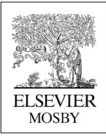




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Neuro-Ophthalmologic Manifestations of Novel Coronavirus



Devin Betsch, MD, Paul R. Freund, MD, MSc, FRCSC*

Department of Ophthalmology & Visual Sciences, Dalhousie University, QEII Health Sciences Centre, 2035-2 West Victoria Building, 1276 South Park Street, Halifax, Nova Scotia B3H 2Y9, Canada

Keywords

• Neuro-ophthalmology • COVID-19 • Coronavirus

Key points

- COVID-19 has been found to have many neuro-ophthalmologic associations, including cranial nerve palsies, Miller Fisher and Guillain-Barré syndromes, optic neuritis, intracranial hypertension, and sequelae from cerebrovascular events.
- Management of neuro-ophthalmology patients during the COVID-19 pandemic has brought about interesting discussions, including use of immunosuppressive agents, increasing usage of telehealth, and prone positioning as it relates to ischemic optic neuropathy.
- More research needs to be done to better characterize the relationship between COVID-19 and rare neuro-ophthalmologic presentations.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been found to have many systemic manifestations. Of these, ocular presentations associated with COVID-19 have been identified as clinicians' familiarity with the disease has increased since the start of the pandemic in early 2020, with a rapidly evolving body of literature. Neuro-ophthalmology has been affected, because of neuro-ophthalmic manifestations of COVID-19, and adaptations in delivery of health care and treatment of preexisting conditions.

Literature emerging on the topic of COVID-19-related thrombotic events has highlighted the relationship between coronavirus infection and

*Corresponding author. *E-mail address:* pfreund@dal.ca

hypercoagulability. The increased risk of arterial and venous thrombosis is thought to be caused by inflammation, platelet activation, endothelial dysfunction, and stasis [1]. Patients with COVID-19 infections have been found to have elevated D dimer levels, thrombocytopenia, and prolonged prothrombin time/international normalized ratio [2–7]. These patients can develop venous thromboembolism, myocardial infarction, stroke, and limb ischemia, even when anticoagulated [1,8–11]. It is possible that a similar mechanism may account for some of the suspected neuro-ophthalmologic associations, such as cranial neuropathies, which often occur in the context of ischemia.

Beyond the neuro-ophthalmic conditions that have been associated with COVID-19 infection, neuro-ophthalmologists care of uninfected patients also has been drastically altered, with a significant shift toward telemedicine and optimizing the management of preexisting conditions given the concern regarding immunosuppression during the current COVID-19 pandemic.

ARTICLE BODY

Neuro-ophthalmic presentations

Cranial nerve palsies

Cranial nerve abnormalities, including anosmia and hypogeusia, have been reported in association with COVID-19, and are accepted symptoms of infection. Based on these findings, it is postulated that the olfactory bulb may serve as an entry point for SARS-CoV-2 into the nervous system [12]. Although less common, there have been reports of isolated oculomotor, trochlear, and abducens nerve palsies in patients with COVID-19.

Faucher and colleagues [13] documented an isolated, partial left oculomotor nerve palsy (impaired adduction and supraduction of the left eye without ptosis or mydriasis) in a 21-year-old man with no other comorbidities that developed 16 days after developing respiratory symptoms. He had a positive polymerase chain reaction (PCR) testing to SARS-CoV-2. His clinical course involved 6 days of intubation and intensive care unit care. MRI showed a few arterial microectasia, but no involvement of the oculomotor nerve. Extensive serologic testing was negative. His symptoms of diplopia resolved within 7 days. Belghmaidi and colleagues [14] described a similar presentation with a partial left oculomotor nerve palsy (lacking ptosis or mydriasis) in a 23-year-old women with no medical comorbidities, preceded by 3 days of fever, anosmia, and cough. Her MRI/MR angiography imaging and serologic testing for a cause was unremarkable apart from positive PCR testing for SARS-CoV-2. She recovered within 6 days of onset. Fitzpatrick and colleagues [15] reported a 67-year-old man with no medical comorbidities who developed a pupil-sparing oculomotor nerve palsy 4 days after being diagnosed with COVID-19. His MRI brain showed only nonspecific microvascular changes and serology was noncontributory. His diplopia improved over 1 month, and the nerve palsy had completely resolved by 2 months. Similarly, Wei and colleagues [16] reported a 62-year-old man who presented with a 5-day history of an isolated pupil-sparing oculomotor nerve palsy with complete ptosis and loss of adduction

and supraduction. His medical history was significant for well-controlled type 2 diabetes mellitus, hypertension, and a prior lacunar infarct, but he did not have any respiratory symptoms on presentation. MRI/MR angiography imaging did not show any acute infarct or aneurysmal cause. He developed dyspnea on Day 2 of his admission and was confirmed to have COVID-19 before rapidly deteriorating and passing away on Day 12.

Paresis of the trochlear nerve also has been reported. Oliveira and colleagues [17] report a case of a 69-year-old White man with a history of hypertension who presented with fever, abdominal pain, chest pain without cough or dyspnea, and a mild occipital headache. Eleven days after the onset of symptoms, he woke with worsening headache and acute onset of binocular diplopia. His neurologic examination was consistent with bilateral trochlear nerve palsies. PCR testing was positive for COVID-19. An MRI with angiography and vessel wall imaging showed findings consistent with vasculitis affecting the vertebro-basilar system and fourth cranial nerve nuclei. His diplopia resolved after a 5-day course of intravenous (IV) methylprednisolone.

Likewise, isolated, unilateral abducens nerve palsies have been reported in patients with active SARS-CoV-2 infections. One case involved an otherwise healthy 32-year-old man, who developed binocular horizontal diplopia after 3 days of progressively worsening upper respiratory tract infectious symptoms [18]. He was ultimately hospitalized for treatment of acute respiratory failure and tested positive for SARS-CoV-2. Five weeks after the onset of diplopia, an ocular examination confirmed a complete left abducens nerve palsy, and MRI imaging at that time showed atrophy of the left lateral rectus consistent with denervation of the muscle. The remainder of his ophthalmologic examination was within normal limits.

Another case involved a 71-year-old woman who presented with cough and fever several days before developing diplopia [19]. She was found to have a complete abducens nerve palsy of the right eye. Nasal swab for SARS-CoV-2 PCR was positive. Axial T1 fat-saturated postcontrast MRI sequences showed bilateral enhancement of the optic nerve sheaths and Tenon capsule. She was treated with hydroxychloroquine. On follow-up 2 weeks after her initial presentation, she reported subjective improvement in her diplopia.

Two additional brief reports documented isolated abducens nerve palsies in SARS-CoV-2 PCR-positive patients: one in a 43-year-old woman who had negative serologic studies for other infectious and inflammatory causes and a normal contrast-enhanced MRI study of the brain and orbits; and the other a 52-year-old man who was only seen via telehealth consultation and declined further investigations [20]. Follow-up was not provided for the 43-year-old patient, but the 52 year old had a resolution of his abducens nerve palsy 14 days after onset.

All but one of the patients with cranial nerve palsies had developed upper respiratory tract infectious symptoms several days before the onset of diplopia. MRI findings were varied, making establishment of a potential mechanism for SARS-CoV-2 causing cranial nerve palsies somewhat challenging. Current

hypotheses include direct viral invasion and injury of the nervous system versus indirect autoimmune and neuroinflammatory pathways [21,22]. The speed of recovery seems to be rapid: 2/3 of the patients with CN3 palsies recovered within 2 weeks (and the third by 2 months); the patient with the central nervous system vasculitis and bilateral CN4 palsies recovered within 5 days; and 2/3 of the patients with CN6 palsies with reported follow-up had rapid recovery within 14 days of symptom onset. This is comparable with the speed of recovery from anosmia and ageusia, suggesting a common underlying pathophysiology [23].

Guillain-Barré and Miller Fisher syndrome

The first case of a patient presenting with Guillain-Barré (GB) associated with SARS-CoV-2 infection occurred in January 2020, after the patient returned from travel in Wuhan, China [24]. This 61-year-old woman first developed symptoms of bilateral lower limb weakness and generalized fatigue before she developed fever and cough 7 days later. The temporal relationship suggested a parainfectious process, rather than the postinfectious onset of GB classically associated with *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, or other viral and bacterial triggers [25].

A second case of ascending muscle weakness developed in a 54-year-old woman who had been diagnosed with COVID-19 3 weeks prior, after experiencing anosmia and hypogeusia. Electrophysiologic studies demonstrated segmental demyelinating polyneuropathy. Cerebrospinal fluid (CSF) analysis showed albuminocytologic dissociation, consistent with GB. Her neurologic symptoms significantly improved with IV immunoglobulin [26].

Dinkin and colleagues [19] reported a 36-year-old man with a history of infantile strabismus who presented with diplopia, left ptosis, and mydriasis, consistent with a left oculomotor nerve palsy. He also had bilateral abduction deficits suggestive of abducens nerve palsies, lower limb hyporeflexia and hypesthesia, and gait ataxia. He had experienced self-limited cough, myalgias, and fever 4 days prior, and was positive for COVID-19. His MRI showed enlargement and enhancement of the left oculomotor nerve. He was admitted to the hospital and treated for presumed Miller Fisher syndrome (MFS; ganglioside antibody negative) and COVID-19, with IV immunoglobulin for 3 days and hydroxychloroquine for 5 days, respectively. His neurologic deficits had improved at the time of discharge.

Gutierrez-Ortiz and colleagues [27] described two cases of COVID-19 associated with MFS and polyneuritis cranialis. The first was a 50-year-old man who presented with MFS. PCR was positive for SARS-CoV-2. His neurologic findings consisted of a right internuclear ophthalmoplegia, anosmia, ageusia, ataxia, and areflexia that developed 5 days after developing fever, malaise, and cough. He was positive for anti-GD1b ganglioside antibodies, rather than anti-GQ1b, which is more commonly associated with MFS. He was treated with IV immunoglobulin and made a near complete neurologic recovery. The second case occurred in a 39-year-old man who was diagnosed with

polyneuritis cranialis and COVID-19 after presenting with diarrhea, fever, and malaise, followed 3 days later by bilateral abducens nerve palsies, ageusia, and areflexia. Ganglioside antibody testing was not performed. He was treated with acetaminophen and had complete resolution of symptoms. Both patients had albuminocytologic dissociation on initial work-up.

Of the five cases described, four developed neurologic symptoms after the onset of viral upper respiratory symptoms, within a range of 3 days to 3 weeks. One presented with physical examination findings consistent with GB before the onset of any symptoms known to be associated with SARS-CoV-2 infection. All had favorable outcomes despite their diagnoses of COVID-19. It is suspected that these cases of GB and MFS represent a similar immune response to other postviral cases of GBS/MFS because of molecular mimicry from the COVID-19 spike protein [27,28]. The short time frame between onset of COVID-19 symptoms and GBS/MFS may be caused by an underestimation of the actual date of infection because of the asymptomatic incubation period between SARS-CoV-2 infection and development of respiratory symptoms.

Optic neuritis

There have been several reports of optic neuritis in patients with concomitant SARS-CoV-2 infection and no known prior history of autoimmune or demyelinating disease. Two cases of inflammatory optic neuritis have occurred in the setting of panuveitis. One involved a 60-year-old woman who presented with left eye pain, redness, and blurred vision 2 weeks following a respiratory infection with associated sinusitis and conjunctivitis [29]. On examination, she was found to have panuveitis and optic disk swelling. Work-up for toxoplasmosis, human immunodeficiency virus, and syphilis were negative. She developed worsening respiratory symptoms 10 days after initial presentation and ultimately was diagnosed with COVID-19 after confirmatory PCR testing. Although her visual acuity significantly improved after treatment with hydroxychloroquine and systemic steroids, she had significant optic nerve atrophy at the time of discharge.

A second report described a woman in her late 50s who was admitted for bilateral COVID-19-positive pneumonia and developed a red eye with decreased vision (hand motion acuity), pain with extraocular movements, and a relative afferent pupillary defect [30]. On slit lamp examination, she had nongranulomatous anterior chamber reaction and keratic precipitates, mild vitritis, disk edema with peripapillary hemorrhages, and vessel narrowing in the inferior retina. MRI brain and orbits with contrast, CSF analysis, and serologic investigations for other inflammatory or infectious causes were negative. Despite treatment with topical and oral steroids, on Day 30, she had persistent papillitis and retinal vasculitis on fluorescein angiography. By Day 48, the panuveitis had resolved and the patient was left with optic atrophy and unchanged hand motion visual acuity.

Reports also exist of demyelinating optic neuritis in patients presenting with decreased vision and pain with extraocular movements, with and without other

focal neurologic symptoms and signs. Zhou and colleagues [31] reported a case of 26-year-old man presenting with severe, sequential bilateral optic neuritis preceded by several days of dry cough. On examination, his Best Corrected Visual Acuity (BCVA) was hand motion OD and 20/250 OS with a right afferent pupillary defect and bilateral disk edema with retinal perivenous hemorrhages. MRI brain and orbits showed bilateral enhancement of the optic nerves and patchy T2 hyperintensities in the lower cervical and upper thoracic spinal cord. Myelin oligodendrocyte glycoprotein (MOG) antibody testing and PCR for SARS-CoV-2 were positive. His visual acuity recovered, and his fundus abnormalities resolved with a 5-day course of IV solumedrol with no pulmonary compromise.

A second report of MOG-optic neuritis has been described in a 44-year-old man, 2 weeks after developing symptoms of dyspnea and cough with a positive COVID-19 PCR test [32]. He reported pain with eye movements and was found to have BCVA 20/200 OD and 20/30 OS, a right afferent pupillary defect, generalized reduction in his visual field OD, and a superior arcuate visual field defect OS. Extensive investigations were significant for positive anti-MOG antibodies and bilateral postcontrast enhancement of the optic nerves with no other radiographic evidence of demyelination.

A third report of optic neuritis as a presenting symptom of multiple sclerosis (MS) in association with COVID-19 infection has also been documented [33]. A 29-year-old woman presented with painful right eye movements and decreased vision, BCVA 20/200, and a right afferent pupillary defect on her initial examination. She also was found to have signs of pyramidal tract dysfunction on examination. Her MRI demonstrated right optic nerve enhancement, nonenhancing and enhancing supratentorial periventricular demyelinating lesions, and a normal spinal cord MRI. She was found to also have oligoclonal bands in the CSF, meeting the MacDonald criteria for a diagnosis of MS.

A case of acute disseminated encephalomyelitis was diagnosed in a 64-year-old woman who presented to care with bilateral hand motion vision loss after having flulike symptoms with anosmia and ageusia 2 weeks prior [34]. She had poorly reactive pupils bilaterally, a right abdominal sensory level, and left-sided lower limb hyperreflexia with a positive Babinski sign. She had multiple enhancing lesions on MRI brain, including bilateral optic nerve involvement, and a spinal cord lesion at T8 (not longitudinally extensive). CSF analyses showed lymphocytic pleocytosis and mild hyperproteinorachia with no oligoclonal banding. NMO and MOG antibodies were negative. She responded well to IV solumedrol and immunoglobulins with improvement to visual acuity of 20/30 OU within 14 days and had improving radiographic findings.

It has been previously established that SARS-CoV-2 enters cells by binding to the ACE2 receptor [35,36]. Given that ACE2 has been found on choroidal cells and neurons, direct viral invasion has been proposed as a mechanism for the development of uveitis and optic neuritis. The optic nerve atrophy that was found in the patients who recovered from panuveitis with optic neuritis could

potentially be explained by an ischemic event, because the virus has a documented prothrombotic effect and endotheliumtropism [29]. In the case of patients with MOG-associated and MS-associated optic neuritis, and acute disseminated encephalomyelitis, the relationship between viral prodrome and parainfectious or postinfectious demyelinating syndromes has been well established in the literature [37,38]. Molecular mimicry is the most widely accepted mechanism, whereby viral antigens initiate a robust immune response against endogenous central nervous system proteins, including MOG and myelin [38]. However, the patient who was diagnosed with MS after developing optic neuritis had radiographic evidence of active and inactive demyelinating lesions, suggesting that her MS disease likely preceded her SARS-CoV-2 infection, although one cannot exclude that the infection did not trigger the episode of optic neuritis.

Intracranial hypertension

Intracranial hypertension attributed to idiopathic (IIH) and secondary causes has been associated with COVID-19. Noro and colleagues [39] reported a non-obese 35-year-old woman who presented with fever, dyspnea, headache, and fatigue. A lumbar puncture showed an elevated opening pressure of 40 cm H₂O. No evidence existed of thrombosis or secondary causes on MRI/MR venography. She also tested positive for SARS-CoV-2, and ultimately was admitted to hospital for worsening headache and confusion. Her symptoms resolved within 2 days of supportive care.

Secondary intracranial hypertension caused by multisystem inflammatory syndrome in children was reported in a 14-year-old girl who presented with fever, rash, dyspnea, headache, and diarrhea [40]. She was admitted to the hospital for respiratory decline and septic shock. During her admission, she developed a right abducens nerve palsy and bilateral papilledema with disk hemorrhages. Lumbar puncture confirmed elevated intracranial pressure and MRI/MR venography was supportive of the same. Although her nasopharyngeal PCR was negative, qualitative IgG was positive for SARS-CoV-2. Two months postdischarge, after poor compliance with acetazolamide, her disk edema and nerve palsy had resolved.

Silva and colleagues [41] published a cross-sectional study investigating the characteristics of headache and CSF analysis in COVID-19 patients. They included patients who underwent lumbar puncture over a defined period of 2 months for neurologic signs and symptoms that had a confirmed diagnosis of COVID-19. Of the 56 participants, 13 (23.2%) underwent lumbar puncture as part of the work-up for a new and persistent headache. Most of those patients (11/13) had complete or partial improvement in their headache. CSF analysis was normal in all patients, and six patients had opening pressures greater than 25 cm H₂O.

Cerebral venous sinus thrombosis (CVST) is a rare cause of secondary intracranial hypertension but is a significant concern given that SAR-CoV-2 induces a hypercoagulable state and the risk of significant morbidity if CVST is

unrecognized or untreated [42]. Multiple reports exist of CVST associated with COVID, but there is a paucity of ophthalmic examinations in the reports to assess for papilledema and other findings of neuro-ophthalmic interest. This may reflect that these patients were admitted to high-acuity COVID-19 wards with reduced access to ophthalmology consultations [43–45]. Practitioners should have a high index of suspicion to rule out CVST with venography and ensure appropriate anticoagulation is instituted.

Beyond the direct causative effect of SARS-CoV-2 inducing intracranial hypertension through the aforementioned mechanisms, changes in health care delivery and biopsychosocial effects of pandemic restrictions have been associated with more severe presentations or worsening disease in patients with new or previously diagnosed IHH, respectively [46]. A tertiary center in Birmingham, UK found a 4.7-times increase in their rate of CSF diversion procedures, which included 21% of their patients with newly diagnosed IHH. Conclusions were limited because of the retrospective nature of the report, but it is likely a combination of decreased or delayed access to emergency care, limited clinical examinations (because guidelines have suggested minimizing fundoscopy and visual field testing to minimize exposures for health care workers), and weight gain caused by pandemic lockdowns and increased anxiety and depression in patients. This highlights the importance of ensuring that clinical care for non-COVID-19-related presentations is not compromised as health care systems evolve and adapt to COVID-19 restrictions.

Other manifestations

In addition to the ischemic and hemorrhagic cerebrovascular complications of COVID-19, there is a higher rate of posterior reversible encephalopathy syndrome (PRES) in the setting of acute SARS-CoV-2 infections [47]. PRES is a disorder of presumed vascular dysregulation commonly associated with hypertension, and with severe infections/sepsis, autoimmune disease, and immunomodulator use, many of the features that exist in COVID-19 patients. Of the COVID-19 associated cases with PRES, transient visual loss has been reported and a hallucinatory palinopsia, a completely novel presentation of PRES [48,49].

Management changes

Prone positioning

In light of the number of SARS-CoV-2 cases requiring ventilation and prone positioning to improve oxygenation, there has been discussion on the multi-system side effects of maintaining such a position for extended periods [50,51]. One such complication is orbital compartment syndrome, which can develop secondary to direct pressure on the globe and orbit in a patient lacking cushioned eye protection. Sun and colleagues [50] reported two cases of orbital compartment syndrome in patients who had between four and nine sessions of 18-hour prone positioning while admitted under the critical care service. Both patients had periorbital edema and a two- to three-fold increase in intraocular pressure while laying prone versus supine. They also had indistinct optic disk

margins and retinal hemorrhages, which was believed to be most consistent with papillophlebitis from a combination of coagulopathy secondary to COVID-19 infection and the prolonged prone positioning.

Other concerns with prone positioning include ocular surface disease, acute angle-closure glaucoma, vascular occlusion, and ischemic optic neuropathy [51]. Ischemic optic neuropathy can result from a combination of prone positioning and systemic hypotension from sepsis or iatrogenic causes. Although there have not been any documented cases of ischemic optic neuropathy attributed to prone positioning in COVID-19 patients, heightened awareness has been recommended, given the risk of significant morbidity.

Immunosuppression

The COVID-19 pandemic posed a dilemma among patients and health care staff alike in regard to the use of immunosuppressive agents. Early in the pandemic, there was concern regarding increased risk of SARS-CoV-2 infection in patients with neuromyelitis optica spectrum disorders and other autoimmune conditions being treated with immunosuppressive agents, because of the associated increased susceptibility to infection. This concern was speculative and given that no data existed at the time to support this hypothesis, it was not recommended to prophylactically change treatment regimens [52]. As the pandemic has progressed, these concerns have not been borne out, and evidence suggests patients on immunosuppressive agents are not at higher risk of COVID-19 [53].

Salama and colleagues [54] conducted a survey that was distributed among 186 randomly selected patients with neuromyelitis optica spectrum disorders to gain more understanding of patient perspectives surrounding use of immunosuppressive therapies during the COVID-19 pandemic. Most patients (85%) had not considered stopping their medication, although some had delayed rituximab infusions. Approximately one-third of patients were maintaining in-person clinic visits, whereas the remainder were communicating with their health care provider via telephone, email, or telemedicine. Overall, it was concluded that most patients did not alter their medication schedule despite concern about acquiring COVID-19.

Telehealth

In light of the current pandemic, physicians are turning to telehealth as a safer alternative to providing in-person visits. However, the practice of neuro-ophthalmology poses an interesting challenge to this transition, given the benefit of physical examination findings and timely diagnostic testing on differentiation of benign from sinister underlying etiologies [55]. Certain aspects of the physical examination, such as visual acuity and a testing for an afferent pupillary defect, are performed by the patient via videoconferencing with detailed instruction [56,57]. However, fundoscopy and quantification of strabismus currently requires in-person assessment and subtle findings, such as nystagmus, may be missed depending on the quality of the video connection. Practical considerations, such as lack of access to appropriate technology, may preclude the

use of telehealth visits in some patients. Remote visual field testing has shown similar reliability to Humphrey visual fields in pilot studies but is not yet readily available [55]. Artificial intelligence optic disk analysis and digital fundus photography are on the horizon, but currently cannot replace clinic visits [58].

Although consultations often are best served by an office visit, appropriate triaging and prescreening of appointments (eg, to appropriately arrange laboratory testing or imaging by the referring physician) allows telemedicine to reduce the need for in-person visits [55,58]. Videoconferencing has gained popularity in medical education and research, with entire large-scale conferences being held via online platforms. As technology evolves and matches the demand for online visits, it certainly is possible that these innovations will propel the field into an era where comprehensive virtual visits become commonplace, pandemic notwithstanding.

RELEVANCE

As more time passes, clinicians are seeing an increasing number of neuro-ophthalmologic conditions presenting in patients with SARS-CoV-2. However, true associations and mechanisms are theoretic and based on extrapolations from a limited, although increasing, number of cases. As more data are accumulated, these relationships will become better characterized. One also has to consider the possibility that the timing of COVID-19 infection and the various neuro-ophthalmologic presentations have overlapped coincidentally, rather than because of the SARS-CoV-2 virus being a causative factor. However, given the restrictions and attempts to limit exposure to COVID-19 patients with abbreviated physical examinations or lack of manpower because of hospital capacity issues, there may also be underreporting of subtle neuro-ophthalmic presentations.

This review summarizes what is known about the relationship between SARS-CoV-2 and neuro-ophthalmology, in hopes that clinicians will have a higher index of suspicion to investigate for concomitant COVID-19 infection in patients, because many of the patients had little or no respiratory symptoms when they developed their neuro-ophthalmic concerns. Given the extensive contact tracing and isolation associated with testing positive for COVID-19, it is also conceivable that patients may underreport these symptoms. Thus, health care providers must remain vigilant and informed on the conditions that may be associated with SARS-CoV-2 infection.

Immunosuppressive medications are still being widely used during the pandemic. There has been no evidence to date to suggest preemptively stopping or changing a patient's immunosuppressive therapy during this time. Even those with proven SARS-CoV-2 infection are assessed on a case-by-case basis, taking into account the patient's comorbidities and severity of the sequelae associated with undertreating their neuro-ophthalmologic disease.

In regard to the changes in patient care, telehealth has been well received by health care providers and patients alike. There is a need for further research on

the topic to analyze cost-effectiveness and overall efficacy, and validate tools, such as visual field testing, to allow their implantation in a clinical setting.

SUMMARY

Although these neuro-ophthalmic findings may be unrelated to SARS-CoV-2 infection, health care providers should still consider them as potential manifestations of infection and exercise caution when seeing patients who present with these findings. As more reports of neuro-ophthalmic presentations in the setting of COVID-19 infections are published, the body of evidence from which to draw from will become more robust. In turn, the quality of data on the topic of neuro-ophthalmology and COVID-19 will improve, such that more definitive conclusions can be drawn about underlying mechanisms of these associations.

CLINICAL CARE POINTS

- Optic nerve and other cranial nerves can be affected in COVID-19 infections, but these cranial neuropathies may spontaneously recover.
- Clinicians should have a high index of suspicion for central venous sinus thrombosis in patients at risk for COVID-19 infections, especially in patients with atypical features for idiopathic intracranial hypertension.
- While tele-ophthalmology cannot replace in person examinations, its use in the appropriate clinical settings can improve patient access while minimizing risk of exposure to the patient and clinician.

Disclosure

The authors have nothing to disclose.

References

- [1] Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol* 2020;75:2950–73.
- [2] Lippi G, Plebani M, Michael Henry B. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta* 2020;506:145–8.
- [3] Lippi G, Favaloro EJ. D-dimer is Associated with Severity of Coronavirus Disease 2019: A Pooled Analysis. *Thromb Haemost* 2020;120(5):876–8.
- [4] Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med* 2020;58(7):1116–20.
- [5] Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. *Clin Chem Lab Med* 2020;58(7):1131–4.
- [6] Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8(5):475–81.
- [7] Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *J Med Virol* 2020;92(7):791–6.
- [8] Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med* 2020;382:e60.
- [9] Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020;18:1743–6.

- [10] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683–90.
- [11] Levi M, Thachil J, Iba T, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 2020;7:e438–40.
- [12] Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol* 2020;92:552–5.
- [13] Faucher A, Rey PA, Aguadisch E, et al. Isolated post SARS-CoV-2 diplopia. *J Neurol* 2020;267(11):3128–9.
- [14] Belghmaidi S, Nassih H, Boutgayout S, et al. Third cranial nerve palsy presenting with unilateral diplopia and strabismus in a 24-year-old woman with COVID-19. *Am J Case Rep* 2020;21:e925897.
- [15] Fitzpatrick JC, Comstock JM, Longmuir RA, et al. Cranial nerve III palsy in the setting of COVID 19 infection. *J Neuroophthalmol* 2020; <https://doi.org/10.1097/WNO.0000000000001160>.
- [16] Wei H, Yin H, Huang M, et al. The 2019 novel coronavirus pneumonia with onset of oculomotor nerve palsy: a case study. *J Neurol* 2020;267(5):1550–3.
- [17] Oliveira RMC, Santos DH, Olivetti BC, et al. Bilateral trochlear nerve palsy due to cerebral vasculitis related to COVID-19 infection. *Arq Neuropsiquiatr* 2020;78(6):385–6.
- [18] Falcone MM, Rong AJ, Salazar H, et al. Acute abducens nerve palsy in a patient with the novel coronavirus disease [COVID-19]. *J AAPOS* 2020;24:216–7.
- [19] Dinkin M, Gao V, Kahan J, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology* 2020;95(5):221–3.
- [20] Greer CE, Bhatt JM, Oliveira CA, et al. Isolated cranial nerve 6 palsy in 6 patients with COVID-19 infection. *J Neuroophthalmol* 2020;40(4):520–2.
- [21] Vonck K, Garrez I, De Herdt V, et al. Neurological manifestations and neuro-invasive mechanisms of the severe acute respiratory syndrome coronavirus type 2. *Eur J Neurol* 2020;27(8):1578–87.
- [22] Costello F, Dalakas MC. Cranial neuropathies and COVID-19: neurotropism and autoimmunity. *Neurology* 2020;95(5):195–6.
- [23] Lee Y, Min P, Lee S, et al. Prevalence and duration of acute loss of smell or taste in COVID-19 patients. *J Korean Med Sci* 2020;35(18):e174.
- [24] Zhao H, Shen D, Zhou H, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol* 2020;19(5):383–4.
- [25] Hughes RA, Hadden RD, Gregson NA, et al. Pathogenesis of Guillain-Barré syndrome. *J Neuroimmunol* 1999;100(1–2):74–97.
- [26] Scheidl E, Canseco DD, Hadji-Naumov A, et al. Guillain-Barré syndrome during SARS-CoV-2 pandemic: a case report and review of recent literature. *J Peripher Nerv Syst* 2020;25(2):204–7.
- [27] Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. *Neurology* 2020;95(5):e601–5.
- [28] Dalakas MC. Guillain-Barré syndrome: the first documented COVID-19-triggered autoimmune neurologic disease: more to come with myositis in the offing. *Neurol Neuroimmunol Neuroinflamm* 2020;7(5):e781.
- [29] Benito-Pascual B, Gegúndez JA, Díaz-Valle D. Panuveitis and optic neuritis as a possible initial presentation of the novel coronavirus disease 2019 (COVID-19). *Ocul Immunol Inflamm* 2020;28(6):922–5.
- [30] François J, Collery AS, Hayek G, et al. Coronavirus disease 2019-associated ocular neuropathy with panuveitis: a case report. *JAMA Ophthalmol* 2020;139(2):247–9.
- [31] Zhou S, Jones-Lopez EC, Soneji DJ, et al. Myelin oligodendrocyte glycoprotein antibody-associated optic neuritis and myelitis in COVID-19. *J Neuroophthalmol* 2020;40(3):398–402.
- [32] Sawalha K, Adeodokun S, Kamoga GR. COVID-19-induced acute bilateral optic neuritis. *J Investig Med High Impact Case Rep* 2020;8:2324709620976018.

- [33] Palao M, Fernández-Díaz E, Gracia-Gil J, et al. Multiple sclerosis following SARS-CoV-2 infection. *Mult Scler Relat Disord* 2020;45:102377.
- [34] Novi G, Rossi T, Pedemonte E, et al. Acute disseminated encephalomyelitis after SARS-CoV-2 infection. *Neurol Neuroimmunol Neuroinflamm* 2020;7(5):e797.
- [35] Seah I, Agrawal R. Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. *Ocul Immunol Inflamm* 2020;28(3):391–5.
- [36] Conde Cardona G, Quintana Pájaro LD, Quintero Marzola ID, et al. Neurotropism of SARS-CoV 2: mechanisms and manifestations. *J Neurol Sci* 2020; <https://doi.org/10.1016/j.jns.2020.116824>.
- [37] Leake JA, Albani S, Kao AS. Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. *Pediatr Infect Dis J* 2004;23:756–64.
- [38] Kuerten S, Lichtenegger FS, Faas S. MBP-PLP fusion protein induced EAE in C57BL/6 mice. *J Neuroimmunol* 2006;177:99–111.
- [39] Noro F, Cardoso FM, Marchiori E. COVID-19 and benign intracranial hypertension: a case report. *Rev Soc Bras Med Trop* 2020;53:e20200325.
- [40] Verkuil LD, Liu GT, Brahma VL, et al. Pseudotumor cerebri syndrome associated with MIS-C: a case report. *Lancet* 2020;396(10250):532.
- [41] Silva MTT, Lima MA, Torezani G, et al. Isolated intracranial hypertension associated with COVID-19. *Cephalalgia* 2020;40(13):1452–8.
- [42] Medicherla CB, Pauley RA, de Havenon A, et al. Cerebral venous sinus thrombosis in the COVID-19 pandemic. *J Neuroophthalmol* 2020;40(4):457–62.
- [43] Klein DE, Libman R, Kirsch C, et al. Cerebral venous thrombosis: a typical presentation of COVID-19 in the young. *J Stroke Cerebrovasc Dis* 2020;29(8):104989.
- [44] Hughes C, Nichols T, Pike M, et al. Cerebral venous sinus thrombosis as a presentation of COVID-19. *Eur J Case Rep Intern Med* 2020;7(5):001691.
- [45] Dakay K, Cooper J, Bloomfield J, et al. Cerebral venous sinus thrombosis in COVID-19 infection: a case series and review of the literature. *J Stroke Cerebrovasc Dis* 2021;30(1):105434.
- [46] Thaller M, Tsermoulas G, Sun R, et al. Negative impact of COVID-19 lockdown on papilloedema and idiopathic intracranial hypertension. *J Neurol Neurosurg Psychiatry* 2020; <https://doi.org/10.1136/jnnp-2020-325519>.
- [47] Parauda SC, Gao Y, Gewirtz AN, et al. Posterior reversible encephalopathy syndrome in patients with COVID-19. *J Neurol Sci* 2020;416:117019.
- [48] Kaya Y, Kara S, Akinci C, et al. Transient cortical blindness in COVID-19 pneumonia; a PRES-like syndrome: case report. *J Neurol Sci* 2020;413:116858.
- [49] Ghosh R, Lahiri D, Dubey S, et al. Hallucinatory Palinopsia in COVID-19-induced posterior reversible encephalopathy syndrome. *J Neuroophthalmol* 2020;40(4):523–6.
- [50] Sun L, Hymowitz M, Pomeranz HD. Eye protection for patients with COVID-19 undergoing prolonged prone-position ventilation. *JAMA Ophthalmol* 2020;e204988; <https://doi.org/10.1001/jamaophthalmol.2020.4988>.
- [51] Sanghi P, Malik M, Hossain IT, et al. Ocular complications in the prone position in the critical care setting: the COVID-19 pandemic. *J Intensive Care Med* 2020;28:885066620959031.
- [52] Carnero Contentti E, Correa J. Immunosuppression during the COVID-19 pandemic in neuromyelitis optica spectrum disorders patients: a new challenge. *Mult Scler Relat Disord* 2020;41:102097.
- [53] Fan M, Qiu W, Bu B, et al. Risk of COVID-19 infection in MS and neuromyelitis optica spectrum disorders. *Neurol Neuroimmunol Neuroinflamm* 2020;7(5):e787.
- [54] Salama S, Giovannoni G, Hawkes CH, et al. Changes in patient and physician attitudes resulting from COVID-19 in neuromyelitis optica spectrum disorder and multiple sclerosis. *Mult Scler Relat Disord* 2020;42:102259.

- [55] François J, Collery AS, Hayek G, et al. Tele-neuro-ophthalmology: vision for 20/20 and beyond. *J Neuroophthalmol* 2020;40(3):378–84.
- [56] Al Hussona M, Maher M, Chan D, et al. The virtual neurologic exam: instructional videos and guidance for the COVID-19 Era. *Can J Neurol Sci* 2020;47(5):598–603.
- [57] Lai KE, Ko MW, Rucker JC, et al. Tele-neuro-ophthalmology during the age of COVID-19. *J Neuroophthalmol* 2020;40(3):292–304.
- [58] Grossman SN, Calix R, Tow S, et al. Neuro-ophthalmology in the era of COVID-19: future implications of a public health crisis. *Ophthalmology* 2020;127(9):e72–4.