

## Myths and Truths of the association of retinal vascular occlusion with COVID-19

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#### **Summary Statement**

The association of retinal vascular occlusion with COVID-19 is weak on the basis of the published scientific evidences until today. Hence, it is not warranted to change the management strategies in these cases at this point.

#### **Abstract**

**Purpose:** To critically review data published in the recent past to scrutinize a causal relationship between retinal vascular occlusion and COVID-19.

Method: A comprehensive literature search was performed on Pubmed with the key words retinal vascular occlusion, retinal vein occlusion, retinal artery occlusion and COVID-19.

Results: A total of 17 case reports were published during this period and 10 were on retinal vein occlusion and 7 on retinal artery occlusion. Most of the published reports lacked convincing evidences in one or the other aspects such as insufficient laboratory workup or presence of multiple confounding risk factors.

Conclusion: In this index manuscript, strength of the data is insufficient to establish a definitive cause-and-effect relationship of retinal vascular occlusive disorders with COVID-19. Hence, clinicians can continue to manage these cases according to the standard guidelines until there are more robust evidences to support this association to alter the diagnostic and treatment modalities.

Keywords: COVID-19; Retinal vein occlusion; Retinal artery occlusion

## **Introduction**

The surge in coronavirus disease of 2019 (COVID-19) cases had initially created a frenzy among the medical community with its unpredictable nature and course. As the pandemic progressed, a better understanding of its manifestations and treatment protocol has brought down the morbidity and mortality. COVID-19 associated retinal vascular occlusions (arterial and venous) has been debated extensively during multiple virtual scientific meetings, based on the assumption of causal relationship. There are very few published case reports based on such similar assumptions. The data though is too scattered in the form of case reports to allow clinicians to

decide on diagnosis and treatment algorithm. The aim of the index article is to critically analyze the strength of this association and understand if ophthalmologists need to alter their management strategy.

### **Method of Literature Search**

We performed a Pubmed literature search on July 01, 2021 with the keywords: retinal vein occlusion (RVO), retinal artery occlusion (RAO), retinal vascular occlusion and COVID-19. We found 31 articles which were published during the period of October 2020 to May 2021. We have included only 17 articles which were claimed by the authors to have a causal association with COVID-19. Amongst these reports, 10 were RVOs {7 central retinal vein occlusions (CRVO), one hemi-retinal vein occlusion (HRVO), one probable HRVO and one branch retinal vein occlusion (BRVO)}, 6 central retinal artery occlusions (CRAO) and one cilioretinal artery occlusion. (Supplementary table 1, <http://links.lww.com/IAE/B582>)

Based on the current understanding of the pathophysiology of COVID-19, coagulation and inflammatory parameters were considered as major determinants to assess the causality of this association. Furthermore, confounding factors were analyzed in each case. Only patients with deranged coagulation and inflammatory parameters at the time of retinal vascular occlusion with no confounding factors were considered as possible true association.

### **Results**

The following are the key cumulative clinical information extracted from the published data. (Supplementary table 1)

**Age group-** The age range was between 17-74 years. RAO cases were in the age group of 26-61 years as compared to RVOs between 17-74 years.

**Sex-** Eleven males and 6 females.

**Bilateral involvement-** Four cases had bilateral involvement. Amongst these cases, 2 were CRVO and two were CRAO.

**Onset of vascular occlusion-** The onset was between 3 to 60 days from the start of clinical symptoms of COVID-19 or a positive real-time polymerase chain reaction (RT-PCR). Three cases had IgG positivity at the time of onset of vascular occlusion. In one case RT-PCR was negative at the time of ocular complaints.

**Best corrected visual acuity (BCVA) -** It was 20/20 to 20/200 in vein occlusion cases and no light perception (NLP) to counting fingers (CF) in cases of artery occlusion. All the retinal vein occlusion cases improved to near normal visual acuity. However, none of the cases due to artery occlusion showed any significant improvement.

**Imaging evidences-** Most of the patients underwent either fundus photo or bedside ophthalmoscopic examination. In addition, majority of them underwent fundus fluorescein angiography (FFA) and/or optical coherence tomography (OCT). Five of the cases revealed cystoid macular edema (CME) on OCT in the RVO group and two patients revealed paracentral acute middle maculopathy (PAMM) in the RAO group.

**Prothrombotic parameters-** Special emphasis was given to D-dimer as it was considered a key parameter in the COVID-19 pathogenesis. The coagulation profile was deranged in 9 cases, normal in 6 cases and it was not done in 2 cases.

**Inflammatory markers-** Information about inflammatory markers was not available for 3 patients, normal in 6 patients and deranged in 8 patients.

**Management-** Amongst the five RVO cases which had CME, three were treated with anti-vascular endothelial growth factor (anti-VEGF) injections, one was treated with intravitreal dexamethasone implant and one was treated only with an antiplatelet drug (aspirin 150 mg/day). Amongst these cases, one patient was also treated with oral steroids along with anti-VEGF. One patient with impending CRVO was treated with intravenous methyl prednisolone (IVMP) and oral steroids. The remaining of the RVO cases were not given any specific ocular therapy. Amongst the CRAO cases, two were given routine CRAO treatment which included ocular massage, intraocular pressure (IOP) lowering drugs and hyperbaric oxygen. One patient with bilateral CRAO was treated with 6 mg dexamethasone and 75 mg aspirin. Apart from these two patients who received aspirin, none of the patients received anticoagulation therapy specifically for the management of retinal vascular occlusion.

**Comorbidities and risk factors-** Out of the 17 patients, 9 had co-morbid conditions with hypertension being the most common (4 cases). Two cases had no mention of comorbid conditions and six cases were supposedly healthy patients with no co-morbid conditions. Other than hypertension, non-insulin dependent diabetes mellitus (NIDDM), hyperlipidemia, sickle cell disease, marijuana use, chronic smoking, hyperuricemia, polycystic ovarian disease (PCOD) and arsenic intake were the risk factors.

## **Discussion**

### **Scrutinizing the association**

#### **CRVO**

The strongest association of COVID-19 and RVO is probably from the case reports by Invernizi and Gaba et al., as both the reports had abnormal coagulation and inflammatory profiles

consistent with the pathogenic cascade of CRVO.<sup>1-2</sup> Furthermore, the case report by Gaba et al. had significant systemic thrombosis at multiple sites due to COVID-19 (no history of previous coagulation disorders) strengthening the possibility of a COVID induced thrombotic RVO. However, rest reports lacked the strength of association based on the scientific evidences mentioned.

The case report by Lorca et al., had no venous tortuosity which is a major characteristic of CRVO. Furthermore, the eye had vitreous hemorrhage and HBA1c was 13% which points more towards diabetic retinopathy.<sup>3</sup> The youngest patient, 17 years of age described by Walinjkar et al., had PCOD and history of arsenic intake in the form of a homeopathic medication as risk factors.<sup>4</sup> Arsenic has been known to induce platelet aggregation and venous thrombosis.<sup>5</sup> Furthermore, PCOD by itself is a cause of venous thrombosis.<sup>6</sup> The case by Yahalomi et al. showed the typical non ischemic CRVO picture but lacked evidence to consider it as a COVID associated vein occlusion as the coagulation profile was normal and inflammatory markers were not reported.<sup>7</sup> The case described by Sheth et al. spared the superotemporal sector of the retina (a possible HCRVO<sup>8</sup>) and FFA showed vasculitic changes; the author too did mention it as a vasculitic RVO. But, COVID-19 inflammatory markers were normal which weakened the possibility of a COVID induced vasculitic RVO. Furthermore, the study lacked D-dimer values.<sup>9</sup> The case described by Finn et al. had normal coagulation and inflammatory profile and the authors themselves mentioned that a causal relationship cannot be established.<sup>10</sup> Although the case report by Venkatesh et al., had deranged D-Dimer values which could be an aggravating factor, the patient had preexisting mild non proliferative diabetic retinopathy which weakens the direct causal relationship with COVID -19 as patient already had microangiopathy in the form of diabetic retinopathy which per se can lead to venous occlusion.<sup>11</sup> The report by Raval et al., had

no derangement of coagulation and inflammatory parameters.<sup>12</sup> The case described by Duff et al lacked reports on coagulation and inflammatory profiles. Furthermore, the patient had history of hyperlipidemia.<sup>13</sup>

## **CRAO**

The case reported by Turedi et al. lacked the classic CRAO finding. The findings were significantly more of PAMM. Despite the COVID-19 anticoagulation therapy for 14 days, the fact that the patient developed CRAO makes it less likely to be COVID induced. There was no mention of systemic co-morbidities by the authors.<sup>14</sup> The case report by Murchison et al. had history of cannabis usage and hypertension, both of which are risk factors of CRAO.<sup>15-16</sup> The strongest association of COVID-19 and RAO is probably from the case reports by Ozsaygili et al., as the report had deranged coagulation and inflammatory profiles with no systemic co-morbidity.<sup>17</sup> Bilateral CRAO described by Maneesh et al., had normal coagulation and inflammatory profiles. Furthermore, at the time of presentation patient was RT-PCR negative.<sup>18</sup> All other cases had deranged coagulation and inflammatory profiles, but they also had systemic risk factors that could cause retinal artery occlusion independently, which weakens the COVID-19 association.<sup>19-21</sup>

Until the date this article was being prepared, 182 million people have been affected with COVID-19 worldwide<sup>22</sup> and we have only 17 case reports of retinal vascular occlusion in the published literature with possible association of COVID-19. The estimated prevalence of CRVO is 0.8/ 1000 in the non-COVID era.<sup>23</sup> Similarly, the incidence of CRAO is 1 in 100,000<sup>24</sup> which makes it difficult to attribute retinal vascular occlusion to COVID-19 when the disease has been



much more common in the non-COVID-19 era. Recently Sunny et al also analyzed 66 patients of CRVO who presented to their center and concluded that the occurrence of CRVO could be a coincidence in these at-risk COVID-19 positive patients.<sup>25</sup> However, we need to agree on the fact that thromboembolic phenomenon post cytokine storm is seen most often in moderate to severe COVID-19 cases where ophthalmological examination may not be practical and patients in such critical conditions may also not be able to detect decreased vision. Complete spectrum of lab investigations, ophthalmic examination and clinical documentation would be able to shed some light on this association in the future.<sup>26</sup>

## **Conclusion**

To summarize, the incidence of COVID-19 related retinal vascular occlusion is extremely low and the strength of association is weak based on the current published data. COVID-19 induced pro-thrombosis and inflammation were considered as background hypothesis to explain the causal relationship but prothrombotic and inflammatory markers were normal or missing in half of the reports along with systemic confounding factors in majority of the cases. We agree that we are still in the process of understanding COVID-19 and its microvascular complications.<sup>26</sup> This review should be considered as an index manuscript based on the scrutiny of available evidences till date. Clinicians can continue to manage these patients according to the standard guidelines until there are more robust evidences to support this association to alter the diagnostic and treatment approach.

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