The novel coronavirus, severe acute respiratory syndrome-2 (SARS-CoV-2) has spread internationally and caused the deadliest pandemic of recent times. The first outbreak was documented in Wuhan, China, in December 2019. By March 10, 2021, there had been over 117 million cases and over 2.6 million deaths worldwide (1). In the United States alone, the country with the highest disease burden, there were 29 million cases and over 520,000 deaths by that time (1).

The COVID-19 pandemic will likely be one of the defining phenomena of this decade, its impact reaching every sector of the society. In the United States, the longstanding public health emergency has pushed several regional medical systems to the brink of collapse. The death toll has steadily crept higher. The global economy has fallen into the worst recession since the Great Depression (2). Life has been indelibly changed by the pandemic. At this time, we do not yet have a cure for the virus, although several medications such as remdesivir, dexamethasone, and immunomodulators such as baricitinib and tocilizumab have been shown to improve morbidity and mortality, in studies. By early March 2021, the FDA had issued emergency use authorizations for 3 different COVID-19 vaccines. However, it is likely that even with the availability of vaccines, COVID-19 and its complications will continue to pose public health challenges in the future.

Early on in the pandemic, health officials warned the public to remain vigilant for flu-like signs and symptoms: fever, cough, sore throat, and shortness of breath. COVID-19 was conceptualized as a respiratory illness, leading to pneumonia or acute respiratory distress syndrome in severe cases. Although SARS-CoV-2 most commonly impacts the respiratory system, as the months of the pandemic have gone on, it has become clear that COVID-19 can impact various other systems of the body. Patients have presented with gastrointestinal symptoms such as nausea, vomiting, and diarrhea, and SARS-CoV-2 has been identified in the stools of infected patients (3). Renal and cardiac complications have been described as well (4). Dermatologic signs, such as urticaria and “COVID toes,” have been identified in infected patients (5,6). Patients with COVID-19 have been found to have coagulopathy, leading to venous and arterial
thrombosis (7). One study found the incidence of venous and arterial thrombotic events to be greater than 30% in hospitalized COVID-positive patients (8).

Patients infected with SARS-CoV-2 often have neurologic manifestations of disease. According to one retrospective study of 214 COVID-positive patients in Wuhan, China, 36% of patients had neurologic signs and symptoms (9). An even higher number, 57.4%, was reported in a study performed in Spain (10). Among these are nonspecific symptoms such as headache, anosmia, ageusia, dizziness, and myalgias, which seem to be common even in milder cases of COVID-19 (10–14). Importantly, headache and other neurologic symptoms may sometimes manifest early in COVID-19 before respiratory symptoms or chest imaging abnormalities are noted (9). In addition, more severe neurologic manifestations have been reported, including stroke, encephalopathy, encephalitis, myelitis, neuropathies, and rhabdomyolysis (15). It is worth highlighting the significant number of COVID-positive patients who have developed ischemic stroke. According to a retrospective study performed in Wuhan, China, of 219 patients with the novel coronavirus, 4.6% experienced acute ischemic stroke (16). Alarming, young patients are at increased risk for stroke when infected with COVID-19. A case series performed at a New York City hospital described 5 patients younger than the age of 50 who presented with large vessel ischemic strokes and tested positive for COVID-19, during a 2-week period (17). This represented a 7-fold increase in the previous rate of large vessel ischemic stroke in young patients. At the same hospital, during the previous 12 months, the average number of patients younger than 50 years of age who presented with large vessel strokes during any 2-week interval was much lower, at 0.73. In addition, a number of cases of COVID-induced Guillain–Barré syndrome have been documented in the literature (18–21).

It is well documented that COVID-19 has the ability to impact the eyes. Eye pain is a common early symptom of coronavirus infection (22); although, it is unclear whether this is due to direct eye involvement or represents a nonspecific manifestation of disease, as headache for instance is also common, with reported frequency in different studies ranging from 6.5% to 70.3% (23) and a recent meta-analysis putting it at 12% (24). Early in the pandemic, “conjunctival congestion” was noted in patients in Wuhan, China (14). One retrospective study of COVID-positive patients in Hubei province, China, found that one-third of patients with COVID-19 had ocular abnormalities consistent with viral conjunctivitis, including conjunctival hyperemia, chemosis, and epiphora (25). Conjunctival swabs and tear samples of infected patients have tested positive for SARS-CoV-2, and the virus can be transmitted through contact with mucosal membranes (26). It is currently unclear whether unique retinal findings can be identified in COVID-positive patients, although notably, SARS-CoV-2 entry proteins ACE2 and Tmprss2 are expressed in small amounts in the human retina (27). A study by Marinho and colleagues described 12 COVID-positive patients who were found to have hyper-reflective lesions at the level of the ganglion cell and inner plexiform layers on the OCT macula, 4 of whom had cotton wool spots and retinal hemorrhages on fundus examination (28). However, this study has generated significant controversy, as other groups have argued that common and normal OCT anatomic findings were misinterpreted in this report (29–31).

Given the ability of the novel coronavirus to impact the neurologic system and the eye, it should not come as a surprise that patients have presented with neuro-ophthalmic signs and symptoms as well. The purpose of this article is to describe the afferent and efferent neuro-ophthalmic conditions associated with COVID-19 documented in the literature thus far.

**AFFERENT NEURO-OPHTHALMIC COMPLICATIONS**

Afferent neuro-ophthalmic complications associated with coronavirus disease 19 include optic neuritis, papillitis, papilledema, visual disturbance associated with posterior reversible encephalopathy syndrome (PRES), and vision loss caused by stroke.

Whether the optic pathways can be directly infected by SARS-CoV-2 is currently unclear. However, in animal models, there is past documentation of optic neuritis caused by coronaviruses. In animal species (murine and feline), coronaviruses can cause severe ocular and neuro-ophthalmic disease, including anterior uveitis, retinitis, vasculitis, and optic neuritis (32). A 2008 experiment by Shindler et al used the murine coronavirus MHV-A59 to create a viral-induced optic neuritis model (33).

**Optic Neuritis**

Several cases of COVID-associated optic neuritis have been documented in the literature thus far. Zhou et al published a case report of a young man who developed myelin oligodendrocyte glycoprotein (MOG) antibody–associated optic neuritis, in the setting of COVID-19 infection (34). This 26-year-old patient presented with the complaint of bilateral vision loss, which was preceded by a dry cough, bilateral pain with eye movements, numbness on the soles of his feet, and neck discomfort with forward flexion. On examination, he had hand motion (HM) acuity in the right eye and 20/250 in the left eye. Disc edema was present in both eyes, with retinal hemorrhages in the right eye. MRI orbits showed bilateral enhancement and thickening of his optic nerves, from the globes to their prechiasmal segments. MRI of the spine showed T2 hyperintensities in the cervical and thoracic spinal cord. After a broad work-up, he tested positive for SARS-CoV-2 by nasopharyngeal PCR and also for anti-MOG antibodies in the serum. His treatment consisted of intravenous followed by oral steroids. Within 3
weeks, he had a significant improvement in his vision in both eyes, with resolution of his disc edema. MOG antibody–associated optic neuritis in the setting of COV-ID infection is an example of a parainfectious demyelinating syndrome with a prodromal viral illness. This could be related to molecular mimicry by viral antigens triggering an immune response directed toward central nervous system (CNS) myelin proteins, including MOG (34), although other mechanisms are possible such as targeting of latent autoimmune disease to areas of viral injury. There is a high likelihood that there will be an increased incidence in demyelinating CNS disease as the pandemic continues and more people are infected with the virus.

Novi et al documented a case of a 64-year-old woman who experienced bilateral optic neuritis in the setting of acute disseminated encephalomyelitis (ADEM) associated with COVID infection (35). The patient experienced flu-like symptoms, anosmia, and ageusia, and three weeks later had bilateral vision loss and a sensory deficit in the right leg. She had HM vision bilaterally, as well as behavioral abnormalities, headache, and a positive Babinski sign. MRI brain showed T1 post-Gd enhancing lesions, and MRI spine showed a spinal cord lesion at the T8 level. Lumbar puncture yielded cerebrospinal fluid (CSF) with a lymphocytic pleocytosis, elevated protein, and SARS-CoV-2 positivity. Identiﬁcal immunoglobulin G oligoclonal bands were identiﬁed in the CSF and serum (mirror pattern). She was diagnosed with ADEM, and started on high dose IV steroids and IV immunoglobulin, with signiﬁcant vision improvement.

**Papillophlebitis**

Papillophlebitis, a condition characterized by optic disc edema and venous congestion, has also been associated with COVID-19 infection. Insausti-Garcia et al described the case of a 40-year-old man who presented with a slight decrease in visual field sensitivity of the left eye. Six weeks prior, he had experienced high fever, cough, and myalgias. On examination, he was 20/20 in both eyes, with left disc edema, dilated and tortuous retinal vessels, and retinal hemorrhages (36). On visual field testing, there was diffuse decrease in left eye sensitivity, with a central scotoma, and increase in the size of the blind spot. A thorough work-up was performed, revealing antibodies to SARS-CoV-2 and persistently elevated coagulation system markers: D-dimer, fibrinogen, and C-Reactive Protein (CRP). It is likely that COVID-associated coagulopathy and inﬂammation predisposed the patient to papillophlebitis.

**Papilledema**

There have been reports of patients who have developed papilledema in the setting of COVID-induced intracranial hypertension (IIH). Verkuil et al documented the case of a 14-year-old-girl who was diagnosed with secondary pseudotumor cerebri syndrome (PCS), in the setting of multisystem inflammatory syndrome in children, a pediatric condition associated with SARS-CoV-2 infection (37). During her hospitalization, she was found to have new esotropia, sixth nerve palsy, bilateral papilledema, and left disk hemorrhages. Lumbar puncture demonstrated an elevated opening pressure of 36 cm H2O. MRI/MRV of the brain showed findings consistent with increased intracranial pressure: globe ﬂattening, dilatation of the optic nerve sheaths, mild ﬂattening of the pituitary gland, and narrowing of the transverse venous sinuses. She tested positive for SARS-CoV-2 antibodies. The mechanism for the IIH in this patient was unclear.

A recent report by Mukharesh et al describes 7 postpubertal patients with new or worsening without venous sinus thrombosis or meningoencephalitis (38). Potential mechanisms by which PCS could develop in patients with COVID-19 include dysregulation of CSF dynamics in the setting of choroid plexus epithelium and meningeal infection (39,40) or quarantine-related lifestyle modiﬁcations promoting weight gain. However, in this case series, most patients developed new PCS or worsening of pre-existing idiopathic IIH in conjunction with or shortly after acquiring COVID-19 without signiﬁcant recent weight gain (or even after recently having lost substantial weight).

Two other recent articles also report cases of PCS developing secondary to COVID-19 infection (41,42). Unfortunately, the study by Thaller et al mentions COVID-19–associated PCS but does not provide further detail (41). In the study by Silva et al, 13 patients underwent lumbar puncture for new persistent headache associated with COVID-19 infection; of these, opening pressure greater than 20 cmH2O was present in 11 patients, and in 6 patients it was greater than 25 cmH2O, none of whom had a CSF pleocytosis or protein elevation (42). These patients were not systematically evaluated from a neuro-ophthalmic perspective, but papilledema was noted in 2 individuals (Figs. 1 and 2).
Recognition that SARS-CoV-2 has tropism for the choroid plexus epithelium suggests a biologically plausible mechanism by which viral infection may dysregulate CSF hydrodynamics (39,40). The vulnerability of choroid plexus epithelium, meninges, and brain vasculature may be attributable to their expression of SARS-CoV-2 entry proteins ACE2 and TMPRSS2. In addition, COVID-19–infected CSF barrier cells display an altered proinflammatory transcription profile not seen in healthy controls or a comparator case with influenza (40). The above-mentioned cases did not involve cerebral venous sinus thrombosis; however, coagulopathy and resultant cerebral venous sinus thrombosis (CVST) have been identified in COVID-positive patients (43,44). Papilledema could be seen in patients with COVID-associated CVST.

Posterior Reversible Encephalopathy Syndrome
Visual disturbance secondary to PRES has been observed in association with COVID-19. Ghosh et al documented the case of a 33-year-old woman who experienced hallucinatory palinopsia, in the setting of COVID-associated PRES (45). She complained of after images, such as a television news anchor who appeared abruptly in her visual field when she was looking at a wall and persisted for 5–15 minutes. On a thorough work-up, she was only positive for SARS-CoV-2. MRI of the brain showed T2 and FLAIR hyperintensity involving the bilateral parieto-occipital regions and bilateral frontal, parietal, and temporal gray–white interfaces, indicative of PRES. PRES has been reported in cases of COVID-19, but the pathogenesis remains unclear (45).

Stroke
Vision loss caused by stroke is another afferent system complication documented in association with COVID-19 infection. Cyr et al published 2 cases of COVID-positive patients with severe bilateral vision loss caused by cerebrovascular accidents (CVAs) (46). In one case, a 61-year-old diabetic man developed fever, myalgias, and cough, and 5 days later, he had sudden, bilateral, painless vision loss with no light perception (LP) vision in both eyes. He had bilateral ground glass opacities on chest X-ray. On computed tomography (CT) of the head without contrast, he had loss of gray–white matter differentiation, indicating cytotoxic edema in the bilateral occipital territories, and bilateral occipital ischemic stroke. He tested positive for SARS-CoV-2 and passed away 3 days after admission. In the second case, a 34-year-old woman with a history of systemic lupus erythematosus, hypertension, end-stage renal disease on hemodialysis, and prior CVA developed pneumonia and was found to be COVID-positive. She was admitted to the hospital, and during the second week of her stay, she experienced sudden, bilateral, painless vision loss. She had LP vision in both eyes. MRI of the brain without contrast showed an acute infarct in the right frontal lobe, along the territory of the right middle cerebral artery, acute left posterior temporal–occipital infarction after the posterior cerebral artery, and chronic infarction in the right temporal–parietal and bilateral medial occipital lobes. On MRA of the brain, she had an occlusion of the M2 branches of the right middle cerebral artery. Both of these cases illustrate the fact that patients with pre-existing endothelial dysfunction may have increased risk for thrombotic occlusive events, in the setting of COVID-19 infection. Bondira et al described a patient complaining of inability to read associated with a right homonymous hemianopsia and a subtle left superior homonymous quadrantanopsia resulting from bilateral occipital lobe infarctions in the setting of COVID-19 infection (47).

Efferent Neuro-ophthalmic Complications
Efferent neuro-ophthalmic complications associated with COVID-19 include cranial neuropahties, Miller Fisher syndrome, Adie’s tonic pupil, ocular myasthenia gravis (MG), nystagmus, and other eye movement disorders.

Cranial Neuropathies
There are a number of reports of patients who presented with new onset sixth nerve palsies, developed in the setting of COVID-19 infection. Dinkin et al reported the case of a 71-year-old woman with a history of hypertension who presented with diplopia and was found to have right eye abduction...
deficits consistent with a sixth nerve palsy (48). Because of her cough and fever, she was sent to the emergency department (ED), where she was found to be febrile, hypoxemic, with bilateral airspace opacities on chest X-ray. MRI showed enhancement of her optic nerve sheaths and posterior Tenon capsules. Her nasal swab was positive for SARS-CoV-2. She experienced gradual improvement of her diplopia over a 2-week period (Fig. 3). Falcone et al reported a similar case of a 32-year-old man who experienced new onset binocular, horizontal diplopia, which began 3 days after upper respiratory symptoms (49). He tested positive for SARS-CoV-2, subsequently developed acute hypoxemic respiratory failure and was hospitalized. On discharge, 5 weeks later, his diplopia persisted. On examination, he had a complete left eye abduction deficit, consistent with left sixth nerve palsy. MRI orbits showed an atrophic left lateral rectus muscle, which displayed T2 hyperintensity.

Greer et al reported 2 cases of patients who presented with sixth nerve palsies, in the setting of COVID infection (50). One patient was a 43-year-old woman with a history of well-controlled hypertension who presented to the ED with acute onset binocular, horizontal diplopia. Before her presentation, she had experienced 3 days of fever, cough, fatigue, and lightheadedness. On examination, she had a right eye abduction deficit. She tested positive for SARS-CoV-2. MRI of the brain and orbits was unremarkable. The second patient was a 52-year-old man with a history of well-controlled hypertension who complained of new horizontal, binocular diplopia. He also reported concurrent fever, anosmia, ageusia, myalgias, headache, and fatigue. New York City was experiencing the peak of its pandemic, and hospitals were overwhelmed with COVID patients at the time; consequently, patients were encouraged to remain at home unless experiencing distress. As a result, this patient was evaluated by telemedicine and found to have an isolated sixth nerve palsy on self-performed alternate cover testing. By the time of his 6 day follow-up, his diplopia, fever, myalgias, and fatigue had resolved, but his anosmia and ageusia persisted.

**Miller Fisher Syndrome**

Miller Fisher syndrome, a condition characterized by ophthalmoplegia, loss of tendon reflexes, and acute onset ataxia, has been observed in a number of patients diagnosed with COVID-19. In a case documented by Gutierrez-Ortiz et al (51), a 50-year-old man presented to an ED with acute onset vertical diplopia, perioral paresthesias, and gait instability. Five days before presentation, he had fever, cough, anosmia, ageusia, headache, malaise, and low back pain. On examination, he had a broad-based ataxic gait and absent deep tendon reflexes in upper and lower limbs. He also had a right hypertropia, right eye limitations in adduction and depression, and left nystagmus, consistent with a right internuclear ophthalmoplegia and right fascicular oculomotor palsy. He tested positive for SARS-CoV-2, and bloodwork showed antibodies to the ganglioside GD1b complex. He was diagnosed with COVID-associated Miller Fisher syndrome and treated with intravenous immunoglobulin, with dramatic improvement in his cranial neuropathies and ataxia. In a case described by Dinkin et al (48), a 36-year-old man presented with left ptosis, diplopia, and bilateral distal leg paresthesias 4 days after the onset of fever, cough, and myalgias. A partial left oculomotor palsy and bilateral abducens palsies were found on examination, as were lower extremity hyporeflexia and hypesthesia, and ataxia. Eye movements significantly worsened the next day. Nasal swab for SARS-CoV-2 PCR was positive. MRI revealed enhancement, T2 hyperintensity, and enlargement of the left oculomotor nerve. There was partial improvement after IV immunoglobulin for presumed Miller Fisher syndrome, although a ganglioside panel was negative.

Reyes-Bueno et al (52) reported the case of a 51-year-old woman who developed diarrhea, cough, and throat pain after contact with a COVID-positive individual. Two weeks later, she developed pain in all 4 limbs, followed by weakness in the lower limbs, loss of the ability to walk, and binocular diplopia. On examination, she had a left sixth nerve palsy, global areflexia, weakness, and SARS-CoV-2 antibodies in the serum. She was diagnosed with Miller Fisher Syndrome.

*FIG. 3.* A 71-year-old woman presented with 2 days of painless diplopia and was found to have a right abducens palsy. She also reported 3 days of fever and cough and tested positive for COVID-19. She was admitted to the hospital for 6 days and then discharged home. **A.** Two weeks after hospitalization, an efferent examination was performed by televisit on Zoom. The center image shows a cross cover test (with assistance from her husband). Note the limitation of abduction in right gaze. **B.** Coronal T1 postcontrast MRI revealed enhancement within the optic nerve sheaths (yellow arrows), more prominently on the right. The abducens palsy resolved within 4 months.
Fisher syndrome in the setting of COVID-19 infection, treated with IV immunoglobulin, with improvement of her diplopia, pain, and facial and limb paresis.

**Myasthenia Gravis**

There are reports of MG with prominent ocular symptoms manifesting in association with COVID infection. Restivo et al documented 3 cases of middle-aged patients with no history of MG who developed diplopia and muscular fatigability, one of whom also noted bilateral ptosis. All patients demonstrated decrement on repetitive nerve stimulation (2 of the facial nerve) and elevated acetylcholine receptor antibody levels (53). Two of the patients developed dysphagia, one of whom developed respiratory failure requiring mechanical ventilation. Thymoma was excluded in all 3 patients. Improvement was observed with prednisone and pyridostigmine in the mildest case, with IVIG in the second case and with plasmapheresis in the patient requiring ventilation.

**Adie’s Pupils**

Pupillary abnormalities have been observed in COVID patients. Ortiz-Seller et al (54) reported the case of a patient who developed bilateral Adie’s pupils, in the setting of COVID infection. A 51-year-old woman tested positive for SARS-CoV-2 after experiencing fever, cough, and headache. Two days after onset of symptoms, she developed retro-orbital pain and reading impairment. On ophthalmic examination, she had poorly reactive pupils, light-near dissociation, and dilation that were more pronounced in bright illumination. In addition, she had yellowish creamy chorioretinal lesions indicative of a new chorioretinitis. On prior eye examination, she had normal pupillary responses and fundus examination. Dilute 0.1% pilocarpine was placed into both eyes, and constriction of both pupils demonstrated a hypersensitive response, indicating bilateral Adie’s pupils. A thorough work-up was only positive for SARS-CoV-2. After she was started on prednisone, she experienced full recovery within a few weeks. Past studies have shown that viral infections, such as herpes zoster, chicken pox, measles, influenza, and viral hepatitis, can also cause Adie’s pupils, presumably through direct infection of the ciliary ganglion (55,56). Some authors postulate that viral infection can lead to denervation of the postganglionic parasympathetic supply to the pupillary sphincter (54).

**Nystagmus and Other Eye Movement Disorders**

Nystagmus and eye movement disorders have been observed in patients with COVID infection. Ayuso et al (57) reported the case of a 72-year-old woman who developed downbeat nystagmus in the setting of rhombencephalitis associated with COVID infection. She was admitted to the hospital with delirium and fever, found to have SARS-CoV-2 associated pneumonia, and later developed oscillop-
<table>
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<th>Mechanism of Disease</th>
<th>Clinical Features</th>
<th>Possible Examination Signs</th>
<th>Possible Study Results</th>
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<tr>
<td>Triggered autoimmunity/immunologic upregulation</td>
<td>Optic neuritis ± acute disseminated encephalomyelitis (ADEM)</td>
<td>Vision loss</td>
<td>MRI brain—optic nerve enhancement (long segment) ± bilateral T2 and FLAIR white matter lesions + anti-MOG antibodies CSF lymphocytic pleocytosis and elevated protein</td>
</tr>
<tr>
<td>Miller Fisher syndrome</td>
<td>Ophthalmoplegia</td>
<td>Loss of tendon reflexes Ataxia Weakness in limbs</td>
<td>+ antiganglioside antibodies Elevated CSF protein MRI brain enhancement and enlargement of cranial nerves</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Muscle fatigability Respiratory failure</td>
<td>+ACh receptor antibodies or MusK antibodies Decrement on repetitive nerve stimulation</td>
<td></td>
</tr>
<tr>
<td>Rhombencephalitis or cerebellitis</td>
<td>Downbeat or upbeat nystagmus Ocular flutter Opsoclonus Smooth pursuit impairment Ataxia Altered sensation in extremities</td>
<td>+ antiganglioside antibodies MRI brain—hypointense lesions in the brainstem and cerebellum</td>
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<tr>
<td>Pediatric multisystem inflammatory syndrome w/associated intracranial hypertension</td>
<td>Papilledema Esotropia</td>
<td>Elevated inflammatory markers Multisystem involvement (2 or more organ systems) Lumbar puncture—elevated opening pressure MRI brain—dilatation of optic nerve sheaths, globe flattening, and partially empty sella MRV head—transverse venous sinus stenosis</td>
<td></td>
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<tr>
<td>Vasodilation and vascular permeability</td>
<td>Ischemic stroke</td>
<td>Vision loss</td>
<td>MRI brain—acute temporal, parietal, or occipital infarct</td>
</tr>
<tr>
<td>Endothelial dysfunction and/or coagulopathy</td>
<td>Ischemic stroke</td>
<td>Vision loss Visual field defects (homonymous hemianopia)</td>
<td>MRI brain—acute temporal, parietal, or occipital infarct MRI head—arterial occlusion</td>
</tr>
<tr>
<td>Cerebral venous sinus thrombosis</td>
<td>Papilledema</td>
<td>MRI brain</td>
<td>MRA head—loss of high flow signal from sinus</td>
</tr>
<tr>
<td>Papillophlebitis</td>
<td>Disc edema Dilated, tortuous retinal vessels Venous congestion Visual field defects</td>
<td>Elevated D-dimer, fibrinogen, and CRP</td>
<td></td>
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<tr>
<td>Posterior reversible encephalopathy syndrome (PRES)</td>
<td>Visual field loss (homonymous hemianopia)</td>
<td>MRI brain—T2 and FLAIR hyperintensity involving parieto-occipital regions and vasogenic edema</td>
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</table>
can cause upregulation and misdirection of adaptive immune responses. The documented anti-ganglioside antibodies in Miller Fisher Syndrome, the anti-MOG-antibodies in MOG-associated optic neuritis (and other reported cases of transverse myelitis associated with both MOG and aquaporin 4 antibodies after COVID-19 infection), and anti-AChR antibodies in MG demonstrate the fact that SARS-CoV-2 has the potential to stimulate autoantibody production (34). Garvin et al (64) proposed the idea that a bradykinin storm is the mechanism by which systemic damage takes place in COVID patients. According to this theory, SARS-CoV-2 causes levels of ACE to decrease in cells, whereas ACE2 increases, which in turn increases the levels of bradykinin in cells. The resultant bradykinin storm promotes vasodilation and vascular permeability, which causes swelling and inflammation of surrounding tissues. In severe cases of COVID, fluid that has leaked into the lungs could combine with excess hyaluronic acid, creating a gelatinous substance that prevents oxygen uptake and carbon dioxide release, leading to respiratory

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Direct viral neurotropism</td>
<td>New or worsening IIH (Direct infection of choroid plexus)</td>
<td>Papilledema Esotropia</td>
<td>MRI brain—dilated, tortuous optic nerve sheaths; globe flattening; and empty sella MRV head—transverse venous sinus stenosis Elevated opening pressure on lumbar puncture</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>Ptosis Extraocular motility deficits</td>
<td>MRI brain—cranial nerve enhancement or extraocular muscle atrophy</td>
<td></td>
</tr>
<tr>
<td>Adie’s pupil</td>
<td>Poor pupillary constriction to light, light-near dissociation</td>
<td>Constriction of pupils with dilute 0.1% pilocarpine</td>
<td></td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; IIH, intracranial hypertension.

**TABLE 2.** Symptoms that preceded neuro-ophthalmic conditions and clinical signs noted on presentation

<table>
<thead>
<tr>
<th>Neuro-Ophthalmic Condition</th>
<th>Symptoms and Clinical Signs</th>
</tr>
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<tbody>
<tr>
<td>Optic neuritis ± ADEM</td>
<td>Dry cough, flu-like symptoms, anosmia, and ageusia</td>
</tr>
<tr>
<td>Papillophlebitis</td>
<td>Fever, cough, and myalgias; elevated D-dimer, fibrinogen, and C-Reactive Protein (CRP)</td>
</tr>
<tr>
<td>MISC-C w/intracranial hypertension</td>
<td>Fever, dyspnea, respiratory failure, leukopenia, increased C-Reactive Protein (CRP) and fibrinogen, and CT chest with ground glass opacities</td>
</tr>
<tr>
<td>PRES w/visual disturbance</td>
<td>Fever, myalgias, cough, tachypnea, respiratory failure; elevated White Blood Cells (WBC), Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), Lactate Dehydrogenase (LDH), C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR); and Chest X-Ray with ground glass opacities</td>
</tr>
<tr>
<td>Stroke w/vision loss</td>
<td>Fever, myalgias, cough, tachypnea, respiratory failure; elevated White Blood Cells (WBC), Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), Lactate Dehydrogenase (LDH), C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR); and Chest X-Ray with ground glass opacities</td>
</tr>
<tr>
<td>Cranial nerve 6 palsy</td>
<td>Fever, cough, anosmia, ageusia, myalgias, hypoxemia, respiratory failure, and Chest X-Ray with airspace opacities</td>
</tr>
<tr>
<td>Miller Fisher syndrome</td>
<td>Fever, cough, myalgias, lymphopenia, and elevated C-Reactive Protein (CRP)</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Fever, CT with bilateral interstitial pneumonia, and respiratory failure</td>
</tr>
<tr>
<td>Adie’s pupils</td>
<td>Fever and cough</td>
</tr>
<tr>
<td>Rhombencephalitis w/nystagmus</td>
<td>Fever, cough, myalgias, dyspnea, tachypnea, and CXR with bilateral interstitial pneumonia; elevated C-Reactive Protein (CRP), Gamma-Glutamyl Transferase (GGT), and Alanine Transaminase (ALT)</td>
</tr>
<tr>
<td>Encephalitis w/saccadic intrusions</td>
<td>Fever, acute respiratory distress syndrome, CSF lymphocytic pleocytosis, and elevated protein</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; CT, computed tomography; MOG, myelin oligodendrocyte glycoprotein; PRES, posterior reversible encephalopathy syndrome.
Proponents of this hypothesis also assert that a bradykinin storm could cause cardiac dysfunction and neurologic issues including encephalopathy, dizziness, headache, ischemia, and cognitive impairment.

Endothelial dysfunction and coagulopathy both contribute to the development of neurologic disease experienced by COVID-positive patients. Angiotensin-converting enzyme 2 (ACE2) is the main functional receptor for SARS-CoV-2 and present on multiple structures, including the brain, heart, nasopharynx, lungs, arteries, and veins (65). Binding of the SARS-CoV-2 spike protein to cell membranes is necessary for cellular entry (66). The endothelial dysfunction that accompanies COVID infection may be explained by the uniquely high density of ACE2 receptors present on endothelial cells (65). The significant presence of these receptors causes endothelial cells to be particularly vulnerable to SARS-CoV-2 binding, and there is subsequent impairment of the function of arteries and veins. Endotheliitis and endothelial alterations result in microvascular dysfunction, including vasoconstriction, ischemia, tissue edema, and a procoagulant state (36). In addition, the cytokine storm hypothesis suggests that elevated cytokine levels caused by COVID infection cause a systemic inflammatory response syndrome, which in turn activates the coagulation cascade, generating a hypercoagulable state (36,65). As a result, patients are at risk for venous and arterial thrombotic events such as acute pulmonary embolism, deep-vein thrombosis, ischemic stroke, myocardial infarction, and/or systemic arterial embolism (8). The contribution of the systemic inflammatory response has led to the use of corticosteroids in patients with COVID-19, with promising results in hospitalized patients (67).

Proponents of the direct viral neurotropism hypothesis suggest that SARS-CoV-2 directly invades neuronal tissues. ACE2, the main functional receptor for SARS-CoV-2, is present in the brain (9). If SARS-CoV-2 directly enters the brain, it could do so hematogenously, by infection of the choroid plexus or meninges, or by spread through the olfactory nerves. Through the study of animal models, researchers learned that other coronaviruses, SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV), may enter the brain through the olfactory nerves and later spread to other regions including the thalamus and brainstem (68). Some researchers hypothesize that the anosmia frequently experienced by COVID patients is evidence of direct viral invasion of the nasal mucosa, by ACE2 receptors on the basal layer of the nasal epithelium, with subsequent viral extension to the olfactory bulb (69). However, gene expression analysis highlights an issue with this theory: ACE2 and transmembrane serine protease 2, proteins involved in SARS-CoV-2 cellular infection, are expressed in the supportive cells of the olfactory epithelium, but not the olfactory sensory neurons (70). Therefore, anosmia does not prove direct CNS invasion by SARS-CoV-2. Research continues on the mechanisms of SARS-CoV-2–induced neurologic disease.

**CONCLUSION**

As a scientific community, we are continuing to learn more about COVID-19’s pathogenesis, clinical presentation, natural course, and management in real time. Our knowledge of neuro-ophthalmic manifestations of COVID-19 also continues to evolve.

It is important that COVID-19 is kept on the differential when evaluating neuro-ophthalmic patients during the pandemic. When patients present with new neuro-ophthalmic complaints, such as vision decrease, eye pain, diplopia, or changes in eye movements, viral testing should be considered. If fever or respiratory symptoms are also present, COVID testing is highly advisable. Thorough neurologic work-up should be pursued in patients.
including MRI brain, lumbar puncture with opening pressure and CSF analysis, and autoantibody panels. The goal of this comprehensive evaluation is to accurately characterize neurologic disease associated with viral infection and clarify mechanisms of disease. The current literature shows that patients who present with new optic neuritis, papillophlebitis, papiledema, PRES, stroke, cranial neuropathy, Miller Fisher Syndrome, Guillain–Barré syndrome, Myasthenia Gravis, Adie’s pupils, nystagmus, or other eye movement abnormalities may have an underlying COVID-19 diagnosis. Proposed mechanisms of COVID-associated neurologic disease include immunologic upregulation, vasodilation and vascular permeability, endothelial dysfunction, coagulopathy, and direct viral neurotropism. Our review includes cases of neuro-opthalmic disease that occurred in the setting of symptomatic COVID-19 infection. Given the timing of the onset of these neuro-opthalmic conditions, we have high suspicion that COVID-19 infection contributed to their development. Most of the cases of the neuro-opthalmic conditions we described were closely preceded by classical COVID-19 symptoms such as fever and cough. Admittedly, although we suspect that these neuro-opthalmic diseases were manifestations of COVID-19 infection, this is not known with absolute certainty. It is difficult to prove a true association, let alone a direct causal link, between these entities and COVID-19. As the pandemic becomes more and more widespread, there will undoubtedly be some cases of neuro-opthalmic disease that have a coincidental relationship with COVID-19 infection. Physicians should remain attentive to the timing of the onset of neuro-opthalmic symptoms, in relation to the onset of COVID-19 symptoms, when working to identify cases that are truly associated. To confirm relationships between neuro-opthalmic conditions and COVID-19, physicians can seek out proof of SARS-CoV-2 within the nervous system (i.e., CSF analysis). On a large scale, population studies can investigate the prevalence of neuro-ophthalmic manifestations of COVID-19. As the pandemic becomes more and more prevalent in a large number of people who have been infected with COVID-19 worldwide, valuable research will undoubtedly continue over the next several years, including epidemiologic studies that provide the prevalence of neuro-opthalmic manifestations of COVID-19.

We do not yet know the long-term neuro-opthalmic impacts of the COVID-19 pandemic. The medical community is realizing that although COVID was previously conceptualized as an acute viral illness, many patients are experiencing unexpected, chronic symptoms, which have been coined “long COVID” (71). It is possible that we may also see neuro-ophthalmic complications of COVID that persist, months after initial viral infection. Nonetheless, as more of the population is vaccinated against the virus over time, we are hopeful that the suffering caused by the COVID-19 pandemic will soon cease.

REFERENCES


