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Clinical Neurology and Neurosurgery 201 (2021) 106440

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Case Report

Monocular visual loss as the presenting symptom of COVID-19 infection

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Central nervous system
Cerebrovascular disease
Central retinal artery occlusion

ABSTRACT

Background and Importance: Additional time is needed to determine the exact impact of COVID-19 on acute cerebrovascular disease incidence, but recently published data has correlated COVID-19 to large vessel occlusion strokes. Clinical Presentation: We report the first case of central retinal artery occlusion (CRAO) as the initial manifestation of COVID-19 infection. Subsequent neuroimaging revealed a large thrombus extending into the internal carotid artery. Conclusion: This case illustrates the need to suspect COVID-19 infection in patients presenting with retinal arterial occlusion, including individuals who are asymptomatic or minimally symptomatic for COVID-19 infection.

1. Case presentation

A patient in his fifth decade was evaluated in the Wills Eye Emergency Room for acute onset of right, painless visual loss the prior day. The patient denied any past episodes of transient visual loss, diplopia, headache, weakness, sensory changes, facial weakness, or slurred speech. The patient's past medical history is significant for hypertension, tobacco use, and occasional marijuana use. He had stopped smoking 2 weeks prior to presentation. He denied the use of any systemic medications. On review of systems, he confirmed mild pharyngitis and diarrhea for 2–3 days but denied fever, cough, changes in smell or taste, confusion, or respiratory complaints.

On examination, blood pressure was 174/107 mm Hg, pulse oximetry was 97 % on room air, and he was afebrile (36.8 °C). Vision was hand motions on the right and 20/20 on the left. A prominent afferent pupillary defect was present on the right. His extraocular motility was normal and the anterior segment was unremarkable except for nuclear sclerotic cataracts. A central retinal artery occlusion (CRAO) was present on the right (Fig. 1). No embolic plaques were present. On the left, arteriovenous nicking was present with one questionable cotton wool spot and a flame hemorrhage. His neurologic exam was otherwise normal.

Based on neuroscience hospital policies, the patient underwent quantitative RNA testing for the SARS COVID-19 and was confirmed positive.

The patient was admitted to the neurology service for further workup. His telemetry was unremarkable. On brain MRI, there was no evidence of acute ischemic stroke or hemorrhage. A long segment filling defect involving the mid and distal portions of the right common carotid artery extending to the communicating segment of the right internal carotid artery (ICA) was noted on CT angiography (CTA) (Fig. 2). On high resolution CTA images, decreased flow was also noted in the right ophthalmic artery (Fig. 2B). Poor flow was also noted on MR angiography (MRA) (Fig. 3). Flow in the ICA reconstituted distal to this point via filling from the right posterior communicating artery (Fig. 3). No significant calcifications were noted.

Pertinent laboratory results included a mildly elevated prothrombin time (14.6, normal 9.4–13.0 sec) and international normalized ratio (INR) (1.29, normal 0.83–1.14), with a normal partial prothrombin time. The low density lipoprotein and hemoglobin A1c were normal at 90 mg/dL and 5.4, respectively. Abnormal studies included elevated levels of D-dimer (450, normal <230 ng/mL DDU), fibrinogen (545,

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https://doi.org/10.1016/j.clineuro.2020.106440
Received 10 August 2020; Received in revised form 6 December 2020; Accepted 10 December 2020
Available online 15 December 2020

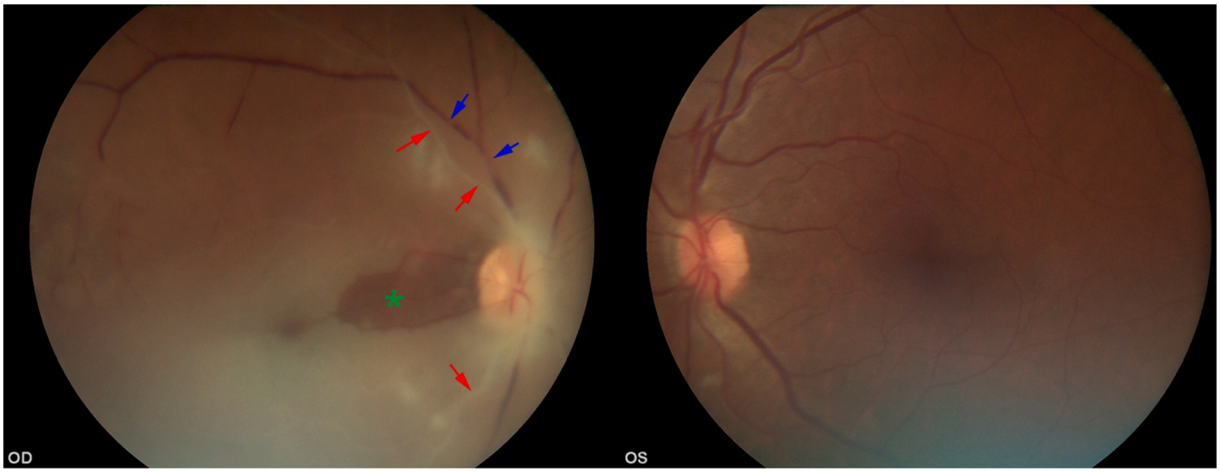

Fig. 1. Handheld digital fundus photos performed at bedside two days after admission. Left: The right fundus with nonperfused retinal arteries (red arrows) and "boxcar" defects in the retinal veins (blue arrows). Cilioretinal artery sparing (green asterisk) is present but does not extend into the fovea. Note the diffuse nerve fiber later edema manifesting as retinal whitening along with a foveal "cherry red spot". Right: The left fundus shows arteriovenous nicking consistent with hypertension. A flame hemorrhage is presnt along the superior arcade and questionable cotton-wool spot may be present inferior to the optic disc, consistent with hypertensive retinopathy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

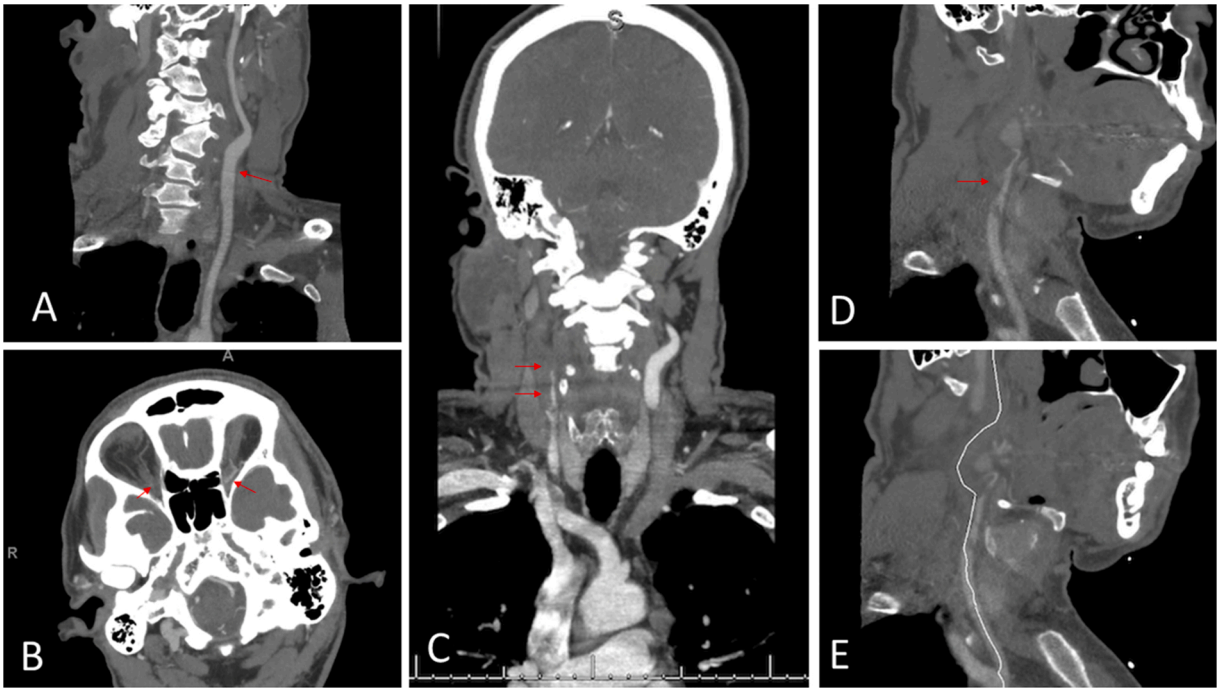

Fig. 2. **A.** Coronal CTA of normal left internal carotid artery (arrow). **B.** Axial CTA at the level of the right ophthalmic artery showing diminished flow compared to the left (arrows). **C.** Coronal and **D.** Sagittal CTA images of right internal carotid artery demonstrating extensive thrombus and cervical occlusion (arrows). **E.** Normal left arterial flow traced in white.The tracing in white illustrates normal left arterial flow.

normal 170−460 mg/dL), lactate dehydrogenase (272, normal 125–240 IU/L), and C-reactive protein (2.10, normal $\leq$ 0.80 mg/dL).

Upon review of imaging, the patient was immediately started on therapeutic low molecular weight heparin (LMWH) and transferred to the neurocritical care unit for closer monitoring. He remained stable with no new ophthalmologic or neurologic symptoms. The patient remained afebrile and his oxygen saturation remained >95 % on room air throughout his admission. LMWH was continued with a plan for repeat imaging and transition to direct oral anticoagulant.

2. Discussion

Additional time is needed to determine the exact impact of COVID-19 on acute cerebrovascular disease incidence, but recently published data has correlated COVID-19 to large vessel occlusion strokes [1]. Viruses, including COVID-19, can penetrate the central nervous system (CNS) (neuroinvasion), infect neurons and glial cells (neurotropism), and contribute to or cause neurological disease (neurovirulence) [2]. Access may be achieved via two main routes: hematogenously or transneuronally through the olfactory bulb. COVID-19 can also bind the angiotensin converting enzyme 2 (ACE-2) receptors that are present in the CNS, which are also involved in the autoregulation of the cerebral

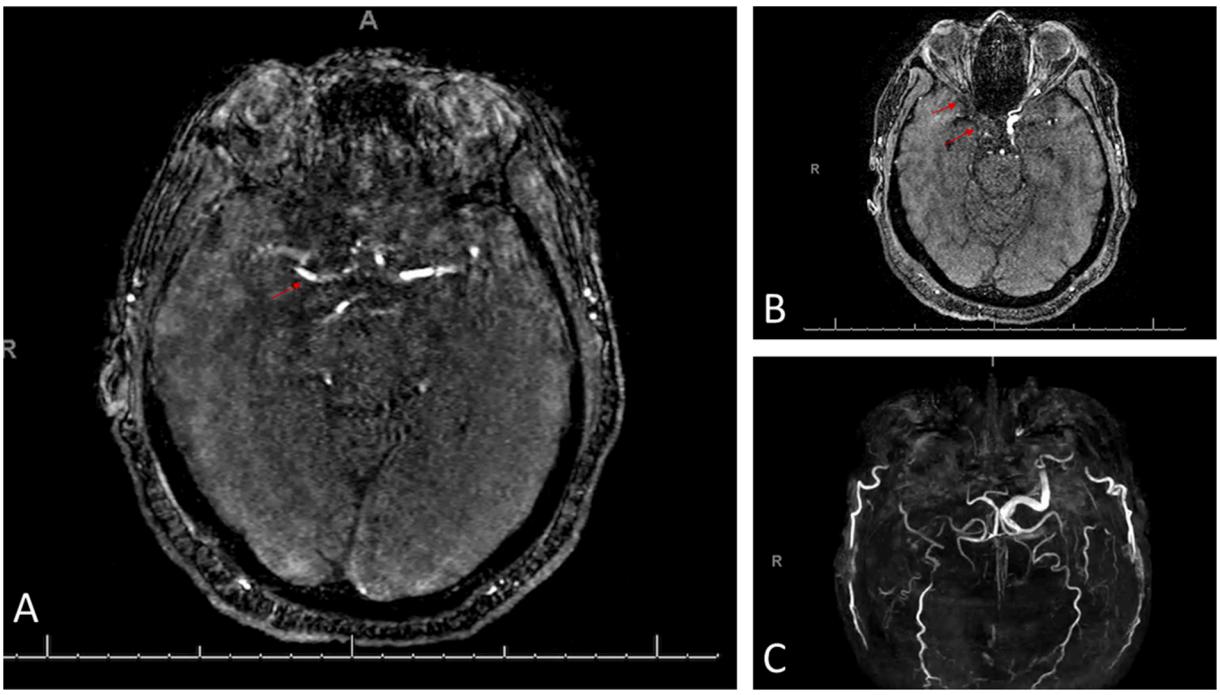

Fig. 3. A. Axial MRA image depicting supraclinoid carotid artery reconstitution through the posterior communicating artery (arrow). **B.** Axial MRA showing lack of flow in the right ophthalmic artery (arrows), compared to left normal side. **C.** 3D MRA reconstruction depicting attenuated flow in the right hemisphere.

perfusion pressure [3]. In addition to common cardiovascular comorbidities in the elderly COVID-19 positive population, mechanisms for ischemic stroke in infected patients of all age groups include hypercoagulability from pro-inflammatory state, infection-induced disseminated intravascular coagulation, and embolism from virus-related cardiac injury. These mechanisms may contribute to the development of variable pathologies that could result in either unilateral or bilateral vision loss, including, including ophthalmic artery occlusion, [4] central retinal artery occlusion [5], central retinal vein occlusion [6], optic neuropathy [7], occipital cortical infarct [8], or acute macular neuroretinopathy [9]. In our patient, the hypercoagulable state caused by virus-induced cytokine storm likely triggered the formation of the internal carotid artery thrombus that led to a CRAO [10].

CRAO causes retinal ischemia, and prompt medical treatment is warranted to prevent irreversible retinal cell death and ultimately blindness. The retinal cells can sustain ischemic conditions for approximately 2 h;beyond that window the damage may be irreversible [11]. Hyperbaric oxygen therapy (HBOT) may be used as an adjunct to thrombolytic treatment [12].

In retrospective studies, critically-ill COVID-19 patients had increased proinflammatory cytokines, including interleukin 2 (IL-2) and tumor necrosis factor α4 (TNF-α4), which can upregulate the coagulation system [13].

In this case, visual loss occurred secondary to occlusion of the internal carotid artery extending into the skull base. The clinical findings were consistent with a CRAO rather than ophthalmic artery (OA) occlusion, either because of partial backfilling of the OA from the posterior communicating artery or secondary to an embolism from the carotid artery thrombus lodged in the central retinal artery posterior to the lamina cribrosa; in this case, partial occlusion of the OA cannot be rules out. Hemispheric stroke was averted because of reperfusion of the ICA at the level of the anterior clinoid process.

The neuroscience hospital policies at our institutions mandate rapid SARS COVID-19 testing in any patient presenting with symptoms of an acute cerebrovascular event. This policy also includes any patient presenting with an ophthalmic or retinal artery occlusion based on recent data.

Outcomes in available COVID-19 patient data do not suggest clear benefit over risk of therapeutic anticoagulation for primary stroke prevention. However, assuming low risk of hemorrhage conversion, therapeutic anticoagulation is frequently initiated for secondary stroke prevention in the critically ill with significantly elevated D-Dimer levels and no other clear etiology of ischemic stroke.

Recent studies of infected patients with cerebrovascular disease revealed the possibility of large vessel occlusion and significant thrombosis in the relatively asymptomatic patient with low D-Dimer levels. When initiating anticoagulation in the COVID-19 patient for secondary stroke prevention, low molecular weight heparin is often preferred to unfractionated heparin given consistent immediate therapeutic levels, reduced nursing and phlebotomy staff exposure, and anti-inflammatory properties. Patients can later be transitioned to ideally a direct acting oral anticoagulant if there are no contraindications.

This case illustrates the need to suspect COVID-19 infection in patients presenting with retinal arterial occlusion, including individuals who are asymptomatic or minimally symptomatic for COVID-19 infection.

Funding statement

This research received no specific grant from any funding agency in public, commercial, or not-for-profit sectors.

Data sharing statement

The relevant anonymized patient-level data are available on reasonable request from the authors.

Ethical approval

All procedures performed in the studies involving human participants were per the ethical standards of the Institutional Review Board (IRB) or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

The study protocol was reviewed and approved by the Thomas Jefferson University Institutional Review Board. Following our institutional guidelines, all protected health information was removed, and individual patient consent was obtained.

CRediT authorship contribution statement

Ann P. Murchison: Conceptualization, Data curation, Methodology, Resources, Writing - original draft, Writing - review & editing. **Ahmad Sweid:** Data curation, Writing - original draft, Writing - review & editing. **Robin Dharia:** Data curation, Writing - original draft, Writing - review & editing. **Thana N. Theofanis:** Data curation, Writing - original draft, Writing - review & editing. **Stavropoula I. Tjoumakaris:** Conceptualization, Data curation, Methodology, Resources, Writing - original draft, Writing - review & editing. **Pascal M. Jabbour:** Conceptualization, Data curation, Methodology, Resources, Writing - original draft, Writing - review & editing. **Jurij R. Bilyk:** Conceptualization, Data curation, Methodology, Resources, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Acknowledgments

None.

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