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NEUROPATHOLOGY AND BRAIN DISORDERS: MIGRAINE HEADACHE

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ABSTRACT

Migraine headache is a prevelant brain disorder and common form of pain with high rates of disability. Originally thought to be a vascular disorder, it is now believed have neurological involvement, leading to the modern neurogenic theory. Many preliminary migraine symptoms are neurological, as well as the aura phase that involves visual disturbances. In the promonitory phase before headache and during the actual headache phase, specific brain regions are activated, with distinct patterns of neuronal activation. Cortical spreading depression (CSD) is an electrophysiological phenomenon involving the spread of a depolarization wave across cerebral gray matter, which disrupts the ionic gradient of the brain and depresses signalling. It is likely that an altered state of brain excitability activates the trigeminovascular system (TVS), leading to vasodilation and plasma estravastion of meningeal vessels. However, migraine is a complex disorder with complicated symptomatolgy, and the pathophysiology is unknown. This paper discusses the combination of vascular and neurogenic components in the pathophysiology of migraine headache.

KEYWORDS: *migraine, headache, neurovascular, neurology, brain disorder, inflammation, CNS*

INTRODUCTION

Headaches are prevalent neurological disorders and common forms of pain which contribute greatly to worldwide levels of disability. Primary headaches cause episodic and chronic head pain that are not a symptom of another disease or medical condition and migraine headache is the most common form, characterized by pulsating head pain that is unilateral and diverse symptoms that are grouped into four phases.

The premonitory phase consists of "warning" symptoms of an impending migraine, which can include changes in mood and energy levels, food cravings, and excessive yawning (1). Following this is the aura phase involving visual disturbances that affects between 15-30% of migraine patients and occurs just before the migraine (2). The next phase is the actual headache, with throbbing head pain that can range in intensity, that lasts between 4-72 hours. During the headache, there may be nausea, vomiting, and sensitivity to light, sound, smell, and touch (allodynia) (3). Finally, the post-headache phase concludes the migraine with symptoms such as fatigue, mood changes, and cognitive impairments (4).

Migraine can be triggered by endogenous or exogenous agents, including menstruation, stress, certain foods such as cheeses or processed meats, alcohol (particularly red wine), or changes in weather or sleep, amongst others (5). Females

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have a higher incidence of migraine, usually being affected two to three times more than males (6,7), implicating sex hormones in the pathogenesis of this disorder (8).

'Triptans' are widely used to treat migraine and can be effective in terminating an attack or decreasing the severity of symptoms (9). Triptans belong to a family of serotonin (5-HT)1b-receptor agonists and include sumatriptan, zolmitriptan, rizatriptan, eletriptan, and naratriptan (4). However, these medications are not effective for all patients (10), and there is a need for new treatment development.

Migraine is highly prevalent around the world and a major contributor to disability (11). In American migraine studies, about 12% of Americans reported experiencing migraine in the span of a year, with women three times more affected than men (12-14). Migraine negatively impacts work and school activities, family, and social relationships, and even the economic status of individual sufferers (15). Despite its high prevalence and intensive research efforts, the pathophysiological basis of migraine headaches is still unknown. This paper will discuss the combination of vascular and neurogenic components in the pathophysiology of migraine headaches.

The vascular theory

Until recently, the vascular system was believed to be the main mechanism inducing primary headaches such as migraine and cluster headaches. The fact that vasodilation could initiate headache (16), and that vasoconstrictors could arrest it (17), were convincing factors for the vascular basis of migraine.

In migraine, there is cerebral and meningeal arterial vasodilation and medications for vasoconstriction, such as triptans, are used to treat migraine. In line with this, vasodilators, substances that dilate blood vessels, can induce headaches such as cluster headaches and migraine (18).

The vasogenic theory is based on the correlation of migraine and variations in vascular caliber, but this does not indicate causation. Additionally, actual dilation of the vasculature is not correlated directly with pain, and so there must be other factors involved in this regard. There is bidirectional communication between the cells in blood vessels and neurons, with release and response of mediators including cytokines, adenosine triphosphate (ATP), nitric oxide (NO), norepinephrine, and calcitonin gene-related peptide (CGRP), and the two systems likely interact in the pathophysiology of headache (4). Integrating the vascular basis of migraine with nervous system interaction led to the neurovascular theory, a more appropriate approach to explain the pathogenesis of migraine.

The neurogenic theory

A more complete explanation of migraine pathophysiology is the neurogenic theory, which has gained evidence as the basis of migraine. It helps to explain many characteristics of migraine attacks that the vascular theory cannot.

For example, ergotamine-derived triptan medication used in treating migraine attacks functions on vasoconstriction and is not effective for all headache patients (19,20). The premonitory phase cannot be explained by changes in vasculature and triptans have no effect on symptoms during this stage. Chemical compounds and hormones play a role, as serotonin and estrogen can contract and constrict blood vessels. Neuronal genes have been implicated in migraine and evidence continues to support neuronal involvement during migraine aura and attack (21).

Triptans are not able to abort the premonitory symptoms of the first phase of a migraine attack, implicating that vasoconstriction does not create these symptoms (22). Many of these symptoms are neurological. The phase that follows, the aura phase, involves visual and sensory symptoms that are not vascular in nature (21).

Imaging studies have shown that migraine involves distinct patterns of neuronal activation. Studies using positron emission tomography (PET) identified specific brainstem regions that became activated during migraine attack, demonstrating periaqueductal gray (PAG), dorsal raphe (DR), and locus coeruleus (LC) activation (23,24). The premonitory symptoms could involve the hypothalamus, which has been seen to increase in activity in the time proceeding the migraine attack, along with elevated functional coupling to the trigeminal nucleus caudalis (TNC) (25). The hypothalamic nuclei is an important brain region for internal homeostatic regulation, where neurons function in diurnal, circadian, and circannual rhythms and hormonal regulation (26). Oscillations in these activities can alter functional connections in other areas of the brain, including subcortical and brainstem regions, with heightened reactions to sensory stimuli that could be involved in the provocation and termination of migraine attacks (27-29).

Cortical spreading depression (CSD) is believed to be the underlying cause of migraine with aura and could be a key player in overall migraine pathophysiology (30,31). It is an electrophysiological phenomenon in which a depolarization wave spreads across cerebral gray matter, disrupting ionic gradients and depressing electrocortical signals, which is then followed by a period of hyperpolarization (32).

CSD has also been hypothesized to initiate activation of the trigeminovascular system (TVS), that comprises neurons originating in the trigeminal ganglion that innervate cerebral vasculature, including the dura mater and large venous sinuses (33). Stimulation of dura mater in the vicinity of sinuses and blood vessels can produce migraine-like pain (34).

TVS activation is involved in the pathogenesis of migraine attack. The cervical nerve root projections come together in the TNC, which is connected by fibers to the thalamus and the sensory cortex, and subcortical regions (35).

The ganglion neurons produce neurotransmitters and vasoactive neuropeptides such as substance P, CGRP, and neurokinin A. Levels of CGRP were substantially elevated in patient jugular venous blood during migraine attacks (36) and intravenous administration of human alpha-CGRP can induce migraine headache (37).

Serotonin, estrogen, and stress

The monoamine transmitter 5-HT is believed to play a central role in migraine pathophysiology, although the exact role of serotonergic mechanisms is unclear. By injection, it has been found to induce migraine-like symptoms (17) and elevated levels of the 5-HT catabolite 5-hydroxyindoleacetic acid (5-HIAA) were found in patient urine during migraine attacks (38). Other studies showed lower plasma 5-HT levels in the intervals between attacks, with increasing levels during the actual migraine attacks (39). However, studies investigating brain levels of 5-HT have been inconclusive, having shown conflicting results of higher and lower levels (40). Triptans are a family of 5-HT1b receptor agonists and are the most effective treatment for migraine, however the exact modes of function are still unclear, and studies show complex mechanisms. It is believed cerebral 5-HT levels in migraine patients could be low in the periods between attacks, with elevated levels during the attack, although more conclusive evidence must be gathered from further studies (40).

Female hormones and the menstrual cycle are factors that can provoke headache. Estrogen levels vary during the lifetime of women, often in patterns correlating with symptom severity, development, and cessation of migraine. At the age of puberty, the rate of migraine in females increases significantly while the male rate remains relatively unchanged (41). During the fertile period and cyclic fluctuations of estrogen levels (42), the prevalence rate is much higher in females and remains so until post-menopause, when estrogen levels are low and female migraine improves (43).

Those who suffer from migraine often have sensitivity to various triggers, suggesting that maladaptive changes are involved in the nervous system of these individuals. Stress is a common trigger, with one study finding that 80% of patients indicate stress as a provoking factor (5). Stress can trigger a cascade of responses in the body, affecting hormone levels by activating the hypothalamic-pituitary-adrenocortical axis (HPA) and the sympathetic nervous system, with the release of stress hormones such as corticotrophin releasing hormone (CRH), cortisol, and epinephrine (44,45).

The stress response can cause biochemical changes and lead to the sensitization of afferent nociceptors (46). Migraine pain is referred to as dysfunctional pain of the nociceptive pain system because it is not caused by injury, but instead by sensitized peripheral nociceptors (47). Additionally, stress can affect migraine and pain sensitization by altering the immune system, as some proinflammatory mediators, including interleukin-1 (IL-1) and IL-6, are involved in pain transmission and sensitization (48). Elevated levels of intracranial inflammatory mediators, such as nerve growth factor (NGF), Substance P, and CGRP circulate during migraine and can sensitize primary afferent nociceptors (49-51). Mast cells and macrophages release proinflammatory mediators that can sensitize meningeal nociceptors, including 5-HT, histamine, and prostaglandins (52-54,46).

CONCLUSIONS

Migraine is a complex disorder, with a multifactorial origin and complicated symptomatology. Originally believed to be a vascular disorder due to meningeal vasodilation, modern studies have shown the neurological implications involved, with affected functioning of multiple cortical, subcortical, and brainstem regions (55).

The vasculature nature and neurogenic implications cannot be denied; however, the precise pathophysiology of migraine remains unknown. Most likely, a brain state of altered excitability leads to the activation of the TVS, resulting in vasodilation and plasma extravasation of meningeal vessels, likely affecting genetically susceptible individuals (3,56). Further research can hopefully discover the mechanisms involved in the activation of brain regions implicated in producing migraine.

Conflict of interest

The author declares that they have no conflict of interest.

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