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Headache in Post-COVID-19 Patients: Toward a Better Understanding About its Clinical Characteristics, Pathophysiological Mechanisms and Treatment

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Introduction
SARS-COV-2 virus accomit not only the respiratory tract, causing also systemic manifestations, such as neurological disturban-ces. Headache is one of the most common neurological symptoms of acute and post-acute phases of COVID-19 disease. The persistence of headache weeks or months after the infection has been observed among a significant number of patients, presen-ting as a worsening of a preexisting primary headache or manifesting as a new dysfunction in those without preliminary ante-cedents of headache syndromes. Furthermore, it has been observed that this cephalea may persist in an indeterminate period and associated with other manifestations of the long-COVID syndrome, such as hyposmia, cognitive disturbances and fatigue. **Objectives**
This summary aims to analyze the presence of persistent headache in individuals previously infected by the SARS-COV-2 virus, summarizing and discussing their pathophysiological mechanisms to improve different approaches to the treatment of this disease.
Methods
A systematic review of literature was performed based on research in PubMed, ScienceDirect and BVS databases, using the boolean operator "and" and the describers "persistent headache" and "COVID". Filters were used to select articles, as review and systematic review article type and English language. 67 articles were obtained in the PubMed database, 264 in the BVS database and 249 in the ScienceDirect database, of which 8 were used.
Results
Studies related that persistent headache after an infection by COVID commits patients that had severe and non-severe forms of the disease. These headaches manifest in different forms, without a specific clinical phenotype. Tension-type-like, migraine-like and new daily persistent headache (NDPH) are the most frequent presentations, and the topography is generally bilateral with frontal or periocular predominance, but the headache can also appear in considerable frequency with a occipital or temporal predominance, with a moderate or severe intensity. Recent discoveries associate the post-COVID cephalea pathophysiology with an activation of the trigeminovascular system in individuals genetically predisposed to develop migraine, since the SARS-COV-2 protein was found in trigeminal branches and in the trigeminal ganglion. Besides that, a prolonged immune system activation with bio-humoral response is also associated with the pathophysiology of the disturbance, once inflammatory cytokines manifest in altered blood levels in those cases. Patients with bilateral headache (93% of the sample used in the study) had higher levels of IL-6 when compared with the amount with unilateral headache. Furthermore, neuroinvasion via the connection between SARS-COV-2 to angiotensin-converting enzyme 2 receptors and via endothelial cells in the blood- brain barrier is another possible pathophysiological mechanism. However, the mechanism is still not established, and the treatment recommendations follow pre-existing protocols for primary headache disorders, considering the phenotype and other symptoms associated with the long-COVID syndrome, but non-steroidal anti inflammatory drugs and tricyclic antidepressants showed a positive prognostic in cases in general.
Conclusions
Although many hypothesis have arisen in recent studies, the certain and established pathophysiological mechanisms remain unclear. Therefore, most recommendations are based on determined lines of treatment for primary phenotype headaches with the same clinical characteristics, such as tension-type and migraine-like headaches. While data is still lacking, those are safe recommendations that lead to the most favorable prognostic. More research is necessary to exhibit the relationship between the infection, the variants of the virus and the different phenotypes and pathophysiological mechanisms of post-COVID headache, so that specific treatments can be determined to improve the prognosis of the patients.

Keywords: Long-Covid; Pathophysiology; Persistent Headache; Sars-Cov- 2; Treatment.