**Headache**
*Series Editor:* Paolo Martelletti

Aynur Özge
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# Headache Disorders in Pandemic Conditions

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# Headache

**Series Editor**
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The purpose of this Series, endorsed by the European Headache Federation (EHF), is to describe in detail all aspects of headache disorders that are of importance in primary care and the hospital setting, including pathophysiology, diagnosis, management, comorbidities, and issues in particular patient groups. A key feature of the Series is its multidisciplinary approach, and it will have wide appeal to internists, rheumatologists, neurologists, pain doctors, general practitioners, primary care givers, and pediatricians. Readers will find that the Series assists not only in understanding, recognizing, and treating the primary headache disorders, but also in identifying the potentially dangerous underlying causes of secondary headache disorders and avoiding mismanagement and overuse of medications for acute headache, which are major risk factors for disease aggravation. Each volume is designed to meet the needs of both more experienced professionals and medical students, residents, and trainees.

Aynur Özge • Derya Uludüz
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Editors

# Headache Disorders in Pandemic Conditions

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# Foreword

In the last 2 years, clinical medicine has had to face an epochal change for which it was by no means prepared. In the previous 20 years, it had prioritised the development of areas deemed ethically strategic for maintaining the well-being of humans in old age, neglecting the area of infectious diseases, not only by failing to develop innovative drugs, but also by not developing health emergency plans for disaster situations such as this SARS-CoV2 zoonosis, which to date has killed 6.7M people, infected 656M and necessitated the rapid development of vaccines administered 13B times.

The appearance on the scene, in a violent and rapid but not entirely unexpected manner, of COVID-19, has overturned all the management potential of public health facilities, changing their operational priorities from the area of non-communicable diseases towards communicable ones, in a sudden but equally rapid manner.

As a result, the focus of clinical and basic research has reverted haphazardly and at times too enthusiastically, to the exuberant growth of scientific publications that has occurred during this pandemic, unfortunately also producing scientific literature of not very high quality.

In this perspective of critically reappraising the scientific evidence accumulated to date, we can welcome this sixteenth volume of the Headache Series to guide us along the ideal path outlined by the headache symptom, one of the relevant clinical signs, although not pathognomonic, at least for the initial diagnosis of COVID-19. The appearance of COVID-19 on the scene, in a violent and rapid but not entirely unexpected manner, has disrupted the management potential of public health facilities, shifting their operational priorities from non-communicable diseases to communicable ones, in a sudden and equally rapid manner.

As a result, the focus of clinical and basic research has haphazardly and at times too enthusiastically reverted to the exuberant growth of scientific publications that have occurred during this pandemic, unfortunately also producing scientific literature of less than ideal quality.

In this perspective of critically reappraising the scientific evidence accumulated to date, we can welcome this seventeenth volume of the Headache Series to guide us along the ideal path outlined by the headache symptom, one of the relevant

clinical signs, although not pathognomonic, at least for the initial diagnosis of COVID-19. However, as we proceed down this path, we delve into the varied clinical evolutions of the complications or the Long-Covid, and then further towards the side-effect alerts of the vaccines themselves.

Thus, to better understand not only the weight of headache within the SARS-CoV2 infection, but especially in the context of the modern concept of One Health, the value of this clinical marker is of inestimable importance, which must now be properly captured and transferred into good clinical practice, not only of experts, not only of researchers, but above all of the huge mass of silent public health workers, the emergency room and internal medicine doctors, who from the first hour are entrenched on the front line of this world war that still today, 2 years after its beginning, seems not to have been won at all, on the contrary.

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# Chapter 1
# Clinical Update on the COVID-19 Pandemic

**Müge Ayhan, Belgin Coşkun, and Rahmet Güner**

In December 2019, cases of pneumonia with unknown etiology have been reported in Wuhan, China [1]. On February 11, 2020, the World Health Organization (WHO) named the pneumonia with unknown etiology as coronavirus disease 2019 (COVID-19) [1]. Before this time, the coronaviruses we know of such as HCoV-NL63, HCoV-OC43, HCoV-229E, and HKU1 are viruses that cause upper respiratory tract infections with mild symptoms for humans. These viruses may lead to a more serious, rare clinical course in infants, children, and the elderly. Coronaviruses were first isolated by Tyrrell and Bynoe in 1965 and by Hamre and Procknow in 1966 in human embryonic ciliated trachea, nasal epithelium, and human kidney cell cultures [2, 3].

Coronaviruses are members of *Coronaviridae* family and *Orthocoronavirinae* subfamily. The *Orthocoronavirinae* subfamily is classified into four genera and several subgenera under these four genera. Among *Alphacoronavirus* (alphaCoV), *Betacoronavirus* (betaCoV), *Deltacoronavirus* (deltaCoV), and *Gamakoronavirus* (gammaCoV), only alfaCoV and betaCoV cause infection in humans (Fig. 1.1) [4]. Each human coronaviruses can cause severe respiratory disease. It affects all age groups, but a more severe clinical course can be observed in people with underlying diseases. SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) are the more serious strains. They can cause pneumonia in humans [5]. SARS-CoV and MERS-CoV are highly pathogenic with zoonotic origin. They have caused epidemics in the past two decades. SARS-CoV was first observed in China in 2003

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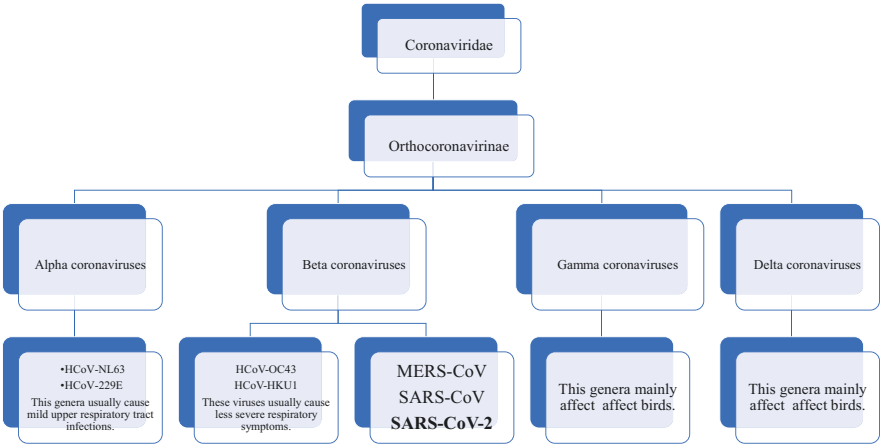


**Fig. 1.1** Shows the status of SARS-CoV-2 in entire coronavirus family

and spread to all countries [5, 6]. In this pandemic, febrile patients have had severe acute respiratory distress syndrome (ARDS), which could present with pneumonia. The most common symptoms in patients presenting with pneumonia are cough and dyspnea. About 10 years after this outbreak, a man who was hospitalized in Saudi Arabia died of severe pneumonia and kidney failure. A novel coronavirus was isolated from this patient's respiratory sample. This coronavirus has been named MERS-CoV. As of June 2020, 2562 confirmed cases of MERS-CoV have been registered, with a fatality rate of 32.7% [7]. SARS-CoV and MERS-CoV were transmitted to humans through market civets and one-humped Arabian camels, respectively. Both viruses are thought to have originated from bats [8]. Both SARS-CoV and MERS-CoV have high fatality rates (about 35% and 10%, respectively) [6, 9]. In the last days of December 2019, a group of pneumoniae patients in which etiology was unknown were observed in Wuhan China and were reported to WHO. One week later, a coronavirus, which was later named SARS-CoV-2, was isolated from respiratory tract specimens of those patients. The genome of the SARS-CoV-2 had 79% similarity to the SARS-CoV genome [9]. This latest coronavirus has infected more people than its two previous predecessors.

## 1.1 Structure of Coronaviruses and SARS-CoV-2

SARS-CoV-2 has a genome that is sized~ 30,000 bases belonging to *Coronaviridae* family of the order of *Nidovirales* [10]. Coronaviruses (27–32 kb) are enveloped, positive polarity, spherical RNA viruses with a single-stranded RNA genome. Coronaviruses have the largest RNA genome among RNA viruses known to date. In conserved genes (ORF1ab, spike, envelope, membrane, and nucleocapsid) and under the nucleocapsid gene in coronavirus strains, a variable number of small open

reading frames (ORFs) exist [11]. The viral genome has got distinctive features. One of distinctive features is a special N-terminal fragment within the spike protein.

The nucleocapsid (N) protein, transmembrane (M) protein, envelope (E) protein, and spike (S) protein are the major structural gene proteins in coronaviruses. They are located in the 5′-3′ arrangement as S, E, M, and N [4, 12]. All of these structural proteins are encoded within the 3′ end of the viral genome [13]. The M protein determines the shape of the viral envelope and is the most abundant protein. This protein crosses the membrane bilayer three times and forms a short NH2-terminal outside of the virus domain and a long COOH terminal (cytoplasmic domain) within the virion [11]. The virus binds to host cell surface receptors via the S protein. After attachment, fusion followed by viral entry occurs. In some coronaviruses, the S protein is also known to mediate cell-cell fusion. This fusion between infected and uninfected cells results in the formation of multinucleated giant cells that allow the virus to avoid virus-neutralizing antibodies and allow direct viral spread [12]. The spike (S) protein is a type I membrane glycoprotein, and it constitutes peplomers. The main inducer and target of neutralizing antibodies against SARS-CoV-2 is S protein [11]. Envelope proteins determine the formation and composition of the coronaviral membrane. It is thought that there is a molecular interaction between these proteins. M, without the need for S, virus particles play a dominant role in intracellular formation. If tunicamycin is present in the medium, the coronavirus grows and produces spike-free, non-infectious virions containing M but lacking S [14].

The N protein is the protein that shapes the nucleocapsid. It is effective in binding to the coronavirus RNA genome, in the replication of viral RNA, and in the host's cellular immune response to viral infection [15].

The E protein is the most mysterious and smallest of the major structural proteins. E protein is excessively expressed in SARS-CoV-2-infected cells, but a small portion of these proteins are located in the virion envelope. In previous studies, three roles of the CoV E protein have been defined. First, M and E proteins are known to play a role in the interaction between their cytoplasmic tails. This indicates that Protein E contributes to viral assembly and budding. Second, the hydrophobic domain of this protein is required for virus assembly. Third, it takes role in disease pathogenesis [15, 16]. SARS-CoV-2 genome is similar to other coronaviruses and contains at least ten open reading frames (ORFs). Two-thirds of the 5′-terminal end of the ORF1a/b genome encode the two large polyproteins that make up the viral replicase-transcriptase complex, while the other ORFs in the remaining third encode four major structural proteins (N, M, E, S) as well as accessory proteins that do not participate in viral replication and whose functions are not fully understood. In addition to capsid-forming major structural proteins, the viral genome encodes many non-structural proteins (NSPs) that play various roles in replication and virus particle formation processes. These proteins regulate early transcription regulation, helicase activity, and immunomodulation and are involved in viral pathogenesis by modulating gene transactivation and counteracting antiviral response [17].

## 1.2 Clinical Presentation of COVID-19

The disease may be asymptomatic, or it may result in death due to severe symptoms [18]. Out of total confirmed COVID-19 cases, 87% were reported between the ages of 30 and 79. Approximately half of the cases have one or more underlying medical conditions such as cardiovascular diseases, diabetes, and hypertension [19]. COVID-19 signs and symptoms occur after 5 days of incubation period. The median time before onset of symptoms from the COVID-19 incubation is 5.1 days, and infected patients show symptoms for 11.5 days. The duration of symptoms varies according to the person's immune system and age.

The most common symptoms are fever, cough, and dyspnea [20]. The elderly is at a higher risk for severe disease because of higher frequency of comorbidities. Younger adults were hospitalized for severe illness during the pandemic, but this has been less frequently. There have been reports of taste and smell disturbances documented in the early course of disease.

As its name suggests, SARS-CoV-2 often causes ARDS in patients and affects the lungs. But in addition, clinicians all over the world have reported the damaging effects of COVID-19 on vital organs such as the gastrointestinal tract, liver, blood vessels, brain, kidney, and heart [10]. Gastrointestinal symptoms can be noted in almost 40% of patients. Loss of appetite, vomiting, and diarrhea may be observed. Up to 10% of patients who have gastrointestinal symptoms are not accompanied by fever or respiratory symptoms [5]. Liver injury can also be observed. Regarding liver injury, multiple reasons have been supposed such as drug toxicity, and immune-mediated cytokine storm have been accused for that injury [21]. It has been reported that COVID-19 patients are at risk for severe coagulopathy especially in patients with comorbid diseases (e.g., hypertension, obesity, cancer, congestive heart failure). In addition, it has been reported that disseminated intravascular coagulation is observed more frequently in deceased patients than in surviving patients [10]. It is thought that cytokine storm and increased D-Dimer levels in with severe disease are the cause of the increased coagulopathy observed in COVID-19 patients [14]. While both venous and arterial thrombosis cases were reported, most of the venous thrombosis cases were reported as pulmonary thromboembolism [22]. Cardiovascular complications are one of the most important causes of mortality in COVID-19 patients. These complications are arrhythmias, myocardial infarction, and myocardial injury. It is known that progressive cardiac involvement is observed in SARS-CoV-2 infection with symptoms of acute coronary syndrome and various increased blood biomarkers. However, in patients with cardiac involvement, the symptoms can sometimes be obscure. Abnormal heart rate, sinus tachycardia, and prolonged QTc interval have been reported previously in patients with COVID-19. The use of hydroxychloroquine and azithromycin, tried for the treatment of COVID-19 in the early stages of the pandemic, has also been associated with QTc interval prolongation. Some serum biomarkers as plasma cardiac specific troponin and N-terminal pro hormone brain natriuretic peptide are elevated in patients who develop

myocardial injury due to COVID-19. Increased ferritin, D-Dimer, lactate dehydrogenase, and interleukin levels are associated with cytokine storm and associated COVID-19 complications [10].

In addition, dermatological manifestations such as erythematous rashes and urticaria have been reported in COVID-19 patients. Hair loss was also reported as a frequent symptom of post-COVID-19 syndrome [23].

In addition to the signs and symptoms observed in all these organs and systems, various neurological involvements have also been reported. In this section, neurological signs and symptoms due to COVID-19 have been discussed in detail.

### *1.2.1 CNS-Associated Sign and Symptoms*

Studies reported several CNS-related manifestations such as epilepsy, headache, ataxia, dizziness, impaired consciousness, acute cerebrovascular disease, acute disseminated encephalomyelitis (ADEM), multiple sclerosis, and viral encephalitis [18].

Headache is one of the most common symptoms of systemic viral infections. However, the relationship between systemic infections and headache has not been fully investigated. Fever, pyrogens, direct effects of microorganisms, and various immune mediators (cyclooxygenase-2/prostaglandin E2 system, cytokines, nitric oxide system, glutamate, and reactive oxygen species) are among the factors blamed for headache that develops during viral infections [24]. In different studies, headache in COVID-19 patients is between 6.5% and 23%. Acute infections, especially in elderly individuals, increase the risk of delirium and confusion. As disease severity increases in COVID-19 patients, the risk of delirium and confusion increases [18]. Intracerebral hemorrhage (ICH) in a COVID-19 patient is reported. ICH may be associated with dysfunction of angiotensin II (ACE2) receptors located on cerebrovascular endothelial cells [25]. Vessel stroke was reported in COVID-19 [26]. It is a very important complication of COVID-19. The stroke mortality rate is reported to be 46% [27]. Thromboembolic events due to COVID-19 trigger stroke. Due to viral infections, the coagulation system is disrupted, and the natural anticoagulant mechanisms are downregulated [28]. Another hypothesis for the development of stroke is cerebrovascular dysfunction due to the cytokine storm that develops during COVID-19 [29]. So viral infections can trigger cerebrovascular diseases such as ischemic stroke [29].

Seizures can occur for different reasons, such as encephalitis, electrolyte imbalance, and metabolic/hypoxic/toxic encephalopathy. There are case reports of recurrent tonic-clonic seizures in COVID-19 patients with no family or personal history of epilepsy/seizures [18]. Various hypotheses have been developed to explain this situation. First hypothesis is the release of inflammatory cytokines, tumor necrotizing factor alpha, and granulocyte stimulating factor in COVID-19. For this reason, glutamate receptor is activated which leads to episodic seizures. It was thought that

this situation might trigger neuronal hyperexcitability [30]. The second hypothesis of seizures is encephalitis. Invasion of the virus to brain tissue can cause encephalitis. In addition to these hypotheses, seizures due to the side effects of antiviral agents including ribavirin and lopinavir/ritonavir used in the treatment of COVID-19 may also be associated [18].

Patients with COVID-19-associated meningoencephalitis may present with different clinical manifestations such as headache, fever, seizures, and coma. There are hypotheses that meningoencephalitis may be due to direct invasion of the virus or immune-mediated inflammatory injury [31].

A case of acute necrotizing encephalopathy (ANE) in COVID-19 was reported [32]. ANE is a progressive neurodegenerative disorder. It is rare. During febrile diseases, cytokines are released uncontrollably. Uncontrolled cytokine release causes the formation of multiple, symmetrical areas of edema and necrosis in the CNS. This can cause ANE [18].

As a result of brain biopsies, coronavirus antigen and RNA were detected in active demyelinating plaques. For this reason, it has been reported that coronaviruses may play a role in the etiology and pathology of multiple sclerosis [33].

Coronaviruses affect host proteases such as endosomal cathepsins, furin, trypsin, and cell surface transmembrane proteases or serin proteases. These proteases play an important role in the pathogenesis of neurogenerative diseases. For this reason, Parkinson's and Alzheimer's diseases have also been associated with COVID-19 [34].

Serotonin level has an important role in mood disorder. There are reports that cytokine increase also causes depression-like symptoms. It is known to cause mood disorders through viral infections, cytokine increase, and downregulation of serotonin. Depression-like symptoms seen in COVID-19 patients may be related to this condition. In addition, social isolation and loneliness experienced during the pandemic contribute to mood disorders [34].

ADEM is a demyelinating disease that can be seen after viral infections. Case reports related to COVID-19 have been reported in the literature. ADEM progresses with encephalopathy and multifocal deficits. High-dose methylprednisolone and intravenous immunoglobulin are used in the treatment of the case [35].

### *1.2.2 PNS-Associated Signs and Symptoms*

There are a lot of PNS-associated signs and symptoms in COVID-19 such as muscle pain, Guillain-Barre syndrome (GBS), hyposmia/anosmia, and hypogeusia/ageusia [18]. Ageusia and anosmia are the most common PNS-associated symptoms of SARS-COV-2. Anosmia has been reported in 40% of patients infected with SARS-CoV-2 [36]. These symptoms are usually associated with nasal obstruction and increased nasal secretion [18]. Anosmia mechanisms in COVID-19 are not clear yet. But there are several hypotheses. In animal studies, it has been shown that the coronavirus spreads to the brain by the transneuronal route. The virus passes through the

olfactory pathways and invades the olfactory neuroepithelium [37]. Olfactory neuroepithelial damage causes anosmia. Another hypotheses regarding the mechanism of anosmia is inflammation in the olfactory nerve is one of the causes of anosmia [38].

GBS is a polyradiculoneuropathy, which occurs because of inflammatory processes. There are several studies that report on the role of viral infections in the etiology of GBS [39]. Cases of COVID-19 associated GBS have been reported in the literature [40]. In the previous studies, there was no difference in clinical presentation and disease severity between COVID-19-related GBS and non-COVID-19-related GBS [39].

It has been shown that viral infections are the etiology of most neurological diseases. SARS-CoV-2 is one of these viruses. In addition to direct neuroinvasion, it has a great contribution in the development of neurological symptoms, cytokine storm, vasculitis development, and thromboembolic events. Neurological symptoms in COVID-19 can be mild or life-threatening. Symptoms may occur during the course of COVID-19, as well as after COVID-19. Therefore, patients with neurological symptoms should be evaluated for COVID-19 regardless of whether they have respiratory symptoms.

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# Chapter 2
# One Health: Lessons from 2 Years' Experience of the COVID-19 Pandemic


**Raymond Klevor and Najib Kissani**

## 2.1 Introduction

In December 2019, a pneumonia outbreak was reported in Wuhan, China. On December 31, 2019, the outbreak was traced to a novel strain of coronavirus, which was given the interim name 2019-nCoV by the World Health Organization (WHO). On March 11, 2020, this new infection was dubbed a pandemic [1]. Since then, the coronavirus disease 2019 (COVID-19) virus has become one of the recent catastrophes in recent history with exponential morbidity and mortality and other direct and indirect impacts on the world.

This pandemic has shown us the likelihood of similar catastrophic events. As such, it seems important to review events leading up to the pandemic, as well as during the pandemic in order to learn from our successes and failures. An important lesson that seems obvious is the concept of One Health. This concept relates to the collaborative efforts needed to combat issues of common interest. One Health, despite its precedence of the pandemic, has become an issue of renewed interest seeing as the COVID-19 virus is purported to be due to a species jump. This not being the only such hazardous incident; it is imperative that all and sundry be involved in combatting global health issues.

In this chapter, we give a detailed description of the pandemic, the challenges faced in curbing the spread of the COVID-19 virus, and the lessons we could learn from these experiences.

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## 2.2 Increasing Threat of Species Jump of Zoonotic Infections

For a zoonotic infection to jump species and affect humans, it must undergo mutations that allow it to be pathogenic to humans. Several infections such as tuberculosis and influenza in humans today, it has been suggested, evolved from animal infections due to agriculture and domestication of animals. Together with a number of factors, these infections have spanned the globe and remain of important interest for modern medicine. Global travel, climate change, poverty, and social inequalities are only a few of these factors driving the increased emergence of new infections. Also, insufficiencies in infrastructure for animal and human health and especially their fragmentation are crucial to the emergence and cross of species boundaries. Several infections in recent years have drawn our attention to the potential of pandemics due to this cross. In fact, infections such as human immunodeficiency virus/acquired immune deficiency syndrome (HIV-AIDS), Middle East respiratory syndrome (MERS), and monkey pox, have been due to this phenomenon. HIV-AIDS remains pandemic and is an important cause of mortality in several parts of the world [2].

The COVID-19 infection is the most recent incident of species jump resulting in global devastating consequences [3]. This phenomenon is reported to be inherently unpredictable, and viruses with ribonucleic acid (RNA), the COVID-19 virus being one of these, are the most likely to be pathogen [4]. This fact underscores the need for a global approach to microbial agents and to health in general and could be achieved through the One Health strategy.

## 2.3 The COVID-19 Pandemic

### *2.3.1 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)*

The coronavirus pandemic is due to an RNA virus belonging to the family of *Coronaviridae* [5]. These species have been reported in bats and other mammals as well as in birds [6, 7]. A number of these coronaviruses have been shown to cause disease in humans as well [8]. The COVID-19 pandemic based on several reports was due to a species jump from bats to humans in a Wuhan wet market. Since then, the virus has circulated around the globe to infect over 500 million people and to cause over six million deaths [9, 10].

### *2.3.2 Epidemiology*

Several factors hamper efforts to have exact figures of the case numbers. Reporting issues remain of concern, sometimes with difficulties confirming direct links between the infection and symptoms or deaths. Several studies have tackled the

problem of coming to near-exact estimates with one study claiming over 40% of the global population was infected at least once by November 14, 2021. The majority of these infections occurred in south Asia, with sub-Saharan Africa having the highest infection rate [11]. It seems that given the wide symptom presentation of the infection, it is likely published figures are an underestimation of the real number of cases [12].

### *2.3.3 Transmission*

Human-human transmission of the infection involves the inhalation of inoculum of virus-containing droplets from an infected person. Also, any physical contact that brings a healthy person within a 1-meter perimeter of an infected person, whether it involved mucosal surfaces or skin, has the potential for being a means of transmission of the virus [13, 14]. Inert surfaces could also serve as contaminating surfaces. The possibility of fecal-oral and sexual transmission has been reported but seems to be less important than the other means of transmission [15].

### *2.3.4 Declaration of a Pandemic*

Despite efforts deployed by the Chinese government, the COVID-19 virus spread beyond the borders of the country, and the first case of the infection was reported in Thailand on January 13, 2020 [16]. On March 11, 2020, WHO declared COVID-19 a pandemic. By then, there were more than 118,000 cases in 114 countries, and 4291 people had lost their lives [17]. In the Director-General's speech, he decried alarming levels of inaction which were the root cause of the spread. To this end, nations were forced to take drastic action including quarantining and lockdowns, the use of personal protective equipment, distancing, and sanitization of surfaces. These measures came at a great cost to individuals, nations, and the world as a whole.

### *2.3.5 Virus Mutations*

Mutations occur spontaneously in organisms. In the case of viruses, these mutations could alter the virulence of the organism and lead to important clinical implications. This has led to monitoring for variants of the SARS-CoV-2 variants. The variants have been grouped into three: variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs). VOCs are those variants whose mutations confer an increased transmissibility and virulence such that public health measures in place are rendered less effective. Omicron is a VOC. VOIs are those variants with mutations known to increase their virulence with findings of

significant community transmission or multiple clusters. Epsilon is one such variant. VUM are those whose mutations are suspected to confer them with increased virulence but for which no epidemiological evidence exists as yet [18].

### 2.3.6 Infodemic and Politics

Besides the science of viral infections and research to understand and treat the illness, a lot was going on outside of science that compounded the facts of the pandemic. The pandemic was a period of political tug-of-war among countries and among scientists and politicians. These heated exchanges potentially soured relationships among countries and led to loss of trust in scientists and politicians. This gave rise to extremist ideations which became front and center in everyday discussions during the pandemic. Misinformation and infodemic became synonymous of the pandemic. The encounter between the pandemic and Internet gave rise to wild theorizing and even hate messaging. The excess of information meant that people would have to wade through hundreds and thousands of items before they got to the right source [19].

### 2.3.7 Health Impact

These issues, together with the restrictions of the pandemic itself and uncertainties of the future, have led to serious impact on health. Patients with chronic illnesses have found it difficult to have access to their physicians and to medications. This has potentially compounded health issues for patients and families [20]. Also, challenges facing industry resulted in disruptions in the manufacture and distribution of essential drugs.

The demands on healthcare workers were excessive, if not exorbitant. The reception of COVID-19 patients in excess with the continuous need for care made the experience challenging for healthcare workers. The enormous workload aside, healthcare workers were at times left to cater to patients with limited resources with which to work or without sufficient protection for themselves.

Inconducive work environment for healthcare workers, an intimidating hospital setting for patients, changes in work prospects in general, uncertainties about the future, the fear of infection and of death, and the loss of dear ones constituted challenging realities during the pandemic and potentially led to serious mental health impacts. Some people found themselves separated from their families as was the case of people trapped outside their countries during the lockdown. Depression, anxiety, psychoses, and suicide were rampant during this period.

### *2.3.8 Socioeconomic Impact*

The impact of the pandemic on the economy has been dire. The pandemic has resulted in slowing of production, demand, and distribution of goods and services. Individuals, families, small businesses, and national economies have suffered from drastic measures during confinement and limitation of mobility during the pandemic. Many workers lost their jobs, and many enterprises were driven out of business [21]. Livelihoods were lost, and food systems were placed under jeopardy [22]. The pandemic also took a toll on education with many students in poor-resource setting suffering more because of inability to switch to online classroom learning [23].

### *2.3.9 Vaccination*

One sore subject during the pandemic is vaccination. Given the extenuating circumstances and the urgent need for vaccines, a lot was done to cut through the red tape and ensure safe and effective vaccines were available to the population in record-breaking time. Unfortunately, so much disinformation around the vaccines has emerged. Conspiratorial theories have enmeshed these vaccines with a high rate of vaccine hesitancy around the world [24]. Different vaccines have been fabricated with mRNA vaccines in the United States by Pfizer-BioNTech and Moderna and by CureVac in Europe. Other vaccines using human or primate adenovirus vectors have been developed by Janssen-Johnson & Johnson, AstraZeneca, Sputnik V, and CanSino. Bharat Biotech, Sinopharm, and Sinovac have fabricated COVID-19 vaccines using an inactivated whole-virus SARS-CoV-2 [25].

## 2.4 Disparities During the COVID-19 Pandemic

Disparities during the pandemic entail differences in disease risk and susceptibility, access to healthcare and management, and impact on health and sustenance engendered by the COVID-19 pandemic. These differences could be due to differences in geographical location, race, gender, age, level of education, socioeconomic status, political affiliation, faith, and sexual orientation. For example, several studies have identified racial and ethnic minority groups and low socioeconomic status to be associated with higher rates of infection, hospitalization, and death [26, 27]. These disparities have also been associated with gender, with females being harder hit by loss of jobs. Students from poorer countries tend to suffer more from school closure [28]. COVID-19 testing and vaccine access are unfortunately low in poorer parts of

the world [29, 30]. These disparities have far-reaching consequences in various domains both in the present and in the future. A solution that stands to avert the dire consequences and ensure better preparedness, if not an avoidance of disaster, is the One Health concept.

## 2.5 One Health

### *2.5.1 The Concept*

One Health is a concept that has been present for decades now and has seen a revival during the pandemic. In fact, the American Veterinary Medical Association dubs One Health "the new professional imperative" [31]. This concept entails the integration of all aspects of health and all the players in healthcare into one robust system capable of dealing with each individual holistically and with health needs of the world at large. In fact, the WHO definition of health has always pointed to the need to look at the well-being of the individual beyond the mere absence of illness. Furthermore, it is imperative to see the continuum between the individual and his environment and as such integrate the environment into the concept of health. The result of such an approach is One Health, which according to the Centers for Disease Control and Prevention (CDC) is "a collaborative, multisectoral, and transdisciplinary approach – working at the local, regional, national, and global levels – with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment" [32]. According to the WHO, it "is an approach to designing and implementing programs, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes" [33].

This approach to human health bears the mark of responsibility and is a moral duty for humans. It also comes naturally as a more effective manner of preventing human disease in as much as humans are in continuous contact with animals and the environment at large. The effective approach of preventing rabies in humans, for example, is to vaccinate dogs against the disease. As such, professionals in the management of human disease would have to collaborate with professionals in the management of animal disease. This collaborative effort would also necessarily have to be backed and sanctioned by political authority to ensure effective participation. One Health lends itself well to this pandemic era. The impact of COVID-19 on other illnesses and on different domains other than health makes this approach an imperative.

### *2.5.2 Implementation*

To this end, a quadripartite memorandum of understanding was entered into by the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE), the UN Environment Program (UNEP), and

the World Health Organization (WHO), to strengthen cooperation to sustainably balance and optimize the health of humans, animals, plants, and the environment [34].

### 2.5.3 Challenges to One Health and Their Solutions

Despite the attractiveness of the One Health concept, there are several challenges faced in its implementation. One such challenge is the lack of awareness. This stems from the absence or inadequate discussion of the subject during the training years of medical professionals. Also, the apparent silence on the subject in the media and in continuing medical education for health professionals contributes to difficulties implementing One Health. The advent of the COVID-19 pandemic has raised the awareness of the general public of the dangers of neglect of environmental and animal health on human health. As such, this pandemic is the best time to entrench the subject and ensure its implementation around the world. To arrive at this, leadership is crucial.

Lack of leadership is another cause of the absence of a strong One Health strategy. This concept has been in circulation for some time now, and yet the lack of proper leadership to ensure its effective implementation has led to an inadequate curbing of COVID-19 after its initial presentation in Wuhan. Contradictory messaging among scientists and politicization of the pandemic have led to distrust in established institutions.

Furthermore, a disease-care mindset is detrimental to the concept of One Health. Medicine should be prevention-oriented. Also, bias toward clinical care is an inadequate approach to the challenges of human health. An effective strategy would be to integrate management and preventive approaches which precede occurrence of disease, as well as the contribution of other non-clinical professionals.

In addition, the increasing fragmentation of specialist fields, though advantageous, has the undesired effect of leading to a narrowed view of the patient and his condition. To counter this, it is important for different specialists to collaborate in patient care and research to ensure a holistic approach to patient health.

Finally, lack of resources remains an issue of concern for the implementation of One Health. This is especially true for resource-limited areas of the world, especially in Africa and Asia. Competing priorities, though an issue globally, means for poor countries that they would have to deal with more basic needs of people first. An effective One Health strategy then must go beyond individual national frontiers and allow for a global approach which subsumes the needs of resource-limited countries. This is probably the most important lesson that the pandemic has shown us, in that what happens in one corner of the world today could potentially have devastating effects on the whole world.

## 2.6 Headache Medicine, COVID-19, and One Health

Headache is a common condition that could be managed by the general practitioner or the neurologist. It remains a great source of handicap and a real public health problem [35, 36]. The cross between headache and the COVID-19 pandemic is threefold. Firstly, structural changes in healthcare systems to combat the pandemic led to temporary abandon of headache patients. Patients no longer had access to their physicians or to drugs. This led to increased morbidity of headache syndromes. Secondly, there is the effect of lifestyle changes, psychological factors, and COVID-19 restriction and preventive measures on extant headache syndromes or the triggering of headache by these factors. Thirdly, there is the direct causality between COVID-19 infection and headache. The latter is due either to the flu-like mechanisms of COVID-19 infection or to its neurotropism [37].

In the spirit of One Health, headache management requires a structured approach which brings together various professionals, researchers, and other stakeholders in order for justice to be duly done to this challenging issue. Headache lends itself well to management in primary health facilities with referrals reserved for difficult cases [38]. E-health could also be another means, other than traditional consultations, to the management of headaches [39].

## 2.7 Conclusion

The COVID-19 pandemic is a lesson for public health. The challenges faced during this period have given us a real-life experience of the continuum of human, animal, plant, and environmental health. To this end, One Health, a concept which embraces the active participation of the various aspects of health and encourages interprofessional collaboration, is a much-needed solution. This concept, though in practice, was not fully functional around the globe and probably facilitated the spread of the virus. Given the growing numbers of animal-to-human species jumps of infections in recent times, the implementation of One Health is an emergency. For this to succeed, all medical domains must take part in the discussion and enactment of One Health strategies. And, beyond infections, the concept of One Health calls on all professionals managing patients, whether in the headache clinic or elsewhere, to embrace holistic approaches to patient management.

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# Chapter 3
# Historical Lessons from the Pandemics

**Okan Bölükbaşı**

*The plague was waiting for steam, electricity, the railroad and the highs iron-hulled ships.*
*In front of the great black terror, it is no longer the false and hissing on the stalks, it is the backfire of the combine harvester launched at full speed in the middle of the wheat.*
*P. Deville* [1].

One would have thought the fight was definitively won, but it was counting without a major change occurring in the late 1960s: the appearance of a globalized epidemiological environment specific to the Anthropocene. Industrial revolution resulted in a geological change. Today, new plagues appear. They are transmitted by wild animals, in contact with our domestic animals. While biodiversity is experiencing massive decline everywhere, are we witnessing the last outbreak of the plagues with the emergence of the Ebola or Zika viruses? The next plague certain? And, above all, can we prevent it? As humans, where are we now? Greenfeld is not optimistic:

> *Investigating the anthropologic, historical, genetic, medical, and social science aspects of plague pandemics can promote us to greater understanding of the interplay between history of humanity, and medical science. You are here because of your ancestors' immune systems. Somehow, because of better nutrition or greater intelligence or geographic circumstance or, most likely, just plain dumb luck, whatever ailments, diseases, and infections your predecessors were stricken with weren't fatal, and those forebears successfully reproduced. The odds against that confluence of genetic good fortune are incalculable; statistically, a German Jew probably had a better chance of surviving the Holocaust.* [2]

How did Hernan Cortes and his 600 men defeated the whole Aztec empire? Yes, they had better weaponry, war dogs, and horses, but famine and smallpox were the real power of Spanish forces. This fact repeated itself throughout the whole history

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of plagues. It is clear that the world is in the era of pandemic, if we consider the outbreaks of the last 20 years. First, an influenza pandemic (H1N1 of 2009), then a severe acute respiratory syndrome (SARS of 2013), a chikungunya pandemic (2014), a pandemic-like Ebola outbreak (2014), and a Zika pandemic (2015). But it must be kept in mind that specific organisms causing pandemics were all around us for millennia without causing an outbreak.

Agriculture, development of cities, and domestication of animals provided opportunity for old organisms to use new hosts like humans. Growing exploitation of once-wild animals and progressive shrinkage of forests with the effects of climate change result in exponential rise of new outbreaks. Then SARS, now COVID-19 is related with large animal markets in overcrowded cities. Human-wild animal contacts caused four zoonotic pandemics and a nearly pandemic just in the last two decades. The horrific reminisces of the past like diphtheria, whooping cough, measles, smallpox, plague, tuberculosis, dysentery, cholera, malaria, typhus, and influenza epidemics are still fresh in the memory of many parts of the world. Any fever, headache, sore throat, or cough was enough to trigger a shock of terror telltaling for the possibility of an epidemic disease in the Old World. Today, it can be regarded as an overreactive attitude of the fear of disease.

Why is Asia so important in the context of plagues? We have to consider vast geographic, climatic, and ethnic features with the progressive effects of colonialism, mercantilism, and economy politique.

> *Southeast Asia is often referred to as a "land of contrasts". And this is not just a tourist cliché, so great is the diversity of landscapes and human societies encountered. It only takes a day's drive to pass from the poor rural world of the mountains to the large urban centers bristling with buildings and traversed by suspended highways, passing through the rice fields intensive use of alluvial plains and deltas. Southeast Asia is also a biodiversity hotspot. Its big biological richness – marked by strong endemism – results from a history complex geological background. This region consists of several sets biogeographical formations, the North and the South being separated by a border named Wallace line, named after Alfred Wallace, co-discoverer with Charles Darwin's theory of evolution by natural selection. It's also a center for the diversification of murine rodents, rats and mice. … Southeast Asia is also unique in terms of the imprint it has left trade, colonization and imperialism. … By promoting exchanges of infectious diseases between Europe, Africa and Asia, this colonization will have health consequences dramatic.* [1]

Now, we can make an add to this forecast of Moran in 2016, "Covid-19 pandemic."

## 3.1 The Rise of Plague and Black Death

> *September 1664; the plague was returned again in Holland;...some said from Italy, others from the Levant...; others said it brought from Candia; others from Cyprus. It matter not from whence it come...*
>
> D. Dafoe [3].

The Plague of Athens (430–423 BCE) resulted in the decline of Greek culture. It was the first recorded pandemic known in history. Exact cause of this outbreak remained unknown. From the middle of the sixth century to the eighth, one of the first great epidemics to affect the entire Mediterranean region was the plague of Justinian. According to the contemporary Procopius, this plague, at its peak, would have killed almost 10,000 people a day. The most recent estimates indicate that a proportion of 15–40% of the population at the time would have found the death. This plague also contributed to the fall of the Roman Empire. For historians, this period marks the end of antiquity and the early medieval world. Procopius mentions a resemblance to those of later plagues, such as the Black Death of the fourteenth and seventeenth centuries. But it is often overlooked that other sixth-century writers also recorded the pandemic, especially John of Ephesus. He was a cleric who witnessed the plague firsthand in his travels to Alexandria, Palestine, Mesopotamia, and Syria. Procopius, for his part, gives us an invaluable perspective from the capital, Constantinople, where he remained throughout the course of the epidemic. Based on the descriptions of these authors and others, there is little disputing that the disease that struck in 541–542 featured bubonic plague: both Procopius and John of Ephesus mention the bubones, or swellings in the groin, that became a signature symptom of the pandemic [4].

In the first book of Chronicles, King David persuaded God to spare Jerusalem from a pestilence that had already killed 70,000 Israelites. Similar statements in the Testaments were a source of fundamentalist actions of religious people and some clerics including perhaps the Flagellant movement, which played such a central role in how medieval Christian society responded to the Black Death. The epic movie of Ingmar Bergman, *The Seventh Seal*, gives a vividly detailed description of the collapsing social order and acts of religious fanatics, namely, "flagellants" of that era [4, 5] (Fig. 3.1).

Ibn Battuta, an Arab traveler and scholar, on returning to homeland from India by Spice Route, reported hearings about an outbreak of plague in 1347–1348. Bubonic plague remains the prototype of severe outbreak of disease with very high mortality and inexorable spread. The Black Death was the most famous pandemic of bubonic plague of the mid-fourth century. Presentation and spread features illustrate how human activities and commerce can cause the dissemination of a fatal disease even if primarily a zoonotic infection [6].

Attitudes of Islamic authorities about plagues are somewhat conflicting. Sometimes the plague is regarded as destiny, an order of almighty God. But there were also very famous words of Muhammad about outbreaks: "If you hear of it (the plague) in a land, do not approach it; but if it breaks out in a land and you are already there, then do not leave in flight from it." This practical approach was a way to quarantine Arabia, which as yet was unaffected by the plague. But this did not prevent outbreaks of plague to devastate the Islamic lands in later centuries. Such traditions and religious comments prevented organized efforts to cope with plague and effective measures for sanitation regulations, perhaps, in particular, outbreaks of which seem to have accompanied the first Muslim conquests of Byzantine and Eastern lands [4].

**Fig. 3.1** Flagellants. Nuremberg Chronicles, 1493, woodcut print, unknown artist. Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Mongolcatapult.jpg. Public Domain

By the sixteenth century, when Christian rules of quarantine and other prophylactic measures against plague had been conducted firmly, Muslim views hardened against efforts to escape the verdicts of Allah. This is well illustrated by the Ottoman Sultan's response to a request from the imperial diplomate to Constantinople for permission to change his residence because plague had broken out in the house given to him. "Is not the plague in my own palace, yet I do not think of moving?" Muslims regarded Christian health measures as exaggerated. By that, they exposed themselves to heavier losses from plague than prevailed among their Christian and Jewish neighbors. Black Death was not a singular outbreak, but it started as a new disease and continued for many centuries, killing 40–60% of the total population in Afro-Eurasia. The Ottoman and Turkish experience of plague (from c 1340s to c1940s; 600 years of uninterrupted plagues) is the longest continuous manifestation of plague in recorded human history. Religious debates on plague and the measures to take against it were of paramount importance in the Ottoman Empire until the 1838 quarantine reforms. The Ottomans, with some objections from the elites recorded sometimes, did not show interest to the newer European quarantine until after the beginning of the nineteenth century [7, 8]. In less than 5 years, the entire

Mediterranean and Western areas were devastated by the plague. In the eighteenth century, there are some reports about the plague in the busy port of Izmir in Asia Minor, Anatolia. The disease came via caravan routes from the Anatolian plateau and spread from Izmir by sea to the other ports. Between 1713 and 1792, only 20 years, Izmir was entirely plague-free, and in the nine periods of epidemic, death tolls ranged up to 35 percent of the entire population of the city. The plague bacillus is still very present in the populations of marmots from the plains of Central Asia [1, 4].

## 3.2 Pneumonic Plague of Manchuria and COVID-19: Important Lessons About Humiliation

In the beginning of the twentieth century, an outbreak of pneumonic plague paralyzed Manchuria, killing more than 60,000 people (or may be more). China was labeled as "Sick Man of the Far East" because of an "epidemic" of opium addiction, malnutrition, lack of hygiene awareness, infectious diseases, and corrupted Qing Dynasty government. "The Sick Man" description was originally used for the Ottoman Empire by the West. But after this plague of pneumonia in 1911, China slowly reconstructed its public health policy, despite "all the odds"; civil wars, famines, invasions by foreign armies, and frequent change in the state regime. In the beginning of the COVID-19 outbreak, Western media accused China about the handling of the situation in Wuhan by using the humiliating label of "Sick Man of Asia." But China successfully controlled the SARS and COVID-19 outbreaks than the Westerners did. The real "Sick Man" is United States, today, in regard to control of pandemic and international status. But why is China in the center of newly emerging pandemics frequently? Increased population density and the cumulative impact of imperialism of the nineteenth century may be the force major of the problem. In 1911, *Yersinia pestis* traveled through the newly opened China Eastern Railway. In 2020, COVID-19 virus (SARS Cov2) travelled from Wuhan via high-speed trains and direct transcontinental flights. Even today, scientists couldn't be sure on the causative factors and vectors of 1911 pneumonic plague of Manchuria. For COVID-19, debate is still going on about the same problem. In the Manchurian plague, Manchuria was divided by Russian- and Japanese-controlled zones. Despite the objections of Russian and Japanese scientists, because they believed that the way of transmission was by rats and fleas, Chinese researchers advocated on the use of face masks because of their discovery of the way of transmission as "airborne," directly lung to lung. Chinese authorities strictly followed countermeasures like the use of face masks. Success of this measure was understood after the alarming death rates of foreign doctors who were working without masks [9] (Fig. 3.2).

**Fig. 3.2** Plague Workers Mukden, Manchuria. Presumably Mukden Plague Hospital. All are wearing cloth masks over their faces (By Scottish missionary Dugald Christie). https://commons.wikimedia.org/w/index.php?search=first+face+mask+manchurian+plague&title=Special:MediaSearch&go=Go&type=image. Public Domain

## 3.3 Effects of Colonization, North and South America Examples

During the Aztecs' counterattack to the Spaniards and Cortes in Mexico City, Aztecs were suffering from smallpox epidemic, killing many of them. The paralyzing effect of a lethal epidemic was devastating for the Aztecs. They did not and could not pursue the defeated and demoralized Spaniards, giving them time to reorganize, gather Indian allies, and attack the city again with eventual victory. Smallpox was nearly harmless for men of Cortes. For Aztecs, it was a horrible shock to witness that their gods were powerless in the presence of God. They converted to Christianity without hesitation in the face of this defeat, ineffectiveness, and humiliation and surrendered unconsciously to their brutal, unmerciful enemies for total annihilation of their culture and population [5].

World conquest and colonization by Europeans inoculated many infectious disease in these colonies. The most catastrophic epidemics in human history are associated with these great explorations with the arrival of Christopher Columbus in the West Indies in 1492. This exploration put an end the nearly 15,000 years of isolation

of the Americas, paving the way for many invaders, leading to a demographic and civilizational holocaust. It is estimated that nearly 50 million Native Americans have perished in the hundred years since the first contact with invaders. Epidemiologically, the European invasion of the Americas is a rapid and violent collision, which is the most catastrophic example in history [1, 5].

Immunities of the Americans were naive against infectious agents from Europe. New infectious diseases like smallpox, measles, or dysentery devastated vulnerable Native American populations, which have low genetic diversity in mainly for immune genes. Spanish clerks observed a one-third reduction of the indigenous population as a result of the latest epidemics of that era. The bubonic plague, the chickenpox, cholera, diphtheria, influenza, leprosy, malaria, tuberculosis, measles, smallpox, typhoid fever, whooping cough, and typhus spread in the Americas. Leptospirosis and fasciolosis were brought by the Spaniards also, during their colonization of the Andean regions [1, 10].

## 3.4 The Emergence of Smallpox

The emergence of pets associated with domestication can take even more complex paths, as evidenced by the example of smallpox, one of those terrible diseases that affected the history of human populations with measles, the Black Death, typhus, yellow fever, or cholera. The observation of smallpox symptoms in Egyptian mummies dating back to a little more than a millennium before Christ suggested that smallpox originated in this country. However, historians of medicine point out that the descriptions of this disease are curiously absent from medical books in Greek and Roman writings. The first unequivocal descriptions of the symptoms of this disease appear in fourth century AD in China and then in the seventh century in India, but it is likely that the treatises on medicine Chinese and Indian have reported more than a millennium BCE. At present, the Chinese origin of smallpox is therefore favored by historians, who hypothesize that the Egyptians of the first millennium could have been infected during wars conducted against invaders from the East and Asia. Smallpox was firstly recorded in China as far back as 1122 BCE. Use of inoculation to prevent disease appeared in Chinese medical text as early as 590 BCE. It was reported in India, also including variolation. It was believed that before the development of agriculture, smallpox never occurred in the Western world. Prescence of smallpox reported in Mesopotamia, Egypt, and Indus River Valley in the second millennium BCE. Ebers Papyrus, especially the Sanskrit medical text Sushruta Samhita (as back as 1500 BCE), gives a detailed clinical description of smallpox. A transmission linked to the ecological proximity between wild animals, domestic animal, and humans therefore contributed to the emergence of smallpox in Asia [1, 4, 5, 11].

## 3.5 Measles

Historically, the first scientific description of the syndrome resembling measles was given by Rhazes, who lived in the ninth century in Iran. This renowned doctor is widwey quoted in medical books, until the end of the 17th century. Measles outbreaks are more clearly and more surely identified from the eleventh and twelfth centuries. The source of the virus was domestic bovids. But why did this emergence occur a millennium ago only, while bovids have been domesticated more than 10,000 years ago in the first center of origin of agriculture? The mathematical models of epidemiology explain that a naive population of at least 250,000 to 500,000 people is needed to maintain the virus of the measles. This size of population was reached only after the first urban civilizations appear in the Middle East, from 3000 to 2500 years BCE [1].

## 3.6 The World After Black Death

Bocaccio is one of the greatest writers in describing the catastrophic effects of a pandemic in a society. He gave the most vivid documentation of the plague: aristocratic presentations, acts of clerics, corrupted state institutions, increased marital problems, broken business deals, relations of Christians with Jews and Muslims in Florence, peasants and their landlords dying alone or among others, breakdown of trust, alienation of human interactions, and alteration of the social fabric had been successfully pictured. Ignorance of physicians and widespread fear became a reservoir for further mistreatment of the sick poor, those who did not have the luxury to flight. Bocaccio grouped the people according to their response to the pandemic. The plague was the final test of fine line between knowledge and ignorance, truth and deception. It can be used also to test the limits of greed and compassion. He was among the first to publicize the changing response to disease. Only after *The Decameron* did physicians began to publish their experiences. However, plague became a litmus paper, showing inadequancies of the physicians of the period. Doctors were wearing protective clothes with a long cape, mask, and bill-like portion over the mouth and nose containing aromatic substances (partly to block out the putrid smell of decaying corpses). This funny suites can be regarded as the first hazmat suit of the epoch, although they did not have any protection at all [12, 13].

Education and practice of physicians changed dramatically after frequent outbreaks of plague. There is, then, good evidence that medical education was becoming more common in early fourteenth-century Aragon. Academic formation unquestionably produced an elite who possessed a common scientific book-learned culture; furthermore, the wide circulation of medical books in the Crown suggest that this culture could be shared by practitioners who did not have such an education. We might wonder, therefore, whether two types of medicine and of practitioners were current in the kingdom – one learned and theoretical and the other

traditional and empirical – and perhaps two corresponding patient populations. But it is clear that this medical formations would be distorted after succeeding catastrophic waves of the plague and failure to make any success [14]. During the Black Death era, some physicians and their medical books were regarded as authoritative. Galen and Avicenna for the European and Muslim world played this role, as Caraka did for the Indians, whereas in China, some local doctors shared canonical status. Medical experience was then interpreted in terms of theory (surely, "four humor" doctrine) and cures inflicted accordingly [5]. But ongoing outbreaks of plague shook the principles of classic authorities like Galen. He was (Galen and "four humor" theory) subject to emendation, though it was not before the seventeenth century that the theory of humors on which he had based his medical practice began to be widely questioned among European doctors. For Asians, medical ideas and practices, once they achieved a classical definition, continued to stay conservatively [14].

## 3.7 Cadavers from Victims of Cholera in the Unyielding Studies of Anatomy

*Vibrio cholerae* is named after F. Pacini (1812–1883) because of his clear observations on cholera pathology and identification of microbe in the mid-1850s. But Pacini's huge contribution was neglected until Koch, because Pacini was living in Florence, which is not the center of the scientific milieu. Robert Koch succeeded to isolate *Vibrio cholerae* in 1883–1884 in endemics of Egypt and Calcutta. Before the rise of pathological anatomy, dead bodies from cholera were frequently subjected to dissection by ambitious scientists. Anatomists Caspar Bartholin and Jean Riolan were leading "practicing" scientists of that era. In the second pandemic of cholera (1830–1837) in New York, London, and Paris, cholera was not seen as a disease but a mass poisoning by doctors to collect cadavers for dissection studies. But anatomical studies failed to show any cause for the disease until the birth of microbiology as a laboratory discipline [15].

We cannot ignore the role of cholera in the history of many nations in the nineteenth century. After 1817, Asiatic cholera spread to every civilized nation in the world. The importance of cholera was not decreased especially in the Third World today. The first pandemic was the worst for Russia (1841–1851) with over a million deaths. Huge economic burden and governmental deficiencies were among the long list of reasons paving the way to Soviet Revolution. Cholera devastated the already-weakened Russian social structure. In contrast to European cholera epidemics, cholera in Russia affected rural and slum regions of workers primarily. There was a crisis in feudal order. Tsarist government offered more restrictions than taking sanitary measures and social reforms. But at the same time, cholera was the demonstrator of the success of newly erected academic medicine of Russia [16].

Epidemic cholera reached Mexico in 1883 but only after the late-nineteenth-century researchers began to develop germ theory. Despite John Snow's discovery of drinking contaminated water as a cause of cholera (1854), it was accepted by the medical communities only after two decades. Cholera returned to Latin America abruptly in 1991. In people's memory, it was a long-forgotten disease of the far past; news media announced it as a nineteenth-century disease [17].

## 3.8 The Birth of Bioterrorism and Biological Warfare

In 1346, Caffa, a Genoese colony near the Black Sea, was under siege by Khan Janibek's army of Golden Horde. Both of the Tatar warriors and the defending people of Caffa were affected with the sudden outbreak of plague at the same time. Chronicles of the time make it possible to accurately trace the route of the epidemic. The Tatar army hurled plague-infected cadavers with catapults into the besieged city, thereby transmitting the disease to the inhabitants. Fleeing survivors of the siege spread plague from Caffa to the whole Mediterranean ports. This may be the first biological warfare ever, with the use of the Black Death. But today, it is believed that the event was unimportant, in the general spread of the plague pandemic. There is an interesting miniature showing this type of assault in the book of Rashid al-Din Hamadani (1247–1318, Ilkhanate State, Iran), *Jami al-tawarikh* (*A Compendium of Chronicles*) [5, 6, 8, 18] (Fig. 3.3).

**Fig. 3.3** Tatar Army (Golden Horde) besieging a city with catapults. Jami al-Tawarikh, Edinburgh Extract. Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Mongolcatapult.jpg. Public Domain

## 3.9 World War II, Opening the Doors of Hell

The Kwantung Army was an army group of Imperial Japanese Army from 1919 to 1945. This army became involved in many of the worst Japanese war crimes before and during World War II (WWII). A very famous part of it was "Unit 731." This unit did many research activities on human subjects mainly inmates of prisoners of war (POW) and civil people including children without any consent. The main research subject was biological warfares. Both the United States (US) and her Western allies remained silent about the Imperial Japanese Army's medical atrocities, which some of them executed upon the US and allied POWs, during WWII. Thousands of Japanese doctors, researchers, and medical workers enrolled in these "research" programs which consisted of inhumane methods of experimentation. They infected POWs and sometimes civil people of Chinese cities with virulent strains of plague, anthrax, gonorrhea, syphilis, tuberculosis, cholera, and many other bacteria. Inmates were often subjected to vivisections without any anesthesia in order to observe the real time effects of these fatal procedures and diseases. After WWII, none of them were interrogated or convicted for their horrible, heinous crimes. They continued to their practice of profession in post-war Japanese institutions. Some of them took highly respected positions in universities or state hospitals. Post-1945, the US-Japan friendship covered up all the atrocities of Unit 731, and in return, the Japanese gave the Americans their secret data and counsel on lethal human experiment and germ warfare. The continuing prescence of cultured and disseminated bacteria of Unit 731, is a dangerous legacy of Japan's biological warfare program in the Japanese occupied regions of China. Even today, some mice and rats in rodent populations in parts of northeastern China and east-central Zhejiang Province test positive for bloodstream antibodies to plague bacillus originally dispersed by Unit 731 and Unit 1644. It is currently thought that the total number of persons in China who died as a result of Japan's biowarfare program reached a minimum cumulative figure of nearly 600,000 [2, 19]. The United States established a biological weapons research and development facility at Camp Detrick, Maryland. This was the first of many biological warfare centers. Several species of bacteria and fungi were released by aerosolization over New York, San Francisco, and other several cities in between 1949 and 1968. The aim of these "studies" was to analyze the spread and survival of biological agents. The United states was also accused of the release of dengue fever virus in Cuba. Cuba has been subjected to a massive number of outbreaks of human and crop diseases, seemingly related to unnatural causes during the 1960s and 1990s. North Korea accused the United States for using bioweapons (germ warfare) against its population by airplanes [6, 9].

## 3.10 Conclusions

In the history of past epidemics, the novel coronavirus found its antecedent, the Spanish Flu. But this is not a virtue in itself. Plagues of the past were known by heart, yet it is hard to describe how unprepared they left us. Some suggest the words of the Camus in *The Plague* – "a plague never disappears, but can lie dormant only to reappear once again for the education of men" – means a call, a call for reeducation of the people in an existential kind of learning even in tragic situations like the COVID-19 outbreak. Everyone's life in this planet is closely related to another's life so tragically [20].

History reminds us that epidemics can serve as a reminder to restructure health politics, industry, education, and global measures to exploitation of lands, oceans, and whole social life. Fear of plagues was a constant threat to humanity throughout the whole history. Examination and investigation of a specific epidemic and people's response to it can supply enormous data on organization and structure of a particular society.

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# Chapter 4
# Nervous System Involvement and Clinical Manifestations of COVID-19

**Ömer Karadaş, Akçay Övünç Karadaş, and Javid Shafiyev**

## 4.1 Introduction

Causing global attention, the coronavirus disease 2019 (COVID-19) epidemic emerged in December 2019 in Wuhan, China. The virus is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Coronaviruses are a large family of viruses that are common in humans and animals. The word corona takes its name from the shape of the virus and means "crown" or "ring of light" in Latin. The virus can pass from animals to humans, which scientists believe is the current spread. However, the source is still unknown [2]. COVID-19 infection symptoms appear after an incubation period of about 5 days. The most common symptoms of COVID-19 are fever, cough, and fatigue. Apart from these, headache, dyspnea, and diarrhea are other findings of the disease. Pneumonia, acute respiratory distress syndrome, and multiorgan failure may develop in most severe cases [3]. The technical term "severe acute respiratory syndrome (SARS) coronavirus 2(CoV-2)" is used to describe this new type of coronavirus. The disease caused by the SARS-CoV-2 virus was named as COVID-19, which means "coronavirus disease 2019", since it was first seen in 2019 by the World Health Organization (WHO). The novel CoV 2019 (SARS-CoV-2) is the pathogen of the ongoing novel pneumonia outbreak and is the seventh known CoV that can infect humans; the other pathogens are HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, and MERS-CoV [1].

Patients infected with SARS-CoV-2 have symptoms of varying degrees: fever, a mild cough to pneumonia, and extensive involvement of multiple organ functions

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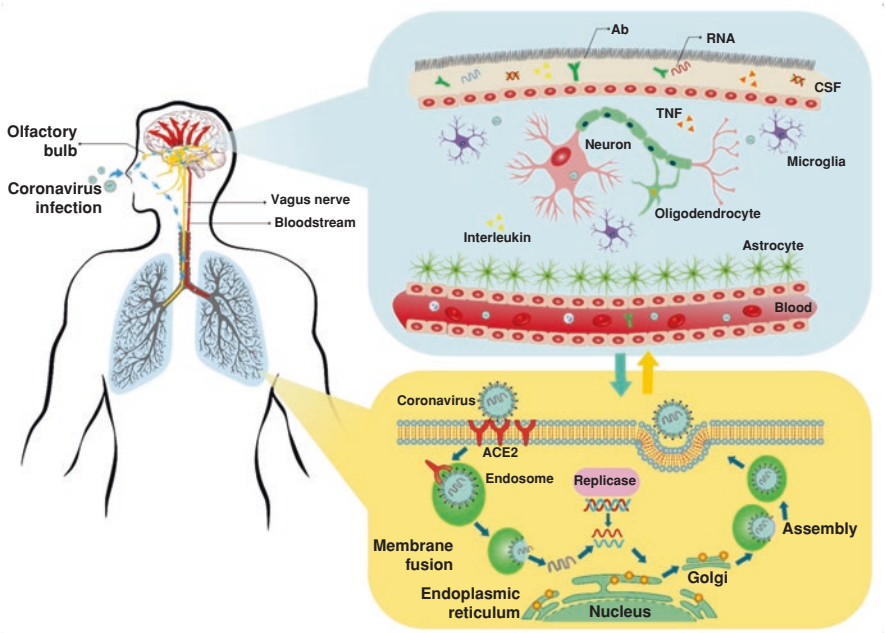


**Fig. 4.1** Neurological damage mechanism of coronavirus infections. Coronaviruses can cause nerve damage via direct blood circulation pathways, neuronal pathways, hypoxia, immune damage, ACE2, and other mechanisms. While coronaviruses can enter the nervous system directly through the olfactory nerve, they cause neurological disorders by entering the nervous system through blood circulation and neuronal pathways. *Ab* antibody, *ACE2* angiotensin-converting enzyme 2, *CSF* cerebrospinal fluid, *ER* endoplasmic reticulum, *TNF* tumor necrosis factor

with a mortality rate of 2–4% [1]. Neurotropic and neuroinvasive properties of the coronavirus have also been described. After the coronavirus binds to ACE2 receptors in the nasal epithelium in nasal infection, it reaches the central nervous system (CNS) through olfaction through the nerves and can then cause inflammation and demyelination (Fig. 4.1) [3]. Patients who are affected more severly develop neurological symptoms more than patients who have mild or moderate disease. Also autopsy reports have revealed brain tissue edema and partial neuronal degeneration in deceased patients [1]. Recent clinical data have revealed that some patients with COVID-19 have symptoms (headache, epilepsy, and disturbed consciousness) similar to intracranial infections. Additionally, many patients report a sudden loss of smell or taste. It is therefore likely that anosmia and dysgeusia might be observed in patients with COVID-19. In fact, some even develop COVID-19-related symptoms only after showing neurologic symptoms. A case of viral encephalitis caused by the novel CoV attacking the CNS was reported from Beijing Ditan Hospital. The presence of SARS-CoV-2 in the cerebrospinal fluid by genome sequencing had supported the theory that this new pneumonia virus can also cause nervous system damage. It is therefore likely that other pathogenic bacteria may destroy the

blood-brain barrier, and secondary intracranial infections may cause headaches, projectile vomiting, vision loss, and limb convulsions in patients with severe COVID-19 symptoms [1].

## 4.2 Clinical Findings

Although respiratory symptoms of COVID-19 are prominent, it has been understood that COVID-19 causes significant neurological symptoms. Additionally, this virus has also been detected in CSF and appears to cause nervous system damage. The pathological mechanism of COVID-19 is similar to SARS and MERS viruses. Similar to other coronaviruses such as SARS and MERS, SARS-CoV-2 can affect the nervous system's hematogenous or retrograde neuronal route. On the other hand, it is thought that COVID-19 may disrupt the blood-brain barrier [3]. A comprehensive review of the neurological disorders reported during the current COVID-19 pandemic shows that infection with SARS-CoV-2 affects the central nervous system (CNS), peripheral nervous system (PNS), and musculature. CNS manifestations include headache and decreased responsiveness, which are considered the first indicators of potential neurological involvement; anosmia, hyposmia, and hypogesic dysgeusia are common early signs of coronavirus infection [4]. In addition to these early symptoms, more serious neurological involvements can be observed in the later stages of the disease. Patients with a diagnosis of COVID-19 have been reported to develop clinical manifestations such as viral encephalitis, infectious toxic encephalopathy, acute cerebrovascular disease, epileptic seizures, and meningitis [5]. There are many studies in the literature on the neurological manifestations of COVID-19. According to the first prospective study conducted by Ömer Karadaş et al., they reported that 34.7% of hospitalized patients with a diagnosis of COVID-19 had neurological signs and symptoms. They reported that the most common of these symptoms with a rate of 26.7% was headache (Table 4.1). It has been observed that the rates of appetite and weight loss are significantly increased in patients with headache compared to those without headache [3]. In addition, results have been published showing that neurological signs and symptoms may be related to the severity of COVID-19, and when compared with patients with COVID-19 whose clinical condition is not bad, it has been observed that patients with poor clinical status often have neurological symptoms manifesting acute cerebrovascular diseases, impaired consciousness, and skeletal muscle symptoms [5]. The most common neurological symptoms are headache, muscle pain, sleep disturbance, unconsciousness, smell and taste disorders, dizziness, and cerebrovascular diseases. In particular, it has been shown that the headache characteristic is different from other primary headaches and is more localized in the frontal and occipital regions [3].

CoV infections can affect the nervous system, and it is currently believed that CoV in concert with host immune mechanisms may turn these infections into

**Table 4.1** Neurological findings [3]

| Signs and symptoms | All patients ($N = 239$) |
|---|---|
| Fever | 79 (33.1%) |
| Headache | 64 (26.7%) |
| Trigeminal neuralgia | 8 (3.3%) |
| Glossopharyngeal neuralgia | 9 (3.7%) |
| Vasoglossopharyngeal neuralgia | 2 (0.8%) |
| Pain with eye movements | 3 (1.3%) |
| Dizziness | 16 (6.7%) |
| Tinnitus | 5 (2.1%) |
| Lack of hearing | 3 (1.3%) |
| Visual defect | 8 (3.3%) |
| Numbness in tongue | 4 (1.7) |
| Sound bifurcation | 3 (1.3%) |
| Numbness in the face area | 8 (3.3%) |
| Smell disorder | 18 (7.5%) |
| Taste disorder | 16 (6.7%) |
| Cerebrovascular disorders | 9 (3.8%) |
| Hemorrhagic CVD | 2 (0.8% |
| Ischemic CVD | 7 (2.9%) |
| Unconsciousness-confusion | 23 (9.6%) |
| Sleeping disorder | 30 (12.6%) |
| Orthostatic hypertension | 8 (3.3%) |
| Balance disorder | 6 (2.5%) |
| Muscle pain | 36 (15.1) |
| Guillain-Barré syndrome | 1 (0.4%) |
| Restless legs syndrome | 4 (1.7%) |
| Nausea | 13 (5.43%) |
| Diarrhea | 13 (5.4%) |

persistent infections that may lead to neurological diseases. Patients with CoV infections should be evaluated early for neurological symptoms, including headache, consciousness disorder, paresthesia, and other pathological signs. Timely analysis of cerebrospinal fluid and awareness and management of infection-related neurological complications are key to improving the prognosis of critically ill patients [6]. In the early symptomatic phase of SARS-CoV-2 infection, more than 1200 patients reported from hospitals in Wuhan; 88%–92% had fever, 67–69% had cough, 26–51% had fatigue, and 36% had muscle pain. Beijing hospitals reported a cohort of 262 confirmed cases that 6.5% had headache, compared with 6–8% in Wuhan, and 13% developed cerebrovascular disease. Chen et al. studied initial symptoms in 113 terminally ill COVID-19 patients, compared with 161 patients who recovered. Early change of consciousness was seen in fatal cases (22%) and in convalescents (1%). Mao et al. found impaired consciousness in 14.8% of 214 patients hospitalized for severe illness and 2.4% in non-severe infections. Therefore, early onset of headache and decreased response to treatment are indicators of potential neurological involvement in COVID-19 patients [7].

While the neurological manifestations of COVID-19 have not yet been properly investigated, it is highly likely that some of these patients, particularly those suffering from a severe illness, will have CNS involvement and neurological manifestations. Precise and targeted documentation of neurological symptoms (e.g., headache, dizziness, etc.) and signs (e.g., altered mental status, meningeal signs, etc.); detailed clinical, neurological, and electrophysiological investigations (e.g., EEG status change); attempts to isolate SARS-CoV-2 from CSF; and autopsies of COVID-19 victims may clarify the roles of this virus in causing neurological symptoms [6].

## 4.3 Pathophysıology

CoV have an average diameter of 100 nm with shapes of spherical or oval. There are large spikes of viral membrane glycoproteins on the surface, and when observed by electron microscopy, these negatively stained virus particles show a typical crown-like shape. CoV is a positive-sense single-stranded RNA virus, which harbors the largest genome among currently known RNA viruses, with a genome length of about 26–32 kb. CoV are neurotropic and can invade nervous tissues and cause infections of immune-functioning macrophages, microglia, or astrocytes in the CNS [1]. Pathological mechanisms found for other known coronavirus subtypes may also be considered for COVID-19. SARS-CoV-1 and SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE2) as a receptor to infect ciliary bronchial epithelial cells and type II pneumocytes. This explains the severity of pulmonary involvement. SARS-CoV-2 has a higher affinity for the ACE2 receptor found on neurons and endothelial cells than SARS-CoV-1, indicating that SARS-CoV-2 may have higher neuroinvasive potential compared to previous coronaviruses [7]. The entry point for SARS-COV-2 is ACE2, and it has almost a ubiquitous presence in human organs including the lung parenchyma, gastrointestinal tract, nasal mucosa, renal and urinary tract, human airway epithelia, lymphoid tissues, reproductive organs, vascular endothelium, and brain. The virus is believed to enter chiefly through the nasal mucosa or the gastrointestinal tract due to the higher expression of protein hACE2. The intriguing part though is that recently reported studies have noted altered mental health in some COVID-19 patients showing symptoms like anosmia and ageusia, thereby indicating a neuroinvasive nature of the virus [8]. According to the data obtained, neurological involvement is not uncommon in human coronavirus infections. There are publications reporting that virus is detected in cerebrospinal fluid (CSF) in SARS-CoV patients. Recent publications have described early changes in smell and taste, as well as neurological manifestations involving the central nervous system (CNS), peripheral nervous system (PNS), and muscle in COVID-19 [7]. Cerebrovascular disease, in particular large-vessel ischemic strokes, and less frequently cerebral venous thrombosis, intracerebral hemorrhage, and subarachnoid hemorrhage, usually occurs as part of a thrombotic state induced by viral attachment to ACE2 receptors in endothelium causing widespread endotheliitis, coagulopathy, and arterial and venous thromboses (Fig. 4.2). Acute

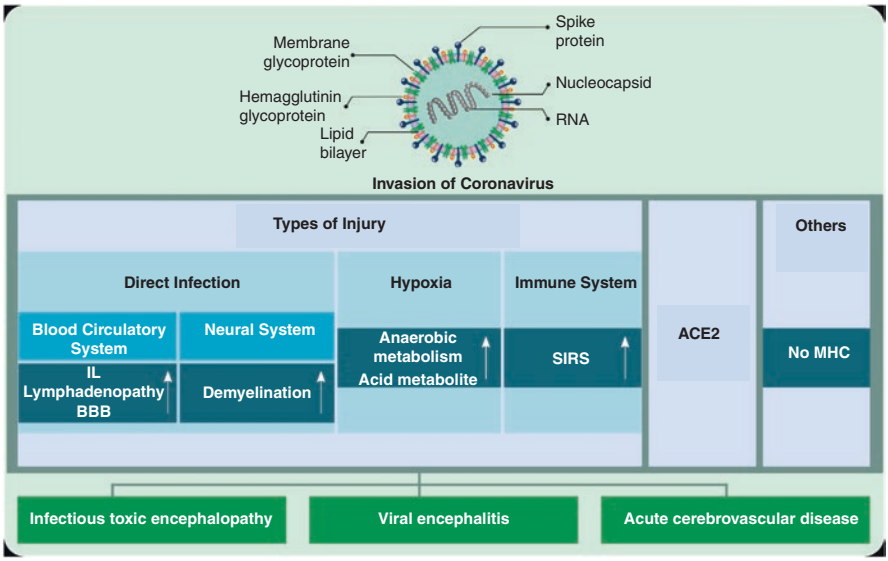


**Fig. 4.2** Pathogenesis of nervous system injury caused by coronaviruses. *ACE2* Angiotensin-converting enzyme 2, *BBB* blood-brain barrier, *IL* interleukin, *MHC* major histocompatibility complexes, *SIRS* systemic inflammatory response syndrome

hemorrhagic necrotizing encephalopathy is associated with cytokine storm. Frontal hypoperfusion syndrome has been reported. There are isolated reports of seizures, encephalopathy, meningitis, encephalitis, and myelitis [7]. Studies indicate that cytokines such as IL-6 and TNF-α are pain mediators in neurovascular inflammation. It has been reported that cytokines such as IL-6 are particularly painful mediators in migraine and that IL-6 levels are significantly higher in some headache patients. IL-6 is a proinflammatory cytokine released from T cells and macrophages as a stimulator of the immune response. It is known to cause inflammation in conditions such as infection and trauma. In addition, this cytokine, which is an important mediator of fever and acute phase response, easily crosses the blood-brain barrier, and initiates PGE2 synthesis in the hypothalamus, has been found to be produced by smooth muscle cells of many blood vessels [3]. The expression and function of ACE2 proteins are reduced following SARS-CoV-2 infection. So that the expression of ACE2 in patients with hypertension is already low, SARS-CoV-2 infection is more likely to induce cerebral hemorrhage in such patients. As a second line of evidence suggesting that SARS-CoV-2 infection may induce cerebral hemorrhage, patients with COVID-19 often suffer from coagulopathy and prolonged prothrombin time, [6, 8], both of which are also contributing factors to secondary cerebral hemorrhage. In contrast, no cases of secondary cerebral infarctions have been reported in patients with COVID-19. COVID-19 may cause an increase in D-dimers [6], which leads easily to thrombotic vascular events. Recent studies have reported cases of secondary cerebral infarction in SARS. Hence, we speculate that COVID-19 also has the potential to induce cerebral venous and/or arterial infarctions [9].

## 4.4 Treatment

**Olfactory and Gustatory Dysfunctions** A multicenter, specifically designed prospective European study performed on 417 mild and moderate COVID-19 patients showed that 86 and 88% of patients reported olfactory and gustatory dysfunctions, respectively. Limited evidence-based treatments exist for anosmia. However, smell and taste dysfunctions are self-limiting in the great majority of COVID-19 patients and do not require specific treatments [10].

**Headache** There is some evidence for pharmacological and non-pharmacological treatments for COVID-19 headache. As cases and studies on COVID-19 headache increase, solid evidence is reached. In light of the information obtained according to available data, some conclusions have been reached. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used in the treatment of acute headaches. However, upon the development of severe symptoms in a few individuals using ibuprofen during COVID-19 infection, concern has arisen that nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen may cause poor clinical outcomes. The proposed mechanism is thought to be that NSAIDs increase the expression of angiotensin converting enzyme 2, so COVID-19 enters the cell through these receptors and leads to a severe disease course. As data on this subject increases, it has been stated by competent institutions in the world that there is no relationship between the use of NSAIDs and the worsening of clinical outcomes. It has even been stated that intermittent use of NSAIDs may be beneficial for patients with COVID-19 [11].

**Impaired Consciousness and Delirium** It has been suggested that the implementation of excellent delirium prevention and management at the bedside should be a priority during the COVID-19 pandemic. A study from a palliative care hospital revealed that agitation could respond well to benzodiazepines. It should be kept in mind that benzodiazepines may be dangerous for patients with respiratory failure who are not ventilated, and special attention is needed. For everything else, even if it has been suggested that hyperactive delirium could require a more aggressive management in these patients, COVID-19-related delirium should be treated like delirium due to other causes [10].

**Ischemic Stroke** The procoagulant pattern of COVID-19 patients may justify the clinical reports of thromboembolic complications, including stroke, during the course of the disease. COVID-19 patients who have ARDS showed a procoagulant profile characterized by an increased clot strength due to both platelet and fibrinogen contribution, elevated D-dimer levels, and hyperfibrinogenemia (possibly linked to increased interleukin-6, a powerful pro-inflammatory cytokine). An aggressive antithrombotic therapy may be warranted (i.e., low-molecular-weight heparin, 6000 IU, two times a day) in most severe cases. Further studies are also needed to assess the best prophylaxis and treatment of this condition. A randomized controlled trial is being planned to study whether prophylactic-dose enoxaparin

(versus no treatment) may reduce early, all-cause mortality and unplanned hospitalizations in adult symptomatic ambulatory COVID-19 patients with no other indications to receive anticoagulation.

In another study, it was shown that coagulation dysfunction is common in patients with COVID-19, especially fibrinogen and D-dimer elevation, and the degree of elevation is related to the severity of the disease. During recovery, fibrinogen and activated partial thromboplastin time also return to normal.

Importantly, even if some adaptations in the real-life management of stroke may be needed, COVID-19 pandemic should not alter the inclusion and exclusion criteria for acute stroke treatments, such as systemic fibrinolysis and mechanical thrombectomy. This also applies to stroke patients with suspected or confirmed SARS-Cov-2 infection [10].

**Epilepsy** When treating epilepsy in a given patient with SARS-Cov-2 infection, it is important to check the pharmacological interactions between antiepileptic drugs and the drugs used to treat COVID-19 in that subject. A special attention is needed for carbamazepine, phenytoin, phenobarbital, and primidone.

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# Chapter 5
# Clinical Pictures and Diagnostic Features of COVID-19 Headache


**Arife Çimen Atalar and Betül Baykan**

## 5.1 Introduction

Coronavirus disease 19 (COVID-19), caused by a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is mainly characterized by respiratory system involvement and other related symptoms such as myalgia, fever, and fatigue [1]. However, various neurological manifestations related to the involvement of both the central and peripheral nervous systems with different mechanisms have also been reported since the emergence of the pandemic [2–10]. Headache is among the top five prevalent neurological symptoms at the acute phase of COVID-19 [11, 12], with a wide estimated prevalence range of 6.5–70.3%, depending on the different designs of studies, but the most frequently reported rates are between 10 and 20% [13–16]. Prominent headache can occur in the early phase of the infection, sometimes as an initial symptom before the emergence of other respiratory and systemic symptoms or as an isolated symptom during the course of the disease [17–19].

There is no definite causative/temporal relationship between headache and fever or respiratory symptoms; hence, headache can present independently from fever in many patients infected with SARS-CoV-2. The current view points out to different pathophysiological mechanisms of headache emergence in these patients, which will be discussed elsewhere in this book [17, 20–22].

Although "headache attributed to systemic infections" (code 9.2.2.1) is well-known and has a special subheading in the International Classification of Headache

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Disorders-3 (ICHD-3) [23], COVID-19-related headache has some unique traits and is more common than other viral infection-related headaches [17, 24–27]. Furthermore, the existence of headache in patients with COVID-19 might also have prognostic implications, such as lower risk of mortality for patients with coexistent headache compared to patients without headache for hospitalized patients [15]. These points clearly indicated the importance of this new headache emerging in the last years.

In the following subsections, the clinical phenotypes of COVID-19 headache will be discussed in detail, and the differentiating features will be highlighted to propose a set of diagnostic criteria to enhance the scientific interest. Topics including red flags associated with headaches, secondary headache disorders related to COVID-19, and treatment of this headache will be discussed in other chapters.

## 5.2 Clinical Characteristics and Prognostic Implications of COVID-19 Headache

Headache associated with COVID-19 has some distinctive features from other infection-related headaches and has different clinical phenotypes with their own characteristics, as shown by related research and expert opinions [16, 24, 28, 29].

The prominent type of COVID-19-related headache that draws attention usually emerges at the early phases of infection, at the acute setting, and sometimes can be the only symptom of COVID-19, which could have a diagnostic value for the prompt recognition of these patients at the emergency departments (ED) and outpatient clinics [17, 24]. Severe, bilateral, long-lasting, and analgesic-resistant headache, together with anosmia and ageusia, might be the only complaint in these patients. Therefore, a detailed, in-depth questioning of headache is essential for early diagnosis of COVID-19 (Fig. 5.1) [24, 28].

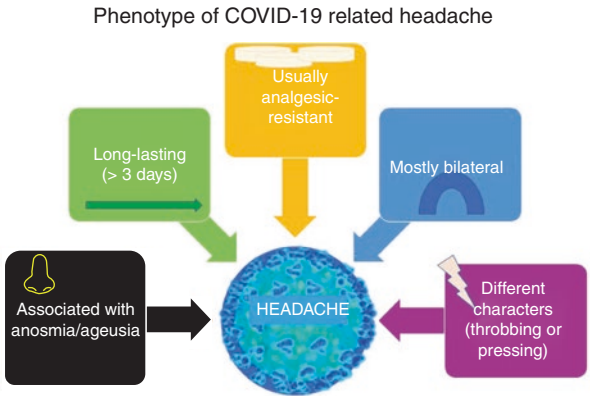


**Fig. 5.1** Phenotypical characteristics of COVID-19-related headache

Particularly, frequent existence of associated anosmia and ageusia (around 67–74%) with headache is remarkable in these patients as a diverse feature [15, 24, 29, 30]. Although the exact mechanisms of acute COVID-19-related headache are still not revealed, it is possible that the direct involvement of trigeminal nerve endings in the nasal or oral cavity could lead to frequent co-occurrence of anosmia/ageusia in association with this headache [24, 31]. In addition to anosmia and ageusia, the presence of gastrointestinal complaints such as nausea, diarrhea, and abdominal pain (up to 70% in COVID-19-positive patients with headache) might also be closely related with acute COVID-19 headaches [24], which points out to the presence of intriguing underlying pathophysiological mechanisms that need further investigation [24, 32]. Other associated symptoms such as photophobia and phonophobia (up to 63.9% and 67.9%, respectively, variable reported rates in different studies) are also very remarkable in COVID-19 patients with headache [20, 24, 27, 31].

Looking from the perspective of gender, an interesting observation is that in the male gender, COVID-19-related headaches are also highly reported unlike the other types of headaches (such as primary headache disorders, migraine, etc.), which are mainly dominant in the female gender [24]. A possible hypothesis for this interesting finding is that males have a higher risk of having COVID-19 (about 56–73% of patients with COVID-19 are male) due to several reasons such as having comorbid diseases (hypertension, atherosclerosis, coronary artery disease, etc.), role of hormonal factors (protective role of female hormones), and different immune activity levels between genders (females having more efficient immune system activity related to genetic factors) [13, 24, 33, 34]. Despite this important observation, the majority of patients with COVID-19-related headaches are still mainly consisted of females [15, 20, 35].

Most of the patients with a symptom of headache have a milder disease progression, underlining the prognostic importance of headache symptom in COVID-19 patients, which can be summarized as the presence of headache points out to a better prognosis [12, 15, 28]. Shorter disease duration of COVID-19 was reported in patients with a symptom of headache (23.9 ± 11.6 vs. 31.2 ± 12.0 days) in line with this observation [28]. Another related remarkable finding is that the presence of headache has an independent role in predicting lower risk of mortality in hospitalized patients and these patients had a different profile from other patients without headache. Headache as an initial symptom of COVID-19 at the acute period was more prevalently reported in non-hospitalized patients (57.97%) compared to hospitalized (31.11%) patients according to a meta-analysis. It is possible that headache might be underreported at the COVID-19 onset in hospitalized patients than other severe and disturbing COVID-19-associated symptoms (such as respiratory failure or fever) [12]. In a hospital-based study, patients with headache had more frequent anosmia (46.7% vs 18.7%) and myalgia (40.1% vs 19.1%) and were more dominantly female (58.4 vs 38.7%) and less disabled (mean modified Rankin scale; 0.14 vs 0.75) compared to patients without headache [15]. The overall hospital mortality rate was found to be 20.0% in the total number of patients, whereas it was only 5.8% in patients with a headache symptom. Moreover, patients without headache

had shown higher C-reactive protein (CRP) levels (median; 73.40 vs 40.55 mg/L), abnormal platelet values (median;194.000 vs 197.500 × $10^9$/L), lymphopenia (median; 940.00 vs 1117.00 × $10^9$/L), and higher D-dimer levels (median; 855 vs 550 ng/dL, RV: <500) at admission, which might reflect the role of cytokine storm determined in COVID-19 patients [15]. In another study by the same group on hospitalized patients, having headache with migraine phenotype was found to be related to more severe hematologic and inflammatory biomarkers and a worse clinical manifestation of COVID-19 compared to the tension-type phenotype, emphasizing the role of headache phenotype on the clinical course of COVID-19 [36].

## 5.3 Phenotypes of COVID-19 Headaches

There are a handful of detailed studies investigating the phenotypes of COVID-related headaches. A summary of related selected eligible studies on this topic is given in Table 5.1.

The most remarkable and striking features of COVID-related headaches can be emphasized as being bilateral (mostly frontal or frontotemporal location), long-lasting, pressing/pulsating in quality, and partially/completely resistant to analgesic treatments [26, 31, 37]. Anosmia, ageusia, and gastrointestinal complaints (such as nausea, diarrhea, vomiting, etc.) frequently accompany the headache, as well as photo- and phonophobia [15, 24].

Headache mainly manifests in two different phenotypes as migraine-like and tension-type, suggesting different underlying pathophysiological mechanisms or severity grades based on the individuals' immune-genetic background and/or viral load [25, 27, 30, 36]. Although tension-type characteristics are more commonly observed in some studies, patients manifesting with the so-called migraine phenotype are also not rare, up to 25%, according to these studies [24, 27, 30, 38]. One third of the patients might also show a combination of migraine and tension-type headache phenotypes [31]. Understandably, patients showing migrainous characteristics can experience more intense and treatment-resistant headache attacks, causing a serious disability. In addition, this severe phenotype seems to be related to a worse clinical manifestation of COVID-19, including an association with hematologic and inflammatory markers of the disease [36]. It is tempting to speculate that there might be associations of SARS-CoV-2 load and its variants with headache phenotypes, but these points were not investigated yet.

Interestingly, a "new-onset" headache type different from the previous headache experiences has also been described by some patients with preexisting primary headaches [18, 24, 26, 30, 35, 39]. It should also be emphasized that even patients without any primary headache disorder (such as migraine) can develop a de novo migraine like headache during the course of COVID-19, which could be explained by the possible activation of the trigeminovascular system [27, 28].

**Table 5.1** Selected important studies reporting the clinical characteristics of COVID-19-related headache

| Author/year/ setting | No. of pts./no. of pts. with H. | f/m | Time course of H. | Prior H. history (PHH) | Phenotype definitions of H | Quality of H |
|---|---|---|---|---|---|---|
| Uygun O et al./2020/ Web-based [24] | 3458/1968 pts. (262 with COVID-19 +) | 2341/1171 COVID-19 pts.: 48.1% m | ˃72 h: 10.3%/4.1% (COVID-19+ vs - group) | 116pts (COVID-19 + group) | 54.7% TTH 36.3% M in total pts. | -With vs without PHH; 32.5% pulsating 43.7% pressing 2.3% fiery 16.1% stabbing |
| López JT et al./2020/HI [27] | 106 COVID-19 pts | 64.2% f | –38.7% within 24 h; –62.3% within 48 h; –73.6% within 72 h | 48.2% (18 M, 30 TTH, 3 C, 2 M + TTH, 1 hypnic, 1 cluster) –26.4% H as first symptoms | 54% TTH 25% M | 75% pressing 21.7% pulsating 14.2% stabbing 2.8% burning 64.1% severe H 32.1% moderate 3.8% mild H |
| Planchuelo-Gómez Á et al./2020/HI [36] | 106 COVID-19 pts | 64.2% f | Not reported | 57.5% (28 TTH, 16 M, 2 TTH + M, 15 other) | 1. Phenotype: M 2. Phenotype: TTH 3. Phenotype: COVID-19 specific | 1. Pulsating 2. Pressing 3. Pressing, intense, hypersensitive to stimuli |
| García-Azorín D et al./2020/HI [35] | 576/130 (22.6%) (COVID-19 pts) | 63.5% f (in 104 pts) | – 42.3% recent-onset – 17.3% progressive – 4.8% sudden – 26% H as the first symptom | 57.7% M 16.3% TTH 28.8% | 49% change in the pattern of a preexisting H 37.5% worst H ever | Not reported |

(continued)

**Table 5.1** (continued)

| Author/year/setting | No. of pts./no. of pts. with H. | f/m | Time course of H. | Prior H. history (PHH) | Phenotype definitions of H | Quality of H |
|---|---|---|---|---|---|---|
| Porta-Etessam J et al./2020/web-based [20] | 112 HCP/112 | 81.3% f | Mean time from onset of COVID-19: 3.9 ± 6 days | 17.9% M<br>7.1% TTH<br>0.9% cluster H | 1. H due to PPE use<br>2. Less specific H with pressing quality<br>3. COVID-19-related H<br>4. In PPH, H compatible with their previous H | 80.4% pressing<br>10.7% stabbing<br>7.4% pulsating<br>1.8% electric-shock like |
| Trigo J et al./2020/HI, OP, ES [15] | 576/137 (23.7%) | 43.3% f (total pts)<br>58.4% f in pts. with H | 26% H as the first symptom | 10.9% | H pts. are younger, ↑f, less disabled, ↓ rates of HT, smoking habits, cardiac disorders, chronic neurological disorders | Not reported |
| García-Azorín D et al./2021/HI, OP [31] | 2194/514 (23.4%)<br>[23.7% OP,22.6% HI] | 72.1% f | 27.9% H as the first symptoms.<br>H started within;<br>1. Day: 40.7%<br>≥ 5.d: 23.1%<br>H dur (n = 390);<br>1–6 h: 49%<br>7–12 h:14.6%<br>13–18 h: 3.6%<br>19–24 h: 32.8% | 48.7% all pts.<br>[56.1% HI, 47.7% OP]<br>18.1% M<br>21.6% TTH | – Median intensity 7/10<br>– more intense in f<br>– 61.1%, red flags of H (+)<br>– 26%, "worst H ever"<br>– H frequency and phenotype similar in HI and OP | 74.7% pressing<br>14.8% throbbing<br>15.7% stabbing<br>0.9% electric<br>2.1% burning |
| Sampaio Rocha-Filho PA et al./2020/HI [29] | 73 /47 (64.4%) | 63% m | Median H onset 1 (1.5–2) day<br>Continuous H: 15% | 30 (64%)<br>(18 TTH, 12 M) | M like 51%<br>TTH like 40%<br>Cough H 26% | 51% pulsatile<br>43% pressing<br>4% stabbing |
| Sampaio Rocha-Filho PA et al./2022/HI, OP [30] | 288/199 (69.1%) | 55.8% f (in pts. with H) | Median H dur: 7 (4.5–12.5) days | 46.2%<br>–78.3% different from previous H | -Most frequent H phenotype; non-M, severe, and different from previous H<br>-M like phenotype:49.3% | Median intensity: 8 (5.5–9.5) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Caronna E et al./2020/ES, 6 weeks follow-up in HI and ICS [28] | 130/97 (74.6%) | 50.8/49.2% (all pts) 57.7% f (H pts) | 49.5% constant 29.3% ≤ 4 h 21.2% ˃4 h H is a prodromal symptom in pts. with severe pain | 19.6% of H pts. had episodic M history | 24.7% had severe pain with M-like features (f and younger pts. and not with a PHH) | 70.1% pressing 19.6% throbbing 10.3% other Pain: moderate 50.6%/24.7% for both severe and mild |
| Membrilla JA et al./2020/ES [26] | 145/99 (68.3%) (45 confirmed COVID-19) | 63.6% f | H as first symptom:24.2% -H onset with/after other symptoms: 57.6/18.2% -H lasting ≥24 h without remission: 45.5% | 33.3% PHH (25.3% M) –H different from previous H attacks: 84.9% –80% of pts. with previous M had pain ≥24 h | Holocranial/bilateral F, moderate/severe pain, pressing; M-like features are not rare – In pts. with PHH; longer, more severe and presents earlier | *89.9% VAS ≥ 5 *60.6% VAS ≥ 7 *73.7% pressing *14.1% throbbing *11.1% stabbing *1% burning |
| Magdy R et al./2020/HI, OP [18] | 172 | 37.2/67.8% | H onset; with/before/after other COVID-19 symptom; 57/28.5/14.5% Median frequency: 7 (3–7) attacks/w Median dur: 6 (2–16) h | 52.9% (26.2% M, 46 26.7% TTH) COVID-19 H ↑ in pts. with PHH (52.9 vs 47.1%) | COVID-19-related H; diffuse, pressing with a median intensity of 7 and a median frequency of 7 attacks/w | 40.7% pressing 26.2% exploding 16.9% dull 16.3% throbbing Median VAS: 7 (5–8) |
| Karadaş O et al./2021/HI [25] | 287/83 (28.9%) | 42/58% | Mean H dur: 9 ± 5.2 h Mean H frequency: 5.10 ± 2.39 days | PHH in pts. with/without H: 14.5/10.3% PHH in f/m 25.7/6.3% | H in COVID-19: New onset, bilateral (F) throbbing, severe, long-lasting attacks accompanied by pulmonary involvement and ↑IL-6 levels | 56.6% throbbing 25.3% pressing 8.4% stabbing 9.6% other |

(continued)

**Table 5.1** (continued)

| Author/year/setting | No. of pts./no. of pts. with H. | f/m | Time course of H. | Prior H. history (PHH) | Phenotype definitions of H | Quality of H |
|---|---|---|---|---|---|---|
| Al-Hashel JY et al./2021/OP [39] | 121/ 121 | 83.5/16.5% | H days ↑ after COVID-19: 11.09 ± 8.45 d<br>Mean H days/month: 4.44 ± 1.68<br>Mean H attack dur: 14.17 ± 15.46 h | 73.6% PHH; 64.5% M, 9.1% TTH. 26.4% de novo H (started during COVID-19 and continued post-COVID-19) | -De novo H: Severe, M phenotype (62.5%)<br>-H in pts. with PPH: TTH pts.; H severity ↑ (66.7%), frequency↑ (55.6%), ↑ analgesic use (55.6%) M pts.; ↑attack severity (41.2%), ↑ H frequency, ↑analgesic use (41.2%) | -De novo H; Throbbing: 50% Pressing: 34.4% Exploding: 9.4% Dull aching: 6.2% |

| Author/year/setting | Localization of H | Anosmia/ageusia | Photo-/phono-/osmophobia | Other remarkable findings | Treatment response/prognosis | Notes |
|---|---|---|---|---|---|---|
| Uygun O et al./2020/Web-based [24] | (COVID-19+ vs - group) 85/64% bilateral Not significant | –60.4% in all COVID + pts.<br>-In pts. with H; 74/20% Significant (COVID-19+ vs – Group) | (In pts. with vs without PHH) Phonophobia 67/67.9% Photophobia 63.9/63% | (COVID-19+ vs - group) 70/53% GIS symptoms 40% fever | (COVID-19+ vs – group) 18/8% analgesic resistant | 22.5% of the COVID-19 pts. with PHH had no H during COVID |
| López JT et al./2020/HI [27] | 85% bilateral 83% F 41.5% periocular 32.1% T 15.1% Hemicranial | Not reported | *45.3% photophobia *39.6% phonophobia *1.8% osmophobia | Not reported | Not reported | –45.5% had persistent H at the time of interview |

| | | | | | | |
|---|---|---|---|---|---|---|
| Planchuelo-Gómez Á et al./2020/HI [36] | – M phenotype: F<br>– COVID-19 specific: bilateral (diffuse) F | Not reported | Photophobia/ phonophobia related to ↑ disability and intensity of H | Not reported | M type phenotype: treatment resistant | 1. L and GFR ↓<br>2. Lower CRP and PCT values<br>3. L, PCT, CRP ↑ |
| García-Azorín D et al./2020/HI [35] | 15.4% strictly Uni | 64.4% anosmia | Not reported | 89.4% fever<br>5.8% autonomic features<br>37.5% precipitated by sneeze, cough, exercise | 14.4% treatment resistant | FHH 37.5% |
| Porta-Etessam J et al./2020/ web-based [20] | 46% hemicranial<br>42.5% holocranial<br>17.7% O | Not reported | 41% phonophobia<br>28.6% photophobia<br>9.8% osmophobia | 19.6% autonomic features<br>60% ↑by act.<br>18.7% nausea<br>3.6% vomiting<br>4.4% allodynia | 15% H not resolved | – 39.9% H due to PPE use<br>– H not related to fever: 88.4% |
| Trigo J et al./2020/ HI, OP, ES [15] | Not reported | 46.7% anosmia | ↑ odds of H in hospitalized pts.; anosmia, f, myalgia, fever | H is related to low mortality | Not reported | Also in pts. with H: CRP, PLT, lymphocyte levels, D-dimer are ↓ |
| García-Azorín D et al./2021/HI, OP [31] | 18.7% holocranial<br>80.1% bilateral<br>19.2% Uni<br>70.9% F<br>43.9% T<br>(433 pts) | 60% anosmia [64.5% HI, 58.7% OP]<br>($n$ = 448) | 33.3% photophobia [45.7% HI, 29.6% OP]<br>147 (32.3%) phonophobia [39% HI, 30.2% OP]<br>3.7% osmophobia | 66.9% avoidance of act<br>16.4% nausea<br>4.6% vomiting<br>24.8% autonomic symptoms | H ≥ 1 month: 12.9%<br>Median dur of H: 7 days<br>Symptomatic. Medication needed: 94.5% | 25.5% had FHM<br>15.6% H is the most bothersome symptom |

(continued)

**Table 5.1** (continued)

| Author/year/setting | Localization of H | Anosmia/ageusia | Photo-/phono-/osmophobia | Other remarkable findings | Treatment response/prognosis | Notes |
|---|---|---|---|---|---|---|
| Sampaio Rocha-Filho PA et al./2020/HI [29] | 80% F<br>55% T<br>49% P<br>36% O<br>94% bilateral | – 33% H + hypo-/anosmia<br>– 34% H+ hypo/ageusia - pts. with hyposmia/anosmia more often in H | 45% photophobia<br>30% phonophobia | 53% worsening with physical act<br>32% nausea<br>11% vomiting | H↑ in pts. with hypo/anosmia and/or hypo/ageusia | – pts with PHM have a M-phenotype of COVID-19 related H<br>– pts with H are younger |
| Sampaio Rocha-Filho PA et al./2022/HI, OP [30] | Not reported | 80.4/53.9% hypo/anosmia in pts. with vs without H<br>–67% in total pts | 48.7% photophobia | 42.7% nausea | 13.6% H continued after acute phase<br>–10.1% H dur ≥ 3 months | H frequency ↑: f, pts. with fever, sore throat, anosmia/ageusia and myalgia |
| Caronna E et al./2020/ES, 6 weeks follow-up in HI and ICS [28] | 47.4% F<br>38.1% holocranial<br>14.5% other | Anosmia/ageusia: 54.6%/18.2% (with/without H) | 10/97 pts. photo/phonophobia | In pts. with H;<br>– 25 nausea / vomiting<br>– 12 worsening with act<br>– 4 vertigo<br>– 3 neck stiffness | – Acute treatment ineffective; Baseline/after 6 w (32.1/28.6%)<br>– 50% of these pts. had no PHH | Clinical dur of COVID-19 is ↓ in H pts. (23.9 ± 11.6 vs. 31.2 ± 12.0 d)<br>-H pts.; younger, f, ↑ PHH,<br>–37.8% of followed pts. had H after 6 w (60.7% daily H) |
| Membrilla JA et al./2020/ES [26] | 86.9% bilateral<br>34.3% F<br>34.3% holocranial<br>12.1% P<br>9.1% O | 49.5% anosmia<br>-anosmia ↑ in pts. with PMH (68 vs 43.2%) | –29.3% photophobia<br>–27.3% phonophobia<br>–9.1% osmophobia | 45.5% H↑ with physical act<br>43.4% H↑ with coughing | Pain relief with<br>1. Step analgesics:<br>Complete:26.3%<br>Partial: 53.5% | –18.2%, fever as the most frequent H trigger |

| | | | | | | |
|---|---|---|---|---|---|---|
| Magdy R et al./2020/HI, OP [18] | 52.9% diffuse<br>23.3% F<br>18% T<br>5.8% O | Not reported | Not reported | 49.2% H ↑ with fever | Response to analgesics;<br>Moderate: 46.5%<br>Excellent: 32.6%<br>Poor: 20.9% | ↑ COVID-19 H attacks in pts. with comorbidities, PHH, dehydration<br>– Fever, dehydration, f gender are predictors of ↑intensity of COVID-19 H |
| Karadaş O et al./2021/HI [25] | 54% F<br>15.6% O<br>3.6% FT<br>92.8% bilateral<br>7.2% Uni | 8.9% hyposmia in pts. with H | 30.1% Photophobia<br>27.7% phonophobia<br>2.4% osmophobia | 14.5% aggravation by physical act<br>10.8% vertigo/ Dizziness<br>36.1% nausea<br>6% vomiting<br>25.3% diarrhea in pts. with H | – 59% paracetamol responsive<br>– 34.9% GON responsive | 2 H clusters:<br>1—severe, long-dur, frequent H, not responsive to paracetamol (85%), IL-6↑, pulmonary infiltration<br>2—moderate (96%) paracetamol responsive H |
| Al-Hashel JY et al./2021/OP [39] | -De novo H:<br>40.6% T<br>40.6% Bi-F<br>9.3% O<br>9.3% diffuse | Not reported | De novo H;<br>– 22.2% Photophobia<br>– 38.9% phonophobia | De novo H;<br>– 11.1% diarrhea<br>– 11.1% dizziness | De novo H; resolved within 1 month (56.3%) | Young m pts. (<40 years of age) with COVID -19 tend to have worse H (longer dur, more severe) |

*act* Activity, *C* cervicogenic, *CS* cross-sectional, *ES* emergency setting, *dur* duration, *f* female, *F* frontal, *FHH* family history of headache, *FHM* family history of migraine, *FT* frontotemporal, *GIS* gastrointestinal symptoms, *GFR* glomerular filtration rate, *GON* great occipital nerve blockage, *h* hours, *H* headache, *HCP* health care professionals, *HI* hospital inpatient setting, *HT* hypertension, *ICS* intensive care setting, *L* lymphopenia, *m* male, *M* migraine, *NA* not applicable, *O* occipital, *OP* outpatient setting, *pts* patients, *P* parietal, *PCT* procalcitonin, *PHH* prior headache history, *PHM* prior history of migraine, *PLT* platelet, *PPE* personal protective equipment, *T* temporal, *TTH* tension type headache, *Uni* unilateral, *VAS* visual analog scale, *w* week, ↓ decreased; ↑ increased

## 5.4 Patients with a Preexisting Primary Headache Disorder

As already mentioned, patients with a previously diagnosed primary headache disorder might complain from a new onset headache with different characteristics or experience changes in their usual headache attack patterns during the course of COVID-19 pandemic [35]. In a large survey study, where 44.3% of the COVID-19 positive patients had a primary headache disorder diagnosis, 79.5% described a new emerging headache different from their usual attacks and 50% of these headaches were described as "totally different", whereas this statement was true for 13.9% in patients without COVID-19 but with a previous primary headache history [24].

The pattern of preexisting headache attacks might change and evolve into a more severe, frequent, longer, and resistant headache affecting the individuals' quality of life in the most bothersome way [18, 26, 31]. Particularly in patients with a preexisting migraine, headache attack duration might increase, being sometimes persistent and resistant to analgesic use. In line with this, those patients with migraine features at the baseline reported more frequently to have post-COVID persistent headache [40]. The increased severity of migraine attacks after COVID-19 was especially more prominent in the female gender [24, 39].

On the other hand, at least half of patients with preexisting primary headache disorders did not experience any changes in their usual headache attacks during the pandemic [24]. Moreover, some patients (up to 1/3 of all patients) might not have any headache attacks at all, if they are not infected during the COVID-19 pandemic [24]. Although there is not an exact explication for the lack of headache in these patients, individual differences and avoiding social stressful interactions due to social isolation might be responsible [24]. Lockdown measures due to the COVID-19 could have affected the course of primary headaches, migraine in particular, in terms of reduced migraine triggers (such as reduced stress, regular sleep, regular meals at home, etc.) and increased self-care at home [41]. However, increased perceived levels of stress along with restriction of regular medical visits and suspension of in-person treatment protocols might have had a negative impact, leading to the increase of headache attack frequency/severity and even transforming into chronic migraine in some patients with episodic migraine [39].

## 5.5 Triggers of Headache

Since the details of the triggering factors and pathogenesis of COVID-19 will be discussed in other chapters, we will give a brief summary of the triggering factors for headache here.

Several triggers were proposed for the emergence of headache in COVID-19 patients. Stress is one of the most remarkable triggers for headache followed by the infection itself (and related factors such as fever, dehydration, coughing, hypoxia), medications used for the treatment of COVID-19, social isolation and related

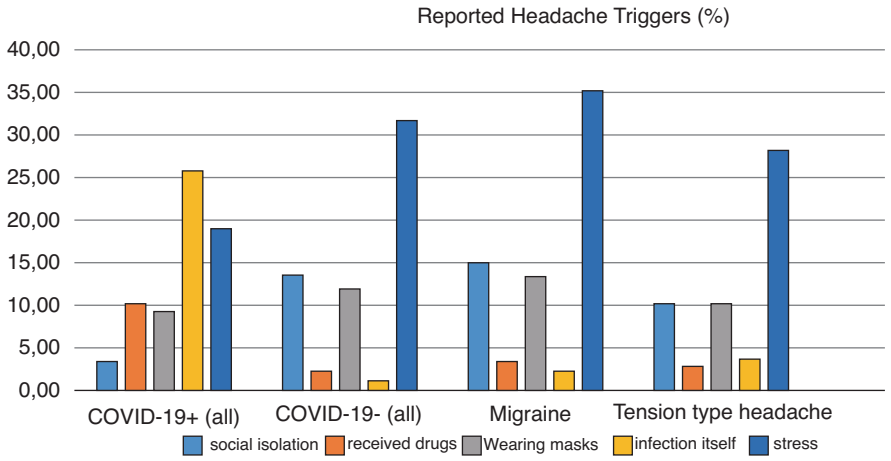


**Fig. 5.2** Triggers of headache in regard to COVID-19 and to previous headache types during the pandemic*. **previously unpublished new analysis from the data of Uygun Ö* et al. *Headache characteristics in COVID-19 pandemic-a survey study. J Headache Pain. 2020 Oct 13;21(1):121*

factors, use of personal protective equipment (PPE), and other similar protective masks [24, 30, 38, 42] (Fig. 5.2).

Fever, as a trigger of COVID-19-related headache, is still a question of debate, since some studies report fever as a trigger of headache, whereas others disclose no definite relationship between fever and headache [15, 20, 28]. Dehydration and hypoxia are also blamed in the etiopathogenesis of headache as underlying mechanisms and as triggers according to some studies without definite evidence [18, 43, 44]. Finally, there are several studies about the role of wearing of PPE such as N95 face masks as a triggering factor for developing de novo PPE-associated headaches or worsening of preexisting primary headache disorders as shown in a variety of studies [17, 42]. De novo PPE-associated headaches may present as both migrainous and tension-type phenotypes, and external compression might be responsible for the headache. The course of the PPE-related headache is broadly favorable, and the majority of these headaches remit and do not persist [42].

## 5.6 Course of Headache in COVID-19 Patients

Headache related to COVID-19 is not specific only to the early phases but might persist after the infection as a chronic sequela. There are only a few studies on the long- term course of headache after COVID-19 yet, but the available data points out to the presence of an elongated and persistent headache in some patients [40]. The prevalence of post-COVID headache was reported between 8% and 15% during the

initial 6 months after acute COVID-19 in a meta-analysis [12]. Although the majority of headaches resolve within the first 2 weeks after COVID-19 [28, 40], it might be persistent and difficult to treat and might evolve into a chronic pattern in some patients.

In a study where patients with acute COVID-19-related headaches were evaluated after 6 weeks, one third of followed-up patients were still suffering from persistent disabling daily headaches, with partial or poor response to acute medications [28]. A larger study with 9 months of follow-up reported that patients suffering from persistent headache after 9 months showed some clinical characteristics such as being older, more frequently female, having less frequent pneumonia, milder headache, and more likely have a throbbing quality of headache. Photophobia/phonophobia and worsening by physical activity were also more common, but pressing quality of pain was less commonly observed in these patients [40]. It is remarkable that the presence of migrainous features at the baseline was more frequently related to persistent headaches after acute COVID-19, and 16% of patients with acute-onset COVID-19-related headache might still suffer from ongoing headaches after 9 months [40].

In patients who develop "de novo" headache after COVID-19 (mostly manifesting with a migraine phenotype), headache resolves within 1 month in 56.3%, whereas in the rest, it might be continuous up to 3 months. There is no difference of headache as a post-COVID symptom between hospitalized and non-hospitalized patient groups [39].

## 5.7 The Need for New Criteria to Focus on COVID-19-Related Headache in the International Classification of Headache Disorders-3

COVID-19-related headache is a global healthcare problem at the moment, both in the acute and other phases of the infection, with a serious disability potential [11, 31]. Due to its unique characteristics, high frequency, and potential to highlight the underlying mechanisms of viral infection-related headaches, COVID-19 headache deserves a separate subheading in ICHD-3 classification, apart from the highly nonspecific title of acute headache attributed to systemic viral infection (code 9.2.2.1).

For this purpose, we have proposed a set of preliminary criteria to guide the clinicians working in the field and dealing with COVID-19-related headaches [37] (Table 5.2).

For this important headache, bilateral location, longer duration, and poor response to analgesics combined with frequent anosmia and ageusia are the keystones of the proposed criteria. Headache might be new emerging or should have different characteristics from the previous headache attacks. Besides, a causative temporal relationship with an established COVID-19 diagnosis is a prerequisite for the definition.

**Table 5.2** Proposed ICHD-3 criteria for COVID-19-related headaches[a] (Headache attributed to COVID-19)[a]

| |
|---|
| (A) The presence of a headache fulfilling all of the below criteria in C |
| (B) The presence of a laboratory confirmed COVID-19 as the causative disorder (PCR or IG evidence) |
| (C) Evidence of causation demonstrated by all of the following: |
| (1) Headache has developed in temporal relation to the onset of COVID-19 (−2 + 9 days) |
| a. Either new emerging headache |
| b. New emerging headache has different characteristics in a patient with a known/diagnosed type of primary headache |
| (2) It resolves in 1 month in parallel with clinical and laboratory improvement (di-dimer, etc.) |
| (3) Headache has at least two of the following characteristics |
| a. Bilateral (frontal or frontotemporal location predominant) |
| b. Long-lasting (>48 h) |
| c. Resistant to simple analgesics (or to previously successful drugs for primary headache sufferers) |
| d. Association with ageusia/anosmia |
| (D) Not better accounted for by another ICHD-3 diagnosis |

[a] *with Editors permission adapted from Baykan B.* et al. *Urgent Need for ICHD Criteria for COVID-19-Related Headache: Scrutinized Classification Opens the Way for Research. Noro Psikiyatr Ars. 2021 Mar 8;58(1):79–80*

The information related to the pathophysiological basis of COVID-19 headache is still scarce, though there are several proposed hypotheses. Invasion of peripheral trigeminal nerve endings by the SARS-CoV-2 both directly and through the vasculopathy by involvement of endothelial cells (with high expression of ACE2) and release of pro-inflammatory mediators and cytokines triggering perivascular trigeminal nerve endings are some of these proposed mechanisms [17]. We believe this topic requires further focused and in-depth studies, and establishing a standard set of criteria for COVID-19-related headache might open the way for further appropriately designed scientific research.

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# Chapter 6
# Secondary Headache Disorders Attributed to COVID-19 Complications


**Hamit Genç and Derya Uludüz**

## 6.1 Introduction

The clinical presentation of COVID-19 is heterogeneous with a wide range of symptoms and diseases observed and can continue even months after the onset [1]. Neurological manifestation of COVID-19 can be scrutinized in three categories: central nervous system (CNS) (headache, dizziness, encephalopathy, seizure, cerebrovascular disease), peripheral nervous system (PNS) (anosmia, ageusia, visual impairment, neuropathic pain, Guillain-Barré syndrome, and its variants), and skeletal muscle damage [2]. Neurological complications during the viral invasion may occur due to hypoxia, systemic inflammatory process, postviral immune-mediated complications, and vascular complications [3].

Headache is deemed the most common and sometimes the first neurological presentation of the disease [1, 4]. It is estimated that there is a fivefold increase in headaches in the regions affected by the COVID-19 pandemic [5]. Headache frequencies are variable and were observed at 25.2% in a meta-analysis of 104,751 infected patients [6]. Headache in early stages can be attributed to excessive secretion of pro-inflammatory mediators and cytokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α) [7]. The release of these pro-inflammatory mediators and cytokines may activate perivascular trigeminal nerve terminations during COVID-19 infection [8]. Headache may also occur due to overstimulation of the trigeminovascular system with inflammation in the endothelial cells of the vessel wall due to the direct invasion of peripheral trigeminal nerve terminations in the nasal cavity. Overactivation of those angiotensin-converting enzyme 2 (ACE2)

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receptors, nitric oxide (NO), and calcitonin gene-related peptide (CGRP) release resulting from hypoxia, cortical spreading depression, and disruption of the blood-brain barrier (BBB) are other possible pathophysiological mechanisms [9].

Headache, anosmia, and ageusia generally appear in the early stages of the symptomatic phase (within 1–2 days on average) and are more common in less severe cases [10]. Anosmia-ageusia with headache in the acute phase is the primary indicator of COVID-19; it is observed at a rate of 74.5% in COVID-19-positive patients [11]. This relationship of anosmia and ageusia with headache and their emergence in similar periods suggests that there may be common underlying pathophysiological mechanisms. It has been hypothesized that SARS-CoV-2 has neurotrophic properties and can flood peripheral nerve endings and penetrate the central nervous system by transsynaptic paths. The anatomical structure of the trigeminal nerve branches is thought to provide a path between the nasal epithelium and the central nervous system. This may explain the anosmia complaints seen in COVID-19 [12]. Another issue suggestive of the neurotropism of COVID-19 is the frequency of phonophobia in headache patients [10]. Researchers reported phonophobia in up to 67% of COVID-19-positive patients with headache, particularly in patients with hyposmia/anosmia and hypogeusia/ageusia [10, 11, 13].

## 6.2 Primary Headache Subtypes Observed in COVID-19 Patients

Headache was the most widespread symptom, along with anosmia in a meta-analysis of 1420 mild-to-moderate COVID-19 patients. The prevalence of pain was higher in women, young people, and those with a previous history of headache [14]. Headache attributed to COVID-19 was observed less frequently in men and older patients [13, 15]. Genetic, hormonal, and psychosocial dissimilarities can explain potential causes for disparity between the sexes range [16].

The type of headache observed in the acute period in patients with COVID-19 is generally tension-type headache (TTH) (17.1–64%) [10, 11, 13]. **Migraine** (14–36.3%) [10, 11, 13, 17], **primary cough headache** (5.4%) [10], **headache secondary to systemic viral infection** [17], **cluster headache** [18], and **trigeminal and occipital neuralgia** [1] are other types of headaches in COVID-19. Migraine-like and TTH-like pain have also been reported in some studies (Table 6.1) [10, 19]. Pain is generally mild-to-moderate severity (47–75.2%) [10, 11, 13], bilaterally located (88.9–94%) [10, 13], and pulsatile (50.9–58.7) [10, 11, 13]. The mean onset time of headache is 1.7 days; pain continues for an average of 2–4 days [13], but 15% of patients had persistent headache lasting at least 15 days. In patients whose headache is not steady, attacks proceed for an average of 120 minutes [10]. 44.3–64% of patients have a previous history of headaches [10, 11, 20]. The pain intensity was severe in 23.4–53% of patients [10, 11, 13] and very intense in 2.3% [11], and pain influenced 52.8% of daily activities [21].

**Table 6.1** Headache types can be observed due to COVID-19 disease

| |
|---|
| *Primary headaches* |
| *Tension-type headache [10, 11, 13] |
| *Migraine [10, 11, 13, 17] |
| *Probable tension-type headache [10, 19] |
| *Probable migraine [10, 19] |
| *Cluster headache [18] |
| *Trigeminal neuralgia [1] |
| *Occipital neuralgia [1] |
| *Primary cough headache [10, 15] |
| *New daily persistent headache (NPDH) [19] |
| *External-pressure headache [23] |
| *Possible secondary headaches attributed to COVID-19 complications* |
| *Headache-related COVID-19 (headache attributed to systemic viral infection) [17, 23] |
| *Headache attributed to increased cerebrospinal fluid (CSF) pressure [23] |
| *Headache attributed to low CSF pressure [23] |
| *Headache attributed to intracranial hypertension secondary to metabolic, toxic, or hormonal causes [20, 23, 25] |
| *Headache attributed to hypoxia and/or hypercapnia [23, 34] |
| #Headache attributed to psychiatric disorder [23] |
| #Headache attributed to depressive disorder [37, 38] |
| #Headache attributed to panic disorder [38] |
| #Headache attributed to generalized anxiety disorder [38] |
| #Headache attributed to posttraumatic stress disorder [50] |
| *Headache attributed to substance withdrawal [23, 53] |
| *Headache attributed to hypertensive encephalopathy [23, 56] |
| *Headache attributed to viral meningitis or encephalitis [23, 58] |
| *Headache attributed to acute rhinosinusitis [60, 61] |
| *Headache attributed to reversible cerebral vasoconstriction syndrome [63] |
| *Acute headache attributed to non-traumatic subarachnoid hemorrhage [65] |
| *Headache attributed to cerebral venous thrombosis [67, 68] |
| *Headache attributed to pituitary apoplexy [69, 70] |
| #Headache attributed to other metabolic or systemic disorder [20, 25] |
| *Headache attributed to secondary angiitis of the central nervous system [73] |
| *Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure [74] |
| *Headache attributed to the occasional use of non-headache medication [75] |
| *Painful optic neuritis [76] |
| *Newly defined* |
| Headache attributed to personal protection equipment (PPE) [28] |
| **Please see ICHD-3 criteria*<br>*#Please see appendix of ICHD-3 criteria* |

## 6.3 Other Primary Headache Subtypes

### *6.3.1 Primary Cough Headache*

The authors have classified headaches due to COVID-19 in two stages of the disease. In phase I (the influenza-like phase), it is seen as **acute headache attributed to systemic viral infection**, **primary cough headache**, **tension-type headache**, and **headache attributed to heterophoria**. In phase II (the cytokine storm phase), **headache attributed to hypoxia** and **new-onset headache** occur (Table 6.1) [15]. Cough headaches are too common in men and people over 40. Cough triggers headaches in COVID-19 patients who have previously had migraine or tension-type headaches. Secondary outcomes of cytokine release syndrome (CRS) in COVID-19 may be responsible for the underlying pathophysiologies and boost other inflammatory markers, such as D-dimer and CGRP, which play a position in headache [20]. CGRP is a neuropeptide with an essential position in migraine pathophysiology and has a suspicious connection to transient receptor potential (TRP) channels [22]. Possible viral activation of TRP channels is implicated in anosmia, cough, and gastrointestinal disturbances in patients with COVID-19. This activation then results in the release of CGRP in some patients. Releasing of CGRP is thought to facilitate the T cell response toward a more pro-inflammatory state characterized by Th17 and IL-17 [20]. In patients with cough-triggered headache, possible intracranial lesions such as middle cranial fossa or posterior fossa tumors, midbrain cyst, reversible cerebral vasoconstriction syndrome, subdural hematoma, cerebral aneurysms, Arnold Chiari malformation type 1, spontaneous intracranial hypotension, carotid or vertebrobasilar diseases, basilar impression, and platybasia must be ruled out [23]. However, it led to diagnostic limitations as COVID-19 protocols for imaging have increased the magnetic resonance imaging (MRI) threshold in the studies [24]. Although there is not enough data, the headache types of some patients may be "headache attributed to increased cerebrospinal fluid (CSF) pressure" or "Headache attributed to low CSF pressure," according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria (Table 6.1) [23]. Considering the hypoxic, toxic, and metabolic disorders that COVID-19 may cause in patients, headache in these patients should be evaluated in terms of "headache attributed to intracranial hypertension secondary to metabolic, toxic, or hormonal cause" (Table 6.1) [20, 23, 25].

### *6.3.2 New Daily Persistent Headache (NPDH)*

**NDPH** is a primary headache belonging to the chronic daily headache (CDH) group, characterized as a marked and clearly remembered beginning, becoming continuous, and lasting pain within 24 hours and permanent for over 3 months [23]. Various triggers associated with NDPH have been reported, such as most commonly

recent infection episodes or stressful life events [26]. Persistent headache that develops during or after acute infection and persists after the resolution of the disease remains relatively common, suggesting that infection triggers the development of NDPH [27]. 12.6–39.1% of COVID-19 patients have new-onset headaches [7–9], and 10% have headaches lasting longer than 3 months [21]. Persistent headaches at rates of 60.7% after an acute episode of COVID-19 have been reported, and some of these also met the NPDH diagnostic criteria (Table 6.1) [19].

### *6.3.3 External-Pressure Headache/Personal Protection Equipment (PPE) Headache*

Ong et al. described a new type of **PPE-related headache** in staff working in COVID-19 services (Table 6.1). This survey-based study found de novo PPE-related headaches in 81% of the participants. It was also stated that preexisting headaches, especially migraines, were exacerbated in some patients [28]. It was confined that this was due to prolonged mask usage that touches the scalp or using a double mask. Some masks may cause breathing difficulties, especially during periods of exertion [29]. Furthermore, factors such as mechanical squeeze triggered by PPE, hypoxemia, and hypercarbia are other factors responsible for the pathogenesis of headache [28]. Considering the mechanical pressure and compression caused by PPE, occasionally headaches in these patients are classified as "external-pressure headache" according to ICHD-3 criteria (Table 6.1) [23]. However, patients were not evaluated for this concern in studies. For PPEs, it has been suggested that it can initiate neural activity by stimulating trigeminal and occipital nerve terminations through compression and peripheral sensation [28]. In a study, the higher frequency of allodynia in patients with worsening migraine seems to support this [29]. When we consider the role of trigeminovascular system activation in the pathophysiology of migraine, we can think that PPEs may lead to migraine activation [30]. Besides, it has been reported that the use of disinfectants in patients with osmophobia is one of the reasons for deteriorating migraine attacks [29].

## 6.4 Secondary Headache Subtypes Observed in COVID-19 Patients

### *6.4.1 Systemic Viral Infection and Headache*

While 78.5–85.2% of the patients reported pain different from the pain they had experienced before [10, 11, 13, 21], 12.6–25.7% developed de novo pain [10, 13]. It is emphasized that headache is 1.7–2.2 times more common in COVID-19 patients than other non-COVID-19 viral infections (other respiratory viral infections) [6].

Thus, some studies have investigated the characteristics of headache attributed to COVID-19. The most striking features of headache are these: usually on bilateral frontal and temporal localization; sudden and gradual onset; lasting longer than 72 h; an intermittent, mild, and vague type of pain; mainly during night period; resistant to analgesics; exacerbated by exercise and coughing; relieved by sleep; and high recurrence rate limited to the active phase of COVID-19 [9, 24]. Another study evaluated the distinctive variants of headache attributed to COVID-19, bilateral localization, duration over 72 h, male gender, analgesic resistance, gastrointestinal symptoms, and presence of anosmia/ageusia; factors that increase the hazard of headache due to COVID-19 infection were emphasized [31]. No relationship between headache and Valsalva maneuvers was found except for exercise and coughing [17]. Pain may be accompanied by nausea and vomiting, photophobia, phonophobia, osmophobia, and allodynia, but trigeminal autonomic symptoms are infrequent [10, 11, 13, 17]. This different pain phenotype attributed to COVID-19 may correspond to the diagnosis of **acute or chronic headache attributed to systemic viral infection**, according to the ICHD-3 criteria (Table 6.1) [17, 23]. The precise mechanisms of headache attributed to systemic infection have not yet been thoroughly studied. Nevertheless, it may occur due to fever and exogenous or endogenous pyrogens, direct effects of microorganisms, and activation of various immunoinflammatory mediators [32].

### *6.4.2 Hypoxia/Hypercapnia and Headache*

In severe cases of COVID-19, patients have severe dyspnea and hypoxemia and require an intensive care unit. Cardiovascular diseases, hypertension, diabetes mellitus, chronic lung disorder, systemic malignancies, and chronic renal failure are comorbid conditions monitored [33]. Headache secondary to hypoxemia developing in alveolar tissues may occur during COVID-19 infection **(headache attributed to hypoxia and/or hypercapnia)** (Table 6.1) [23, 34]**.** Hypoxia to ischemia and ischemia may also lead to headache by increasing free radicals [34, 35]. However, headache characteristics of patients have not been adequately questioned in studies. This may be because most studies have focused on COVID-19 symptoms in general, and the frequency of headaches has been underestimated because of respiratory symptoms that cause patients to be hospitalized most frequently [10].

### *6.4.3 Psychiatric Disorders and Headache*

The lack of treatment, uncertainty in the process, fear of death, social isolation, and economic problems, especially in the initial phases of the COVID-19 pandemic, have led to an increased incidence of psychiatric disorders such as panic, anxiety, and depression [36]. Perlis et al. found that the prevalence of these symptoms among COVID-19 patients was 52.4%, and the existence of headache was more highly

associated with moderate or severe depressive symptoms [37]. In another study, researchers reported that the probability of anxiety disorder and depression increased 2.2–4 times in patients with headache, especially in individuals with migraine and chronic TTH, compared to healthy controls [38]. Individuals with migraine may experience intense anxiety and are more likely to commit suicide [39]. Although it has not been studied in detail, headache types in these patients may fit classifications as "headache attributed to depressive disorder," "headache attributed to panic disorder," and "headache attributed to generalized anxiety disorder" according to the ICHD-3 criteria (Table 6.1) [23]. It is unclear whether the psychiatric symptoms are due to the psychosocial problems caused by the pandemic or to the direct effects of the virus on the central nervous system [40]. Mental stress, intense anxiety, and lifestyle modifications are likely causes of headaches [41]. In addition, the ongoing neuroinflammation and cytokine release in COVID-19 can affect the metabolism of neurotransmitters such as serotonin, dopamine, and glutamate through synthesis, release, and reuptake [42]. As a result, any neurotransmitter deterioration may lead to psychiatric symptoms. Disease severity, hospitalization, previous mental disorders, female gender, infected individuals in the family, post-infection physical pain, and raised inflammatory markers play a vital role in developing depression and anxiety in COVID-19 patients [43, 44].

Another common psychiatric disorder in recovering COVID-19 patients is posttraumatic stress disorder (PTSD) [44]. PTSD is characterized by severe anxiety, flashbacks, nightmares, and emotional numbness following a typically traumatic event, such as death, grave violence, sexual or physical attack, or a fight. Fear of pain is hypothesized to contribute significantly to the development of chronic pain. Augmented anxiety, fear, and stress increase perceived pain intensity and decrease pain tolerance [45]. PTSD seems more in those with severe respiratory distress than those without respiratory symptoms [46]. This shows that hypoxemia may also have an effect in addition to the aforementioned pathophysiological mechanisms that can cause psychiatric symptoms [47]. The incidence of PTSD among COVID-19 patients ranged from 20% to 30% [48]. A study is demonstrated that young age, gender, obesity, severe respiratory symptoms, and comorbid psychiatric condition lead to hospitalization and intensive care unit care as risk factors [49]. Persistent symptoms such as headache, anosmia, fatigue, shortness of breath, sleep problems, chest ache, cough, and mental health problems that can be observed after COVID-19 substantially impact the quality of life caused by PTSD [50]. Therefore, patients who develop a headache after COVID-19 should also be evaluated in terms of "headache attributed to posttraumatic stress disorder" according to ICHD-3 criteria (Table 6.1) [23].

### *6.4.4 Substance Withdrawal and Headache*

Illicit substances, particularly opioids, seriously impair lung function by reducing immune function [51]. COVID-19 patients with comorbid substance abuse disorder had a higher rate of hospitalization and death than patients without a history of

substance abuse [52]. Isolation practices and restrictions, especially in the pandemic's early stages, led to an inability to obtain addictive substances in this group of patients and the subsequent emergence of alarming withdrawal symptoms in these patients [53]. COVID-19-positive patients with headache and a history of substance use should be evaluated in terms of "headache attributed to substance withdrawal" according to the ICHD-3 criteria (Table 6.1). However, there is insufficient information in the literature.

### 6.4.5 Encephalopathy and Headache

*Encephalopathy* is a change in one or more brain functions such as altered consciousness, confusion, seizures, and acute focal disorders caused by systemic disease and is typically reversible. A study detected headache and encephalopathy in 40% of COVID-19 patients, but the particulars and diagnostic criteria are not disclosed [4]. Saniasiaya and Kulasegarah suggested that headache may occur due to mechanisms such as inflammation in neural nerves, hypoxia, hypercoagulopathy, and re-exposure of the brain to the pathogen [54]. Although encephalopathy is reversible, it can be prolonged in severe COVID-19 patients and is a risk factor for poor outcomes. In patients with encephalopathy, there is no evidence of brain inflammation shown on imaging or CSF. Patients who developed unexplained encephalopathic features showed leptomeningeal enhancement on brain MRI (62%), perfusion abnormalities on MRI (100%), and ischemic cerebrovascular attack (23%) [55].

Posterior reversible leukoencephalopathy (PRES) is a potential neurological complication associated with COVID-19 characterized by headache, altered consciousness, visual impairment, and seizures (according to ICHD-3 criteria, "headache attributed to hypertensive encephalopathy") (Table 6.1). The cytokine storm of COVID-19 can cause endothelial dysfunction leading to increased permeability of the BBB and sensitization to blood pressure changes [56]. Renal failure may be another explanation because renal failure is a familiar complication associated with critically ill patients with COVID-19 [57]. Compared with other etiologies, there are higher bleeding rates in neuroimaging cases of PRES due to COVID-19 [56].

### 6.4.6 Viral Meningitis/Encephalitis and Headache

Intracranial infections in COVID-19 patients are reported very seldom. Clinically, it may present as encephalitis, meningoencephalitis, or meningitis. According to ICHD-3 criteria, "headache attributed to viral meningitis or encephalitis" should be suspected when symptoms of fever, neck stiffness, light sensitivity, and nausea and/or vomiting are observed in COVID-19 patients (Table 6.1). Meningitis and/or

encephalitis diagnosis can be confirmed through histology studies or findings of inflammatory cells in the CSF. The genetic material of SARS-CoV-2 was found in the CSF of a patient with clinical meningoencephalitis [58]. This suggests that COVID-19 may lead to a direct central nervous system infection. Underlying pathophysiological mechanisms are developing cytokine release after SARS-CoV-2 infection and secondary of this disruption of the BBB and injury to the brain parenchyma [59].

Another recently reported secondary infection is rhino-orbital mucormycosis, a deadly angio-invasive disease caused by mold fungi such as *Rhizopus*, *Mucor*, *Rhizomucor*, and *Cunninghamella* and usually affecting immunocompromised patients. Diabetes mellitus (DM) and corticosteroids appear to be risk elements, because there was DM in 80% of cases. Also, 76.3% of mucormycosis and COVID-19 patients used corticosteroids as treatment [60]. One study suggested that patients with both head and face pain should be suspected of mucormycosis [61]. This type of pain can be examined under the subtitle "headache attributed to acute rhinosinusitis" according to ICHD-3 criteria (Table 6.1).

### *6.4.7 Subarachnoid Hemorrhage/Reversible Vasoconstriction Syndrome and Headache*

Reversible vasoconstriction syndrome (RVCS) is one of the rare neurological complications of COVID-19. COVID-19 does not directly cause global or segmental vasoconstriction. However, downregulation of ACE2 receptors leads to overactivation of the classical renin-angiotensin axis, resulting in vasoconstriction and/or sympathetic hypertonia of cerebral vessels [62]. RCVS can lead to complications such as seizures, ischemic stroke, intracerebral hemorrhage, PRES, and convexity subarachnoid hemorrhage (cSAH). Recurrent thunderclap headaches are typical for RCVS. In a study, it was emphasized that even in the mild course of COVID-19, especially in young patients, recurrent headaches and thunder headaches should be a warning that it is a typical symptom of RCVS [63]. This headache is evaluated under the subtitle "headache attributed to reversible cerebral vasoconstriction syndrome" according to ICHD-3 criteria (Table 6.1).

Intracranial hemorrhage is infrequent in patients with COVID-19 [64]. It was observed as the second common finding in neuroimaging studies in patients with neurological involvement with COVID-19 [65]. Intracranial hemorrhage is commonly associated with risk factors such as arterial hypertension and anticoagulation therapy [64]. A higher incidence of aneurysmal SAH is suspected in patients with COVID-19 [65]. Acute onset of thunderclap headache is typical for SAH, which is classified as an "Acute headache attributed to non-traumatic subarachnoid hemorrhage" according to the ICHD-3 criteria (Table 6.1). The pain has been reported to be holocephalic and progressive in a few cases [63, 65]. It may present a complication of RVCS, especially in patients younger than 60 years of age, and is usually localized at the level of convexity.

### 6.4.8 Stroke/Cerebral Venous Sinus Thrombosis and Headache

The most common types of acute stroke are ischemic and hemorrhagic. Ischemic stroke is probably the most common type of stroke [66]. Cerebral venous sinus thrombosis (CVST) is 0.08% in hospitalized patients infected with COVID-19, accounting for 4.2% of all cerebrovascular events in the context of COVID-19 infection. CVST evolves within 1–8 weeks after respiratory or systemic symptoms of SARS-CoV-2 infection [67]. Systemic inflammation, cytokine release, direct immune-mediated postinfectious mechanism, and endotheliitis may cause arterial and venous thrombosis in COVID-19 patients [56]. All CVST cases have been reported in individuals with headache **(headache attributed to cerebral venous thrombosis according to ICHD-3)** (Table 6.1) [23, 68]. With the presence of headache, seizures, focal neurological signs, encephalopathy, or mental status change in the acute and subacute stage of COVID-19, CVST should be suspected, and intracerebral vascular imaging (e.g., CT or MR venography) should be performed. As CVST is one of the few causes of cerebral hemorrhage needing anticoagulation therapy, diagnostic confidence is essential to initiate proper treatment.

### 6.4.9 Pituitary Apoplexy and Headache

Pituitary apoplexy is a rare disorder resulting from ischemia or bleeding in a pituitary adenoma or, infrequently, a physiologically enlarged pituitary gland. It is observed in roughly 2–12% of all patients with pituitary adenoma. Pituitary apoplexy usually presents with a sudden onset of severe headache. Rapidly progressive visual disturbances, nausea, pituitary hormone lacks, and intracranial hypertension symptoms can follow headaches. Pituitary apoplexy has been reported in a few cases of COVID-19 [69, 70]. Taneja et al. also described ischemic pituitary apoplexy in a 74-year-old female patient who presented with acute and new-onset, very painful (the most excruciating pain in her life) headache accompanied by nausea and vomiting [70]. The acute-onset, severe headache described in these cases is classified as a "headache attributed to pituitary apoplexy" according to the ICHD-3 criteria (Table 6.1). SARS-CoV-2 can precipitate pituitary infarction and/or hemorrhage, combined with overstimulation of the pituitary gland, and influence the coagulation cascade by provoking thrombocytopenia and platelet dysfunction in the setting of acute infection [71].

### 6.4.10 Metabolic or Systemic Disorders and Headache

Headache in SARS-CoV-2 infection may occur as a result of more general indirect mechanisms that are not specific to the disease, including hypoxia, dehydration, systemic inflammation, and metabolic disorders [20]. This situation can be

evaluated under the subtitle of "headache attributed to other metabolic or systemic disorder" according to the ICHD-3 criteria (Table 6.1). Systemic metabolic changes, such as fluid and electrolyte imbalance, hormonal dysfunction, and accumulation of toxic metabolites, reduce cerebral perfusion. It may cause some nonspecific neurological presentations of the disease such as headache, confusion, and agitation [25]. The autopsy examinations of brain tissue performed in patients who died from acute COVID-19 determined that they had serious diseases and that most had systemic and metabolic disorders that were not specific to pathology before death [72].

### *6.4.11 Other Complications and Headache*

CNS angiitis can occur due to some conditions such as inflammatory, infectious, malignant, or toxic. Headache is the dominant symptom in the patients, but CNS angiitis has no specific features [23]. CNS angiitis secondary to COVID-19 was reported in a 28-year-old man who presented with intense headache, dysarthria, and deviation of lip rhyme to the left (headache attributed to secondary angiitis of the central nervous system according to ICHD-3) (Table 6.1) [23, 73].

In addition, the prevalence of Bell's palsy in patients infected with SARS-CoV-2 was found to be 0.08%, and recurrence was 8.6% in those diagnosed with Bell's palsy before infection [77]. In one case, left retro-auricular pain and taste perversion with facial paralysis on the left side in a patient infected with SARS-CoV-2 have been reported **(headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure according to ICHD-3 appendix criteria)** (Table 6.1) [23, 74].

Another point that is neglected when evaluating headaches secondary to COVID-19 complications is that, although rare, headache can be seen as a side effect of drugs used in the treatment **(headache attributed to the occasional use of non-headache medication according to ICHD-3)** (Table 6.1). Headache can be observed in patients at varying rates as a side effect of drugs such as ivermectin, azithromycin, remdesivir, posaconazole, and tocilizumab, which are used to manage complications and treat the infection [75].

Finally, cases of optic neuritis have been reported in some COVID-19-positive patients. 92.2% of optic neuritis patients have eye pain that worsens with eye movement **(painful optic neuritis according to ICHD-3)** (Table 6.1). However, there is no evidence of human coronaviruses' etiological role in acute monosymptomatic optic neuritis [76].

## 6.5 Conclusion

Headache is one of the most common neurological complications of the COVID-19 disease and may cause different pain phenotypes in patients in acute, subacute, and chronic phases. Headache, anosmia, and ageusia usually occur in the early stages of

the symptomatic phase of mild-moderate COVID-19. A systemic inflammatory process, hypoxia, vascular complications, and postviral immune-mediated complications can cause headaches in COVID-19-positive patients. The features of headache attributed to COVID-19 headache are usually bilateral frontal and temporal localization; showing sudden and gradual onset; lasting longer than 72 h; having an intermittent, mild, and vague type of pain; showing evening preference; being resistant to analgesics; exacerbated by exercise and coughing; relieved by sleep; and showing high recurrence rate limited to the active phase of COVID-19. Besides this, SARS-CoV-2 can also trigger some primary headache subtypes such as TTH and migraine. In the studies, while the headaches observed in the early period of the COVID-19 infection were well examined, headaches secondary to complications of COVID-19 observed in the later period of the disease have not been adequately investigated. Reasons for this are the following:

1. Preceding severe symptoms such as pulmonary and cardiac in patients than headache complaints
2. Inability of patients with encephalopathy to express headache, if any
3. Being the high threshold for advanced examinations such as neuroimaging and CSF analysis to minimize the risk of transmission, especially in the early period of the pandemic

Although some secondary headache subtypes can observe together with COVID-19 complications, the relationship between some complications of COVID-19 and headache is still not proven. Secondary headache disorders attributed to COVID-19 complications should be suspected in patients of the male gender, older age, acute onset, progressive and severe headache, a thunderclap headache, epileptic seizure, impaired consciousness, focal neurological deficit, and history of concomitant comorbid disease. In these patients, detailed medical history, neurological examination, and neuroimaging methods should be designed for the suspected diagnosis. Psychiatric complications of the disease should not be overlooked. Psychosocial rehabilitation should be provided by furnishing necessary consultations with appropriate individuals. In patients with severe COVID-19 infection, although the risk of headache secondary to COVID-19 complications is higher, it should be kept in mind that even mild-moderate COVID-19 disease may present with severe symptoms, and a complete neurological evaluation should be performed in all patients.

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# Chapter 7
# COVID-19 Vaccine-Related Headache


**Esme Ekizoglu and Mine Sezgin**

## 7.1 Introduction

Vaccination against coronavirus disease 2019 (COVID-19) has a crucial role to achieve population immunity and restrict the spread of the disastrous pandemic declared on March 2020. Vaccines are indeed one of the greatest triumphs of modern medicine and undoubtedly the most cost-effective lifesaving device in the history. Numerous vaccines against COVID-19 are still in clinical development, and some of them are currently in use. Although their safety and efficacy are well documented, randomized controlled trials and further clinical studies reported various systemic adverse reactions following vaccination [1]. Neurological side effects to SARS-CoV-2 vaccines are generally mild, short-lasting, self-limiting, and mostly manageable. Headache is reported as the most frequent neurological symptom seen after SARS-CoV-2 vaccination according to the available data [2]. Moreover, headache is an overlap symptom for COVID-19 and also for COVID-19 vaccination. Therefore, knowledge of characteristics of headache seen following vaccination seems to be crucial to differentiate vaccine-related headache from headache related to COVID-19 itself.

## 7.2 Mechanisms of Headache Related to Vaccination

Headache related to vaccination was reported so far with various types of viral vaccines at different rates: after adenovirus-vectored (AdV) Ebola virus vaccine in 46%, measles-mumps-rubella vaccine in 35%, and inactivated influenza vaccine in

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7–31.8% of the participants. It was also seen following vaccination against human papillomavirus and varicella-zoster virus [3, 4]. However, the mechanisms underlying vaccine-related headaches are not clearly illuminated.

To date, COVID-19 vaccines globally in use have one of the following technologies: viral vector-based, mRNA-based, DNA-based, whole inactivated virus, and protein subunit vaccines [5]. Numerous studies were performed to better understand the virus, and the S protein is the key target of the vaccines for SARS-CoV-2. Murine challenge models and also clinical trials detected potent humoral and cellular immune responses elicited by vaccines encoding S protein. Beside S protein, other proteins (M protein, N protein, non-structural proteins (nsps), and accessory proteins) may also serve as antigens [6].

There are several possible mechanisms underlying COVID-19 vaccine-related headache. A pro-inflammatory state occurring following vaccination, similar to that in COVID-19-related headache with high levels of pro-inflammatory cytokines, may have the predominant role [7]. Furthermore, fever accompanying more frequently COVID-19 vaccine-related headache may support the role of inflammation, leading to the development of vaccine-related headache. On the other hand, COVID-19 vaccines with inactivated virus include adjuvants, which may promote headache following vaccination. Although rare, vaccine-induced blood clotting events were also defined, and some vaccine-related secondary headache conditions were reported, which will be further presented in this chapter.

## 7.3 Frequency of Headache Related to COVID-19 Vaccines

Clinical trials revealed an acceptable safety profile with high antibody responses [8]. Post-authorization observational studies reported similar rates of adverse events with clinical trials. However, there were significant differences among vaccine platforms, and the dosage was closely related to the occurrence of headache as an adverse reaction (Tables 7.1 and 7.2) [5, 9, 10].

The pooled rates of systemic and local adverse events were found to be lower among inactivated vaccines (21.0%, 23.7%), protein subunit vaccines (22.3%, 33.0%), and DNA vaccines (29.3%, 39.5%), compared to mRNA vaccines (83.3%, 89.4%), non-replicating vector vaccines (66.3%, 55.9%), and virus-like particle vaccines (78.9%, 100.0%) [5]. Similar to these findings, headache was less reported in subjects vaccinated with inactivated virus, as well as all other types of side effects. This may be related to the mature technology, the mechanism, the alum-adjuvants, or other factors [9]. However, vaccine-related adverse events depend also on dosage. Regardless of the vaccine identity, subjects experienced more headache following the second dose of mRNA vaccines on both clinical trials and post-authorization studies [5]. The impact of the route of administration was also evaluated. A study

**Table 7.1** Frequency of headache based on data from clinical trials

| Vaccine platform | Vaccine type | Age, years | Number of subjects | Headache | RR |
|---|---|---|---|---|---|
| mRNA | BNT162b2 | 18–55 | Dose1: 2238<br>Dose 2: 2045 | Dose 1: 959 (42.9)<br>Dose 2: 1085 (53.1) | Dose 1: 1.2<br>Dose 2: 2.2 |
| | | ≥56 | Dose 1: 1802<br>Dose 2:1660 | Dose 1: 454 (25.2)<br>Dose 2: 647 (39.0) | Dose 1: 2.3<br>Dose 2: 2.8 |
| mRNA | mRNA-1273 | 18–64 | Dose 1: 11401<br>Dose 2: 10357 | Dose 1: 4031 (35.4)<br>Dose 2: 6500 (62.8) | Dose 1: 1.2<br>Dose 2: 12.6 |
| | | ≥65 | Dose 1: 3761<br>Dose 2: 3745 | Dose 1: 921 (24.5)<br>Dose 2: 1665 (46.4) | Dose 1: 1.3<br>Dose 2: 2.6 |
| Non-replicating viral vector | ChAdOx1-nCoV-19 | 18–55 | Dose 1:99;<br>Dose 2: 100 | Dose 1: 53 (53.5)<br>Dose 2: 28 (28) | – |
| | | ≥56 | Dose 1: 155<br>Dose 2: 153 | Dose 1: 50 (32.3)<br>Dose 2: 28 (18.3) | – |
| Non-replicating viral vector | Ad26.CoV2.S | 18–59 | Dose 1: 2036 | Dose 1: 905 (44.4) | Dose 1: 1.8 |
| | | ≥60 | Dose 1: 1320 | Dose 1: 401 (30.4) | Dose 1: 1.4 |
| Inactivated | CoronaVac | 18–59 | Dose 1: 6585<br>Dose 2: 5811 | Dose 1: 2049 (31.1)<br>Dose 2: 1399 (24.1) | Dose 1: 1<br>Dose 2: 1 |
| | | ≥60 | Dose 1: 149<br>Dose 2: 149 | Dose 1: 5 (3.4)<br>Dose 2: 4 (2.7) | Dose 1: 2.9<br>Dose 2: 0.7 |
| Protein subunit | NVX-CoV2373 | 18–59 | Dose 1: 139<br>Dose 2: 137 | Dose 1: 40 (28.7)<br>Dose 2: 68 (49.9) | Dose 1: 1.1<br>Dose 2: 3.4 |
| | | 60–84 | Dose 1: 116<br>Dose 2: 113 | Dose 1: 19 (16.4)<br>Dose 2: 6 (5) | Dose 1: 1.1<br>Dose 2: 0.5 |

evaluating the safety of an aerosolized form of adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults reported headache in 46 (35%) participants following vaccination, similar to other studies investigating viral vector based COVID-19 vaccines [11].

Interestingly, clinical trials showed that frequency of headache as well as other side effects decreased with age in all vaccine platforms. Binding-antibody levels were found to be low after COVID-19 vaccination in subjects older than 70 years, a finding that suggests lower immune responses in elderly, causing fewer adverse events [9].

However, findings based on the data of vaccines in real-world registries (VAERS) was somewhat surprising. Researchers exploring these big data, of 11,936 participants, found out lower rates of adverse events in the real world than those reported in clinical trials, and headache had the highest incidence (16.53%) among other adverse events [12]. In children, COVID-19 vaccines showed also good safety profiles according to VAERS reports, and mRNA vaccine-related headache was reported in only 13.9% and 19.8% of the children, being more frequent following second dose than the first dose [13].

**Table 7.2** Frequency of headache reported in post-authorization active surveillance studies among the general population

| Vaccine platform | Vaccine type | Study group | Number of subjects | Age, years | Headache |
|---|---|---|---|---|---|
| mRNA | BNT162b2 | GP | Dose 1: 1659724 Dose 2: 971375 | ≥16 | Dose 1: 409359 (24.7%) Dose 2: 392266 (40.4%) |
| mRNA | mRNA-1273 | GP | Dose 1: 1984194 Dose 2: 949497 | ≥18 | Dose 1: 534248 (26.9%) Dose 2: 504739 (53.2%) |
| mRNA | BNT162b2 | GP | Dose 1: 282103 Dose 2: 28207 | Dose 1: Median 64 Dose 2: Median 59 | Dose 1: 21910 (7.8%) Dose 2: 3731 (13.2%) |
| mRNA | BNT162b2 | HWs | 277 | 20–69 | 67 (24.2%) |
| mRNA | BNT162b2 | HWs | 80 | 35.83 ± 10.99 (mean ± SD) | 6 (7.5%) |
| mRNA | BNT162b2 | HWs | 52 | ≥19 | 15 (28.8%) |
| Non-replicating viral vector | Gam-COVID-Vac | GP | Dose 1: 2558 Dose 2: 1288 | 18–89 | Dose 1: 473 (18.5%) Dose 2: 282 (21.9%) |
| Non-replicating viral vector | ChAdOx1 nCoV-19 | GP | 345,280 | Median: 65 | 78,734 (22.8%) |
| Non-replicating viral vector | ChAdOx1 nCoV-19 | HWs | 5589 | 20-69 | 3887 (69.5%) |
| Non-replicating viral vector | ChAdOx1 nCoV-19 | HWs | 2005 | NA | 870 (43.4%) |
| Non-replicating viral vector | ChAdOx1 nCoV-19 | HWs | 1403 | 35.84 ± 11.13 (mean ± SD) | 726 (50.7%) |
| Non-replicating viral vector | ChAdOx1 nCoV-19 | HWs | 1639 | Median: 32 | 807 (49.2%) |
| Non-replicating viral vector | ChAdOx1 nCoV-19 | HWs | 2426 | ≥19 | 1747 (72.0%) |
| Inactivated | CoronaVac | HWs | Dose 1: 1526 Dose 2: 1397 | Dose 1: 35.4 ± 8.9 (mean ± SD) Dose 2: NA | Dose 1: 92 (6.0%) Dose 2: 48 (3.4%) |
| Inactivated | BBIBP-CorV | HWs | 4458 | NA | 8 (0.18%) |
| Inactivated | CoronaVac | HWs | 1819 | ≥18 | Dose 1: 244 (43.9%) Dose 2: 139 (25%) |

*GP* General population, *HWs* healthcare workers

## 7.4 Clinical Features of Headache Following Vaccination with COVID-19 Vaccines

To date, few studies focused on headache following COVID-19 vaccines and evaluated in detail clinical characteristics of headache. Headache starts within 24–48 h after the vaccine injection and resolves spontaneously and lasts less than 24 h, in the majority of cases. However, long-lasting headaches following vaccination are also reported. A multicenter observational study showed that headache started within 24 h after vaccination in 80% and lasted less than 22 h in 80% and more than 36 h in only 10% of the participants vaccinated with mRNA vaccine. Interestingly, headache occurred in multiple episodes in one third of the subjects [14]. Another study showed that the latency from vaccination to the occurrence of headaches was 18 h with a duration of 14 h on average [2]. In a survey study addressing healthcare workers, temporal characteristics of headache related to inactivated virus vaccine showed moderate differences from those of the headache related to mRNA vaccine. The headache occurred 1.8 ± 3.5 (median, 1; IQR, 0–2) days later after vaccination and lasted less than 24 h in 61.1% and more than 3 days in 25.9% of the subjects. However, it was overall shorter than COVID-19-related headache experienced by the same population [10].

In subjects having migraine, headache attacks began within the first 24 h of vaccine in the half of the participants following mRNA or DNA viral vector vaccines administration. These attacks lasted more than 24 h up to 7 days in 46.1% of the migraineurs [15]. It seems reasonable to suggest that COVID-19 vaccine-related headache potentiates migraine pathways and causes longer duration of attacks.

Although there are cases perceiving mild or very severe headache following vaccination, the severity of vaccine-related headache seems to be predominantly moderate. COVID-19 vaccine-related headache was less severe than COVID-19-related headache and migraine pain, whereas it was more severe than tension-type headache attacks in healthcare workers who received inactivated virus vaccine [10]. Studies investigating mRNA vaccine-related headache disclosed that the headache was moderate in nearly half of the cases (in 46.2% of the subjects). However, the pain affected routine physical activity in 42.8% of all study group [14]. A study focusing the effects of COVID-19 vaccines in migraineurs found that the character of headache following vaccination was different from migraine attacks and pain intensity was higher in more than half of the participants [15]. The severity of headache was also related to dosage; a higher severity following the second dose of the mRNA vaccine compared to the first one and between the first dose of the AdV vaccine and the second dose of the mRNA vaccine was observed [16].

The rates of areal location of the headache showed more or less a similar distribution on frontal and temporal areas and at the back of the head (38%, 32%, 23%, respectively) [14]. COVID-19 inactivated virus vaccine-related headache was mostly bilateral (70%) similar to the location of tension-type headache and contrary to migraine attacks in the same population [10]. Headache following mRNA vaccine was also bilateral in most of the participants (73.1%). Studies investigating

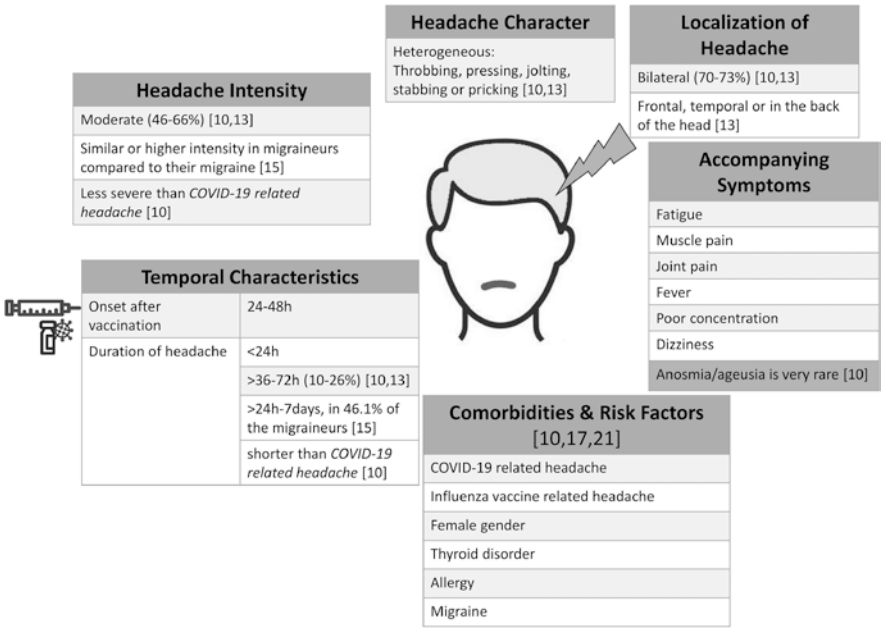


**Fig. 7.1** Clinical features associated with COVID-19 vaccine-related headache

subjects who received mRNA or inactivated virus vaccines reported heterogeneous headache characters. It was mostly pressing in mRNA vaccine group, whereas mostly throbbing in inactivated virus vaccine group [10, 14]. Furthermore, symptoms such as fatigue, muscle pain, joint pain, or fever were found to be associated with COVID-19 vaccine-related headache [10, 14, 15]. Poor concentration and dizziness were also observed in cases with headache following vaccination [14], whereas sensitivity to noise, light, or odors typical for migraine was less frequently reported by vaccinees receiving mRNA or inactivated virus vaccines [10, 14]. Moreover, anosmia or ageusia, typical symptoms for COVID-19-related headache, accompanied rarely vaccine-related headache [10]. Clinical features associated with COVID-19 vaccine-related headache are given in Fig. 7.1.

## 7.5 Comorbidities and Immunization History

Preexisting primary headache disorders like migraine or tension-type headache were also found to be more often present in cases having COVID-19 vaccine-related headache after either mRNA or inactivated virus vaccines [10, 14]. The duration of headache after vaccination was also significantly longer and more severe in subjects with migraine than those without this disorder [14]. Other diseases such as thyroid, pancreas, pulmonary, and vascular disorders showed also significant association

with vaccine-related headache [10, 14]. Furthermore, severe COVID-19 and COVID-19-related headache were reported more frequently in the group experiencing COVID-19 vaccine-related headache when compared to those without COVID-19 vaccine-related headache in healthcare workers [10]. Moreover, history of headache following other types of vaccines such as influenza vaccine was found to be a risk factor increasing 4.8-fold (CI, 2.84–8.23) the risk for experiencing COVID-19 inactivated virus vaccine-related headache [10].

## 7.6 Gender Differences and Headache Characteristics in Specific Subpopulations

Even though headache related to COVID-19 itself showed a male predilection, significant female dominance was found in subjects experiencing inactivated virus or mRNA vaccine-related headache [10, 17]. Moreover, women had a more severe headache in comparison to men. However, a gender difference in terms of the latency and the duration of headache was not notified [14]. On the other hand, this significant difference in the prevalence of headache in terms of gender disappeared in the population older than 75 years [18] and was particularly remarkable in young adults (18–30 years old) [19].

Furthermore, headache following vaccination with COVID-19 mRNA vaccines was less commonly seen among pregnant women after both doses in comparison to non-pregnant women, as well as myalgia and arthralgia. The prevalence of headache was similar in each trimester of pregnancy [20]. However, side effects following COVID-19 mRNA vaccine, such as headache, fatigue, arthralgia, and muscle pain, showed higher frequencies and tended to be more severe in individuals with different allergy histories than those without any allergy disorder. These side effects showed also a female dominance in allergic individuals [21].

## 7.7 Treatment

Unfortunately, there is not yet an established algorithm designated for the treatment of headache following COVID-19 vaccination. Studies focusing on COVID-19 vaccine-related headache reported that paracetamol and nonsteroidal anti-inflammatory drugs (particularly ibuprofen) were the mostly used painkillers [10, 14]. A recent survey study disclosed improvement without analgesics in almost one-third of subjects and a significant improvement of vaccine-related headache with painkillers in comparison to COVID-19-related headache [10], whereas migraineurs reported that the attacks after vaccination were different than their routine migraine attacks, with a lower responsiveness to painkillers almost in half of the patients [15].

## 7.8 Secondary Headaches

Secondary headaches are primarily related to underlying critical conditions, and secondary headaches associated with COVID-19 vaccines are also compatible with this rule of thumb. Although rare, life-threatening secondary headaches were also reported following COVID-19 immunization with vaccines, and emerging evidence has shown that the etiology of secondary headaches following vaccination is cerebral venous thrombosis, in most of the cases [22].

Cerebral venous thrombosis is accompanied by severe thrombocytopenia because of the presence of antiplatelet factor 4 antibodies in some cases. This clinical entity is called as vaccine-associated immune thrombosis and thrombocytopenia (VITT), in other words, thrombosis in thrombocytopenia syndrome [23, 24]. While thrombocytopenia is a key characteristic, the female to male ratio is 2:1. According to the literature, differentiation between primary and secondary type of headaches following COVID-19 vaccination may be done according to some clue clinical features. Especially delayed-onset headaches after COVID-19 vaccine should be evaluated thoroughly for secondary and life-threatening causes. Other indicators for secondary headaches seem to be female gender and being younger than 60 years old [22]. Furthermore, persistent headaches despite painkillers should raise concern regarding secondary etiologies [25].

The diagnosis of VITT requires the presence of antibodies against platelet factor 4 (PF4), determined using enzyme-linked immunosorbent assays (ELISAs) [26]. Furthermore, D-dimer levels are elevated in these patients, and it was shown that they are fourfold higher in subjects diagnosed with VITT [27]. Considering the underlying pathophysiology, treatment options targeting the immune system might be beneficial such as intravenous immunoglobulin (IVIG) and steroids in patients with VITT-related cerebral venous thrombosis [27].

Increased risk of ischemic stroke after BNT162b2 mRNA vaccination was also reported in a study including 9,513,625 participants. However, this study was a self-control retrospective study, and COVID-19-related vascular events have been found higher in the same population. Finally, there is not enough data regarding the clinical features including the presence of headaches in this population [28]. Furthermore, other etiologies underlying secondary headaches associated with COVID-19 vaccines have been rarely reported, such as a 45-year-old male patient diagnosed with Tolosa-Hunt syndrome following an mRNA-based COVID-19 vaccine [29].

## 7.9 Conclusion

COVID-19 vaccine-related headache is frequently seen and seems to be elicited by the pro-inflammatory state following vaccination. Fortunately, studies showed that this particular headache starting in general with a latency of 24–48 h and showing

heterogeneous character has a self-limiting course and is mostly mild and short-lasting. There is not yet an established algorithm for the treatment of headache following COVID-19 vaccination, a considerable percentage of the cases recovers without medication, and standard painkillers may be effective for the relief. Although rare, secondary headaches related to COVID-19 vaccine should also be considered in patients with long-lasting and treatment-resistant headaches.

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# Chapter 8
# Pathophysiology and Inflammatory Mechanisms of COVID-19 Headache

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## 8.1 Introduction

After the introduction of SARS-CoV-2 in late 2019, humans faced numerous sets of symptoms, together with pandemic conditions. In the beginning, the emerging clinical picture was expected to be a sole respiratory disorder like SARS-CoV-1, MERS-CoV, and other previous coronavirus diseases. However, different presentations of neurological involvement have gained particular attention over time with an increasing number of cases.

Headache, including post-covid headache, is one of the most frequent and well-recognized symptoms due to its high prevalence between 34 and 71.1%, and it is ascribed to different pathophysiological mechanisms [1]. Headache may manifest secondary headache features and/or migraine-like characteristics. New persistent headache with gradual or rapid onset, unresponsive to analgesics, located bilaterally or diffuse, with pressing quality and associated with multisystemic symptoms (e.g., anosmia/ageusia, diarrhea, loss of appetite, and weight loss) in the absence of prior headache history was emphasized in recent case series and raised the need for identification of new criteria specific to "headache attributed to COVID-19" [2, 3].

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On the other hand, headaches that persist beyond or emerge after the acute phase of the disease was referred to as post-COVID headache, and a greater number of presentations have been identified under this term [4]. The patients described late-onset new daily persistent headache or migraine-like headache without a prior history, together with various systemic symptoms occasionally [2]. The presence of headache during the acute phase of COVID-19 is one of the risk factors for the long-COVID syndrome. Additionally, headache is the second most important symptom of the long-COVID syndrome after fatigue [5].

Underlying pathophysiological mechanisms urge upon three mechanisms: direct invasion of trigeminal nerve endings in the nasal cavity, vascular pathogenesis, and triggering of trigeminal nerve endings via proinflammatory mediators and cytokines [1] (Fig. 8.1). As the theory of vascular pathogenesis also depends on diffuse endothelial inflammation associated with SARS-CoV-2, it would be reasonable to argue that inflammation plays a central role in the pathophysiology of COVID-19-related headache [6].

From the beginning of the pandemic, angiotensin-converting enzyme 2 (ACE2), which cleaves angiotensin II (Ang II) and acts oppositely via resultant substrates, has been recognized as the potential gate for SARS-CoV-2. Downregulation of ACE2 secondary to SARS-CoV-2 invasion is considered to result in an unbalanced Ang II activity and provoke a series of reactions acting in an inflammatory cascade.

In the following sections, the downstream effects of this inflammatory cascade will be discussed in detail.

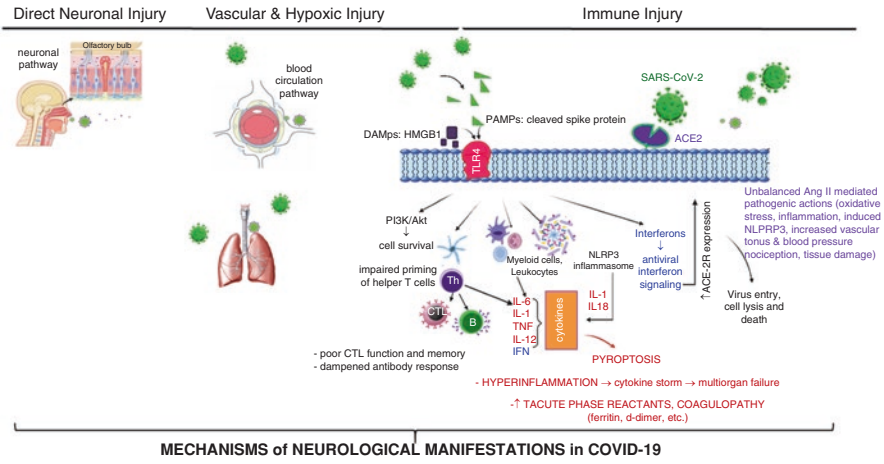


**Fig. 8.1** The pathophysiological mechanisms underlying neurological manifestations in COVID-19

## 8.2 Inflammatory Response to SARS-CoV-2

Inflammation plays a well-regulated role in homeostatic processes but is also a powerful weapon for the immune system to use in defense against invading foreigners. When both innate and acquired immune system elements recognize an antigen of a pathogen, including viruses, an inflammatory response through various pathways is activated. It is very important that the inflammatory response fades and returns to the normal state when the threat is eliminated. Whether due to microbial or sterile origin, an inflammatory response that cannot be controlled in terms of severity or duration may cause more damage to the tissue than the agent itself.

The body's encounter with microbial agents, including viruses, occurs in three main ways. Foreign organisms that enter the body through the skin, respiratory system, or gastrointestinal tract are first recognized by the innate immune system through their common molecular patterns. Tissue macrophages and neutrophils build the first line of defense after antigen binding, which induces a proinflammatory stimulus of damage-associated molecular patterns (DAMP) or pathogen-associated molecular patterns (PAMP). While macrophages stimulated by cytokines immediately begin phagocytosis, the migration of neutrophils from the blood to the site of inflammation occurs over time. At this stage, an increase in blood flow occurs with vascular changes, endothelial permeability increases, and the migration of neutrophils toward the area occurs. During this migration, adhesion molecules expressed on the endothelial surface and chemokines that mediate the orientation of cells are important mediators.

NLRP-3 inflammasome is another proinflammatory molecule whose production is stimulated in the cell as a result of the binding of antigen to pattern recognition receptors (PRR) such as toll-like receptor (TLR)-4 during the activation of innate immunity. NLRP-3, a tripartite protein, consists of the amino-terminal pyrin domain (PYD), the central nucleotide-binding and oligomerization domain (NOD; aka the NACHT domain), and a C-terminal leucine-rich repeat (LRR) domain [7]. NLRP-3 inflammasome is one of the most important molecules in the cell regulating innate immunity against microbial infection and cell damage by caspase-1 activation and IL-1β/IL-18 production. NLRP-3 can also induce cytokine storm by inducing fibrosis and severe tissue damage [8]. Another effect of the inflammasome is on clot formation. The inflammasome is activated in a ROS-dependent manner by the binding of increased circulating thrombin to its receptors on platelets. IL-6, which is stimulated by IL-1β, causes the conversion of prothrombin to thrombin and clot formation via tissue factor, leading to the development of disseminated intravascular coagulation (DIC) [9].

Inflammation against microbial agents causes stimulation of different components according to the agent. In extracellular bacterial infections, complement and antibody-mediated responses are prominent. As cellular elements, CD4+ T helper lymphocytes regulate the response through proinflammatory cytokine production. On the other hand, in intracellular bacteria and viral infections, cellular immunity is at the forefront, and the response of macrophages, natural killer (NK) cells, and

cytotoxic T lymphocytes (CTL) is effective. Another important element in the innate immune response against viruses is type 1 interferons. Type 1 interferons inhibit local viral replication and increase the effect by initiating a systemic viral response. Antibodies' neutralizing effects are also important in the response to viruses. Viruses try to escape from the immune system by making antigenic changes such as shift and drift, suppressing antigen presentation, changing the cytokine and cytokine receptor profile, and causing the death of functional immune cells.

COVID-19 is an immune system disease that begins as a viral infection but is characterized by an extreme host response followed by inflammation and severe stimulation of the hemostatic pathways [10]. Following the infection of the pneumocytes by the virus, the stimulation of the intracellular inflammasome causes IL-1β and IL-18 levels to increase. Activated macrophages both support IL-6 production and accelerate the development of lung damage by causing macrophages to accumulate in the lungs. As a result of inappropriate priming and dysfunctional responses of T lymphocytes, in which antigen-presenting cells present the antigen, especially CTL functions are impaired, and enzymatic and cellular mechanisms that are involved in viral clearance are suppressed [11].

There are many molecular and epigenetic factors such as genetic variations in inflammasome components, changes in the number and functions of lung epithelial and immune cells, comorbidities and currently used treatments, and gender that regulate the development of COVID-19 caused by SARS-CoV-2 infection [12]. Although many candidates have been focused on the viral entry to the cell, recent studies reveal that angiotensin-converting enzyme-2 (ACE2) receptors are mainly responsible for this entry. Since ACE2 receptors are expressed in many organs of the body, both virus internalization and replication occur after binding, and many systemic effects related to ACE2 dysregulation occur [13]. Following viral replication, the presentation of antigen to T lymphocytes via antigen-presenting cells causes the production of proinflammatory cytokines, while stimulation of cytotoxic T lymphocytes works to eliminate infected cells by lytic mechanisms. B lymphocytes that recognize the antigen contribute to the neutralization of the virus by producing antibodies [14]. At this stage, hyperinflammatory acute-phase reactants such as ferritin, d-dimer, and CRP increase in the circulation through the stimulation of cytokines and contribute to the pathogenesis. If the virus cannot be cleared by these first-line reactions, proinflammatory cytokines, especially IL-6, trigger an irreversible cascade called a cytokine storm. Cytokine storm triggers both cytotoxicity-mediated and enzymatic tissue damage and the development of capillary leak syndrome because of endothelial dysfunction, leading to acute respiratory distress syndrome (ARDS) and multiorgan failure [15].

Intracellular iron stored in ferritin has become one of the most interesting players in cell survival, with both beneficial and harmful roles. Cellular iron storage is regulated by transport proteins variably expressed in meningeal cells and glia [16]. Mislocalization of iron in the cell may contribute to the pathogenesis of many neurological disorders including migraine, through stimulation of proinflammatory pathways, oxidative stress, and also via ferroptosis [17]. Ferritin has an important place among acute-phase reactants that increase during the pathogenesis of

COVID-19. Increased circulating ferritin levels trigger inflammation and contribute to the development of cytokine storm and also ferroptosis at the cellular level [18]. High ferritin levels were found to be related to disease severity and prognosis [19]. Another remarkable result of the ferritin increase is coagulopathy, which is the main complication in COVID-19 pathogenesis.

Although SARS-CoV-2 infection is asymptomatic or mild in especially young people, it is observed that a hyper-inflammatory response occurs in 10–30% of patients as a result of genetic, phenotypic, and environmental factors [20]. Again, similar effects are also decisive for prolonged (or long) COVID, which can be seen up to 30% after the COVID-19 disease [20]. It is known that the absence of regulatory factors such as TGF-β and IL-10, which restores immune homeostasis, and the presence of autoantibodies together with T and B lymphocytes are important in the development of prolonged COVID. Autoantibodies can cause various chronic effects, especially by playing a role in the long-term suppression of type I interferons.

## 8.3 COVID-19 Headache and Inflammation

Headache is highly expectable at onset and during COVID-19. Since SARS-CoV-2 prefers nasal mucosa for entry, and nasal mucosa is covered by trigeminal afferents along with olfactory neurons, one can argue that headache is inevitable for this disease, from the starting point. There is not enough evidence regarding the expression of the gatekeeping molecule ACE2 on trigeminal nerve endings, although some reports indicating direct invasion of cerebral parenchyma exist [21]. However, it's a well-known fact that direct irritation of trigeminal nerve endings is not a prerequisite for trigeminovascular activation, and after 2.5 years of experience, indirect mechanisms including inflammation seem to play a major role regarding neurological symptoms associated with COVID-19 [1].

Angiotensin-converting enzyme-2 (ACE2), the most striking actor as the host receptor for SARS-CoV-2, is a transmembrane metalloproteinase that degrades angiotensin II (Ang II) resulting in the formation of angiotensin 1–7 (Ang 1–7) [22]. Its expression has been demonstrated in a wide range of tissues including oral and nasal epithelia, pneumocytes of the respiratory system, vascular endothelium, and smooth muscle cells [23]. It is also expressed in the brain, mainly in the neurons of the motor cortex, basal ganglia, thalamus, nucleus ambiguus, dorsal raphe nucleus, and solitary tractus [24].

The binding of SARS-CoV-2 to ACE2 initiates a series of reactions including direct viral invasion and vasculopathy or neuroinflammatory activation through pro-inflammatory mediators composing the pathophysiological mechanisms underlying COVID19-related headache [1, 6].

In this section, inflammation and consequent mechanisms will be discussed as potential underlying pathophysiology of COVID-19-associated headache.

In case of an attack, two major molecule groups play a pivotal role in the innate immune response of the host. The first major molecule group is pathogen-associated

molecular patterns (PAMPs), and the second one is damage-associated molecular patterns (DAMPs), which are produced during infections and/or tissue damage [25].

Once SARS-CoV-2 binds to ACE2, internalization and functional downregulation of the receptor occurs, which results in uncontrolled activity of Ang II/AT1R and downstream [1]. Ang II, a well-known component of the renin-angiotensin system, maintains vascular tonus and blood pressure, as well as electrolyte homeostasis, but also takes further part in the induction of inflammation, the production of reactive oxygen species, the activation of NLRP3 inflammasome, and the regulation of nociception [22, 25]. Trigeminal ganglion, which mainly controls intracellular modulatory mechanisms and intercellular signaling rather than acting as a central transition gate for peripheral stimuli, has already been demonstrated to release numerous neuropeptides including Ang II [26]. Close localization of Ang II with the most pronounced nociceptive mediators like CGRP and SP makes it a potential regulator of nociception and subsequent headache [27]. Recently decreased levels of Ang II were demonstrated in COVID-19 cases with headache when compared to the ones without headache [25]. Diminution of Ang II levels in this group was explained as a secondary outcome following increased circulating ACE2 in patients' sera due to the binding of SARS-CoV-2 to the membrane-bound form [28]. For their cohort, the authors concluded that Ang II was not responsible for the trigeminal nociception [25].

Considering sACE2 as a host receptor, it is plausible to expect an excessive viral entry throughout the blood circulation and contribution to viremia, as well as a worse disease prognosis [29]. On the other hand, as a defender of the organism against Ang II and its detrimental effects, increased sACE2 in the circulation might result in the magnified activity of the protective Ang I-MasR (mitochondrial assembly receptor) axis together with fewer amounts of Ang II [1, 22, 25]. Demonstration of higher ACE2 levels in 48 COVID-19 patients with headache as opposed to the 40 cases without headache in the presence of favorable disease course without any ARDS may be supportive of this latter hypothesis [25]. However, headache in that cohort was associated with increased frequency of pulmonary involvement and stronger inflammatory response, to which the contribution of ACE2 seemed still reasonable.

PAMPs and DAMPs as mentioned above principally serve as boosters for the generation of an important actor of the innate immune system, so-called the inflammasome [9]. Inflammasome activation takes place after two steps. The first step involves binding to a pattern recognition receptor such as toll-like receptor (TLR)-4 occurs, which results in the synthesis of pro-IL-1β and pro-IL-18. The second step necessitates another signal to induce inflammasome formation and processing of former compounds [9, 30].

High mobility group box-1 (HMGB1), a member of DAMPS, is an intranuclear protein existing in numerous eukaryotic cells [25]. In addition to the regulation of essential genomic events as a DNA binding protein, it could also be transported to the extracellular space where it behaves as an efficacious proinflammatory mediator [9]. In COVID-19, HMGB1 is suggested to have a critical role in the inflammatory response inside the lungs of COVID-19 patients. It is placed in the proximity of IL-6

and gives rise to ARDS/acute lung injury (ALI) by activation of inflammasome throughout the lungs [31]. It also induces mechanical hypersensitivity and mediates nociceptive action through pattern recognition receptors like RAGE (receptor for advanced glycation end-products), TLR4, and TLR2 and enhances neuron-glia signaling via immune cells and glial cells, again expressing these receptors [32, 33]. In capsaicin responsive primary afferent neurons, HMGB1 was shown to increase calcium mobilization and neuronal excitability via RAGE, and RAGE together with TLR4 has already been demonstrated in sensory neurons of DRG and trigeminal neurons. In experimental models of neuropathic pain, blocking RAGE and TLRs is known to lessen pain behavior and hypersensitivity, whereas dealing with trigeminal nerve with antiHMGB1 antibody suppresses macrophage-glia activation along with inhibition of pain behavior [33]. In a retrospective cohort of hospitalized COVID-19 patients with moderate disease, cases with headaches were found to have higher levels of HMGB1 when compared to the ones without headache. HMGB1 showed 68% sensitivity and 80% sensitivity while classifying the group according to headache and was negatively associated with paracetamol response. As denoted by the authors, the findings listed above suggested a key role for HMGB-1 in COVID-19-related headache, which would probably make it a potential therapeutic target in the near future [25].

Another component of the inflammasome complex, named NOD-like receptor protein-3 (NLRP3), has also been involved in COVID-19-associated headache, concerning its contribution demonstrated in experimental headache models. NLRP3 serves as a sensor within the inflammasome complex, the master regulator of IL1-β. It reacts to many signals including ion exchange mediated by viral particles, such as viroporin E and accessory protein 3a, during SARS-CoV-2 infection [34]. NLRP3 activation necessitates two steps, of which the first generates transcriptional upregulation of NLRP3 and pro-IL-1β via NF-κB-dependent way, and the second induces oligomerization and activation of the NLRP3 inflammasome complex in response to activation signals mentioned above [9]. The final result is the production and release of proinflammatory cytokines, IL-1β, IL-18, IL-6, tumor necrosis factor, prostaglandins, leukotrienes, etc. and perpetuation of inflammation which may sometimes progress to a hyperinflammatory state named "the cytokine storm" for COVID-19 [6, 35]. Proinflammatory process triggered by IL-1β in experimental models is known to take part in trigeminal satellite cell activation and induce cross-excitation of neurons together with satellite glial cells in the trigeminal ganglion [33]. A migraine-relevant pain mouse model (NTG stimulation) revealed increased NLRP3 expression in association with IL-1β activation, which indicates upregulation of NLRP3 inflammasome expression. Inhibition of NLRP3 and IL-1β in that model resulted in the recovery of hyperalgesia and ceased the increase in biomarkers regarding central sensitization of chronic migraine [36].

In COVID-19 patients with headache, NLRP3 levels were found to be significantly higher than patients without headache, which correlated with both headache duration and hospital stay [25].

More familiar molecules, like IL-6 and CGRP, which are involved in the pathophysiology of primary headache disorders, have also been proposed as potential

contributors of COVID-19-related headache. Particularly IL-6, which is a steady marker of COVID-19 disease activity, was studied in large cohorts of patients with COVID-19-related headache [25, 37]. Beyond its capability of activating perivascular trigeminal nociceptors throughout the meninges and triggering headache, which was established in several preclinical pain models, it acted as a key molecule in both central and peripheral neuroinflammation regarding various neurological manifestations during COVID-19 disease [38–40]. Increased levels were detected in patients with COVID-19 headache, in comparison to the ones without headache, and cluster analysis in another cohort reported its positive correlation with VAS scores [25]. The latter study, which further classified headache of COVID-19 patients in terms of intensity, frequency, duration, treatment response, and accompanying pulmonary involvement, revealed that headache patients with cluster 1-type headache exhibited poorer features in terms of all mentioned headache parameters, together with significantly higher IL-6 levels and pulmonary involvement [37].

CGRP has a well-established role in trigeminovascular activation and migraine and is known to be increased in response to IL-6 and TNF-α [1]. Co-localization of its receptors with ACE and SARS-CoV-2 binding subunits in the cells of TG makes it an attractive molecule in the pathogenesis of COVID-19-associated headache [24]. However, studies evaluating CGRP levels in COVID-19-associated headache failed to illustrate such a relationship. In the case series of 88 hospitalized COVID-19 patients with and without a headache, no difference was demonstrated between the groups in terms of CGRP levels [25].

In conclusion, host immune response, innate immunity, and cytokines significantly contribute to headache symptom seen in both acute COVID-19 and long-COVID syndrome. Elucidating underlying mechanisms of COVID-19 headache will be helpful to understand and find novel therapeutic targets for other secondary headaches as well as primary headaches.

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# Chapter 9
# COVID-19 Microbiome Alterations

**Meltem Yalınay**

## 9.1 Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by a novel coronavirus severe acute respiratory syndrome. Coronavirus type 2 (SARS-CoV-2) is classified as a pandemic by the World Health Organization. So far, there have been 600 million reported cases and six million deaths throughout the world. SARS-CoV-2 infection is characterized by different clinical syndromes differing greatly from asymptomatic ailment or symptoms similar to mild influenza to severe pneumonia and acute respiratory distress syndrome [1]. This RNA virus primarily infects the respiratory tract and causes various severity levels in patients depending on the host immunity.

Covid-19-diagnosed patients are mainly asymptomatic (80%) and tend to show only mild respiratory and/or gastrointestinal symptoms. However, the remaining 20% of cases develop acute respiratory distress syndrome urging hospitalization and oxygen support, and 25% of the patients in the aforementioned segment need critical care. Such remarkable difference in individual's presentations and symptoms of COVID-19 stems from the heterogeneous immune status and personal reactions against SARS-CoV-2 infection [2].

The human gastrointestinal tract is inhabited by the largest microbial community within the human body containing trillions of microbes called gut microbiota and is the largest immune organ in the human body with its significant microbial community. Trillions of microorganisms, bacteria, fungi, viruses, and algae, are collectively found nearly everywhere on human beings essentially at the gut.

Gut microbiota is considered to be crucial on host metabolic functions with its unique and diversified composition [3]. This complex ecosystem has several

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features, such as nutrient absorption, regulation of the host immunity, and antagonistic effect against pathogen colonization. Thus, a tremendous amount of evidence has highlighted the crucial role of the gut microbiota on health and disease [3]. The gut microbiota regulates immune responses fighting against infections of pathogens [4].

Significant number of scientific research revealed a reciprocal reaction between gut microbiota and many organs within the human body such as the intestines, lungs, brain, and skin. The fact that gut microbial alteration is a key factor in the pathogenesis of many local and systemic disorders has been scientifically validated for more than a decade. Consequently, profound comprehension of the mechanisms affecting gut microbial symbiosis/dysbiosis is essential with respect to clinical and health-related examinations and research [4]. The genome of these microorganisms is considered as the microbiome. Microbiome is a significant factor on host immunity [5]. By far accumulating evidence suggests that the gut microbiome is broadly altered in patients with COVID-19 and that the gut microbiome configurations are linked with immune responses and disease presentations in COVID-19 [6].

The SARS-CoV-2 infection course is crucial for the alterations in the ecology and dynamics of human gut microbiome. Regardles of time, it influences the health of the host. With this respect, microbiome modulation-based approaches are of utmost importance for the personalized medicine purposes.

## 9.2 Gut Microbiome

Gut microbiome is comprised of diverse microorganisms involving genetic components and microbial biodiversity with distinctive functions. In the gut, resilience is interconnected to the functional core microbiota [6]. If the microbiota composition is due to *Firmicutes* and *Bacteriodetes* and the symbiotic phylogenetic taxa ratios are in balance, this will have been defined as eubiosis. Vigorous immune response depends on the gut microbiota eubiosis. If that is not the case, the imbalance of *Firmicutes* and *Bacteriodetes* gives rise to dysbiosis. Gut microbiota composition has direct influence on related organs. If a systemic ilnesss is trigerred by the gut microbial dysbiosis, it is known as the gut-origin concept of diseases. The gut microbiota dysbiosis causes low-level proinflammatory response. This proinflammatory response constitutes a vital aspect in the immune-related infections and severity of such.

In COVID-19, the gut-lung axis has a critical importance. The gut microbiome regulates host defenses against viral infections. With this respect, dysbiosis may be a leading factor that triggers the cascade of inflammation and immune imbalances in such patients. The gut microbial fingerprint in COVID-19 patients is likely to be seen as a potential diagnostic, therapeutic, and a prognostic marker [7].

COVID-19 is essentially a lung disease. It is scientifically proven that the gut can affect the lung through the gut-lung axis [8]. Beyond the local immune regulation by the gut microbiota, extensive immune impact of gut microbiota is acknowledged, especially on the pulmonary immune system [9]. Short-chain fatty acids (SCFAs), a

group of prototypic metabolites produced by gut bacteria, translocate across the intestinal barrier, penetrate the systemic circulation, and alter the lung immune reaction [10]. They are mainly produced by bacterial degradation and fermentation of dietary fibers, acting as signaling molecules in the lung on resident antigen-presenting cells to diminish the inflammatory and allergic responses [10, 11]. Decline in the abundance of SCFA-producing bacteria observed in the gut microbiota of patients with COVID-19 can be considered as one of the most important mechanisms affecting the gut-lung crosstalk and thereby disease severity [12].

The gut-brain axis; gut microbiota dysbiosis damages the gut permeability causing translocation of gut microbes and their metabolites into the circulatory system and induce systemic inflammation which, in turn, may influence distal organs such as the brain. In addition, gut microbiota maintains the availability of tryptophan for kynurenine pathway, which is essential for both central nervous and gastrointestinal system in regulating inflammation. SARS-CoV-2 infection damages the gut microbiota, resulting in immune dysfunction with generalized inflammation. Proinflammatory cytokines and microbial products crossing the blood-brain barrier induce the neuroinflammation, which contributes to the pathophysiology of neurodegenerative diseases containing neuropathies. Therefore, both gut-lung and gut-brain axes are involved in COVID-19 severity and extrapulmonary complications. Moreover, gut microbial dysbiosis can be the reason for the neurologic complications encountered in severe COVID-19 patients with the association of dysbiosis-related neuroinflammation [13].

## 9.3 The Gut Microbiome Compositional Changes in COVID-19

### *9.3.1 The Gut Bacterial Microbiome in COVID-19*

The severity of COVID-19 disease is closely associated with gut and lung dysbiosis. The gut microbiome of COVID-19 patients diminishes bacterial diversity in a significant manner. The pathobiont genera seems to go up where the symbionts decline: There is a significantly higher abundance of opportunistic pathogens such as *Streptococcus*, *Rothia*, *Veillonella* and *Actinomyces*, and a lower abundance of bacteria that are beneficial symbionts compared with controls. Furthermore, it is presented that the disease severity of COVID-19 is linked with a predominance of opportunistic pathogens and inversely associated with beneficial commensals [14].

The gut bacterial microbiome of patients with COVID-19 was outstandingly different in comparison to healthy controls characterized by depletion of beneficial commensals and enrichment of opportunistic pathogens in the gut [6]. Dysbiosis in COVID-19 patients was linked with disease severity [15]. It was reported that the change in the number of butyrate-producing bacteria, such as *Faecalibacterium prausnitzii*, *Clostridium leptum*, *Clostridium butyricum*, and *Eubacterium rectale*,

is likely to differentiate critical patients from general patients [15]. Long-lasting changes in the fecal microbiome of the aforementioned patients were encountered upon hospitalization compared to healthy controls [6]. Besides, fecal microbiota changes were seen to be associated with fecal levels of SARS-CoV-2 and COVID-19 severity [6].

The abundance of butyrate-producing bacteria, such as *Faecalibacterium prausnitzii*, *Clostridium butyricum*, *Clostridium leptum*, and *Eubacterium rectale*, considerably diminished in patients with COVID-19 compared to the controls [15]. Contraversely, the abundance of the common opportunistic pathogens *Enterobacteriaceae* and *Enterococcus* rose extensively in patients with COVID-19 compared to the controls [15]. While the genera *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces* were enriched in the feces of these patients at the genus level, the genera *Romboutsia*, *Faecalibacterium*, and *Fusicatenibacter* increased in the feces of healthy controls [16]. Opportunistic bacteria dominate the ecological network of the gut microbiome due to SARS-CoV-2 infection.

There are several researches that highlight the correlation between dysbiosis of the lung microbiome and COVID-19. Gaibani et al. carried out important research comparing the lung microbiome between COVID-19 patients in critical conditions and COVID-19-negative patients with pneumonia using bronchoalveolar lavage samples. COVID-19 patients had a lower microbial diversity with a significantly higher relative abundance of *Pseudomonas* spp. compared with COVID-19-negative pneumonia patients [17]. Contrary to what was being said above, the lung microbiome in COVID-19-negative pneumonia patients indicated a reduction in butyrate-producing organisms from the *Clostridium* cluster XIVa as well as anti-inflammatory organisms such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*. The lung and gut dysbiosis changes the course of the COVID-19 severity and its prognosis.

Gut microbiota composition of patients with COVID-19 during hospitalization is associated with plasma concentrations of several cytokines, chemokines, and inflammation markers, highlighting the fact that the gut microbiota could alter host immune response and potentially influence disease severity and outcomes. Specifically, the depletion of several bacterial species in the COVID-19 cohort was found to be associated with increased concentrations of TNF-α and IL-10 consistent with immunological studies of patients with COVID-19. The data indicate that these depleted taxa are likely to prevent overaggressive inflammation. Depleted gut commensals such as *Bifidobacterium adolescentis*, *F. prausnitzii*, *Eubacterium rectale*, *Blautia obeum*, and *Dorea formicigenerans* are associated with lessening host inflammatory response in other inflammatory-related diseases [18].

Gut microbiota of recovered patients were enriched in species including *Bifidobacterium dentium* and *Lactobacillus ruminis* regardless of antibiotic intake and depleted in *E. rectale*, *R. bromii*, *F. prausnitzii*, and *Bifidobacterium longum* ($p < 0.05$, LEfSe) [18]. Gut microbiome dysbiosis remains to be seen in subjects recovered from COVID-19. This implies that gut microbiome is closely associated to host health in a post-COVID-19 age [19, 20]. Altered gut microbiome composition is strongly associated with persistent symptoms in patients with COVID-19 up to 6 months after clearance of SARS-CoV-2 virus. The gut bacterial microbiome in COVID-19 is defined as decreased diversity and richness and persistent bacterial microbiome dysbiosis even after disease resolution [21].

Several COVID-19 patients informed that they went through systemic and/or organ-specific disorders in the follow-up phase following treatment such as extreme tiredness, sore muscles, sleep deficit, anxiety, depression, diarrhea, dyspnea and joint pains, and poor glycemic controls [22–25], which is commonly accepted as "long COVID." Oddly, the GI tract can also be affected following COVID-19, as demonstrated by a prolonged shedding of viral RNA in stool specimens up to 42 days and the presence of SARS-CoV-2 virus in the gut epithelium up to 90 days after disease resolution [26, 27]. Patients with high SARS-CoV-2 infectivity in the gut showed an elevated abundance of the bacterial species *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, and *Morganella morganii* as well as an increased functional capacity for nucleotide de novo biosynthesis, amino acid biosynthesis, and glycolysis [28]. On the other hand, *Alistipes onderdonkii* has a reverse relation with COVID-19 severity [6]. Intriguingly, indole positive Alistipes species are a part of the serotonin precursor tryptophan metabolism and contribute to maintaining gut immune homeostasis [29, 30].

A relation was found between the hyper-inflammatory response of COVID-19 patients and disrupted gut permeability as well as microbial translocation [31]. Due to translocation of granulocytes and monocytes/macrophages into the gut lumen, the amount of fecal calprotectin increased in the feces of patients [32]. This fact indicates immune dysfunction of the gut and altered gut niche in COVID-19 patients. Therefore, the compositional alterations in the gut microbiome of these patients occur as far as host immune responses are concerned. Hence, SARS-CoV-2 infection diminishes the variety while increasing the abundance of opportunistic pathogens in the gut. To wrap up, patients of aforementioned disease are known to have different fecal microbial composition patterns [6, 13, 15, 16, 18, 28, 33–35]. (Table 9.1).

**Table 9.1** The gut microbiome compositional changes in COVID-19

| Modulation of fecal microbiota | [a]Antibiotics | [a]Antivirals or other drugs | Geographic location | Gastrointestinal symptoms | References |
|---|---|---|---|---|---|
| ↑ *Ruminococcus gnavus*, *Eggerthella*, *Coprobacillus*, *Lachnospiraceae bacterium*, *Clostridium ramosum*, and *Eggerthella lenta*<br>↓ *Alistipes* sp. AP11, *Roseburia intestinalis*, *Burkholderiales bacterium*, *Eubacterium hallii*, *Parasutterella excrementihominis*, *Alistipes indistinctus*, *Coprobacter fastidiosus*, *Eubacterium eligens*, *Bacteriodales bacterium* ph 8, *Bacteroides salyersiae*, *Odoribacter splanchnicus*, *Alistipes shahii*, *Ruminococcus bromii*, and *Bacteroides massiliensis* | None, moxifloxacin, piperacillin/tazobactam, cefuroxime, or levofloxacin | None, lopinavir/ritonavir, Arbidol, or ribavirin | Beijing, China | None, diarrhea, constipation, or abdominal distention | [33] |
| ↑ *Streptococcus*, *Clostridium*, *Haemophilus*, and *Proteobacteria*<br>↓ *Prevotella*, *Akkermansia*, *Paraprevotella*, and *Lachnospira* | Antibiotics (unspecified) | Antivirals (unspecified), corticosteroids, immunoglobulin, traditional Chinese medicine, probiotics, anticoagulation, or tocilizumab (anti-IL6R) | Hefei, China | Diarrhea, nausea, vomiting, anorexia, or abdominal pain | [34] |
| ↑ *Enterococcus* and *Enterobacteriaceae*<br>↓ *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium prausnitzii*, *Clostridium butyricum*, *Clostridium leptum*, and *Eubacterium rectale* | Antibiotics (unspecified) | Antifungal drugs or probiotics | NA | NA | [b] [15] |
| ↑ *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, and *Morganella morganii*<br>↓ *Parabacteroides merdae*, *Bacteroides stercoris*, *Alistipes onderdonkii*, and *Lachnospiraceae bacterium* | NA | NA | Hong Kong, China | None or diarrhea[c] | [28] |

| | | | | | |
|---|---|---|---|---|---|
| ↑ *Streptococcus*, *Rothia*, *Veillonella*, *Erysipelatoclostridium*, and *Actinomyces*<br>↓ *Ruminococcaceae*, *Fusicatenibacter*, *Anaerostipes*, *Agathobacter*, unclassified *Lachnospiraceae*, and *Eubacterium hallii* | NA | NA | Zhejiang, China | None or diarrhea | [16] |
| ↑ *Ruminococcus gnavus*, *Ruminococcus torques*, and *Bacteroides dorei*<br>↓ *Bifidobacterium adolescentis*, *Faecalibacterium prausnitzii*, and *Eubacterium rectale* | Antibiotics (unspecified)<br>None, lopinavir/ritonavir, ribavirin, or oseltamivir | Corticosteroids or proton pump inhibitor | Hong Kong, China | None or diarrhea | [18] |
| ↑ *Clostridium hathewayi*, *Actinomyces viscosus*, and *Bacteroides nordii*<br>↓ *Eubacterium ventriosum*, *Faecalibacterium prausnitzii*, *Roseburia*, and *Lachnospiraceae* | Amoxycillin, clavulanate cephalosporin, or tetracycline | Lopinavir/ritonavir, or ribavirin interferon beta-1b | Hong Kong, China | None or diarrhea | [6] |
| ↑ *Streptococcus*, *Clostridium*, *Lactobacillus*, and *Bifidobacterium*<br>↓ *Bacteroidetes*, *Roseburia*, *Faecalibacterium*, *Coprococcus*, and *Parabacteroides* | NA | NA | Anhui | China NA | [35] |

[a] Single or combination of two or more
[b] Predominant fecal microbiota was detected by qPCR
[c] Change in the microbiota in fecal samples with signature of high SARS-CoV-2 infectivity relative to the fecal samples with signature of low-to-none SARS-CoV-2 infectivity. NA, no information
Available [13]

### 9.3.2 The Gut Mycobiome in COVID-19

The gut mycobiome is a fungal microorganism found at the human gut. Alterations in the gut mycobiome were detected in COVID-19 patients denoted by enrichment of *Candida albicans* and highly heterogeneous mycobiome profiles [6]. The abundance of opportunistic fungal pathogens like *Candida albicans*, *Candida auris*, and *Aspergillus flavus* has risen in feces of COVID-19 patients in the course of the disease [6]. Fungal pathogens associated with pneumonia and respiratory symptoms, *Aspergillus flavus* and *Aspergillus niger*, were encountered in fecal samples from a subset of these patients even after disease resolution [6].

Gut mycobiome is not stable, and extended dysbiosis remained in a significant proportion (30%) of the aforementioned patients [6]. *Aspergillus niger* presence was positively linked with diarrhea. However, the abundance of *Penicillium citrinum* was reversely associated with blood levels of CRP [2]. Aspergillus infections were reported in respiratory tract secretions and tracheal aspirates in patients with COVID-19 [36]. Aspergillus is a genus of fungi giving rise to several pulmonary and respiratory symptoms [36]. Aspergillus may lead to immune dysfunction and affect clinical features and disease course [36]. Candida and Aspergillus spp. have been the specific opportunistic fungal pathogens enriched in COVID-19 patients during the disease course. *Candida albicans* is the widely encountered one, and its colonization can aggravate inflammation in the gut and other tissues [37].

The gut mycobiome in COVID-19 is identified with increased fecal fungal load and beta-diversity (heterogeneity increased), and it is unsteady and keeps on changing after disease resolution. SARS-CoV-2 displays infectivity in the gut. Delayed SARS-CoV-2 viral shedding and persistent gut virome dysbiosis remains to be seen after disease resolution. The gastrointestinal tract epithelial barrier of these patients is weakened [2].

### 9.3.3 The Gut Virome in COVID-19

The gut virome incorporates both RNA and DNA viruses that chronically contaminate their eukaryotic and prokaryotic hosts [38]. Bacteriophages are the most largely encountered group in gut virome. The gut virome serves to modulate the ecology of the co-resident gut bacterial microbiota as well as the immunity of the mammalian host [39]. Escherichia and Enterobacter phages were prominent in COVID-19 patients [2]. Expansion of these phages has been causally implicated in gut inflammation and host interferon response [40], and Microviridae bacteriophages constitute central network nodes [33]. The DNA viruses in the gut of patients with COVID-19 were mainly crAss-like phages (35.48%) and Myoviridae (20.91%) and Siphoviridae (20.43%) family of viruses. Compared with healthy controls, the gut virome composition of patients with COVID-19 changed significantly, especially the crAss-like phages family, from the first time of hospital admission. A stark

association between the composition of virome and bacterial microbiome in COVID-19 patients was reported [33]. A potential correlation is also displayed between the change in virome and bacteriome (like *Tectiviridae* and *Bacteroidaceae*). Combined ecological network analysis of the virome and bacterial microbiome in COVID-19 unveiled three bacterial species, *Faecalibacterium prausnitzii*, *Bacteroides vulgatus*, and *Ruminococcus gnavus* (the abundance of these bacterial species was also associated with COVID-19 and/or disease severity [2]). These bacterial and viral species are considered as key species for mediating microbial-microbial interactions in the gut microbial ecology.

As demonstrated above, the gut-lung axis contains host-microbe and microbe-microbe interactions contributing to immunomodulation. This microbial intercompartmental crosstalk is likely to be realized through bacteriobiota, mycobiota, and virobiota affecting T-helper response pathway leading to acute and chronic respiratory disease. Thus, microbiome regulation through a change in eating habits and biotics can be considered as an alternative for the treatment of respiratory disease. Personalized nutrition therapy is to be applied by profiling the gut microbiota of the patients. Specific probiotics/synbiotics to improve gut dysbiosis is recommended, which shall also improve immune reactions. This also can be performed as a prophylactic strategy in high-risk populations. Undoubtedly, aforementioned approach shall bring along a better management of the disease. Therefore, the gut microbial signature and modifying its function is considered to be essential COVID-19 prevention and treatment.

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# Chapter 10
# Gender Susceptibility and Comorbidities in COVID-19 Headache

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## 10.1 Comorbidities in COVID-19 Headache

Coronavirus disease 2019 (COVID-19) infection has shown a more pronounced effect and severe course in the elderly population at the beginning of the pandemic. The proportion of patients with comorbid diseases in COVID-19 infection increases with age. COVID-19 infection mostly affects the middle-advanced age group. In light of this information, the frequency of COVID-19 headache and comorbid disease arouses curiosity. As the pandemic progresses, the age of COVID-19 infection has become younger as a result of restrictions and vaccination for the elderly population.

Thus, it has also guided new studies on comorbidities and COVID-19 symptoms.

The cases which experience headaches under COVID-19 infection are reported as younger cases compared to those who do not. In addition, the average age of cases with COVID-19 headache in the studies was 50–57 years, which can be defined as the middle age [1–4]. In this age group, many chronic diseases begin.

Charlson Comorbidity Index (CCI) is high in COVID-19 patients with headache [3]. The coexistence of major chronic diseases and COVID-19 headache will be mentioned one by one below. Previous studies on comorbid diseases are summarized in tables below (Tables 10.1, 10.2, and 10.3).

*Hypertension (HT)* is the most common chronic disease in this population. It was expected to be similar in COVID-19 patients. Existing endothelial damage in HT patients may facilitate the invasion of the virus into neuronal tissue in the COVID-19 infection process.

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**Table 10.1** The frequency of HT, DM, CAD, and stroke in patients with COVID-19 headache

| Studies and comorbidities | | With headache ((%(N)) | Without headache ((%(N)) | *P* value |
|---|---|---|---|---|
| *Hypertension (HT)* | | | | |
| Group1 studies[1] | Dos Anjos de Paula RC et al. 2021* | 37.5% | NO DATA | NO DATA |
| | Porta-Etessam J et al. 2020** | 4.5% (5/112) | NO DATA | NO DATA |
| Group2 studies[2] | Trigo J, et al. 2020 | 38% (52/137) | 56.5% (248/439) | <0.001 |
| | Gonzalez -Martinez A et al. 2021 | 27% (13/48) | 48% (160/330) | 0.005 |
| | Membrilla JA et al. 2020 | 15.2% (15/99) | 32.6% (15/46) | 0.016 |
| Group3 studies[3] | Karatas O, et al. 2021 | 39.8% (33/83) | 23% (47/204) | 0.007 |
| *Diabetes mellitus (DM)* | | | | |
| Group1 studies[1] | Dos Anjos de Paula RC et al. 2021* | 37.5% | NO DATA | NO DATA |
| | Porta-Etessam J et al. 2020** | 0% (0/112) | NO DATA | NO DATA |
| Group2 studies[2] | Trigo J, et al. 2020 | 14.6% (20/137) | 21.2% (93/439) | 0.090 |
| | Gonzalez -Martinez A et al. 2021 | 12% (6/48) | 12% (64/331) | 0.322 |
| | Membrilla JA et al. 2020 | 3.0% (3/99) | 2.2% (1/46) | 0.769 |
| Group3 studies[3] | Karatas O, et al. 2021 | 16.9% (14/83) | 7.8% (16/204) | 0.040 |
| *Coroner artery disease (CAD)* | | | | |
| Group1 studies[1] | Dos Anjos de Paula RC et al. 2021* | NO DATA | NO DATA | NO DATA |
| | Porta-Etessam J et al. 2020** | NO DATA | NO DATA | NO DATA |
| Group2 studies[2] | Trigo J, et al. 2020 | 13.9% (19/137) | 30.8% (135/439) | <0.001 |
| | Gonzalez-Martinez A et al. 2021 | NO DATA | NO DATA | NO DATA |
| | Membrilla JA et al. 2020 | 1.0%(1/99) | 2.2% (1/46) | 0.576 |
| Group3 studies[3] | Karatas O, et al. 2021 | 9.6% (8/83) | 4.4% (9/204) | 0.154 |
| *Stroke* | | | | |
| Group1 studies[1] | Dos Anjos de Paula RC et al. 2021* | NO DATA | NO DATA | NO DATA |
| | Porta-Etessam J et al. 2020** | NO DATA | NO DATA | NO DATA |

**Table 10.1** (continued)

| Studies and comorbidities | | With headache ((%(N)) | Without headache ((%(N)) | *P* value |
|---|---|---|---|---|
| Group2 studies[2] | Trigo J, et al. 2020 | NO DATA | NO DATA | NO DATA |
| | Gonzalez -Martinez A et al. 2021 | NO DATA | NO DATA | NO DATA |
| | Membrilla JA et al. 2020 | 0% (0/99) | 2.2% (1/46) | 0.141 |
| Group3 studies[3] | Karatas O, et al. 2021 | 10.8% (9/83) | 1.5% (3/204) | 0.001 |

*(mean age: 53.8) **(mean age: 43.4)
[1] Studies that included only patients with COVID-19 headache
[2] Studies where mean age was higher in patients without headache than with headache
[3] Studies where mean age was similar between with and without headache in COVID

**Table 10.2** The frequency of COPD, cancer, and smoking in patients with COVID-19 headache

| Studies and comorbidities | | With headache ((%(N)) | Without headache ((%(N)) | *P* value |
|---|---|---|---|---|
| *Chronic obstructive pulmonary disease (COPD)* | | | | |
| Group1 studies[1] | Dos Anjos de Paula RC et al. 2021* | NO DATA | NO DATA | NO DATA |
| | Porta-Etessam J et al. 2020** | NO DATA | NO DATA | NO DATA |
| Group2 studies[2] | Trigo J, et al. 2020 | NO DATA | NO DATA | NO DATA |
| | Gonzalez -Martinez A et al. 2021 | NO DATA | NO DATA | NO DATA |
| | Membrilla JA et al. 2020 | NO DATA | NO DATA | NO DATA |
| Group3 studies[3] | Karatas O, et al. 2021 | 10.8% (9/83) | 4.4% (9/204) | 0.077 |
| *Cancer* | | | | |
| Group1 studies[1] | Dos Anjos de Paula RC et al. 2021* | 8.3% (2) | NO DATA | NO DATA |
| | Porta-Etessam J et al. 2020** | NO DATA | NO DATA | NO DATA |
| Group2 studies[2] | Trigo J, et al. 2020 | 13.1% (18/137) | 17.3% (76/439) | 0.249 |
| | Gonzalez -Martinez A et al. 2021 | NO DATA | NO DATA | NO DATA |
| | Membrilla JA et al. 2020 | 2.0% (2/99) | 2.2% (1/46) | >0.999 |
| Group3 studies[3] | Karatas O, et al. 2021 | NO DATA | NO DATA | NO DATA |
| *Smoking* | | | | |
| Group1 studies[1] | Dos Anjos de Paula RC et al. 2021* | 16.6% (4) | NO DATA | NO DATA |
| | Porta-Etessam J et al. 2020** | NO DATA | NO DATA | NO DATA |

(continued)

**Table 10.2** (continued)

| Studies and comorbidities | | With headache ((%(N)) | Without headache ((%(N)) | *P* value |
|---|---|---|---|---|
| Group2 studies[2] | Trigo J, et al. 2020 | 14.6% (20/137) | 22.3% (98/439) | 0.050 |
| | Gonzalez -Martinez A et al. 2021 | 38% (18/47) | 28% /93/329) | 0.173 |
| | Membrilla JA et al. 2020 | NO DATA | NO DATA | NO DATA |
| Group3 studies[3] | Karatas O, et al. 2021 | NO DATA | NO DATA | NO DATA |

*(mean age: 53.8) **(mean age: 43.4)
[1] Studies that included only patients with COVID-19 headache
[2] Studies where mean age was higher in patients without headache than with headache
[3] Studies where mean age was similar between with and without headache in COVID

**Table 10.3** The frequency of obesity and CRF and prior history of headache in patients with COVID-19 headache

| Studies and comorbidities | | With headache ((%(N)) | Without headache ((%(N)) | *P* value |
|---|---|---|---|---|
| *Obesity* | | | | |
| Group1 studies[a] | Dos Anjos de Paula RC et al. 2021* | 12.5 (%) | NO DATA | NO DATA |
| | Porta-Etessam J et al. 2020 ** | NO DATA | NO DATA | NO DATA |
| Group2 studies[b] | Trigo J, et al. 2020 | NO DATA | NO DATA | NO DATA |
| | Gonzalez -Martinez A et al. 2021 | NO DATA | NO DATA | NO DATA |
| | Membrilla JA et al. 2020 | NO DATA | NO DATA | NO DATA |
| Group3 studies[c] | Karatas O, et al. 2021 | 33.7% (28/83) | 24% (49/204) | 0.124 |
| *Chronic renal failure (CRF)* | | | | |
| Group1 studies[a] | Dos Anjos de Paula RC et al. 2021* | 8.3% (2) | NO DATA | NO DATA |
| | Porta-Etessam J et al. 2020** | NO DATA | NO DATA | NO DATA |
| Group2 studies[b] | Trigo J, et al. 2020 | NO DATA | NO DATA | NO DATA |
| | Gonzalez-Martinez A et al. 2021 | 6% (3/48) | 8% (12/323) | 0.424 |
| | Membrilla JA et al. 2020 | NO DATA | NO DATA | NO DATA |
| Group3 studies[c] | Karatas O, et al. 2021 | NO DATA | NO DATA | NO DATA |

**Table 10.3** (continued)

| Studies and comorbidities | | With headache ((%(N)) | Without headache ((%(N)) | *P* value |
|---|---|---|---|---|
| *Prior history of headache* | | | | |
| Group1 studies[a] | Dos Anjos de Paula RC et al. 2021* | NO DATA | NO DATA | NO DATA |
| | Porta-Etessam J et al. 2020** | 25.9% (29/112) | NO DATA | NO DATA |
| | Rocha-Filho PAS et al. 2020 | 64% (30/47) | NO DATA | NO DATA |
| | Uygun Ö et al. 2020 | 44.27% (116/262) | NO DATA | NO DATA |
| Group2 studies[b] | Trigo J, et al. 2020 | 10.9% (15/137) | 3.9% (17/439) | 0.002 |
| | Gonzalez -Martinez A et al. 2021 | NO DATA | 65% (15/23) | NO DATA |
| | Membrilla JA et al. 2020 | 33.3% (33/99) | 6.5% (3/46) | <0.001 |
| Group3 studies[c] | Karatas O, et al. 2021 | 14.5% (12/83) | 10.3% (21/204) | 0.425 |

*(mean age: 53.8) **(mean age: 43.4)
[a] Studies that included only patients with COVID-19 headache
[b] Studies where mean age was higher in patients without headache than with headache
[c] Studies where mean age was similar between with and without headache in COVID

The mechanic effects of hypertension on COVID-19 infection remain controversial. Some studies have shown that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blocker (ARB) agents are widely used in the treatment of HT. These drugs would cause an increase in ACE type 2 (ACE-2) expression [5]. In addition, the increased ACE-2 expression will facilitate the cellular invasion of the virus. Whether this predisposes the host to COVID-19 infection remains controversial [6].

Large-scale studies also support this foresight of HT in COVID-19 disease [7]. Hypertension is the most common chronic disease (27%–39.8%) in patients with COVID-19 headache [2, 3, 8, 9].

In a study conducted in Turkey, the presence of HT is more common in COVID-19 patients with headache than in those without headache. However, the striking feature in this study is that COVID-19 patients with and without headache are in the similar age range (39.8% vs. 23.0%) [9].

The prevalence of hypertension in COVID-19 patients with and without headache varies according to the age group included in the studies. In some studies, since the mean age of COVID-19 patients without headache was higher than those with headache, the frequency of HT was also higher in this non-headache group (48% vs. 27%) (56.5% vs. 38%) [2, 3].

*Diabetes mellitus (DM)* affects millions of people around the world, and the number of diabetic people increases day by day. Also, it is the most common

endocrinological disease with vascular, neuronal, and renal complications and mortal consequences.

Inflammatory dysfunction in diabetic patients may predispose to infections [10]. ACE-2 receptor and furin protease expression increases in diabetic patients [11]. Furin is an enzyme that is defined as type 1 membrane-dependent protease. Binding of the virus to the ACE-2 receptors increases furin production.

New studies suggested that furin facilitates the infective process of the virus. Furin binds to human protease and facilitates virus entry into the host cell and escapes from the immune system in COVID-19 [7, 12, 13].

DM is the second most common chronic disease with the frequency of 12%–16.6% in COVID-19 patients with headache [3, 8]. There are different data worldwide in terms of COVID-19 headache and DM coexistence.

In a large-scale study based in Spain, the frequency of DM in COVID-19 patients was found to be higher in patients without headache than in those with headache (21.2% vs. 14.6%) [2]. However, in a small study based in Spain, the frequency of DM was found to be similar in patients with and without COVID-19 headache (12% vs. 12%, respectively) [3].

In a study conducted in Turkey, patients with and without headache were selected from similar age groups in COVID-19 patients. As a result of the study, the frequency of diabetes was found to be higher in COVID-19 patients with headache (16.9%) than in those without headache (8.7%) [9].

In addition, in a study conducted in Madrid, a younger population was included in the study, and DM was not detected in any patient with COVID-19 headache [14]. As a result, DM coexistence in individuals with COVID-19 headache is under the influence of many factors such as age, gender, and study plan.

*Coronary artery disease (CAD)*: The balance of ACE-1 and ACE-2 regulated by the renin-angiotensin system (RAS) plays a crucial role in the functional continuity of the cardiovascular system. Different products of these enzymes show opposite effects such as vasoconstriction, pro-inflammation, sympathetic nervous system stimulation, vasodilatation, and antithrombotic and antiarrhythmic properties. Therefore, as COVID-19 targets ACE-2 receptors, it is also important to detect cardiac diseases in these patients [10, 15]. The frequency of comorbidity of COVID-19 headache and CAD is 9.6% to 13.9% in studies [2, 9].

In a study including patients of the same age and gender in Turkey, when patients with (9.6%) and without (4.4%) headache due to COVID-19 were compared, CAD rates were found to be similar between the two groups [9]. In another study conducted in Spain, the age range of COVID-19 patients with headache was younger than those without headache. As a result of the study, CAD was found to be significantly lower in cases with headache (13.9%) compared to cases without headache (30.8%) [2].

*Stroke*: There may be a direct and/or indirect relationship between COVID-19 and cerebrovascular diseases. However, the etiology of the coexistence of the two diseases has not been clarified. Concentration of ACE-2 receptors in cardiac cells can increase cardiovascular complications. The pro-inflammatory process that occurs during infection may trigger atherosclerotic complications and cause this

coexistence [7]. There are few studies that address chronic neurological diseases such as stroke in cases with COVID-19 headaches. In a study from in Spain, chronic neurological disease (9.5% vs. 2%) was more common in patients with COVID-19 headache. In another study from Turkey, the frequency of stroke was particularly high (1.5% vs. 10.8%) [2, 9].

*Chronic obstructive pulmonary disease (COPD)* is a comorbid disease associated with prolonged hospitalization and high mortality in COVID-19 patients [16]. COPD is associated with chronic hypoxia, hypercapnia, secondary sleep apnea, and sleep disturbance. Accordingly, there are studies showing the frequency of COPD and headache [17]. The relationship between COVID-19 headache and COPD contains some controversial. In most of the studies, there is no information about COPD in individuals with COVID-19 headache. However, a study conducted in Turkey did not find the significant association between COVID-19 headache and COPD (9.6% vs. 4.9%) [9].

*Cancer*: Cancer patients, especially those with lymphoid and hematopoietic system cancers, are immunocompromised due to immunosuppressive therapies and are in the risk group for COVID-19 [10]. In terms of comorbidity of COVID-19 headache and cancer, the data were very limited, and the frequency was reported as 8.3%–13.1% [8]. The presence of cancer was not observed as a risk factor in COVID-19 headache [2].

*Smoking* is one of the most modifiable risk factors for vascular diseases. Smoking increases platelet adhesion with its nicotine content and causes peripheral vasoconstriction by causing the release of catecholamines. This causes microvascular occlusion and tissue hypoxia. It has an irritant and toxic effect on the bronchial epithelium and alveoli in the respiratory system. It primarily affects the respiratory system with ciliary dysfunction accompanied by inflammation and increased secretion [18]. Also, smoking has been shown to have a poor prognostic effect for COVID-19 [19]. In addition, it has been said that smoking may predispose to neurological findings in COVID-19 [20]. The prevalence of smoking (14.6% to 38%) in COVID-19 patients with headache has been reported. As a result, no significant association was found between COVID-19 headache and smoking [2, 3].

*Obesity*: The obesity was not considered a risk factor for COVID-19 in studies originating from China, Italy, and the United States, but in North America and Europe, the incidence of obese people infected with COVID-19 was higher than those of normal weight [7]. However, while there is not enough data on this subject, the coexistence of COVID-19 headache and obesity is a much more limited field of study. In studies, the prevalence of obesity in cases with COVID-19 headache is between 12.5% and 33.7% [8, 9].

*Chronic renal failure (CRF)*: Isolation of coronavirus from urine samples suggests that the renal system is also a potential target for COVID-19. There is a rise in ACE-2 expression in renal diseases, so these cases are more easily affected by COVID-19 (7). The frequency of CRF in cases with COVID-19 headache has been reported as 6% to 8.3% [3, 8]. But CRF has not been reported as a risk factor for COVID-19 headache [3].

*Headache* is more common in COVID-19 patients with a history of primary headache especially migraine [1, 2].

Goadsby and collages declared that the rise of angiotensin 2 in the blood causes an increase in calcitonin gene-related peptide (CGRP), which has an active role in the etiopathogenesis of migraine [21]. On the other hand, there are publications stating that CGRP is decreased in COVID-19 patients and that COVID-19 headache cannot be associated with CGRP. The role of CGRP in COVID-19 headache is still controversial.

There are studies on pain development and modulation of the renin-angiotensin system (RAS). Angiotensin 2 is said to be a potent inflammatory-immunological response modulator involved in different painful conditions affecting central and peripheral neuronal functions. Increased angiotensin levels in COVID-19 patients may trigger nociceptive stimulation, resulting in increased pain response [22].

COVID-19 headaches are generally in the clinics of tension headache and/or migraine-like headache, and this finding does not arouse much surprise. However, in patients with a history of headache, it is generally observed that the headache character changes during the COVID-19 process [8]. The presence of a history of headache in cases with COVID headache varies between 25.9% and 64% [15, 23].

In addition to many studies showing that a history of headache is more common in cases with COVID-19 headache (10.9% vs. 3.9%, 33.3% vs. 6.5%, 57.2% vs. 42.8%) [2, 24, 25], there are also studies showing the opposite (25% vs. 75%) [8].

## 10.2 Gender Susceptibility in COVID-19 Headache

Clinical manifestation of COVID-19 mostly differs by age, gender, and other comorbidities.

Looking at past case series, it has been observed that the susceptibility of male and female genders to COVID-19 infection is similar in some, while some studies have shown that the prevalence of COVID-19 is more common in men over 50 years of age than in women. There are also publications stating that the disease is four times more common in men, regardless of age [26]. There are many publications showing that COVID-19 is more complicated and severe in men. Mortality rates were also higher in men [27].

While addressing the gender difference in headache due to COVID-19, the unequal distribution of the disease between the sexes is also an important factor. Many mechanisms have been implicated in explaining the difference between the genders.

In order to explain this gender difference, factors such as the anti-inflammatory property acquired by the second X chromosome, the anti-inflammatory properties of sex hormones, and gender-related behaviors were evaluated in previous studies.

ACE-2 is the most studied and most mentioned element in the publications to explain the gender difference in the frequency of being infected with COVID-19,

mortality rates, and accompanying symptoms, especially headache. Expression and activity of the ACE-2 are higher in men than in women [28].

The gene encoding ACE-2 is located on the X chromosome. In females, one of the two X chromosomes is silenced during development; the other is more dominant. X inactivation is to ensure balanced gene expression between the sexes. Nevertheless, some of the genes, most of which are localized on the short arm (p) of the X chromosome, may escape inactivation. This may explain the differences in ACE-2 between the genders [29].

While examining the difference between the genders of headache, it is useful to mention the effect of hormones. While addressing the clinical differences between the genders during the COVID-19 infection and COVID-19 headache, two enzymes under the control of hormones were emphasized. One of them is ACE-2, which we have mentioned at length above, and the other is transmembrane protease serine 2 (TMPRSS2). Estrogens produced by the ovary promote ACE-2 expression. ACE-2 also plays a role in the local response after the virus enters the body. ACE-2 is not only an entry-way aid for viral infection but also a protective factor in the severity of the disease. The absence of an increased pool of ACE-2 in men due to low estrogen increases tissue injury and disease severity in men compared to women with the same viral load [30]. Differences in ACE-2 expression caused by sex hormones may cause this gender disparity in disease severity [31]. TMPRSS2 is another key protein for the spread of COVID in the human body. Androgen receptors play an important role in the transcription of TMPRSS2. Androgens produced by the testicles lead to increased TMPRSS2 expression. While this supports viral entry in men, low androgen levels in women may keep TMPRSS2 expression at low levels, which is more protective for the development of COVID-19 infection [30].

If we look at it in terms of gender difference, the fact that female hormones have a pronounced anti-inflammatory feature may benefit women both in the mild course of the disease and in the development of COVID-19-related headache.

Headaches associated with COVID-19 usually occur early in the disease and tend to be of a migrainous character. It is said that there is no significant relationship between the severity of the disease and the frequency of headache development [1, 8].

It was observed that the severity of migraine ($8.91 \pm 7.18$ vs. $6.33 \pm 6.97$) and the rate of analgesic use ($3.97 \pm 2.60$ vs. $2.42 \pm 2.04$) increased significantly in female patients after COVID-19. While there was a significant increase in the severity of attacks in young patients with tension-type headache after infection ($13.0 \pm 8.30$ vs. $11.75 \pm 7.67$), a significant increase was observed in the use of analgesics in female patients ($3.93 \pm 2.01$ vs. 0). Considering the severity of headache, it tended to be more severe in male patients than in females [32].

In studies investigating patients with headache in the acute phase of the disease, female dominance was mentioned. In the studies of Corona et al. and Toptan et al., the proportion of women with COVID-19 headache was found to be 50.2% and 69.2%, respectively [1, 33].

It has been observed that patients who have had any previous headache, especially migraine, develop headache due to COVID-19 more frequently than without

headache. In the studies, these rates were given as 14.1% vs. 7.8%, 25.3% vs. 6.5%, and 14.5% vs. 10.5%, respectively [9, 21, 24].

There are statements that women are more affected by social isolation and that they develop more anxiety with the difficulties brought by the pandemic. Stress and anxiety, as triggering factors in headache, may affect women more [34, 35]. In addition, it can be said that anxiety is distributed unequally between the sexes, since the health of the family, home arrangement, and the programming of social life are mostly the workload of women and the deteriorating health of one of the family members affects more women negatively.

Although headache is more common in women, there are also publications reporting adverse results in COVID-19 headache. It is possible to explain this male dominance in COVID-19 headache by the fact that the disease affects men more prominently [8, 25]. In different publications, the rates of these male patients are given as 66.6% and 57.8%, respectively [9, 36].

Karadaş et al., in their study that included 287 COVID-19 patients, found that the frequency of having primary headache was similar between patients with and without headache. When patients with COVID-19 headache were examined, it was seen that the history of primary headache was more common in women (25.7% vs. 6.3%). In patients with COVID-19 headache, they did not find a significant difference between the genders in terms of headache phenotype [9].

When examining the long-term effects of COVID-19, different results on gender distribution have been reported. Although some studies have found that post-COVID-19 symptoms are more common in women, there are also publications stating that there is no gender difference [37].

From one point of view, it can be said that the fact that primary headaches are more common in women may cause female predominance in COVID-19 headache.

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# Chapter 11
# Long-Term Effects of COVID-19 and ICU on Headache Disorders


**Cristina Gaglianone, Enrico Bentivegna, and Paolo Martelletti**

## 11.1 Introduction

SARS-Cov-2 infection can present with several manifestations. In particular, symptoms of COVID-19 vary according to the severity of the disease [1]. Although most patients have a favorable evolution, some patients develop extremely severe symptoms and require treatment in an ICU [2]. The most characteristic manifestations are represented by respiratory symptoms (as cough and dyspnea) and fever; however, some patients may develop neurological manifestations, among which headache is not infrequent [3].

Furthermore, COVID-19 infection significantly increased the risk of developing major long-term sequelae: symptoms that persist beyond the onset of infection, called post-COVID-19 syndrome [4], and defined by the National Institute for Health and Care Excellence (NICE) guidelines as "manifestations that develop during or after COVID-19 infection, continue for more than 12 weeks (3 months) and cannot be explained by an alternative diagnosis" [5].

Similarly to the acute phase, also in the post-COVID syndrome various organs and systems such as the respiratory, cardiovascular, neurological, and gastrointestinal systems can be affected [6].

If we consider the huge number of people who have been infected with this virus, it is easy to understand how this aspect could affect a large part of the population. Indeed, more than 500 million people had survived COVID-19 by the end of June 2022 [7].

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This is especially true for those patients who have been hospitalized in the ICU for which it is possible to recognize a post-ICU syndrome [8], a set of symptoms that frequently occur in critically ill patients after discharge from intensive care commonly defined as PICS (post-intensive care syndrome) [9, 10].

## 11.2 COVID-19 and Headache

Among the different manifestations, headache represents a common symptom experienced at the acute phase of the infection [11–14].

No wonder, considering the fact that headache is often referred to as a symptom accompanying viral infections including those caused by respiratory viruses, so much that the International Classification of Headache Disorders 3rd edition (ICHD-3) recognizes viral infections as a possible cause of secondary headache. In this case the headache can be triggered by several mechanisms such as fever and the production of cytokines, including interferon, by the host's immune system [15, 16].

Available reports related to headache prevalence in patients with COVID-19 are summarized in Table 11.1.

Additionally, headache represents a recurring sequela in COVID-19 survivors [13].

Headache can occur in long COVID both in patients who already suffered from migraines and as a new onset symptom. Furthermore, headache associated with

**Table 11.1** Reports on headache prevalence in COVID-19 patients

| |
|---|
| **Prevalence of headache in patients with COVID-19: a systematic review and meta-analysis of 14,275 patients.** |
| *Caronna et al.* |
| **SAMPLE:** 14,275 patients. |
| **HEADACHE PREVALENCE:** 10.1% |
| **Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study** |
| *Tao Chen et al* |
| **SAMPLE:** 1,099 patients |
| **HEADACHE PREVALENCE: 13,65%** |
| **Clinical characteristics of 3062 COVID-19 patients: A meta-analysis** |
| *Jieyun Zhu et al* |
| **SAMPLE:** 3,062 patients |
| **HEADACHE PREVALENCE** |
| **Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China** |
| *Dawei Wang et al* |
| **SIMPLE:** 138 patients |
| **HEADACHE PREVALENCE: 6,5%** |
| **The international European Academy of Neurology survey on neurological symptoms in patients with COVID-19 infection** |
| *E. Moro et al* |
| **SIMPLE:** 2343 phisician (interviewed on patients with COVID-19) |
| **HEADACHE PREVALENCE:** 61,9% |
| **Spectrum of Headaches Associated With SARS-CoV-2 Infection: Study of Healthcare Professionals** |
| *Jesús Porta-Etessam MD et al* |
| **SIMPLE:** 112 patients |
| **HEADACHE PREVALENCE:** 17,9% |

COVID-19 infection would appear to be more resistant to symptomatic therapy which is normally effective in headache patients [17].

Considering that the presence of long-term symptoms can lead to limitations in daily life, it is important to determine whether the development of consequences such as headache could be related to the initial severity of the disease and therefore whether patients admitted to the ICU may be at increased risk of developing symptoms of long COVID and in particular headache. The answers are important to ensure best care for COVID-19 survivors.

## 11.3 Neurological Manifestations: Pathogenetic Mechanisms of Post-ICU Syndrome

Neurological symptoms related to SARS-Cov-2 infection are reported with increasing frequency in the literature, especially for patients admitted to intensive care. Understanding the mechanisms involved not only in neurological manifestations, but more generally in the pathogenesis of long COVID disease, can represent the key to guaranteeing the patient an effective and timely care.

## 11.4 Post-ICU Syndrome

Unfortunately, the sequelae that afflict patients after admission to intensive care are not uncommon. Indeed, it is estimated that this affects about half of the patients who survive intensive care [18]. While the discharge of critically ill patients from intensive care can be a success, we cannot overlook the long-term consequences that determine a reduction in the life quality of patients in terms of both physical and mental health and thus compromising the long-term prognosis. As we have said, the problems that arise on physical and mental level after discharge from intensive care are defined as *post-ICU syndrome*. Furthermore, the post-ICU syndrome (PICS) does not refer only to the patient's health, such as the physical and mental impairments that develop during and after admission to intensive care, but this concept extends to the family sphere including the mental state and the effects on the patient's family so much that it is possible to identify a post-intensive care syndrome affecting family members of these patients known as PICS-F [19].

The manifestations that the patient can present in PICS are mainly physical impairment and cognitive and psychiatric impairment.

Muscle weakness is one of the most characteristic consequences of PICS. This is characterized by polyneuropathy and myopathy (or both) and is linked to several factors such as microvascular and nervous ischemia and prolonged immobility. Muscle weakness also affects respiratory muscles: mechanical ventilation and sedative drugs favor a disuse-mediated atrophy through neural inhibition of the

respiratory muscles leading to a thinning of the diaphragm visible on CT scans in just 2 days [20].

In addition, the severe stress to which these patients are subjected also has consequences on a cognitive and mental level.

Indeed, many of these patients develop memory impairments, executive function deficits, and speech and attention disorders. Very frequent are also anxiety, depression, as well as post-traumatic stress disorder [19].

The risk factors involved in the development of neurological sequelae and cognitive impairment in critically ill patients can be manifold. In addition to the patient's pre-existing conditions, such as previous morbid conditions, advanced age, and pre-existing cognitive deficits, factors such as sepsis, hypoxia (respiratory failure and acute respiratory distress syndrome, cardiac arrest) [10], hypotension, trauma, hypoglycemia, and prolonged mechanical ventilation can play a key role. These conditions can be at the basis of vascular lesions and neuroinflammation which in turn can lead to an interruption of the blood-brain barrier, hyperinflammatory state, and oxidative stress with activation of microglia, mainly at the limbic level [21]. Several researches support the hypothesis of the involvement of the inflammatory response in the development of PICS. A study published in 2018 showed that patients who had higher levels of IL-6 and IL-10 after ICU admission had worse long-term cognitive performance (but not functional status) up to 4 years after discharge from ICU [22].

If all this occurs in patients who have faced with serious illness and have survived, we ought to wonder what the recovery of patients hospitalized for severe COVID will entail. These patients in fact not only suffer the consequences of hospitalization but bear the burden of a disease linked to a pandemic, therefore a completely new and scary situation. Let's remember that, for example, while family support is an important factor in terms of care, these patients have to face this path alone due to the contagiousness and risk of this new infection.

These aspects imply that COVID-19 must be addressed on two levels: one linked to the acute phase and therefore to the immediate threat to life and the other that instead deals with the long-term consequences and by equating the effects on physical and mental health.

However, if it is now established that hospitalization in ICU can be the cause of psycho-physical disorders, the evidence that intensive care can cause the development of headache after the discharge of the patient with COVID-19 is still scarce.

Regarding SARS-Cov-2, the mechanisms by which the virus damages brain tissue can be multiple and schematically described as:

1. *Mechanism of direct damage*:

   - Direct brain invasion and neuronal pathway such as axonal transport along the fibers of the olfactory nerve.
   - ACE2 receptor through which the virus penetrates inside the cells. Indeed, these receptors are expressed in high numbers on glial cells and neurons [23].

2. *Mechanism of indirect damage*:

- Hypoxia: due to exchange disorders in the lungs induced by the pulmonary inflammatory pattern both at the alveolar and interstitial level.
- Immune-meditated neurologic injury: hyperinflammatory syndrome accompanied by massive release of cytokines. This occurs in the most severe cases in the so-called secondary hemophagocytic lymphohistiocytosis (sHLH) characterized by fulminant and fatal hypercytochemia with multi-organ failure [24].

Regarding headache, if in the acute phase purely neurological factors such as micro-emboli in brain tissue, blood-brain barrier dysfunction, and neuroinflammation leading to coagulopathy may contribute to its development, as regards the development of symptoms in the long term, factors related to hospital admission such as mechanical ventilation and medications such as sedatives according to the aforementioned post-intensive therapy syndrome can be involved [4].

A study conducted in 2020 on patients with COVID-19 admitted to the intensive care unit diagnosed with acute cerebrovascular disease describes brain biopsies of these patients with extensive intraparenchymal hemorrhage and fibrin microthrombi observed at different points in the brain tissue. A noteworthy aspect was represented by the alterations in the walls of the small arterioles as capillaries and venules, with endothelial cell injury, degeneration of the neuropil at the level of the capillaries due to edema or extravasation of macromolecules, and local inflammatory state [3].

Microvascular thrombi, systemic inflammation, and direct viral-mediated neurotoxicity are hypothesized to be the possible mechanisms contributing to neuropathology in COVID-19 [25, 26].

These pathophysiological mechanisms could not only explain the increased incidence of cerebrovascular events in patients with COVID-19, but it can represent the cause of neurological manifestations, such as headache, which occur in COVID-19 patients not only in the acute but also in the chronic phase.

Since headache represents one of the most frequent symptoms in COVID-19 infection, it is easy to ask whether this may represent a prognostic factor of the disease. In a prospective study conducted by Caronna and colleagues, 130 patients hospitalized in the ER for COVID-19 were compared (11 patients required hospitalization in the ICU). About 74% of patients had headache as a symptom associated with infection, and of these, 19.6% had a personal history of pre-existing headache in the absence of chronic migraine cases.

Comparing patients with and without headache, it was found that patients who had headache among the symptoms reported at the onset of the disease or at hospitalization had a shorter duration of the disease. According to this study, headache would predict a better prognosis showing a shorter duration of disease of about 1 week [27].

A recent meta-analysis shows that headache is experienced more in non-hospitalized patients than in those hospitalized for COVID-19 (57% vs. 31%) [13]. The study also shows a decreasing prevalence of headache after illness with no significant differences between the two patient groups [27].

Several researches attempted to understand which neurological symptoms were prevalent among those of long COVID. For this purpose, a meta-analysis and systematic review was published in December 2021 [11]. The research included both neuropsychiatric symptoms such as anxiety, panic attacks, depression, sleep disturbances, and post-traumatic stress disorder or symptoms and neurological symptoms such as headache, paresthesia, dizziness, and vertigo. Fatigue, which is a frequent post-COVID symptom, was also reported.

The primary outcome was the pooled prevalence of each symptom, while the secondary outcome was the assessment of disease severity both in terms of ICU admission and World Health Organization (WHO) severity scale [28].

Regarding the prevalence of long COVID symptoms, according to the literature, the most frequent were sleep disturbance (27.4%), fatigue (24.4%), cognitive impairment (20.2%), anxiety (19.1%), and post-traumatic stress (15.7%). Neurological symptoms such as headache, dysgeusia, sensory-motor symptoms, dizziness, and vertigo were less frequent but present in significant quantities with a cumulative prevalence of <10% for each [11].

In particular, of the 51 studies that were included in the research, 15 treated headaches for a total of 4023 patients with a pooled prevalence of 0.066 (95% CI 0.036–0.12%).

Regarding the secondary outcome, there was no difference in the prevalence of any symptoms between hospitalized and non-hospitalized samples (with the exception of anxiety, which was reported more frequently in non-hospitalized samples) or between patients admitted to intensive care or with a “critical” or “severe” disease according to the WHO scale.

The prevalence of symptoms appears to be relatively stable during the first 6 months after infection regardless of the severity of the initial infection. Thus, there would appear to be no significant differences between hospitalized and non-hospitalized patients or between hospitalized and ICU patients [11].

A similar study was published in January 2022 in which 18 studies were analyzed, involving a total of 10,530 patients [4]. Also in this case, the prevalence of neurological and neuropsychiatric symptoms in long COVID was taken as the primary outcome and the difference in terms of prevalence of these symptoms between hospitalized and non-hospitalized patients and between hospitalized and ICU patients as a secondary outcome. The most frequently reported neurological symptoms were fatigue (37%), brain fog (32%), memory issues (28%), attention disorder (22%), myalgia (17%), anosmia (12%), and dysgeusia (10%), while for headache the prevalence was 15%. Among the most frequent neuropsychiatric symptoms, we can find sleep disturbances (31%), anxiety (23%), and depression (17%).

As regards headache, according to the literature, this represented one of the most expressed symptoms in the acute phase together with anosmia and dysgeusia, but its prevalence was lower in the months following the infection: among hospitalized patients it was present in 25% of cases, while a higher percentage was found in the population of patients not hospitalized for COVID-19, equal to 52% [4].

Compared to non-hospitalized patients, patients hospitalized for COVID-19 showed a reduced frequency of headaches at 3 (or more) months after infection. In

accordance with the above, once again headache would seem to be prevalent in the non-hospitalized patient population. Additionally, study groups showed that ICU patients during acute COVID-19 experienced a higher prevalence of fatigue, anxiety, depression, and sleep disturbances as prevalent symptoms than groups with fewer critically ill patients [4].

The cited studies are summarized in Table 11.2.

**Table 11.2** Prevalence of post COVID-19 headache in the literature

| |
|---|
| **Headache: A striking prodromal and persistent symptom, predictive of COVID-19 clinical evolution.** |
| *Caronna et al.* |
| **AIM:** To define headache characteristics and evolution in relation to COVID-19 |
| **SAMPLE:** 130 COVID-19 patients recruited at the ER |
| **FINDING:** |
| 1. 74.6% (97/130) had headache. |
| 2. Clinical duration of COVID-19 was shorter in the headache group (23.9 ± 11.6 vs. 31.2 ± 12.0 days; p = 0.028) |
| 3. Headache associated with COVID-19 is predictive of a shorter duration of the desease. |
| **Headache as an acute and post-COVID-19 symptom in COVID-19 survivors: A meta-analysis of the current literature.** |
| *Fernández-de-Las-Peñas et al.* |
| **AIM:** To synthesize the prevalence of post-COVID headache in hospitalized and non-hospitalized patients recovering from SARS-CoV-2 infection |
| **SAMPLE:** 28 peer-reviewed studies and 7 preprints were included. The sample was 28,438 COVID-19 survivors |
| **FINDING:** |
| ***1.*** The overall prevalence of post-COVID headache was 47.1% (95% CI 35.8–58.6) at onset or hospital admission, 10.2% (95% CI 5.4–18.5) at 30 days, 16.5% (95% CI 5.6–39.7) at 60 days, 10.6% (95% CI 4.7–22.3) at 90 days, and 8.4% (95% CI 4.6–14.8) at ≥180 days after onset/hospital discharge; |
| ***2.*** Headache as a symptom at the acute phase was more prevalent in non-hospitalized (57.97%) than in hospitalized (31.11%) patients; |
| ***3.*** No significant differences in the prevalence of post-COVID headache between hospitalized and non-hospitalized patients were observed at any follow -up period; |
| ***4.*** Headache as a symptom at the acute phase of the disease was more prevalent in non-hospitalized patients (57.97%) than in hospitalized (31.11%) patients. |
| **Persistent neuropsychiatric symptoms after COVID-19: a systematic review and meta-analysis** |
| *Badenoch et al.* |
| **AIM:** To determine the prevalence of neuropsychiatric symptoms in survivors of COVID-19 |
| **SAMPLE:** 51 studies (n = 18917 patients) |
| **FINDING:** |
| ***1.*** The most prevalent neuropsychiatric symptoms werw sleep disturbance [pooled prevalence = 27.4% (95% confidence interval 21.4–34.4%)], fatigue [24.4% (17.5–32.9%)], objective cognitive impairment [20.2% (10.3–35.7%)], anxiety [19.1% (13.3–26.8%)] and post-traumatic stress [15.7% (9.9–24.1%)]. Classically 'neurological' symptoms such as dysgeusia, headache and dizziness/vertigo were less frequent but present in non-negligible amounts (pooled prevalence <10% for each). |
| ***2.*** With the exception of anxiety, which was reported more frequently in non-hospitalized samples, there was no evidence of a differential prevalence of any symptom among hospitalized versus non-hospitalized samples, nor among patients admitted to ICU/having WHO 'critical' or 'severe' illness versus those not requiring ICU. |
| **Mid and long-term neurological and neuropsychiatric manifestations of post-COVID-19 syndrome: A meta-analysis.** |
| *Premraj et al.* |
| **AIM:** To determine the prevalence of neurological and neuropsychiatric symptoms in survivors of COVID-19 |
| **SIMPLE:** 18 studies (n = 10530 patients) |
| **FINDING:** |
| ***1.*** The most frequently reported neurological symptoms were: fatigue (37%), brain fog (32%), memory issues (28%,), attention disorder (22%), myalgia (17%), anosmia (12%), dysgeusia (10%) while for headache the prevalence was 15%. Among the most frequent neuropsychiatric symptoms we can find sleep disturbances (31%), anxiety (23%) and depression (17%); |
| ***2.*** Cohorts with >20% of patients admitted to the ICU during acute COVID-19 experienced higher prevalence of fatigue, anxiety, depression, and sleep disturbances than cohorts with <20% of ICU. |

## 11.5 Conclusions

From a preliminary analysis of the data, it is possible to conclude that:

- Headache represents one of the most frequent symptoms in the acute phases of COVID-19; its prevalence appears to be lower in the months following the infection, while the most frequent symptoms are fatigue, brain fog, sleep disturbances, anxiety, and depression.
- Patients who had headache among the symptoms reported at the onset of the disease or at hospitalization appear to have a shorter duration of the disease.
- Headache is experienced more in non-hospitalized patients than in those hospitalized for COVID-19.

There is so far little evidence that these persistent symptoms, and headache in particular, could be related to the severity of the initial infection. Although, from a first analysis it would seem that the headache that occurs in the post-COVID is not related to the severity of the acute SARS-Cov-2 infection, further studies are needed.

The answer to these issues should be sought in order to be able to recognize patients who are more likely to develop disabling consequences such as headache. This would make it possible to intervene in the preventive phase and improve patient care in the follow-up and when necessary in therapy.

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# Chapter 12
# Nociplastic Pain in COVID-19

**Çile Aktan, Gozde Celik, Didem Tuba Akçalı, and Hayrunnisa Bolay**

## 12.1 Background and Objective

SARS-CoV-2 caused COVID-19 pandemic and it has been continuing for the last 2.5 years. Major symptoms of the infection include fever, sore throat, cough, headache, fatigue, anosmia, ageusia, diarrhea, and anorexia. After acute COVID-19 infection, many patients report ongoing fatigue, shortness of breath, and regional or widespread pain, accompanied by headache [1–5].

Nociplastic pain is due to altered nociception with comorbid sleep disorders, hyperirritability, depression, and anxiety. Management of such a pain syndrome is challenging. The chapter briefly overviews nociplastic pain features of COVID-19 infection.

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## 12.2 Pain in COVID-19

Although the COVID-19 epidemic was first thought to be a respiratory infection only, it has been determined that it affects many systems over time. Patients apply to the doctor with neurological complaints, and headache is among the most common complaints. Neurological and neuropsychiatric symptoms associated with COVID-19, such as chronic pain, depression, and anxiety, have been described and are an area of ongoing research [6–10].

During the pandemic, hospitalized COVID-19 patients had chronic pain, especially nociplastic pain because of disease-related factors, increased anxiety, immobility, and social isolation [8].

The COVID-19-related headache was described as bilateral, throbbing or pressing, long-lasting (>12 h) secondary headache. Accompanying sensory symptoms were anosmia, diarrhea, and weight loss. COVID-19 included characteristics similar to migraine and/or atypical features including anosmia and diarrhea [5]. The throbbing, long-lasting COVID-19-related headache coincides with nociplastic migraine pain.

The most common primary headaches are migraine without aura (MWA) and tension-type headache (TTH). Primary headaches, chronic migraine, tension-type headache, and also chronic cluster headache are all examples of nociplastic pain [1, 3, 5].

According to another study investigating the relationship between COVID-19 and headache, 74.6% of patients suffered headache. Overall, 24.7% had severe pain with migraine-like symptoms. Anosmia/ageusia was more common in headache patients (54.6% vs. 18.2%). The clinical span of COVID-19 was shorter in the headache patients. 37.8% of patients reported a persistent headache after 6 weeks. 50% of them had no previous history of headache. In 21.4% of patients with permanent headache, headache was the first symptom of COVID-19 [11].

Pain is considered “nociceptive” when associated with an ongoing stimulus resulting from tissue damage either actual or threatened, or “neuropathic” when caused by an injury affecting the peripheral or central nervous system. Nociplastic pain has different features from nociceptive and neuropathic pain summarized in Table 12.1 [12–14].

In 2016, the International Association for the Study of Pain (IASP) proposed a third definition, as distinct from nociceptive and neuropathic pain: “nociplastic pain” [15]. Nociplastic pain can be described as pain arising from the modified function of pain-related sensory pathways in the peripheral or central nervous system and causing increased tenderness [16].

Preliminary factors for nociplastic pain are family history of chronic pain, childhood pain, underlying inflammatory diseases, and psychosocial, emotional, sexual, and physical abuse history. Triggering factors might be psychosocial stressors and gastrointestinal infections, as underlying inflammatory rheumatic diseases. Gastrointestinal infections and irritable bowel syndrome are organ-specific triggers [17].

**Table 12.1** Comparison of nociceptive, neuropathic, and nociplastic pain

| | Nociceptive | Neuropathic | Nociplastic |
|---|---|---|---|
| Cause | Tissue damage and activation of nociceptor | Disease or injury to the somatosensory system | Altered central pain processing and nociception |
| Stimulus | Injury inflammation | Neural pinching, irritation | Central nervous system excitability, inhibition |
| Quality | Sharp, stinging, dull ache | Burning, paresthesia, hyperalgesia, allodynia | Non-specific, sharp, paresthesia, dull ache |
| Clinical conditions | Acute trauma<br>Osteoarthritis<br>Rheumatoid arthritis<br>Bursitis | Diabetic neuropathy<br>Carpal tunnel syndrome<br>Complex regional pain syndrome<br>Sciatica | Fibromyalgia<br>Chronic migraine<br>Chronic tension-type headache<br>Chronic cluster headache |
| Management | Exercise<br>NSAID<br>Opioids | Exercise<br>Antiepileptic drugs (gabapentinoids)<br>SNRI | Education<br>Exercise<br>SNRI<br>TCA<br>Ketamine<br>Cannabis<br>Avoid opioids |

NSAIDs: non-steroidal anti-inflammatory drugs; SNRI: serotonin and noradrenaline reuptake inhibitor; TCA: tricyclic antidepressants

Headache is the second most common (64.7%) risk factor for long-lasting COVID-19 headache, consisting of nociplastic pain. Risk factors are female sex, primary headache, and headache during COVID-19 infection [18, 19].

Nociplastic pain is typically defined as dull, deep, and aching pain (terms typically together with nociceptive pain); however, most of the patients describe neuropathic features (e.g., burning or shooting), which resemble fibromyalgia. Headache alters both in site and severity and may be exacerbated by physical action, environmental factors (e.g., weather conditions), or emotional disturbance. Several patients reported dysesthesia, hyperalgesia, or allodynia. Activity-related pain and mechanical hyperalgesia result from mechanoreceptor sensory inputs gaining access to central pain-related neural systems [16].

The widespread pain is related to central sensitization. In post-COVID-19 syndrome a similar widespread pain pattern is acknowledged. Symptoms of fatigue, widespread pain, and cognitive impairment accompany pain that constitute nociplastic pain features [20].

In a study about prevalence of fibromyalgia developing after COVID-19 infections with symptoms, the prevalence of patients reporting fibromyalgia symptoms after COVID-19 was found to be 30%. This study suggests that in COVID-19 patients after recovery, clinical symptoms of fibromyalgia are common and that risk factors are obesity, besides male gender for post-COVID-19 fibromyalgia [21].

A study has shown that the COVID-19 patients had a remarkable prevalence of new-onset pain (65.2% vs. 11.0%) and also new headache (39.1% vs. 2.7%) compared to control group. New-onset chronic pain was more common in COVID-19

patients than in the control group (19.6% vs. 1.4%). No statistically difference was found in mean de novo pain severity and prevention of daily activities among the groups. Pain symptoms in COVID-19 were more commonly located in the head, neck, and lower extremities. New-onset fatigue was more common in hospitalized COVID-19 patients compared to controls (66.8% vs. 2.5%). Patients with anosmia had more new-onset pain compared to patients without anosmia (48.0% vs. 83.3%) [22].

## 12.3 Pain Mechanism in COVID-19

The exact mechanism is not yet known; however, many studies have tried to explain the headache associated with COVID-19. The first possibility might be that SARS-CoV-2 invades the trigeminal nerve endings in the nasal cavity [2]. In the brain (especially in neurons such as motor cortex, caudoputamen, thalamus, raphe nucleus, solitary tract, and nucleus ambiguus), ACE2 expression is detected other than cardiovascular distribution [23]. ACE is a key enzyme that produces angiotensin II (Ang II) and involved in vasoconstriction, pathogenesis of cardiovascular incident, and oxidative stress [2].

The second mechanism is the dysregulation of ACE2/Ang1–7/MasR axis as implicated in stroke, cognitive decline, Alzheimer's and Parkinson's disease, and pain [24]. In rat and human dorsal root ganglia (DRG) neurons, Ang II is locally produced and it is co-localized with substance P and calcitonin gene-related peptide (CGRP) which is an explanation of participation and function of Ang II in the nociception [25]. CGRP is a key neuropeptide in migraine which provokes headache. Ang II increases circulating levels of CGRP.

Another pain mechanism in COVID-19 is vascular pathogenesis where high expression of ACE2 was prominent in endothelial cells, which may cause trigeminovascular activation leading to headache [26]. It has been reported that the cytokine elevation and hypoxia are associated with headache. The virus can invade various tissues in the body and induce different pain manifestations [27]. During viral infection, the cause of myalgia is usually elevated interleukin-6 levels [28].

**Case Vignette**

*A 40-year-old woman was consulted with a bilateral, daily, severe, throbbing headache.*

*Headache increased with movement and was accompanied by photophobia and phonophobia and lasted 12–18 hours. Attack frequency was 20/month and she was using analgesics for every attack, more than 20 pills/month. The pain spread to the neck, back, and shoulders.*

*She had episodic migraine for 4 years.*

*Her history revealed COVID-19 infection 9 months ago and inactivated COVID-19 vaccine injection 1 month ago.*

*The patient had allodynia on the scalp. The greater occipital nerve (GON) region and pericranial area was tender. Her neurological examination was otherwise normal.*

This headache following COVID-19 infection was due to altered nociception, and there was no diagnosed nerve damage, implying that it was nociplastic pain.

After COVID-19 infection, the headache was accompanied by allodynia, long-lasting depression, anxiety, sleep, and memory impairment. In nociplastic pain also these comorbid symptoms are present.

Her episodic migraine responded to NSAIDs; however, long COVID-19 headache did not respond. GON block, supraorbital nerve (SON) block, and pericranial trigger point injections were performed. She was prescribed duloxetine for headache and quetiapine for sleep disturbance. Intravenous lidocaine and steroid infusion were applied with a limited response.

Nociplastic pain features dominated long-lasting COVID-19 headache. Most of the patients did not respond to NSAIDs as the treatment of nociplastic pain involves SNRIs and, GON block, and other treatments.

Post-COVID-19 headache and vaccine-related headache were similar to chronic migraine and more severe. The nociplastic character is common in all of them. COVID-19 vaccines have different side effects and headache is one of the best investigated side effects, such as fatigue, flu-like symptoms, and headache. Vaccine-related headache is defined as bilateral, throbbing or pressing, rarely fiery, stabbing, and/or pricking with an incidence of 30.6%. It is higher in mRNA-based vaccines (39–80%) compared to inactivated vaccines (13%). In patients with primary headache history, 55% reported vaccine-related increase in headache severity and frequency. They also confirmed that they were unresponsive to analgesics. Headaches were not prominent after each vaccination [29].

## 12.4 Treatment of Nociplastic Pain in COVID-19

It is substantial to recognize the nociplastic pain, since treatment is different. Nociceptive pain is less responsive to peripherally acting anti-inflammatory drugs and opioids, surgery, or injections [13].

Damage and pathology-targeted approaches (i.e., surgery, interventional procedures for joint, and anti-inflammatory drugs) should be used for nociceptive pain [14].

The basic treatment for nociplastic pain in COVID-19 is patient education. First of all, education should teach the biopsychosocial model, and patients should be encouraged for good lifetime habits, e.g., stress reduction, physical activity, weight management, and sleep hygiene. Self-care and a strong internal control should be encouraged. Non-pharmacological treatment is preferred because most medications have limited benefit and may cause side effects in nociplastic conditions [13, 14].

Psychological measures might include cognitive behavioral therapies and acceptance-based interventions, mindfulness, psychodynamic therapies, hypnotherapy, and biofeedback. These modalities can be included into a multidisciplinary program.

Dietary manipulation for chronic pain of fibromyalgia is a hypocaloric, raw vegetarian, and low fermentable oligo-, di-, and monosaccharide and polyol (FODMAP) diet, but the evidence was evaluated as being of poor quality [30].

Some patients might benefit from practitioner-administered integrative treatments. For example, acupuncture, massage, and naturopathic therapies may provide some effectiveness.

Nociplastic pain is less responsive to muscle relaxants, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids compared to nociceptive pain. Opioid treatment is strongly discouraged [13].

In nociplastic pain, mainly fibromyalgia, there are medications with regulatory approval which may differ among countries (e.g., pregabalin, duloxetine, and milnacipran approval for fibromyalgia and duloxetine approval for low back pain and musculoskeletal pain) [31].

Tricyclic antidepressants, gabapentinoids, and SNRIs acting on the CNS provide moderate benefits and infrequent side effects; fatigue and cognitive impairment may worsen. In fibromyalgia, chronic low back pain, and headache, small efficacy in pain and function was reported (e.g., 5–20 points on a 0–100 scale) with serotonin–norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, and NSAIDs in the short term. Intermediate to long-term outcomes were not frequently assessed [32].

Ketamine, an NMDA receptor antagonist, administration provided short-lived pain relief in CRPS type I and fibromyalgia patients. Long-term cognitive effects of ketamine and its neurotoxicity are not known. Further studies are needed for evidence-based ketamine treatment in nociplastic pain [33].

Cannabidiol (CBD) alone or CBD/tetrahydrocannabinol (THC) combination holds promise in nociplastic pain; still formal studies are required to use in patients at significant risk for side effects. These products may ease pain and useful for sleep problems and anxiety; in contrast they may exacerbate symptoms such as fatigue, cognitive difficulties, and anxiety. These side effects restrict the use of cannabis for COVID-19 patients [34].

In nociplastic pain of COVID-19, interventional pain treatments appear as an option where medical and noninvasive treatments are insufficient. In a study, it was found that GON blockades for controlling resistant headaches during COVID-19 are effective in pain control [4, 35].

Trans-nasal sphenopalatine ganglion block has been reported in a case report that low back pain in a patient can be modulated by anesthesia of the ganglion. Sphenopalatine ganglion block may alleviate the psychosomatic aspects of pain, but more studies are needed on this subject [36].

It is essential to treat acute pain in COVID- 19 to prevent chronic pain and overuse of analgesics. In patients with fibromyalgia, the amount of trigger and tender points and the severity of pain may increase after COVID-19. Injection of these points with a local anesthetic is quite effective in pain control in some patients.

When the pain is relieved, it becomes easier to adapt to the exercise, and the exercise makes it possible to be pain-free for a longer time [37].

Emerging treatments like neurostimulation methods have potential, still theoretical, and have insufficient evidence for treatment [38].

Transcutaneous Electrical Nerve Stimulation (TENS) is a noninvasive neurostimulation method for nociplastic pain in COVID-19 that is safe, effective, inexpensive, and easily accessible [39].

Opioids are not recommended for treating nociplastic pain. However, during COVID-19 pandemic, opioid dependence was been reported to be increased, and the use of TENS is a good treatment option to avoid opioids [40].

## 12.5 Conclusions

Information on the "COVID-19 and pain" relationship is still under development. Post-COVID-19 pain severity is moderate and significantly interferes with daily activities. Forthcoming studies will better describe the features of pain related to COVID-19 and provide insight into its prevention and treatment. So, COVID-19-related headache is a good clinical scenario for nociplastic pain. Diagnosis is usually by clinical features and treatment must be planned accordingly. In the management of nociplastic pain, individual variability should be kept in mind and a personalized treatment should be administered.

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# Chapter 13
# Effect of Personal Protective Equipment on Headache Disorders


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## 13.1 Introduction

Coronavirus disease 2019 (COVID-19) has resulted in a global pandemic with more than 584 million cases and 6.42 million deaths thus far. It is transmitted via respiratory droplets. In order to reduce transmission risks, it has been mandated for healthcare professionals worldwide to use personal protective equipment (PPE) when providing care to patients with suspected or confirmed COVID-19 infection.

The components of full PPE include the following: a size-appropriate respiratory mask that is pre-fitted for each individual, protective eyewear (wraparound goggles, safety goggles or face shield), gown and gloves. The N95 face mask is the most frequently worn respirator. When donned properly with an adequate seal, it filters off at least 95% of particles that are >0.3 μm which includes COVID-19 virus particles [1, 2]. As such, a fit test is necessary to be conducted for every person [2]. Differing mask types are used in different countries and are each certified via different regulations and institutes. In China, the KN95 mask is regulated by the government under regulations GB2626-2006, GB262-2019 and GB19083-2010, whereas the National Institute for Occupational Safety and Health (NIOSH) approves respirators suitable for use in the United States of America (USA). The European Union uses EN 149:2001 + A1:2009 for harmonised standardisation of PPE-regulated

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masks, for which they classify their respirators into three classes—FFP1, FFP2 and FFP3. FFP3 comprises masks which provide the highest filtration and least inward leakage.

In addition to PPE, powered air-purifying respirator (PAPR) use is compulsory for healthcare professionals involved in aerosol-generating procedures like cardiopulmonary resuscitation or endotracheal intubation because of the elevated COVID-19 transmission risks [3, 4]. In the case of COVID-19, which has a protracted course with a high volume of patients, the usage of the PPE over an extended period is often necessary, which can result in significant physical distress for the user [5–7].

It has previously been well described in literature that the donning of headwear such as helmets or goggles can result in headaches due to their tight bands or straps and due to prolonged compression of peri-cranial soft tissues [8–14]. Likewise, when the N95 mask is worn for a protracted duration, it has limited tolerability. The need for an air tight, snug fit and the accompanying elastic head straps often results in discomfort over the ear lobes and facial pain which contribute to headaches as well [15–17]. Besides pain and discomfort, other unpleasant symptoms such as breathlessness and giddiness have also been reported. For those required to don N95 respirators for prolonged periods, these complaints by users have led to reduced satisfaction and adverse effects on their occupational health [18].

This review aims to discuss the epidemiology, features, postulated aetiopathogenesis, prognosis and management of PPE-associated headaches with proposed further directions for PPE research and development.

### *13.1.1 Epidemiology*

The overall reported incidence of PPE-associated headaches experienced by healthcare workers during the COVID-19 pandemic varies across different studies, ranging from 26.5% to 90.7% [19–31]. The wide range of incidences amongst studies could be attributed to differing working conditions and shift rotations amongst the varying hospitals worldwide. Since the onset of COVID-19 in December 2019, seven studies seeking to explore PPE-associated headache amongst healthcare personnel have been published [20, 28–33]. These studies revealed that certain factors contribute to a higher probability of an individual acquiring de novo PPE-associated headaches.

In general, individuals who suffer from a pre-existing primary headache pathology like tension-type headache or migraine [20, 29] are more prone to developing such headaches. Ramirez et al. (2020) explored other factors which contributed independently to the development of headache and identified the following: the use of a filter mask, contrasted with a surgical mask, individuals with a past medical history of asthma, and being a nurse or healthcare worker [30].

Prolonged duration with joint usage of the N95 respirator and protective eyewear has also been associated with the risk of headaches. When worn beyond 4 h a day

[20], the use of PPE has been described to cause headaches. Notably, Caglar et al. (2020) described that every additional hour of PPE usage was associated with an increased probability of headache by 1.38 times [26]. In a Moroccan study conducted amongst healthcare workers in Casablanca, it was also revealed that working beyond 8 h shifts contributed to de novo PPE-associated headaches [32].

### *13.1.2 Phenotype and Clinical Characteristics*

PPE-associated headaches were not frequently reported prior to the advent of COVID-19. In the past 3 years, the resultant surge of PPE usage amongst healthcare professionals due to the COVID-19 pandemic led to the corresponding observation of this entity. A few studies published recently analysed the clinical characteristics of PPE-associated headaches in healthcare workers [6, 20, 28–32]. In 2021, the HAPPE (headaches associated with personal protective equipment) study was published. This study was conducted in Singapore, and it characterised the phenotypic characteristics of new onset PPE-associated headaches during the COVID-19 pandemic [20]. Following which, various other studies were carried out globally that sought to provide insights about this entity as well.

These studies demonstrated that de novo PPE-associated headaches can manifest with features similar to a migrainous or tension-type headache. In many patients, the headaches also fulfilled criteria for external compression headache (ECH).

The clinical characteristics of de novo PPE-associated headaches that were identified in those studies included the following:

- Location—The headaches were mostly bilateral in nature. Local pressure effects resulting from the protective eyewear and respirators with their elastic straps led to pain commonly described over the head, face and/or neck (see Fig. 13.1) [6, 20, 31, 32].
- Nature of pain—They were described as a ‘pressure’ or ‘pulling’ sensation in most, although some experienced a ‘throbbing’ headache [6, 20, 28, 30].
- Intensity—Most individuals rated their headaches to be in the mild to moderate range in terms of pain score, although some also rated the headaches to be severe [6, 20, 29, 30, 31].
- Duration of attacks—They were reported to range from less than 30 min up to 2 h [6, 20, 29, 31, 32].
- Associated symptoms—It was found that a proportion of participants had characteristics that resembled migrainous symptoms including that of photophobia, phonophobia, nausea and/or vomiting, neck discomfort and sensitivity on movement [6, 20, 28]. Other reported symptoms included fatigue, tachypnoea, giddiness and palpitations [31].

In 2020, two studies published demonstrated that a large proportion of their respondents who developed de novo PPE-associated headaches fulfilled criteria for external compression headache based on the International Classification of

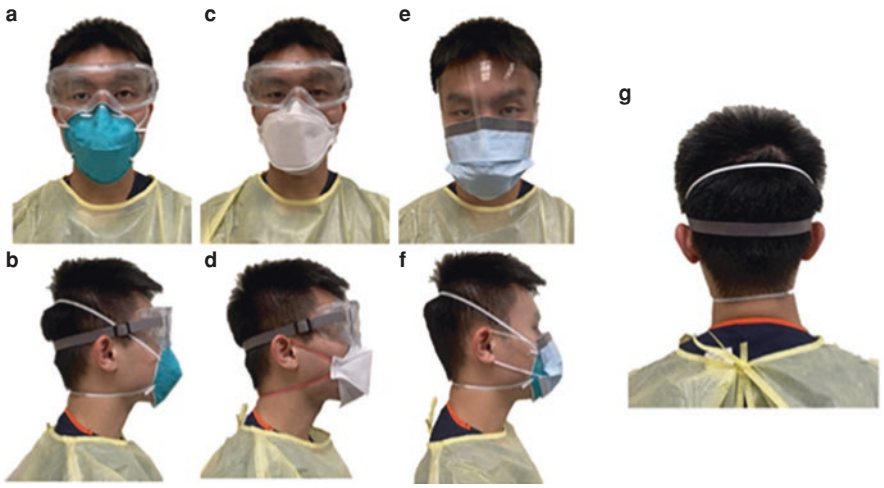


**Fig. 13.1** These photos showcase a healthcare worker who has donned the N95 mask and goggles (**a**–**d**) and N95 mask with a face shield (**e**–**f**). The lateral and posterior profiles of the individual depict the areas of compression sites from the elastic straps of the N95 mask and goggles (**b**, **d**, **f** and **g**). Adapted with permission from [20]

Headache Disorders 3rd Edition (ICHD-3) criteria [20, 32]. Ong et al. (2020) first described the temporal relationship between de novo headache and PPE usage, whereby majority of participants developed bilateral headaches, with onset within 60 min of PPE use. These headaches mostly resolved within 60 min after removal of PPE [20]. Subsequently, Hajjij et al. (2020) also portrayed similarly that their participants experienced frontal and temporal headaches that occurred within 1 h of the donning of PPE, and resolution within 1 h after its removal [32].

### *13.1.3 The Effect on Patients with Pre-existing Headache Disorders*

In patients with a previous history of primary headaches, multiple reports have shown that the clinical history can be affected by the use of PPE [20, 28–32]. Subjects with an antecedent primary headache disorder like migraine or tension-type headache had a higher occurrence of PPE-associated headaches [6], although the incidence of PPE-associated headaches varied amongst different studies conducted across different countries, ranging from 29.0% to 93.5% [6, 20, 29, 33]. The usage of protective eyewear together with a protective mask, worn for more than 4 h, was also found to increase the prevalence of headaches in this subgroup [6, 20, 31].

The studies revealed that an increased frequency of PPE usage correlated with an increased frequency, duration and severity of attacks and the resultant need for more frequent administration of abortive therapy in subjects who had a prior history of

headaches [6]. In these individuals, work performance was also thought to be adversely affected as well, similar to what was previously reported by subjects who did not have a pre-existing headache disorder [6, 20, 30]. However, these could also be confounded by other circumstances, including that of insufficient sleep, physical or psychological stress, erratic meal schedules or dehydration [6, 20, 30–32].

### *13.1.4 Aetio-pathogenesis*

There are several possible mechanisms that may underlie the development of PPE-associated headaches.

Firstly, the mechanical forces produced at areas of contact by PPE may cause focal tissue injury and/or irritate superficial sensory nerves innervating the head and neck regions via compression or traction [10] (see Fig. 13.2). Typical pressure areas include the rim of the equipment, as well as the straps used to secure the protective equipment in place. Amongst the sensory nerves, the trigeminal and occipital nerve branches are the most closely associated with those regions. Furthermore, the physical forces exerted on the head and neck from wearing PPE can trigger tension-type or cervicogenic headache, resulting in peripheral sensitisation and activation of the trigeminocervical complex [34, 35]. Nociceptive traffic is then relayed along the branches of the trigeminal nerve through to the trigeminal ganglia and brainstem and then to the higher cortical areas, generating the sensation of head discomfort [36].

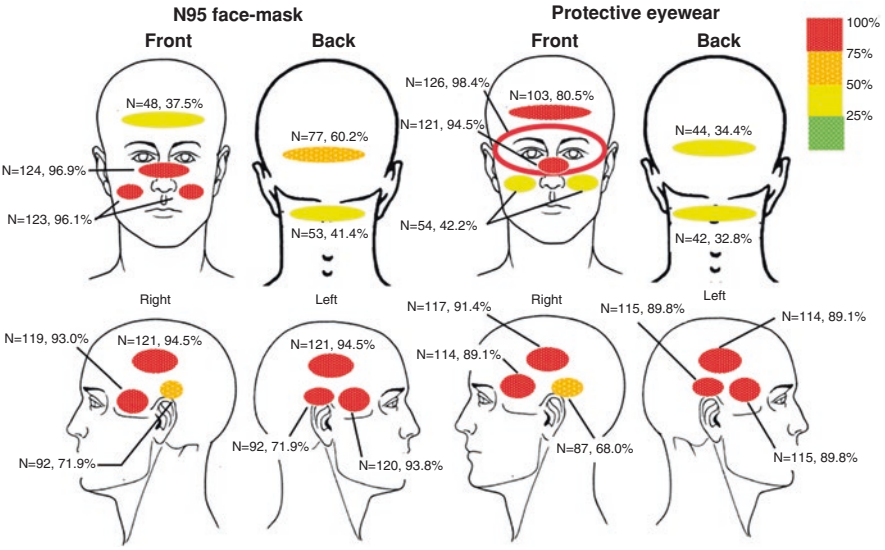


**Fig. 13.2** Frequency distribution of the areas of discomfort experienced by the 128 respondents who reported de novo PEE-related headaches in the HAPPE study. Adapted with permission from [20]

Secondly, hypoxemia and/or hypercapnia may contribute to the causation of PPE-associated headaches although reports are conflicting. In theory, the physiology of respiration could be altered by the N95 respirator due to increased resistance of breathing. This in turn increases usage of respiratory muscles and affects carbon dioxide [37] and oxygen homeostasis [38]. Previously, it has been postulated that hypoxemia and carbon dioxide retention could cause altered cerebral haemodynamics, and this could lead to headache within minutes of donning the N95 respirator [18]. Nevertheless, this was neither shown to cause significant alteration in the aforementioned blood gas concentrations [39] nor result in clinically pertinent effects in healthy individuals. In contrast, there was a report that low physical activity and speaking while wearing respirators could bring about carbon dioxide rebreathing, resulting in discomfort and reduced tolerability.

Bharatendu et al. (2020) added clarity to the relationship between hypercapnia and PPE-associated headaches by documenting the cerebral haemodynamic changes of 154 healthcare workers in Singapore who wore either the N95 respirator alone or in combination with PAPR during the COVID-19 pandemic [3]. They relied on transcranial doppler (TCD) monitoring of the middle cerebral artery to evaluate cerebral haemodynamics and obtain the mean flow velocity (MFV) and pulsatility index (PI) at baseline, 5 min after donning the N95 respirator and 5 min after donning PAPR. These TCD parameters were aptly chosen because they vary with alterations in partial pressure of carbon dioxide in arterial blood and have been validated to be dependable surrogates of cerebral blood flow and vascular tone. Cannula-derived end-tidal carbon dioxide (ETCO2) pressure was also measured. The eventual results showed that donning of the N95 respirator resulted in the elevation of both MFV and ETCO2, while PI was reduced. The likely pathophysiology is that hypercapnia occurred with the increased volume of dead space around the nose and mouth created by the PPE. In addition, an interesting phenomenon was observed with the normalisation of ETCO2 and PI after 5 min in those participants donning both the N95 respirator and PAPR. The most plausible explanation is that PAPR provided positive pressure within the hood that created a state of relative hypocapnia via the positive pressure-assisted exhalation as well as increase in oxygen concentration. These findings allow us to ascribe hypercapnic cerebral vasodilatation as a potential mechanism for PPE-associated headaches and also offered the use of PAPR as a mitigating factor.

The use of PAPR to enhance PPE tolerability was also supported by another study from the same group. The study measured the concentration of ETCO2 in individuals under the four different scenarios—(a) during regular breathing with no mask worn, (b) with donning of the JustAir® PAPR, (c) or KN95 respirator (Emercate, Shenzhen, China) (d) or a valved respirator (model 7502/37082(AAD) (3 M, St. Paul, MN)) [40]. The significant finding was that the donning of JustAir® PAPR not only stayed below the 8-h NIOSH exposure threshold limit value-time-weighted average (TLV-TWA) but also had significantly lower values as compared to the use of the KN95 and valve respirators. Both the use of KN95 and valve respirators resulted in breach of the 8-h NIOSH TLV-TWA.

Aside from respiration, other physiological parameters such as heart rate and perfusion index may also have a role to play. There is evidence that they are altered with PPE use and in themselves can cause a variety of adverse effects, particularly after prolonged working hours. Symptoms include headaches, tiredness, difficulty breathing and palpitations [27].

## 13.2 Investigations and Management

In general, investigations are not routinely required unless there are atypical features or red flags, as there is typically a distinct temporal correlation between the usage of PPE and the development of headache. With regard to blood investigations, Martin-Rodriguez et al. (2021) reported the potential use of creatinine levels in the prediction of PPE-associated headaches in individuals, whereby an increased baseline creatinine compared to that measured after a 4-h shift could be predictive of an increased likelihood of an individual developing PPE-associated headaches [41]. Additional studies and investigations are required to prove the validity and applicability of this preliminary discovery.

Regarding acute abortive therapy required, this varied across the different studies conducted in different regions. In the HAPPE study (2020) conducted in Singapore, most subjects (68.8%) did not require analgesics [20]. In contrast, the studies conducted by Hajjij et al. (2020) and Zaheer et al. (2020) demonstrated that most of their participants required abortive therapy (90.62% in the former and 86.7% in the latter) [29, 32]. The disparity between the studies could be related to the varying demographics and working circumstances amongst the different study populations.

Of all participants who took analgesics, paracetamol was most frequently used, followed by non-steroidal anti-inflammatory drugs (NSAIDs). Opioids were used by respondents in the study published by Hajjij et al. (2020) to a similar degree as that of NSAIDs, though it was not used regularly in the other two studies. The use of triptans was rare, in all three studies [20, 29, 32]. The frequency of analgesics required varied from 1 to 9 days per month mostly [20].

## 13.3 Implications on Quality of Life and Work

In general, the studies demonstrated that those with underlying headache disorders had aggravation of attacks with regard to frequency, reported pain scores and analgesic requirements [20, 28–32], affecting quality of life. The headaches also affected psychosocial wellbeing of individuals with headaches, as described by Ramirez et al. who described elevated stress levels in those groups across various aspects when assessed by the Psychosomatic Problems Questionnaire [30].

With regard to work, it was reported that these headaches could have negative consequences on performance and occupational health [20, 30, 32]. Besides causing headaches, PPE use also led to increased facial pain due to skin tears and damages from direct pressure effects [43], which added to the overall discomfort in the head and neck region. The safety goggles were also frequently reported to cause obscuration of vision and reduced focus which participants felt led to impaired work performance [32]. In the HAPPE study by Ong et al., participants also revealed that headaches affected their productivity and efficiency at work, undermining their job performance [20].

Fortunately, the reports published currently suggest that PPE-associated headaches have a favourable prognosis in general, as the duration of episodes is largely brief with no protracted adverse consequences [6, 20, 28–31, 32]. At this juncture, there are no standardised guidelines or evidence-based treatment strategies for the management of PPE-associated headaches. With COVID-19 that is here to stay, the need for PPE in the long run can result in potential detrimental effects on the quality of life and work productivity in healthcare professionals who suffer from this entity.

## 13.4 Potential Strategies

It is crucial for strategies to be implemented to safeguard the welfare, productivity and comfort of healthcare workers while ensuring that their occupational safety is not compromised, to ensure sustainability in the management of COVID-19 in the long term. As such, we propose certain strategies that can be carried out to reduce the incidence and severity of PPE-associated headaches.

The first-line measures we propose include lifestyle modifications and the avoidance of known headache triggers. Optimisation of sleep and ensuring that an individual gets sufficient hours of rest are important in the management of headaches. In addition, mealtimes should be adhered to strictly, in conjunction with the need to remain adequately hydrated [20, 23, 36].

Other measures to reduce discomfort include methods to reduce mechanical strain from compression over the ears and crown that results from the straps of respirators and protective eyewear. To alleviate the pressure-related effects, the use of topicals like petroleum jelly or alcohol-free film barriers can be considered as well [20].

Finally, a systems-based approach to optimise working conditions for healthcare professionals can be undertaken to help ensure sustainability of the measures in the long run. Measures to regulate and maintain optimal temperature and ventilation can be taken [20, 23], to help ease the discomfort of PPE usage especially in certain regions with high temperatures and humidity. On top of this, the implementation of regular, mandatory breaks and adjustment of work hours to reduce the duration of PPE usage can help to reduce headaches [20]. For healthcare professionals scheduled on longer shifts in whom the above measures are deemed to not be feasible, the use of PAPR should be strongly considered [3, 40].

## 13.5 Future Directions

Studies relating to the COVID-19 pandemic have indeed given us more insight into PPE-associated headaches and it may be opportune to incorporate these findings to further define the entity of ECH. It is important to note that although a large percentage of subjects with PPE-associated headaches fulfilled the criteria for ECH (see Table 13.1), a small subset of subjects did not fall within this group [6, 20]. In those participants, the onset and/or resolution of headaches only occurred beyond 60 min after the donning or doffing of PPE, respectively [6, 20], and hence could not be classified to have ECH. A plausible explanation for this could be due to the duration of PPE that the individual required.

In a study by Farronato et al. (2020) which was conducted amongst dental professionals, it was shown that there was a lack of association between mask donning and headache [25]. An astute observation was made by Farronato and team that dentists usually removed their masks in between patients and hence it was inferred that this could contribute to the above observation [25]. Extrapolating this to the context of COVID-19, the participants in the HAPPE study who did not fulfil criteria for ECH could have used their PPE for a protracted, continuous duration in caring for the sheer number of COVID-19 patients. Coupled with the inability to adjust the fit of protective gear in between patients due to the COVID-19 infectious disease protocol, the prolonged stimulus could have led to more severe headache attacks with prolonged time courses in those subjects [6, 20].

Moving forward, in the next ICHD update, further characterisation of the subtypes of headaches (e.g. migraine or tension-type headaches) could potentially be included in the diagnostic criteria of ECH. In the studies published, a percentage of subjects had headaches with phenotypes that were in keeping with migraines, and another subgroup had tension-type characteristics [20, 28]. The location of pain experienced over the head and neck regions (refer to Fig. 13.2) could be present in either headache subtypes and hence not a useful differentiating factor. Due to the differing management strategies for different types of headaches, it would be beneficial both in terms of diagnostic purposes and administration of therapeutics if the headache subtypes could be identified accurately. Further comprehensive systemic studies to help validate the above would be of benefit in the long run.

Finally, given the persistence of COVID-19 and resultant long-term need for PPE, further consideration should be made to innovate and redesign further

**Table 13.1** International Classification of Headache Disorders 3rd Edition (ICHD-3) (2018) criteria for external compression headache (Adapted with permission from [8])

| |
|---|
| 1. At least two episodes of headache fulfilling criteria 2–4 |
| 2. Brought on by and occurring within 1 h during sustained external compression of the forehead or scalp |
| 3. Maximal at the site of external compression |
| 4. Resolving within 1 h after external compression is relieved |
| 5. Not better accounted for by another ICHD-3 diagnosis |

generations of PPE to improve tolerability for the user. At present, traditional PPE prioritises the importance of a snug fit to ensure safety of the user, forsaking comfort. If not dealt with in the long run, this can lead to problems such as non-compliance and burnout and have serious implications on occupational health, worker productivity and workplace safety. Perhaps, novel material engineering solutions may be the answers to problems like thermal discomfort from trapped air and the mechanical pain from the ubiquitous elastic straps [6, 22, 42]. Collaborations with industries with the relevant expertise can be considered, with the aims to create safe, better tolerated PPEs and achieve enhanced occupational safety and user sustainability in the long term.

## 13.6 Conclusions

The COVID-19 pandemic has resulted in an exponential increase in the need for PPE, and while its use is essential in protecting frontline healthcare workers, it is not without its challenges. PPE-associated headache is one such eminent concern and it is progressively seen by some as a type of secondary headache. The occupational health ramifications from PPE-associated headaches are significant and this entity needs to be adequately recognised so that strategies can be viably and promptly implemented to combat the situation. With COVID-19 that is here to stay, it is crucial for innovations and improvements to happen promptly to improve PPE usability and comfort while upholding conventional safety standards for all.

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# Chapter 14
# Management of Headache Related to COVID-19

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## 14.1 Background

Headache has been described as one of the most disabling symptoms experienced by coronavirus disease 2019 (COVID-19) patients [1]. Its treatment can be subdivided into acute and preventive treatment. All patients should receive acute medications, which may be beneficial for other symptoms, as fever, myalgia, or arthralgia, while preventive treatment is required by just a minority of patients. The median duration of COVID-19 in a multicentric ambispective study that assessed 905 COVID-19 survivors was 14 days [2]. In that study, it was noted that when headache persisted at least 2 months after the acute phase, it adopted a chronic patter and became persistent [2]. This points that the optimal time to evaluate the need for a preventive treatment may be shortly after 2 months.

In the present chapter, management of COVID-19-related headache will be discussed, reviewing the existing evidence regarding acute and preventive treatment of COVID-19 related to COVID-19. Given the lack of randomized controlled trials,

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most of the evidence is indirect from other headache disorders, or based on case reports and case series, where the true effect of the treatments may not be adequately estimated.

## 14.2 Acute Treatment

There is no reason for denying acute treatment to patients with headache during the acute phase of COVID-19 unless these are formally contraindicated. There was an initial concern with the use of non-steroidal anti-inflammatory drugs in patients with COVID-19 [3], which was not lately confirmed based on real-world evidence [4]. From the academic standpoint, the acute phase of COVID-19 and the acute treatment of post-COVID-19 headache could be differentiated, but from the practical perspective, in both cases the employed drugs are similar.

Most treatments are safe and can be used in patients without prior history of allergy or hypersensitivity. Paracetamol/acetaminophen is one of the best tolerated drugs and rarely produces any adverse effects. It should be used with caution in patients with chronic liver disease [5]. Non-steroidal anti-inflammatory drugs (NSAIDs) presented adverse events in 5–28% of patients in migraine trials, the most frequently presented gastrointestinal ones being [6] nausea, vomiting, or epigastralgia; 5–10% of patients complained of dizziness and unsteady gait and <5% presented other adverse effects, including cough or chest pain [7]. Triptans are associated with a 12–36% adverse event rate, the most frequently reported symptoms being fatigue (2–14%), nausea (4–13%), paresthesia (3–11%), or lightheadedness (2–11%) [7, 8]. Older drugs, such as ergots, may be discouraged, given the possibility of severe adverse events, including retroperitoneal, pulmonary, or pericardic fibrosis, in addition to less severe symptoms in 17–41% of patients, the most frequently reported being lightheadedness, dysgeusia, or nausea [9].

Most of the evidence regarding acute medications is indirect, either from other primary headache disorders, as migraine or tension-type headache, or from other COVID-19 symptoms [10, 11]. Regarding the frequency of acute treatment need, in a large study that evaluated 330 patients managed in an outpatient setting and 107 patients hospitalized, 94.5% and 94.4% of them required acute medications to alleviate the headache. The frequency was equally similar in both sexes, being 94.5% in women and 94.5% in men. The most frequently used drugs were acetaminophen in 92.5% of cases, ibuprofen in 17.2% of cases, metamizole in 12.3% of cases, dexketoprofen in 3.9% of cases, triptans in 1.4% of cases, tramadol in 1.2% of cases, naproxen in 1.2% of cases, aspirin in 1.0% of cases, and etoricoxib in 0.5% of cases [1].

In a study done in a third-level headache outpatient clinic that evaluated the first 100 consecutive patients that were referred due to COVID-19-related headache, the frequency of acute medication use reached 93% of patients. The most frequently used treatments were paracetamol (64%), followed by ibuprofen (44%), metamizole

**Table 14.1** Main acute drugs that may be used in the treatment of COVID-19 headache

| Drug | Dose (oral) mg | Specific considerations | Cautions/contraindications |
|---|---|---|---|
| *Analgesics*<br>Paracetamol<br>Metamizole | 1000 mg | Valid for children, pregnant women, and old patients | Liver disease |
| | 575 mg | | Agranulocytosis |
| *NSAIDs*<br>AAS | 500–1000 mg | Mild-to-moderate intensity | Kidney diseases, hypertension, peptic ulcer disease |
| Diclofenac | 50–100 mg | | |
| Ibuprofen | 600–1200 mg | | |
| Naproxen | 550–1100 mg | | |
| *Triptans*<br>Sumatriptan | 50 mg | Intranasal and subcutaneous available | Vasculopathy, coronary artery diseases, stroke, arterial hypertension with need of 3+ antihypertensive drugs |
| Zolmitriptan | 2.5–5 mg | | |
| Almotriptan | 12.5–25 mg | | |
| Rizatriptan | 5–10 mg | | |
| Eletriptan | 20–80 mg | | |
| Naratriptan | 2.5 mg | More prolonged half-life | |
| Frovatriptan | 2.5 mg | | |

(26%), and triptans in 21% of cases. Treatment response was adequate in 37.5% for paracetamol, 35% for NSAIDs, 19% for metamizole, and 38% for triptans. A third of patients needed three or more different acute treatments [12]. This data should be interpreted cautiously, due to the selection bias of patients evaluated in a specialized headache clinic and not in the general population, so the response rate may be probably higher. In another study that evaluated 97 patients that visited the emergency department during the first wave of the pandemic, the response to acute treatment was better in patients with mild-to-moderate headache (65.8%) compared with severe headache (37.5%) [13]. In a study that evaluated the frequency of red flags in 104 patients that were hospitalized due to COVID-19 during the first wave of the pandemic, resistance to acute treatments was reported in 14.4% of patients [14], and in a similar study from the same cohort, which included 107 hospitalized patients and 351 patients managed in an outpatient setting, acute treatment resistance was reported by 19.4% of patients [1].

Table 14.1 summarizes the usual doses, specific considerations, and contraindications of the main acute treatments.

## 14.3 Preventive Treatment

There are no headache-specific trials on the treatment of COVID-19. In headache medicine, most chronic headache disorders are defined by the frequency of headache days per month, rather than for the true chronic nature of the diseases, which in the case of most primary headache disorders is long-lasting. The International Classification of Headache Disorders [15] marks the 3-month period as the agreed

time for most chronic headache disorders, including 9.2.2.2 chronic headache attributed to systemic viral infection [15]. On the other hand, there are several definitions of post-COVID-19 condition. The World Health Organization tried to harmonize its definition and one of the remarkable elements of this definition was the 3 months' item, from the onset of COVID-19 symptoms and the minimum duration of 2 months [16]. These general definitions should be adapted to the specific case of headache. According to the existing evidence, when a patient with persistent post-COVID-19 headache remains symptomatic 2 months after the acute phase, the probability of spontaneous resolution is significantly lower [2], suggesting that waiting for 3 months may not be the best choice.

The pathophysiology of post-COVID-19 headache remains unclear. Some experts may argue that post-COVID-19 headache is in reality a non-previously diagnosed/emerged primary headache disorder. This is supported by the clinical phenotype of headache, which combines phenotypic features of tension-type headache and migraine. Indeed, half of the patients who present headache during the acute phase of COVID-19 fulfill the ICHD criteria of tension-type headache, and a quarter of them fulfill criteria for migraine [17]. Based on this, in clinical practice, preventive treatments of both tension-type headache and migraine have been used with various results. Preventive treatments may be selected based on the clinical phenotype of the headache, regardless of the prior history of these in the patient or her/his family.

### *14.3.1 Amitriptyline*

Taking into account COVID-19 headache phenotype, amitriptyline seems an attractive option, since it is the first-line treatment of tension-type headache [18] and one of the best-established oral preventive treatments of migraine [19]. In addition, amitriptyline has additional benefits that may go beyond headache. It may have some beneficial effect for mood disorders [20], sleep [21], or other painful symptoms, as musculoskeletal pain [22] or neuropathic pain [23].

In a report of three post-COVID-19 headache cases, amitriptyline was used based on the potential benefits on sleep and headache. In a patient with prior history of migraine, it was not beneficial, while botulinum toxin led to the clinical improvement of the patient; in a patient with no prior history of headache, amitriptyline improved both headache and sleep disturbances, and in a third patient with no prior history of headache, neither amitriptyline nor botulinum toxin improved the headache frequency [24].

One study addressed the effectiveness of amitriptyline in the treatment of persistent post-COVID-19 headache in a series of 48 patients from four third-level hospitals. In this study, patients had a baseline frequency of headache days per month of 30 (inter-quartile range (IQR), 30–30) and needed acute medication 12 (IQR, 5–23) days per month. The median reduction of headache days per month was 9.6 after 3 months of amitriptyline use. Regarding response rates, 50% of patients had at least

a 30% response rate, 44% of patients had a 50% response rate, and 21% of patients had a 75% response rate. Only 6% of patients discontinued amitriptyline due to poor tolerability. Prior history of tension-type headache and nausea was associated with a higher probability of response [25].

In the previously mentioned study that assessed the first 100 consecutive patients that had been evaluated in a third-level outpatient clinic, preventive drugs were needed by 76% of patients, amitriptyline being the most frequently employed (66%), followed by anesthetic blockades (18%) and botulinum toxin (11%). Response was evaluated according to the 30%, 50%, and 75% response rate as per International Headache Society recommendations [26], comparing the frequency of headache days per month between weeks 8 and 12 after treatment with the month prior to the treatment onset. Response rates for amitriptyline were 69% for 30% response, 42% for 50% response, and 16% for 75% response [27].

### *14.3.2 Steroids*

Steroids may be another option. In two case reports, including a total of three patients, [28, 29], patients improved after treatment with systemic steroids, while in other series, only 1/5 of patients improved with the use of systemic steroids [27]. In the case of another prevalent COVID-19 symptom, anosmia, intranasal steroids were not superior to olfactory training, in a prospective, randomized, controlled trial that included 100 patients [30]. In an open-label trial high-dose prednisone was not better than low-dose prednisone in 130 patients with persistent dyspnea and diffuse abnormalities of the lung parenchyma [31].

### *14.3.3 Local Treatments*

In addition to oral treatments, anesthetic blockades have proven efficacy in patients with migraine [32, 33] but not clearly in tension-type headache [34]. There is some preliminary evidence regarding the possible benefit of greater occipital nerve blockade in the treatment of headache associated with COVID-19, showing that visual analogue scale decreased 10 days after the blockade in a series of 27 COVID-19 patients [35]. In patients with persistent post-COVID-19 headache, response rates for anesthetic blockades were 50% for 30% response, 37% for 50% response, and 12% for 75% response [27].

Concerning onabotulinumtoxinA, in a series of three patients, two of them were treated with onabotulinumtoxinA with benefit in one of them [13]. In another series, response rates for botulinum toxin were 50% for 30% response, 25% for 50% response, and 12% for 75% response [27]. Both anesthetic blockades and onabotulinumtoxinA may probably be done similarly to other primary headache disorders, adopting special precautions in the case of infected or possibly infected patients [36].

### 14.3.4 Other Treatments

Evidence regarding other oral treatments is even more limited. These could be considered in other patients based on the clinical phenotype. Keeping in mind the possibility of other manifestations in post-COVID-19 patients, treatments should be started at a low dose and progressively tapered to the therapeutic dose. Table 14.2 summarizes the initial doses and the maximum dose that may be reached in the case of adequate tolerability. Many treatments may result beneficial with low doses, so waiting for a minimum of 3–4 weeks may minimize the risk of adverse effects and procure some time to allow the treatment to work [37, 38].

In the selection of the treatment, all other medical conditions and the prior medical history of the patient should be screened, with special attention to contraindications. Valproate should be avoided in women in their reproductive ages. Patients should be informed about the possibility of adverse effects, clarifying that most of them are transient and mild, and that these should disappear upon treatment discontinuation. Table 14.3 summarizes the specific considerations of the some of the different oral preventive medications.

### 14.3.5 Anti-calcitonin Gene-Related Peptide Therapies

There is no evidence in the present regarding the clinical benefit of anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies that antagonize the circulating peptide, including galcanezumab, fremanezumab, or eptinezumab, or its receptor, in

**Table 14.2** Dosage of the main preventive drugs that may be used in the treatment of COVID-19 headache

| Drug | Initial dose (mg) | Standard dose | Maximum dose |
|---|---|---|---|
| Amitriptyline | 10 | 25 | 75 |
| Propranolol | 20 | 60 | 160 |
| Metoprolol | 50 | 100 | 200 |
| Candesartan | 4 | 8–16 | 32 |
| Lisinopril | 2.5 | 5 | 10 |
| Flunarizine | 2.5 | 5 | 10 |
| Lamotrigine | 25 | 100 | 200 |
| Magnesium | 0.5 tablet | 1 tablet | 1 tablet |
| Mirtazapine | 7.5 | 15 | 30 |
| Topiramate | 25 | 100 | 200 |
| Valproate | 300 | 600 | 1500 |
| OnabotulinumtoxinA | 155 | 155–195 units | 195 |

**Table 14.3** Preventive treatments that may be used in COVID-19 headache and their specific considerations (Adapted from Santos-Lasaosa, Guerrero AL and Pozo-Rosich, 37)

| Drug/class | To be considered in patients with | Caution with | Contraindicated in |
|---|---|---|---|
| Amitriptyline | Tension-type-like headache<br>Migraine-like headache<br>Depression<br>Anxiety<br>Insomnia<br>Other painful disorders | Somnolence<br>Constipation<br>Dry mouth<br>Orthostatic hypotension<br>Urinary retention<br>Cognitive impairment | Glaucoma<br>Coronary artery disease<br>Bipolar disorder<br>Pheochromocytoma<br>Pregnancy<br>Epilepsy<br>Prostatic hyperplasia |
| Beta blockers | Migraine-like phenotype<br>Hypertension<br>Tremor<br>Anxiety | Fatigue<br>Hypotension<br>Bradycardia<br>Peripheral vascular disease<br>Diabetes<br>Depression | Severe cardiac failure<br>Bronchial disease<br>Auriculoventricular blockade<br>Pheochromocytoma<br>Severe peripheral arteriopathy |
| Candesartan/ lisinopril | Migraine-like phenotype<br>Hypertension<br>Anxiety | Fatigue<br>Hypotension<br>Hyperkalemia<br>Cough<br>Kidney disease | Bilateral kidney artery disease<br>Pregnancy<br>Hyperaldosteronism<br>Psoriasis<br>Sulfamide hypersensitivity |
| Flunarizine | Migraine-like phenotype<br>Children<br>Insomnia | Overweight<br>Depression<br>Somnolence<br>Galactorrhea<br>Parkinsonism | Depression<br>Cardiac disorders<br>Parkinson<br>Pregnancy |
| Lamotrigine | Migraine-like phenotype | Cutaneous reaction<br>Irritability<br>Insomnia | |
| Magnesium | Pregnant patients | Diarrhea | Kidney disease<br>Myasthenia gravis |
| Mirtazapine | Tension-type-like headache<br>Depression<br>Anxiety<br>Insomnia<br>Other painful disorders | Somnolence<br>Constipation<br>Dry mouth<br>Urinary retention<br>Cognitive impairment | Cardiac disease<br>Pregnancy<br>Prostatic hyperplasia |
| Topiramate | Migraine-like phenotype<br>Overweight<br>Epilepsy | Paresthesia<br>Cognitive impairment<br>Weight loss<br>Gastrointestinal symptoms<br>Depression<br>Dysgeusia | Nephrolithiasis<br>Glaucoma<br>Pregnancy<br>Kidney failure |

(continued)

**Table 14.3** (continued)

| Drug/class | To be considered in patients with | Caution with | Contraindicated in |
|---|---|---|---|
| Valproate | Migraine-like phenotype<br>Epilepsy | Nausea<br>Somnolence<br>Overweight<br>Tremor<br>Alopecia<br>Osteopenia | Pregnancy<br>Hepatic disorders<br>Pancreatitis<br>Thrombocytopenia |
| Venlafaxine | Tension-type-like headache<br>Depression | Fatigue<br>Sexual impotence | Suicidal ideation<br>Pregnancy |

the case of erenumab, and the same applies in the case of gepants. There are theoretical reasons for both antagonizing and not antagonizing CGRP in COVID-19 patients. The main reasons that may support their use would be the pro-inflammatory effect of CGRP, increasing the production of interleukin-6 and polarization of T-cell response towards T helper 17-based responses [38]. On the other hand, CGRP may promote the airway restoration and prevents pulmonary hypertension [38]. CGRP levels have been reported as lower in patients with COVID-19 [39].

## 14.4 Non-pharmacological Treatment

Lifestyle changes may benefit patients, including diet, sleep, and physical exercise; however, the specific impact of each of these interventions is difficult to be measured [40]. Clinical management of post-COVID patients should be multidisciplinary and should evaluate and treat other prevalent symptoms, as fatigue, weakness, myalgia, and cognitive complaints, among others.

## 14.5 Outlook and Future Directions

COVID-19 is an opportunity to improve our knowledge about primary headaches and secondary headache disorders. Its huge prevalence has positioned it as one of the most incident causes of headache, and in post-COVID patients, headache is one of the main symptoms. There is no reason for not sharing our experience in the treatment of these patients. Academic centers should organize themselves to provide the best quality evidence for the clinical management of treatment-resistant COVID-19 patients. Further research is needed to better understand the pathophysiology of COVID-19-related headache and post-COVID condition, which would allow the use of specific and tailored therapies, with fewer adverse effects and better outcomes.

## 14.6 Conclusion

COVID-19-related headache is a prevalent symptom during the acute phase and one of the most frequent and disabling symptoms of the post-COVID condition. Most patients with headache will need acute medications, which may be only partially effective. In the case of insufficient effect, other symptomatic treatments should be offered. The median duration of COVID-19-related headache is between 1 and 2 weeks, so in most patients, preventive treatment will not be necessary. If the headache has not resolved 2 months after the acute phase, then it is highly likely that the headache will adopt a chronic pattern. Evidence regarding preventive medications is limited and based on observational studies. In most studies post-COVID headache has been treated according to its clinical phenotype. Amitriptyline is one of the most frequently employed therapies, based on its possible benefit for both tension-type headache and migraine. Some patients may experience a positive or even optima response; however some cases are treatment resistant. Evidence regarding other treatment options is even more limited, but some selected patients may improve with anesthetic blockades, other oral preventive mediations, or onabotulinumtoxinA.

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# Chapter 15
# Headache Features in Children and Adolescents with COVID-19

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## 15.1 Neurological Signs of COVID-19 Infection in Children

Fever is the most frequent sign of presentation, followed by cough, rhinorrhea, and sore throat. Other frequent symptoms are headache, diarrhea, vomiting, fatigue, myalgia, tachypnea, tachycardia, and rash [1].

Children with COVID-19 infection may develop neurological manifestations, ranging from common symptoms, such as anosmia and ageusia and headache, to more severe consequences, like ADEM (acute disseminated encephalomyelitis), Guillan-Barrè Syndrome, acute transverse myelitis, cerebrovascular accidents, impaired consciousness, and skeletal muscle injury [2]. However, a severe course is

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quite rare and neurological involvement is significantly more common among patients with underlying neurological disorders [3].

As a new disease entity, unique in the pediatric population, Multisystem Hyperinflammatory Syndrome in Children (MIS-C) represents a serious complication of COVID-19 infection in children [4]. Neurologic findings in MIS-C include, among others, seizure, stroke, and aseptic meningitis. CNS involvement is generally mild and transient, with severe involvement in 8% of patients, as reported in a recent comprehensive review [5].

This may include stroke, mild-to-severe acute encephalopathy, demyelinating lesions, fulminant cerebral edema, headache, delirium, loss of consciousness, inability to walk or crawl, and neck pain. Neurological dysfunction is more prevalent in MIS-C than in severe cases of COVID-19.

Finally, "long COVID-19," characterized by persistent symptoms for more than three months, mainly affects people 12 years of age and older.

This condition, with a wide range of symptoms, including fatigue, shortness of breath, "brain fog" and depression, impairs the patient's ability to resume normal activities, and thus it shows substantial long-term morbidity [6].

## 15.2 Headache and COVID-19 Infection in Children

Headache represents the most common neurological symptom of COVID-19 infection [7].

### *15.2.1 Epidemiology*

As reported in a systematic review concerning the early spread of COVID-19 among affected children, the prevalence of headache was estimated to be around 67% [8]. A 2021 systematic review and meta-analysis of 15 published MIS-C studies, with a total of 785 pediatric patients, found that 27% of the children developed headache [9]. Headache was also the most frequent symptom in a series of 58 children with COVID-19-related MIS-C, since it affected 26% of patients [10]. In addition to these previously exposed, other studies conducted among COVID-19 infected children show that headache is the prevalent neurological symptom [11–14] (Table 15.1).

**Table 1** Headache prevalence in children with COVID-19 infection

| No. | Authors | Title | Journal | Pub. Date | Study | Age | No. patients | Patients presenting with headache: prevalence (No.) | Other neurological symptoms |
|---|---|---|---|---|---|---|---|---|---|
| [8] | Badal S, Thapa Bajgain K, Badal S, Thapa R, Bajgain BB, Santana MJ. | Prevalence, clinical characteristics, and outcomes of pediatric COVID19: A systematic review and meta-analysis. | J Clin Virol. | 2021 Feb. | Systematic review and meta-analysis | 0–21 | 1810 | 67% (117 on 175 ca.) | Not Mentioned |
| [9] | Nepal G, Shrestha GS, Rehrig JH, Gajurel BP, Ojha R, Agrawal A, et al. | Neurological Manifestations of COVID19 Associated Multi-system Inflammatory Syndrome in Children: A Systematic Review and Meta-analysis. | J Nepal Health Res Counc. | 2021 Apr. | Systematic review and meta-analysis | 0–18 | 785 | 27% (211) | Meningism 17.1%, Encephalopathy 7.6% seizures, cerebellar ataxia, muscle weakness, myopathic and neuropathic changes. |
| [10] | Whittaker, E.; Bamford, A.; Kenny, J.; Kaforou, M.; Jones, C.E.; Shah, P, et al. | Clinical Characteristics of 58 Children with a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 | JAMA | 2020 | Case series | 5.7–14 | 58 | 26% (15) | Seizures |
| [11] | Sandoval F, Julio K, Méndez G, Valderas C, Echeverría AC, Perinetti MJ, et al. | Neurologic features associated with SARSCoV-2 infection in children: a case series report. | J Child Neurol. | 2021 | Case series | 0–18 | 90 | 9% (8) | Encephalopathy Seizures Muscle weakness |

(continued)

**Table 15.1** (continued)

| No. | Authors | Title | Journal | Pub. Date | Study | Age | No. patients | Patients presenting with headache: prevalence (No.) | Other neurological symptoms |
|---|---|---|---|---|---|---|---|---|---|
| [12] | Zhu L, Wang J, Huang R, Liu L, Zhao H, Wu C, Zhu C | Clinical characteristics of a case series of children with coronavirus disease 2019 | Pediatr Pulmonol | 2020 Jun. | Case series | 0–18 | 10 | 20% (2) | Not Mentioned |
| [13] | Foster CE, Moulton EA, Munoz FM, Hulten KG, Versalovic J, Dunn J, Revell P, Koy TH, Arrington AS, Marquez L, Campbell J. | Coronavirus Disease 2019 in Children Cared for at Texas Children's Hospital: Initial Clinical Characteristics and Outcomes | J Pediatric Infect Dis Soc. | 2020 Jul. | Retrospective study | <21 | 57 | 24,5% (14) | Not Mentioned |
| [14] | Mannheim J, Gretsch S, Layden JE, Fricchione MJ | Characteristics of Hospitalized Pediatric Coronavirus Disease 2019 Cases in Chicago, Illinois, March–April 2020 | J Pediatric Infect Dis Soc | 2020 Nov. | Case series | <17 | 64 | 28% (18) | Not Mentioned |

### *15.2.2 Pathophysiology*

The main targets required for COVID-19 invasion are two cellular membrane proteins, angiotensin-converting enzyme 2 (ACE2) receptor, and transmembrane serine protease 2 (TMPRSS2) [15]. Both proteins can be expressed in the CNS, although the degree of expression is unclear, particularly for the trigeminal nerve. Investigating the pathophysiological mechanisms underlying the headache linked to COVID-19 infection, in fact, it is essential to consider the aspect of trigeminovascular activation in the context of the viral infection and the consequent host immune response.

#### 15.2.2.1 Systemic Inflammation

Among the possible pathophysiological mechanisms involved in the COVID-19 headache, elevated levels of acute innate inflammatory markers have been associated with serious neurologic insults in adults [16, 17].

Several studies have evaluated the association of COVID-related headache with the systemic levels of pro-inflammatory factors, such as serum high mobility group box-1 (HMGB1), NOD-like receptor pyrin domain-containing 3 (NDRP3), IL-6 [18–20], angiotensin-converting enzyme 2 (ACE2), calcitonin gene-related peptide (CGRP) [21, 22], and anti-inflammatory factors such as interleukin 10 (IL-10) [23]. The systemic inflammatory response to infection is considered important for the onset of headache associated with systemic viral infection [24], despite that the results of the above-cited studies have been inconsistent and controversial, confirming the need for further data.

#### 15.2.2.2 Local Inflammatory Process, Direct Viral Injury, and Vascular Inflammation

In terms of local inflammatory mechanisms, an association was found between COVID-19 headache, anosmia, and ageusia [25–27] leading to the hypothesis that damage to the olfactory pathway and inflammation of the nasal cavity can activate the trigeminal system and cause headache [28]. In this regard, the data about direct viral damage due to invasion of neuronal tissues seem controversial [29–31]. On the other hand, the involvement of the mucosal COVID-19 infection of the upper respiratory tract with the subsequent release of local inflammatory mediators may lead to both anosmia-ageusia and activation of trigeminal nociceptors causing headache. Viral infection can also lead to endotheliitis and vascular injury at the same level, thus activating the perivascular trigeminal nociceptors involved in the genesis of headache.

Although the pathophysiological mechanisms behind COVID-19 headache are likely related to trigeminal activation and local inflammation also in the pediatric population, data remain scarce in children, confirming the need for further studies and evaluations, especially within childhood-specific clinical pictures such as MIS-C [32].

### *15.2.3 Clinical Characteristics*

Currently, data on headache linked to COVID-19 infection, its clinical features, nature (primary or secondary), and onset (acute/sub-acute) are still limited, especially in the pediatric population. Among adults, those with a previous history of headache are more likely to suffer from headaches in the acute and post-acute phases of COVID-19 infection [33]. Migraine patients, in the acute phase, usually experience headaches that are more intense than usual and characterized by a longer duration [34], while, in the post-acute phase of the infection persisting headache is usually observed, with an increase in frequency and intensity of the attacks [35]. In the adult population, secondary headache linked to COVID-19 during the acute phase of the infection could show a migraine or tension-type headache phenotype (in 25% and 54% of cases, respectively) [36]. These patients, even without a previous history of headache disorders, may experience a migraine-like persistent headache in the post-acute phase of the infection (40%) [37].

Data about children are still scarce, probably since most of the clinical trials were conducted during the first wave of the pandemic and focused primarily on the prevalence of headaches and other symptoms that occurred during the infection. Pediatric COVID-19 headache features and characteristics need to be evaluated in further studies involving patient cohorts with controlled similar parameters such as disease course, comorbidities, headache severity, and treatment pathway.

## 15.3 Social Impact of COVID-19 Pandemic on Primary Headache Disorders

Currently, in the aspect of social Impact of COVID-19 Pandemic on Primary Headache Disorders in Children we can say that, the available data on children and headaches during the COVID-19 pandemic mainly concern primary headache disorders not related to the infection itself.

### *15.3.1 Trend of Headache Disorders During the Pandemic in Children*

A major multicenter study was conducted in patients (from 5 to 18 years of age) referred to nine different pediatric headache centers [38]. It was based on the administration of an online questionnaire that considered the average of “frequency of headache attack before lockdown” and “monthly medication intake for the attack before lockdown.” A headache severity index was defined. Only children and adolescents with a diagnosis of migraine (with or without aura) or tension-type

headache according to the ICHD-3 criteria [39], with a disease history of at least 1 year, were included. The topics of the questionnaire were: features of headache, type of headache, duration of the headache from the first attack, variation of attack intensity during the lockdown, number of attacks per month before the lockdown and during the lockdown, and therapy for the attacks. Patients reported improvement in 46% of cases, while 39% expressed a stable trend and 15% a worsening of the headache. Regarding the intensity of the attacks, 49% of patients defined it as stable while 38% reported an improvement. Only in 13% of patients attack intensity worsened. As for the frequency of the attacks, the average value before the pandemic was higher than 7 attacks per month, while it dropped to 5.4 attacks per month during the lockdown. Patients who had a long history of headache disorders showed a lower improvement in the intensity and frequency of the attacks. Improvement in headache observed during lockdown involved both migraine and tension-type headache, although these were more pronounced in patients with migraine, particularly those with chronic migraine.

The mean use of symptomatic drugs reduced from 4.8/month prior to the pandemic to 2.1/month during the pandemic. It was shown that the general improvement of headache during the lockdown was not influenced by prophylaxis therapy (amitriptyline, flunarizine, topiramate, valproate, and nutraceutics), while the release of school-related stress represented the main factor explaining the outcome.

Another Italian survey of 142 children (mean age 15 years) recruited during the 2020 lockdown showed an improvement in migraine [40]. The familiar and environmental exposure to COVID-19 was evaluated, together with school activities, leisure activities, anxious symptoms during the emergency, frequency, and intensity of the attacks before and during the lockdown. Before COVID-19 pandemic, 63% of the patients suffered from migraine without aura and 52% from migraine with aura. Fifty-two percent of patients lived in the initial Italian geographical hotspot of COVID-19 spread, 8% had at least one relative positive to the virus, 42% had at least one parent who needed to travel for work in COVID-19 area, 88% interrupted school activities at the time of the study. All the patients who reported a worsening before COVID-19 pandemic had a reduction in intensity of the attacks during the lockdown and 50% showed a reduced frequency. Anxiety symptoms worsened in only 26% of cases (37 patients), remaining stable in 73% (104). All these studies suggest that the primary headache course in children and adolescents is deeply influenced by stress factors, whose release during the lockdown led to headache improvement.

### *15.3.2 Social Impact*

To better understand the real impact of social stressors in modifying the course of headache disorders, is important to consider the health and lifestyle implications that lockdown measures have had on children.

#### 15.3.2.1 School Activities and Socialization

As for children and adolescents, a significant change was the interruption of school activities with the introduction of online courses. Several studies [41–46] have emphasized the role of different risk factors for migraine in children. School stress, dysfunctional family situation, anxiety, altered sleep, and insufficient leisure time have been associated with migraine onset and severity. In children, migraine tends to have a seasonal pattern throughout the year, likely associated with school attendance with an increased risk of chronicity during the winter months, when school activities are intensified. The COVID-19 pandemic was a global emergency that created individual and collective psychological reactions and a source of stress that could have affected children suffering from primary headache. From this point of view, we could have expected a worsening of children's headache. What can explain headache improvement? Most patients reported a reduction in school effort, since they were required only to attend online lessons. Interestingly, patients with worsening headaches during lockdown were those who continued to feel stress at school.

#### 15.3.2.2 The Use of Face Masks

According to parents' and pediatricians' surveys [47], complaints about the use of the face mask are frequently reported: symptoms are attributed to the mask for more than 80%, and headache disorders have been reported for almost half of the children. Unfortunately, we do not know if these children had already had a diagnosis of headache. Interestingly, during the pandemic the prevalence of headache did not change, as compared to that before the pandemic (up to 50% in over 7 year old children). The possibility that headache can be due to the mask use seems more conceivable in children using FFP2-type masks. Mechanical factors, hypoxia, hypercapnia, stress, and discomfort in speaking are some of the possible mechanisms complained by children. We should consider that mask also hinders nonverbal communication, facial expression, social smile, facial recognition, and tends to modify teacher's voice, which can be important, especially for children with preexisting difficulties. All these features can increase social stress that, on its turn, leads to the development of headache disorders.

#### 15.3.2.3 Additional Factors

In addition, children can undergo several other stressors related to the pandemic, such as the risk of infection, the constant alarming information broadcast by media or even by family members, and the health situation of family members, especially grandparents who are at higher risk [48]. Extracurricular activities are interrupted or limited, and interactions with peers are diminished; so, as we said previously regarding the impact of COVID-19 pandemic on young and adolescents, all this

background can potentially trigger headache disorders in children. Interestingly, the relationship between this new "pandemic lifestyle" and headache disorders has been emphasized [49]. School changes, home changes, and psychological changes may trigger the onset of migraine or other types of headaches even in those children and adolescents who have never had headache before. Some solutions have been proposed, such as modifying the brightness of the screens and using artificial tears in children—especially those with chronic migraine—who complain of altered vision and worsening headache due to the more frequent computer use during a pandemic, better ergonomics in chairs and desks to cope with prolonged sitting and altered postures.

## 15.4 Vaccination Against SARS-COV-2 and Headache

A worsening trend of primary headache after COVID-19 vaccination has been shown in adult patients [50]. With the recent inclusion of children in vaccination programs around the world, the number of papers demonstrating the safety and efficacy of vaccination at all ages of life is growing. However, only general information on adverse events is available in pediatric vaccination and there have not been studies concerning changes in headache course, either in children with a history of primary headache or in newly diagnosed children.

Hause et al. reviewed the adverse events after receipt of Pfizer-BioNTech COVID-19 vaccine (BNT162b2) [51]. In order to investigate the safety of the vaccine in children aged 5–11 years, they enrolled 42504 children who were asked to report any adverse event, divided into local effects on the injection site and systemic reactions (mild, moderate, or severe), during the week after dose I and after dose II. Four thousand two hundred forty-nine children reported adverse events: while 98% had no serious event, 2% showed serious reactions. In this last group, there were only 10 patients (10%) with severe symptoms regarding headache.

In another similar study, between October 2020 and January 2021, a total of 2260 adolescents (from 12 to 15 years of age) underwent a double-blind randomized study, with 1131 receiving BNT162b2 and 1129 receiving placebo [52]. Headache and tiredness were the most commonly reported systemic events. After injection of BNT162b2, severe tiredness and severe headache were reported less frequently in 12–15 year olds than in 16–25 year old participants. One BNT162b2 recipient in the 16–25 year old cohort stopped getting vaccinated due to severe pain at the injection site and vaccine-related headaches one day after the first dose.

Symptoms resolved within 1 day. A second randomized controlled trial studied a total of 3732 participants aged 12–17 years [53]. They were randomly assigned to receive either Moderna vaccine, named mRNA-1273, (2489 participants) or a placebo (1243 participants). Headache was reported in 44.6% of children in the mRNA-1273 group after the first dose and in 70.2% after the second dose, as compared with 38.5% and 30.2%, respectively, in the placebo group.

A comprehensive review studied the safety and efficacy of Pfizer vaccination in pediatrics, and the conclusion was in line with that of the above-reported studies [54]. Although the most common adverse event was injection site pain, headache was also frequently reported, often associated with fever and fatigue.

It could be interesting to investigate whether and how vaccination can change the course of a primary headache. at this moment, however, no data are yet available on this issue, especially regarding the pediatric population, making this topic worthy of further studies.

## 15.5 Conclusions

Most available studies concern adulthood, while there is still a lack of information about children. Nevertheless, it is widely accepted that the social consequences of the whole COVID-19 pandemic have an enormous impact on headache courses even in children. While, during the first half of 2020 improvement of headache disorders in previously affected children was mainly related to release from stress, data about the second wave, from November 2020 to January 2021, are still emerging. In adults, the prolongation of pandemic seems to have had a negative impact on migraineurs, due to the restriction of the public medical services that worsened the management of chronic diseases, such as headache [55]. We could expect the same consequence also in pediatric population, but this need to be confirmed. Future research should also be addressed to characterize "COVID-related" headache in children and adolescents, with particular attention to its own features and risk factors, in order to either add a "new" headache in the ICHD3 or include it within the chapter of "headache attributed to systemic viral infection" [39].

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# Chapter 16
# Changes in Migraine in the COVID-19 Pandemic Era


**Amanda Macone and Sait Ashina**

## 16.1 Introduction

COVID-19 was first declared a global pandemic by the World Health Organization on March 11, 2020 [1], and shortly thereafter, hospitals and healthcare systems halted all non-essential procedures as many parts of the world entered into an initial quarantine period. As such, access to medical care for many patients became limited, and for migraine patients, procedures such as onabotulinumtoxinA and peripheral nerve blocks became delayed or cancelled [2]. Additionally, concerns arose during the early pandemic regarding the safety of medications commonly used in the treatment of migraine, such as non-steroidal anti-inflammatory drugs (NSAIDs), creating confusion and directly affecting management of migraine and other headache disorders [3]. Studies have emerged since the early pandemic, highlighting some of the difficulties that patients with chronic neurological diseases have experienced [4]. Social isolation in the setting of restrictive measures, economic instability, fear of the contagion itself, and an influx of frequently contradictory information from media outlets contributed to anxiety, depression, sleep disturbances, and changes in physical activity in the general population [5, 6]. Over the course of this chapter, we discuss the impact of the pandemic on primary headache disorders, with a particular focus on migraine.

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## 16.2 Migraine in the Early Pandemic

Migraine is the second most common primary headache disorder, associated with substantial disability and great impact on quality of life [7, 8]. The severity of migraine can be influenced by a number of modifiable, external factors, including psychiatric comorbidities and sleep disorders [9–12]. In previous pandemics, such as the 2003 outbreak of severe acute respiratory syndrome (SARS) and the 2014 outbreak of Ebola, quarantine has been associated with several negative psychological effects, such as post-traumatic stress disorder (PTSD) [5, 13]. As such, it would be reasonable to assume that migraine patients would be at increased risk for worsening following COVID-19 restrictions. Studies investigating the impact of the early quarantine period on migraine patients however had varying results. While a number of studies did note worsening in migraine frequency and severity [14–18], a number of other studies found the migraine course to be stable [19–24] or even improved [25–30] during the early quarantine period. This suggests that the course of disease for any migraine patient during the pandemic is more individualized, with certain factors correlating with improvement or worsening during this period.

### *16.2.1 Factors Leading to Improvement in Migraine*

There were a number of studies that noted initial improvement in migraine symptomology during the early quarantine period of the pandemic. Of those, two were longitudinal, observational cohort studies [27, 30], and four were retrospective, cross-sectional studies [25, 26, 28, 29]. Key factors that played a role in the initial improvement experienced by some migraineurs included reductions in stress due to decreased social requirements, ability to work remotely, and the increased ability to format the structure of one's daily routine (Table 16.1).

One Italian study found a direct correlation between reduced headache frequency and severity, and the number of days the participant was able to stay home during the early quarantine period [25]. In support of the positive impact remote working

**Table 16.1** Factors affecting migraine during the COVID-19 pandemic

| Migraine improvement | Migraine exacerbation |
|---|---|
| Reduced stress | Disrupted sleep |
| Reduced anxiety/depression | Increased anxiety/depression |
| Remote work/days at home | In-person work |
| Decreased social requirements | Social isolation |
| Reduction in perceived school workload | Concern regarding pandemic |
| Flexibility in daily schedule | Uncertainty regarding the future |
| Familial support | Economic hardship |
| | Disruption in medical care |

may have had on migraine patients during the early pandemic, an additional study found that individuals with migraine, who were required to present for in-person work, noted an increase in their migraine frequency and severity [14].

Many studies noting reductions in migraine intensity and frequency during the early pandemic also found correlations between migraine severity and reported levels of anxiety or depression. In those that noted reductions in stress and migraine frequency, it was postulated that these initial stress reductions in the early quarantine period were likely impart due to the ability to work from home, increased control over the formatting of one's day, and reduced social requirements, despite the uncertainties of the pandemic at the time [20, 23, 25, 26, 28, 30].

These positive findings of stress reduction in the early pandemic were also observed in the pediatric population with remote learning. Two pediatric studies noted that during the early quarantine period with the initiation of remote learning, children overall noted an improvement in their migraine frequency and severity [28, 29]. One of the studies found that a reduction in headache frequency correlated to perceived reductions by the students in school effort and associated anxiety. Conversely, in children that had worsening of their migraine, correlations were found with older age and increases in anxiety and depression [29]. It was therefore postulated that reduced daily environmental challenges and pressures from transitioning to remote learning may have assisted in the observed initial improvement.

Additional factors, such as the presence of familial support during quarantine, were found to correlate with improvements in migraine patients [22]. It was acknowledged in these early studies that improvement was not experienced by all migraine patients though, and that the initial improvement seen in some participants may change over time as the pandemic continues, due to economic instability, prolonged social isolation, and uncertainty about the future [23, 30]. These initial suspicions were supported by subsequent studies, noting increases in psychological comorbidities and migraine symptoms as the pandemic continued [31, 32]. In the remaining part of the chapter, we will discuss some of the factors that have negatively impacted migraine patients and the longer lasting impact of the pandemic on this population.

### *16.2.2 Factors Contributing to Migraine Exacerbation*

While some migraineurs did experience an initial period of improvement due to reductions in stress during the early lockdown period, for many individuals with migraine, the impact of the pandemic was negative due to increases in underlying anxiety or depression, loneliness due to social isolation, economic uncertainties, disruption in sleep pattern, and lack of access to medical care (Table 16.1).

A number of studies found that individuals who experienced higher levels of anxiety [14, 16–18, 21, 23, 24, 28] or depression [14, 18, 26] during the pandemic were significantly more likely to have worsening of their migraine. Additionally,

one cross-sectional study noted that migraine patients appeared to be at higher risk than non-migraine patients to developing anxiety during the pandemic [24]. Some factors identified as contributing to increases in anxiety, depression, and higher level of migraine disability were general feelings of loneliness and lower levels of social support compared to non-migraine controls [15]. Migraine patients were also found to display higher levels of psychological distress than non-migraine patients in one case control study from China, noting they spent more time watching media coverage and had greater levels of concern regarding the pandemic [16]. When patients using the Migraine Buddy app [33] were surveyed on factors that they subjectively felt were contributing to stress during the pandemic, they identified social isolation, excessive information, access to essentials such as food and medicine, and financial concerns as significant contributors. Of these individuals, 58.1% also noted experiencing disruptions in their medical care [17].

Additional factors identified as contributing to increasing migraine disability were decreases in sleep quality [14, 18, 19, 21, 23, 24], economic hardship such as job loss [24], and severity of the pandemic in the region [22, 25]. It was observed in at least two studies that participants living in regions with higher numbers of COVID-19 cases in the community at the time were more likely to have an increase in headache frequency [25], severity, and duration [22] compared to participants in other regions. It was additionally noted that participants who described "disgust" towards the pandemic, or concern regarding their future, had higher rates of headache frequency [16, 25] and intensity [23].

Disruption of care was also experienced by a large percentage of the population during the early pandemic, including those experiencing migraine, resulting in increased headache frequency, severity, and level of disability.

## 16.3 Disruptions in Migraine Management

During the early pandemic, the World Health Organization (WHO) Pulse Survey on Continuity of Essential Health Services noted that 48% of responding countries reported at least partial disruption to services for non-communicable diseases and mental health [34]. A subsequent global survey focused on the disruption of neurological services during the pandemic, including 43 countries, had 69% of respondents report disruption of services at their facilities. These care disruptions were also experienced by many headache medicine clinics in the early pandemic [35]. In one retrospective, cross-sectional study from Kuwait, a significant number of patients reported worsening of their migraine during the early pandemic, as well as difficulties accessing care. 61.5% of them reported not communicating with their neurologists during this period, 66.1% reported cancellation of their scheduled botulinum toxin injections, 58.7% reported overuse of analgesics, and 25.1% reported additional difficulties accessing their typical medications [14].

Patients particularly impacted by disruptions in care were those receiving botulinum toxin injections or peripheral nerve blocks. For many practices, these procedural services were initially postponed or severely reduced [2, 35, 36]. In chronic migraine or high-frequency episodic migraine patients who had their botulinum toxin injections involuntarily postponed, migraine exacerbations were seen. In two cross-sectional studies assessing outcomes of migraine patients who had delay in scheduled botulinum toxin injections, there was a notable increase in number of headache days per month, number of migraine days per month [37], number of days of acute medication use, number of acute medications used per month, and level of headache-related disability [38].

Migraine patients with care disruptions other than a delay in procedural therapy reported having worse outcomes as well. In at least two retrospective reviews, they found that enrolled migraine patients noted more issues than non-migraine patients with maintaining usual therapeutic care during the pandemic [15, 24]. Some patients faced medication shortages [21], and those who were unable to continue on their typical preventative therapy reported higher levels of acute headache medication use, placing them at increased risk for medication overuse headache and chronic migraine [23, 24].

Attempt to mitigate this disruption was mainly through the implementation of telemedicine [39], and a large number of those who were able to utilize telemedicine did find it a useful alternative to in-person visits, at times noting that without this option they would have missed medical care [24]. Patients who were able to access care and continue on their preventative treatments were found to have better outcomes. One longitudinal, observational cohort study of patients receiving calcitonin-gene-related peptide monoclonal antibody agents (CGRP MABs) found that during the pandemic patients continued to have reductions in headache frequency and severity in line with expectations based on clinical trial data [27].

## 16.4 Impact of COVID-19 Infection and Vaccination on Migraine

In addition to the psychosocial and economic difficulties due to the pandemic, a number of migraine patients also experienced COVID-19 infection, resulting for some in worsening of their headaches [14, 32]. It has been suggested in a number of studies that while anyone in the general population is at risk of developing headaches acutely during COVID-19 infection, those with underlying headache disorders, such as migraine, appear to be at higher risk [40–45].

Patients with underlying primary headache disorders often describe their headache with acute COVID-19 infection to be different than their typical headaches [43, 46, 47] and appear to be more likely to experience pulsing pain [46] and a lack of response to analgesics [40]. In particular, it has been described that migraine

patients may be more likely to experience earlier headache onset, longer headache duration, and higher pain intensity with acute COVID-19 infection than those without a migraine history [48].

After the acute COVID-19 infection subsides, a number of patients may continue with lasting changes in their headaches, either experienced as an exacerbation of their underlying migraine or with a compilation of other symptoms described as long COVID [41, 49]. One cross-sectional study of patients presenting to a headache clinic within 3 months of their COVID-19 infection found that the majority of the participants had a preceding diagnosis of migraine (64.5%) and reported a significant increase in acute headache medication use. They also found that patients with underlying primary headache disorders were more likely to have an ongoing headache more than 1 month after their COVID-19 infection than those without a history of a primary headache disorder, with a noted increase in headache attack frequency and severity from baseline [49]. There has also been at least one study suggesting that an underlying diagnosis of migraine may predispose individuals to experience a higher number of symptoms secondary to long COVID than individuals without migraine [50].

The first vaccinations became available for COVID-19 infection in late 2020, and since, there have been a few observational studies [51–54] suggesting that individuals with underlying primary headache disorders appear more likely to experience headache in association with COVID-19 vaccination than those without a prior headache history.

Three of the four studies focused on individuals who received mRNA COVID-19 vaccination [51–53], with one cross-sectional study including patients who received non-replicating DNA viral vector vaccines [54]. No difference was noted between patients with a history of migraine and those without a headache history in the timing of headache onset after vaccination [51, 53]. Results on headache duration are mixed, with one study noting patients with migraine were more likely to experience longer headaches than those without a migraine history [51], and another noting no difference in headache duration between groups [53]. Overall, headache duration for most participants was short-lived, lasting less than a day in duration. One study noted that headache intensity post-vaccination appears higher in those with a migraine history compared to those without [51], and in some studies participants reported that their headaches associated with COVID-19 vaccination differed from their typical headaches [52, 54].

As such, it is important that patients with underlying primary headache disorders, such as migraine, have access to readily available medical care. Also, one should consider the possibility of acute COVID-19 infection when a patient presents to the ED or calls the clinic with an exacerbation in their underlying headache disorder, particularly if new features are described. Future areas of research may include assessment of whether medications for management of acute COVID-19 infection could have an impact on the course of migraine or headache associated with acute COVID-19 infection.

## 16.5 Late Pandemic Observations

As alluded to earlier in the chapter, as the pandemic continued, many of the initial improvements experienced in migraine patients due to decreases in stress from remote work and decreased social demands began to decline as anxiety, depression, uncertainty regarding the future, economic concerns, ongoing social restrictions, and effects of the pandemic itself became more prominent [31, 32].

A follow-up study on an Italian population assessed during the first wave of the pandemic [25] found that headache-related outcomes worsened as the pandemic continued [31]. This follow-up, cross-sectional study took place during the second lockdown period in Italy and found that participants had higher levels of stress, anger, and disgust towards to the pandemic. They also had a significant increase in their headache frequency, headache intensity, and acute medication use compared to both their pre-pandemic baseline and the first lockdown period. Increases in frequency were most noticeable in the episodic migraine patients, noting increases in stress and perception of pandemic risk correlated with worsening in migraine symptoms.

It is therefore not surprising that during the pandemic two separate studies noted higher numbers of individuals transitioning from episodic to chronic migraine than expected based on general estimates in the population. In a retrospective, cross-sectional study by Al-Hashel et al., 10.3% of participants were reported to transform into chronic migraine during lockdown [14]. In a retrospective cohort study from Colombia, the percentage of patients meeting criteria for chronic migraine increased by 21.4% after a 12-week period [18]. These findings are much higher than the general estimate of 2.5% of migraine patients transitioning to chronic migraine annually [55]. One study found that higher levels of anxiety, depression, disordered sleep, female sex, and unemployment at the beginning of the pandemic were factors associated with increased progression to chronic migraine during the pandemic [18].

## 16.6 Conclusion

Differences in individual resilience, social restrictions, access to hospital care and medications, and availability of remote services such as telemedicine have varied significantly throughout the pandemic, likely contributing to the multifactorial and evolving experience witnessed in migraineurs. Differences in socioeconomic measures taken, pandemic burden, culture, and economic impact likely all played a part in the range of experiences in those with primary headache disorders. While a number of studies were initially mixed in their results at the beginning of the pandemic, with a number noting improvement during the initial lockdown period due to decreases in stress from reduced societal requirements, these improvements for many were ultimately short-lived. As the pandemic continued, uncertainty regarding the future, economic hardships such as unemployment, disruption in care, and

possible COVID-19 infection led to worsening in migraine disability and symptomology for many individuals. Additionally, a number of migraine patients, along with the general population as a whole, experienced negative psychological effects, such as PTSD, anxiety, and depression [5, 31].

Fortunately, in most of the world at this time strict quarantine regulations are no longer in place, and medical access has improved through the resumption of procedural-based care and increased availability for in-person clinic visits. These are positive changes and have likely started to help reverse some of the negative consequences experienced by many from restrictive social measures and disruptions in care during the first year of the pandemic in particular. Additionally, new treatment strategies have become available to assist in treating those with acute COVID-19 infection, as well as vaccinations to help decrease the spread of infection. Telemedicine has also proven to be a useful tool that is now available at many institutions, and headache medicine has been able to make adaptations at many institutions should restrictive measures from this pandemic or a future pandemic occur.

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# Chapter 17
# NSAIDs, CGRP Monoclonal Antibodies, and COVID-19

**Berkay Alpay, Bariscan Cimen, and Yildirim Sara**

## 17.1 Introduction

SARS-CoV-2 is a member of Coronaviridae family and notorious for COVID-19 pandemic. Coagulopathy and thrombosis are important clinical presentations of COVID-19, related to pulmonary injury and inflammation. SARS-CoV-2 virus exploits angiotensin-converting enzyme 2 (ACE-2) and transmembrane protease serine 2 (TMPRSS2) as a means of cellular entry. The ubiquitous expression of ACE-2 on lung and heart vascular endothelium can explain the trophism of the virus primarily to these tissues. During inflammatory processes, ADAM17 (A disintegrin and metalloproteinase 17) expression is increased and its increase stimulates the release of strong pro-inflammatory mediators like TNF-α and IL-6 and also cleaves off membrane-bound ACE-2. ACE-2 cleavage may account for increased local angiotensin [1–8] concentrations, which can promote vasoconstriction, inflammation, and thrombosis. Pro-inflammatory cytokines and neutrophil infiltration give rise to endothelial dysfunction, further contributing to thrombotic processes.

An overwhelming number of clinical reports show that SARS-CoV-2 also generates a cytokine storm, characterized by an aberrant increase in cytokine levels. Along with increased cytokine levels, local inflammatory reactions are also initiated. Main agents of this local inflammation are arachidonic acid pathway products, such as prostaglandins, thromboxanes, and leukotrienes through cyclooxygenase

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(COX) and lipoxygenase pathways. Prostaglandins and thromboxane can amplify cytokine responses, recruit inflammatory cells, and induce transcription of pro-inflammatory genes. Besides, thromboxanes and E, I, and H series prostaglandins are also well-established prothrombotic agents. Specifically, PGE2 is shown to increase in many viral diseases, including CMV, EBV, HSV, RSV, and SARS-CoV-2 [1]. PGE2 is implicated in prothrombotic processes by decreasing the activation threshold of platelets [2]. Therefore, PGE2 can be a key player in COVID-19-associated intravascular thrombosis. Furthermore, COX-pathway products are also a strong inducer of local inflammation via their chemoattractant properties. Vijay et al. have drawn attention to PGD2 by showing that it can attract macrophages and induce IFN-γ production following coronavirus infection [3]. Inflammatory substances released by the newly recruited immune cells lead to endothelial damage, contributing to the increased thrombosis risk. Prostaglandins seem to be a significant contributor in COVID-19 patients with increased coagulopathy tendencies, microthromboses, and higher D-dimer levels. Given that COX-pathway products contribute significantly to COVID-19-related coagulopathy and systemic inflammation, nonsteroidal anti-inflammatory drugs (NSAIDs) have been subjects of vigorous medical discussion in terms of their risks and benefits in COVID-19 management.

## 17.2 NSAIDs, Paracetamol, and COVID-19

NSAIDs are well-known and widely used inhibitors of COX enzymes. In 2015, Qiao et al. reported ibuprofen may upregulate ACE-2 enzyme expression in animal experiments [4]. Interestingly this animal study with a single type of NSAID, ibuprofen, led clinicians and scientists to the misinterpretation as to all NSAIDs may worsen COVID-19 prognosis by increasing the target protein of viral cell entry. Another concern in this regard was the speculation that NSAIDs may mask and/or delay initial trivial symptoms of SARS-CoV-2 infection, thus diverting people from getting tested for the disease. Consequently, in March 2020, French health authorities advised against using all NSAIDs due to possible disease aggravation. Only in one study, Jeong et al. mentioned NSAID use before a week of hospital admission resulted in worse clinical outcomes (sepsis, mechanical ventilation use, intensive care unit admission, in-hospital death) with, interestingly, no association with cardiovascular complications [5]. However, another South Korean case-control study of approximately 11,000 patients with acetylsalicylic acid (ASA) exposure 14 days before having tested positive for COVID-19 revealed no such correlation. As of May 2022, all recent human studies demonstrated that NSAID usage in COVID-19 disease did not negatively affect parameters such as infection susceptibility, progression, prognosis, hospitalization, and mortality [6, 7].

Since COVID-19 patients displayed high coagulopathy rates, low-dose ASA usage became a point of discussion. Any study so far did not expose any negative outcomes in COVID-19 patients treated with low-dose ASA. And even in some

studies, a beneficial effect on mortality with low-dose ASA was demonstrated [8, 9]. A retrospective study from Israel demonstrated that patients on low-dose ASA for primary cardiovascular disease prevention were less likely to test positive and quicker to test negative after a COVID-19 diagnosis [10]. Still, this study may be confounded by the fact that patients on low-dose ASA may have been more adherent to conventional preventive measures of the COVID-19 pandemic. Osborne et al. and several other authors found that COVID-19 was less likely to result in death in chronic ASA users [11, 12]. However, all of these studies were retrospective in nature and some of them were conducted on homogenous samples. RECOVERY trial, a randomized controlled trial testing the effects of acute 150 mg ASA used in hospitalized COVID-19 patients, detected no difference in mortality rate and the composite outcome of mechanical ventilation and death [13]. Readers must keep in mind that these studies were mostly conducted on patients with multiple drug regimens, which means patients were already receiving other drugs and may not have benefitted from ASA itself at all. Cautiousness is advised against possible side effects, such as bleeding, and recommended risk-benefit ratio assessment in individual patients with COVID-19.

In a cohort of 28,856 patients, Campbell et al. did not find any increased risk of all-cause mortality in COVID-19-positive patients that were on chronic NSAID (ASA, ibuprofen, naproxen, meloxicam, celecoxib, diclofenac) or paracetamol use [14]. In the meta-analysis study by Zhou et al., it was reported that ibuprofen, ASA, and COX-2 inhibitors can be safely used in COVID-19-positive patients [15]. In a randomized clinical trial conducted on mild and moderate COVID-19 in-patients, the indomethacin group exhibited lesser oxygen desaturation issues and their symptoms resolved faster than the paracetamol group [16]. In their randomized controlled trial, Guzman-Esquivel et al. revealed that mefenamic acid shortened the duration of COVID-19-related symptoms in ambulatory COVID-19 patients also receiving antiviral therapies [17]. Asadi et al. reported that hospitalized COVID-19 patients that were receiving naproxen twice a day were approximately twice as likely to be free of pulmonary symptoms (cough and shortness of breath) as compared to the placebo arm [18]. In the current literature, there is no completed clinical trial regarding the safety of paracetamol use in COVID-19. Yet, Leal et al. showed that paracetamol usage can decrease ACE-2 expression and can be associated with a lower risk of infection [19]. Diclofenac, both in acute and chronic use, was not found to be associated with increased mortality [14, 20].

NSAIDs are ubiquitously utilized in many inflammatory disorders, and due to their COX-pathway inhibition capabilities, their role in systemic COVID-19 management is seriously considered. Studies mentioned above reported that NSAID use of COVID-19 decreased mortality, morbidity, and duration of hospitalization in hospitalized patients. In the same manner, NSAIDs shortened the duration of COVID-19-related symptoms and the period of test positivity in ambulatory patients. Moreover, NSAID use has not been associated with any deterioration of COVID-19 disease (Table 17.1).

**Table 17.1** Clinical drug recommendations for COVID-19 and COVID-19-related headaches

| Drugs | Usage for COVID-19 | Chronic medicine users diagnosed with COVID-19 | Usage for COVID-19 headache |
|---|---|---|---|
| Acetylsalicylic acid | No reduction in 28-day mortality in hospitalized COVID-19 patients and a slight increase in alive discharging probability [13] Beneficial effects of therapeutic low-dose ASA on mortality were demonstrated [8, 9] | Chronic low dose was not associated with a lower risk of COVID-19 hospitalization and severe COVID-19 prognosis [21] Patients on chronic low-dose ASA were less likely to test positive and quicker to test negative [10] | NA |
| Ibuprofen | No increased mortality rates or an increased risk for respiratory support [22] | Chronic use is not associated with worse COVID-19 disease outcomes [6] | Suggestion of continuing if already using [23] |
| Indomethacin | In hospitalized COVID-19 patients it is associated with significant symptomatic relief and improved oxygen saturation levels according to the paracetamol group [16] | NA | Suggestion for refractory COVID or post-COVID headache [24] |
| Diclofenac | No association with higher mortality or increased severity of COVID-19 [20] | No significant differences in mortality at 30 days [14] | NA |
| Meloxicam | No association with increased COVID-19 severity, all-cause mortality, or invasive ventilation in COVID-19 in-patients [25] | No significant differences in mortality at 30 days [14] | NA |
| Celecoxib | The adjuvant treatment promotes recovery and reduces the mortality rate of the elderly [26] | No significant differences in mortality at 30 days [14] | NA |
| Paracetamol | Putative protective effect of paracetamol against SARS-CoV-2 infection and safe for COVID-19 [19] | No significant differences in mortality at 30 days [14] | Suggestion as first-line therapy before NSAIDs [27] |
| CGRP receptor antagonists | The safety and efficacy trial of zavegepant is an ongoing project | Suggestion of not discontinuing CGRP antagonists [28] | Can be an option for the refractory, persistent, and severe COVID headache |
| CGRP monoclonal antibodies | NA | Safe in clinical practice in terms of COVID-19 infection susceptibility and hospitalization [29] | Can be an option for the refractory, persistent, and severe COVID headache |

*NA* Not available

## 17.3 NSAIDs, Paracetamol, and COVID-19-Related Headaches

NSAIDs are widely used for the management of various headache types, and they can be easily reached by patients all over the world. COVID-19 patients can also exhibit excruciating headaches, both simultaneously with the disease or after convalescence. Headache frequency is reported to be 12% in the overall patient population and 29% in hospitalized COVID-19 patients in a meta-analysis [30]. COVID-19 patients with headaches are significantly more likely to present with a more serious set of clinical symptoms such as anosmia, gastrointestinal symptoms, and pulmonary involvement [31]. Headaches are most of the time frontally localized, pressing or pulsating, and moderate to severe in intensity and last more than 72 h. On the other hand, 25% of COVID-19-related headache patients exhibit migraine-like pain, that is, a debilitating single-sided headache associated with photophobia and phonophobia [32]. This serious clinical presentation causes a huge disability and a lower quality of life in a considerable part of COVID-19 sufferers, thus requiring to be promptly addressed.

COVID-19-related secondary headaches are reported to be generally irresponsive to paracetamol treatment [31]. A study from Brazil identified the therapeutic potential of indomethacin on the post-COVID headache that is resistant to paracetamol and other NSAIDs [24]. Guzman-Esquivel et al. found mefenamic acid to be beneficial in terms of shortening the duration of headaches in mildly and moderately severe COVID-19 patients [17]. Ozkan et al. reported a patient with treatment-resistant COVID-19-related headache abruptly ceasing with anti-CGRP (calcitonin gene-related peptide) mAbs (monoclonal antibodies) [33]. In the case of pediatric patients, Mishra et al. advised the administration of paracetamol as the first-line headache treatment within the context of COVID-19 [34]. In addition, cerebral venous thrombosis can be a differential diagnosis in the treatment-resistant headache of COVID-19 patients as indicated by a case report [35].

During the pandemic, an unprecedented vaccination campaign was carried out with inactivated, adenovirus-associated, spike-protein-based, or brand-new mRNA vaccines. Headache is reported to be the third most common symptom in vaccinated individuals. Onset of the post-vaccination headache falls mostly within the first 24 h of vaccination. Most of the time, the post-vaccination headache was bilateral, frontally located, pressing or pulsating, and moderate in intensity. However, one-third of the vaccinated individuals reported a migraine-like headache [36]. Headache incidence was found to be higher in migraineurs and non-migrainous headache patients as opposed to vaccinated individuals without any previous headache diagnosis. Critically, 2.2% of people vaccinated with adenovirus-associated vaccine and 1% of people vaccinated with mRNA-based vaccine were reported to suffer from cerebral venous thrombosis [37]. Considering that cerebral venous thrombosis mostly presents with headaches, people with headaches after vaccination should be evaluated with scrutiny in that regard.

In an observational study, ibuprofen was the most used painkiller, followed by paracetamol and metamizole, as reported by the patients. When they were asked to rate the efficacy of pain killers, they ranked acetylsalicylic acid as the most effective painkiller, followed by ibuprofen and paracetamol [38]. In another study, ASA, loxoprofen, and ibuprofen were found to be more effective in shortening post-vaccination headache duration than paracetamol [39]. Therefore, NSAIDs can be a viable option for combatting post-vaccination headaches.

Approximately one-third of the COVID-19-related headaches persisted after the COVID-19 disease convalescence [40]. Patients that had persistent COVID-19 headaches were more likely to be female and have a previous headache diagnosis and to have presented with headaches on their first admission. More than half of the patients complained of daily headaches. This persistent headache was more resistant to acute pain management at the time of the diagnosis [41]. The number of patients with persistent COVID-19 headache was reported to decrease over a course of several months [42]. Currently, there is no clear data about how to treat persistent COVID-19 headaches. In the case of pharmacological resistance, pericranial nerve blocks can be utilized as well. Besides, Dono et al. have mentioned in their case report that they have treated two such patients with high-dose parenteral corticosteroids [43].

As a summary, NSAIDs are found to be safe and therapeutically effective in COVID-19-related headaches (Table 17.1).

## 17.4 CGRP and COVID-19

Calcitonin gene-related peptide (CGRP) was identified in the late twentieth century as a vasodilatory, angiogenic, and immune-modulating peptide, which is primarily located in the peripheral and central sensory nervous system. Increased CGRP release by trigeminal nerves plays a crucial role in migraine pathophysiology and CGRP antagonists are useful for migraine prophylaxis. Apart from the treatment choices for migraine prophylaxis, CGRP plays a role in systemic arterial hypertension, pulmonary hypertension, heart failure, and systemic or local inflammation. The reason why CGRP came into question again with the COVID-19 pandemics is that the CGRP receptor can stimulate pro-inflammatory cytokines including IL-6 and polarization of $T_h17$-based (T helper 17) T cell response [44]. Regarding the therapeutical role of CGRP, clinical investigations are still in progress despite conflicting opinions concerning its status in COVID-19.

There are two main conflicting camps of thought regarding the role of CGRP in COVID-19 disease. One group proposes that diminished CGRP function is responsible for the clinical presentation of the disease. In COVID-19 pneumonia, CGRP serum levels were found to be lower in hospitalized COVID-19 patients as compared to healthy controls. Since CGRP is a vasodilatory peptide, this reduction may be a partial contributor to pulmonary hypertension secondary to blunted

vasodilatory response, epithelial dysfunction, and angiodysgenesis in hospitalized COVID-19 patients. Furthermore, CGRP attenuates type-2 cytokine release (IL-4, IL-5, IL-9, and IL-13) and T helper type 2 ($T_H2$) proliferation [44]. As an example, in animal models of allergy and RSV infection, serum CGRP is found to be lower and airway responsiveness improved upon restoration of CGRP levels [45]. Experiments conducted on pulmonary hypertensive rats with chronic hypoxia displayed lower serum CGRP levels. Increasing serum CGRP levels by continuous infusion of CGRP analogs were therapeutically effective in dilating pulmonary vessels, rescuing the animal from pulmonary hypertension [46]. Additionally, CGRP is also well known for its positive inotropic effects. Theoretically, this effect may be beneficial for pulmonary functioning by increasing right ventricular function.

The other group maintains that excessive CGRP production causes the cardiopulmonary impairment of COVID-19. In line with this conviction, in a lung injury model CGRP inhibition restored pulmonary function, edema, and inflammation [47]. CGRP can stimulate the production of a wide range of pro-inflammatory cytokines, such as IL-6, a cytokine very closely correlated with disease severity [48]. In accordance with these pathophysiological mechanisms, CGRP antagonism may be espoused as a therapeutical measure against COVID-19 pneumonia. However, no study managed to demonstrate the therapeutical efficacy of CGRP antagonism in COVID-19 so far. Currently, there is only one Phase 3 clinical trial of Biohaven Pharmaceuticals Inc., researching the efficacy of intranasal zavegepant in COVID-19 pneumonia, results of which are yet to be published.

Concerning the role of CGRP in COVID-19, serum CGRP levels may not exactly reflect local CGRP concentrations and function. Therefore, the potential therapeutic benefits of CGRP agonism or antagonism must not be evaluated depending on solely serum CGRP levels. CGRP receptor subtypes, local production, and compensatory receptor upregulation secondary to serum CGRP depletion should be taken into account as confounding factors. Ultimately, how CGRP is involved in COVID-19 remains elusive due to the scarcity of experimental evidence.

Another crucial question was if CGRP antagonists and CGRP mAbs (monoclonal antibodies) were safe during the pandemic (Table 17.1). Blocking the activity of CGRP (receptor antagonism or CGRP mAbs) is the mainstay of migraine therapy. Studies conducted on migraineurs treated with CGRP mAbs showed no change in clinical outcomes such as disease susceptibility, severity, morbidity, and mortality. In a longitudinal observational study conducted on migraine patients using CGRP monoclonal antibodies, PandeMig, the authors did not detect any adverse outcome related to COVID-19 pneumonia [49]. Angus-Leppan et al. have advised migraineurs not to discontinue CGRP mAbs, as they are totally safe regarding COVID-19 [28]. Likewise, Caronna et al. indicated that CGRP mAbs are safe and were not associated with susceptibility to or aggravation of COVID-19 disease [29]. Additionally, CGRP mAbs are not associated with any safety or efficacy concerns regarding COVID-19 vaccination according to a preliminary report [50]. In conclusion, there is no harm in continuing the treatment of patients who are currently using CGRP mAbs as well as in starting CGRP mAb treatment.

## 17.5 CGRP and COVID-19-Related Headaches

CGRP is firmly identified in the migraine headache pathophysiology. CGRP is claimed to be implicated in COVID-19-related headaches [33]. In response to viral infection, pulmonary nerve endings adjacent to pulmonary vessels release CGRP. It can be hypothesized that elevated levels of CGRP can cause headaches in predisposed patients. However, this hypothesis is in direct contradiction with the data of Ochoa-Callejero et al., which reports lower levels of serum CGRP in COVID-19 patients [51]. Another study attempted to clarify the issue and found no statistically significant correlation between serum CGRP levels and headache [31]. Additionally, Souza et al. suggested that SARS-CoV-2 can invade the trigeminal nerve endings and along with an increase in the inflammatory cytokines results in a migraine-like headache [52].

A primary headache exacerbation should be discerned from a new-onset headache secondary to COVID-19. Grassini et al. published a case report of a migraine patient on CGRP mAbs (erenumab) where the patient displayed increased migraine attack frequency after contracting mild COVID-19 disease. When the dose of erenumab was doubled this patient's attack frequency considerably decreased [53]. Both CGRP receptor antagonists and monoclonal antibodies can be safely used in the COVID-19 pandemic because there is no associated higher risk of worse clinical outcomes or mortality related to COVID-19 disease [28] (Table 17.1).

In conclusion, COVID-19 is a pandemic afflicting millions worldwide and one of the greatest health concerns of our time. It has a very diverse clinical course, encompassing cardiopulmonary dysfunction, coagulopathy, and disabling cephalgia. Despite newly developed antiviral treatments, patients are still in need of regimens that would support their care. In the light of emerging clinical evidence, NSAIDs and paracetamol seem to be valid choices for alleviation of systemic symptoms without significant risk of worse clinical outcomes. Besides, patients can be administered with these drugs in case of both primary headache exacerbations and headaches related to COVID-19. Additionally, no supportive evidence for CGRP mAbs is present for uses other than headaches in COVID-19, and patients that are on CGRP mAbs can continue their therapies safely.

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# Chapter 18
# COVID-19 Headache Manifestations in the Elderly

**Nil Tekin and Aynur Özge**

## 18.1 Introduction

### *18.1.1 Current Status of COVID-19 Infections in the Elderly*

The novel coronavirus-2 with the common names SARS-Cov-2 has spread all over the world starting from China in late 2019. Subsequently, all age groups but specifically elderly national health and care systems had, to cope with primary and secondary hits from the SARS-Cov-2-related disease called COVID-19. Later, they had to deal with primary and secondary illnesses resulting from the SARS-Cov-2 related disease called COVID-19 [1].

Primary consequences of this pandemic infection affected people of every age across the globe. Elderly peoples specifically patients with dementia had several types of comorbidities had to polypharmacy leading to more susceptible to COVID-19 infections with more severe symptoms and worse prognosis [2]. In addition to acute phases, post-acute and chronic phases created some unusual troubles stemming from prolonged bedding and respiratory, cardiovascular, psychosocial, and neurological complications including several types of cognitive dysfunctions.

As it is known, it is important to apply standard isolation precautions, especially in elderly and chronically ill populations, and special attention and effort should be made to reduce transmission [3]. However, secondary consequences of the pandemic infection created big troubles on the regular follow-up visits by the healthcare system affecting specifically chronic diseases, especially in the elderly [3].

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Elderlies staying in "nursing homes" or "own homes" were deprived of physical visits by friends and relatives due to COVID-19 containment measures and had very limited access to the system. The WHO stated in its 2020 report that "the elderly with cognitive impairment or dementia during the epidemic and quarantine either experience more anxiety, anger, stress, agitation or, on the contrary, become more withdrawn when they are hospitalized during the pandemic process" [1, 4].

It is known that COVID-19 has higher mortality rates in the elderly. COVID-19 should be monitored more closely in this population. Of course, the efficacy of vaccines in the elderly is not as well-known as in adults. However, the most important issue that will determine the future of the elderly is the vaccination of the whole world as soon as possible. In addition, more studies are needed on the problems that arise in the long-term follow-up of the elderly who have had COVID-19 [5].

### *18.1.2 Impact of COVID-19 on Mental Health and Aging*

Neurodegenerative diseases and inflammatory-mediated neurological disorders have also been recognized as a potential risk factor for COVID-19 infection. CNS symptoms such as ischemic stroke, encephalitis, encephalopathy, and epileptic seizure have been observed following COVID-19 infection. There are several case studies linking COVID-19 infection with stroke. The most common neurological sign associated with COVID-19 infection on brain imaging in hospitalized patients is acute stroke. For example, in an observational study, an elderly male patient with no symptoms specific to COVID-19 other than shortness of breath presented with dysarthria, disorientation, and weakness in the left upper extremity. Many factors have been proposed that contribute to ischemic stroke associated with COVID-19. The exact mechanism is not yet known [6].

Almost one-third of the cases develop neurological manifestations related to COVID-19 including headache, dizziness, encephalopathy, acute myelitis, cerebrovascular accident, and encephalitis in the short term. On the other hand, there are several long-term effects reported including headache, asthenia, cognitive disturbances named as "foggy brain," etc. [7].

### *18.1.3 Headache in the Natural Course of COVID-19*

Headache is among the most common but less focused presentation of COVID-19 infection, commonly mimicking migraine or TTH (tension-type headache) in the elderly population. Headache develops generally within 72 h of COVID-19 infection onset in most cases and might be the presenting symptom at least in a quarter of patients. Pain location was generally frontal, bilateral, severe, but less complicated with common associated symptoms and focal neurological symptoms when it was not related to a secondary reason [8, 9]. Even though headache disorders

attributed to COVID-19 infection pointed to the rubric diagnostic criteria of ICHD-3 (International Classification of Headache Disorders) classification subtitle 9.2.2.1 (acute headache attributed to systemic viral infection), there are several cases where the mentioned criteria are unmet and some new specific emerging criteria are proposed [9].

The real reasons of the COVID-19-related headache are not completely explained yet but the involvement of the trigeminocervical complex and hyperinflammatory response including inflammasome activation was implicated and pointed additionally to as some potential effect of increased coagulation [10, 11]. The close relation between headache and anosmia/ageusia may give us some clues and support a direct invasion of cranial nerves by the virus but subsequent studies did not put forward the real importance of it. To conceive appropriately designed comparable translational studies, the acceptance of ICHD criteria will be guiding the researcher and open some new windows to the mysteries of the triggering mechanisms of viruses for the headache mechanisms far from a neuroinflammation [9].

Comprehensive case series supported that headaches occur in almost one of every four confirmed COVID-19 cases independent of age. In less than 10% of the cases headache is the first or early onset symptom of the disease with specific phenotypic features including forehead located, commonly pressing quality but severe headache attacks accompany lots of migraine symptoms without any proven secondary reasons need to intervention by medical or other procedures but not a predictor of poor outcome. The elderly with dementia with COVID-19 infections presented headache symptoms at any stage of the disease, and the following are the frequencies and type of red flags in differential diagnosis in patients with COVID-19 infection: fever (59.2%), worst headache ever experienced (26.0%), wake-up headache (21.2%), precipitation by cough or Valsalva maneuver (21.5%), resistance to current headache management (19.4%), precipitation or aggravation by sitting upright or standing (14.5%), progressive headache disorders (13.1%), precipitation by bending (12.9%), associated confusion state (6.2%), sudden onset of headache (5.8%), precipitation by lying horizontally (5.5%), and loss of consciousness (0.5%) [12].

Headache is also the second most common presentation of long-term effects in COVID-19 patients especially in almost 44% of the elderly population, and several comorbidities including brain fog or altered mental status merit more comprehensive longitudinal studies to explore their real importance especially in the elderly population including dementia cases [13].

### *18.1.4 Cognitive Dysfunction on Primary or Secondary Headache Disorders in the Elderly*

There are several reports suggesting impaired cognition is not only related to secondary causes of headache disorders but also primary headache disorders including migraine. Supporting data reveals migraine is associated with attention deficits,

executive dysfunctions, and disturbed processing speed and memory especially chronic and comorbid cases with increasing frequency in the elderly. However, there is no clear association between migraine and dementia up to now. Additionally, even with some supportive reports, there is no consensus about the cognitive dysfunction in patients with neither tension-type headaches nor cluster headaches. On the other hand, several secondary headache syndromes relevant to clinicians managing headache disorders are associated with poorer cognitive performance or distinctive cognitive patterns, including those attributed to chronic cerebral or systemic vascular disorders (CADASIL, MELAS, RVCS-LM, and cerebral amyloid angiopathy), trauma, and derangements of intracranial pressure and volume, including frontotemporal brain sagging syndrome (FBSS). Brain imaging to search for the stigmata of spontaneous intracranial hypotension should be considered in patients with postural headaches, and a behavioral variant frontotemporal dementia phenotype as FBSS might improve with blood patch and/or repair of CSF leaks [14].

There are some growing evidences on post-COVID-19 headaches and post-acute sequelae SARS-CoV-2 infection (PASC), and potential associations between post-COVID-19 headaches and PASC cognitive impairment are important topics that need to be discussed. There are several potential reasons for decreased cognitive dysfunction potentially leading to dementia related to COVID-19 infection or triggered by the post-infection phases. Some of them are listed here:

- Hypoxia and cerebral hypoperfusion secondary to cardiorespiratory disease leading to known hypoxic-ischemic brain injury and documented diffuse white matter damage in neuroimaging
- Increased coagulopathy, with thrombotic occlusion of cerebral blood vessels leading to the cerebral artery or venous thrombosis, sometimes presented with disseminated intravascular coagulation
- Cerebral microvascular damage and dysfunction leading to neuroinflammation, pericyte damage, BBB leakiness, neurovascular dysfunction, impaired autoregulation, impaired vascular/para-vascular drainage, and overreactive neurodegeneration
- Dysregulation of the renin-angiotensin system leading to loss of regulatory RAS and overactivity of classical RAS signaling and several endpoints of the body including the CNS
- Rarely encephalitis or post-infective encephalitis leading to CNS viral neuroinvasion via olfactory nerve fibers or vasculature/post-infective immune injury to the CNS [15]

Neurobiological differences of natural course in each step of the process mentioned before explains potential reasons of interpersonal and intrapersonal changes. Additionally, apolipoprotein polymorphism related to the natural course of COVID-19 infection and postinfection cognitive decline is far from a coincidence. It is revealed that APOE ε4 individuals have the lowest ACE-2 receptor activity than others. It is closely related to the changes in basement membrane formation causing brain-blood barrier (BBB) leakage promoted by a change in pericyte function. These changes cause reduced cerebral blood flow and also increased subcortical ischemic white matter lesions commonly reported in these cases. There are also

several supportive clues for increased and overreactive neuroinflammation closely related to ApoE4 care and comorbid vascular and metabolic changes mentioned before [10, 11, 15].

### *18.1.5 Effects of Lockdown on the Headache and Mental Health in the Elderly*

There are several reports about the increased resilience of the elderly with or without headache disorders during lockdown and post-COVID crisis. However, the elderly who had any type of headache disorders were more vulnerable than their peers without painful syndromes. On the other hand, dementia patients and their caregivers faced various challenges during the pandemic. Also, during lockdown in Italy, more than 60% of caregivers of dementia patients were reported to have stress-related symptoms. While neuropsychiatric symptoms increased in dementia patients with COVID-19 infection in lockdown, stress levels increased in caregivers [16].

Even in the first days of the pandemic some of the authors took this interaction and proposed some solution-based interventions like telemedicine, online follow-up treatment, and some tools for self-evaluation [17]. On the other hand, except for some educated and technology-adapted elderly population, most of the population are not aware of this intention. Regarding to technological richness and flexibility some cases decreased lockdown related cognitive and emotional burdens. We need more data about the long-term effect both of lockdown and socialization made through virtual platforms.

### *18.1.6 Short- and Long-Term Effect of ICU and Severe Pulmonary Disease in Elderly Headache*

There are many studies on the elderly hospitalized due to COVID-19 infection. However, limited information is available on the characteristics and clinical outcomes of elderly patients hospitalized in intensive care units (ICU) due to COVID-19 infection [18]. Compared with younger patients in some studies, shortness of breath has been reported to be a factor associated with worse prognosis in the elderly. In addition, while 37% of the patients did not have fever and shortness of breath, the presence of delirium correlated with worsening of the clinical course, admission to the ICU, and death [18]. Headache, which is among the clinical findings, was found to be associated with a low mortality risk in hospitalized COVID-19 patients [19]. Another study found that the presence of headaches in hospitalized COVID-19 patients was independently associated with lower mortality and lower ICU admission. On the other hand, patients with headaches described a high degree of disability and the need for acute treatment was frequent [12].

Headache is also defined as a common post-COVID-19 sequela experienced by those with COVID-19 infection [20]. In the outpatient follow-up after hospitalizations, those with severe illness during acute COVID-19 and/or those who need an intensive care unit and those who are most susceptible to complications (e.g., the elderly, those with multiple-organ comorbidities, etc.) should be prioritized [21].

The incidence of post-COVID headaches decreased after the acute phase; it has been demonstrated by a meta-analysis that it remained stable in different follow-up periods during the first 6 months after COVID infection. This duration was similar in hospitalized or outpatient COVID-19 patients. This supports the notion that headache is a common post-COVID symptom experienced in patients with severe symptoms (hospitalized) and in patients with moderate to mild symptoms (not hospitalized) [20, 21].

Guidelines issued by the British Thoracic Society to evaluate survivors of COVID-19 infection in the first 3 months are based on the severity of acute COVID-19 after hospital discharge and whether the patient has been hospitalized in the ICU. In addition to this 12-week evaluation, an earlier clinical evaluation 4–6 weeks after discharge is recommended for those with severe acute illness (those with severe pneumonia, those requiring an ICU, the elderly, or those with multiple comorbidities) for rehabilitation needs [21].

### *18.1.7 Effect of COVID-19 Vaccines on Headache in the Elderly*

After the novel SARS-CoV-2 virus infection spread all over the world, vaccines have brought us a ray of hope to effectively fight against the deadly pandemic of COVID-19 and hope to save lives. Many vaccines have been granted emergency use authorizations by many countries based on different mechanisms and methods. In the last 2 years, a wide spectrum of neurological complications is continuously being reported following COVID-19 vaccination including some neurological adverse events like fever and chills, headache, fatigue, myalgia and arthralgia, or local injection site effects like swelling, redness, or pain. The most devastating neurological post-vaccination complication is cerebral venous sinus thrombosis causing focal neurological symptoms including headache. Fortunately, robust central nervous system damage complications like post-vaccinal encephalitis, acute transverse myelitis, acute disseminated encephalomyelitis, neuroleptic malignant syndrome, delirium, or progressive dementia are reported rarely in the process [22].

To confirm the hypothesis of a causal relationship between vaccine administration and worsening of headaches in patients with preexisting migraine, the clinical pattern of headache attacks following COVID-19 vaccine administration (regardless of vaccine type) in a large sample of headache patients was investigated. The main finding relates to perceived headaches. 57.60% of the patients named the post-vaccination attacks as more severe. This may be related to inflammatory production. Randomized controlled trials (RCTs) have also shown an increase in attack duration

and intensity after COVID-19 vaccine in preexisting headaches. A high percentage of migraine patients with headache clinical practice reported headache episodes in the days following vaccination. In general, worse pain intensity, prolongation of attack duration, and worse response to painkillers were observed, unlike before. Given the high prevalence of migraine in general, awareness of the possibility of worsening headaches following COVID-19 vaccination may allow both patients and physicians to consciously confront this clinical situation [23]. It is also closely related to the female gender, previous primary headache disorder history, known COVID-19-related headache disorders, and comorbid thyroid disorders in addition to headache complications of previous influenza vaccines [24].

Both primary and secondary headache diagnoses should be discussed, provided there is solid evidence that COVID-19 vaccine administration can cause headaches. Due to both the high prevalence of migraine (12–14%) and the high prevalence of COVID-19 vaccine administration in the world, it is necessary to be aware that several million patients may be under a high disability burden at the same time for a certain period of time. It is important to spread the awareness that the existing headache may worsen following the administration of the COVID-19 vaccine in migraine patients. Awareness of this situation by clinicians may reduce the waste of resources for inappropriate health services. On the other hand, migraine patients should be informed and reassured about the possibility of increased headache severity after vaccination [25].

### *18.1.8 Long-Term Neurocognitive Consequences of COVID-19 Including Dementia*

COVID-19 infections created several types of neurocognitive symptoms including dementia via direct invasion of the central nervous system (encephalitis, stroke, consciousness disorders, etc.) or indirect effects via vascular complications, lockdown, long COVID, vaccines, etc. Some retrospective studies supported the increased ratio of neurocognitive dysfunction including clinical dementia during the pandemic days than before. Together with the indirect effect of the virus including anxiety, isolation, personal protective equipment uses, limited exercise, vaccines, etc., dementia progression had increased. Taking account of variables with formal or informal caregivers related to COVID-19 infections and other social problems, clinical dementia progression from the prodromal stage could be imagined. On the other hand, ACE-2 receptor polymorphism, apolipoprotein E (ApoE) genotype, hospitalization or the ICU requirement, and comorbid vascular and neurological disorders explain the changing ratio both of the new onset dementia diagnosis and previous dementia prognosis [16].

There is no consensus about the middle- or long-term consequences of COVID-19 infection on the neurodegenerative conditions including Alzheimer's disease because of the known systemic inflammation and other unknown reasons. Literature suggested mechanisms of potential causes of reported mental illness and dementia

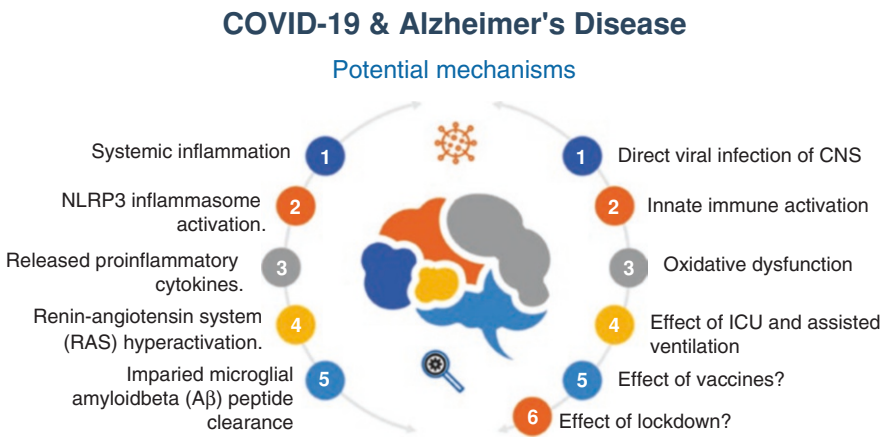


**Fig. 18.1** Potential mechanisms of COVID-19 infection causing neurodegeneration including Alzheimer's disease

like consequences including NLRP3 inflammasome activation-related to IL-1β release, different level renin-angiotensin system hyperactivation, ineffective immune activation, unregulated oxidative stress, direct viral infection, and direct cytolytic β-cell damage caused by blood-brain barrier degeneration somewhere. At this step, some types of anti-inflammatory therapies, including TNF-α inhibitors and nonsteroidal anti-inflammatory drugs, antioxidants such as the vitamin E family, nutritional intervention, physical activity, blood glucose control, and vaccination, are proposed as preventive measures to minimize AD risk in COVID-19 patients [10, 25] (Fig. 18.1).

Current reports revealed that severe COVID-19 infection process is associated with an increased risk of long-term cognitive decline in the elderly population rather than a coincidence [dementia 25 (10.50%) vs. 9 (0.69%), $p < 0.001$, and mild cognitive impairment (MCI) 60 (25.21%) vs. 63 (4.84%), $p < 0.001$], and controls [dementia 25 (10.50%) vs. 0 (0%), $p < 0.001$, and MCI 60 (25.21%) vs. 20 (4.29%), $p < 0.001$)]. Some associated factors like the severity of COVID-19 infection including pulmonary involvement, delirium, and Chronic obstructive pulmonary disease (COPD) were risk factors of current cognitive impairment. On the other hand, low education level, severe COVID-19, delirium, hypertension, and COPD were accepted as potential risk factors of longitudinal cognitive decline accordingly [26].

### *18.1.9 Unusual Presentations of Headache in Dementia*

It is known that more than 50 million people are live with dementia all over the world excepting prodromal or preclinical stages. Additionally, it has been reported that patients with severe cognitive impairment due to AD and related dementias, therefore represent one of the populations at greatest risk of negative outcomes

during quarantine and long-term effects of COVID-19. At this stage, drugs for management of dementia, comorbid disorders, and COVID-10 infection have to be taken into account [1].

A recent report supported that an altered mental status of acute onset may be a leading symptom of COVID-19 especially in older age or dementia cases. Among these symptoms, confusion, agitation, and disorientation appeared before other respiratory symptoms or fever is commonly presented in dementia cases. In all cases, developed biomarkers evidents of severe COVID-19 infections on the process and commonly complicated with painful disorders including headaches reported [27].

### *18.1.10 Emergency Room Tips and Traps for Elderly Cases with COVID-19*

Current reports suggested that COVID-19 admissions were enriched for minority ethnic groups and for those with dementia, obesity, and diabetes when compared to non-COVID-19 pandemic admissions, especially in the elderly, but had lower rates of malignancy. It is also correlated with the increased prevalence of dementia among COVID-19 admissions that could reflect outbreaks in nursing homes or difficulty shielding effectively when reliant on external caregivers [28].

An important cause of ER visits in the elderly is delirium with or without previous dementia diagnosis. Delirium is among the most frequent neuropsychiatric manifestation of COVID-19 especially in the elderly, occurring in 37–42% of hospitalized patients and also around 3% of total cases, which is an important prognostic factor predicting poorer outcome. There are several reports suggesting the increased frequency of delirium in pandemic days compared to pre-pandemic days correlated with previous psychiatric disorders, dementia, and/or neurological comorbidities including headache disorders, independent of the severity of the pre-existing COVID-19 infection [29].

### *18.1.11 Social and Medical Aspects of Pain Disorders in Nursing Homes in the Pandemic Era*

Despite their active needs, a definitive approach to managing chronic pain in the elderly in nursing home has not been fully demonstrated. Appropriate pain management is challenging due to concerns about potential adverse effects. Uncertain guidelines on specific treatment practices and duration of treatment and limited treatment options are major barriers in nursing homes. A wide variety of clinician prescribing habits for pain control among nursing home residents are also important. In this case, fragility, decrease in functionality, and medical complications are also effective. All these difficulties complicate the successful implementation of comprehensive chronic pain management [30, 31].

The COVID-19 pandemic has also adversely affected the fragile elderly living in nursing homes beyond physical health, including social isolation, loneliness, and depression. Many residents in nursing homes have experienced physical, emotional, and psychological trauma from active COVID-19 infection, repeated testing for the virus, as well as lack of visitation by family members. It has been reported that anxiety and depression symptoms and chronic pain symptoms exacerbated during the COVID-19 pandemic. Also, it has been stated that this situation may cause an increase in the need for all pain relievers, including opioids. As a result, this process has made the management of chronic pain in nursing homes even more complicated and difficult. Multidisciplinary teamwork, support of relatives, and regular follow-up of patients at risk are important in solving problems. The patient with chronic pain is at risk of functional and emotional decline and potentially an increase in the long-term healthcare burden during the pandemic process. Clinical decisions regarding pain management strategies should be based on balancing the risks [30, 31].

### *18.1.12 Telemedicine-Based Tools, Artificial Intelligence, and Suggestions for Physicians*

Current development on telemedicine-based awareness, education, diagnosis, and management has been widened in the last 2 years with pandemic new life experiments. On the other hand, expert statistics opened new era for defining prognosis or mortality before they happened. Some important cohorts suggested that the age > 65, concomitant headache, nursing home residency, associated dyspnea, altered mental status, consolidation, hypoxemia (<88 $O_2$ saturation), status of oxygen in the hospitalization (yno2), coronary artery disease, diabetes, alcohol, hypertension, stroke, dementia, prothrombin, and CRP were accepted positively correlated with mortality among patients with COVID-19. There are several applications of machine-learning-based approaches to predict hospital mortality or natural history of the diseases in patients with COVID-19 and identification of the most important predictors from clinical, comorbidities, and blood chemical variables provided from blood samples, CSF, neurophysiological screens, care systems, etc. in order to determine the high- and low-risk survivors as well [32].

The COVID-19 pandemic has spurred the use of telemedicine, changing the delivery of medical services. However, accessing these benefits requires extensive logistics to ensure successful implementation. Its benefits are specific to different medical applications. Telemedicine must be fully integrated into healthcare systems to ensure maximum effect and smooth functioning. The main barriers identified include the lack of political support and a lack of understanding of the applications and usefulness of telemedicine. More information on costs and required resources are needed to ensure its effective implementation [33].

### *18.1.13 Frailty as a Hidden Factor of Dementia and Headache Disorders*

Hospital-based series reported that headache is the most important and presenting symptom, especially in patients older than 65. In patients with dementia, difficulties in the evaluation of symptoms and additional barriers relating to isolation strategies are encountered. Additionally, age-related physiological changes; some common comorbidities like heart diseases, lung diseases, hypertension, diabetes mellitus, and obesity; smoking history; dementia; multiple drug use; nursing home; and other potential reasons of increased virus load also have to be considered for the elderly during evaluation. An important hospital-based report showed that headache and altered mental status are the most common symptoms in elderly cases with COVID-19. These reports also suggested that impaired mental status is closely related to headache, Acute respiratory distress syndrome (ARDS), comorbid dementia, and cerebrovascular disorders, but long-term consequences of headache and cognition disorders need to be clarified. However, it is reported that associated headache symptoms and related disorders have a favorable outcome on the natural history of the COVID-19 infection process according to current literature. On the other hand, altered mental status not only the infection phase but also the post-infection phase with or without focal neurological sequelae like hemiparesis was associated with a less favorable outcome. Moreover, preexisting dementia or cerebrovascular disorders increased the ratio of poor outcome and mortality [32–34]. We need more comprehensive long-term data for defining the exact role of frailty on headache symptoms of dementia cases in addition to making clear uncommon presentations.

### *18.1.14 Management of Headache Disorders in the Elderly with COVID-19*

There is no specific management of headache disorders in the elderly with COVID-19. However, some important reports showed that an appropriate management has to be considered according to phenotypic presentation of the mentioned headache disorders and known comorbid medical conditions of the cases. The elderly population merits much more attention to psychopharmacology and early evaluation of interventional procedures like peripheral nerve blockage because of there is no systemic side effect potentially cause to crossing side effects of current antiviral and metabolic drugs. On the other hand, there is no suggested data that requires extra attention to acetaminophen, NSAIDs, 5-HT 1B/1D/1F receptor agonists, CGRP monoclonal antibodies, or onabotulinumtoxinA procedures according to current literature [11].

### *18.1.15 Future Directions and Unanswered Questions*

- Which cases are more suspectable for headache disorders in elderly or dementia cases?
- Are there any specific biomarkers in detecting headache symptoms on dementia cases?
- Long-term consequences of overreacting neuroinflammation on neurodegeneration including AD.
- Exploring the exact role of and consequences of ACE-2, ADAM-17, or ApoE4 polymorphism potentially opens a window to management strategies together with a satisfactory explanation to personal changes in prognosis not only for the acute infection process but also long-term disorders.
- Long-term consequences of the changed daily routine with limited action and social network on the frailty causing dementia in the elderly population.
- Long-term consequences of refractory headache disorders on the natural history of AD.

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# Chapter 19
# COVID-19 Headache During Pregnancy and Breastfeeding


**Füsun Mayda Domaç**

## 19.1 Introduction

During pregnancy, there are differences in immune responses, physiological changes in cardiac system such as heart rate and changes in respiratory system due to the anatomical position of the diaphragm, and decreased capacity of the lungs which may lead to a high risky and sensitive period for both the initiation and the complications of any infectious diseases as well as SARS-CoV-2 infection [1–4]. But at the beginning of the pandemia it has been reported that the risk for COVID-19 infection for pregnant women was not different from the non-pregnant ones [5–7]. In a prospective cohort study, during follow-up for 10 weeks, pregnant women had a 1% risk of coronavirus infection and 35% of the patients seemed to be asymptomatic [7]. Developed symptoms during the infection for non-pregnant women were also similar to pregnant women [6]. Though being pregnant did not seem to make an effect on the development or the initiation time of the symptoms, stillbirth and preterm birth ratios were found to be higher in the infected patients than the patients without COVID-19 infection [4, 8–10]. Vertical transmission was found to be rare in coronavirus disease but maternal effects of the disease seemed to be higher especially in the last trimester of the pregnancy [11]. Management of coronavirus disease is similar in pregnant individuals and in non-pregnant ones [12]. But it must be kept in mind that the progress of the disease may be more severe and the need for mechanical ventilation may be earlier for pregnant women [8].

As more experiences and knowledge about the clinical state and progress of the coronavirus disease have increased, it was seen that symptoms showing the involvement of the nervous system both peripheral and central may also accompany

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COVID-19 infection and headache was observed to be the commonest complaints among them [13–16]. Even though the pathophysiology of headache due to coronavirus disease is not clear yet, it is suspected that peripheral endings of the trigeminal nerve may be activated by the virus directly. Elevation of cytokines leading to proinflammation, hypoxia, or vasculopathy is another accused mechanism [14].

In this chapter it was aimed to investigate the relation of headache with SARS-CoV-2 infection during pregnancy and breastfeeding.

### *19.1.1 Lockdown and Headache*

Lockdown following the beginning of pandemia has brought several problems. Sleep disturbances like insomnia and sleep-wake disorders, psychological problems like depression, anxiety disorders, and stress have increased which had a negative effect on premorbid headache disorders [17, 18]. Though the data in pregnancy and breastfeeding is lacking, excessive computer use, changes in lifestyle (sleep, food, exercise, etc.), and increase in attention to the news of coronavirus disease were thought to be the main factors that have increased the incidence of headache attacks [19]. But, effects of lockdown or quarantine on comorbid headache disorders are conflicting. In the study of Delussi et al. most of the patients did not report a difference in the number of headache attacks between prequarantine and quarantine periods except the patients suffering from an increase in the frequency and the severity of migraine headaches from the northern part of Italy where the diffusion of pandemia was high [20]. In another study it was found that migraine attacks and pain intensity have decreased during pandemia which may be due to the lessened triggering factors while resting at home. Lesser depression and anxiety was found to be in correlation with lesser migraine attacks [21].

### *19.1.2 Vaccination and Headache During Pregnancy and Breastfeeding*

Recent studies have reported that pregnant women who were not vaccinated had severe COVID-19 infection with a high ratio of hospital admission and critical care as well as perinatal deaths [22, 23]. Due to the probability of being a severe disease, pregnant women were recommended to be vaccinated against COVID-19 by the World Health Organization [24]. In several countries some of the pregnants were vaccinated and no increasement was found as severe complications that might affect fetuses or severe adverse effects on pregnant women after vaccination [25].

Komine-Aizawa et al. have documented the results of vaccination (two doses) of pregnant individuals and found that pain on the vaccine administered area was the most frequent (90%) local adverse reaction. Symptoms associated with pregnancy

such as bleeding, amniorrhexis, decrease of fetal movements, or increase in blood pressure of the mother were seen in 1%. Systemic reactions were seen as fever (which was found to be approximately 4 times higher than the first vaccination), fatigue and/or malaise (approximately 2 times higher at the second vaccination), and arthralgia (approximately 4 times higher at the second dose). Among the frequent symptoms headache was found to be seen in 14.13% after the first vaccination. Like the other symptoms headache seemed to develop more commonly after the second dose with a ratio of 38.28% [26]. Increase of headache occurrence after the second dose of vaccination was also shown in another study [27].

These results were not found to be different with nonpregnant women [25]. Compared to housewives and self-employed pregnant women, healthcare workers and public servants seemed to be have participated more in vaccination. The trimester of the pregnancy had also an effect on the participation of vaccination and it was high in both the second and the third trimesters [26].

In a systematic review it was also reported that after first vaccination with mRNA vaccines, transient headache has developed in 8% to 20% of pregnant women and 32% to 65% after the second dose. Antibody transmission through placenta was shown as antibodies were detected in the neonates whose mothers were vaccinated. The number of vaccination was important for the appearance of antibody. After a single dose 43.6% of the neonates had antibody, while it was detected in 98.5% of the neonates whose mothers had vaccination twice [28].

Vaccination for SARS-CoV-2 is also thought to be effective during breastfeeding and also suspected to be protective for the baby via the antibodies that occur in the breastmilk [11]. Side effects due to vaccination were similar in pregnants as nonpregnants. Headache was one of the most common complaints after vaccination. After the second dose headache was seen more than the first one [27]. Some patients have complained of a reduction in the amount of breastmilk after the first dose of vaccination and the number of women with this complaint has increased after the second dose [29]. Nevertheless, vaccination during pregnancy and breastfeeding should be applied after a risk-benefit decision [30].

### *19.1.3 Headache and COVID-19 Infection During Pregnancy and Breastfeeding*

COVID-19-related headache mostly presents like tension-type headache and approximately ¼ of the patients represents headache as migraine-like [31, 32]. After recovering from the infection some patients may still continue suffering from headache [31].

From the beginning of the pandemia, several reports from several countries have also documented headache during coronavirus disease. In some studies headache was found to be a less common symptom [4, 33], while some studies have shown that headache seemed to be one of the commonest symptoms in COVID-19

infection [34–36]. Hernandez-Cruz et al. observed headache as a significant symptom in infected pregnant women. They have found that patients whose PCR test was positive for coronavirus had headache more and they suspected that headache must not be overestimated in pregnancy and PCR test should be applied [36].

Çakırca et al. from Turkey have documented 75 pregnant patients infected with SARS-CoV-2 virus, nearly half of whom were at their third trimester. Among these patients headache was the third most common symptom and half of the patients complained of headache [35].

Montinelli et al. have investigated the pregnant individuals hospitalized with the diagnosis of coronavirus disease either positive or suspected positive and compared them with nonhospitalized infected patients. Headache was seen in 80% of the hospitalized and 71.9% in nonhospitalized pregnant women, while the ratio was 62% in nonpregnant women [34].

Several mechanisms are accused for the tendency for thromboembolism during coronavirus disease [37]. Pregnancy is also accepted as a prothrombotic state. Thus, it was suspected that risk of thromboembolic events would be triggered by SARS-CoV-2 during pregnancy but no events have been reported. Nevertheless, it must be kept in mind that secondary headaches can develop due to cerebrovascular events in pregnant women with COVID-19 infection, and if "red flags" exist, appropriate examinations should be made. Venous sinus thrombosis and ischemic stroke must be differentiated in patients with coronavirus disease especially when neurological symptoms accompany newly onset headache in temporal relation with the infection [37, 38]. Headache can also be due to hemorrhagic stroke which may be due to endothelial damage, vasculitis, or cytokine storm in COVID-19 disease [39]. Chan et al. presented a case with coronavirus disease who had acute onset neurological symptoms and headache and was diagnosed as pituitary apoplexy in the third trimester of pregnancy [40]. Preeclampsia can also develop in symptomatic patients with COVID-19 infection. Investigation of the placentas of the patients revealed highly fibrinoid deposition which was suspected to be a result of vascular malperfusion of the mother [41, 42].

It is not clear whether the virus is transmitted vertically through breastmilk. Some recent studies did not find signs of positivity for SARS-CoV-2 in the breastmilk of the infected patients [43, 44], while in some cases PCR test was positive for the virus in the specimen of breastmilk [45–47]. Jafari et al. also found SARS-CoV-2 in breastmilk and they have suggested that even low percentages may be adequate for vertical transmission [4].

In postpartum period coronavirus disease can also be a reason for secondary headaches. Cerebrovascular events induced by viral infection can also present with headache with accompanying neurological symptoms. Subarachnoid and intracerebral hemorrhages were reported in a case with coronavirus disease after the first week of delivery [48]. As postpartum period can be a hypercoagulopathic state, increased thromboembolic events and ischemic stroke were also reported after COVID-19 infection [49, 50]. Posterior reversible encephalopathy was reported in a postpartum woman, which was suggested to develop due to an upsurge on blood pressure caused by coronavirus disease [51].

As a conclusion, headache during pregnancy and puerperium must be followed up and secondary etiologies should be ruled out. COVID-19-related headache seems to be transient but may last longer in some patients. Pre-existing headache attacks may increase in frequency and intensity. If headache persists, nonpharmacological treatments can be applied and also appropriate pharmacological treatments depending on the type of headache can be suspected in case of need.

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# Chapter 20
# The Changing Nature of Headache Practice in the Pandemic Era


**Necdet Karli and Emel Oguz-Akarsu**

## 20.1 Introduction

The last weeks of 2019 and early days of 2020 have been a major turning point in modern time history. Humanity was faced with one of its greatest challenges and problems unprepared. Coronavirus disease 2019 (COVID-19) has emerged from Wuhan, China, and quickly spread all over the world resulting in the World Health Organization (WHO) to call it as a pandemic. All the countries, governments, political systems, communities, and the healthcare systems were caught unprepared to such a devastating pandemic. It posed an enormous burden on people, individuals, economy, and social life but health system being the most. The modern healthcare system was designed for protective healthcare and has a limited number of outpatient and inpatient clinics, but it has nowhere foreseen a possibility of such a huge demand. Such a disease resulting in billions of sick people, affecting many different organs of the body, needed a higher number of doctors and healthcare workers as well as higher numbers of intensive care unit (ICU) beds and intensive care equipments and a higher capacity of inpatient clinics and medical kits for patient care. Faced with such a devastating condition healthcare managers diverted doctors and other medical staff to the emergency departments, ICUs, and COVID-19 inpatient clinics and outpatient clinics. Both to help the war against COVID-19 and to protect healthcare professionals from increased COVID-19 risk, outpatient clinics, some inward clinics, and many primary care facilities were closed. This situation caused a handicapped health service, particularly to the patients suffering from chronic diseases. Headache and pain were the leading ones among many others.

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## 20.2 Pandemic and Headache

Headache sufferers compose the majority of neurology and pain outpatient clinics [1]. They need frequent visits in order to comply with the changing frequency, severity, and burden of headache as well as to arrange the medication according to these changing parameters. The pandemic has caused a major obstacle in receiving the medical care that headache sufferers needed. Many patients could not reach healthcare facilities. The lucky ones who could be able to reach a hospital could not see a specialist. Both the indirect effects of pandemic (anxiety, social isolation, economic loss) and direct effects of COVID-19 (causing headache, increased frequency and severity of headache) increased the need for headache healthcare [2]. This made the neurology and headache specialists to seek the opportunities of giving remote healthcare services. Among them telephone calls, video calls, and video meetings (e-consultation) were the most popular ones.

## 20.3 Telemedicine and Headache

Telephone calls have been used for a long time by physicians and healthcare workers which can be accepted a traditional way now. However, video calls and meetings with patients and their families appeared as a new and remote way of physician visits and consultations. There had been limited studies and guidelines before the pandemic investigating how to and whether they are safe or reliable. In those studies telemedicine was found to be both satisfactory and reliable with similar outcomes as in face-to-face visits [3, 4]. The European Headache Federation and American Academy of Neurology were among the associations that tried to set up guidelines for telemedicine in headache and neurology even before the pandemic [5, 6]. Through the pandemic many studies have been published showing the reliability, practicality, and safety of telemedicine with similar outcomes with visiting outpatient clinics [7, 8]. These studies showed none of telemedicine or traditional visits were superior to each other. Besides, Müller et al. reported that telemedicine saved up to 300 euros and 8 h of travel time for people residing in the remote regions of their countries [8].

## 20.4 Benefits and Concerns About Telemedicine and Headache

Telemedicine has a lot of benefits that consist of improved access to specialist care and avoidance of travel and decreased costs. Despite its many benefits, telemedicine might have weaknesses in patients with red flags and may be unsuitable for first visits and unsuitable for patients who do not want to share personal data (Fig. 20.1).

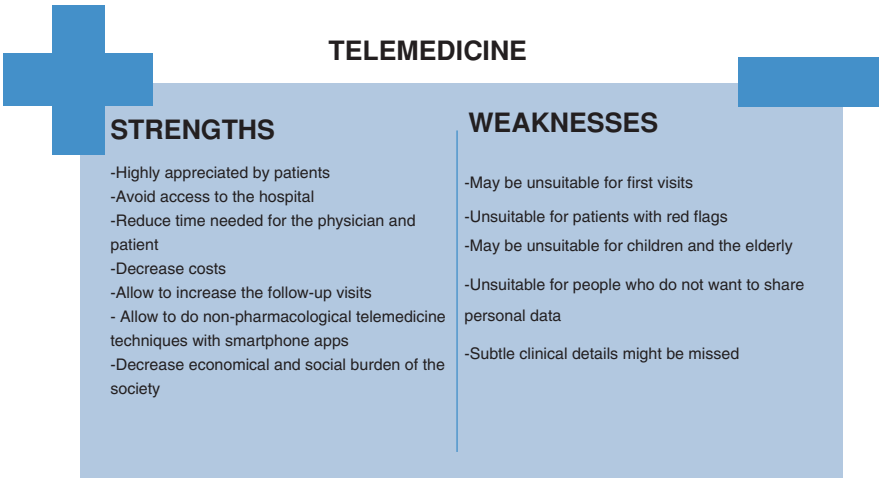


**Fig. 20.1** The strengths and weaknesses of telemedicine

Second opinion and follow-up visit evaluations are easy to do with telemedicine, either phone calls or video calls or meetings. However, the first evaluation is the problematic one with telemedicine. Neurologic examination requires physical contact in some aspects. To decide the strength of every muscle, checking for neck stiffness; to evaluate deep tendon reflexes, looking for Babinski and other reflexes; and to do fundoscopy, examining vestibular system and checking for trigger points need face-to-face evaluation and physical visits. Even though some of these examinations are neglectable, fundus oculi examination, vestibular system evaluation, pathological reflex evaluation, and trigger point examinations must be evaluated for a headache patient. The good part is primary headache diagnosis mostly depends on a good history taking. In many headache sufferers headache can be easily differentiated by a headache expert—whether it is primary or secondary. More than 90% of headache patients' headache, admitting to an outpatient clinic, is primary. Those showing red flags need to be examined face-to-face and requires neuroimaging [9]. Physicians can feel more relaxed about patients without any red flag. Müller et al. reported that 20,000 telemedicine consultations were needed to miss one secondary headache, which implicates that telemedicine is a safe method.

As the pandemic evolved a number of solutions have been developed for remote neurological examination. Al Hussona et al. proposed a virtual neurologic exam in a well-lit room, in front of a web camera with a third party (a family member) [10]. They defined remote neurologic exam in detail. The neurological exam described by them seems sufficient for a headache patient without a red flag. In the case of the presence of a red flag, patients may be scheduled for a routine, traditional exam or can be directly referred for neuroimaging. Another major problem is fundoscopy. Developing technology investing in smart phone applications and tools was reported by Evans et al. [11]. There are very good reasons to be optimistic about remote fundoscopy in the near future. Taken all together, first visit by telemedicine seems

to be practical and safe. In the near future remote virtual neurologic exam will improve and would help us to deliver healthcare to those residing in remote parts of the countries and those who cannot reach the health centers.

Follow-up visits seem much easier compared to the first evaluation. A headache expert needs to know headache frequency, duration, severity, associated features, acute medication intake, emergency department visits, and preventive and acute treatment side effects for monitoring the patient. These data are sufficient to evaluate the treatment response and side effects. During the last decade e-diaries and smart phone applications have been developed for keeping headache records. E-diaries have already been used in many headache studies, proving their reliability and safety and even using algorithms to differentiate migraine and other headaches [12–15]. Therefore, for telemedicine purposes, e-diaries not only give the frequency, duration, and the characteristics of headache attacks and the other aforementioned headache features, but the headache type as well, without any review of a headache expert. It is already shown that remote monitoring with e-diaries might be superior to traditional monitoring [16]. Using e-diaries and telemedicine can substantially reduce the time needed for a physician or any healthcare giver to do the follow-up visits of a headache sufferer, decreasing the headache outpatient clinics' burden along with the economic and social burden of the individual and the society. However, there are still some limitations of remote monitoring. First of all smart phones or computers equipped with web cams with a good Internet connection are the absolute musts of remote monitoring. It is still difficult for some remote parts of countries to get high-quality Internet connection. In poor countries smart phones or computers are way too far to buy. Elderly and those adults unfamiliar to technology or those who do not want to share personal data for safety reasons might hinder the use of remote monitoring. However, as the technology improves, all those concerns might not be a problem anymore. Telemedicine is also accepted as a feasible method in pediatric headache [17].

## 20.5 Cost-Effectiveness of Telemedicine

Telemedicine is also a cost-effective method. The time- and money-consuming nature of traditional visits increase the costs of healthcare both for the patient and healthcare payers. Patients trying to reach headache specialists spend time and money as the distance to go grow larger. In Norway, 300 euros and 8 h of travel time had been saved by telemedicine. We can add the time saved by healthcare providers to that as well [8]. In some poor countries or countries with geographical difficulties telemedicine can be life saver. Adcock et al. reported that telemedicine is an acceptable and feasible method of delivering educational neurology topics relevant to rural communities [18]. They did this study in rural regions of Guatemala and headache and seizures were the most common problems. Telemedicine may help to reach the headache patients who do not have the chance to see a headache specialist.

## 20.6 Non-pharmacological Telemedicine Techniques

It is known that relaxation techniques such as yoga, breathing exercises, neurofeedback programs, and behavioral therapies reduce the frequency and severity of migraine attacks. During the previous years some smart phone apps, delivering, teaching, and showing these techniques, have been invented. These non-pharmacological telemedicine techniques, along with traditional treatment, might increase the success of headache management. Still large-scale studies are needed, and some studies showed the benefits of smart phone apps similar to the in-patient techniques [19, 20]. However, most of these apps are commercial and lack scientific efficacy, reliability, and safety studies. Scientific studies in large scales needed to accept these apps as a reliable tool and position them in headache guidelines.

## 20.7 Conclusion

Humanity suffered a lot during COVID-19 in many ways. It reminded us of the forgotten realities of life: disasters and contagious diseases throughout the world. As all other crisis during history it has also brought some opportunities and new ways of approaches. Telemedicine is the new future of health in many ways. It might provide many benefits to the poor, rural residents, and disabled people, sparing them time, money, and energy in going to the health system. Headache is one of the leading disorders causing burden to the individual, society, and health system. As its nature is compliant with telemedicine, it has a great capacity to adopt telemedicine. However, large-scale studies are needed for the implementation of telemedicine into daily headache practice.

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# Chapter 21
# New Trends in Headache Education and Telehealth During the COVID-19 Pandemic

**Elif Kocasoy Orhan and H. Macit Selekler**

This section will focus on two issues related to each other. First, telemedicine's situation in evaluating neurological patients, especially headache patients, will be mentioned, and second, information about the essentials of training health workers during the epidemic is provided. How can we solve that with telemedicine?

## 21.1 Telehealth During the COVID-19 Pandemic

The COVID-19 pandemic, which started at the end of 2019, had a significant impact on the world in a short time. As in every field, it disrupted the health system and educational activities at all levels. Patients' access to hospitals was restricted. There were uncertainties regarding the follow-up and treatment of chronic diseases.

It was reported that services for patients with neurological disorders were spoiled by 75%. Travel restrictions due to lockdowns (81.7%) and service closures (65.4%) were the leading causes of failure [1].

For healthcare delivery, circumstances have raised possibilities other than "face-to-face evaluation." The World Health Organization demanded peculiar communication technologies such as telehealth or mobile phone application [2]. Better data and evidence on the use of standard and innovative forms can be put forward to decrease the effects of the pandemic on service interruptions.

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Telemedicine, called telehealth, refers to the two-way transmission of the voice and image of the patient and the doctor in real time using "telecommunication systems" in the same environment and not face-to-face. Telemedicine was introduced in the 1970s to improve information and communication technologies and facilitate patient care and access to medical information, so it is not a new practice for physicians [3, 4].

However, some uncertainties about actual effectiveness and reliability compared to face-to-face visits have not become widespread due to licensing restrictions on technological and organizational issues [5, 6].

Despite technological advances, its use remained limited in the pre-pandemic period. In a study (survey conducted by the Global Observatory-2009), its use was found to be approximately 33% in 114 countries [7]. While it is a promising application to increase productivity for those with ease of service and access, technological literacy was necessary for this method to become widespread. Overall, educational shortcomings and technical barriers have hampered the general use of telemedicine [8].

Regarding neurological diseases, telemedicine applications have started to be used primarily in evaluating stroke patients. It has been shown that the "tele-stroke" application gives a chance for early intervention in stroke patients [9, 10].

Apart from stroke, it has been shown that telemedicine methods can be helpful in the evaluation of chronic diseases such as Parkinson's and multiple sclerosis [11]. Similarly, numerous studies have been conducted on telemedicine applications in the follow-up of headache and migraine patients [12–14].

With the emergence of the COVID-19 pandemic, the place of telemedicine in health services and education has expanded rapidly. That caused as an essential alternative in these areas. However, over the past decade, clinical trials have shown that patients realize telemedicine is cost-effective and valuable (especially when using tablet computers as an alternative to traditional telehealth technologies). Satisfaction rates have demonstrated comparable results to conventional face-to-face visits [13].

Regarding headache patients, research from the American Headache Association identified the need for remote consultation with a higher frequency than other neurological patients, raising the need for a correct approach to virtual management [15].

Telemedicine is as effective as face-to-face interviews in evaluating headache patients living in rural areas. It has been shown to provide savings when assessing travel costs [16].

A comparable situation applies to the routine evaluation of the child patient group with headaches. It was reported that there is an elevated level of the physician, patient, and family satisfaction and savings with remote counseling during the pandemic period. On average, 85–90% of patients reported to continue remote counseling after the pandemic [17, 18].

Telemedicine facilitates patients' access in different locations and conditions to evaluations in various specialties. This technology seems suitable especially for the follow-up of primary type headaches such as migraine that do not require physical

examination after the first examination. Thus, the physician can determine the patient's headache, medications, response to treatment, follow-up, and treatment planning. The patient and physician can also use their time better. In the pre-pandemic period, Friedman et al. showed that office visits took longer than telemedicine evaluations in their study [19]. The same study revealed that despite this shorter telemedicine visit, patients were satisfied with these visits. Similarly, it was reported that the improvement in migraine-related disability did not differ between patients evaluated by telemedicine visits and patients hospitalized for severe migraine attacks. Although patients may have concerns about their data, not being in a hospital environment and being unable to be examined, and "technological concerns" about sound, camera use, and security, telemedicine seems to be a viable method for evaluating patients with headaches. Although there is a need for multi-center studies that evaluate patients with different types of headaches to evaluate safety and efficacy better, it has played an essential role in the follow-up of non-emergency patients, especially during the pandemic period. From the physician's perspective, telemedicine visits can increase productivity by contributing to good time management.

One of the critical points to be emphasized is that patients who will be evaluated for the first time and whose treatment will be changed are more suitable for face-to-face visits. In addition, face-to-face evaluations should be preferred in patients with limited or inadequate access to technology. In today's conditions, telemedicine can be used effectively in the follow-up of patients with headaches whose diagnosis is determined, and treatment is planned. In light of this information, it should be considered that evaluating patients with headaches with hybrid methods, considering the patient's characteristics, may be a correct approach [12, 13, 19].

## 21.2 Tele-education of Health Professionals During the COVID-19 Pandemic

This section will review telemedicine's effect on training health workers throughout the pandemic. We had chosen the most appropriate methods for patients' diagnosis and treatment. When the headache patient shows up with accompanying symptoms, the physician interested in the case must have adequate education and experience to evaluate the circumstance. Accordingly, education on headaches must have an important place both in medical schools in the training process and in specialty training.

Studies on migraine education were conducted with pre-pandemic primary care physicians (PCP) and family physicians. Options such as being a web-based source that could be accessed during patient evaluation make participants feel safer. Having algorithms showing diagnosis and treatment options, having a helpline where they can reach the relevant specialist, and conducting training sessions that can be accessed later have come to the fore [20].

It is understood that the content and information developed by a professional association such as the International Headache Society about headache classification and treatments are essential in terms of standardization [21].

Especially headaches could be a good candidate for telemedicine after the first visit (physical, systemic, and neurologic examinations have been done). Therefore, twenty-first-century neurologists need to use telemedicine effectively in their clinical careers. In the future, this affair is a candidate to become part of practical applications. Our experience with telemedicine-teleneurology in outpatient clinics for evaluating neurological patients before the pandemic has been insufficient. Knowing this hiatus, the American Academy of Neurology, Telemedicine Working Group, planned to introduce the first modeling for a teleneurology curriculum in 2017 for neurology residents [22].

A pilot study among the neurology residents in the pre-pandemic period showed that residents received a limited telemedicine education. In the pandemic period, their knowledge of essential telemedicine topics both theoretically and practically increased [23].

It is emphasized that the most criticized issue of neurology residents regarding telemedicine is the inability to perform an adequate and accurate neurological examination. In addition, the neurologists participating in this study drew attention to the need for caregiver support in inpatient evaluation [23].

While the efforts of neurologists on telemedicine before the pandemic were progressing slowly, with the COVID-19 pandemic, mandatory changes in patient profiles, working conditions, and training curricula have emerged. Our students and colleagues faced some difficulties with their education in this process. Similar to the profound impact of the pandemic on patients, it has been demonstrated that residents in surgical and clinical branches do not receive adequate training and need to extend their training periods [24]. In addition, the COVID-19 pandemic has been shown to have adverse psychological effects on health professionals and deficiencies and difficulties in practical application [25–28].

The decrease in outpatient clinic patients due to the pandemic, the necessity of working residents and specialists in COVID wards, and intensive care have affected the quality of education in both surgical and internal sciences and led to a decrease in experience [24].

The effects of the pandemic being felt worldwide have necessitated changes in medical education. Virtual courses adapted within classical medical education have been shown to provide some advantages. It has been reported that the virtual neurology elective course, which offers inter-institutional sharing opportunities that students and educators can attend from various cities all over the world, has developed an increase in knowledge, skills, and confidence for students at all levels. In addition, allowing faculty members to move their clinical expertise to the virtual platform enabled them to experience virtual teaching models [29].

The coronavirus pandemic has changed the medical faculty's curriculum and educational styles. Still, it seems to be a technological necessity that these changes continue to be developed in the future.

In the future, it seems necessary to create algorithms prepared by experts to use Internet-based tools and video consultancy by health professionals in training and patient follow-up.

Artificial intelligence modeling can also be done with telemedicine information obtained by considering headache diaries, treatments, and recommendations. Previous studies have shown that the treatment algorithm prepared for primary headaches has similar results to a general practitioner's evaluation of the same patient [16, 30]. Studies indicate that telemedicine-telehealth applications will be a part of our education and daily practice in the post-pandemic period [31].

Different scenarios can be written about how telemedicine methods will take shape in the future. Still, it seems ideal to handle the diagnosis and treatment algorithms created by health authorities that can replace personal counseling or social media sharing, especially in headaches. So far, the data suggest that patients and physicians will accept this situation. It should be kept in mind that some negativities and disadvantageous situations may arise. Although the history of telemedicine dates back 50 years, the pandemic has accelerated its spread.

We follow these developments in our country as well. Headache cases were presented by experienced headache specialists and discussed by viewers who are largely composed of neurology residents and neurology consultants. Various staff physicians related to painful conditions, primary care physicians, and interns had got the opportunity to come with us easily.

The meetings mentioned above were organized every week. Two groups of moderators from headache and algology branches run the sessions. In these online interactive meetings, we review current issues related to headache and pain. Our goal is to actively use telemedicine methods in headache education and to reduce the possible negative effects of the pandemic period on education.

We benefited from telemedicine for headache and pain education. Global Migraine and Pain Summit organized regular meetings available for Turkey and Azerbaijan. The program also drew the attention of Turkish physicians practicing in Europe and Turkic countries such as Kazakhstan. The technical team recorded all sessions and loaded them on the website. After two seasons of the program (2000–2021 and 2021–2022), the growing interest in the sessions made us think of subtitling the recordings in different languages. We would also like to reach the Middle East and Asia.

The program begins with the presentation of the headache cases of the day and continues with a discussion of diagnosis and treatment options. The session includes two speakers and two moderators. Participating physicians are primarily neurology residents and consultants. Staff physicians related to pain (from fields such as orthopedics and physical medicine and rehabilitation), primary care physicians, and medical students also joined the sessions.

The most critical concern was the 1-h time limit. Sometimes it was difficult to interrupt ongoing discussions to stay within the time limit. The time issue was also the problem that forced moderators to skip some critical questions coming from the audience. However, in the long run, moderators acquired the experience to tackle the issue professionally.

Humankind's struggle with COVID-19 popularized telemedicine, which is likely to become a revolutionary phenomenon.

When neurological diseases are considered, it has been shown that face-to-face evaluation and examination can be successfully applied, especially in the follow-up of primary headache patients, except for clinical pictures and emergencies where it is indispensable. Within education systems, education with telemedicine is becoming more attractive and necessary for students, residents, and specialists.

As a result, telemedicine in headaches is a part of the hybrid system for patients and physicians. In the future, we will see how the hybrid system we are talking about today will be shaped and developed using correctly selected methods for the correct set of patients. In addition, telemedicine programs and the courses related to their use will also find their place in the systems that regulate medical education-resident training and will probably be integrated. What is fundamental is that telemedicine practices should be based on solid and evidence-based scientific foundations and be used safely.

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# Chapter 22
# Interventional Management Strategies of Pain for the Pandemic Era

**Halil Cetingok and N. Suleyman Ozyalcin**

## 22.1 COVID-19 and Healthcare in the Pandemic Era

One of the greatest disasters that mankind has experienced recently has been the COVID-19 pandemic. According to the weekly epidemiological update on the COVID-19 report of the World Health Organization dated June 1, over 526 million confirmed cases and over 6 million deaths have been reported globally [1]. The global coronavirus disease 2019 has significantly affected both social life and healthcare all over the world.

All elective, surgical, and interventional procedures and face-to-face patient-doctor interviews were canceled or postponed at the beginning of the pandemic to avoid the risk of COVID-19 and to limit the spread of the disease. Despite the unfavorable effects of the pandemic, physicians should continue to provide medical services safely. Therefore, to meet the current need, telemedicine has become of fundamental importance. Telemedicine is a term that describes providing remote medical support to patients through digital communication technologies such as phone conversation, video conferencing, e-mail, and text messages [2]. It has provided important benefits such as mitigating the risk of disease spread and reducing the need for personal protective equipment. Telemedicine has also been very useful in triaging patients and deciding the need for face-to-face interviews, informing and consenting before interventional procedures, and post-interventional follow-up [2].

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With the rapid spread of the pandemic, it has become a common approach to symptom screening of both patients and healthcare professionals before the scheduled visits and diagnostic testing of all COVID-19 contacts and symptomatic or high-risk individuals and for everyone else to be evaluated as COVID positive.

## 22.2 Chronic Pain and Pain Medicine in the Pandemic Era

Approximately 45–75% of the patients who apply to the emergency department present with complaints of pain, and nearly half of them have moderate-to-severe pain [3]. Chronic pain is one of the most common causes of disability. It causes significant physical and emotional suffering, reduces the quality of life, and limits daily activities [4]. Chronic pain is the most common coexisting condition for cancer, diabetes, coronary artery disease, and chronic obstructive pulmonary disease [5].

In chronic pain patients, whose interventional pain treatments are postponed or canceled, the most frequently used alternative treatment approach was the more intensive use of opioids. But this is not an optimal strategy, because there are numerous opioid-associated side effects and especially the potential risk of opioid dependence and opioid use disorder [6].

Chronic pain has a depressing effect on immunity and may cause immunosuppression in some patients [5]. On the other hand, opioids which are the most commonly used drugs in chronic pain may have similar immunosuppressive effects on immunity and increase the risk for infections. The activation of opioid receptors causes a decrease in the number of macrophages and phagocytic activity [6]. Although there are different studies on the effects of opioid types on the immune system, fentanyl and morphine cause more immunosuppression than others, and buprenorphine seems to be the safest alternative [7]. Apart from these generalizations, there is no evidence that opioid use exacerbates disease severity in COVID-19 patients. As a result, it does not seem possible to make clear recommendations on the use of opioids in the treatment of chronic pain during the pandemic [2].

There may be some drug interactions between opioids and some drugs used in the treatment of COVID-19. CYP3A4 and CYP2D6 enzymes play an important role in the bioelimination of opioids. Ritonavir inhibits CYP3A4; so it increases the opioid plasma levels and consequently increases the risk of opioid-induced respiratory depression and overdose [2, 8]. Lopinavir may cause the induction of CYP-450 enzymes and cause a decrease in opioid plasma levels [9]. Tapentadol, morphine, and buprenorphine are independent of CYP450 enzyme activity and create safe alternatives in concomitant antiviral use for COVID-19 [10].

At the beginning of the pandemic, some health professionals from the French Ministry of Health stated that due to the effects of ibuprofen and the other nonsteroidal anti-inflammatory drugs (NSAIDs) increasing angiotensin-converting enzyme (ACE) levels, the COVID-19 disease may progress more severely [11].

Therefore, it is recommended not to use ibuprofen and other NSAIDs. However, no scientific data was found to support this idea, and it continued to be used for the treatment of pain in patients with NSAID indications [5].

## 22.3 Interventional Pain Management (IPM) in the Pandemic Era

Even if the medical pain treatment options, especially NSAIDs and opioids, are fully used despite the doubts about them, adequate pain palliation may not be provided sometimes. In such cases, it is necessary to use other options in addition to pharmacotherapy. Under normal conditions, the first treatment alternatives that come to mind are physical therapy, manual therapy, chiropractic adjustments, acupuncture, etc. But such treatments were also restricted within the scope of general infection protection measures, especially in the early stages of the pandemic. Even if these treatments are fully achieved, most chronic pain syndromes do not respond adequately.

As a result, IPM procedures constitute one of the invaluable and powerful treatment alternatives for these patients who were evaluated with telemedicine and whose cause of the pain was determined with the help of radiology. The effective and appropriate use of IPM procedures provides benefits in enabling patients to avoid negative effects of chronic pain such as functional loss and psychosomatic exposure and in reducing the negative effects of opioids during the pandemic (immune suppression, addiction, and abuse) or in avoiding situations that increase the risk of COVID, such as the need for face-to-face treatment in the hospital setting, such as physical therapy [4].

At the beginning of April 2020, all non-urgent interventional and surgical procedures were postponed or canceled due to the rapid increase in COVID-19 cases worldwide. The main purposes of this were to limit the contact and spread of COVID-19, to use insufficient personal protective equipment effectively, and to gain time to predict the unknown future of the pandemic. Since IPM services are seen as elective, most of them were closed during this period.

The European Society of Regional Anaesthesia and Pain Therapy (ESRA) and the American Society of Regional Anesthesia and Pain Medicine (ASRA) recommended classifying patients as elective, semi-urgent, or urgent while triaging the patients for the timing of interventional pain treatment procedures [12]. We look at the explanation and examples of this classification [2, 6]:

1. Elective: the patient could wait >4 weeks. There is no concern that the delay may damage the patient. It should be postponed. Examples include any pain condition that is stable and can be managed with alternatives.
2. Semi-urgent: the patient could not wait for >2–4 weeks. There is a worry that the delay may damage the patient. It should be decided on a case-by-case basis.

Examples include cancer pain, cluster headache, trigeminal neuralgia, acute herpes zoster or intractable postherpetic neuralgia, acute herniated disc or worsening lumbar radiculopathy, and early phase of the complex regional pain syndrome (CRPS). Intervention examples include neurolytic procedures for refractory cancer pain, epidural steroid injections for acute disc herniation, replacement of neuromodulation systems, and sympathetic blocks for early CRPS.

3. Urgent: the patient could not wait. There is a significant apprehension that the delay may damage the patient. It should proceed with caution. Examples include infection or migration of spinal cord stimulation (SCS) that leads to neurological deficits and intrathecal pump (ITP) malfunction. Intervention examples include epidural catheter for rib fractures, vertebral augmentation, and removal of infected ITP or SCS.

Elective interventional pain treatments were resumed after the global lockdown was relieved. When an indication for interventional pain treatment is given to a patient, the first thing to do is to determine the COVID-19 risk status of the patient. In terms of possible COVID-19 infection, interventional procedure risk classification according to the American Society of Interventional Pain Physicians (ASIPP) is as follows [4, 6, 13]:

- Low: Age 45–64 years, body mass index 24.9–29.9, hemoglobin A1c 5.7–6.49, or blood glucose 100–120 mg/dL; no pulmonary-cardiovascular-renal-hepatic disease; not immunosuppressed
- Moderate: Age 65–74 years, body mass index 30.0–39.9, hemoglobin A1c 6.5–8.49, or blood glucose 120 to 160 mg/dL; mild to moderate pulmonary-cardiovascular-renal-hepatic disease; mild immunosuppressed
- High: Age > 75 years, body mass index ≥40, hemoglobin A1c ≥8.5, or blood glucose >160 mg/dL; severe pulmonary-cardiovascular-renal-hepatic disease; moderate-severe immunosuppressed (active cancer treatment, organ transplantation, AIDS, etc.)

When scheduling procedures, the first thing to do should be to assess patients in terms of COVID-19 risk. This evaluation should be done using telemedicine without meeting with the patient. The patient should be questioned in terms of whether they are positive for COVID-19, whether there are positive cases around them, whether they have COVID-19 symptoms, and their past infection and vaccination status. In addition, patients should be reminded that they should measure their body temperature at home and inform the IPM team when there is a risky situation for COVID (such as fever and other infectious symptoms, COVID-positive patient contact) [3, 14]. If pain interventions with a high risk of aerosolization and requiring intubation are planned, patients should be provided with a COVID-19 test 48 h before the procedure [3, 14]. All patients should be reviewed for the last time for COVID-19 symptoms (fever, chills, sweats, cough, shortness of breath, difficulty breathing, sore throat, or new loss of taste or smell) on the day of the procedure [3, 4, 14].

### *22.3.1 Procedural Precautions and Personal Protective Equipment (PPE) Requirements*

Interventional pain management procedures can be classified in three different ways: short or prolonged, percutaneous or surgical procedures, and aerosol-generating or non-aerosol-generating procedures [2].

Most of the pain procedures (short and percutaneous) do not generate aerosol and hence standard PPE (a surgical cap, surgical mask, and gloves) is generally considered sufficient [3, 5]. Epidural injections, facet joint interventions, and major joint injections can be given as examples.

Prolonged percutaneous neuraxial procedures such as spinal cord stimulation trials or kyphoplasty require a gown in addition to the standard PPE [3, 5]. These procedures also do not require intubation and do not generate aerosols. But an N95 respirator mask can be used instead of a surgical mask.

Surgical procedures may require intubation and so lead to aerosol generation. Goggles, eye-face shield, and an N95 mask should be used in addition to standard PPE [3, 5]. If general anesthesia is required, intubation should be carried out using rapid-sequence induction and minimal use of bag-mask ventilation [3].

In general, all patients must wear a surgical mask for the duration of the intervention. Only the patient and the limited number of pain team personnel should be allowed into the operation room. COVID-19 can survive on surfaces such as steel, glass, and plastic [15]. So the ultrasound machine and transducers should be protected from contamination using a cover. Because the ultrasound gel is easily contaminated, single-use gel packets should be used [15].

### *22.3.2 Interventional Pain Management Procedures During the COVID-19 Pandemic*

It is an important issue whether the drugs and methods used in interventional pain management procedures may be used safely during the COVID-19 pandemic period (Fig. 22.1).

#### 22.3.2.1 Steroid Injections and COVID-19

Corticosteroids are the commonly used agents in the interventional pain procedures such as epidural interventions, peripheral nerve blocks, and joint injections. Steroids have many mechanisms of action such as nerve membrane stabilization, inhibition of neural protein synthesis, blockade of phospholipase A2 enzyme, suppression of neuronal pain transmission, and suppression of sensitized dorsal horn neurons [16].


**Fig. 22.1** Practical points about interventional pain managements in the COVID-19 pandemic

Corticosteroids have anti-inflammatory and immunosuppressive effects. They impair the immune functions of the inflammatory cells (neutrophils, lymphocytes, macrophages, mast cells) and mediators [17]. Meta-analysis of orally administered corticosteroid versus placebo demonstrates an increased risk of an influenza infection within the steroid group [18].

There are suspicions that epidural steroid injections may have immunosuppressive effects and reduce the effectiveness of COVID-19 vaccines. Considering the available literature, the following results will be instructive in this regard.

As yet, there is no evidence in the literature regarding whether an injection of corticosteroids increases the risk of severe COVID-19 infection. Even if epidural or intra-articular steroids may be absorbed systemically, they are unlikely to cause

similar immunosuppressive effects associated with high-dose systemic steroid use [19]. However, considering that corticosteroids may have immunosuppressant effects, it may be a suitable way not to apply unless necessary. For example, in patients who are already at risk of immunosuppression, other alternatives may be considered instead of using steroids, or the procedure may be delayed.

A systematic review that evaluated the clinical benefits of steroids used in chronic noncancer pain management showed local anesthetics alone appear to reduce pain without the use of steroids [20]. It is important to note that for many injections, such as trigger point injections, there are no benefits to adding steroids to local anesthetics [21, 22].

Corticosteroid-related immunosuppression appears to be dose-dependent and lower doses may diminish the risk of immunosuppression [23]. The use of a short-acting steroid with the lowest effective dose is more reasonable during COVID-19 time. Dexamethasone and betamethasone have been shown to have a shorter duration of systemic effect and may be favored over other steroids for injections [19, 23].

Although it is known that long-term high-dose steroid use adversely affects the vaccine-based immunity, there is no evidence that epidural single-dose steroid injection will impact vaccine responsiveness [19]. In addition, there is no evidence that epidural steroid injections increase the risk of adverse events from COVID-19 vaccination. However, given the deadly risks posed by the COVID-19 pandemic, interventional pain physicians should not use the steroid less than 2 weeks before and less than 1 week after a COVID-19 mRNA vaccine dose for elective pain treatment interventions [24].

#### 22.3.2.2 Local Anesthetics and COVID-19

Local anesthetics (LA) are indispensable agents of pain management interventions. They block voltage-gated sodium channels in the nerve sheath and thus prevent the production of action potentials or block the neurotransmission of the generated stimulus. Local anesthetics decrease the polymorphonuclear leukocytes' adherence, migration, and accumulation at the site of inflammation [25]. Because of these effects, local anesthetic agents suppress the excessive inflammatory response without significantly impairing the patient's immune system. Theoretically, local anesthetics at high systemic concentrations might risk infection, so it is best to use the lowest effective volume and lowest effective concentration of local anesthetics for pain injections.

#### 22.3.2.3 Regenerative Medicine and COVID-19

Regenerative medicine is one of the approaches that has become popular in recent years and is widely used in the treatment of chronic pain conditions. Mesenchymal stem cells (MSC) and platelet-rich plasma (PRP) are effective in treating especially tendon, cartilage, bone, joint, and muscle damage [26]. Obtaining the aspirate to be

injected from allogeneic tissues taken from the patient, such as blood or adipose tissue, minimizes the risk of side effects and systemic complications.

Regenerative medicine methods are mainly compared with steroid-based injections in the literature, and some studies have reported that they provide superior and long-acting results than steroids. On the other hand, especially the immune-regulatory effects of MSC have been tried in the treatment of COVID-19-related immune dysregulation and evidence has been obtained that it is beneficial [27]. Considering the immunosuppressive effects of steroids and local anesthetics, which are two important actors of pain treatment interventions, the use of regenerative medicine methods such as MSC or PRP, which may even have positive benefits over COVID-19, has expanded during the pandemic.

Dextrose does not have a deleterious effect on the immune system. It is a safe drug with no effect on the patient's systemic physiology. Dextrose alone or combined with LAs is a good option during the COVID-19 pandemic.

Regenerative medicine is a safe and effective therapy and may be a good alternative for steroids, local anesthetics, and opioids.

#### 22.3.2.4 Ozone Injections and COVID-19

Ozone (O3) is a molecule consisting of three oxygen atoms [28]. It has been described as the anti-inflammatory, analgesic, anti-edema, and muscle relaxant effects of injected medical ozone [29]. Because of these effects, medical ozone injections have been used for treating various musculoskeletal and spinal diseases such as arthritis, tendonitis, myositis, fasciitis, neuritis, or herniated disc [29].

Ozone is a powerful oxidant. When ozone gas is delivered to human tissues, it releases reactive oxygen species and lipid oxidation products [30]. As a result of the activation of different biochemical pathways, it causes immune-stimulating, antimicrobial, and antioxidant effects. Ozone seems to have antiviral activity by inhibiting viral replication and exerts its lethal effect [31]. Thanks to these antiviral effects, ozone therapy has been shown to be effective in the COVID-19 treatment.

Due to its positive benefits in the treatment of COVID-19, the use of medical ozone therapy in interventional pain procedures seems safe. Contrary to the immunosuppressive effects of steroids, the presence of immune stimulants and antiviral effects makes medical ozone injections more prominent via pandemic.

#### 22.3.2.5 Radiofrequency and COVID-19

Radiofrequency (RF) technology generates radio waves by electric current to inhibit pain transmission. Conventional RF uses a continuous voltage that increases tissue temperature above 50 °C and damages the neural structures that function in the pain pathway [32]. Since the thermal lesion formed here can also affect the motor nerves,

it is not available in some regions. Since the effect obtained with conventional radiofrequency therapy is local thermal damage, no significant systemic effect is expected. Therefore, there is no evidence that radiofrequency ablation may pose a risk during the COVID-19 pandemic [33].

Pulsed radiofrequency (PRF) uses a discontinuous voltage that not to increase tissue temperature (stays under 42 °C) and provides analgesic effect without damaging the neuronal structures. Therefore, it is possible to use it in almost every region. The efficacy of PRF may be secondary to magnetic field exposure as opposed to thermal coagulation. It also provides analgesia without the need for medication. After using pulsed radiofrequency, inflammatory mediators increase such as TNFα, IL- 1β, and superoxide dismutase and then it goes back to their basal levels [33]. As a result, pulse radiofrequency therapy is a safe method in interventional pain treatment during the pandemic.

#### 22.3.2.6 Intrathecal Drug Delivery System (IDDS) and COVID-19

IDDS is one of the most efficacious solutions that come to mind, especially in patients with severe cancer pain resistant to conservative treatments. It can also be applied in cases such as complex regional pain syndrome, axial low back pain, and postherpetic neuralgia among noncancer pain syndromes [34].

Intubation and extubation are considered high risk in pandemic conditions, because they cause aerosol propagation. Thus, general anesthesia should be avoided when possible during IDDS implantation. Infection is a major complication of IDDS and can either occur at the site of the pump or meningitis. However, there is no evidence that IDDS poses an additional risk of infection in terms of COVID-19.

Intrathecal opioids administered by IDDS for a long time suggest the immunosuppressive effects of opioids. However, considering that the intrathecal dose is much less than the oral opioid dose that should be taken for a similar effect, it seems to be safe.

#### 22.3.2.7 Neurostimulation and COVID-19

Spinal cord stimulation (SCS) is a safe and minimally invasive intervention. Long-term use of high-dose opioids or corticosteroid injections can cause depressing effects on the immunity, but on the contrary, SCS is not associated with immunological dysfunction [35]. There is no evidence in the literature that neuromodulation procedures cause immune suppression or increase the risk of systemic infection. From this point of view, SCS seems like a safe procedure under pandemic conditions. Besides, local infections may develop at a rate of 3–7%, since it is a minimally invasive surgical procedure [36]. SCS can be applied in pandemic conditions with meticulous evaluation and correct indication.

### 22.3.3 How Was Interventional Pain Practice Affected in the Pandemic Era?

COVID-19 has made an intense impact on the interventional pain management (IPM) community and has put interventional pain practices under considerable financial loss [37]. Global lockdown and restrictions for the pandemic have disrupted interventional pain management practices and decreased the number of pain procedures [38].

A survey conducted by the American Society of Interventional Pain Physicians (ASIPP) revealed the early phase of devastating effects of COVID-19 on interventional pain management (IPM) in April 2020 [39]. According to the results of the research, 98% of the practicing physicians were affected, 91% were affected financially, and 88% of the physicians had performed significantly less interventional procedures.

The other early survey about the impact of the COVID-19 pandemic on interventional pain practice was applied to Spine Intervention Society members by Lisa et al. in June 2020 [40]. The data obtained in this study are summarized in Fig. 22.2.

The last and most extensive survey was performed approximately 15 months after the onset of the COVID-19 pandemic by Manchikanti et al. [37]. This survey confirmed the significant impact of COVID-19 on interventional pain management practices with detrimental effects. According to this survey, respondents reported reduction in income of 88%, a decrease in revenue of 98.8%, and a decline in procedures of 69% [37].

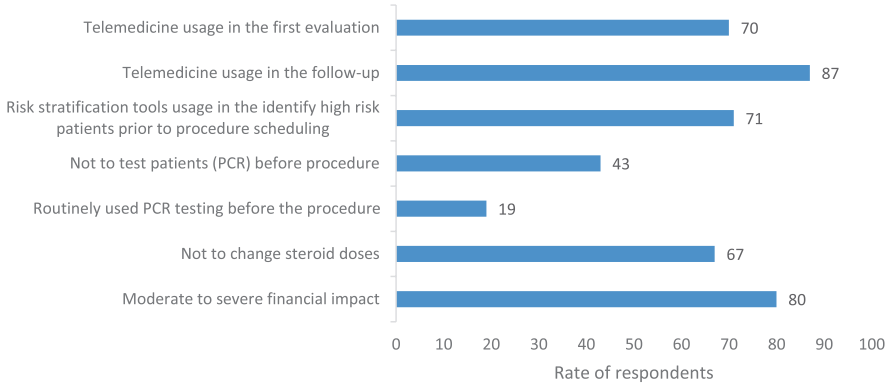


**Fig. 22.2** Early survey about the impact of COVID-19 pandemic on interventional pain practice by Lisa et al. [40]

## 22.4 Conclusion

Although the whole society is affected by the COVID-19 pandemic, the most profound effects were seen in the health system. Telemedicine, infection control methods, personal protective equipment, surgical and N95 masks, PCR tests, mRNA-based vaccines came into our lives. Chronic pain syndromes, which are the leading causes of disability, and interventional pain treatment practice were deeply affected in this period. Especially at the beginning of the pandemic, global lockdown and restrictions have disrupted interventional pain management practices.

We have had basic approaches during the pandemic period: use general infection prevention measures and personal protective equipment widely; triage patients to classify as elective, semi-urgent, or urgent before the interventional procedure; evaluate the risk of COVID-19 at every stage and apply PCR test when necessary; and not to prefer drugs and methods that adversely affect the immune system or if it is necessary to use them utilize as low a dose as possible in the interventions.

The effects of the pandemic have not yet completely disappeared. A new wave of COVID-19 or pandemics due to another infectious agent may occur at any time. As healthcare systems and healthcare professionals, we have learned a lot from the COVID-19 pandemic. We should use what we have learned and be prepared for new disasters.

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