Review Article

Update on coronavirus disease and retinal artery occlusion

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ABSTRACT

Background: The novel coronavirus disease 2019 (COVID-19) is significant not only for its life-threatening impact, but also for its association with serious eye disorders, including retinal artery occlusion. This language-inclusive narrative review analyzed the available clinical literature on retinal artery occlusion linked to COVID-19, highlighting it as a serious vision-threatening complication of this disease during the recent pandemic.

Methods: A targeted literature search was conducted in the PubMed / MEDLINE and Google Scholar databases from January 1, 2020, to January 1, 2025, to gather the most recent evidence. Studies were identified through various combinations of the following search terms: "eye diseases in COVID-19," "ocular findings," "ocular manifestations in COVID-19," "posterior segment alterations in COVID-19," and "retinal artery occlusion in COVID-19." Articles with relevant clinical significance were selected for review. The reference lists of these papers also manually checked for other relevant papers. We included case reports, case series, and both prospective and retrospective studies that reported cases of central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO) in patients of any age, sex, and race with confirmed COVID-19.

Results: We found 27 records, of which 21 reported cases of CRAO in patients with COVID-19. The mean (standard deviation) age of these patients was 54.1 (13.4) years (range: 30–77 years). Off the 21 patients, 18 (86%) were men and three (14%) were women. In three cases, bilateral involvement was noted; in one such instance, CRAO was diagnosed sequentially: in the left eye while the patient had COVID-19, and in the right eye 1.5 months later. Among the cases of unilateral CRAO, the left eye was the most frequently affected. Additionally, four cases of BRAO were reported in patients with COVID-19, with most of these patients being women. Most of these cases were diagnosed in the left eye within 1 month of a COVID-19 diagnosis. Notably, in the majority of cases involving CRAO or BRAO, vascular thromboembolic events were not reported. Additionally, two case series reported a total of 17 patients with COVID-19 who were diagnosed with CRAO.

Conclusions: Although strong evidence of a causal relationship is lacking, healthcare specialists should be aware that CRAO or BRAO may be ocular complications of COVID-19. This is particularly important with the emergence of new subvariants of SARS-CoV-2 and in asymptomatic patients, and considering the availability of rapid viral antigen tests will make it easier to check if the patient with CRAO or BRAO actually have asymptomatic COVID-19.

KEYWORDS

SARS-CoV-2, COVID-19, ocular manifestations, branch retinal artery occlusion, central retinal artery occlusion

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INTRODUCTION

Central retinal artery occlusion (CRAO) is a vaso-occlusive disorder of the retinal artery, representing a "retinal stroke." It should be considered an ophthalmic emergency, as it can cause profound acute vision loss and even blindness [1]. Its mean standardized incidence rate is 2.00 cases per 100 000 person-years [2]. The first case of CRAO was reported by Van Graefe in 1859 [3]. The pathogenesis of CRAO has varied systemic and local implications. CRAO is most commonly caused by embolism or thrombosis caused by hemodynamic changes or large artery atherosclerosis [4].

On January 30th, 2020, the World Health Organization announced the outbreak of the extremely transmissible novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which represented "a public health emergency of international concern" [5]. Clinical medicine has witnessed an explosion in the number of ocular manifestations, ranging from 2% up to 60%, in patients with COVID-19 since the onset of the global pandemic [6-16]. Currently, available findings highlight a direct impact of SARS-CoV-2 on the surface of the eye, usually clinically seen as viral conjunctivitis [16-18], as well as an indirect impact on intraocular structures [16, 19, 20].

SARS-CoV-2 plays an important role in the pathophysiology of several conditions and can be life-threatening. However, it also plays a role in the pathophysiology of sight-threatening disorders of the eye [19, 20], such as retinal artery occlusion [17, 19, 20]. This is potentiated by prone positioning in the critical care setting [21]. In this language-inclusive narrative review, we aimed to analyze the clinical data available in the literature regarding retinal artery occlusion associated with COVID-19 as a serious sight-threatening complication during the recent pandemic.

METHODS

A targeted literature search was conducted using the PubMed / MEDLINE and Google Scholar databases from January 1, 2020, to January 1, 2025, to retrieve the most recent evidence. Papers were identified by using various combinations of the following search terms: "eye diseases in COVID-19," "ocular findings," "ocular manifestations in COVID-19," "posterior segment alterations in COVID-19," and "retinal artery occlusion in COVID-19."

Articles with acceptable clinical relevance were selected for review. The reference lists of these papers also manually checked for other relevant papers. We included case reports, case series, and any prospective or retrospective studies reporting central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO) in patients of any age, sex, and race with confirmed COVID-19.

Descriptive statistics were derived from the individual patient data reported in the included publications. Each patient was counted once, including those with bilateral involvement, and summary statistics were based on the information available in the original reports.

RESULTS

We identified 27 papers, including two cases series [22, 23] and 25 case reports, representing 21 patients with COVID-19 who had been diagnosed with CRAO [24-44] and four who had been diagnosed with BRAO [45-48]. Table 1 summarizes demographic and clinical characteristic of cases [24-44] with CRAO who had a mean (standard deviation) age of 54.1 (13.4) years (range: 30–77 years). Of the 21 patients with CRAO, 18 (86%) were men and three (14%) were women. Three had bilateral involvement [35, 36, 44]. In one of these patients, the bilateral CRAO was detected in a sequential order, where the left eye developed CRAO simultaneous with COVID-19, and CRAO was detected in the right eye 1.5 months later [36]. Among the patients with unilateral CRAO [24-34, 37-43], the left eye was the most frequently affected [25, 27, 29, 32, 34, 39, 41-43].

Acharya et al. [24] presented the first case of COVID-10-associated CRAO in a 60-year-old Hispanic male who was diagnosed with CRAO on the 12th day of hospitalization for COVID-19. The authors stated that this diagnosis has not been described in the natural history of COVID-19 up to that point, and was associated with poor visual outcomes. Multiple similar cases were subsequently presented by different researchers [25-34], some of which were associated with remarkable neuroradiological findings, such as internal carotid artery obstruction [30-32, 40, 49, 50].

Lecler et al. [50] reported nine consecutive patients with severe COVID-19 who exhibited abnormalities on globe magnetic resonance imaging. Among them, one was diagnosed with unilateral CRAO through fluorescein angiography. However, due to insufficient data about this patient, this case was not included. Murchison et al. [31] diagnosed CRAO as the initial manifestation of COVID-19 with a large thrombus extending into the internal carotid artery revealed by neuroimaging (Table 1). Another report described a fatal case, in which a 77-year-old male hospitalized with moderate COVID-19 developed severe disease with a devastating "thromboembolic storm," which included right eye CRAO during the recovery stage of COVID-19, on the 16th day since symptoms started [33] (Table 1).

Another case of CRAO was documented in an otherwise healthy 63-year-old male who was admitted to the intensive care unit on the 21 days since recovery from COVID-19 [34] (Table 1). Bilateral cases of CRAO were also documented in different periods of COVID-19 [35, 36, 44] (Table 1).

Table 2 summarizes the demographic and clinical characteristic of the four reported cases of BRAO that were diagnosed in patients with COVID-19 [45-48]. Three of the four patients were women [45-47] and the left eye was affected in three cases [45, 46, 48], mostly within 1 month of a COVID-19 diagnosis [46-48].

Table 1. Characteristics of reported cases [24-44] of CRAO associated with COVID- 2019

Author (Year)	Age (y) /Sex / Race	Laterality	Time interval	Severity of COVID-19	Vascular thromboembolic events	Relevant note
Acharya et al. (2020) [24]	60 / M / Hispanic	RE	12 days	Severe	No	-
Montesel et al (2020) [25]	59 / M / African	LE	17 days	Severe	No	Acute renal injury requiring hemodialysis.
Turedi and Onal Gunay (2021) [26]	54 / M / Turkic	RE	14 days	Mild	No	-
Latigan et al. (2021) [27]	31/ W / Russian	LE	> 21 days	Moderate	No	Hypercoagulation.
Ucar and Centinkaya (2021) [28]	54 / M / Turkic	RE	21 days	Mild	No	-
Been Sayeed et al. (2021) [29]	38 / M / Bangali	LE	7 days	Severe (Fatal)	Acute ischemic stroke.	Diabetes mellitus.
Sweid et al. (2020) [30]	59 / M / NA	Unilateral	Simultaneous	Mild	Internal carotid artery occlusion.	Hypertension.
Murchison et al. (2021) [31]	50 / M / NA	RE	Asymptomatic	NA	Internal carotid artery occlusion.	Hypertension.
Paul et al. (2022) [32]	30 / M / Indian	LE	3 months	Mild	Ophthalmic artery occlusion, posterior ciliary artery occlusion, and proven internal carotid artery occlusion.	Ischemic stroke with right hemiparesis, global aphasia, and right upper motor neuron facial palsy. Cilioretinal artery occlusion.
Jervis et al. (2022) [33]	77 / M / NA	RE	16 days	Moderate turned into severe(Fatal)	Spleen, kidneys, and peripheral vasculature "thromboembolic storm."	Rheumatoid arthritis, diabetes mellitus, and hypertension.
Shroff et al. (2022) [34]	63 / M / Indian	LE	21 days	Severe	No	-
Bapaye et al. (2021) [35]	42 / M / Indian	Bilateral	1-month	Moderate	No	-
Karahan et al. (2021) [36]	61 / M / Turkic	Bilateral	Left eye with simultaneousinvolvement, but RE with 1.5 months interval.	Moderate	No	Asthma.
Walinjkar (2021) [37]	66 / M / Indian	RE	-	Asymptomatic	No	Simultaneous central retinal vein occlusion.
Sanjay et al. (2021) [38]	66 / M / Indian	RE	4 days	Mild	No	Bilateral panuveitis.
Raj et al. (2021) [39]	37 / M / Indian	LE	14 days	Severe	No	Cavernous sinus thrombosis.
Larochelle et al. (2022) [40]	68 / M / Caucasian	RE	3 days	Severe	Acute kidney injury, atrial fibrillation.	Internal carotid artery occlusion and sixth cranial nerve palsy.
Yalcinbayir et al. (2023) [41]	66 / M / Turkic	LE	14 days	Mild	No	-
Heidarzadeh et al. (2023) [42]	44 / M / Persian	LE	21 days	Severe	No	Pneumonia and uveitis.
de Oliveria et al. (2023) [43]	68 / W / Brazilian	LE	23 days	Severe	Elevated fibrinogen.	Hypertension.
Blyden et al. (2024) [44]	44 / W / NA	Bilateral	19 days	Severe	Elevated platelet.	Type 2 diabetes mellitus.

Note: CRAO, central retinal artery occlusion; COVID-19, coronavirus disease 2019; y, year-old; M, man; W; woman; NA, not available; Time interval, the time interval between COVID-19 infection and the onset of CRAO; LE, left eye; RE, right eye.

Table 2. Characteristics of reported cases [45-48] of BRAO associated with COVID- 2019

Author (Year)	Age (y) / Sex / Race	Laterality	Time interval	COVID-19 Severity	Vascular thromboembolic events	Relevant note
Uzun et al. (2021) [45]	65 / W / Turkic	LE	5 weeks	Mild	No	-
Nourinia et al. (2021) [46]	60 / W / Persian	LE	10 days	Severe	No	Meningoencephalitis
Ates et al. (2021) [47]	34 / W / Turkic	RE	25 days	Mild	No	-
Jiang et al. (2024) [48]	79 / M / Chinese	LE	2 weeks	Mild	No	Hypertension

Note: BRAO, branch retinal artery occlusion; COVID-19, coronavirus disease 2019; Y, year-old; M, man; W; woman; Time interval, the time interval between COVID-19 infection and the onset of branch retinal artery occlusion; LE, left eye; RE, right eye.

The two case series described 17 patients with COVID-19 who had been diagnosed with CRAO [22, 23]. A retrospective study evaluating the frequency of SARS-CoV-2 among 15 patients (7 males and 8 females) with CRAO, who attended a tertiary referral hospital between March and November 2020, demonstrated no infection by SARS-CoV-2 before episodes of CRAO. However, the authors stated that their results required further comprehensive assessment taking into account confounding factors [22]. Likely explanations for this lack of correlation are that COVID-19 rarely manifests solely with CRAO, or that the majority of CRAO cases were diagnosed in patients with severe COVID-19 [24, 25, 29, 34, 39, 40, 42-44] who were hospitalized in non-ophthalmic medical centers, including intensive care units. A multicenter retrospective study of COVID-19-related retinal vascular occlusions, diagnosed during March 2020 and September 2021 [23], documented two cases with CRAO among 15 eligible cases. The authors concluded that occlusion could manifest simultaneously with COVID-19 or weeks later, typically affecting patients younger than 60 years [23].

DISCUSSION

Current clinical evidence suggests a potential link between COVID-19 and CRAO or BRAO. Reports indicate that patients with COVID-19 may develop CRAO or BRAO, regardless of the severity of their COVID-19 symptoms, as cases ranged from asymptomatic individuals to those with critical illness [22, 23, 24-44, 45-48].

The pathogenesis of CRAO has varied systemic and local implications. CRAO is most commonly caused by embolism or thrombosis associated with hemodynamic changes or atherosclerosis [4]. CRAO is hypothesized to result from thromboembolism in addition to inflammation and hypercoagulation secondary to SARS-CoV-2 infection [51-59]. Increasing evidence indicates that this virus could also cause vaso-occlusion of the retinal artery [16, 22-50] due to its thromboembolic effects [49]. The proposed mechanism of destructive impact is as follows: the virus reaches the intraocular structures through the bloodstream [60], targeting tissues expressing angiotensin-converting enzyme 2 [61], including the retinal vascular network and retinal pigment epithelium [62, 63]. After binding to this receptor, it then triggers a cascade of inflammatory events, which is followed by endothelial dysfunction [51, 52], platelet activation, and hypercoagulability [53], leading to thrombotic complications [64]. A number of recent studies have shown different vascular and retinal abnormalities with clinical and subclinical manifestations detected in cases of mild and severe COVID-19 [65-75], which have also been confirmed by a postmortem study [76, 77].

Recently Abbati et al. [78] described the first case of a 6-year-old otherwise healthy girl who was diagnosed with CRAO after a 1-day fever. The authors stated that this has not been reported in the natural history of COVID-19 in the pediatric population and was associated with poor visual outcomes [78]. These findings suggest that SARS-CoV-2 could potentially cause CRAO in any age group. While the mean age of patients with CRAO and COVID-19 described in included case reports was 54.1 years [24-44], almost all cases were ≥ 30 years. A recent study funded by the National Institutes of Health [77] provided new evidence of the direct impact of SARS-CoV-2 infection on the arteries of the heart, which increase the risk of heart attack and stroke [77]. With this in mind, it should be considered that CRAO and the resulting retinal ischemia [49] represents a "retinal stroke."

COVID-19 remains a significant and evolving issue. It is important to stay informed about the disease and be aware of any emerging symptoms. [79]. This is particularly important given the possibility of reinfection and the current circulation of various subtypes of SARS-CoV-2 such as the emerging subvariant BA.2.86, also known as "Pirola." This subvariant has a significant number of mutations that may enhance its ability to evade the immune system [80]. Reinfection may result in more chronic, multi-organ complications, which could have serious implications for ocular health [81].

Recent reviews, such as those by Stawowski et al. [79], Ng et al. [81], Eissa et al. [82], Patel et al. [83], Parmar et al. [84], and Salvetat and Zeppieri [85], have covered a significant number of studies that have evaluated the ocular manifestations of COVID-19. The general consensus is that CRAO could occur in patients with COVID-19. Further supportive data for this notion were reported by Micevych and Stewart [86]. However, the evidence regarding COVID-19-associated CRAO remains inconclusive due to the limited number of reported cases [49]. This highlights the need for big data [87, 88] and multicenter cohort studies to verify causal relationships.

This review summarized the demographic and clinical characteristics of patients who developed CRAO or BRAO in connection with COVID-19, as reported in the scientific literature over the past 5 years. However, the absence of a systematic review search strategy may have led to the oversight of some important studies on this topic. Furthermore, the existing evidence was primarily derived from case reports and case series, making it difficult to draw definitive conclusions about the causal relationship of COVID-19 with CRAO or BRAO. Consequently, further research, including systematic reviews and meta-analyses, is necessary to establish clearer conclusions. Additionally, multicenter cohort studies are needed to verify causal relationships between COVID-19 disease and retinal vascular occlusive diseases.

CONCLUSIONS

Despite the lack of strong evidence confirming a causal relationship, healthcare specialists should remain vigilant regarding cases of CRAO or BRAO as potential ocular complications associated with COVID-19. This is particularly important with the emergence of new subvariants of SARS-CoV-2 and in asymptomatic patients. With using available rapid antigen tests for SARS-CoV-2, establishing whether CRAO or BRAO are complications of infection with this virus will be facilitated. Early identification and prompt management of patients with COVID-19 exhibiting ocular manifestations—particularly those that threaten vision—can reduce ocular complications, mitigate the severity of the viral disease, facilitate quicker recovery, and help prevent the spread of infection within both the medical and general communities.

ETHICAL DECLARATIONS

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