Neuroradiologic Imaging of Neurologic and Neuro-ophthalmic Complications of Coronavirus-19 Infection

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Background: To review the literature and provide a summary of COVID-19–related neurologic and neuro-ophthalmic complications.

Methods: The currently available literature was reviewed on PubMed and Google Scholar using the following keywords for searches: CNS, Neuro-Ophthalmology, COVID-19, SARS-CoV-2, coronavirus, optic neuritis, pseudotumor cerebri, Acute Disseminated Encephalomyelitis, posterior reversible encephalopathy syndrome (PRES), meningitis, encephalitis, acute necrotizing hemorrhagic encephalopathy, and Guillain-Barré and Miller Fisher syndromes.

Results: Neuroradiologic findings of neurologic and neuro-ophthalmologic complications in relationship to COVID-19 infection were reviewed. Afferent visual pathway–related disorders with relevant imaging manifestations included fundus nodules on MRI, papilledema and pseudotumor cerebri syndrome, optic neuritis, Acute Disseminated Encephalomyelitis, vascular injury with thromboembolism and infarct, leukoencephalopathy, gray matter hypoxic injury, hemorrhage, infectious meningitis/encephalitis, acute necrotizing hemorrhagic encephalopathy, and PRES. Efferent visual pathway–related complications with relevant imaging manifestations were also reviewed, including orbital abnormalities, cranial neuropathy, Guillain-Barré and Miller Fisher syndromes, and nystagmus and other eye movement abnormalities related to rhombencephalitis.

Conclusion: COVID-19 can cause central and peripheral nervous system disease, including along both the afferent and efferent components of visual axis. Manifestations of disease and long-term sequelae continue to be studied and described. Familiarity with the wide variety of neurologic, ophthalmic, and neuroradiologic presentations can promote prompt and appropriate treatment and continue building a framework to understand the underlying mechanism of disease.
encephalopathy (2,5,8–16). COVID-19–related central nervous system disease has been broadly categorized by Moonis et al as direct infection by neuroinvasion or endo-
thelioptahy, parainfectious immune response resulting in coagulopathy and cytokine storm, delayed postinfectious immune activation and complications of prolonged, severe illness, though these categories likely overlap and are still under investigation (17).

Review of the neuroradiology of neurologic and neuro-
ophthalmologic disease will be discussed along the afferent
and efferent visual pathway. From the afferent perspective,
these include fundus nodules on MRI, papilledema and
pseudotumor cerebri syndrome, optic neuritis, acute demy-
elinating encephalomyelitis (ADEM), vascular injury with
thromboembolism and infarct, leukoencephalopathy, hem-
orrhage, gray matter hypoxia, infectious meningitis/ ence-
phalitis, acute necrotizing hemorrhagic encephalopa-
thy, and posterior reversible encephalopathy syndrome
(PRES). The neuroradiology of severe cerebral complica-
tions of COVID-19 will be described, although these have
not been well correlated with neuro-ophthalmic sequelae
yet to familiarize readers with their appearance. Efferent
neuro-ophthalmic complications with relevant imaging
include orbital abnormalities, cranial neuropathy,
Guillain–Barré and Miller Fisher syndromes, and nystag-
mus and other eye movement abnormalities related to
rhombencephalitis.

**AFFERENT VISUAL SYSTEM**

**Fundus Nodules on MRI**

In a retrospective study reviewing 129 severely ill patients
with COVID-19 who underwent MRI examinations, Lecler
et al found 9 patients (7%) had T2/Fluid-attenuated
inversion recovery image (FLAIR) hyperintense, nonen-
hancing nodules in the posterior globe. One patient had a
central artery occlusion identified on fluorescein angiogram,
and 1 had keratitis. Although the etiology of these nodules
is unknown, the authors suggest an ophthalmic examination
is warranted (7).

**Papilledema**

Several publications report new-onset papilledema during
COVID-19 infection in conjunction with new or worsened
pseudotumor cerebri (18–20). Imaging findings include
dilated, tortuous optic nerve sheaths and an empty sella
(21). The mechanism may be unique to COVID-19 infec-
tion because many patients lacked classic risk factors,
including weight gain or exposure to tetracyclines or vita-
min A derivatives. In addition, Verkuil et al described a 14-
year-old girl diagnosed with COVID-19–related multisys-
tem inflammatory syndrome in children who developed
secondary pseudotumor cerebri. A brain MRI/MR
venogram suggested increased intracranial pressure, and
lumbar puncture confirmed this with opening pressure of
36 cmH2O (22). Several hypotheses for the development of
pseudotumor cerebri have been postulated. SARS-CoV-2
may directly dysregulate cerebral spinal fluid (CSF) hydro-
dynamics, as the virus has a choroid plexus epithelial, men-
ingeal, and brain vasculature tropism (cells which express
SARS-CoV-2 entry proteins angiotensin converting enzyme
2 [ACE2] and transmembrane protease serine 2
[TMPRSS2]). Choroid plexus epithelial cell tropism has
been demonstrated in vitro (23,24). COVID-19–infected
CSF barrier cells also display a proinflammatory transcrip-
tion profile not seen in healthy controls or in comparison
with influenza (24).

COVID-19–related cerebral venous thrombosis from
hypercoagulability has been reported but is less common
than arterial thrombosis (17,25). Cavalcanti et al reported
3 young patients with cerebral venous thrombosis, 2 of whom
presented with intraparenchymal hemorrhage from venous
infarct who were not candidates for thrombectomy. The
superficial and deep venous systems were involved. One
patient demonstrated a hyperdense superior sagittal sinus on
a noncontrast head computed tomography (CT) and non-
filling of the sinus and several cortical veins on CT venogram
and was brought to angiography for thrombectomy in the
setting of rapid decompensation. Despite radiographically
satisfactory thrombectomy and initial neurologic improve-
ment, the patient died from cardiac arrest hours later (26).

**Optic Neuritis and Acute Disseminated
Encephalomyelitis (ADEM)**

Multiple cases of COVID-19–related optic neuritis have
been reported in the literature (Fig. 1). Zhou et al described
a 26-year-old man with flu-like symptoms, bilateral vision
loss, pain with eye movement, neck discomfort with for-
ward flexion, and numbness on the soles of both feet. Orbital
MRI revealed enlargement and enhancement of retrolublar,
intracanalicular, and intracranial optic nerves. Cervicothoracic
MRI showed multiple intramedullary T2 hyperintensity
foci. Nasopharyngeal reverse transcriptase polymerase
chain reaction (RT-PCR) testing confirmed infection,
and myelin oligodendrocyte glycoprotein antibo-
dies were identified. The authors suggested a parainfec-
tious demyelinating syndrome (27). Other cases of optic
neuritis have been reported with aquaporin-4 antibodies
(5,28).

Optic neuritis has also been reported in COVID-19–
related ADEM. Novi et al described a 64-year-old woman
with bilateral vision loss and right lower extremity sensory
loss. MRI showed optic nerve T2/short tau inversion
recovery (STIR) hyperintensity, multiple enhancing paren-
chymal lesions, and a T2 hyperintense, enhancing cord
lesion at T8. CSF analysis revealed a lymphocytic pleocy-
tosis, elevated protein, and SARS-CoV-2 PCR positivity.
Identical immunoglobulin-G oligoclonal bands were
identified in the CSF and serum, and a diagnosis of ADEM was made (29).

Parsons et al reported a 51-year-old woman with COVID-19 infection, intubated and sedated for 18 days, and nonresponsive on sedative weaning (Glasgow Coma Scale = 3) who had flaccid muscle tone and depressed deep tendon reflexes. A brain MRI on hospital day 24 demonstrated T2/FLAIR hyperintense foci in the deep and juxta-cortical white matter, some of which demonstrated faint reduced diffusivity and enhanced, minimal interventricular hemorrhage. CSF analysis was negative for viral RNA, and 4 oligoclonal bands were present in CSF and serum. The patient improved after 5 days of intravenous steroids and 5 days of intravenous immunoglobulin (IVIg) and was diagnosed with ADEM. Repeat MRI examinations showed slowly progressive involvement of the deep white matter and resolution of restricted diffusion. This report illustrated that ADEM should be considered a treatable cause of profound encephalopathy in COVID-19 infection (30).

Vascular Injury, Thromboembolism, and Infarct

Early in the pandemic, acute thromboembolic infarcts were the most recognized severe neurologic sequela of COVID-19. A retrospective study of the Wuhan outbreak showed the incidence of stroke in hospitalized patients approached 5%, and the youngest patient was 55-year-old (31). In April 2020, the New England Journal of Medicine reported large-vessel strokes in 5 patients 33–49 years old, markedly younger than the typical cohort for this disease (10). In a retrospective study of 3,218 patients admitted for COVID-19 infection to New York City hospitals, Jain et al found the incidence of stroke to be 1.1%. Of the 3,218 patients, 38 neuroimaging studies were positive, including 17 large infarcts, 9 lacunar infarcts, and 9 hemorrhagic strokes. Forty-seven percent of patients with large infarcts and 55.5% of patients with hemorrhagic infarcts died during hospitalization. Direct viral injury and a proinflammatory state have been hypothesized as mechanisms of vascular injury. The spike binding protein of the SARS-CoV-2 virus has a strong affinity for the angiotensin-converting enzyme receptor on many human cell types, including the vascular endothelium and may cause direct injury (32). In addition to viral endotheliopathy, proinflammatory hypercoagulability even without cytokine storm can result in thrombus formation. Patients with COVID-19 thromboembolism may have a high clot burden within the great vessels, pulmonary arteries, and lower extremity veins (Moonis). Acute thromboembolic disease is responsible for large-vessel occlusion, branch vessel occlusions, small-vessel occlusions, territorial, watershed and multivessel infarcts (Fig. 2) (13,17,32).

Specific to the visual cortex, Cyr et al reported 2 patients with severe bilateral vision loss from ischemic stroke. One patient infarcted the bilateral visual cortex. The second patient was a young woman with a history of systemic lupus erythematosus complicated by end-stage renal disease requiring hemodialysis, hypertension, and prior infarct. Her pre-existing conditions suggest baseline endothelial dysfunction that may have increased her risk for thrombotic occlusive events during COVID-19 infection (33). Bondira et al described a second case of bioccipital infarcts in a patient after prolonged hospitalization for COVID-19 infection (34).

Posterior Reversible Encephalopathy Syndrome

PRES is clinically characterized by a headache, seizure, altered mentation, and vision changes and radiologically characterized by white matter vasogenic edema in the territory of the posterior circulation, predominantly affecting the parieto-occipital white matter (35). Ghosh et al reported a 33-year-old woman with COVID-19–associated PRES. A brain MRI showed T2/FLAIR hyperintensity predominantly in the parieto-occipital parenchyma (36) (Figs. 1–3).

NEUROIMAGING OF SEVERE COVID-19

Leukoencephalopathy and Microhemorrhage

More subtle examples of vascular injury and thrombosis came to attention after severely ill patients with COVID-19 remained unresponsive after weaning of sedation (13,17,37). In a French observational series, Helms et al reported that of 58 patients admitted to the intensive care unit (ICU) for COVID-19–related acute respiratory distress...
syndrome (ARDS), 14% percent had neurologic symptoms on admission and 67% had neurologic symptoms when sedation was withdrawn (38). Microhemorrhage on susceptibility-weighted imaging (SWI) has become a hallmark of severely ill patients with COVID-19 with neurologic deficits and attributed to microvascular injury (Fig. 3). Conklin et al described microvascular injury in the corpus callosum, subcortical, and deep white matter in 69% of a cohort of 16 ICU patients. Radiologic–pathologic correlation from a single autopsy revealed mixed pathology of microhemorrhage identified on SWI and microscopic ischemic lesions beyond the resolution of MRI. A similar neuroanatomical distribution of microvascular lesions has been seen as a rare complication of cerebral hypoxia in ARDS, high-altitude exposure, and extracorporeal membrane oxygenation. The authors suggest a role for both hypoxic microvascular injury and endothelial dysfunction (39–41).

The leukoencephalopathy identified in severely ill patients is characterized by symmetric and confluent T2/FLAIR hyperintense signal in the deep white matter with sparing of the juxtacortical white matter (Fig. 4) (13,17,37). The etiology is likely multifactorial, and multiple hypotheses have been explored, including microvascular injury from endothelial dysfunction, delayed posthypoxic leukoencephalopathy, critical illness–related encephalopathy, cytokine storm, and infectious and autoimmune encephalitis. Assessment is further clouded by complex clinical courses and multidrug regimens (13,37,39,42). However, hypoxic–ischemic injury has remained a common theme and is supported by radiographic and pathologic findings (37,38,42).

In a retrospective study, Rapalino et al evaluated COVID-19-related leukoencephalopathy with and without diffusion restriction in 27 ICU patients, 26 of whom were intubated on admission. Seven patients (26%) had diffuse, symmetric T2/FLAIR hyperintensity in the deep white matter and middle cerebellar peduncle with faint diffusion restriction, greater than nonrestricting patients. Objective measurements of oxygenation were not statistically different for patients with or without restricted diffusion which seems to contradict the hypoxia hypothesis. However, patients with restricted diffusion had statistically significant higher BMI (36 vs 28 kg/m², P < 0.01) which may have contributed to baseline microangiopathy (42). Before the pandemic, Lampe et al described deep white matter abnormalities in patients with obesity and suggested proinflammatory cytokines may play a role, which, coupled with the predisposition for border-zone ischemia in the deep white matter and the cerebellar peduncles, may account for the greater severity of disease in patients with COVID-19–related leukoencephalopathy with restricted diffusion (42,43).

In a small case series, Rapalino et al used magnetic resonance spectroscopy to compare white matter metabolites of 3 patients with COVID-19 neurologic manifestations and 2 patients with severe neurologic illness not related to COVID-19 infection. The metabolic patterns suggested the possibility of 3 physiologic processes: anaerobic metabolism, neuronal dysfunction and injury, and increased membrane destruction and turn over (42).

In an interesting twist on leukoencephalopathy predisposition, Zhang et al reported the development acute
FIG. 3. A 69-year-old woman with a history of chronic obstructive pulmonary disease hospitalized for COVID-19 pneumonia complicated by ARDS and acute kidney injury requiring hemodialysis presented with left-sided weakness. A. Susceptibility-weighted images of a brain MRI shows hemorrhagic conversion of a right middle cerebral artery stroke stroke (asterisk) and microhemorrhage in the corpus callosum (solid thin arrow), the posterior limb of the internal capsule (arrowhead), and cortex and subcortical white matter (solid thick arrow). B. The same patient also demonstrated interventricular hemorrhage layering in the occipital horns of the lateral ventricles (solid thin arrow) and additional foci of cortical/subcortical microhemorrhage (solid thick arrow).

multi-infarct encephalopathy in a woman with asymptomatic cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The woman had a history of hyperlipidemia and hypertension and presented with fever, dysphagia, dysarthria, and encephalopathy. Her brain MRI showed diffuse subcortical white matter T2/FLAIR hyperintensity in the frontal, parietal, and temporal white matter and deep gray nuclei with patchy restricted diffusion similar in appearance to CADASIL. Subsequent genetic testing revealed a pathogenic variant in the NOTCH3 gene with a heterozygous missense mutation, consistent with CADASIL. The authors suggested this may be a sudden onset of symptomatic CADASIL or a combination of underlying disease and immune response, such as cytokine storm (44).

Global Hypoxic Injury
Acute global hypoxic injury can result in cortical and deep gray matter restricted diffusion (17). Kandemirli et al found that in a cohort of 235 ICU patients, 21% developed neurologic symptoms; 54% of the patients were able to have a brain MRI, and 10 of these patients had cortical restricted diffusion and T2/FLAIR hyperintensity, leptomeningeal enhancement, and cortical microhemorrhage. The authors discussed the differential of hypoxic injury as well as critical illness–related encephalopathy, cytokine storm syndrome, and infectious and autoimmune encephalitis, although the only abnormality in 4 of the 10 CSF analyses was elevated protein alone (13). In a French observational series, a brain MRI was performed on 13 encephalopathic ICU patients after sedation weaning. Of the 11 studies performed with perfusion imaging, all patients demonstrated bilateral frontotemporal hypoperfusion (38). In the retrospective cohort of 3,218 inpatients, Jain et al reported hypoxic ischemic in 5% of the 38 positive neuroimaging studies (32). Visual dysfunction can be part of the neurologic manifestations of severe hypoxia, but this has not been systematically assessed (Figs. 4, 5).

Infectious Meningitis and Encephalitis
Direct neuroinvasion has been hypothesized because of the presence of viral RNA detected using RT-PCR in CSF analysis in isolated cases, although it bears emphasis that this is not a validated test, and CSF RT-PCR was negative in many cases with neurologic disease. Moriguichi et al reported the first case of meningocencephalitis in a 24-year-old man with flu-like symptoms and seizures. A brain MRI showed right mesial temporal T2/FLAIR hyperintensity, and viral RNA was detected in the CSF by RT-PCR (45). Larger cohorts have since questioned direct neuroinvasion; in a prospective study of 606 hospitalized patients with COVID-19 with new neurologic symptoms, no diagnosis of meningocencephalitis was made, and CSF of 18 patients were all negative for viral RNA by PCR (46,47). In the retrospective cohort of 3,218 inpatients, Jain et al (32) reported encephalitis in 1 of the 38 positive neuroimaging studies. On a review of 142 brain autopsies in the literature, mild focal perivascular, parenchymal, and leptomeningeal T-cell infiltrates were described without clear vasculitis or meningocencephalitis (48). Immunohistochemistry staining for antibodies within the brain has been negative with the exception of 1 report by Matschke et al who found viral proteins and RNA within the medulla and vagus and glossopharyngeal nerves. To conclude, infectious meningitis or encephalitis is, at the least, an uncommon presentation of COVID-19 (49).

Poyiadji et al published the first neurologic manifestation of the disease in the United States on March 31, 2020, describing a 58-year-old airline worker with fever, cough, and altered mental status. A brain MRI demonstrated bilateral thalamic and medial temporal FLAIR hyperintensity with mass effect and bithalamic hemorrhage, compatible with acute hemorrhagic necrotizing encephalopathy, a rare and fulminant complication of viral infection related to cytokine storm and breakdown of the blood–brain barrier (50).

EFFERENT VISUAL SYSTEM
COVID-19–related efferent neuro-ophtalmic complications include cranial neuropathies, Miller Fisher syndrome, and nystagmus and eye movement disorders related to brainstem abnormalities (5).
Cranial Neuropathy

Multiple COVID-19–related cranial neuropathies have been described related to dysfunction of the extraocular muscles, particularly new-onset abducens palsies (51–53). Dinkin et al described 2 patients with new diplopia with COVID-19 infection. A 71-year-old woman with hypertension presented with new-onset diplopia and a right eye abduction deficit, consistent with an abducens palsy. Orbital MRI showed enhancement of the optic nerve sheath and the posterior Tenon capsule. The authors postulate the palsy may be secondary to immune-mediated acute demyelinating inflammatory neuropathy (51).

Guillain–Barré and Miller Fisher Syndromes

Multiple publications have reported patients presenting with COVID-19–related Guillain–Barré syndrome, an inflammatory polyradiculoneuropathy that occurs as a postviral inflammatory process (Fig. 5) (54). Caress et al reviewed 37 patients with Guillain–Barré syndrome associated with Covid-19 and compared with patients with contemporaneous non–COVID-19 Guillain–Barré syndrome (55).

Multiple publications of COVID-19–related Miller Fisher syndrome report presentations of ophthalmoplegia, loss of tendon reflexes, and acute onset ataxia with complete or incomplete response to treatment with IVlg. Gutierrez-Ortiz et al described a 50-year-old man with COVID-19–related cranial neuropathies and ataxia with ganglioside GD1b complex antibodies who recovered completely with IVlg treatment (56). Dinkin et al described a 36-year-old man with flu-like symptoms, left ptosis, diplopia, and distal lower extremity areflexia, diagnosed with presumed Miller Fisher syndrome with a negative ganglioside panel. An orbital MRI showed left oculomotor nerve enlargement and enhancement within the superior orbital fissure and orbit. The patient partially improved with IVlg (51). Reyes-Bueno et al described a 51-year-old woman with a left abducens palsy, global areflexia, and weakness who presented with new-onset diplopia and a right eye abduction deficit, consistent with an abducens palsy. Orbital MRI showed enhancement of the optic nerve sheath and the posterior Tenon capsule. The authors postulate the palsy may be secondary to immune-mediated acute demyelinating inflammatory neuropathy (51).
was diagnosed with COVID-19–related Miller Fisher syndrome and improved with IVIg (57).

**Nystagmus and Other Eye Movement Disorders**

Nystagmus and other eye movement disorders have been associated with COVID-19 infection. For example, Ayuso et al described a 72-year-old woman with downbeat nystagmus. A brain MRI showed vermian and right flocculus T2/FLAIR hyperintensity. She tested positive for anti-GD1a IgG antibodies, was treated with steroids, and diagnosed with postinfectious immune-mediated thombocapillitis (58). Several publications have described eye movement disorders secondary to central nervous system dysfunction, including brainstem inflammation (59), severe encephalitis (60), brainstem encephalitis (61), and a presumed parainfectious cerebellitis causing opsoclonus–myoclonus–ataxia syndrome (62).

**ORBIT**

**Orbital Myositis, Cellulitis, and Sinusitis**

Turbin et al. described 2 cases of orbital cellulitis, sinusitis, and intracranial abnormalities in 2 adolescents with COVID-19. Radiographic findings simulated fungal infection; however, workup for allergic and invasive fungal disease remained negative (63). Several cases of COVID-19–related orbital inflammation and orbital myositis have recently emerged in the literature (64–66). Multiple cases of post–COVID-19 mucormycosis have been recently reported with high morbidity and mortality (67,68).

**CONCLUSION**

COVID-19 can cause central and peripheral nervous system disease, including along both the afferent and efferent visual axis. Familiarity with the wide variety of neurologic, ophthalmic, and neuroradiologic presentations can promote prompt and appropriate treatment and contribute to building a framework to understand the underlying mechanisms of disease. Hypotheses may continue to evolve as long-term sequelae are reported and analyzed.

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Marsiglia et al.: J Neuro-Ophthalmol 2021; 41: 452-460
Disease of the Year: COVID-19

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