

Headache and COVID-19: An Unholy Alliance

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ABBREVIATIONS: SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Coronavirus Disease 2019; ICHD-3: International Classification of Headache Disorders; TTH: Tension-Type Headaches; NSAIDS: Non-steroidal anti-inflammatory Drugs; TMPRSS2: Transmembrane Protease, Serine 2 ACE2 Cellular Receptor Angiotensin-Converting Enzyme 2; WHO: World Health Organization; ICHD-3: International Classification of Headache Disorders; ACE2: Cellular Receptor Angiotensin-Converting Enzyme 2; TTH: Tension-Type Headaches

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case of SARS-CoV-2 was officially reported in December 2019 from Wuhan, China [1]. After its spread to more than 200 countries, On March 11th, 2020, the World health organization (WHO) has declared the novel coronavirus (COVID-19) outbreak a global pandemic [2]. Globally, it has affected more than 262 million people to date, causing fatality in more than 5.2 million patients [3]. The novel coronavirus primarily affected the respiratory and cardiovascular system, but frequent neurological manifestations and complications of COVID-19 infection have been reported in the literature, including headache, anosmia/hyposmia, acute myelitis, encephalitis, acute hemorrhagic necrotizing encephalopathy, and cerebrovascular accidents. Headache is one of the most frequent neurological symptoms reported by COVID-19 patients. COVID-19 headache can persist as a de-novo post-Covid-19 headache as well [4,5] Broadly COVID-19 headache falls under the classification of 'Headache attributed to systemic viral infection 9.2.2' as per international classification of headache disorders 3rd edition (ICHD-3) [2,4].

SARS-CoV2 primarily attacks the respiratory epithelium. It invades the human host cells by binding to the cellular receptor angiotensin-converting enzyme 2 (ACE2) and by serine proteases

TMPRSS2 for spike (S) protein binding. Although SARS-CoV-2 was not considered neurotropic in the early phase, invasion of the ACE2 receptors in glial cells and spinal neurons is postulated to be one of the reasons for the neurological manifestation of the COVID-19 infection. Animal models predicted SARS-CoV-2 to spread through the olfactory bulb, and consequently, it reaches the central nervous system (CNS). Respiratory centers in the human brain, including the nucleus ambiguus and solitary tract, are also postulated to be the target of SARS-CoV-2, suggesting central hypoventilation seen in COVID-19 respiratory failure. The role of dysregulation of ACE2/Angiotensin1-7/MasR axis is the current research nucleus for COVID-19 headache due to the angiotensin-converting enzyme 2 (ACE2) receptor's high affinity for SARS-CoV-2 [6]. COVID-19's Headache pathophysiology is hypothesized to be through activation of peripheral trigeminal nerve endings by the virus directly or through the vasculopathy and increased circulating pro-inflammatory cytokines and hypoxia [9].

COVID-19 headaches are diffuse with pressing quality in the frontal, temporoparietal and periorbital region [4]. Phenotype resembles that of migraine and tension-type headaches (TTH) [7]. Headaches are moderate to severe in intensity [8,9] and are commonly associated with lethargy, cough, photophobia, phonophobia, anosmia, and ageusia [10].

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Al-Hashel et al. [5] reported in his study that 32/121 COVID-19 patients had de-novo post-Covid headache. In contrast, patients with preexisting migraine and TTH after recovery had worsening headaches, an increased frequency of attacks, and increased analgesic intake. De novo headaches resolved within one month mostly, and males were more affected [5]. In a separate study by Magdy R et al., fever, dehydration, and female gender were predictors of higher intensity of COVID-19 related headache [9]. ICHD-3's validation study for COVID-19 headache in 106 hospitalized patients showed headache as the most bothersome symptom in 19 % of patients with a median disability scale of 60/100 [4].

NSAIDs (nonsteroidal anti-inflammatory drugs) and acetaminophen are the first-line drugs against COVID-19 headaches [11]. Initially, the role of NSAIDs, especially ibuprofen, was contested as it increased ACE2 levels [12]. However, it was argued to be a weak bias as the trial was on diabetic rats, and the increase in ACE2 was seen in rats' hearts only [11]. By far, indomethacin showed promising results in COVID-19 headaches, which are refractory to other therapies. Besides COX-1 and COX-2 inhibition, indomethacin exerts its anti-inflammatory action by inhibiting IL-6, TNF, and superoxide radicals as well. It also inhibits viral protein synthesis, established in studies against herpesvirus 6, hepatitis B virus, and cytomegalovirus [13].

Headache is one of the cardinal symptoms of COVID-19 infection, with a reported cumulative prevalence of 25.26%. As per García-Azorín et al. [7] 6% of patients reported headache as the first COVID-19 symptom [7]. Unfortunately, there is currently a lack of a better COVID-19 headache definition, and it falls under the broad ICHD-3 classification for 'Headache attributed to systemic viral infection 9.2.2'. Mutiawati et al. [14] found headaches to be 1.7-fold more prevalent in patients with COVID-19 than those with non-COVID-19 respiratory viral infections. Therefore, it is worth suggesting that once we have attained robust evolution data on COVID-19 headaches along with a better understanding of pathophysiology, a revised subclassification in ICHD-3's 9.2.2 section should be considered to diagnose COVID-19 headache from other viral headaches.

A new subclassification will give physicians a better sense to diagnose de novo acute and chronic COVID-19 headaches from different primary and secondary causes of headaches. More importantly, this will help in future treatment trials specifically for de-novo post-Covid-19 headaches.

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