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Pathophysiology of cluster headache

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Cluster headache is severe, unilateral headache disorder belonging to the group known as the trigeminal autonomic cephalalgia. Cluster headache is characterized by strictly unilateral head pain that occurs in association with cranial autonomic symptoms, and has a striking circannual and circadian periodicity. Pathophysiology of cluster headache is poorly understood. Activation of trigeminal-autonomic reflex results in severe trigeminal distribution pain and autonomic symptoms. Circadian biological changes and neuroendocrine disturbances have suggested a pivotal role of hypothalamus in cluster headache and, neuroimaging studies have corroborated hypothalamic involvement in cluster headache. However, recent imaging studies suggested that multiple cortical pain matrix areas are also involved in the cluster headache pathogenesis.

Key Words: Cluster headache, Pathophysiology, Trigeminal autonomic cephalalgia, Hypothalamus

Introduction

Cluster headache (CH) is a primary headache disorder that presents with severe recurrent unilateral head pain accompanied by ipsilateral cranial autonomic symptoms. Prevalence of CH is approximately 0.1% of the population and mostly affects men with a typical age of onset between 20 and 40 years. Although uncommon, CH is the most common of the trigeminal autonomic cephalalgia (TAC). The TACs include cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and hemicrania continua. Pathophysiology of CH is complex and underlying mechanisms poorly understood. Clinical and basic research have suggested integral involvement of the trigeminovascular and cranial parasympathetic systems in CH. Activation of these pathways provides the anatomic basis for the expression of first-division trigeminal pain and ipsilateral autonomic symptoms that occur during cluster attacks. Circannual and circadian periodicity and the functional imaging studies implicate the hypothalamus as major role to CH. On top of that, recent neuroimaging studies have suggested that the disturbance in multiple pain matrix may give rise to a permissive state and result in disinhibition of the hypothalamic-trigeminal pathway, which seems necessary for CH pain to begin.[1]

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Epidemiology and genetics

CH is a very rare disorder. Meta-analysis reported a lifetime prevalence of 124 per 100,000 persons and a 1-year prevalence of 53 per 100,000 persons.[2] Men are

affected 4.3 times as often as women, and episodic CH is more frequent than chronic CH with a ratio of 6:1 in western population. Although the first attacks usually occur between the ages of 20 and 40 years, some case study suggested that onset of disease may span from early childhood until the ninth decade of life. Genetic basis has been suggested by family and twin studies, but the mode of transmission seems to vary and heritability is unclear. Twin and family studies have suggested a heritable component, and it was estimated that first-degree relatives of CH patients have a 5-18 fold increased risk and second-degree relatives have a 1-3 fold increased risk.[3] However, genetic background of CH remains largely unexplored until recently. Molecular genetic investigations of CH have been hampered by the complex nature of the disorder and very low prevalence of CH. Therefore, the number of genetic association studies investigating genetic polymorphisms implicated in the pathogenesis of CH is limited. A missense single nucleotide polymorphism in the HCRTR2 gene that encodes the hypocretin receptor 2 has been suggested to be the genetic factor associated with cluster headache which may affect the hypothalamic hypocretin system in different studies, but not confirmed in a recent meta-analysis.[4] No associations or conflicting results were found for variants in CACNA1A, NOS, MTHFR, PR3, SERPINA, and ADH4 genes. Pharmacogenetic studies have suggested that G protein beta3 polymorphism may modify treatment response to triptans among CH patients by altering the signal transduction cascade via G protein-coupled receptors.[5] Genetic studies in CH are very difficult due to the complex nature of the disorder and the low prevalence of CH.

Pathophysiology

The pathophysiology of CH remains poorly understood. Any pathophysiologic model for CH must explain three major features of CH, unilateral trigeminal distribution of the pain, the ipsilateral autonomic manifestations, and the tendency for attacks to cluster with circadian and circannual consistency. Several possible mechanisms have been proposed, based on clinical as well as electrophysiological, endocrinologic, and animal studies.

1. Trigeminovascular system and Trigeminal–autonomic reflex

Clinical phenotype of cluster headache has been suggested as a process involving trigeminal-autonomic activation (considered on the background of the anatomy and physiology of the trigeminovascular system, and its reflex connections with the cranial parasympathetic autonomic outflow).[6] The pain-sensitive innervation of intracranial structures has cell bodies in the trigeminal ganglion and is mainly innervated by the ophthalmic division of trigeminal nerve. Cerebral vessels and dura maters are innervated by trigeminal ganglion. The cranial parasympathetic innervation of intracranial vessels arises from neurons located in the superior salivatory nucleus in brainstem. Parasympathetic vasomotor efferents innervate the cerebral blood vessels, and secretomotor efferents innervate both the lacrimal and nasal mucosal glands, which provides the cranial autonomic symptoms (lacrimation, nasal congestion, rhinorrhea) in patients with cluster headache. Stimulation of the trigeminal ganglion causes cerebral vasodilatory response with an increase in cerebral blood flow. This effect is mediated by activation of trigeminal afferents with release of calcitonin gene-related peptide (CGRP), as well as through stimulation of parasympathetic outflow, which is accomplished through functional reflex between the nuclei of the trigeminovascular (trigeminal nucleus caudalis) and parasympathetic (superior salivatory nucleus) system. Cranial parasympathetic autonomic vasodilator pathway from the superior salivatory nucleus can be activated with stimulation of a trigeminovascular nociceptive input.[6] Activation of trigeminovascular system has been suggested by marked increase in the level of CGRP in the cranial venous circulation during attacks of CH as well as migraine.[7] Parasympathetic activation in humans has been demonstrated by elevated level of vasoactive intestinal peptide (VIP) during attacks of CH,

however, in patients with migraine, levels of VIP remain relatively unchanged unless there are accompanying signs of autonomic activation.[8] In conclusion, there are integral involvement of the trigeminovascular and cranial parasympathetic systems in CH. Activation of these pathways provides the anatomic basis for the expression of first-division trigeminal pain and ipsilateral autonomic symptoms that occur during cluster attacks. However, elevated CGRP level have also been documented during migraine attack, therefore, although the peripheral trigeminal nerve might be involved in CH, its activation alone cannot account for CH.

2. The hypothalamus and periodicity

The relapsing-remitting course, seasonal variation, and the clockwise regularity of single episodes are characteristics of CH, and suggest that a biological clock in the hypothalamus is involved in the pathogenesis of CH.[9] Lowered concentration of testosterone in the plasma of men with CH, reduced response to thyrotropin-releasing hormone, and other circadian irregularities in CH supports the involvement of hypothalamus in CH. Neuroimaging studies have corroborated clinical and neuroendocrinological data indicating hypothalamic involvement in CH. PET study has confirmed ipsilateral hypothalamic activation during CH attack.[10] Magnetic resonance spectroscopy (MRS) studies documented lower hypothalamic N-acetylaspartate/creatine ratios in CH patients, which indicating neuronal dysfunction in the hypothalamus in patients with CH.[11] Sensory information from trigeminal territories is conveyed to the posterior hypothalamus via the trigemino-hypothalamic tract.[12] Stimulation of the posterior hypothalamus modulates the activity of trigeminal nucleus caudalis neurons. In PET study of patients with chronic cluster headache, hypothalamic stimulation induced activation in both the ipsilateral hypothalamic grey and the ipsilateral trigeminal system, documenting a connection between the hypothalamus and the trigeminal system.[13] Therefore, it was initially suggested that the hypothalamus had a permissive or triggering role in CH. However, recent researches suggest other interpretations. If the hypothalamus is the trigger site, hypothalamic stimulation would trigger CH pain attacks, but this has not been documented. Other hypothesis about the role of hypothalamus in CH and TAC is that hypothalamus plays a major part in terminating attack and regulating the duration of attack, rather than triggering attacks.[14]

3. Recent neuroimaging studies

The findings of recent neuroimaging studies have shown several major development regarding pathophysiology of CH. Structural neuroimaging studies have observed significant gray matter volume and white matter microstructural differences in frontal pain areas, which suggests that the descending pain modulation system is structurally impaired in CH.[15] Resting-state functional MRI studies have reported significant hypothalamic functional connectivity differences in CH patients.[16] CH associated changes in hypothalamic functional connectivity primarily involved frontal pain modulatory, occipital, and cerebellar areas.[1] Therefore, CH appears to involve structural and functional changes in the descending pain modulation network and changes in the functional link between the hypothalamus and forebrain as well as cerebellar and occipital areas.

Conclusions

Pathophysiology of CH is complex and underlying mechanisms poorly understood. Acute attack of pain may be regarded as a manifestation of the trigeminal-autonomic reflex. Circannual and circadian periodicity and the functional imaging studies implicate the hypothalamus as major brain region for cluster headache. However, recent imaging studies suggested that multiple cortical pain matrix area involved in the CH pathogenesis. Disturbance in the interaction between multiple pain matrix may give rise to a permissive state and result in disinhibition of the hypothalamic-trigeminal pathway, which seems necessary for CH pain to begin.

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