Ophthalmic and neuro-ophthalmic manifestations and findings in COVID-19: a review

Samiha Fahad Khayyat1, Meshari Saeed Alzahrani1*, Salah Hassan Khafaji1, Muhammad Irfanullah Siddiqui2

ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by a highly infectious enveloped RNA virus named severe acute respiratory syndrome coronavirus 2. In the emerging COVID-19, ocular and neuro-ophthalmic manifestations were described in the literature. These signs and symptoms may be the result of range of pathophysiological mechanisms that occurs during the acute illness but are still not well understood. In this review, we will discuss the ocular and neuro-ophthalmic manifestations and findings associated with COVID-19 infection.

Keywords: COVID-19, neuro-ophthalmic manifestations, ocular manifestations.

Introduction

The coronavirus disease 2019 (COVID-19) outbreak began in Wuhan, China, in December 2019, and the World Health Organization (WHO) revealed it is a pandemic on 11 March 2020. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped RNA virus that causes the infection [1-3]. According to the data reported by the WHO on 18 February 2021, COVID-19 has reached 109,594,835 confirmed cases and caused 2,424,060 deaths across 223 different countries (WHO). Fever, cough, shortness of breath, and fatigue are considered the most common symptoms; in addition, the disease had a negative impact on cardiovascular, neurological, hematological, and renal systems [2,3]. Involvement of the ocular system is rare compared to the typical features and it is not well understood [3,4]. Patients who have ocular symptoms can complain of pain, redness, congestion, dryness, foreign body sensation in the eyes, and neuro-ophthalmiological presentations, such as optic neuritis and third, sixth, and seventh cranial nerve palsy [5-7]. In this review, we aim to outline the ocular and neuro-ophthalmic manifestations and findings that have been reported in COVID-19 patients.

Method

A literature search was carried out in PubMed/Medline and Google Scholar databases using keywords such as COVID-19, neuro-ophthalmic manifestations, and ocular manifestations. Articles the have been published from 2019 to January 2021 were included. The search in the original review retrieved 2,288 articles, of which 2040 were excluded based on the title and 199 after reading the abstract. Of the remaining 248 articles, 221 were excluded after reading the full text as they did not focus on the topic or were not written in English. The reference lists in full-text articles were scanned to obtain additional citations. The finding from 36 articles is summarized and discussed.

Discussion

Ocular manifestations

Conjunctivitis

 Conjunctivitis is considered the most common ocular manifestation in COVID-19 and the conjunctival tissue is thought to be a potential portal of entry for COVID-19. It can present as conjunctival congestion, red eye, dry eye, foreign body sensation, itching, tearing, and floaters.

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Two published reports had two patients showing signs and symptoms suggestive of conjunctivitis shortly before the onset of COVID-19 symptoms [8,9]. A study conducted at Madrid, Spain, showed that 35 patients out of 301 (11.65%) had acute conjunctivitis, and mucopurulent discharge was the most common symptom (100%), followed by tearing (62.8%) and foreign body sensation (57.1%) [10]. Another study conducted in Wuhan, China, reported that 27 out of 535 COVID-19 patients (5%) complained of conjunctival congestion with 4 of them presenting with conjunctivitis as their initial presentation [11]. A retrospective cross-sectional study carried out on patients with mild COVID-19 symptoms revealed that 11 patients complained of ocular manifestations with 8 out of 11 complaining of conjunctival secretions, 3 had ocular burning sensation, 1 patient complained of epiphora, and another patient complained of hordeolum [12]. Additionally, two studies showed that conjunctivitis can present as a late ocular manifestation in patients with severe COVID-19 symptoms [13,14] (Table 1).

### Table 1. Case summaries of conjunctivitis and panuveitis during COVID-19.

<table>
<thead>
<tr>
<th>First author</th>
<th>Number of patients</th>
<th>Manifestations</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidder et al. [5]</td>
<td>1</td>
<td>Kawasaki-like syndrome and nonexudative conjunctivitis</td>
<td>45-year-old male presented with COVID-19 and Kawasaki like symptoms, had peri-orbital rash involving the upper and lower eyelids, bilateral diffuse conjunctival hyperemia, and chemosis consistent with nonexudative conjunctivitis. On examination, he had bilateral superficial keratitis, with symmetric Anterior chamber (AC) inflammation.</td>
</tr>
<tr>
<td>Vilaroz et al. [12]</td>
<td>127</td>
<td>Conjunctivitis</td>
<td>11 patients out of 127 complained of ocular manifestations. Eight patients had conjunctival congestion, three patients had ocular burning sensation, one patient with burning eye, and one patient with hordeolum. 5 out of 11 patients developed ocular manifestation before any COVID-19-related symptoms.</td>
</tr>
<tr>
<td>Guemes-Vilahoz et al. [10]</td>
<td>301</td>
<td>Conjunctivitis</td>
<td>35 patients out of 301 had acute conjunctivitis; the most common symptoms reported were mucopurulent discharge (100%), tearing (62.8%), and foreign body sensation (57.1%).</td>
</tr>
<tr>
<td>Navel et al. [13]</td>
<td>1</td>
<td>Hemorrhagic conjunctivitis and pseudomembranous</td>
<td>63-year-old male with COVID-19 in the ICU, developed conjunctival hyperemia and clear secretions on day 17 post-admission; 2 days later, he had follicles, petechiae, tarsal hemorrhages, chemosis and pseudomembranes.</td>
</tr>
<tr>
<td>Mendez et al. [15]</td>
<td>1</td>
<td>Episcleritis</td>
<td>31-year-old female tested positive for COVID-19. 10 days later she developed red eye, foreign body sensation, epiphora in the left eye, and was diagnosed as a case of nodular episcleritis.</td>
</tr>
<tr>
<td>Daruich et al. [8]</td>
<td>1</td>
<td>Conjunctivitis</td>
<td>27-year-old male complaining of red left eye with foreign body sensation, on exam showed left eyelid edema and moderate conjunctival hyperemia. Few hours later he had fever cough and dyspnea and has tested positive for COVID-19.</td>
</tr>
<tr>
<td>Ahuja et al. [9]</td>
<td>1</td>
<td>Conjunctivitis with phlebitis</td>
<td>53-year-old male complaining of left eye irritation and upper lid swelling since 1 day; on examination, the left upper eyelid was red, swollen, and had crusting in the eyelashes with mild inflammation and injection of the conjunctiva. The following day he tested for SARS-CoV-2 PCR and came out positive.</td>
</tr>
<tr>
<td>Nayak et al. [14]</td>
<td>1</td>
<td>Conjunctivitis</td>
<td>65-year-old male with COVID-19 was intubated and mechanically ventilated; 7 days later, he developed redness and severe infection of the right eye. Torchlight examination showed severe follicular reaction in lower palpebral conjunctiva with conjunctival prolapse.</td>
</tr>
<tr>
<td>Lim et al. [16]</td>
<td>2</td>
<td>Conjunctivitis</td>
<td><strong>Case 1:</strong> 38-year-old male with COVID-19, developed bilateral eye redness 1 day later. Slit lamp examination revealed bilateral follicular conjunctivitis with mild chemosis of left eye. <strong>Case 2:</strong> 27-year-old male with COVID-19 complained of bilateral eye redness and discomfort. Slit lamp examination showed bilateral follicular conjunctivitis which was worse in the right eye.</td>
</tr>
<tr>
<td>Francois et al. [17]</td>
<td>1</td>
<td>Panuveitis</td>
<td>Woman in her late 50s with COVID-19 developed redness and blurred vision in her right eye 2 days later. Slit lamp examination revealed mild anterior chamber inflammation. Fundus examination showed pupillary edema and mild vitreous inflammation.</td>
</tr>
<tr>
<td>Turbin et al. [6]</td>
<td>2</td>
<td>Orbital cellulitis</td>
<td><strong>Case 1:</strong> 12-year-old male with 3 days of painful unilateral orbital swelling patient. On examination, severe unilateral right upper and lower eyelid edema with mild erythema were noted. 14 days later, pre-operative PCR for SARS-CoV-2 was positive prior to concurrent endoscopic sinus debridement. <strong>Case 2:</strong> 15-year-old male with progressive painful unilateral orbital swelling, severe right-sided upper and lower eyelid and periorbital edema with mild non-chomotic conjunctival hyperemia and proptosis. PCR for SARS-CoV-2, within 19 hours of his presentation, was positive.</td>
</tr>
</tbody>
</table>
Coronavirus disease 2019 (COVID-19) has shown in animals the capabilities of causing anterior uveitis and choroiditis; these manifestations have rarely been described in humans [7]. Two published case reports have reported anterior uveitis with COVID-19 symptoms; the first case was a 30-year-old female patient diagnosed as a case of conjunctivitis with positive COVID-19 Polymerase chain reaction (PCR) for SARS-CoV-2 developed blurred vision in her right eye; after 2 weeks, her slit lamp examination revealed conjunctivitis and acute uveitis of the right eye with the presence of diffuse white pigmentary precipitates in the anterior capsule [18]. The second case report was a 54-year-old who presented with multisystem inflammatory syndrome due to COVID-19; 2 weeks later, she developed bilateral blurred vision and was diagnosed with bilateral anterior uveitis [19] (Table 2).

### Ocular manifestations in hospitalized patients

A cross-sectional study of 142 patients found a high frequency of ocular manifestations in hospitalized COVID-19 patients. Conjunctival hyperemia is considered as the most common ocular symptoms (28.9%), followed by chemosis, tearing, and eye irritation (15.5%, 23.2%, and 13.4%, respectively). This study also demonstrated a higher frequency of ocular finding in patients admitted to the intensive care unit (ICU) compared to those in other wards. Moreover, the patients admitted to the ICU were associated with increased risk of developing chemosis [28].

Wu et al. [29] reported that the patients with conjunctivitis are more likely to have higher levels of procalcitonin, white blood cell, neutrophil counts, higher lactate dehydrogenase activity, and C-reactive protein compared to those without ocular symptoms, suggesting that ocular abnormalities occurred more frequently in patients with more severe COVID-19.

However, a cross-sectional study on 301 patients found no relationship between the COVID-19 severity score and the presence of conjunctivitis ($p = 0.17$), which is considered a rapid self-limited conjunctivitis that did not have any impact on visual acuity, did not associate with short-term complications, and can be improved without treatments [10].

### Table 2. Case summaries of neuro-ophthalmological manifestations during COVID-19.

<table>
<thead>
<tr>
<th>First author</th>
<th>Number of patients</th>
<th>Manifestations</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Khan et al. [20]</td>
<td>1</td>
<td>Optic neuritis associated with MOG-AD</td>
<td>11-year-old male patient tested positive for COVID-19 and presented with optic neuritis; MOG antibody was positive. MRI findings were consistent with MOG-AD and bilateral asymmetrical optic neuritis.</td>
</tr>
<tr>
<td>Selvaraj et al. [21]</td>
<td>1</td>
<td>Acute vision loss</td>
<td>A female in her 50s, a confirmed COVID-19 case, had painless right eye monocular visual disturbance and other neurological symptoms. Her vision spontaneously improved during her hospitalization.</td>
</tr>
<tr>
<td>Falcone et al. [22]</td>
<td>1</td>
<td>Abducens palsy</td>
<td>A 32-year-old male patient presented with upper respiratory illness and painless acute binocular horizontal diplopia. He tested positive for COVID-19. On MRI, there was atrophic left lateral rectus muscle.</td>
</tr>
<tr>
<td>Francis et al. [23]</td>
<td>1</td>
<td>Abducens palsy and anosmia</td>
<td>A 69-year-old female patient developed painless binocular horizontal diplopia 8 days after being testing positive for SARS-CoV-2 infection. Her only COVID-19 symptom was anosmia. 5 weeks later at follow-up, the patient’s diplopia resolved.</td>
</tr>
<tr>
<td>Belghmaidi et al. [4]</td>
<td>1</td>
<td>Oculomotor palsy</td>
<td>A 24-year-old female patient presented with acute diplopia and strabismus on the left eye 3 days after the start of general symptoms. Nasopharyngeal swab for COVID-19 RT-PCR was positive.</td>
</tr>
<tr>
<td>Gutiérrez-Ortiz et al. [24]</td>
<td>2</td>
<td>Miller Fisher syndrome and polyneuritis cranialis</td>
<td>Case 1: A 50-year-old male presented with right internuclear ophthalmoplegia, right fascicular oculomotor palsy, ataxia, and areflexia, followed by few days of typical COVID-19 symptoms. He tested positive for COVID-19.</td>
</tr>
<tr>
<td>Restivo et al. [26]</td>
<td>3</td>
<td>Myasthenia Gravis</td>
<td>Three patients with positive COVID-19 test developed symptoms suggestive of myasthenia gravis. Electromyography (EMG) with repetitive stimulation showed decrement and concentration of acetylcholine was elevated.</td>
</tr>
<tr>
<td>Novi et al. [27]</td>
<td>1</td>
<td>Acute disseminated encephalomyelitis</td>
<td>64-year-old female developed bilateral severe vision impairment associated with sensory loss of right leg, left-sided lower limb hyper-reflexia with the Babinski sign 2 weeks after COVID-19 infection, Cerebrospinal fluid (CSF) sample was positive for SARS-CoV2, and serum SARS-CoV2 was positive for IGG antibodies.</td>
</tr>
</tbody>
</table>
**Ocular findings among pediatrics**

Ocular pathology could be produced in children due to SARS-CoV-2 infection, which appears after several weeks of the acute disease phase [30]. A prospective observational study found that 17 children with COVID-19 had ocular findings, out of which five had ocular hyperemia, three had bilateral acute conjunctivitis, and two had unilateral episcleritis. Only one patient presented with unilateral optic neuritis and had visual symptoms as unilateral inferior temporal quadrantanopia. Additionally, only one patient had unilateral retinal vasculitis which was observed through ocular fundus examination. In addition, six patients diagnosed with COVID-19 associated with pediatric inflammatory multisystem syndrome (Kawasaki-like disease). They showed mild follicular conjunctivitis, but no findings of anterior uveitis were compared to Kawasaki disease [30].

There was also only one case reported of an infected 2-year-old child characterized by conjunctivitis and eyelid dermatitis without any other symptom [31]. Another study was conducted on 216 pediatric patients with COVID-19, demonstrating that 22.7% of the children showed various ocular manifestations and 9 children had ocular complaints upon initial presentation. Common ocular manifestations were conjunctival discharge, eye rubbing, conjunctival congestion, ocular pain, eyelid swelling, and tearing. Children with systemic symptoms were nearly twice as likely to develop ocular symptoms. Most ocular symptoms were mild where 46.9% of the patients recovered without treatment, while 8 children had persistent eye rubbing, and only 1 child completely recovered. Only 7 days was the median duration of ocular symptoms [32].

**Retinal findings**

Retinal changes during COVID-19 have been observed in several studies. In a study conducted on 18 hospitalized patients with severe COVID-19, 10 had abnormal dilated eye examination with the main findings being flame-shaped hemorrhages in 4 patients, followed by cotton wool spots in 3 patients. Other retinal findings in the study included retinal sectorial pallor, peripheral retinal hemorrhages, and macular hemorrhages with hard exudates [3]. Additionally, two published case reports reported retinal changes in patients who have ocular manifestations during COVID-19 infection; the first was a 59-year-old female with a known case of controlled type 2 diabetes mellitus who presented with sudden bilateral blurred vision with COVID-19 symptoms. On fundal examination the patient had dot-and-blot hemorrhages with mild optic disk hyperemia in both eyes. The second case was a 40-year-old male who was diagnosed with COVID-19; 1 day later he developed bilateral painless blurred vision. On his fundus examination, bilateral dilated tortuous veins, dot-and-blot hemorrhages with cotton wool spots and optic disk edema were noted [33,34]. Another study reported that the peripapillary retinal nerve fiber layer in a total of 32 patients with COVID-19 had a significant thinning in the inferonasal quadrant versus 34 health individuals (111.97 ± 17.58 μm vs. 121 ± 20.47 μm ; p = 0.04) [35].

**Neuro-ophthalmological manifestations**

Several neuro-ophthalmological manifestations are associated with COVID-19. Table 2 shows the signs and symptoms reported, including diplopia, ptosis, ophthalmoplegia, and vision loss. The pathophysiology behind these manifestations is still not fully understood [7].

**Optic neuritis**

A study reported a 26-year-old male patient with bilateral severe optic neuritis and myelitis [36]. On examination, he had vision loss and disk edema in both eyes which raised suspicion for myelin oligodendrocyte glycoprotein-AD Myelin oligodendrocyte glycoprotein antibody disease (MOG-AD). He tested positive for MOG IgG and for COVID-19 oropharyngeal swab.

**Miller Fischer syndrome**

Two cases were reported with ocular motility deficits after resolution of typical COVID-19 symptoms, which were associated with hyporeflexia and paresthesia. These findings were suggestive of Miller Fisher syndrome, a variant of the Guillain-Barre syndrome [37,24]. A 36-year-old positive COVID-19 male patient presented with left ptosis, diplopia, and bilateral distal leg paresthesia [37]. On examination, he had left eye ptosis, mydriasis, and limitations in depression and adduction. Other neurological findings included ataxic gait and hyporeflexia. Another case was reported on a 50-year-old man who presented having diplopia, paresthesia, and gait instability associated with confirmed COVID-19 infection [24]. On examination, he had right hypertropia with and left nystagmus, ataxic gait, and absent deep tendon reflex on both upper and lower extremities. He tested positive for antibodies to ganglioside GD1b complex.

**Cranial nerve palsies**

Diplopia and ptosis have been described in association with the diagnosis of COVID-19 infection. Several cases were reported with sixth nerve palsies associated with the diagnosis of COVID-19 [4,23,2]. One case reported a 32-year-old male patient who presented with horizontal diplopia and tested positive for COVID-19 infection [22]. On examination, he was found to have binocular diplopia and a limitation to abduction in the left eye. 5 weeks later, his visuals symptoms persisted, and on Magnetic resonance imaging (MRI), it showed left lateral rectus muscle atrophy. Another case was reported on a 69-year-old female patient with positive COVID-19 infection who presented with painless acute binocular horizontal diplopia and inability to abduct. Interestingly,
her only COVID-19 symptom was anosmia. On follow-up, 5 weeks later, her diplopia had resolved [23]. In addition, third cranial palsy was also reported in a 24-year-old female patient [4]. She presented with acute diplopia and strabismus on the left eye accompanied by COVID-19 infection. On neurological examination, she had limitations in up-gaze, adduction, and down gaze of the left eye. Incomplete third nerve palsy was diagnosed. MRI was unremarkable.

Vision loss

Visual loss is a possible serious neuro-ophthalmological presentation in COVID-19 patients. One published article reported two case reports with visual loss secondary to ischemic stroke [38]. The first was a 61-year-old male patient with positive COVID-19 infection presenting with bilateral sudden vision loss [38]. On examination, he was disoriented and on visual acuity there was no light perception in both eyes. Computed tomography scan (CT-scan) with no contrast revealed low attenuation changes and loss of gray/white matter differentiation consistent with cytotoxic edema within bilateral occipital polar regions with no hemorrhage. The second case was a 34-year-old female patient who tested positive for COVID-19 and was complaining of sudden, bilateral, and painless loss of vision [38]. On examination, she was awake and oriented. On visual acuity, she had light perception in both eyes. The rest of the ophthalmological exam was unremarkable. Her MRI without contrast revealed multiple acute infarcts in the right frontal lobe, left posterior temporal-parietal lobe, and bilateral occipital lobes.

Conclusion

Significant challenges have been created/increased among the general population and healthcare providers due to the rapid progression of the COVID-19 crisis worldwide. There have been several published reports of variants ocular manifestations in some COVID-19 patients, which were found to be presented as the initial or exclusive complaints. Other studies recorded eye redness and irritation in COVID-19 patients, suggesting that conjunctivitis could be an ocular manifestation of SARS-CoV-2 infection. Patients with COVID-19 could be firstly examined or evaluated by the ophthalmologists due to conjunctivitis, which is a common eye condition. Thus, patients with viral conjunctivitis’ symptoms or signs should be examined with special care.

However, ophthalmological and neuro-ophthalmological symptoms and signs should not be neglected. Ophthalmology at the frontline has played a crucial role in confronting COVID-19 and they have learned and discovered information about the disease as a new pathology and have explored its extrapulmonary manifestations to evaluate patients effectively.

In our opinion, the major ocular and neuro-ophthalmological manifestations report lack due to safety issues concerning detailed ophthalmological examination. On the other hand, more cases infected with COVID-19 reported that the disease restricts them to utilize ocular examination and also restricts ophthalmologist’s visit to the ICU.

We suggest that future prospective studies with methodical collection and data reporting are needed for evaluation of ocular involvement and to detect their real incidence in COVID-19 patients.

More efforts and precautions are required to prevent and stop the outspread of COVID-19, proper therapeutic approaches should be provided, and effective communication between the patients and healthcare professional must be carried out.

List of Abbreviations

AC  Anterior chamber
CSF  Cerebrospinal fluid
CT-scan  Computed tomography scan
COVID-19  Coronavirus disease 2019
EMG  Electromyography
ICU  Intensive care unit
MRI  Magnetic resonance imaging
MOG  Myelin oligodendrocyte glycoprotein
MOG-AD  Myelin oligodendrocyte glycoprotein antibody disease
PCR  Polymerase chain reaction
SARS-CoV-2  Severe acute respiratory syndrome coronavirus 2
WHO  World health organization

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent to participate

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Ethical approval

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References

Ophthalmic and neuro-ophthalmic


