraine critical.[6-8]

The clinical phases of a migraine attack are as follows; (1) Premonitory phase: Up to a third of people have premonitory symptoms hours to days before the onset of an aura or headache. These symptoms may include tiredness, irritability, loss of concentration, a stiff neck, and food cravings; (2) Migraine aura: Up to one-third of people have aura symptoms for at least some time which can last up to 1 hour. Symptoms can be visual, sensory, or motor. There are no associated focal neurological symptoms in migraine without Aura; (3) Headache phase: The throbbing pain usually starts on one side and spreads across the head. Headaches can be accompanied by fatigue, nausea, vomiting, or dizziness. There may be hypersensitivity to anything that touches the head. Symptoms may last from 4 to 72 hours (usually about a day); (4) recovery phase: Irritability, fatigue, or depression may take hours or days to resolve.

The diagnosis of migraine is made from the medical history and physical examination. The differential diagnosis is confirmed by imaging and EEG. Functional neuroimaging and genetic studies are advancing the understanding of the mechanisms involved in migraine attacks and the individual variants involved with disease susceptibility. Migraine management includes avoiding triggers (e.g., darkening the room or applying ice). Sleep can provide some relief with the onset of acute migraine. Pharmacological management for the treatment and prevention of migraine is available and individualized.

Chronic migraines usually start as episodic migraines that increase in frequency over time. Chronic migraines occur at least 15 days a month (may occur every day or nearly every day) for more than 3 months. Chronic migraines are associated with the overuse of migraine analgesic drugs (sometimes called rebound headaches), obesity, and excessive use of caffeine. Treatment is similar to episodic migraine. Injections with botulinum toxin A are approved for preventing chronic migraines. Individuals with chronic migraine who are unresponsive to medical treatment should be evaluated for intracranial hypertension without papilledema and possible venous sinus stenosis.[9-13]

Cluster headaches

Cluster headaches are one of a group of rare disorders known as trigeminal autonomic cephalgia. They occur on one side of the head, mainly in males between the ages of 20 and 50. The pain may alternate sides with each episode of severe, stabbing, throbbing headaches. These unusual headaches occur in clusters (up to eight attacks per day) and last for minutes to hours over several days, followed by long periods of spontaneous remission. Cluster headaches have episodic and chronic forms with extreme pain intensity and short duration. If cluster attacks occur more frequently without sustained spontaneous remission, they are classified as chronic cluster headaches (10% to 20% of cases). The triggers are similar to migraine headache triggers.

Trigeminal activation occurs, but the mechanism is unclear. Functional imaging suggests a role for the posterior hypothalamus and activation of the pain neuromatrix concomitant with the involvement of the opioid system. Pathogenic mechanisms of pain are related to the release of vasoactive peptides and the formation of neurogenic inflammation. Autonomic dysfunction is characterized by a lack of sympathetic activity and parasympathetic activation. Headache attacks usually begin without warning. There is a unilateral trigeminal distribution of severe pain with ipsilateral autonomic manifestations, including tearing of the affected side, ipsilateral eye ptosis, and congestion of the nasal mucosa. Pain often radiates to the midface and teeth. Prophylactic medications and trigger avoidance are used to treat cluster headaches. Acute attacks are managed with oxygen inhalation, inhaled sumatriptan or ergotamine administration, and nerve stimulation. New drugs are being investigated. Chronic paroxysmal hemicrania (CPH) is a cluster headache with the unilateral headache associated with autonomic features (lacrimation or rhinorrhea) that occurs with daily frequency (4 to 12 per day) but of shorter duration (20 to 120 minutes). The remission phase is often shorter. Attacks occur in men and women from the age of 30 to 40 years. The

symptoms are similar to cluster headaches. Like cluster headaches, there are episodic and chronic forms. The pathophysiology involves impaired sympathetic hyperactivity, but the mechanism differs from cluster headache in that there is effective symptom relief with indomethacin.[14-17]

Tension-type headache

Tension-type headache (TTH) is the most common type of recurring headache. It's not a vascular headache or a migraine. The mean age of onset is during the second decade of life. Usually mild to moderate bilateral headaches with a feeling of tight bands or pressure around the head. The onset of pain is usually gradual. Episodic tension-type headache occurs less than 15 days per month and may last for a few hours or several days. It is not made worse by physical activity and can be triggered by sleep disturbances (insomnia). Chronic tension-type headache develops from episodic TTH and occurs at least 15 days per month for at least 3 months. Many people experience tension-type headaches and migraines.

Central and peripheral mechanisms work to cause tension headaches. The central mechanism may involve hypersensitivity of pain fibers from the trigeminal nerve leading to central sensitization with deficits in descending pain inhibitory pathways within the brainstem. Peripheral sensitization of myofascial sensory afferents may lead to muscle hypersensitivity and the development of chronic TTH. Headache sufferers have more localized pain and pericranial muscle tenderness.

Mild headaches are treated with ice, and more severe forms are treated with aspirin or other nonsteroidal anti-inflammatory drugs. Chronic TTH is best managed with tricyclic antidepressants and behavioral and relaxation therapy. Some individuals benefit from botulinum toxin A injection. Long-term use of analgesics or other drugs, such as muscle relaxants, antihistamines, sedatives, caffeine, and ergot alkaloids, should be avoided.[18-20]

2. Conclusion

Primary headache syndrome is a chronic recurrent type not associated with structural abnormalities or systemic disease and includes migraine, cluster, paroxysmal hemicrania, and tension headaches.

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