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Neuroinflammation and glial activation in the pathophysiology of migraine: a systematic review

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Introduction
Migraine is a multifactorial neurological disorder associated with central sensitization and the dysfunction of neuroimmune mechanisms. In this context, neuroinflammation and glial activation stand out due to the release of pro-inflammatory mediators capable of perpetuating neuronal excitability and contributing to the chronification of attacks.

Objective
To evaluate the role of neuroinflammation and glial activation in the pathophysiology of migraine and its relationship with central sensitization and the chronification of attacks.

Methods
A systematic review guided by the question: "Are neuroinflammation and glial activation associated with central sensitization and the chronification of attacks in migraine?". The question was structured using the PICO strategy: population (patients with migraine), intervention (neuroinflammation and glial activation), comparison (individuals without migraine and/or without evidence of neuroinflammatory activation), and outcome (central sensitization and chronification of attacks). The literature search was conducted in the PubMed database using DeCS/MeSH descriptors and free terms related to the topic ("Migraine Disorders OR migraine" AND "neuroinflammation OR glial activation" AND "central sensitization"). Original articles in English published within the last 5 years were included. Selection followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A total of 43 studies were identified, of which 18 met the eligibility criteria and were included in the analysis.

Results
Studies demonstrate that neuroinflammation and glial activation play a central role in trigeminovascular sensitization and migraine chronification. Experimental models induced by nitroglycerin or inflammatory soup demonstrated microglial activation in the spinal trigeminal nucleus caudalis and the trigeminocervical complex, associated with an increase in pro-inflammatory mediators, such as interleukin-1 beta (IL-1). Microglial receptors, such as transient receptor potential vanilloid 2 (TRPV2), purinergic receptor P2X4 (P2X4R), and purinergic receptor P2Y14 (P2Y14), participate in the activation of inflammatory pathways related to the NLR family pyrin domain containing 3 (NLRP3) inflammasome and the phosphorylation of extracellular signal-regulated kinase (ERK), contributing to mechanical allodynia and neuronal hyperexcitability. Furthermore, meningeal inflammation promotes the sensitization of trigeminal nociceptors and an increased release of calcitonin gene-related peptide (CGRP).

Conclusion
Neuroinflammation and glial activation play a fundamental role in the pathophysiology of migraine. The involvement of microglial receptors, inflammatory pathways, the NLRP3 inflammasome, and mediators such as CGRP demonstrates that neuroimmune mechanisms are directly related to central sensitization and the chronification of attacks, highlighting potential therapeutic targets for the management of the disease.

Keywords:
Migraine
Central sensitization
Neuroinflammation
CGRP
Glial activation

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