COVID-19, Eye Pain, Headache, and Beyond

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ABSTRACT

Background:

SARS-CoV-2, which causes COVID-19, emerged in December 2019 and became a devastating pandemic. While its respiratory effects can be deadly and debilitating, it can lead to other systemic disorders, such as those causing eye pain and headache. This literature review aims to describe presentations of eye pain and headache in relation to COVID-19, with an emphasis on how these disorders help us to understand the pathophysiology of COVID-19.

Evidence acquisition:

Literature was mined from the PubMed database using the key terms: “eye pain”, “conjunctivitis”, “episcleritis”, “optic neuritis”, “migraine”, and “headache” in conjunction with “COVID-19” and “SARS-CoV-2”. With the exception of general background pathology, articles that pre-dated 2006 were excluded. Case reports, literature reviews, and meta-analysis were all included. Where SARS-CoV-2 research was deficient, pathology of other known viruses was considered. Reports of ocular manifestations of vision loss in the absence of eye pain were excluded. The primary search was conducted in June 2021.

Results:

The literature search led to a focused review of COVID-19 associated with conjunctivitis, episcleritis, scleritis, optic neuritis, and myelin oligodendrocyte glycoprotein-associated optic neuritis. Four distinct COVID-19-related headache phenotypes were identified and discussed.

Conclusions:

Eye pain in the setting of COVID-19 presents as conjunctivitis, episcleritis, scleritis, or optic neuritis. These presentations add to a more complete picture of SARS-CoV-2 viral transmission and mechanism of host infection. Furthermore, eye pain during COVID-19 may
provide evidence of hypersensitivity type reactions, neurovirulence, and incitement of either novel or subclinical autoimmune processes. Additionally, investigation of headaches associated with COVID-19 demonstrated four distinct phenotypes that follow ICHD-3 categories: headaches associated with personal protective equipment, migraine, tension type headaches, and COVID-19 specific headache. Early identification of headache class could assist in predicting the clinical course of disease. Finally, investigation into the COVID-19 associated headache phenotype of those with a history of migraine may have broader implications adding to a more general understanding of migraine pathology.
INTRODUCTION

In December 2019, a local outbreak of pneumonia in Wuhan, China was quickly discovered to be caused by a novel coronavirus, identified as Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2).\(^1\) SARS-CoV-2 causes the disease COVID-19, which may result in fatal pneumonia and respiratory distress. This deadly virus quickly spread throughout China and worldwide, disrupting the health and livelihood of millions and devastating local and global economies. Globally, from December 2019 to June 2021, there have been over 180 million confirmed cases of COVID-19, including 3.9 million deaths.\(^2\)

Research during the pandemic has been divided between vaccine development and combatting the evolving symptomology of the disease. As the initial focal point of the infection and a significant cause of disease mortality, the respiratory system has been the primary focus. While these efforts are paramount, a more complete picture of the transmission, pathogenicity, and long-term systemic effects of SARS-CoV-2 is necessary. In this context, the manifestations of COVID-19 in eye pain and headache were considered in an effort to better understand disease transmission, presenting features, and infective mechanisms.

METHODS

Literature was mined from the PubMed database using the key terms: “eye pain”, “conjunctivitis”, “episcleritis”, “optic neuritis”, “migraine”, and “headache” in conjunction with “COVID-19” and “SARS-CoV-2”. Where SARS-CoV-2 research was deficient, pathology of other known viruses was considered. Reports of ocular manifestations of vision loss in the absence of eye pain were excluded. The primary search was conducted in June 2021.
RESULTS

Eye Pain

There are many causes of eye pain in an ophthalmology clinic. The most frequent include dry eyes, conjunctivitis, episcleritis/scleritis, and neuro-ophthalmic entities, such as optic neuritis (ON).³

Conjunctivitis

Clinical studies examining incidence of conjunctivitis in COVID-19 are variable. One of the largest studies was conducted in China involving 1099 participants, with only 0.8% diagnosed with conjunctivitis.⁴ Two smaller series reported prevalence around 3%.⁵,⁶ However, more recent research has suggested higher rates of 11.6%.⁷ Within this study by Güemes-Villahoz et al., there was no relationship between COVID-19 severity and presence of conjunctivitis nor was there a difference in incidence between men and women. However, men with acute conjunctivitis were more likely to present with moderate COVID-19 disease compared to mild disease in women.⁷

Several case studies have reported conjunctivitis as the sole symptom of COVID-19.⁸,⁹ Of those, only one case report describes acute conjunctivitis in a child whose only presenting symptoms were conjunctivitis and eyelid dermatitis.¹⁰

Episcleritis and Scleritis

In June 2020, the first case of episcleritis in a patient with COVID-19 was reported (Table 1).¹¹ Seven days after onset of COVID-19 symptoms, the patient presented with symptoms of red eye, foreign-body-sensation, and photophobia without loss of visual acuity. Elevated epibulbar area with hyperemia was appreciated and the patient was diagnosed with acute nodular episcleritis.¹¹
A September 2020 case report described episcleritis presenting a few days before respiratory symptoms. In addition to episcleritis, anterior and posterior scleritis have also been reported.

**Optic Neuritis**

While incidence of ON associated with COVID-19 infection remains low, there is an increasing number of case reports of ON in the setting of COVID-19 (Table 2). Many cases describe symptoms of ON as the first manifestation of SARS-CoV-2 infection, however, there are reports of ON in the post-infective period. Benito-Pascual et al described unilateral ON and panuveitis as a presenting manifestation, prior to onset of pulmonary symptoms. Interestingly, many of the reported cases of SARS-CoV-2 associated ON are positive for myelin oligodendrocyte glycoprotein (MOG) IgG antibodies.

**Headache**

Prevalence of headache associated with COVID-19 has been variably reported, though commonly described in 6.5-13% of cases. Higher rates (23%) were indicated in hospitalized patients in Spain, and even higher rates (~70%) have been reported among healthcare workers in the Netherlands and Spain. However, a recent meta-analysis of 6335 COVID-19 positive patients estimated incidence to be 12%, consistent with an earlier meta-analysis of 3598 patients.

**Categories of headache**

Within the literature, four distinct phenotypes of COVID-19 associated headache predominate (Table 3). The first phenotype describes headaches associated with use of personal protective equipment (PPE). The third edition of the International Classification of Headache Disorders (ICHD-3) classifies this type of headache as an external pressure headache.
conducted with healthcare workers in Singapore during the COVID-19 outbreak found nearly 82% of respondents reporting de novo PPE associated headache. PPE associated headache was more frequent with use of N95 face mask and protective eyewear for greater than four hours per day or among those with a prior history of headache. The mechanism of onset is external compression causing local tissue damage and irritation of underlying superficial cervical and trigeminal sensory nerves. This peripheral stimulation by PPE may induce further nociceptive signal transmission, central sensitization, and ultimately activation of the trigemino cervicical complex resulting in headache.

The second headache phenotype includes individuals with a history of migraine. Among patients with a history of migraine, 92% report COVID-19 headache as atypical from their usual headache. Nevertheless, patients reporting a history of migraine were more likely to report earlier, longer, more intense headaches than those without prior migraine. Those with prior migraines had higher incidences of nausea, vomiting, photophobia, phonophobia, worsening pain with physical activity, and pulsatile pain resulting in disability from headache alone, consistent with migraine defined by ICHD-3. Visual aura symptoms, which are often associated with migraine, from COVID-19 associated headache have not yet been described.

Patients within this phenotype have shown hematologic and inflammatory biomarkers of thrombocytopenia, lymphopenia, hyperferritinemia, and both elevated c-reactive protein (CRP) and procalcitonin (PCT). These biomarkers are known to be associated with more severe COVID-19 infection; thus, headache severity may be a useful tool in determining overall infection prognosis.

The third group of headache phenotypes includes tension type headache (TTH), further described as pressing in quality with no aggravation upon movement and of mild to moderate
intensity, consistent with ICHD-3.\textsuperscript{38} In contrast to migraine presentation, TTH in the setting of COVID-19 has been linked to lower PCT and CRP, suggesting a milder course of infection.\textsuperscript{33,35,43}

The final headache phenotype describes a COVID-19 specific headache. Pain is bilateral and more diffuse with typically frontal localization. Quality is pressing, intense, and exacerbated with activity and head movement. Phonophobia may occur but overall the headache is less likely to present with photophobia, nausea, and vomiting.\textsuperscript{33,35} This category of headache has been associated with elevated glomerular filtration rate, lymphopenia, elevated PCT, and elevated CRP.\textsuperscript{33}

**DISCUSSION**

Eye pain and headache are common in COVID-19. The pathophysiology of these disorders may contribute to a deeper understanding of the transmission and mechanism of infection of SARS-CoV-2.

While viruses are a common initiator of conjunctivitis, ocular transmission of SARS-CoV-2 has been debated in the literature; the results of which may have substantial public health implications. Delving into the mechanism of coronavirus infection and transmission may clarify the situation.

Coronaviruses contain four principle structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). M, E, and N proteins contribute to virion structure and assembly, while S protein allows binding to host cells.\textsuperscript{44} Fusion of the virion to the host is initiated by host transmembrane serum protease 2 (TMPRSS2) cleaving the S protein into S1 and S2 polypeptide subunits. Infection is facilitated by the S1 subunit binding to host angiotensin converting enzyme-2 (ACE2).\textsuperscript{44} Thus, SARS-CoV-2 associated conjunctivitis would require the
expression of ACE2 and TMPRSS2 on the conjunctiva. Zhou et al demonstrated ACE2 expression in conjunctival, limbic, and corneal cells and TMPRSS2 expression in the conjunctiva.45 In contrast, other research has exhibited expression of mRNA for ACE2 in corneal cells but found no evidence of conjunctival expression.46,47

Systemically, early research on SARS-CoV-2 found ACE2 highly expressed in the lungs, heart, esophagus, kidney, bladder, liver, and ileum; these findings illustrating a potential relationship between ACE2 expression and clinical symptoms of hepatic failure, respiratory injury, or diarrhea.48,49 However, more recent studies have found ACE2 to be lowly expressed, especially in the lung.49,50 Thus, other membrane proteins have been suggested as potential co-receptors to assist ACE2 in SARS-CoV-2 infection.46,49 Analysis of single cell co-expression patterns of 400 membrane proteins and 51 known viral receptors revealed Glutamyl Aminopeptidase (ENPEP), alanyl aminopeptidase (ANPEP) and dipeptidyl peptidase 4 (DPP4) as the most likely auxiliary proteins.49 However, it remains unclear whether these peptidases are expressed on the conjunctival epithelium.51

Clinically, conjunctivitis in the setting of COVID-19 has been demonstrated. A retrospective analysis with COVID-19 patients in Hubei Province, China was performed to investigate ocular manifestations. During the treatment period, 31.6% (n=38) of the patients demonstrated ocular manifestations consistent with conjunctivitis. Furthermore, 5.2% of the patients yielded positive reverse transcription-polymerase chain reaction (RT-PCR) findings of SARS-CoV-2 in conjunctival specimens.52

Using animal models to investigate ocular transmission could also prove useful in settling these controversies; however, to date, there has been only one such study conducted in rhesus monkeys. Rhesus monkeys were inoculated with SARS-CoV-2 either via the conjunctiva or
intratracheally. Continuous viral load was detected in nasal and throat swabs following both inoculation routes 1-7 days post inoculation. Conjunctival viral load could only be detected in the conjunctival inoculated animal on post inoculation day one. Both routes yielded distinct viral distribution consistent with local anatomical structure. Notably the conjunctival inoculated animal demonstrated viral load in tissues of the nasolacrimal system, suggesting the lacrimal duct may be a conduit for viral transmission from ocular to respiratory tissues.53

Chest radiographs demonstrated relatively mild and local interstitial pneumonia in the conjunctival infected monkey, unlike the intratracheally inoculated monkey that developed moderate and diffuse interstitial pneumonia with increased inflammation, exudation, and diffuse lesions. While viral load via conjunctival inoculation was significant enough to result in systemic infection, it is possible that viral particles were quantitatively reduced in transit to yield a milder respiratory disease. Conjunctivitis, however, was not reported, which is not surprising considering the transient detection of conjunctival viral load.53

Unlike conjunctivitis, episcleritis is attributed to a vascular inflammatory response rather than direct ocular inoculation. Most cases of episcleritis are idiopathic, however 26% to 36% arise secondarily from systemic disorders, such as collagen vascular diseases, autoimmune disorders, or infection.54 While systemic autoimmune disorders are a more common cause of episcleral vascular insult, many infectious agents are causal.54–57

Among various ocular findings and symptoms of patients with COVID-19, episcleritis has been found to be associated with elevated D-dimer.58 Considering this vascular immune reaction mechanism and the high incidence (31%) of thrombotic complications in ICU patients with COVID-19, episcleritis in the setting of SARS-CoV-2 could potentially be initiated by immune complex deposition or coagulation dysfunction.59 This is not a completely novel viral expression.
Episcleritis in hepatitis C viral infection has been linked to cryoglobulin immune complex deposition in primarily small vessels resulting in inflammatory response and wide-spread secondary vasculitis.\(^5\) Additionally, mechanism of secondary episcleritis in autoimmune disorders has been attributed to hypersensitivity type reactions.\(^5^4\)

ON is a manifestation of central nervous system (CNS) inflammation, most often found in individuals with systemic inflammatory or autoimmune disorders, though infectious ON also occurs.\(^1^6\) As ACE2 receptors are known to exist on both neurons and endothelial cells, direct infection is possible.\(^1^8\) Postmortem examination of a patient with COVID-19 in conjunction with clinically worsening neurologic symptoms revealed the virus in neural and capillary endothelial tissue, suggestive of viral neurotropism.\(^6^0\)

There are two primary routes of viral entry into the CNS: hematogenous dissemination and neuronal retrograde dissemination.\(^6^1,6^2\) The first requires virus in the bloodstream that can either infect endothelial cells of the blood brain barrier (BBB) or leukocytes that transcytose through the BBB, allowing entry to the CNS.\(^6^1,6^2\) It has been postulated that SARS-CoV-1 is capable of infecting endothelial cells of the BBB, facilitating viral entry.\(^6^3\) SARS-CoV-2 has been found to infect tissue-resident macrophages of the lymph nodes and spleen, indicating that it may also infect leukocytes.\(^6^4\) Following 15 autopsies, SARS-CoV-1 viral components were discovered in circulating monocytes, lymphocytes, lymphoid tissue, and macrophages in various organ systems.\(^6^5\) Considering these findings of SARS-CoV pathogenicity, it is possible that the innate immune system is utilized by SARS-CoV-2 as a somal cargo system through the BBB into the CNS.

Somal transport and endothelial disruption of the BBB are not the only mechanisms by which viruses cause neurotropism. Some viruses are capable of infecting peripheral nerves to gain
access to the CNS through retrograde axonal transsynaptic neuronal dissemination. Human Coronavirus OC43 in mice has been shown to neuropropagate from the nasal cavity to the olfactory bulb, piriform cortex, and ultimately the brainstem by passive diffusion and axonal transport strategies. SARS-CoV-2 viral neurotropism through one or several of these mechanisms is likely considering the presentation of ON and other CNS disorders in the setting of COVID-19 disease.

Many cases of ON associated with COVID-19 are associated with myelin oligodendrocyte glycoprotein (MOG) antibody disease (MOGAD). MOG is solely expressed on oligodendrocytes and may act as an adhesion molecule to regulate microtubule stability and mediate the complement cascade. MOGAD can present without apparent cause; however, it has been described in postinfectious demyelinating disease following infection with herpes simplex virus, Epstein-Barr virus, and Lyme disease. The mechanism of injury is believed to be molecular mimicry wherein viral antigens induce an autoimmune response. Furthermore, acute disseminated encephalomyelitis (ADEM), another clinical feature of MOGAD, has a strong association with viral illness. Leake et al. reported that 93% of patients with ADEM reported a history of viral illness within three weeks of neurological symptoms.

SARS-CoV-2 has demonstrated an ability to dysregulate the immune system with reports of Miller Fisher syndrome, Guillain-Barre syndrome, Kawasaki syndrome, and anti-phospholipid antibody syndrome, the latter resulting in thrombosis. Considering SARS-CoV-2 virus’s affinity and access to the CNS in addition to prominent immune and vascular dysregulation abilities, it is surprising that ON is not more commonly observed. It is unclear as to whether COVID-19 patients presenting with ON and MOGAD housed a subclinical predisposition to MOGAD, or if the virus is capable of inciting a novel autoimmune process.
ON provides valuable insight into viral neurotropism and autoimmune dysregulation; likewise, investigation into headache symptomology may further support and explore SARS-CoV-2 pathogenesis. There are three theories to pathogenesis of headache from COVID-19 infection. The first suggests viral entry into the nasal cavity leading to direct invasion of trigeminal nerve endings (similar to neuronal retrograde dissemination previously discussed). ACE2 receptors are known to express on glial cells and CNS neurons. While ACE2 expression has not yet been reported on the peripheral trigeminal nerve, it has been located on the sensory trigeminal nucleus.

ACE2 is the key enzyme in producing angiotensin II and upholds a prominent role in the renin-angiotensin-aldosterone system (RAAS) which maintains fluid homeostasis. Dysregulation of RAAS has been linked to pain, and antagonism of RAAS is clinically beneficial in treating migraine, neuropathic, and nociceptive pain. In human and rat thoracic dorsal root ganglion, angiotensin II was found to be both locally produced and colocalized with Substance P and calcitonin gene-related peptide (CGRP), suggesting angiotensin II may participate in nociceptive regulation. CGRP is well known for provocation of migraine, and its antagonism is also an effective migraine treatment. Angiotensin II has shown a dose-dependent increase in CGRP, further suggesting a role of angiotensin II and RAAS in headache pathology. Considering these associations, dysfunction of ACE2 inducing RAAS and angiotensin II destabilization could potentially result in a secondary nociceptive response.

The second mechanism for COVID-19 associated headache concerns vascular pathogenesis. SARS-CoV-2 has demonstrated an affinity for dysregulation and infection of diffuse systemic endothelial cells. The endothelium participates pivotally in homeostasis, more specifically thrombosis and fibrinolysis, vasodilation/constriction, and inflammation. Thrombosis, shock, and multi-organ system dysregulation associated with COVID-19 has been
attributed to this endothelial dysregulation.\textsuperscript{75} Resulting oxidative stress, free radical formation, and unbalanced vasoconstriction secondary to ACE2 downregulation and internalization could lead to vasculopathy. In the setting of perivascular trigeminal nerve fibers this vasculopathy may result in COVID-19 associated headache.\textsuperscript{69}

The third postulated mechanism for COVID-19 associated headache assumes pro-inflammatory mediators and cytokines directly stimulating perivascular trigeminal nerve fibers.\textsuperscript{69} The headache phase of migraine is believed to originate from mechanical, electrical, or chemical activation of nociceptive nerves of intracranial vasculature and the meninges. Stimulated release of vasoactive neuropeptides, Substance P and CGRP, from the trigeminal ganglion access the dura through the trigeminal nerve, primarily the ophthalmic division (V1).\textsuperscript{77} Furthermore, trigeminal neurovascular activation has been linked to pro-inflammatory mediators such as IL-1 beta, IL-6, NF-\textsuperscript{kb}, and nitric oxide (NO).\textsuperscript{69,78} It is possible that the cytokine storm associated with severe COVID-19 disease could chemically activate perivascular trigeminal nerve nociception producing headache. Resulting meningeal inflammation may contribute to the COVID-19 specific headache phenotype considering the defining symptoms of pain with head movement, photophobia, and phonophobia.\textsuperscript{35,79}

While it may not be considered a common mechanism, COVID-19 headache experienced by migraine sufferers may be connected to genetics. A large-scale genome-wide association study conducted in 2016 identified 38 distinct loci associated with migraine.\textsuperscript{80} While the associated genes are primarily involved in vascular function, 11 of the genes are involved in metal ion homeostasis.\textsuperscript{80,81} With this discovery, it has been hypothesized that metal ion dyshomeostasis may indicate susceptibility for migraine.\textsuperscript{81} In this context, research demonstrating that SARS-CoV-2 targets the human metalloproteome may be relevant.\textsuperscript{82} SARS-CoV-2 viral affinity for zinc disrupts
normal cell activity by affecting zinc-binding protein domains and causing strong intracellular zinc disturbances.\textsuperscript{82} This disturbance, in combination with genetic susceptibility for dysregulated metal ion homeostasis in familial migraine, may contribute to the COVID-19 headache phenotype described in individuals with a history of migraine.

**CONCLUSION**

As COVID-19 continues to devastate global health and global economies, we continue to learn about its association with systemic disorders. Investigation into the relationship of COVID-19 and disorders such as eye pain and headache could provide insight into viral transmission and disease pathophysiology. Some of these disorders may be a first presentation of SARS-CoV-2, while many present soon after infection and others may linger chronically, such as headache. The visual system has helped to delineate the pathophysiology of COVID-19 and inversely the study of COVID-19-related headache may provide insight into the pathophysiology of migraine.
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Table 1. Summary of previous case reports of episcleritis and scleritis associated with COVID-19.

<table>
<thead>
<tr>
<th>Study</th>
<th>Disorder</th>
<th>Gender</th>
<th>Age (y)</th>
<th>Visual symptom onset in relation to COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otaif 2020 et al.(^{12})</td>
<td>Episcleritis</td>
<td>Male</td>
<td>29</td>
<td>Eye redness and foreign body sensation five days before respiratory symptoms and fever</td>
</tr>
<tr>
<td>Mendez Mangana 2020 et al.(^{11})</td>
<td>Episcleritis</td>
<td>Female</td>
<td>31</td>
<td>Eye redness, foreign body sensation, epiphoria, and photophobia seven days after cough and myalgia</td>
</tr>
<tr>
<td>Collange 2020 et al.(^{14})</td>
<td>Posterior scleritis</td>
<td>Male</td>
<td>56</td>
<td>MRI during admission showed posterior scleritis</td>
</tr>
</tbody>
</table>
| Feizi 2021 et al.\(^{13}\) | Anterior scleritis | Two cases (female and male) | Case 1: 67  Case 2: 33 | Case 1: necrotizing anterior scleritis both eyes 3 weeks after COVID-19 onset  
  Case 2: sectoral anterior scleritis 2 weeks after COVID-19 onset |
Table 2. Summary of previous case reports of optic neuritis associated with COVID-19.

<table>
<thead>
<tr>
<th>Study</th>
<th>Gender</th>
<th>Age</th>
<th>Visual symptom onset in relation to COVID-19</th>
<th>Antibodies associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azab 2021 et al.</td>
<td>Male</td>
<td>32</td>
<td>Two weeks post-COVID-19 infection</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kogure 2021 et al.</td>
<td>Male</td>
<td>47</td>
<td>Asymptomatic of respiratory symptoms; COVID-19+ the same day (had contact at home for two days)</td>
<td>MOG-IgG +; AQP4-IgG -</td>
</tr>
<tr>
<td>Parvez 2021 et al.</td>
<td>Female</td>
<td>10</td>
<td>Simultaneous; asymptomatic of respiratory symptoms</td>
<td>MOG-IgG -; AQP4-IgG -</td>
</tr>
<tr>
<td>Zoric 2021 et al.</td>
<td>Male</td>
<td>63</td>
<td>Five weeks post-COVID-19 infection</td>
<td>MOG-IgG +; AQP4-IgG -</td>
</tr>
<tr>
<td>Rodriguez-Rodriguez 2021 et al.</td>
<td>Female</td>
<td>55</td>
<td>Simultaneous; asymptomatic of respiratory symptoms</td>
<td>Not reported</td>
</tr>
<tr>
<td>Sardar 2021 et al.</td>
<td>Female</td>
<td>38</td>
<td>Two weeks post-COVID-19 infection</td>
<td>AQP4-IgG -; MOG-IgG not reported</td>
</tr>
<tr>
<td>Sharma 2021 et al.</td>
<td>Female</td>
<td>22</td>
<td>Ten days post-COVID-19 infection</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mabrouki 2021 et al.</td>
<td>Female</td>
<td>60</td>
<td>Two weeks post-COVID-19 infection</td>
<td>MOG-IgG -; AQP4-IgG -</td>
</tr>
<tr>
<td>Sawalha 2020 et al.</td>
<td>Male</td>
<td>44</td>
<td>Two weeks post-COVID-19 infection</td>
<td>MOG-IgG +; AQP4-IgG -</td>
</tr>
<tr>
<td>Study</td>
<td>Gender</td>
<td>Age</td>
<td>Symptom Onset Description</td>
<td>Immunological Findings</td>
</tr>
<tr>
<td>---------------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td>Benito-Pascual 2020 et al.(^{18})</td>
<td>Female</td>
<td>60</td>
<td>Ten days prior to respiratory symptoms</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ruijter 2020 et al.(^{21})</td>
<td>Male</td>
<td>15</td>
<td>A few weeks after presumed COVID-19 infection</td>
<td>MOG-IgG +; AQP4-IgG -</td>
</tr>
<tr>
<td>Woodhall 2020 et al.(^{25})</td>
<td>Female</td>
<td>39</td>
<td>Six days after COVID-19; had a prior history of relapsing MOG Ab disease</td>
<td>MOG-IgG serological reversion</td>
</tr>
<tr>
<td>Zhou 2020 et al.(^{19})</td>
<td>Male</td>
<td>26</td>
<td>Few days post development of dry cough</td>
<td>MOG-IgG +; AQP4-IgG -</td>
</tr>
</tbody>
</table>

MOG-IgG = myelin oligodendrocyte glycoprotein immunoglobulin G; AQP4-IgG = aquaporin-4 immunoglobulin G
Table 3. Summary of headache syndromes that predominate in the setting of COVID-19 disease.

<table>
<thead>
<tr>
<th>Headache Syndromes</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPE associated</td>
<td>External pressure headache(^{38})</td>
</tr>
<tr>
<td>Migraine (occurring in those with a history of migraine)</td>
<td>Transformation of a patient’s typical migraine pattern, though still with migrainous features(^{33,35,38,42})</td>
</tr>
<tr>
<td>Tension type headache</td>
<td>Consistent with ICHD-3 tension-type headache(^{33,35,38,43})</td>
</tr>
<tr>
<td>COVID-19 specific headache</td>
<td>Occurs in patients without a history of headache and resembles migraine, though often lacks photophobia, nausea, and vomiting(^{33,38})</td>
</tr>
</tbody>
</table>

PPE=personal protective equipment; ICHD-3=International Classification of Headache Disorders, 3\(^{rd}\) edition