Section Editors: Bart Chwalisz, MD
Marc J. Dinkin, MD

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

Marcela Marsiglia, MD, PhD, Bart K. Chwalisz, MD, Mary Maher, MD

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 sequela 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.

Journal of Neuro-Ophthalmology 2021;41:452–460
doi: 10.1097/WNO.0000000000001454

Department of Radiology (M. Marsiglia), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; Department of Neurology (BKC), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; Department of Ophthalmology (BKC), Massachusetts Eye & Ear, Harvard Medical School, Boston, Massachusetts; and Department of Radiology/Division of Neuroradiology (M. Maher), University of Pennsylvania Medical Center, Philadelphia, Pennsylvania.

The authors report no conflicts of interest.

Address correspondence to Mary Maher, MD, Department of Radiology/Division of Neuroradiology, University of Pennsylvania Medical Center, 3400 Spruce Street, 219 Dulles Building, Philadelphia, PA 19104; E-mail: mary.maher@pennmedicine.upenn.edu

BACKGROUND

Infection by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also known as "COVID-19," was first described in Wuhan in China's Hubei Province in December 2019 as an illness that caused difficulty breathing. The disease spread worldwide and was declared a global pandemic on March 11, 2020. Since then, and as of this article, 202,658,082 COVID-19 cases and 4,293,491 COVID-19–related deaths have been reported worldwide (1).

Acute and chronic neurologic and neuro-ophthalmic symptoms continue to be described and characterized as our understanding of infection and postinfectious complications evolve. Mao et al first described neurologic symptoms on March 17, 2020, in a multicenter retrospective review of admitted patients in Wuhan, China, between January and February 2020. Of the 214 admitted patients, 36.4% had neurologic manifestations of disease, more common in severely ill patients (2). Although data since this first publication have varied, neurologic sequelae have remained a common theme, and severity of neurologic disease has typically (but not always) mirrored the severity of systemic disease. Ocular manifestations were described early in the pandemic (3,4), and detailed descriptions of neuro-ophthalmic manifestations have since been reported (5–7).

A range of neurologic and neuro-ophthalmic symptoms have been reported: anosmia, ageusia, headache, dizziness, myalgias, diplopia, focal neurologic deficits, and

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 endotheliopathy, 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 demyelinating encephalomyelitis (ADEM), vascular Injury with thromboembolism and infarct, leukoencephalopathy, hemorrhage, gray matter hypoxia, infectious meningitis/encephalitis, acute necrotizing hemorrhagic encephalopathy, and posterior reversible encephalopathy syndrome (PRES). The neuroradiology of severe cerebral complications 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 nystagmus 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, nonenhancing 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 infection because many patients lacked classic risk factors, including weight gain or exposure to tetracyclines or vitamin A derivatives. In addition, Verkuil et al described a 14-year-old girl diagnosed with COVID-19–related multisystem 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 cmH_2O (22). Several hypotheses for the development of pseudotumor cerebri have been postulated. SARS-CoV-2 may directly dysregulate cerebral spinal fluid (CSF) hydrodynamics, as the virus has a choroid plexus epithelial, meningeal, 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 transcription 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 nonfilling 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 improvement, 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 forward flexion, and numbness on the soles of both feet. Orbital MRI revealed enlargement and enhancement of retrobulbar, 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 antibodies were identified. The authors suggested a parainfectious 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 parenchymal lesions, and a T2 hyperintense, enhancing cord lesion at T8. CSF analysis revealed a lymphocytic pleocytosis, 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 juxtacortical 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 hypercoaguability 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, and 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

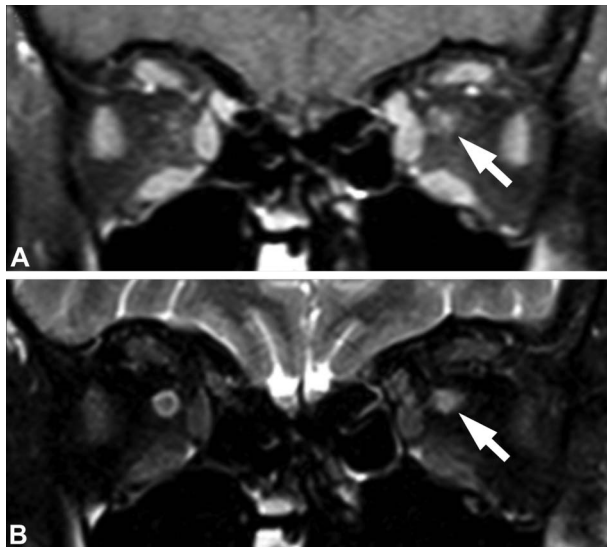

FIG. 1. A 34-year-old man with a history of COVID-19 infection 2 months before presented with left blurry vision loss and bumping into things for 1 month. Physical examination revealed papilledema and relative afferent pupillary defect in the left eye. An orbital MRI demonstrates (**A**) enhancement (*arrow*) and (**B**) T2/STIR hyperintense signal (*arrow*) of the left retrobulbar optic nerve. STIR, short tau inversion recovery.

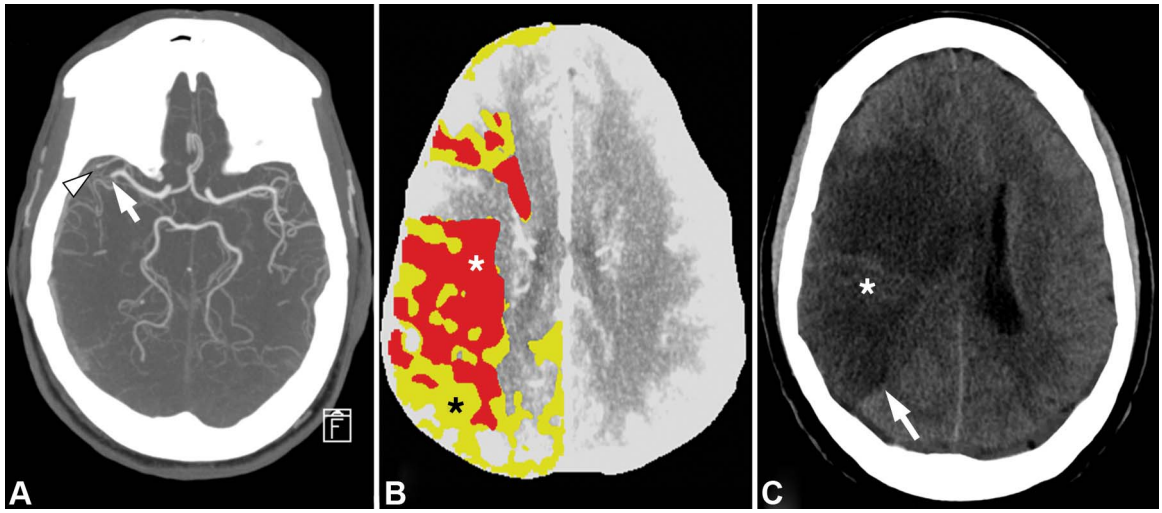

FIG. 2. A 58-year-old man with a history of heart failure and asthma developed new left-sided weakness while hospitalized for COVID-19 pneumonia, sepsis, and acute kidney injury. **A**. A head CT angiography (CTA) demonstrates a superior M2 branch cut off (arrowhead) and an inferior M2 branch cut off (arrow) of the right middle cerebral artery. **B**. CT Perfusion (CTP) shows a core infarct (white asterisk) and surrounding penumbra (black asterisk) in the right middle cerebral artery distribution. The patient was taken to interventional neuroradiology for mechanical thrombectomy with incomplete recanalization. **C**. Several days later, the follow-up head CT demonstrates evolution of the infarct with loss of gray–white differentiation and edema (*arrow*). Linear hyperdensity may reflect petechial hemorrhage (asterisk). CT, computed tomography.

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 hypoxemic 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/m^2, $P < 0.01$) 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

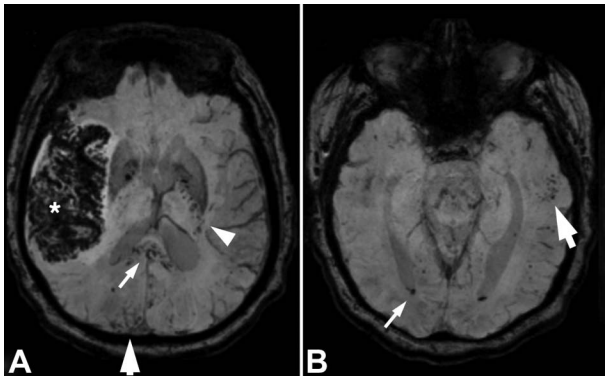

FIG. 3. A 69-year-old woman with a history of chronic obstructive pulmonary disease hospitalized for COVID-19 pneumonia complicated by ARDS and acute kidney injury requiring hemodialysis presented with left-sided weakness. **A**. Susceptibility-weighted images of a brain MRI shows hemorrhagic conversion 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. Moriguchi et al reported the first case of meningoencephalitis 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 meningoencephalitis 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 meningoencephalitis (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-ophthalmic complications include cranial neuropathies, Miller Fisher syndrome, and nystagmus and eye movement disorders related to brainstem abnormalities (5).

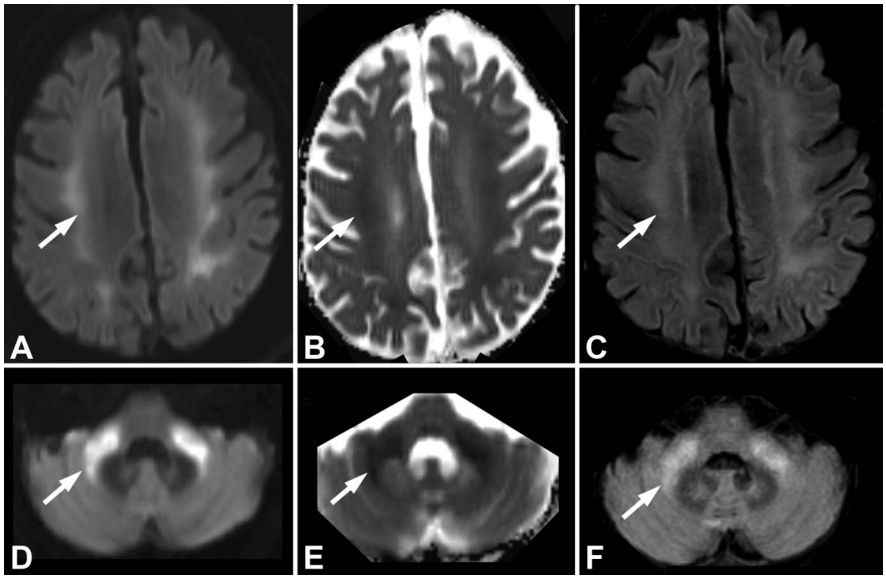

FIG. 4. A 62-year-old man with a history of obstructive sleep apnea, hyperlipidemia, and obesity was hospitalized for COVID-19 pneumonia complicated by respiratory failure requiring intubation and was nonresponsive after sedation weaning. A brain MRI reveals leukoencephalopathy with faint diffusion restriction in the supratentorial deep white matter with (**A**) elevated signal on diffusion-weighted imaging (DWI) (arrow) with corresponding (**B**) low apparent diffusion co-efficient (ADC) (arrow) and (**C**) T2/FLAIR hyperintense signal (arrow). There is a similar pattern of leukoencephalopathy signal abnormality in the middle cerebellar peduncles with (**D**) elevated signal on DWI (arrow), (**E**) low ADC and (**F**) T2/FLAIR hyperintensity.

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).

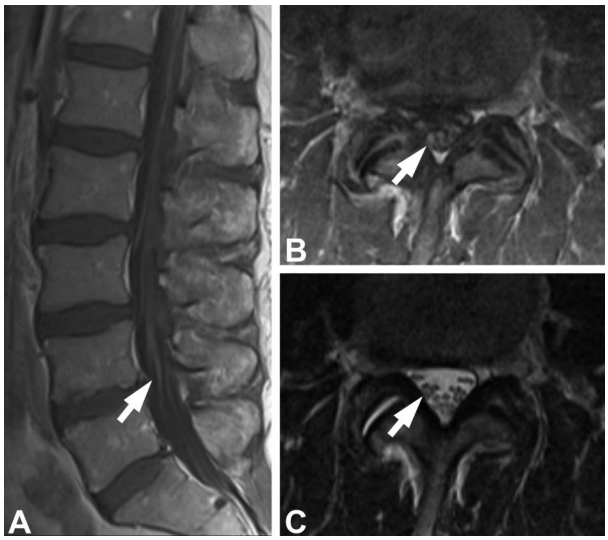

FIG. 5. A 63-year-old man with a history of COVID-19 infection 2 weeks before presented with difficulty urinating. Physical examination reveals diminished vibration and pinprick sensation. A lumbar spine MRI demonstrates thickening and enhancement of the cauda equina nerve roots (*arrows*) on (**A**) T1 sagittal and (**B**) axial sequences. **C**. A T2 axial sequence demonstrates nerve root thickening (*arrow*).

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 presentaions of ophthalmoplegia, loss of tendon reflexes, and acute onset ataxia with complete or incomplete response to treatment with IVIg. 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 IVIg treatment (56). Dinkin et al described a 36-year-old man with flu-like symptoms, left ptosis, diplopia, and distal lower extremity paresthesia, 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 IVIg (51). Reyes-Bueno et al described a 51-year-old woman with a left abducens palsy, global areflexia, and weakness who

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 rhombencephalitis (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.

REFERENCES

1. Johns Hopkins coronavirus Resource center web site. Available at: https://coronavirus.jhu.edu/map.html. Accessed July 22, 2021.
2. **Mao L**, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:683–690.
3. **Wu P**, Duan F, Luo C, Liu Q, Qu X, Liang L, Wu K. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020;138:575–578.
4. **Guan WJ**, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–1720.
5. **Tisdale AK**, Dinkin M, Chwalisz BK. Afferent and efferent neuro-ophthalmic complications of coronavirus disease 19. J Neuroophthalmol. 2021;41:154–165.
6. **Marinho PM**, Marcos AAA, Romano AC, Nascimento H, Belfort R Jr. Retinal findings in patients with COVID-19. Lancet. 2020;395:1610.
7. **Lecler A**, Cotton F, Lersy F, Kremer S, Héran F; SFNR's COVID Study Group. Ocular MRI findings in patients with severe COVID-19: a retrospective multicenter observational study. Radiology. 2021;299:E226–E229.
8. **Singhal AB**, Gonzalez RG, Chwalisz BK, Mukerji SS. Case 26-2020: a 60-year-old woman with altered mental status and weakness on the left side. N Engl J Med. 2020;383:764–773.
9. **Romero-Sánchez CM**, Díaz-Maroto I, Fernández-Díaz E, Sánchez-Larsen Á, Layos-Romero A, García-García J, González E, Redondo-Peñas I, Perona-Moratalla AB, Del Valle-Pérez JA, Gracia-Gil J, Rojas-Bartolomé L, Feria-Vilar I, Monteagudo M, Palao M, Palazón-García E, Alcahut-Rodríguez C, Sopelana-Garay D, Moreno Y, Ahmad J, Segura T. Neurologic manifestations in hospitalized patients with COVID-19: the ALBACOVID registry. Neurology. 2020;95:e1060–e1070.
10. **Oxley TJ**, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, Skliut M, Weinberger J, Dangayach NS, Bederson JB, Tuhrim S, Fifi JT. Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med. 2020;382:e60.
11. **Harapan BN**, Yoo HJ. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). J Neurol. 2021;268:3059–3071.
12. **Asadi-Pooya AA**, Simani L. Central nervous system manifestations of COVID-19: a systematic review. J Neurol Sci. 2020;413:116832.
13. **Kandemirli SG**, Dogan L, Sarikaya ZT, Kara S, Akinci C, Kaya D, Kaya Y, Yildirim D, Tuzuner F, Yildirim MS, Ozluk E, Gucyetmez B, Karaarslan E, Koyluoglu I, Demirel Kaya HS, Mammadov O, Kisa Ozdemir I, Afsar N, Citci Yalcinkaya B, Rasimoglu S, Guduk DE, Kedir Jima A, Ilksoz A, Ersoz V, Yonca Eren M, Celtik N, Arslan S, Korkmazer B, Dincer SS, Gulek E, Dikmen I, Yazici M, Unsal S, Ljama T, Demirel I, Ayyildiz A, Kesimci I, Bolsoy Deveci S, Tutuncu M, Kizilkilic O, Telci L, Zengin R, Dincer A, Akinci IO, Kocer N. Brain MRI findings in patients in the intensive care unit with COVID-19 infection. Radiology. 2020;297:E232–E235.
14. **Morfopoulou S**, Brown JR, Davies EG, Anderson G, Virasami A, Qasim W, Chong WK, Hubank M, Plagnol V, Desforges M, Jacques TS, Talbot PJ, Breuer J. Human coronavirus OC43 associated with Fatal encephalitis. N Eng J Med 2016;375:497–498.
15. **Tsai LK**, Hsieh ST, Chang YC. Neurological manifestations in severe acute respiratory syndrome. Acta Neurol Taiwan 2005;14:113–119.
16. **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Specialty Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033–1034.
17. **Moonis G**, Filippi CG, Kirsch CFE, Mohan S, Stein EG, Hirsch JA, Mahajan A. The Spectrum of neuroimaging findings on CT and MRI in adults with COVID-19. AJR Am J Roentgenol. 2021 217:959–974.
18. **Mukharesh L**, Bouffard M, Prasad S, Datta S, Chwalisz BK. Pseudotumor Cerebri Syndrome with COVID: Coincidence or not? Poster presented at: North American Neuro-Ophthalmologic Society (NANOS) February 20-23, 2021; Virtual meeting.
19. **Thaller M**, Tsermoulas G, Sun R, Mollan SP, Sinclair AJ. Negative impact of COVID-19 lockdown on papilloedema and idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry. 2021;92:795–797.

20. **Silva MTT**, Lima MA, Torezani G, Soares CN, Dantas C, Brandão CO, Espíndola O, Siqueira MM, Araujo AQ. Isolated intracranial hypertension associated with COVID-19. Cephalalgia. 2020;40:1452–1458.
21. **Noro F**, Cardoso FM, Marchiori E. COVID-19 and benign intracranial hypertension: a case report. Rev Soc Bras Med Trop. 2020;53:e20200325.
22. **Verkuil LD**, Liu GT, Brahma VL, Avery RA. Pseudotumor cerebri syndrome associated with MIS-C: a case report. Lancet. 2020;396:532.
23. **Jacob F**, Pather SR, Huang WK, Zhang F, Wong SZH, Zhou H, Cubitt B, Fan W, Chen CZ, Xu M, Pradhan M, Zhang DY, Zheng W, Bang AG, Song H, Carlos de la Torre J, Ming GL. Human pluripotent stem cell-derived neural cells and brain organoids reveal SARS-CoV-2 neurotropism predominates in choroid plexus epithelium. Cell Stem Cell. 2020;27:937–950.
24. **Yang AC**, Kern F, Losada PM, Agam MR, Maat CA, Schmartz GP, Fehlmann T, Stein JA, Schaum N, Lee DP, Calcuttawala K, Vest RT, Berdnik D, Lu N, Hahn O, Gate D, McNerney MW, Channappa D, Cobos I, Ludwig N, Schulz-Schaeffer WJ, Keller A, Wyss-Coray T. Dysregulation of brain and choroid plexus cell types in severe COVID-19. Nature. 2021;595:565–571.
25. **Hemasian H**, Ansari B. First case of Covid-19 presented with cerebral venous thrombosis: a rare and dreaded case. Rev Neurol (Paris). 2020;176:521–523.
26. **Cavalcanti DD**, Raz E, Shapiro M, Dehkharghani S, Yaghi S, Lillemoe K, Nossek E, Torres J, Jain R, Riina HA, Radmanesh A, Nelson PK. Cerebral venous thrombosis associated with COVID-19. AJNR Am J Neuroradiol. 2020;41:1370–1376.
27. **Zhou S**, Jones-Lopez EC, Soneji DJ, Azevedo CJ, Patel VR. Myelin Oligodendrocyte Glycoprotein antibody-associated optic neuritis and myelitis in COVID-19. J Neuroophthalmol. 2020;40:398–402.
28. **Rafique S**, Wasim A, Sultan T, Ahmad A. Post-COVID neuromyelitis optica Spectrum disorder. J Coll Physicians Surg Pak. 2021;31:138–140.
29. **Novi G**, Rossi T, Pedemonte E, Saitta L, Rolla C, Roccatagliata L, Inglese M, Farinini D. Acute disseminated encephalomyelitis after SARS-CoV-2 infection. Neurol Neuroimmunol Neuroinflamm. 2020;7:e797.
30. **Parsons T**, Banks S, Bae C, Gelber J, Alahmadi H, Tichauer M. COVID-19-associated acute disseminated encephalomyelitis (ADEM). J Neurol. 2020;267:2799–2802.
31. **Li Y**, Li M, Wang M, Zhou Y, Chang J, Xian Y, Wang D, Mao L, Jin H, Hu B. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. Stroke Vasc Neurol. 2020;5:279–284.
32. **Jain R**, Young M, Dogra S, Kennedy H, Nguyen V, Jones S, Bilaloglu S, Hochman K, Raz E, Galetta S, Horwtiz L. COVID-19 related neuroimaging findings: a signal of thromboembolic complications and a strong prognostic marker of poor patient outcome. J Neurol Sci. 2020;414:116923.
33. **Cyr DG**, Vicidomini CM, Siu NY, Elmann SE. Severe bilateral vision loss in 2 patients with coronavirus disease 2019. J Neuroophthalmol. 2020;40:403–405.
34. **Bondira lP**, Lambert-Cheatham NA, Sakuru RC, Polinger-Hyman DJ, Pipitone BD, Arnold KE, Nagia L, Kaufman DI. Inability to read after prolonged COVID-19 hospitalization: MRI with clinical correlation. J Neuroophthalmol. 2021;41:e277–e278.
35. **McKinney AM**, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, Teksam M. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. AJR Am J Roentgenol. 2007;189:904–912.
36. **Ghosh R**, Lahiri D, Dubey S, Ray BK, Benito-Leon J. Hallucinatory palinopsia in COVID-19- Induced posterior reversible encephalopathy syndrome. J Neuroophthalmol. 2020;40:523–526.
37. **Rapalino O**, Pourvaziri A, Maher M, Jaramillo-Cardoso A, Edlow BL, Conklin J, Huang S, Westover B, Romero JM, Halpern E, Gupta R, Pomerantz S, Schaefer P, Gonzalez RG, Mukerji SS, Lev MH. Clinical, imaging, and lab Correlates of severe COVID-19 leukoencephalopathy. AJNR Am J Neuroradiol. 2021;42:632–638.
38. **Helms J**, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C, Fafi-Kremer S, Ohana M, Anheim M, Meziani F. Neurologic Features in severe SARS-CoV-2 infection. N Engl J Med. 2020;382:2268–2270.
39. **Conklin J**, Frosch MP, Mukerji SS, Rapalino O, Maher MD, Schaefer PW, Lev MH, Gonzalez RG, Das S, Champion SN, Magdamo C, Sen P, Harrold GK, Alabsi H, Normandin E, Shaw B, Lemieux JE, Sabeti PC, Branda JA, Brown EN, Westover MB, Huang SY, Edlow BL. Susceptibility-weighted imaging reveals cerebral microvascular injury in severe COVID-19. J Neurol Sci. 2021;421:117308.
40. **Fanou EM**, Coutinho JM, Shannon P, Kiehl TR, Levi MM, Wilcox ME, Aviv RI, Mandell DM. Critical illness-associated cerebral microbleeds. Stroke. 2017;48:1085–1087.
41. **Riech S**, Kallenberg K, Moerer O, Hellen P, Bärtsch P, Quintel M, Knauth M. The pattern of brain microhemorrhages after severe lung failure Resembles the one seen in high-altitude cerebral edema. Crit Care Med. 2015;43:e386–e389.
42. **Rapalino O**, Weerasekera A, Moum SJ, Eikermann-Haerter K, Edlow BL, Fischer D, Torrado-Carvajal A, Loggia ML, Mukerji SS, Schaefer PW, Gonzalez RG, Lev MH, Ratai EM. Brain MR spectroscopic findings in 3 Consecutive patients with COVID-19: preliminary observations. AJNR Am J Neuroradiol. 2021;42:37–41.
43. **Lampe L**, Zhang R, Beyer F, Huhn S, Kharabian Masouleh S, Preusser S, Bazin PL, Schroeter ML, Villringer A, Witte AV. Visceral obesity relates to deep white matter hyperintensities via inflammation. Ann Neurol. 2019;85:194–203.
44. **Zhang T**, Hirsh E, Zandieh S, Rodricks MB. COVID-19-Associated acute multi-infarct encephalopathy in an asymptomatic CADASIL patient. Neurocrit Care. 2021;34:1099–1102.
45. **Moriguchi T**, Harii N, Goto J, Harada D, Sugawara H, Takamino J, Ueno M, Sakata H, Kondo K, Myose N, Nakao A, Takeda M, Haro H, Inoue O, Suzuki-Inoue K, Kubokawa K, Ogihara S, Sasaki T, Kinouchi H, Kojin H, Ito M, Onishi H, Shimizu T, Sasaki Y, Enomoto N, Ishihara H, Furuya S, Yamamoto T, Shimada S. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 2020;94:55–58.
46. **Narula N**, Joseph R, Katyal N, Daouk A, Acharya S, Avula A, Maroun R. Seizure and COVID-19: association and review of potential mechanism. Neurol Psychiatry Brain Res. 2020;38:49–53.
47. **Frontera JA**, Sabadia S, Lalchan R, Fang T, Flusty B, Millar-Vernetti P, Snyder T, Berger S, Yang D, Granger A, Morgan N, Patel P, Gutman J, Melmed K, Agarwal S, Bokhari M, Andino A, Valdes E, Omari M, Kvernland A, Lillemoe K, Chou SH, McNett M, Helbok R, Mainali S, Fink EL, Robertson C, Schober M, Suarez JI, Ziai W, Menon D, Friedman D, Friedman D, Holmes M, Huang J, Thawani S, Howard J, Abou-Fayssal N, Krieger P, Lewis A, Lord AS, Zhou T, Kahn DE, Czeisler BM, Torres J, Yaghi S, Ishida K, Scher E, de Havenon A, Placantonakis D, Liu M, Wisniewski T, Troxel AB, Balcer L, Galetta S. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York city. Neurology. 2021;96:e575–e586.
48. **Mukerji SS**, Solomon IH. What can we learn from brain autopsies in COVID-19? Neurosci Lett. 2021;742:135528.
49. **Matschke J**, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, Mushumba H, Fitzek A, Allweiss L, Dandri M, Dottermusch M, Heinemann A, Pfefferle S, Schwabenland M, Sumner Magruder D, Bonn S, Prinz M, Gerloff C, Püschel K, Krasemann S, Aepfelbacher M, Glatzel M. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol. 2020;19:919–929.
50. **Poyiadji N**, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging Features. Radiology. 2020;296:E119–E120.
51. **Dinkin M**, Gao V, Kahan J, Bobker S, Simonetto M, Wechsler P, Harpe J, Greer C, Mints G, Salama G, Tsiouris AJ, Leifer D. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. Neurology. 2020;95:221–223.

52. **Falcone MM**, Rong AJ, Salazar H, Redick DW, Falcone S, Cavuoto KM. Acute abducens nerve palsy in a patient with the novel coronavirus disease (COVID-19). J AAPOS. 2020;24:216–217.
53. **Greer CE**, Bhatt JM, Oliveira CA, Dinkin MJ. Isolated cranial nerve 6 palsy in 6 patients with COVID-19 infection. J Neuroophthalmol. 2020;40:520–522.
54. **Zhao H**, Shen D, Zhou H, Liu J, Chen S. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020;19:383–384.
55. **Caress JB**, Castoro RJ, Simmons Z, Scelsa SN, Lewis RA, Ahlawat A, Narayanaswami P. COVID-19-associated Guillain-Barré syndrome: the early pandemic experience. Muscle Nerve. 2020;62:485–491.
56. **Gutierrez-Ortiz C**, Mendez A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Manas R, de Aragón-Gómez F, Benito-León J. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. Neurology. 2020;95:e601–e605.
57. **Reyes-Bueno JA**, Garcia-Trujillo L, Urbaneja P, Ciano-Petersen NL, Postigo-Pozo MJ, Martinez-Tomas C, Serrano-Castro PJ. Miller-Fisher syndrome after SARS-CoV-2 infection. Eur J Neurol. 2020;27:1759–1761.
58. **Llorente Ayuso L**, Torres Rubio P, Beijinho do Rosario RF, Giganto Arroyo ML, Sierra- Hidalgo F. Bickerstaff encephalitis after COVID-19. J Neurol. 2021;268:2035–2037.
59. **Wong PF**, Craik S, Newman P, Makan A, Srinivasan K, Crawford E, Dev D, Moudgil H, Ahmad N. Lessons of the month 1: a case of rhombencephalitis as a rare complication of acute COVID-19 infection. Clin Med (Lond). 2020;20:293–294.
60. **Umapathi T**, Quek WMJ, Yen JM, Khin HSW, Mah YY, Chan CYJ, Ling LM, Yu WY. Encephalopathy in COVID-19 patients; viral, parainfectious, or both? eNeurologicalSci. 2020;21:100275.
61. **Khoo A**, McLoughlin B, Cheema S, Weil RS, Lambert C, Manji H, Zandi MS, Morrow JM. Postinfectious brainstem encephalitis associated with SARS-CoV-2. J Neurol Neurosurg Psychiatry. 2020;91:1013–1014.
62. **Sanguinetti SY**, Ramdhani RA. Opsoclonus-myoclonus-ataxia syndrome related to the novel coronavirus (COVID-19). J Neuroophthalmol. 2021;41:e288–e289.
63. **Turbin RE**, Wawrzusin PJ, Sakla NM, Traba CM, Wong KG, Mirani N, Eloy JA, Nimchinsky EA. Orbital cellulitis, sinusitis and intracranial abnormalities in two adolescents with COVID-19. Orbit. 2020;39:305–310.
64. **Mangan MS**, Yildiz E. New onset of unilateral orbital myositis following mild COVID-19 infection. Ocul Immunol Inflamm. 2021:1–2. doi: 10.1080/09273948.2021.1887282.
65. **Eleiwa T**, Abdelrahman SN, ElSheikh RH, Elhusseiny AM. Orbital inflammatory disease associated with COVID-19 infection. J AAPOS. 2021;25:232–234.
66. **Armstrong BK**, Murchison AP, Bilyk JR. Suspected orbital myositis associated with COVID-19. Orbit. 2021;40:532–535.
67. **Sharma K**, Tiwari T, Goyal S, Sharma R. Rhino-orbito-cerebral mucormycosis causing cranial nerve abscess in post-COVID-19 status. BMJ Case Rep. 2021;14:e245756.
68. **Soman R**, Sunavala A. Post COVID-19 mucormycosis in the second Wave-Realities, uncertainties and myths. J Assoc Physicians India. 2021;69:11–12.