▪ Headache Medicine 2026, Supplement ▪ p-ISSN 2178-7468, e-ISSN 2763-6178

Headache Medicine

ID: 262

Microstructural alterations in the periaqueductal gray matter and hypothalamic connectivity in patients with refractory chronic cluster headache

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Introduction
Cluster headache is one of the most severe and disabling forms of primary headache disorder. Recent studies have demonstrated a pathophysiological association with specific neural structures, particularly the hypothalamus, which is considered the central generator of the disease due to its characteristic cyclic pattern. Additionally, the periaqueductal gray matter (PAG), a key modulator of nociceptive transmission, exhibits functional abnormalities and structural alterations in affected individuals, contributing to the hyperexcitability of trigeminal and spinal nociceptive pathways. In this context, evaluating the influence of cellular and structural changes in these regions on clinical refractoriness in the chronic form of cluster headache is of paramount importance.

Objective
To analyze microstructural alterations in the periaqueductal gray matter and hypothalamic connectivity in patients diagnosed with refractory chronic cluster headache.

Methods
A systematic review was conducted using the PubMed, Google Scholar, NIH, and Cochrane databases. Searches employed combinations of the descriptors "Cluster Headache", "Periaqueductal Gray" and "Hypothalamus" in both English and Portuguese. Publications between 2010 and 2026 investigating microstructural alterations in the periaqueductal gray matter and hypothalamic connectivity through advanced neuroimaging techniques in patients with refractory chronic cluster headache were included. Studies focused on episodic cluster headache or pediatric populations were excluded.

Results
The findings suggest the presence of microstructural and functional alterations involving the hypothalamus, the PAG, and pain-modulating neural circuits. Diffusion tensor imaging studies demonstrated reduced fractional anisotropy (FA) and increased mean diffusivity (MD) within the hypothalamus, as well as bilateral increases in thalamic FA, suggesting remodeling of nuclei involved in nociceptive processing. Diffuse white matter abnormalities were identified in limbic, parahippocampal, frontal, and cerebellar regions, with anatomical connections linking these areas to the ipsilateral hypothalamus. Functional analyses revealed reduced connectivity between the central executive network and the salience network, as well as abnormal connectivity between the default mode network and executive brain regions. Studies involving the PAG also demonstrated increased connectivity with nociceptive circuits and sensorimotor regions, including the thalamus, insula, and hypothalamus, which was associated with increased attack frequency. These findings support the hypothesis that dysfunction within hypothalamic, cortical, and PAG-related networks may contribute to the chronification of cluster headache.

Conclusion
Refractoriness in chronic cluster headache appears to be directly associated with anatomical and microstructural alterations of the periaqueductal gray matter and hypothalamic connectivity.

Keywords:
Cluster headache
Hypothalamus
Periaqueductal gray

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