

# The characteristics of headache in COVID-19: A literature review

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) has become outbreak in the world since December 2020. The higher incidence and transmission of COVID-19, the higher virulence of the disease. Besides respiratory manifestations, the most common symptoms in COVID-19 are neurological manifestations. The major neurological manifestations in COVID-19 are headache and dizziness. Headache is more common as chief complaint in emergency room and hospitalized patients than dizziness. Therefore, this review aims to outline the characteristics of headache in COVID-19. The conclusion of this review is that the characteristics of headache in COVID-19 are moderate-severe intensity, frontal-temporal region, pulsatile and tightening quality, constant duration and commonly associate with one or more COVID-19 symptoms.

**Keywords:** coronavirus, coronavirus infections, COVID-19, disease outbreak, headache

## INTRODUCTION

In the end of December 2019, there was a case of pneumonia outbreak in Wuhan which was caused by Coronavirus disease 2019 (COVID-19). The World Health Organization (WHO) named COVID-19 based on its genetic sequence which was found similar with severe acute respiratory syndrome corona virus (SARS-CoV). COVID-19 has been declared as pandemic by WHO on March 11, 2020 [1].

As of May 2<sup>nd</sup>, 2021, WHO reported that there had been increment of COVID-19 cases in nine consecutive months since the pandemic occurred. It was the highest level of new weekly cases of COVID-19 (5.7 million new cases) with 6% increase of death cases from a past week. The South-East Asia was marked higher increase in new cases (19%) and death events (48%) than another region. The largest contribution to the number of new cases (188.2/100,000) and death incident (1.7/100,000) was from India. Indonesia was the second highest contribution of new cas-

es (13.2/100,000) and death incident (0.4/100,000) [2].

There are three ways of COVID-19 in human-to-human transmission, such as direct, contact, and airborne transmission. COVID-19 can invade and replicate in the host cell by angiotensin-converting enzyme 2 (ACE2) receptor which can be observed in oral mucosa, lung, esophagus, ileum, colon, myocardium, kidney and bladder [3]. Besides, brain and spinal have glial cells which also contain ACE receptor [4]. The COVID-19 requires about 5 days until the symptom begins. Epidemiologically, COVID-19 mostly affects male and older age ( $\geq 50$  years old). High hospitalization is higher in patient with comorbid (60-90%). Mostly, the symptom of COVID-19 is in mild manifestation (81%). Flu-like syndromes, such as fever, dry cough, rhinorrhea, breathless and myalgia are frequently found in COVID-19. The other symptoms which can be observed in COVID-19 are headache, gastrointestinal symptoms (nausea, vomiting and diarrhea), fatigue,

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anosmia and ageusia [5]. Recent study found that COVID-19 patients with history of primary headache had new attack of headache (42%), alteration of headache pattern (49%), and the most severe headache attack (39%). Headache was found twice higher in COVID-19 patient than in non-COVID-19 patient (OR: 1.73; 95%CI: 1.94-2.51;  $p$ : 0.04) [6]. The incidence of headache is approximately five-fold in confirmed COVID-19 patient (11.8% vs 2.8; OR: 4.95; 95%CI: 3.50-6.92;  $I^2$ : 55%) [7]. The major neurological complaints of COVID-19 patient are severe intensity of headache with anosmia and ageusia in emergency room [8]. Therefore, this literature review aims to discuss the characteristic headache, including frequency, type, severity and the symptoms which associated with headache in COVID-19 patient.

## MAIN TEXT

### COVID-19

The SARS-CoV-2 is club-like approximately 120nm in diameter with spike protein around envelope protein E. It is a single-stranded Ribonucleic Acid (RNA) which contains approximately 30 kilobase pair genomes and 5' methyl-guanosine cap [1,9]. It can infect easily and adapt the new host because of the recombination and variation of genome [5]. Microscopically, the shape of SARS-CoV-2 looks like a crown so that its name corona based on Latin [9]. SARS-CoV-2 is *Beta-coronavirus* and the third SARS which has severe symptoms and infects human following SARS-CoV epidemic in 2002-2003 and Middle East Respiratory Symptom (MERS) in 2012. Bat is the natural host of SARS-CoV, MERS and COVID-19 [1]. There are two types of SARS-CoV-2, such as type S and L, with type L is more aggressive than type S [9].

SARS-CoV-2 can invade the human cells via ACE2 in oral mucosa, lung, esophagus, ileum, colon, myocardium, kidney and bladder which is cleaved by serine protease TMPRSS2 and binding process with spike protein of virus. The process of translation, proteolysis, replication and translation begin after endocytosis of RNA SARS-CoV-2. Furthermore, the infected host cell can produce hundreds of new virions. Alveolar epithelial type II cells are the most frequent cells which express ACE2 and TMPRSS2. Inflammatory process is triggered by SARS-Cov-2 invasion and replication. The imbalance of type 1 and type 2 T-helper cells which is caused by cytokine storm and hypoxemia may lead to respiratory dysfunction and multiple organ failure [1,5,9].

The classification of COVID-19 had been revised into three parts (suspect, probable and confirm) on August 7<sup>th</sup>, 2020. The criteria of suspected COVID-19, such as fever, cough (or  $\geq 3$  acute symptoms, such as fever, cough, fatigue, headache, myalgia, sore throat,

dyspnoea, gastrointestinal symptoms, altered mental status), history of living/working/traveling within 14 days from high risk of virus transmission area and history of severe acute respiratory illness. The criteria of probable COVID-19, including suspected COVID-19 criteria, anosmia or ageusia with unknown etiology and history of contact with probable/confirmed COVID-19 or suggestive COVID-19 in chest imaging [10]. Confirmed COVID-19 was diagnosed by positive result in Reverse Transcription Polymerase Chain Reaction (rRT-PCR) method [11].

The transmission of COVID-19 can be direct/indirect contact, such as surface contact, droplet, airborne, fecal-oral, blood transfusion, vertical transmission and animal to human [2]. The term of contact is regarded as history of exposure to probable/confirmed COVID-19 in two days before and two weeks following the onset of symptoms by face-to-face more than 15 minutes in a day and within one meter or direct physical contact with probable/confirmed case [10].

The size of droplet is approximately more than 5-10  $\mu\text{m}$ . If the size is  $\leq 5\mu\text{m}$ , it is called droplet nuclei/aerosol. Droplet can be produced by cough, sneeze, talk and sing. It can be transmitted to other person's respiratory system when the distance of each other is about one meter. Aerosol can still be infectious in the air and spread widely especially during medical procedure, such as intubation. COVID-19 can be detected in fomites within 48-72 hours in adequate air temperature and humidity [2].

The initial screening of COVID-19 should be performed in suspected case or in person who has history of contact to probable/confirm COVID-19 [2]. Ag-RDTs (Antigen-detecting Rapid Diagnostic Tests) can be used in the community for screening COVID-19 with Nucleic Acid Amplification Tests (NAATs) like rRT-PCR confirmation. If rRT-PCR is unavailable, the diagnosis of confirmed COVID-19 can be made by using Ag-RDTs which has sensitivity  $\geq 80\%$  and specificity  $\geq 97\%$ . This test should be conducted by trained operators [12].

The risk of transmission is higher when health protocols are not carried out and in poor ventilated room. Therefore, WHO promotes some ways in order to decline the transmission of COVID-19 by washing hand regularly, wearing face mask, avoiding crowded situation and poor ventilated room, and practicing social distancing [2].

### Headache and COVID-19

According to the third edition of the International Classification of Headache Disorders (ICHD-III), headache is classified into primary headache, secondary headache and painful cranial neuropathies, other facial pain and other headache. Headache in COVID-19 is classified in "headache attributed to

systemic viral infection” in ICHD-III. The diagnostic criteria of headache attributed to systemic viral infection are at least two of: headache associates with onset of viral infection, the severity of viral infection is comparable with the severity of headache, the improvement of headache is parallel with the improvement of systemic viral infection, and the characteristic of headache has one or both, such as diffuse pain and/or moderate to severe intensity. Moreover, other cause of headache, such as viral meningitis or encephalitis, should be rule out in order to diagnose headache attributed to systemic viral infection [8]. According to ICHD-III, the symptoms associated with headache, such as fever, light sensitivity and nausea, can suspect viral meningitis or encephalitis [13].

COVID-19 patients commonly enter the emergency department with the chief complaint as fever and cough (88.5% & 80.2%) [14]. Fever (83.3%; 95%CI: 78.4-87.7), cough (60.3%; 95%CI: 54.2-66.3) and fatigue (38%; 95%CI: 29.8-46.5) were the most frequent symptoms observed in China meta-analysis study [15]. Although fever and cough were common in COVID-19, neurological manifestations were also frequently reported (72.1%) [16].

The neurological manifestation of COVID-19 can be classified into three classifications, such as Central Nervous System (CNS), Peripheral Nervous System (PNS) and skeletal muscle injury. CNS manifestation was more common than PNS and skeletal muscle manifestation in COVID-19 (24.8% vs 8.9 vs 10.7%) [14]. Headache was the most common CNS symptom in COVID-19 patient (74.6%) in some previous studies (8,14,17). Barek reported that headache was more often than dizziness (16.2% vs 12.26%) [18]. A study which was involved 1420 COVID-19 patients with mild-moderate symptoms, headache was the most common neurology symptom (70.3%), followed by anosmia (70.2%) and obstruction of nasal (67.8%) [19]. A systematic review in Spain demonstrated that early symptoms of hospitalized COVID-19 patients were neurologic symptoms (57.4%), such as myalgia, headache, and dizziness (17.2% vs 14.1% vs 6.1%). The onset of the symptoms appeared approximately 3.8 days [20]. A retrospective study of 11 hospitals, showed that 16% of COVID-19 manifestations were headache, following confusion (53%) [21]. In contrary, Mao exhibited that dizziness was more common than headache (13.1% vs 16.8%) [22]. A meta-analysis study reported that headache (9.20%) and dizziness (10.00%) were the most frequent CNS symptoms in COVID-19 [23]. A retrospective study of 1034 COVID-19 patients in Tunisia found that the predominant neurological symptom was headache (41.1%) with mild-moderate intensity (59.1%), frontal-temporal region (51.2%) and the onset of headache during the first-3-day of the disease

[16]. Augusto investigated that 64.4% of COVID-patients had headache (95%CI: 52.3-75.3). The migraine phenotype (51%) with severe intensity (53%), bilateral pain (94%) or frontal area (80%) and pulsatile (51%) or tightening quality (43%) were observed as the beginning symptoms of COVID-19 (range 1-20 days) [13,24]. Pulsating quality of headache was more prevalence in COVID-19 patient with history of headache than those without history of headache (50.9% vs 32.5%;  $p$ : 0.008). Moderate intensity (47.7%) was the most predominant intensity of headache, while mild, severe and very severe intensity were about 26.6%, 23.4%, and 2.3%, respectively. There were several variables that could differ the etiology of headache due to COVID-19 and non-COVID-19, such as bilateral headache (OR: 3.37), duration over 3 days (OR: 1.93), male (OR: 2.06) and resistance to analgetic (OR: 2.61) ( $p$ : 0.04) [17]. Toptan explained that the characteristics of headache and migraine-like in COVID-19 were moderate-severe intensity, in frontal-temporal, pulsating, aggravated by activity, improvement in 3 days and associated with photophobia, phonophobia, osmophobia, and nausea [25]. Consistent with previous research, the common characteristics of headache in COVID-19 were moderate intensity (50.6%), frontal area (47.4%), pressing quality (70%), and constant duration (49.5%). 37.8% of COVID-19 patient had headache for 6 weeks [8]. In the other hand, a study which involved 3458 participants in Turkey demonstrated that COVID-19 patient had the same frequency (52.5%), deterioration of severity (72.4%), and duration of headache (66.4%) [17]. A meta-analysis study in Bangladesh revealed that the severity of headache was not correlated with the severity of COVID-19 infection (OR: 1.19;  $p$ : 0.34) [18]. Tension Type Headache (TTH) was more common than migraine-like attack in COVID-19 (54.7% vs 36.3%). Uygun exhibited that longer duration of headache (more than 3 days) was more frequently observed in COVID-19 than in non-COVID-19 [17]. A Tunisia study also reported that headache was more prevalence in COVID-19 patients with respiratory symptoms (dyspnea or cough) than those without respiratory symptoms (59% vs 32.3%;  $p$ : <0.001) [16]. Cough could trigger headache reported in a study (16.4%; 95%CI: 8.8-27%) [24]. Moreover, gastrointestinal symptoms in COVID-19 could increase the incidence of headache (21.62% vs 8.84%;  $p$ : 0.002). Jin suspected that this could be due to electrolyte imbalance [26]. Infection and stress (up to 30%) also triggered headache in COVID-19 patient ( $p$ : 0.0015) [17]. Up to 50% of COVID-19 patients with headache, did not have previous history of headache.<sup>8</sup> Based on the previous history of headache, 80% patient suffered different type of headache with previous headache phenotype [24]. A research in Turkey also exhibited

that different type of headache was found in COVID-19 patient with previous history of headache (79.5%) [17]. However, 83% of the patients with previous history of migraine phenotype had similar phenotype of headache and half of those patients with history of tension-type headache phenotype also had the same tension-type headache phenotype. Physical activity and nausea could worsen in COVID-19 patients with previous history of migraine (83% vs 43%; 58% vs 23%;  $p < 0.05$ ). Younger patient also had headache in COVID-19 significantly (median: 56; IQR: 44-65.5 vs 62; IQR: 52-74.5;  $p: 0.039$ ). Consistently, younger COVID-19 patients were more common having headache than older patients reported in Spain Study (50.6±15.3 vs 63.6±15.7;  $p: <0.0001$ ). Lechien demonstrated that female and younger age (< 60 years) were more frequent having headache than male ( $p: <0.001$ ) [19]. A prospective study exhibited that female was more dominant having severe quality headache than male (57.7% vs 30.3%;  $p: 0.009$ ) [8]. Meanwhile, a cross-sectional study in Brazil demonstrated that there was no different significantly between male and female in having headache (59.6% vs 69.2%;  $p: 0.413$ ) [24]. A US study which compared headache in COVID-19 and in Influenza A-B revealed that the prevalence of headache in COVID-19 was significantly higher than in Influenza A-B (11% vs 3%; OR: 3.9; 95%CI: 1.3-11.5;  $p: 0.01$ ) [27].

COVID-19 infects the central nervous system via cranial nerve, particularly olfactory pathway. The dysfunction of olfactory nerve is related with this entry pathway. This process can affect not only the perception of odors, but also the sense of taste. Both anosmia/hyposmia and ageusia/hypogeusia are common symptoms in COVID-19 (52.7% & 43.9%; 95%CI: 29.6-75.2% & 20.5-68.9%) [24]. Mao also reported that impairment of both taste and smell were dominant PNS symptoms in COVID-19 (5.6% & 5.1%, respectively) [23]. Headache was more frequent in COVID-19 who had anosmia/hyposmia than those who had normosmia (86% vs 51%; OR:5.7; 95%CI: 1.7-19.2;  $p$  value: 0.003). Moreover, headache was also more often in ageusia/hypogeusia than in normogeusia (86% vs 50%; OR: 6.3; 95%CI: 1.9-20;  $p: 0.002$ ). COVID-19 patients who had more frequent headache attack were also observed higher in both anosmia/hyposmia and ageusia/hypogeusia than in

normosmia and normogeusia (83% vs 47%; 95%CI: 1.8-15.9;  $p: 0.002$ ) (24). A study in Spain also found that the incident of headache was significantly higher in patients who had anosmia/ageusia than those in normal (54.6% vs 18.2%;  $p: <0.0001$ ) [8]. Although the exact mechanisms were not fully understood, this neurological symptoms were possibly caused by direct invasion of COVID-19 to the neuron in CNS and PNS, particularly olfactory bulb [24].

The pathophysiology of headache in COVID-19 relates with ACE2. The effect of ACE2 opposes the activity of ACE. Angiotensin II (Ang II) is converted from Angiotensin I (Ang I) by ACE. ACE2 is modulated to alter Ang II forming Ang I-VII whose effects are contrary with Ang II such as, vasodilatation, cardiovascular protection and decrease inflammation process, reactive oxygen species, neurodegeneration, neuronal death and nociception. The binding process between ACE2 and COVID-19 may lead to downregulation of ACE2. This process may result in the decrement of Ang I-VII production and the unbalance of ACE/Ang II activity. Ang II, substance P and Calcitonin Gene-Related Peptide (CGRP) in dorsal root ganglia of trigeminal ganglia contribute to nociception process [13]. CGRP is a neuropeptide which can provoke both migraine and headache [28]. Besides, diffuse endothelial inflammation also relates with headache as ACE2 can also be found in endothelial cell. Therefore, it can activate trigeminovascular and lead to vasculopathy [29]. The trigeminovascular activation may also be mediated by inflammatory mediators such as, interleukin-1 beta, nitric oxide, prostaglandin E2 and nuclear factor-kappa B. Furthermore, these inflammatory mediators contribute in headache process [30].

## CONCLUSIONS

The prevalence of neurological manifestation is quite high in COVID-19. CNS manifestation is more common than PNS and muscle injury manifestation. Headache is the most dominant CNS manifestation of COVID-19. The characteristics of headache, observed in COVID-19, are moderate-severe intensity, frontal-temporal region, pulsatile and tightening quality, constant duration and commonly associate with other COVID-19 symptoms, such as anosmia/hyposmia and ageusia/hypogeusia.

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