Headache Medicine

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Evidence of glymphatic dysfunction in cluster headache: the interface between sleep, circadian rhythms, and hypothalamic activity

Humberto Nunes Filho, Rayan Oliveira Falcão, José Roberto Neto, João Bosco Filho, Ana Luiza Carvalho, Giulia Carolinne Gonçalves, João Gabriel Cunha, Ana Aragão, Eduardo Filho, Maria Guimarães, Clarissa Salgado, Alberto Santana, Renan Brito, Bruna Mendonça Doria de Jesus, Yasmin Gabriele Ferreira Santos

Tiradentes University, Aracaju, Sergipe, Brazil

Humberto Nunes Filho
humbertofilho1005@gmail.com

Introduction
Cluster headache exhibits marked circadian periodicity and is frequently associated with sleep disturbances, suggesting a central role of the hypothalamus and chronobiological mechanisms in its pathophysiology. In parallel, the glymphatic system plays a fundamental role in cerebral homeostasis and metabolite clearance during sleep, and its dysfunction has been associated with neuroinflammatory processes and various pain syndromes. In this context, emerging evidence suggests that glymphatic alterations may act as a potential pathophysiological link between sleep disturbances, circadian dysregulation, and hypothalamic activation in cluster headache.

Objective
Investigate the role of glymphatic system dysfunction as a potential pathophysiological link between sleep disturbances, circadian dysregulation, and hypothalamic activity in cluster headache.

Methods
This systematic review was conducted using publications retrieved from the PubMed and Google Scholar databases between 2015 and 2025. The descriptors "Cluster Headache", "Glymphatic System", "Sleep", "Circadian Rhythm", and "Hypothalamus" were combined using the Boolean operators AND and OR. Original studies published in English addressing chronobiological aspects, sleep disturbances, hypothalamic activity, and glymphatic dysfunction in cluster headache were included. Narrative reviews, editorials, and studies not directly related to the proposed topic were excluded.
Results: Diffusion tensor imaging findings demonstrated a significant reduction in the DTI-ALPS index in patients with cluster headache compared with healthy controls (1.586 vs. 1.786; p=0.044), suggesting persistent impairment of glymphatic function. The index also showed a negative correlation with age (r=-0.549; p=0.042). Clinically, up to 80% of patients identified sleep as the main trigger for headache attacks, exhibiting marked sleep fragmentation and pathological scores on the Pittsburgh Sleep Quality Index (PSQI). Since glymphatic activity depends on the integrity of deep sleep, hypothalamic-driven circadian dysregulation may promote inefficient cerebral clearance, leading to the accumulation of toxic metabolites and oxidative stress, which may amplify and sustain trigeminal nociceptive pathway activation.

Conclusion
Current evidence suggests that glymphatic system dysfunction may represent an important pathophysiological link between sleep disturbances, circadian dysregulation, and hypothalamic activity in cluster headache. Impaired cerebral clearance may contribute to neuroinflammatory processes and the perpetuation of trigeminovascular activation, emerging as a potential therapeutic target for future investigations.

Keywords:
Cluster headache
Circadian rhythm
Glymphatic system

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