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Headaches attributed to COVID-19 infection

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Introduction

Headache has been identified as a common neurologic manifestation of COVID-19 infection in several studies. The prevalence of headache among COVID-19 cases was found to be 25.2% according to a metaanalysis of 104,751 COVID-19 cases from 78 eligible studies [1].

The exact pathogenic mechanism of headache in COVID-19 infection is not clear. During the course of COVID-19, headaches have usually exhibited benign features and have even been counted as a good prognostic factor [2]. However, in some instances, headache could be the symptom of a serious complication.

Acute headache in patients affected by COVID-19 could be attributed to systemic viral infection, viral meningitis or encephalitis, noninfectious inflammatory intracranial disease, cough headache, hypoxia and/or hypercapnia, and increased cerebrospinal fluid (CSF) pressure. However, most COVID-19 headaches are benign and are not serious.

The worsening of COVID-19-related headaches has been found to be higher in patients with existing primary headache group disorders. High pain intensity more frequently afflicts younger males with moderate COVID-19 infections [3].

Most cases of headache are transient and improve along with the improvement of the systemic manifestations of the disease. However, in a subgroup of patients, the headaches may continue for several weeks. Migraineurs are more susceptible to developing headaches in the acute phase of COVID-19 infection and to experience a continuation of headache afterward. In a minority of patients, de novo headaches will develop after the disease.

Development of headache has been observed to be significantly higher in dehydrated patients (defined as serum osmolality of more than 294 mOsm/kg) [4]. Therefore, monitoring of fluid requirements is essential. In one study on 172 patients with COVID-19-induced headache, a previous history of primary headache and dehydration was considered as risk factors for a higher frequency of headache. Fever and dehydration have also been associated with increased pain severity [4]. Another study found that headache prevalence was significantly higher in patients with gastrointestinal (GI) symptoms. The authors suggested that these headaches could be caused by fever and electrolyte imbalances in patients with GI manifestations [5].

Anosmia and ageusia have been reported more frequently in headache patients compared to patients without headache [6]. Involvement of the nasal cavity by the virus and irritation of the branches of the trigeminal nerves which innervate it could be responsible for headache in these patients. In one study, MRI showed evidence of transient olfactory bulb injury in patients with fever and headache, which could indicate the cause of anosmia with headache in these patients [7].

Headaches that occur early in the course of COVID-19 infection may be similar to influenza-type headache and usually will respond well to proper hydration, nonsteroid antiinflammatory drugs, or high-dose acetaminophen. However, the treatment should be continued for a few days after relief to prevent headache recurrence. In many patients, anxiety and concerns about the disease can also provoke or worsen a headache. With this in mind, it could be advisable to add an anxiolytic drug to analgesic mediation. As headache could also be a response to a fever from any cause [8], antipyretic therapy could improve headache symptoms.

A few days after the onset of COVID-19, the body's immune response to it and the accompanying cytokine release could lead to headaches that are more severe than those which can accompany the early course of the disease. Cytokines are involved in the modulation of the pain threshold and sensitization of the trigeminal nerve fibers [8–10]. In this scenario, a headache might become severe and may not respond to simple or combined analgesics. However, this type of headache usually ameliorates in line with an improvement of systemic manifestations.

Headache could be a symptom of a more serious problem, such as cerebral venous thrombosis (CVT) or subarachnoid hemorrhage. There is strong evidence of the possibility of hypercoagulability and vascular endothelial damage and serious vascular consequences of COVID-19. A headache could be a presenting or accompanying symptom of a rare manifestation of

meningitis or meningoencephalitis from COVID-19 infection, although other neurologic symptoms and signs should accompany or follow.

Treatment of headaches caused by serious problems should be directed toward the primary condition. Parenteral analgesics could be of help in patients with severe headaches. A headache in a later phase of COVID-19 may fulfill the criteria for intracranial hypertension; thus, corticosteroids could be helpful for a short period where no contraindications exist. Headache sometimes could be a response to the side effects of drugs used to treat COVID-19 patients.

In conclusion, headaches that accompany COVID-19 infection could have different causes. With the use of ICHD3 criteria, these headaches could be classified as “acute headache attributed to systemic viral infection,” “headache attributed to viral meningitis or encephalitis,” “headache attributed to other noninflammatory intracranial diseases,” “secondary cough headache,” “headache attributed to hypoxia and/or hypercapnia,” “headache attributed to cranial or cervical vascular disorders,” and “headache attributed to increased CSF pressure.” It is important to differentiate between benign headaches and those from serious causes and manage them accordingly.



Unremitting headache after recovery

Studies have reported headaches enduring more than 1 month after recovery from COVID-19 infection [6,11]. In one cohort study, headache resolved in most patients within 1 month after recovery from COVID-19 and in the rest after 3 months. An increase in the severity of migraines was noticed more among females and those who had experienced more severe migraines before COVID-19 infection. Similarly, an increase in attack frequency was noted in patients who had experienced more frequent migraine attacks before infection [3]. This indicates that incidences of persistent headache for over 1 month after COVID recovery, both as new-onset or aggravation of a preexisting migraine, should not be underestimated [3].



Headache after vaccination for COVID-19

Headache has been reported to be among the most frequent adverse effects following COVID-19 immunization. Its incidence has been reported by approximately half of vaccine recipients both in clinical trials and from real-world data [12,13]. The headache typically presents within the first

72 h postvaccination and may be accompanied by fatigue, fever, myalgia, arthralgia, or diarrhea [12]. Although headache is a common symptom after vaccination, it typically presents and resolves within 1 day or a few days [14].

Headache is the most frequent symptom of CVT and it may be isolated or accompanied by other symptoms [13,15,16]. As in other secondary headache disorders, CVT can be recognized by the presence of red flags [14]. Delayed onset of headache following an adenovirus vector-based COVID-19 vaccine has been associated with CVT. Patients with new-onset headache within 1 week of vaccination with an adenovirus vector-based vaccine should receive a thorough clinical evaluation and CVT must be considered in the diagnostic work-up [14]. Diagnostic delay is common in CVT. Because prompt treatment likely will improve the clinical outcome, every physician must be aware of the potential risk of vaccine-related thrombotic complications [14].

The pathophysiology of thrombosis with thrombocytopenia syndrome has been recently discussed. The role of antiplatelet factor-4 antibodies seems causative and includes inducing platelet activation, aggregation, and thrombosis, leading to severe platelet consumption and thrombocytopenia. Evidence discussed in an interim guideline published by the World Health Organization (WHO) states that the treatment should include that for immune-mediated phenomenon and adequate anticoagulation. For the first, intravenous immunoglobulins are the preferred option, while nonheparin-based anticoagulants must be used. Heparin-based anticoagulants and platelet infusion should be avoided [17].



Headache in COVID-19 era caused by lifestyle changes

Aside from headache that is directly related to COVID-19 infection, during the pandemic and subsequent lockdowns, an increase in the number of patients complaining of headache with or without a previous history of migraine or tension-type headache has been reported.

Cervical muscle spasm as a cause of headache

One common trigger for headache is neck muscle spasm and the consequent cervical pain. This can be attributed to poor posture and increased screen time using electronic devices [4]. One study conducted on the work from home population during the COVID pandemic reported a 23.5% incidence of neck pain [18]. Neck pain is a common symptom of overuse of mobile phones and electronic devices [19]. It has also been shown that neck pain itself could trigger or be an accompanying symptom of primary headaches, including migraine [20].

External compression headache

According to ICHD3 criteria, external compression headache results from sustained compression of the pericranial soft tissues, for example, from use of a tight band around the head. This will occur within 1 hour of sustained external compression with maximum severity located at the site of external compression. It generally will resolve within 1 hour after the source of external compression is removed (ICHD3 [21]).

The mandatory use of masks in many societies can be a cause of headache in susceptible persons. This is especially an issue for health care providers who work in hospitals or clinics. Ong et al. [22] studied 158 workers who wore N95 face masks with or without eye protection in Singapore and reported that this type of headache was a complaint in 81.0% of workers. The location was bilateral in all participants and corresponded to the contact areas of the protection equipment. It manifested mainly as a sensation of heaviness and pressure and was less accompanied by pulsation (11.7%).

Headaches due to eye refractory errors

In persons with refractive error of one or both eyes, prolonged visual tasks may induce or aggravate headache. During the pandemic, many people spend more time using electronic devices in teleworking; thus, this type of headache can occur in individuals with preexisting refractory error [21].

Other causes

Stress and anxiety is caused by isolation or fear of COVID-19 infection, as well as emotional and economic problems secondary to loss of employment or a decrease in income. These, in addition to changes in dietary habits and irregular sleep hours, are the common causes that can aggravate the incidence of previous headache.



Suggestions for headache management

General considerations

Methods of mitigating the occurrence or increase in headache include publicizing information about headache triggers, encouragement of effective means of stress management, and maintaining correct posture when using electronic devices. Additional efforts should be to strive for a regular and sufficient sleep cycle, healthy diet, and regular physical activity. Stretching

exercises focusing on the neck and shoulder muscles as well as eye rest when working on electronic devices could be helpful in headache prevention. Access to physicians and health care providers and to medical and psychological consulting, especially by virtual routes, can be very effective in controlling headaches and preventing episodic headaches from becoming chronic ones.

An issue requiring attention is headache in medical staff. This occurs mainly as a consequence of increased work hours in highly stressful situations with the requirement of wearing personal protection equipment. All of these factors should be considered and addressed by management to maintain the welfare of the medical staff.

Drug therapy

There is no specifically approved drug for treatment during the acute phase of a headache, although one study recommended indomethacin [23]. Common NSAIDs also can be used without causing specific adverse effects for the disease. High-dose acetaminophen also could be effective.

For more serious headaches, symptomatic relief might be achieved by the transient use of opioids by parenteral or oral route; however, their abuse always is a concern and they should be used cautiously. Short-term corticosteroids at the lowest effective dosage in oral or intravenous form might be considered for severe headaches that are unresponsive to the previously mentioned drugs, especially during the cytokine release phase. It is essential to discuss the risks and benefits of any prescribed drug with the patient prior to its use [24].

For headaches that persist for more than a few weeks, prophylactic treatments might be needed for headaches that are frequent or bothersome. Such prophylactic drugs should be selected according to the headache type or by similarity of the headache to migraine, tension, or trigeminal autonomic cephalalgias types.

For those with a previous history of a primary headache and aggravation due to a trigger or stimulating factor, a change in dosage or the use of prophylactic drugs might be needed. In this case, physicians should strive to prevent patients from developing chronic or medication overuse headaches and promptly managing them if or when this occurs.

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