

Review

Acute Macular Neuroretinopathy Mediated by COVID-19 Infection: Insights into its Clinical Features and Pathogenesis

Yixuan Xi^{1,2,3}, Ziyi Zhou², Tianfang Chang², Guorui Dou^{2,*}, Zhaojie Chu^{3,4,*}

¹College of Life Sciences, Northwestern University, 710069 Xi'an, Shaanxi, China

²Department of Ophthalmology, Eye Institute of Chinese PLA, Xijing Hospital, Fourth Military Medical University, 710032 Xi'an, Shaanxi, China

³Department of Ophthalmology, First Affiliated Hospital of Northwest University, Xi'an First Hospital, 710002 Xi'an, Shaanxi, China

⁴Shaanxi Institute of Ophthalmology, 710021 Xi'an, Shaanxi, China

*Correspondence: fierywang@126.com (Guorui Dou); chuzhaojie2009@163.com (Zhaojie Chu)

Academic Editor: Gabriella Lupo

Submitted: 3 September 2024 Revised: 21 November 2024 Accepted: 26 November 2024 Published: 24 April 2025

Abstract

Acute macular neuroretinopathy (AMN) is a rare retinal condition that predominantly affects young females. The incidence of AMN increased significantly during the COVID-19 pandemic, thereby providing a unique opportunity to elucidate the etiology of this disease. In the present study, 24 articles reporting 59 patients were reviewed. The average age of the patients was 33.51 ± 14.02 years, ranging from 16 to 75 years, with females comprising 71.19% of the cases. The average duration of ocular symptoms post-infection was 8.22 ± 10.69 days, ranging from 4 to 150 days. This study investigated the potential pathogenesis of AMN, including the impact of COVID-19 on retinal neurovascular structure and function, immune-mediated inflammatory factor production, blood-retinal barrier disruption, and retinal microvascular damage, as well as potential clinical therapeutic interventions. This research provides a theoretical framework that can inform further investigations of AMN.

Keywords: acute macular neuroretinopathy; COVID-19; clinical features; pathogenesis; fundus imaging

1. Introduction

Acute macular neuroretinopathy (AMN) is a rare retinal disease first described by Bos and Deurman [1]. It is most commonly observed in young and healthy females, and is characterized by the sudden onset of monocular or binocular symptoms that can progressively worsen over days or weeks. AMN lesions often exhibit varying shades of reddish-brown, brown, or purple. Imaging with frequency-domain optical coherence tomography (OCT) reveals various abnormal findings, including rupture of the ellipsoid zone, increased reflectivity of the outer nuclear layer, thinning of the outer nuclear layer, decreased reflectivity of the photoreceptor/retinal pigment epithelium (RPE) complex, and extensive loss of the outer retina [2–4]. Clinical associations with AMN include the use of oral contraceptives, and exposure to vasoconstrictive substances such as epinephrine or ephedrine, trauma, shock, intravenous contrast, preeclampsia, postpartum hypotension, and caffeine intake [3,5–9].

An association between the development of AMN and respiratory or influenza-like illnesses was reported previously [10]. COVID-19 has been the most prevalent influenza-like respiratory disease in recent years, and an increased incidence of AMN has been observed in COVID-19 patients and in individuals who received COVID-19 vaccinations [4]. Although this suggests that COVID-19 infection contributes to an increased prevalence of AMN, the potential mechanisms linking these two conditions remain

unclear, thus presenting a challenge for the clinical prevention and treatment of AMN. Investigation and elucidation of the underlying mechanism for COVID-19-induced AMN is therefore of considerable importance for the prevention and treatment of AMN, as well as other ocular complications caused by the COVID-19 pandemic.

Currently, most research suggests the primary mechanism of AMN involves vascular damage to the deep retinal capillary plexus, leading to occlusion of the ocular microvessels. This results in ischemic retinopathy, which triggers retinal hemorrhage, damage to photoreceptors and macula, and ultimately induces AMN [11,12]. However, some studies have reported that patients with AMN often suffer decreased visual acuity, possibly indicating damage to the retinal ganglia and disruption of the blood-brain barrier, although the precise mechanism of AMN is still unclear [7,8,10]. A study has also shown that COVID-19 induces the development of microvascular thrombosis and endothelial cell dysfunction, suggesting a potential link between COVID-19 and AMN [13]. Indeed, there is increasing evidence of an association between COVID-19 and ocular diseases [14]. Transmission of COVID-19 via the ocular surface was postulated during the early stages of the pandemic, with recent findings supporting this hypothesis [15]. Nevertheless, the clinical features, pathogenesis, and treatment of COVID-19-related AMN have yet to be fully characterized.



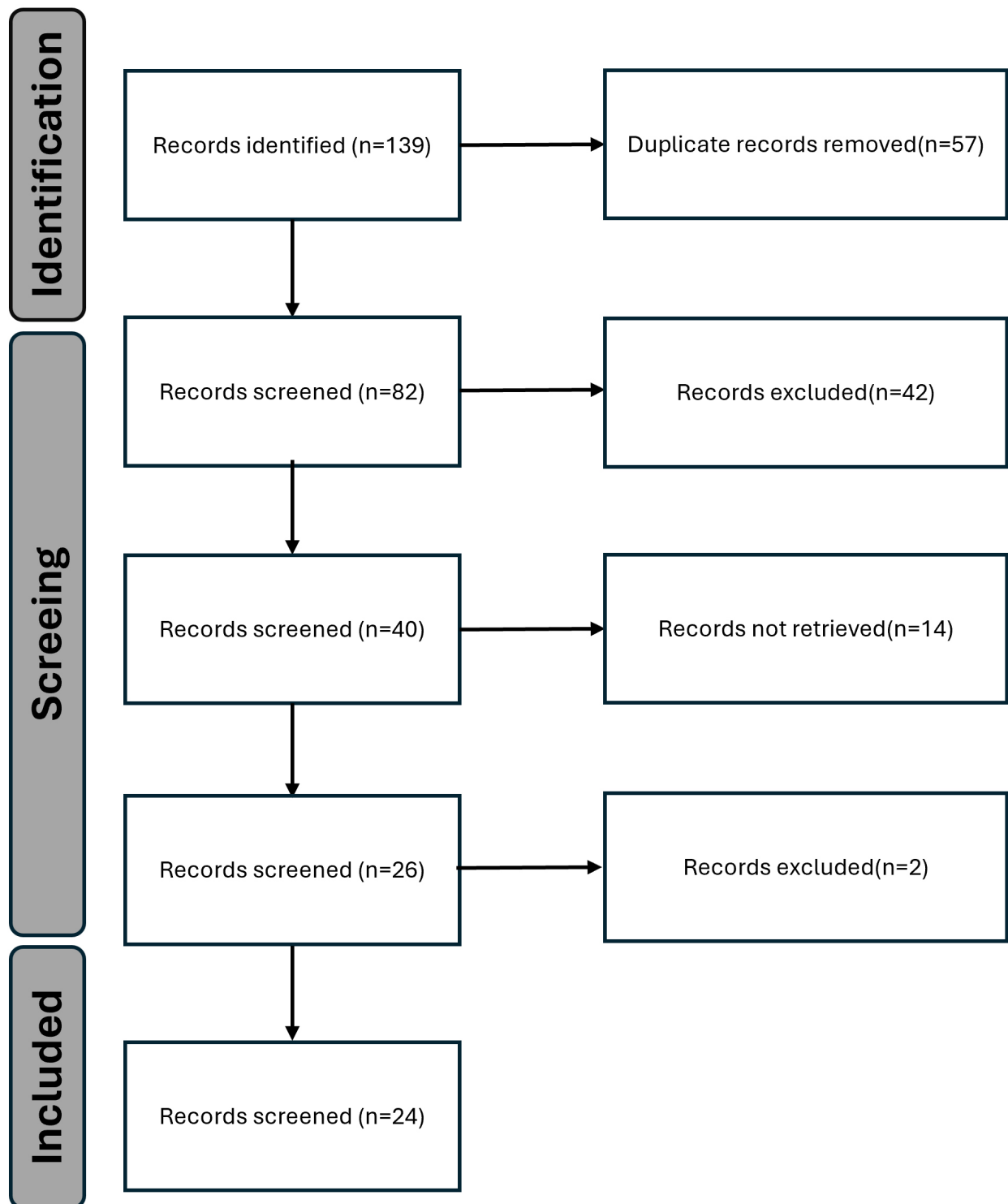


Fig. 1. PRISMA flow diagram showing the process of data collection and selection.

The aim of this review was therefore to compile and analyze the clinical manifestations and diagnostic features of AMN associated with COVID-19, and to compare our findings with those of previous reports. Based on existing studies, we investigated the effects of COVID-19 on the structure and function of the retinal neurovascular unit. These effects may underline potential pathogenic mecha-

nisms involving the secretion of immune storm factors, disruption of the blood-retinal barrier (BRB), and damage to the retinal microvasculature. Our objectives were to provide a theoretical framework and foundation for further investigation of AMN, and to identify areas for possible therapeutic intervention.

Table 1. Clinical presentation in a series of reports on COVID-19-associated AMN.

Article	Sex	Age (years)	Symptoms	¹ Time of onset (days)	Severity of COVID-19	Unilateral or bilateral	Imaging	Follow-up (days)
Ajaz S <i>et al.</i> [16]	Female	28	Paracentral scotoma	NR	NR	OU	OCT, OCTA	35
	Female	22	Paracentral scotoma	NR	NR	OD	OCT, OCTA	60
	Female	27	Paracentral scotoma	NR	NR	OU	OCT, OCTA	NR
Jalink and Bronkhorst [17]	Female	29	Scotomas	14	Moderate	OS	OCT, VF	NR
	Female	40	Scotomas	150	Mild	OD	OCT, VF	NR
	Female	21	Scotomas, photopsias	42	Mild	OD	OCT, VF	90
	Female	42	Scotomas	45	Mild	OD	OCT, VF	NR
Preti <i>et al.</i> [18]	Male	70	Scotomas, diaphoresis	4	Severe	OS	OCT	30
Aidar <i>et al.</i> [19]	Female	71	Blurry vision	14	Moderate	OS	OCT	60
David and Fivga [20]	Female	22	Scotomas	14	Moderate	OU	OCT, OCTA, ICGA	280
Zamani <i>et al.</i> [21]	Female	20	Scotomas	9	Mild	OD	OCT	6
Gascon <i>et al.</i> [22]	Male	53	Scotoma	NR	NR	OS	OCT, ICGA	11
Virgo and Mohamed [23]	Male	32	Paracentral scotoma	16	Moderate	OD	OCT, VF	NR
	Female	37	Paracentral scotoma	35	Mild	OD	OCT, VF	NR
Giacuzzo <i>et al.</i> [24]	Female	23	Paracentral scotoma	14	Moderate	OU	OCT, VF	30
Masjedi <i>et al.</i> [25]	Female	29	Paracentral scotoma	14	Moderate	OS	OCT	90
Bellur S <i>et al.</i> [26]	Female	64	Persistent central vision loss	3	Severe	OU	OCT, OCTA	14
Capuano V <i>et al.</i> [27]	Female	37	Paracentral scotoma	NR	NR	OU	OCT	30
	Male	27	NR	NR	NR	OU	OCT	30
Goyal M <i>et al.</i> [28]	Male	32	Paracentral scotoma	120	Mild	OU	OCT	NR
El Matri <i>et al.</i> [29]	Female	75	Paracentral scotoma	30	Moderate	OD	OCTA	NR
Macé and Pipelart [30]	Female	39	Paracentral scotoma, photopsia	2	Mild	OU	OCTA	30
Diafas A <i>et al.</i> [31]	Male	59	Paracentral scotoma	NR	NR	OU	OCTA	42
Strzalkowski <i>et al.</i> [32]	Female	18	Central scotomas	NR	NR	OU	OCTA	30

Table 1. Continued.

Article	Sex	Age (years)	Symptoms	¹ Time of onset (days)	Severity of COVID-19	Unilateral or bilateral	Imaging	Follow-up (days)
Liu YC <i>et al.</i> [33]	Male	19	NR	5	Moderate	OU	OCTA	NR
	Male	35	Paracentral scotoma	5	Moderate	OU	OCTA, OCT	NR
	Female	17	NR	4	Moderate	OU	OCT	NR
	Male	28	Scotomas	4	Moderate	OU	OCTA, OCT	NR
	Male	37	Decreased vision	2	Moderate	OU	OCT	NR
	Female	49	Blurred vision	5	Moderate	OU	OCTA, FFA	NR
	Female	23	Scotoma, decreased vision	1	Moderate	OU	OCTA, FFA	20
	Female	32	Decreased vision	4	Moderate	OU	OCTA	NR
	Male	16	NR	2	Moderate	OU	OCTA	NR
Kovalchuk <i>et al.</i> [34]	Female	16	Paracentral scotomas	1	Severe	OU	OCTA, OCT	30
Hawley and Han [35]	Female	21	bilateral Paracentral scotomas	2	Severe	OU	OCT	NR
Reddy S <i>et al.</i> [36]	Female	24	scotomas	5	Moderate	OU	OCT, OCTA	NR
Sonmez <i>et al.</i> [37]	Female	41	Paracentral scotoma	30	Moderate	OD	OCTA	30
Feng <i>et al.</i> [38]	Male	34	Paracentral scotoma	2	NR	NR	OCT, OCTA	56
	Male	42	Blurred vision	3	NR	OU	OCT, OCTA	84
	Male	37	Central Scotomas	10	NR	NR	OCT, ICGA	84
	Female	39	Blurred vision, Paracentral scotoma	1	NR	OU	OCT, OCTA	112
	Female	36	Central scotoma	2	NR	OU	OCT, OCTA	105
	Female	41	Decreased vision	3	NR	OU	OCT, ICGA	56
Tang J <i>et al.</i> [39]	Male	27	Scotoma, photopsia	2	Mild	OU	OCT	NR
	Female	25	Scotoma, photopsia	2	Mild	OS	OCT	NR
	Female	27	Scotoma, Decreased vision	2	Severe	OU	OCT	NR
	Female	29	Scotoma, Decreased vision	10	Mild	OU	OCT	NR
	Female	16	Scotoma	2	Severe	OS	OCT	NR
	Female	54	Scotoma	NR	NR	OS	OCT	NR
Average		33.5 (SD 14.02)		8.22 (SD 10.69)	Mild: 28.57% Moderate: 54.28% Severe: 17.14%	OU 67.79% OS 32.21%		59.51 (SD 40.71)

¹ Time of onset: number of days after COVID-19 diagnosis until AMN was identified.

Abbreviations: OCT, Optical Coherence Tomography; OCTA, Optical Coherence Tomography Angiography; FFA, Fluorescein Fundus Angiography; VF, Ventricular Fibrillation; ICGA, Indocyanine Green Angiography; NR, Not Reported; AMN, Acute macular neuroretinopathy; OU, oculus unati; OS, oculus sinister; OD, oculus dextrus.

2. Clinical Features of COVID-19-Associated AMN

Inclusion and Exclusion Criteria for AMN Cases

The inclusion criteria for this literature search were: (1) studies on AMN caused by COVID-19 or SARS-CoV-2 infection; (2) publication between April 2021 and April 2024; (3) original research or case reports. The exclusion criteria were: (1) studies on AMN that were not associated with COVID-19 or SARS-CoV-2 infection; (2) studies related to AMN following COVID-19 vaccination.

The pathogenesis of a disease is closely associated with its clinical manifestations. To elucidate the molecular mechanisms of AMN, it is essential to investigate and identify the epidemic-like characteristics of AMN within the context of the COVID-19 pandemic. The clinical features of AMN induced by COVID-19 were studied by conducting a comprehensive review of relevant articles published in the PubMed database between April 2021 and April 2024. The keywords used in the search were “SARS-CoV-2”, “COVID-19”, and “acute macular neuroretinopathy”. All articles containing these keywords were systematically screened and evaluated, together with their references (Fig. 1). In all, 24 articles [16–39] containing 49 AMN patients were identified. The data collected included the number of cases, patient age and gender, clinical characteristics, time of disease onset after COVID-19 diagnosis, and disease duration (Table 1, Ref. [16–39]). This data was subsequently analyzed using IBM SPSS Statistics software V27.2.1 (IBM Corp., Armonk, NY, USA).

The demographic and clinical characteristics of the patients are shown in Table 1. Among the 49 participants, females predominated and comprised 71.19% of the study cohort. The mean age of patients was 33.51 years, with a range of 16 to 75 years. Data on the time of onset of ocular symptoms post-infection was available for 42 patients. Of these, 39 developed ocular symptoms after a mean of 8.22 days, with a range of 4 to 150 days. In the 3 remaining patients, ocular symptoms manifested concurrently with COVID-19. All patients underwent OCT or OCTA imaging, which revealed abnormalities in all cases. Moreover, we have observed that the severity of COVID-19 is related to the incidence of AMN. Among the 49 patients, 35 patients had reported COVID-19 severity, including 10 mild cases (10/35, 28.57%), 19 moderate cases (19/35, 54.28%), and 6 severe cases (6/35, 17.14%), further indicating the correlation between the incidence of AMN and COVID-19.

The most prevalent ocular manifestation was acute onset of a scotoma (32/49, 65.30%), occasionally associated with blurred vision (6/49, 12.24%), decreased vision (6/49, 12.24%), and photopsia (5/49, 10.20%). Additional reported symptoms included persistent and central vision loss [26]. Among the patients with follow-up data (average follow-up period: 59.51 ± 40.71 days, range 6 to 180 days), 3 recovered completely, 21 experienced a partial recovery, 5 demonstrated no clinical or imaging improvement, and

1 patient succumbed. In most cases, the macular hypo reflectance focus (arrow) was observed by infrared (Fig. 2A), and the corresponding macular optical coherence tomography showed the high reflection of the outer plexiform layer, thinning of the outer nuclear layer (arrow) and interruption of the continuity of the ellipsoid zone (arrow) (Fig. 2B).

The incidence of AMN increased substantially during the COVID-19 pandemic, accompanied by a concomitant rise in related conditions. Because the neurological and vascular clinical manifestations of AMN are more obvious in patients with COVID-19, we hypothesized these may be related to alterations in the retinal neurovascular unit (RNVU) and in the BRB. The specific pathogenesis of AMN is explored in detail in subsequent sections.

3. Pathogenesis of the Retinal Neurovascular Unit is Mediated by COVID-19

3.1 The Retinal Neurovascular Unit is the Primary Target of COVID-19 Infection

The neurovascular unit (NUV) concept was formulated during the initial Stroke Progress Review Group meeting organized by the National Institute of Neurological Disorders and Stroke, a division of the National Institutes of Health (<https://www.ninds.nih.gov>). This concept was developed to highlight the intricate interplay between cerebral cellular components and the brain's vascular network, whose structural and functional impairments underlie many neurodegenerative and neuroinflammatory disorders [40,41]. The NVU denotes the functional coupling and interdependence among neurons, glial cells, and the vascular system [42]. As an extension of the brain, the eye has a similar structure to the NVU, referred to as the RNVU. This consists mainly of retinal neurons, neuroglia and the retinal microvascular system distributed within the corresponding retinal structures [43,44].

COVID-19 enters host cells mainly via the spike (S) protein, which exists as a homotrimer on the viral surface [45,46]. The S protein interacts with angiotensin-converting enzyme 2 (ACE2), which serves as the host receptor for COVID-19. After this interaction, the virus enters the cell through a mechanism facilitated by transmembrane serine protease 2 (TMPRSS2) [47]. Expression of ACE2 has been detected on the surface (cornea and conjunctiva) and on the inside of the eye (iris, trabecular meshwork, and retina) [48–51]. The virus can invade all structures in the retinal tissue, and COVID-19 virus particles have been found in autopsy samples of retinopathy [52]. The S protein interacts with ACE2 and is detected within the deeper ocular structures, specifically in the retinal ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer segment of the photoreceptor [53]. The ACE2 receptor has also been detected at the mRNA and protein levels in rat and porcine retinas [54,55], and its expression in the retina has been demonstrated by *in situ* hybridization. These observations suggest that COVID-19 is located in

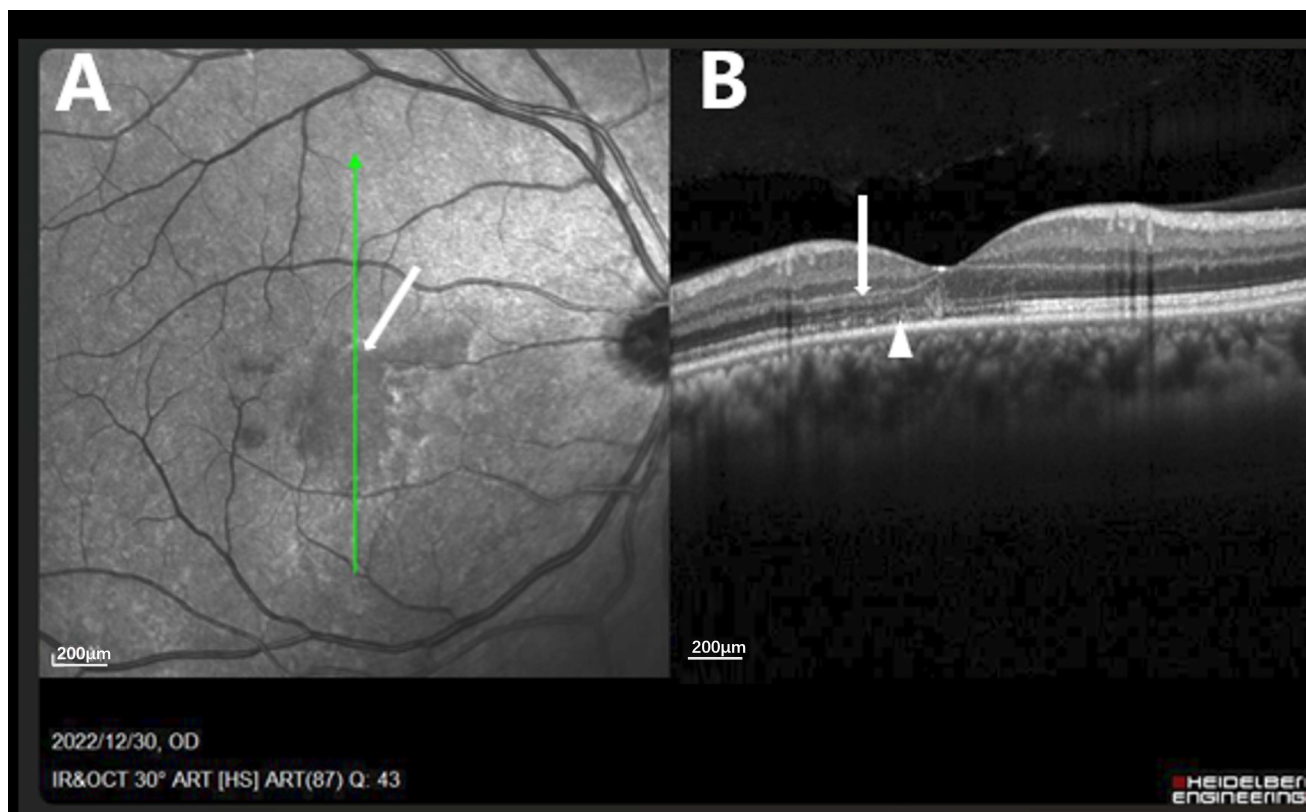


Fig. 2. Infrared and optical coherence tomography images of patient. The infrared image (A) of the eye showed the macular hypo-reflectance focus (arrow), and the corresponding right macular optical coherence tomography (B) showed the high reflection of the outer plexiform layer, thinning of the outer nuclear layer (arrow) and interruption of the continuity of the ellipsoid zone (arrowhead). The scale bar is 200 μm .

the RNUV following infection, and that the interaction between COVID-19 and ACE2 may result in retinal inflammation and significant upregulation of inflammatory cytokines, including TNF- α , IL-6, IL-10, and IL-23 [56,57]. Thus, COVID-19 invasion of the retina, leading to structural and functional alterations in the RNVU, may be a potential mechanism for the pathogenesis of AMN.

3.2 Involvement of Retinal Neurons and their Subsequent Damage

3.2.1 Retinal Ganglion Cell Involvement

Five types of neurons exist in the RNVU: photoreceptors, horizontal cells, bipolar cells, amacrine cells, and ganglion cells. Photoreceptor cells detect light stimuli and transmit signals to bipolar and ganglion cells, which subsequently convey these signals to the central nervous system (CNS) via the optic nerve [58]. Retinal ganglion cells (RGCs) are neural retinal elements that connect visual receptors to the brain to form the neurovisual system. The functional and morphological involvement of RGCs is essential for retinal function, making them critical targets for protective strategies in retinal diseases [59]. The ACE2 receptor is readily detected in eye and brain tissues, and is expressed ubiquitously throughout the human visual system

and CNS [60–63]. COVID-19 exhibits a preferential infection and replication pattern in the RGCs of human retina-like organs. A comparative analysis of differentially expressed genes in retinal organoids revealed the enrichment of TGF- β -responsive genes. TGF- β signaling plays a crucial role in maintaining the immune status of the eye. RGCs inhibit T-cell activation through the secretion of TGF- β . COVID-19 infection of the retina results in apoptosis and damage to RGCs, leading to an increased number of T cells. This process induces the upregulation of immune factors and triggers AMN [64,65].

The optic nerve and the visual circuit of the brain contain significant amounts of ACE2 receptor mRNA and protein [66]. The abundance of ACE2 receptors correlates with the propensity to attract and bind COVID-19, thereby facilitating entry of the virus into human host cells. Elevated expression of ACE2 receptors on the outermost surface of the eye and extending through the RGCs into the brain could potentially impact vision and the CNS, thus contributing to the development of AMN.

3.2.2 Retinal Photoreceptor Involvement

In retinopathy, the vascular system is considered to be the primary site of pathology and is therefore the prin-

cial focus of research for elucidating visual dysfunction. However, the potential contribution of photoreceptor cells, which comprise the majority of retinal structures and drive metabolic activity, remains largely overlooked in the context of vascular disease. Even under conditions that induce the degeneration of photoreceptor cells, little attention has been directed towards damage to retinal capillaries resulting from the decline of photoreceptor cells [48–51,67–69].

The photoreceptor is the predominant cell type in the retina and the most metabolically active neuron in the RNUV, containing at least 75% of the retinal mitochondria. Photoreceptors serve a unique function in the body by absorbing light and transducing it into electrical energy, thereby facilitating vision. Research has found that alterations or impairment of photoreceptors in the retina are related to the pathogenesis of AMN [70–72].

Studies have revealed the presence of defects in the junction between the inner and outer segments of the photoreceptor, attenuation of the outer nuclear layer (ONL) [73–76], thinning of the photoreceptor outer segments, and localized hyper-reflectivity in the outer retina, which subsequently progress to degenerative changes [76–78]. Hansen *et al.* [79] employed adaptive optical scanning ophthalmoscopy (AOSLO) and SD-OCT to examine photoreceptor chimeras in patients with AMN and to evaluate the structures of rods and cones. SD-OCT images showed that the two bands in the outer retina, which are usually associated with the photoreceptor structure, exhibited diminished intensity. Moreover, AOSLO imaging revealed the cone cells exhibited significant structural deterioration in regions with diminished retinal sensitivity, as determined by microperimetry. In retinal organoids infected with COVID-19, the S protein of the virus was predominantly localized in photoreceptors, leading to their structural and functional impairment and consequent retinal dysfunction [63].

The COVID-19 targeting and degeneration of retinal photoreceptors subsequently damages the retinal capillaries, thus potentially affecting the normal functioning of the retina and initiating AMN.

3.3 Retinal Glial Cell Involvement

The glial component of the RNVU is comprised of macroglia (astrocytes and Müller cells), microglia, and oligodendrocytes. These encompass neurons, establish retinal defense structures, and contribute to the maintenance of retinal homeostasis. Glial cells serve as the interface between neurons and the vascular system, and are critical regulators of functional communication [80]. COVID-19 affects not only cells within the retina, but also other retinal cells including Müller cells, microglia, and astrocytes. In patients with COVID-19, binding of ACE2 protein to COVID-19 S protein results in the activation of Müller cells [81–85]. A significant correlation has been observed between Müller cell activation and cone cell alterations [86,87].

Microglial activation is also prominent in the retina following COVID-19 infection. Albertos *et al.* [88] reported the presence of microglial nodules surrounding retinal blood vessels in the superficial vascular plexus, analogous to those observed in the brain tissue of COVID-19 patients. They also noted an increase in the perivascular periphery of all vascular plexuses, and a higher proportion of microglia. Increased levels of pro-inflammatory factors in the blood of COVID-19 patients may facilitate the activation and migration of microglia, potentially affecting the development and function of retinal photoreceptors, RPE, and ganglion cells. This may lead to impaired retinal outcomes and function, thereby inducing AMN [89,90].

The potential mechanism for COVID-19-induced AMN may therefore involve neuronal and glial damage in the RNUV that alters its structure and function, which in turn triggers AMN.

3.4 Involvement of the Retinal Microvasculature and Damage to the BRB

Changes to the retinal microvasculature and disruption of the BRB have been implicated in the pathogenesis of AMN. Inflammatory responses following COVID-19 infection may trigger vascular or embolic events that lead to ischemia in the deep retinal capillary plexus, thereby disrupting the BRB and manifesting as relatively hypodense regions in the retina [91–93]. OCT and OCTA have revealed the presence of superficial or deep capillary plexus (DCP) and choroidal capillary ischemia in AMN [94–97].

Approximately 30% of COVID-19 patients experience complications caused by thrombosis. Inactivation of ACE2 can disrupt the equilibrium of the renin-angiotensin system, resulting in vasoconstriction and inadequate retinal vascular perfusion [98]. This makes patients vulnerable to retinal ischemia, which can potentially lead to AMN. Azar *et al.* [99] proposed that virus-induced endothelial injury may be the primary mechanism underlying the pathogenesis of AMN caused by COVID-19, which could correspond to microvascular damage in the DCP. Using OCTA, Liu *et al.* [100] observed decreased vascular density in the superficial capillary plexus (SCP), DCP, choriocapillaris, and large vessel layer in all AMN cases, with DCP exhibiting the most decrease. This suggests that pathogenesis of the acute phase of AMN may be associated with decreased vascular density resulting from microvascular contractions in the deep retina. A prospective study utilizing OCT to analyze the retinal microcirculation found that changes in macular microvessel density in the plexiform layer served as a clinical marker for the severity of COVID-19, and also indicated possible immune thrombosis [101]. Based on these findings, it was hypothesized that AMN is associated with decreased microvascular circulation.

Damage and destruction of vascular endothelial cells (ECs) plays a crucial role in the impairment of microvascular function. A recent study found that markers associated

with endothelial inflammation and injury pathways, including IL-6, TNF- α , ICAM-1, and caspase-1, were elevated in the pulmonary tissues of individuals with COVID-19 compared to individuals with 2009 H1N1 influenza and to control groups [102]. Motta *et al.* [103] reported that human brain microvascular ECs infected with COVID-19 showed increased cysteine cleavage and apoptotic cell death. Additionally, analysis of RNA sequencing data revealed increased expression of endothelial activation markers such as RELB (p50) and TNF- α . Vascular ECs infected with COVID-19 are stimulated to produce substances that enhance inflammation and form new blood vessels. This increases the expression of certain tight junction proteins (ZO-1, occludin, and claudin-5) and decreases permeability of the blood-brain barrier [104,105]. The resulting increase in plasma angiogenic markers such as VEGF-A enhances endothelial leakage and the infiltration of inflammatory cells [106,107]. Consequently, the damage and death of vascular ECs results in dysfunction of the microvascular circulation, thereby altering the structure of the retina, impairing its function, and inducing AMN.

Microvascular dysfunction is significantly affected by the senescence of vascular ECs. COVID-19 infection specifically elicits this process, which functions as a critical stress response. The aggregate effects of COVID-19-induced senescence and angiogenesis may vary depending on the disease phase. Treatment of human ECs with both TNF- α and IFN- γ enhances the expression of ACE2 receptor, thereby facilitating viral entry through the JAK/STAT1 pathway [108]. Additionally, fluid from virus-infected cells stimulates the formation of neutrophil extracellular traps and platelet activation [109]. D'Agnillo *et al.* [110] reported elevated levels of cellular senescence-related markers, including PAI-1, p21, and sirtuin-1, in the serum and lung ECs of COVID-19 patients. Furthermore, cellular senescence was associated with vascular endothelial inflammation characterized by ICAM-1 and increased VCAM-1 expression, which play crucial roles in promoting leukocyte adhesion to activated ECs [111].

Consequently, one of the potential mechanisms for AMN is that COVID-19 infection induces the senescence or secondary senescence of ECs. This leads to vascular endothelial inflammation and the expression of associated factors, as well as disruption of the BRB, resulting in dysfunction of microvascular circulation and alterations in the structure and function of the retina.

RPE cells are essential for various aspects of eye function, including nutrient transport, light absorption, and the production of cytokines and chemokines. Impairment of RPE function can lead to visual disturbances and potentially trigger the onset of AMN. A recent study of COVID-19-associated AMN found distinctive OCT features, including increased reflectivity in the macular outer plexiform and outer nuclear layers, as well as disruptions in the ellipsoid and interphalangeal regions, as well as in the RPE layers.

Of note, the enhanced reflectivity observed by OCT in the outer retinal layers may be an indirect indicator of damage to nearby photoreceptors and the RPE [112]. These clinical observations suggest that COVID-19 may have a detrimental effect on the RPE, potentially contributing to the development of AMN.

COVID-19 and its spike proteins can induce cellular senescence. Zhang *et al.* [113] demonstrated the S protein of COVID-19 could induce senescence of ARPE-19 cells *in vitro* by increasing the level of cytosolic reactive oxygen species (ROS), endoplasmic reticulum (ER) stress, and activating the NF- κ B pathway. Under stressful conditions, ROS is the primary cause of cellular senescence. COVID-19 infection induces ER stress in cells, which is crucial for viral replication and damage to host cells [114,115]. Furthermore, activation of the NF- κ B pathway is closely associated with COVID-19-induced acute inflammation and the expression of senescence-associated inflammatory factors [116,117]. Based on this evidence, a hypothesis to explain the AMN manifestations of COVID-19 has been proposed. In addition to direct viral damage, the spike proteins of COVID-19 may stimulate increased production of senescence-associated inflammatory factors or acute inflammation, resulting in RPE senescence and injury [118].

3.5 The Immune Response and Cytokine Storm

When the immune system fails to recognize specific body components, it can produce autoantibodies that target cells, tissues, or organs. This phenomenon results in inflammatory reactions, and ultimately leads to the development of autoimmune diseases [119]. The specific pathogenic mechanism associated with COVID-19 infection has yet to be fully elucidated. However, a study has shown that COVID-19 can induce excessive production of inflammatory cytokines [120]. This immune response can facilitate the fight against the virus, or contribute to excessive production of inflammatory chemokines, potentially leading to a “cytokine storm” that exacerbates the patient’s severe condition [121].

COVID-19 infection also damages mitochondrial structure and function, thereby promoting the production of inflammatory cytokines and triggering AMN. Ajaz *et al.* [16] found that COVID-19 appropriates the host mitochondria, which is an essential organelle in innate immune signaling. COVID-19 then induces mitochondrial dysfunction, resulting in oxidative stress and the production of pro-inflammatory cytokines, and subsequently causing damage that affects retinal function.

Finally, the mechanism of COVID-19-induced AMN may not be limited to single cell damage. Rather, COVID-19 could potentially inflict varying degrees of harm on multiple retinal cell types, thus affecting the structure and function of the retina and consequently leading to disease (Fig. 3).

Potential mechanisms of AMN caused by COVID-19

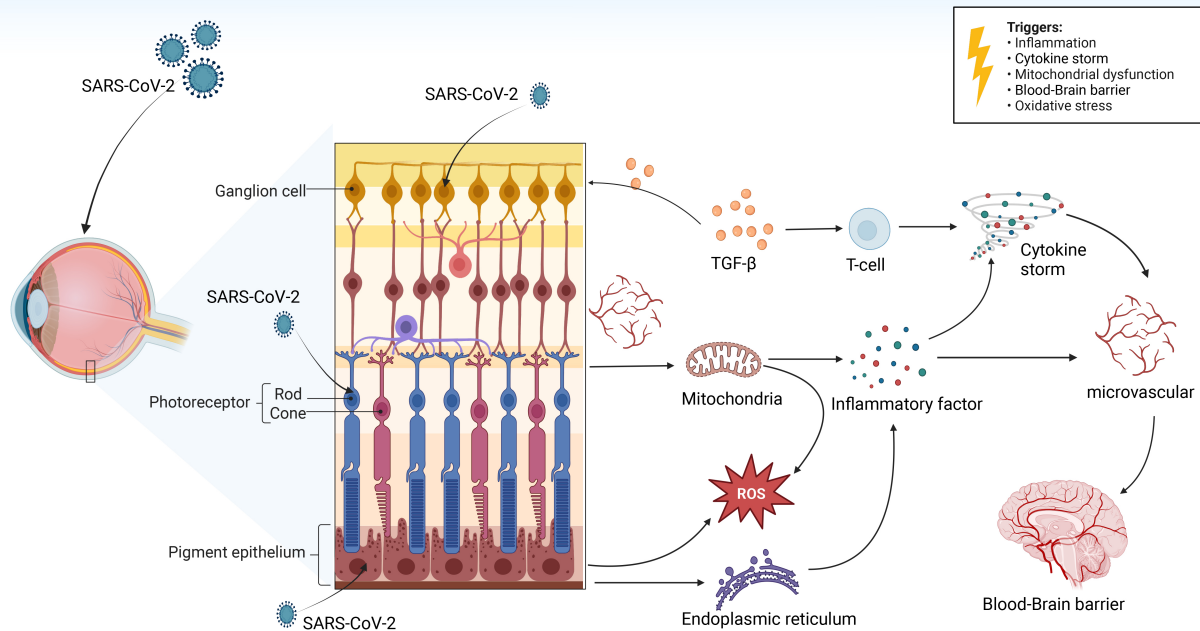


Fig. 3. Proposed mechanisms for AMN caused by COVID-19 infection. COVID-19 infects the inner retina (ganglion cells, photoreceptors, RPE) and recruits TGF- β to the retina. This leads to T-cell activation, mitochondrial dysfunction, and endoplasmic reticulum stress. Subsequently, the upregulation of inflammatory factors triggers a cytokine storm, causing damage to the retinal microvasculature and blood-brain barrier. This affects the visual system and leads to AMN. Created with biorender.com (<https://www.biorender.com>).

4. Current Therapeutic Options

At present, no established treatment exists for COVID-19-related AMN. Consequently, the pharmacological interventions discussed below have proven effective against COVID-19, or represent potential therapeutic approaches.

4.1 Corticosteroids

Corticosteroids have been used extensively to treat cytokine storm syndrome, which is characterized by excessive inflammation resulting from the overproduction of immune cells and cytokines [122]. This syndrome can manifest during various infections or autoimmune conditions, and a significant increase in several cytokines has been observed in a subset of COVID-19 patients [123]. The primary mechanism of corticosteroid action involves the inhibition of viral entry and replication by targeting viral proteins, or by modulating the host immune response to reduce hyperinflammation caused by COVID-19 infection [124–127]. This is achieved by decreasing the expression of two principal proteins utilized by COVID-19 for cellular uptake: TMPRSS2 and ACE2 [128].

Nevertheless, the high dosage and prolonged course of corticosteroids required to treat severe cases can result in adverse effects and undesirable reactions, including longer

virus elimination and increased susceptibility to opportunistic infections. Consequently, attention has turned to the development of corticosteroid-reducing medications (immunomodulators) and novel corticosteroid administration methods aimed at reducing the required dosage and hence the associated drug-induced risks [129].

4.2 Interferons

Interferons are a group of cytokine-signaling mediators that exhibit critical antiviral activity and play significant roles in innate and adaptive cellular immune responses [130]. Their immunomodulatory and antiviral activities are thought to involve activation of the innate immune response after viral infection, inhibition of viral replication, and stimulation of protein synthesis through interaction with toll-like receptors [131]. Interferons are widely used in ophthalmology for the treatment of ocular surface tumors, macular edema, and other anterior and posterior chamber pathologies. Recombinant forms of interferon have also been employed to treat various viral infections and neoplastic diseases [132,133]. The efficacy of interferon β (IFN- β) in treating MERS indicates that it may have potential as an alternative therapy for COVID-19, especially when used in conjunction with other medications. Interferon β 1 (IFN- β 1) is a powerful coronavirus inhibitor and may also be a

safe and effective treatment for COVID-19. Its therapeutic impact can be amplified when administered with drugs such as lopinavir/ritonavir, ribavirin, or remdesivir [134,135].

4.3 Arbidol Hydrochloride

Arbidol hydrochloride is an antiviral drug that inhibits interaction between the spike protein and ACE2 [136]. It has been used extensively in the prevention and treatment of influenza, and is currently being investigated for its potential efficacy against COVID-19 using an identical dosing regimen (200 mg every 8 h). Although preliminary results from a small, non-randomized study has shown promise, further research is needed to comprehensively evaluate its effectiveness [137]. As with other pharmaceutical agents, no ocular adverse effects associated with its use have been reported. Arbidol is a non-nucleoside antiviral agent that prevents viral entry into host cells by inhibiting the virus lipid envelope from fusing with the host cell membrane. Arbidol can also boost the host immune system by inducing the production of interferons and activating macrophages [138].

4.4 Camostat Mesylate

Carmustine mesylate exerts its effect on the host enzyme TMPRSS2, a member of the serine protease family. This mechanism inhibits viral entry and impedes virus-cell membrane fusion, thereby effectively suppressing viral replication [139]. Regulatory approval for this pharmaceutical agent has been received for the treatment of pancreatitis in Japan, and it also exhibits some efficacy against other coronaviruses. However, definitive evidence for its effectiveness against COVID-19 remains to be established [140].

4.5 Tocilizumab

Tocilizumab is an immunomodulatory drug recently approved by the U.S. Food and Drug Administration for Phase III clinical trials of critically ill COVID-19 patients. COVID-19 infection results in compromised vascular integrity, activated coagulation, and increased inflammation due to IL-6 trans-signaling. The therapeutic mechanism of tocilizumab involves the targeting of endothelial IL-6 signaling transduction to mitigate COVID-19-induced cytokine storm symptoms [141]. This medication is typically administered either as a monotherapy or in combination with other drugs to manage various autoimmune disorders, including rheumatoid arthritis [142,143].

5. Conclusions and Perspectives

The presence of COVID-19 in the eye can result in various ocular diseases. AMN is a rare retinal disorder with few cases reported prior to the COVID-19 pandemic. However, the incidence of AMN is significantly higher in patients with COVID-19. This observation suggests the virus plays a crucial role in the increased prevalence of AMN,

highlighting the need for further investigation into its underlying mechanisms in order to improve disease management. In this study, we examined the demographic and clinical characteristics of COVID-19-induced AMN utilizing the existing literature. We comprehensively analysed the potential mechanisms of COVID-19-induced AMN, focusing not only on microvascular damage but also the effects of COVID-19 on immunological factors and the BRB. We posit that COVID-19 induces damage to the retina and retinal cells, resulting in impairment of the microvascular circulation and subsequently triggering the development of AMN. This hypothesis provides a theoretical foundation for further investigation of the specific pathophysiological mechanisms underlying AMN.

The continuous mutation of COVID-19 enhances its immune escape and transmission capabilities, thus underscoring the importance of clinical prevention and treatment strategies. This review examined agents that can effectively reduce viral infection and associated toxicity in COVID-19. However, certain drugs exhibit varying adverse effects that necessitate careful consideration in the clinical setting. These therapeutic interventions may provide a foundation for future clinical treatments.

Author Contributions

Conceptualization, GD and YX; Methodology, YX, GD, and TC; Investigation, YX, and ZZ; Resources, YX; Data curation, YX and ZC; Writing—original draft preparation, ZC and YX; Writing—review and editing, ZC, GD, and YX; Visualization, YX and ZZ; Supervision, GD and ZC; designed the research study, ZC. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Northwestern University Clinical Research.

Acknowledgment

We deeply appreciate Dr. Yannian Hui from Dept. Ophthalmology of Xijing Hospital for his critical thinking and constructive suggestions for this work.

Funding

This study was supported by grants from the National Natural Science Foundation of China (Nos. 82371071, 81970814, and 82000905); clinical AFFMU foundation support (2021JSTS28); Science and Technology Project of Xi'an (22YXYJ0053).

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Bos PJ, Deutman AF. Acute macular neuroretinopathy. *American Journal of Ophthalmology*. 1975; 80: 573–584. [https://doi.org/10.1016/0002-9394\(75\)90387-6](https://doi.org/10.1016/0002-9394(75)90387-6).
- [2] Bhavsar KV, Lin S, Rahimy E, Joseph A, Freund KB, Sarraf D, et al. Acute macular neuroretinopathy: A comprehensive review of the literature. *Survey of Ophthalmology*. 2016; 61: 538–565. <https://doi.org/10.1016/j.survophthal.2016.03.003>.
- [3] Valenzuela DA, Groth S, Taubenslag KJ, Gangaputra S. Acute macular neuroretinopathy following Pfizer-BioNTech COVID-19 vaccination. *American Journal of Ophthalmology Case Reports*. 2021; 24: 101200. <https://doi.org/10.1016/j.ajoc.2021.101200>.
- [4] Yeo S, Kim H, Lee J, Yi J, Chung YR. Retinal vascular occlusions in COVID-19 infection and vaccination: a literature review. *Graefes's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie*. 2023; 261: 1793–1808. <https://doi.org/10.1007/s00417-022-05953-7>.
- [5] Sen M, Honavar SG, Sharma N, Sachdev MS. COVID-19 and Eye: A Review of Ophthalmic Manifestations of COVID-19. *Indian Journal of Ophthalmology*. 2021; 69: 488–509. https://doi.org/10.4103/ijo.IJO_297_21.
- [6] Rauegger T, Blatsios G, Haas G, Putz G, Zehetner C. C-Shaped Scotoma after Complicated Cesarean Section: A Case of Acute Macular Neuroretinopathy. *Case Reports in Ophthalmology*. 2019; 10: 391–396. <https://doi.org/10.1159/000504289>.
- [7] Gupta N, Padidam S, Tewari A. Acute macular neuroretinopathy (AMN) related to energy drink consumption. *BMJ Case Reports*. 2019; 12: e232144. <https://doi.org/10.1136/bcr-2019-232144>.
- [8] Stanescu-Segall D, Yap C, Burton BJL. Acute Macular Neuroretinopathy following Oral Intake of Adrenergic Flu Treatments. *Case Reports in Ophthalmology*. 2018; 9: 322–326. <https://doi.org/10.1159/000487075>.
- [9] Nentwich MM, Leys A, Cramer A, Ulbig MW. Traumatic retinopathy presenting as acute macular neuroretinopathy. *The British Journal of Ophthalmology*. 2013; 97: 1268–1272. <https://doi.org/10.1136/bjophthalmol-2013-303354>.
- [10] Ashfaq I, Vrahimi M, Waugh S, Soomro T, Grinton ME, Browning AC. Acute Macular Neuroretinopathy Associated with Acute Influenza Virus Infection. *Ocular immunology and inflammation*. 2021; 29: 333–339. <https://doi.org/10.1080/09273948.2019.1681470>.
- [11] Nasiri N, Sharifi H, Bazrafshan A, Noori A, Karamouzian M, Sharifi A. Ocular Manifestations of COVID-19: A Systematic Review and Meta-analysis. *Journal of Ophthalmic & Vision Research*. 2021; 16: 103–112. <https://doi.org/10.18502/jovr.v16i1.8256>.
- [12] Yener AU. COVID-19 and the Eye: Ocular Manifestations, Treatment and Protection Measures. *Ocular Immunology and Inflammation*. 2021; 29: 1225–1233. <https://doi.org/10.1080/09273948.2021.1977829>.
- [13] Badawi AE, Elsheikh SS, Addeen SZ, Soliman MA, Abd-Rabu R, Abdella WS, et al. An Ophthalmic Insight into Novel Coronavirus 2019 Disease: A Comprehensive Review of the Ocular Manifestations and Clinical Hazards. *Journal of Current Ophthalmology*. 2020; 32: 315–328. https://doi.org/10.4103/JOCO.JOCO_255_20.
- [14] Lu CW, Liu XF, Jia ZF. 2019-nCoV transmission through the ocular surface must not be ignored. *Lancet (London, England)*. 2020; 395: e39. [https://doi.org/10.1016/S0140-6736\(20\)30313-5](https://doi.org/10.1016/S0140-6736(20)30313-5).
- [15] Azzolini C, Donati S, Premi E, Baj A, Siracusa C, Genoni A, et al. SARS-CoV-2 on Ocular Surfaces in a Cohort of Patients With COVID-19 From the Lombardy Region, Italy. *JAMA Ophthalmology*. 2021; 139: 956–963. <https://doi.org/10.1001/jamaophthalmol.2020.5464>.
- [16] Ajaz S, McPhail MJ, Singh KK, Mujib S, Trovato FM, Napoli S, et al. Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19. *American Journal of Physiology. Cell Physiology*. 2021; 320: C57–C65. <https://doi.org/10.1152/ajpcell.00426.2020>.
- [17] Jalink MB, Bronkhorst IHG. A Sudden Rise of Patients with Acute Macular Neuroretinopathy during the COVID-19 Pandemic. *Case Reports in Ophthalmology*. 2022; 13: 96–103. <https://doi.org/10.1159/000522080>.
- [18] Preti RC, Zacharias LC, Cunha LP, Monteiro MLR. ACUTE MACULAR NEURORETINOPATHY AS THE PRESENTING MANIFESTATION OF COVID-19 INFECTION. *Retinal Cases & Brief Reports*. 2022; 16: 12–15. <https://doi.org/10.1097/ICB.0000000000001050>.
- [19] Aidar MN, Gomes TM, de Almeida MZH, de Andrade EP, Seracarbassa PD. Low Visual Acuity Due to Acute Macular Neuroretinopathy Associated with COVID-19: A Case Report. *The American Journal of Case Reports*. 2021; 22: e931169. <https://doi.org/10.12659/AJCR.931169>.
- [20] David JA, Fivgas GD. Acute macular neuroretinopathy associated with COVID-19 infection. *American Journal of Ophthalmology Case Reports*. 2021; 24: 101232. <https://doi.org/10.1016/j.ajoc.2021.101232>.
- [21] Zamani G, Ataei Azimi S, Aminizadeh A, Shams Abadi E, Kamandi M, Mortazi H, et al. Acute macular neuroretinopathy in a patient with acute myeloid leukemia and deceased by COVID-19: a case report. *Journal of Ophthalmic Inflammation and Infection*. 2021; 10: 39. <https://doi.org/10.1186/s12348-020-00231-1>.
- [22] Gascon P, Briantais A, Bertrand E, Ramtohl P, Comet A, Beylerian M, et al. Covid-19-Associated Retinopathy: A Case Report. *Ocular Immunology and Inflammation*. 2020; 28: 1293–1297. <https://doi.org/10.1080/09273948.2020.1825751>.
- [23] Virgo J, Mohamed M. Paracentral acute middle maculopathy and acute macular neuroretinopathy following SARS-CoV-2 infection. *Eye (London, England)*. 2020; 34: 2352–2353. <https://doi.org/10.1038/s41433-020-1069-8>.
- [24] Giacuzzo C, Eandi CM, Kawasaki A. Bilateral acute macular neuroretinopathy following COVID-19 infection. *Acta Ophthalmologica*. 2022; 100: e611–e612. <https://doi.org/10.1111/aos.14913>.
- [25] Masjedi M, Pourazizi M, Hosseini NS. Acute macular neuroretinopathy as a manifestation of coronavirus disease 2019: A case report. *Clinical Case Reports*. 2021; 9: e04976. <https://doi.org/10.1002/ccr3.4976>.
- [26] Bellur S, Zeleny A, Patronas M, Jiramongkolchai K, Kodati S. Bilateral Acute Macular Neuroretinopathy after COVID-19 Vaccination and Infection. *Ocular Immunology and Inflammation*. 2023; 31: 1222–1225. <https://doi.org/10.1080/09273948.2022.2093753>.
- [27] Capuano V, Forte P, Sacconi R, Miere A, Mehanna CJ, Barone C, et al. Acute macular neuroretinopathy as the first stage of SARS-CoV-2 infection. *European Journal of Ophthalmology*. 2023; 33: NP105–NP111. <https://doi.org/10.1177/11206721221090697>.
- [28] Goyal M, Murthy SI, Annum S. Retinal manifestations in patients following COVID-19 infection: A consecutive case series. *Indian Journal of Ophthalmology*. 2021; 69: 1275–1282. https://doi.org/10.4103/ijo.IJO_403_21.
- [29] El Matri K, Werda S, Chebil A, Falfoul Y, Hassairi A, Bouraoui R, et al. Acute macular outer retinopathy as a presumed manifestation of COVID-19. *Journal Francais D'ophtalmologie*. 2021;

- 44: 1274–1277. <https://doi.org/10.1016/j.jfo.2021.06.002>.
- [30] Macé T, Pipelart V. Acute macular neuroretinopathy and SARS-CoV-2 infection: Case report. *Journal Français D'ophtalmologie*. 2021; 44: e519–e521. <https://doi.org/10.1016/j.jfo.2021.07.004>.
- [31] Diafas A, Ghadiri N, Beare N, Madhusudhan S, Pearce I, Tan SZ. Comment on: 'Paracentral acute middle maculopathy and acute macular neuroretinopathy following SARS-CoV-2 infection'. *Eye (London, England)*. 2022; 36: 1507–1509. <https://doi.org/10.1038/s41433-021-01709-5>.
- [32] Strzalkowski P, Steinberg JS, Dithmar S. COVID-19-associated acute macular neuroretinopathy. *Die Ophthalmologie*. 2023; 120: 767–770. <https://doi.org/10.1007/s00347-022-01704-5>.
- [33] Liu YC, Wu B, Wang Y, Chen S. Detection of macular ganglion cell complex loss and correlation with choroidal thickness in chronic and recurrent central serous chorioretinopathy. *International Journal of Ophthalmology*. 2023; 16: 579–588. <https://doi.org/10.18240/ijo.2023.04.12>.
- [34] Kovalchuk B, Kessler LJ, Auffarth GU, Mayer CS. Paracentral scotomas associated with COVID-19 infection. *Die Ophthalmologie*. 2023; 120: 323–327. <https://doi.org/10.1007/s00347-022-01726-z>.
- [35] Hawley L, Han LS. Acute macular neuroretinopathy following COVID-19 infection. *The New Zealand Medical Journal*. 2022; 135: 105–107. <https://doi.org/10.26635/6965.5835>.
- [36] Reddy S, Garvin A, Weeks JL, West MR. In the Eye of the Cytokine Storm: A Tale of SARS-CoV-2-Induced Acute Macular Neuroretinopathy. *Cureus*. 2023; 15: e36797. <https://doi.org/10.7759/cureus.36797>.
- [37] Sonmez HK, Polat OA, Erkan G. Inner retinal layer ischemia and vision loss after COVID-19 infection: A case report. *Photodiagnosis and Photodynamic Therapy*. 2021; 35: 102406. <https://doi.org/10.1016/j.pdpdt.2021.102406>.
- [38] Feng H, Zhao M, Mo J, Cao X, Chen W, Wang H. The characteristics of acute macular neuroretinopathy following COVID-19 infection. *BMC Ophthalmology*. 2024; 24: 19. <https://doi.org/10.1186/s12886-024-03283-2>.
- [39] Tang J, Li S, Wang Z, Tao Y, Zhang L, Yin H, *et al.* Acute Macular Neuroretinopathy after SARS-CoV-2 Infection: An Analysis of Clinical and Multimodal Imaging Characteristics. *Diagnostics (Basel, Switzerland)*. 2023; 13: 3600. <https://doi.org/10.3390/diagnostics13243600>.
- [40] Reed MJ, Damodarasamy M, Banks WA. The extracellular matrix of the blood-brain barrier: structural and functional roles in health, aging, and Alzheimer's disease. *Tissue Barriers*. 2019; 7: 1651157. <https://doi.org/10.1080/21688370.2019.1651157>.
- [41] Erickson, M. A., & Banks, W. A. Neuroimmune Axes of the Blood-Brain Barriers and Blood-Brain Interfaces: Bases for Physiological Regulation, Disease States, and Pharmacological Interventions. *Pharmacological reviews*. 2018; 70: 278–314. <https://doi.org/10.1124/pr.117.014647>.
- [42] Noonan JE, Lamoureux EL, Sarossy M. Neuronal activity-dependent regulation of retinal blood flow. *Clinical & Experimental Ophthalmology*. 2015; 43: 673–682. <https://doi.org/10.1111/ceo.12530>.
- [43] Hammes HP. Diabetic retinopathy: hyperglycaemia, oxidative stress and beyond. *Diabetologia*. 2018; 61: 29–38. <https://doi.org/10.1007/s00125-017-4435-8>.
- [44] Vecino E, Rodriguez FD, Ruzafa N, Pereiro X, Sharma SC. Glia-neuron interactions in the mammalian retina. *Progress in Retinal and Eye Research*. 2016; 51: 1–40. <https://doi.org/10.1016/j.preteyeres.2015.06.003>.
- [45] Zhou L, Xu Z, Castiglione GM, Soiberman US, Eberhart CG, Duh EJ. ACE2 and TMPRSS2 are expressed on the human ocular surface, suggesting susceptibility to SARS-CoV-2 infection. *The Ocular Surface*. 2020; 18: 537–544. <https://doi.org/10.1016/j.jtos.2020.06.007>.
- [46] Schmitt CA, Bergey CM, Jasinska AJ, Ramensky V, Burt F, Svardal H, *et al.* ACE2 and TMPRSS2 variation in savanna monkeys (*Chlorocebus* spp.): Potential risk for zoonotic/anthropogenic transmission of SARS-CoV-2 and a potential model for functional studies. *PloS One*. 2020; 15: e0235106. <https://doi.org/10.1371/journal.pone.0235106>.
- [47] Napoli PE, Nioi M, d'Aloja E, Fossarello M. The Ocular Surface and the Coronavirus Disease 2019: Does a Dual 'Ocular Route' Exist? *Journal of Clinical Medicine*. 2020; 9: 1269. <https://doi.org/10.3390/jcm9051269>.
- [48] Heegaard S, Rosenberg T, Preising M, Prause JU, Bek T. An unusual retinal vascular morphology in connection with a novel AIPL1 mutation in Leber's congenital amaurosis. *The British Journal of Ophthalmology*. 2003; 87: 980–983. <https://doi.org/10.1136/bjo.87.8.980>.
- [49] Pennesi ME, Nishikawa S, Matthes MT, Yasumura D, LaVail MM. The relationship of photoreceptor degeneration to retinal vascular development and loss in mutant rhodopsin transgenic and RCS rats. *Experimental Eye Research*. 2008; 87: 561–570. <https://doi.org/10.1016/j.exer.2008.09.004>.
- [50] de Gooyer TE, Stevenson KA, Humphries P, Simpson DAC, Curtis TM, Gardiner TA, *et al.* Rod photoreceptor loss in Rho-/- mice reduces retinal hypoxia and hypoxia-regulated gene expression. *Investigative Ophthalmology & Visual Science*. 2006; 47: 5553–5560. <https://doi.org/10.1167/iovs.06-0646>.
- [51] Fernández-Sánchez L, Lax P, Esquivá G, Martín-Nieto J, Pinilla I, Cuenca N. Safranin, a saffron constituent, attenuates retinal degeneration in P23H rats. *PloS One*. 2012; 7: e43074. <https://doi.org/10.1371/journal.pone.0043074>.
- [52] Casagrande M, Fitzek A, Püschel K, Aleshcheva G, Schultheiss HP, Berneking L, *et al.* Detection of SARS-CoV-2 in Human Retinal Biopsies of Deceased COVID-19 Patients. *Ocular Immunology and Inflammation*. 2020; 28: 721–725. <https://doi.org/10.1080/09273798.2020.1770301>.
- [53] Ahmed W, Suri A, Ahmed A. COVID-19 and Acute Macular Neuroretinopathy - An underlying association? *Annals of Medicine and Surgery (2012)*. 2022; 78: 103847. <https://doi.org/10.1016/j.amsu.2022.103847>.
- [54] Tikellis C, Johnston CI, Forbes JM, Burns WC, Thomas MC, Lew RA, *et al.* Identification of angiotensin converting enzyme 2 in the rodent retina. *Current Eye Research*. 2004; 29: 419–427. <https://doi.org/10.1080/02713680490517944>.
- [55] Luhtala S, Vaajanen A, Oksala O, Valjakka J, Vapaatalo H. Activities of angiotensin-converting enzymes ACE1 and ACE2 and inhibition by bioactive peptides in porcine ocular tissues. *Journal of Ocular Pharmacology and Therapeutics: the Official Journal of the Association for Ocular Pharmacology and Therapeutics*. 2009; 25: 23–28. <https://doi.org/10.1089/jop.2008.0081>.
- [56] Reynolds JL, Mahajan SD. SARS-COV2 Alters Blood Brain Barrier Integrity Contributing to Neuro-Inflammation. *Journal of Neuroimmune Pharmacology: the Official Journal of the Society on NeuroImmune Pharmacology*. 2021; 16: 4–6. <https://doi.org/10.1007/s11481-020-09975-y>.
- [57] Alquisiras-Burgos I, Peralta-Arrieta I, Alonso-Palomares LA, Zacapala-Gómez AE, Salmerón-Bárceñas EG, Aguilera P. Neurological Complications Associated with the Blood-Brain Barrier Damage Induced by the Inflammatory Response During SARS-CoV-2 Infection. *Molecular Neurobiology*. 2021; 58: 520–535. <https://doi.org/10.1007/s12035-020-02134-7>.
- [58] Cunha-Vaz J, Bernardes R, Lobo C. Blood-retinal barrier. *European Journal of Ophthalmology*. 2011; 21 Suppl 6: S3–S9. <https://doi.org/10.5301/EJO.2010.6049>.
- [59] Parisi V, Oddone F, Ziccardi L, Roberti G, Coppola G, Manni G. Cytokine and Retinal Ganglion Cells: Effects on Morphology and Function. *Current Neuropharmacology*. 2018; 16: 919–932.

<https://doi.org/10.2174/1570159X15666170703111729>.

- [60] Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infectious Diseases of Poverty*. 2020; 9: 45. <https://doi.org/10.1186/s40249-020-00662-x>.
- [61] Lukiw WJ, Pogue A, Hill JM. SARS-CoV-2 Infectivity and Neurological Targets in the Brain. *Cellular and Molecular Neurobiology*. 2022; 42: 217–224. <https://doi.org/10.1007/s10571-020-00947-7>.
- [62] Edo A, Sugita S, Futatsugi Y, Shio J, Onishi A, Kiuchi Y, *et al*. Capacity of Retinal Ganglion Cells Derived from Human Induced Pluripotent Stem Cells to Suppress T-Cells. *International Journal of Molecular Sciences*. 2020; 21: 7831. <https://doi.org/10.3390/ijms21217831>.
- [63] Menuchin-Lasowski Y, Schreiber A, Lecanda A, Mecate-Zambrano A, Brunotte L, Psathaki OE, *et al*. SARS-CoV-2 infects and replicates in photoreceptor and retinal ganglion cells of human retinal organoids. *Stem Cell Reports*. 2022; 17: 789–803. <https://doi.org/10.1016/j.stemcr.2022.02.015>.
- [64] Bertoli F, Veritti D, Danese C, Samassa F, Sarao V, Rassu N, *et al*. Ocular Findings in COVID-19 Patients: A Review of Direct Manifestations and Indirect Effects on the Eye. *Journal of Ophthalmology*. 2020; 2020: 4827304. <https://doi.org/10.1155/2020/4827304>.
- [65] Zhang BZ, Chu H, Han S, Shuai H, Deng J, Hu YF, *et al*. SARS-CoV-2 infects human neural progenitor cells and brain organoids. *Cell Research*. 2020; 30: 928–931. <https://doi.org/10.1038/s41422-020-0390-x>.
- [66] Lukiw WJ. David Hunter Hubel, the 'Circe effect', and SARS-CoV-2 infection of the human visual system. *Frontiers in Bioscience (Landmark Edition)*. 2022; 27: 7. <https://doi.org/10.31083/j.fbl2701007>.
- [67] de Gooyer TE, Stevenson KA, Humphries P, Simpson DAC, Gardiner TA, Stitt AW. Retinopathy is reduced during experimental diabetes in a mouse model of outer retinal degeneration. *Investigative Ophthalmology & Visual Science*. 2006; 47: 5561–5568. <https://doi.org/10.1167/iovs.06-0647>.
- [68] Penn JS, Li S, Naash MI. Ambient hypoxia reverses retinal vascular attenuation in a transgenic mouse model of autosomal dominant retinitis pigmentosa. *Investigative Ophthalmology & Visual Science*. 2000; 41: 4007–4013.
- [69] Liu H, Tang J, Du Y, Saadane A, Tonade D, Samuels I, *et al*. Photoreceptor Cells Influence Retinal Vascular Degeneration in Mouse Models of Retinal Degeneration and Diabetes. *Investigative Ophthalmology & Visual Science*. 2016; 57: 4272–4281. <https://doi.org/10.1167/iovs.16-19415>.
- [70] Masland RH. The fundamental plan of the retina. *Nature Neuroscience*. 2001; 4: 877–886. <https://doi.org/10.1038/nn0901-877>.
- [71] Ames A, 3rd, Li YY, Heher EC, Kimble CR. Energy metabolism of rabbit retina as related to function: high cost of Na⁺ transport. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 1992; 12: 840–853. <https://doi.org/10.1523/JNEUROSCI.12-03-00840.1992>.
- [72] Demontis GC, Longoni B, Marchiafava PL. Molecular steps involved in light-induced oxidative damage to retinal rods. *Investigative Ophthalmology & Visual Science*. 2002; 43: 2421–2427.
- [73] Grover S, Brar VS, Murthy RK, Chalam KV. Infrared imaging and spectral-domain optical coherence tomography findings correlate with microperimetry in acute macular neuroretinopathy: a case report. *Journal of Medical Case Reports*. 2011; 5: 536. <https://doi.org/10.1186/1752-1947-5-536>.
- [74] Hughes EH, Siow YC, Hunyor AP. Acute macular neuroretinopathy: anatomic localisation of the lesion with high-resolution OCT. *Eye (London, England)*. 2009; 23: 2132–2134. <https://doi.org/10.1038/eye.2008.430>.
- [75] Maschi C, Schneider-Lise B, Paoli V, Gastaud P. Acute macular neuroretinopathy: contribution of spectral-domain optical coherence tomography and multifocal ERG. *Graefes's Archive for Clinical and Experimental Ophthalmology = Albrecht Von Graefes Archiv Fur Klinische Und Experimentelle Ophthalmologie*. 2011; 249: 827–831. <https://doi.org/10.1007/s00417-010-1560-1>.
- [76] Yeh S, Hwang TS, Weleber RG, Watzke RC, Francis PJ. Acute macular outer retinopathy (AMOR): a reappraisal of acute macular neuroretinopathy using multimodality diagnostic testing. *Archives of Ophthalmology (Chicago, Ill.: 1960)*. 2011; 129: 365–368. <https://doi.org/10.1001/archophth.129.3.365>.
- [77] Chan WM, Liu DT, Tong JP, Law RW, Lam DS. Longitudinal findings of acute macular neuroretinopathy with multifocal electroretinogram and optical coherence tomography. *Clinical & Experimental Ophthalmology*. 2005; 33: 439–442. <https://doi.org/10.1111/j.1442-9071.2005.01006.x>.
- [78] Vance SK, Spaide RF, Freund KB, Wiznia R, Cooney MJ. Outer retinal abnormalities in acute macular neuroretinopathy. *Retina (Philadelphia, Pa.)*. 2011; 31: 441–445. <https://doi.org/10.1097/IAE.0b013e3181fe54fa>.
- [79] Hansen SO, Cooper RF, Dubra A, Carroll J, Weinberg DV. Selective cone photoreceptor injury in acute macular neuroretinopathy. *Retina (Philadelphia, Pa.)*. 2013; 33: 1650–1658. <https://doi.org/10.1097/IAE.0b013e31828cd03a>.
- [80] Bilimoria PM, Stevens B. Microglia function during brain development: New insights from animal models. *Brain Research*. 2015; 1617: 7–17. <https://doi.org/10.1016/j.brainres.2014.11.032>.
- [81] Cuenca N, Fernández-Sánchez L, Campello L, Maneu V, De la Villa P, Lax P, *et al*. Cellular responses following retinal injuries and therapeutic approaches for neurodegenerative diseases. *Progress in Retinal and Eye Research*. 2014; 43: 17–75. <https://doi.org/10.1016/j.preteyeres.2014.07.001>.
- [82] Bringmann A, Pannicke T, Grosche J, Francke M, Wiedemann P, Skatchkov SN, *et al*. Müller cells in the healthy and diseased retina. *Progress in Retinal and Eye Research*. 2006; 25: 397–424. <https://doi.org/10.1016/j.preteyeres.2006.05.003>.
- [83] Cuenca N, Ortuño-Lizarán I, Sánchez-Sáez X, Kutsyr O, Albertos-Arranz H, Fernández-Sánchez L, *et al*. Interpretation of OCT and OCTA images from a histological approach: Clinical and experimental implications. *Progress in Retinal and Eye Research*. 2020; 77: 100828. <https://doi.org/10.1016/j.preteyeres.2019.100828>.
- [84] Sethi CS, Lewis GP, Fisher SK, Leitner WP, Mann DL, Luthert PJ, *et al*. Glial remodeling and neural plasticity in human retinal detachment with proliferative vitreoretinopathy. *Investigative Ophthalmology & Visual Science*. 2005; 46: 329–342. <https://doi.org/10.1167/iovs.03-0518>.
- [85] Ramírez JM, Ramírez AI, Salazar JJ, de Hoz R, Triviño A. Changes of astrocytes in retinal ageing and age-related macular degeneration. *Experimental Eye Research*. 2001; 73: 601–615. <https://doi.org/10.1006/exer.2001.1061>.
- [86] Wang Y, Detrick B, Yu ZX, Zhang J, Chesky L, Hooks JJ. The role of apoptosis within the retina of coronavirus-infected mice. *Investigative Ophthalmology & Visual Science*. 2000; 41: 3011–3018.
- [87] Zinkernagel MS, Chinnery HR, Ong ML, Petitjean C, Voigt V, McLenachan S, *et al*. Interferon γ -dependent migration of microglial cells in the retina after systemic cytomegalovirus infection. *The American Journal of Pathology*. 2013; 182: 875–885. <https://doi.org/10.1016/j.ajpath.2012.11.031>.
- [88] Albertos-Arranz H, Martínez-Gil N, Sánchez-Sáez X, Noailles A, Monferrer Aduara C, Remolá Sargues L, *et al*. Microglia activation and neuronal alterations in retinas from COVID-19 patients: correlation with clinical parameters. *Eye and Vi-*

- sion (London, England). 2023; 10: 12. <https://doi.org/10.1186/s40662-023-00329-2>.
- [89] Matschke J, Lütgehetmann M, Hagel C, Sperhake JP, Schröder AS, Edler C, *et al.* Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *The Lancet. Neurology*. 2020; 19: 919–929. [https://doi.org/10.1016/S1474-4422\(20\)30308-2](https://doi.org/10.1016/S1474-4422(20)30308-2).
- [90] Thakur KT, Miller EH, Glendinning MD, Al-Dalahmah O, Banu MA, Boehme AK, *et al.* COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. *Brain: a Journal of Neurology*. 2021; 144: 2696–2708. <https://doi.org/10.1093/brain/awab148>.
- [91] Mambretti M, Huemer J, Torregrossa G, Ullrich M, Findl O, Casalino G. Acute Macular Neuroretinopathy following Coronavirus Disease 2019 Vaccination. *Ocular Immunology and Inflammation*. 2021; 29: 730–733. <https://doi.org/10.1080/09273948.2021.1946567>.
- [92] Vinzamuri S, Pradeep TG, Kotian R. Bilateral paracentral acute middle maculopathy and acute macular neuroretinopathy following COVID-19 vaccination. *Indian Journal of Ophthalmology*. 2021; 69: 2862–2864. https://doi.org/10.4103/ijo.IJO_1333_21.
- [93] Aggarwal K, Agarwal A, Katoch D, Sharma M, Gupta V. Optical coherence tomography angiography features of acute macular neuroretinopathy in dengue fever. *Indian Journal of Ophthalmology*. 2017; 65: 1235–1238. https://doi.org/10.4103/ijo.IJO_485_17.
- [94] Chen YC, Chen SN. Microvascular change in acute macular neuroretinopathy by using optical coherence tomography angiography. *Taiwan Journal of Ophthalmology*. 2019; 9: 118–121. https://doi.org/10.4103/tjo.tjo_83_17.
- [95] Casalino G, Arrigo A, Romano F, Munk MR, Bandello F, Parodi MB. Acute macular neuroretinopathy: pathogenetic insights from optical coherence tomography angiography. *The British Journal of Ophthalmology*. 2019; 103: 410–414. <https://doi.org/10.1136/bjophthalmol-2018-312197>.
- [96] Lee SY, Cheng JL, Gehrs KM, Folk JC, Sohn EH, Russell SR, *et al.* Choroidal Features of Acute Macular Neuroretinopathy via Optical Coherence Tomography Angiography and Correlation With Serial Multimodal Imaging. *JAMA Ophthalmology*. 2017; 135: 1177–1183. <https://doi.org/10.1001/jamaophthalmol.2017.3790>.
- [97] Neri P, Pichi F. COVID-19 and the eye immunity: lesson learned from the past and possible new therapeutic insights. *International Ophthalmology*. 2020; 40: 1057–1060. <https://doi.org/10.1007/s10792-020-01389-2>.
- [98] Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, *et al.* Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis Research*. 2020; 191: 145–147. <https://doi.org/10.1016/j.thromres.2020.04.013>.
- [99] Azar G, Bonnin S, Vasseur V, Faure C, Salviat F, Clermont CV, *et al.* Did the COVID-19 Pandemic Increase the Incidence of Acute Macular Neuroretinopathy? *Journal of Clinical Medicine*. 2021; 10: 5038. <https://doi.org/10.3390/jcm10215038>.
- [100] Liu YC, Wu B, Wang Y, Chen S. Clinical and multimodal imaging features of acute macular neuroretinopathy lesions following recent SARS-CoV-2 infection. *International Journal of Ophthalmology*. 2023; 16: 755–761. <https://doi.org/10.18240/ijo.2023.05.13>.
- [101] Hohberger B, Ganslmayer M, Lucio M, Kruse F, Hoffmanns J, Moritz M, *et al.* Retinal Microcirculation as a Correlate of a Systemic Capillary Impairment After Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Frontiers in Medicine*. 2021; 8: 676554. <https://doi.org/10.3389/fmed.2021.676554>.
- [102] Nagashima S, Mendes MC, Camargo Martins AP, Borges NH, Godoy TM, Miggiolaro AFRDS, *et al.* Endothelial Dysfunction and Thrombosis in Patients With COVID-19-Brief Report. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2020; 40: 2404–2407. <https://doi.org/10.1161/ATVBAHA.120.314860>.
- [103] Motta CS, Torices S, da Rosa BG, Marcos AC, Alvarez-Rosa L, Siqueira M, *et al.* Human Brain Microvascular Endothelial Cells Exposure to SARS-CoV-2 Leads to Inflammatory Activation through NF- κ B Non-Canonical Pathway and Mitochondrial Remodeling. *Viruses*. 2023; 15: 745. <https://doi.org/10.3390/v15030745>.
- [104] Caccuri F, Bugatti A, Zani A, De Palma A, Di Silvestre D, Manocha E, *et al.* SARS-CoV-2 Infection Remodels the Phenotype and Promotes Angiogenesis of Primary Human Lung Endothelial Cells. *Microorganisms*. 2021; 9: 1438. <https://doi.org/10.3390/microorganisms9071438>.
- [105] Yang RC, Huang K, Zhang HP, Li L, Zhang YF, Tan C, *et al.* SARS-CoV-2 productively infects human brain microvascular endothelial cells. *Journal of Neuroinflammation*. 2022; 19: 149. <https://doi.org/10.1186/s12974-022-02514-x>.
- [106] Pine AB, Meizlish ML, Goshua G, Chang CH, Zhang H, Bishai J, *et al.* Circulating markers of angiogenesis and endotheliopathy in COVID-19. *Pulmonary Circulation*. 2020; 10: 2045894020966547. <https://doi.org/10.1177/2045894020966547>.
- [107] Filbin MR. Insights into Endotheliopathy in COVID-19. *American Journal of Respiratory and Critical Care Medicine*. 2022; 206: 926–928. <https://doi.org/10.1164/rccm.202207-1258ED>.
- [108] Kandhaya-Pillai R, Yang X, Tchkonja T, Martin GM, Kirkland JL, Oshima J. TNF- α /IFN- γ synergy amplifies senescence-associated inflammation and SARS-CoV-2 receptor expression via hyper-activated JAK/STAT1. *Aging Cell*. 2022; 21: e13646. <https://doi.org/10.1111/acer.13646>.
- [109] Lee S, Yu Y, Trimpert J, Benthani F, Mairhofer M, Richter-Pechanska P, *et al.* Virus-induced senescence is a driver and therapeutic target in COVID-19. *Nature*. 2021; 599: 283–289. <https://doi.org/10.1038/s41586-021-03995-1>.
- [110] D’Agnillo F, Walters KA, Xiao Y, Sheng ZM, Scherler K, Park J, *et al.* Lung epithelial and endothelial damage, loss of tissue repair, inhibition of fibrinolysis, and cellular senescence in fatal COVID-19. *Science Translational Medicine*. 2021; 13: eabj7790. <https://doi.org/10.1126/scitranslmed.abj7790>.
- [111] Meyer K, Patra T, Vijayamahantesh, Ray R. SARS-CoV-2 Spike Protein Induces Paracrine Senescence and Leukocyte Adhesion in Endothelial Cells. *Journal of Virology*. 2021; 95: e0079421. <https://doi.org/10.1128/JVI.00794-21>.
- [112] Xu B, Zhang J, Zhang Y, Cheng Y, Huang Q. Transient Increase in Patient Numbers with “Acute Macular Neuroretinopathy” Post SARS-CoV-2 Infection-Case Series During the First Surge of Infection in December 2022. *Journal of Inflammation Research*. 2023; 16: 2763–2771. <https://doi.org/10.2147/JIR.S413050>.
- [113] Zhang Y, Peng X, Xue M, Liu J, Shang G, Jiang M, *et al.* SARS-COV-2 spike protein promotes RPE cell senescence via the ROS/P53/P21 pathway. *Biogerontology*. 2023; 24: 813–827. <https://doi.org/10.1007/s10522-023-10019-0>.
- [114] Rashid F, Dzakah EE, Wang H, Tang S. The ORF8 protein of SARS-CoV-2 induced endoplasmic reticulum stress and mediated immune evasion by antagonizing production of interferon beta. *Virus Research*. 2021; 296: 198350. <https://doi.org/10.1016/j.virusres.2021.198350>.
- [115] Santerre M, Arjona SP, Allen CN, Shcherbik N, Sawaya BE. Why do SARS-CoV-2 NSPs rush to the ER? *Journal of Neurology*. 2021; 268: 2013–2022. <https://doi.org/10.1007/s00415-020-10197-8>.
- [116] Goel S, Saheb Sharif-Askari F, Saheb Sharif Askari N, Madkhana B, Alwaa AM, Mahboub B, *et al.* SARS-CoV-2 Switches

- 'on' MAPK and NFκB Signaling via the Reduction of Nuclear DUSP1 and DUSP5 Expression. *Frontiers in Pharmacology*. 2021; 12: 631879. <https://doi.org/10.3389/fphar.2021.631879>.
- [117] Zaffagni M, Harris JM, Patop IL, Pamudurti NR, Nguyen S, Kadener S. SARS-CoV-2 Nsp14 mediates the effects of viral infection on the host cell transcriptome. *eLife*. 2022; 11: e71945. <https://doi.org/10.7554/eLife.71945>.
- [118] Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, *et al.* Extrapulmonary manifestations of COVID-19. *Nature Medicine*. 2020; 26: 1017–1032. <https://doi.org/10.1038/s41591-020-0968-3>.
- [119] Betterle C. Le malattie autoimmuni. Padova: Piccin. 2017.
- [120] Infantino M, Damiani A, Gobbi FL, Grossi V, Lari B, Macchia D, *et al.* Serological Assays for SARS-CoV-2 Infectious Disease: Benefits, Limitations and Perspectives. *The Israel Medical Association Journal: IMAJ*. 2020; 22: 203–210.
- [121] Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Seminars in Immunopathology*. 2017; 39: 529–539. <https://doi.org/10.1007/s00281-017-0629-x>.
- [122] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet (London, England)*. 2020; 395: 1033–1034. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0).
- [123] Yang Y, Shen C, Li J, Yuan J, Yang M, Wang F, *et al.* Exuberant elevation of ip-10, mcp-3 and il-1ra during sars-cov-2 infection is associated with disease severity and fatal outcome. *medRxiv*. 2020. (preprint) <https://doi.org/10.1101/2020.03.02.20029975>.
- [124] Campos DMDO, Fulco UL, de Oliveira CBS, Oliveira JIN. SARS-CoV-2 virus infection: Targets and antiviral pharmacological strategies. *Journal of Evidence-based Medicine*. 2020; 13: 255–260. <https://doi.org/10.1111/jebm.12414>.
- [125] Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). *StatPearls*. 2023; .
- [126] Asselah T, Durantel D, Pasmant E, Lau G, Schinazi RF. COVID-19: Discovery, diagnostics and drug development. *Journal of Hepatology*. 2021; 74: 168–184. <https://doi.org/10.1016/j.jhep.2020.09.031>.
- [127] Rocha SM, Fagre AC, Latham AS, Cummings JE, Aboellail TA, Reigan P, *et al.* A Novel Glucocorticoid and Androgen Receptor Modulator Reduces Viral Entry and Innate Immune Inflammatory Responses in the Syrian Hamster Model of SARS-CoV-2 Infection. *Frontiers in Immunology*. 2022; 13: 811430. <https://doi.org/10.3389/fimmu.2022.811430>.
- [128] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020; 323: 1824–1836. <https://doi.org/10.1001/jama.2020.6019>.
- [129] Le Page C, Génin P, Baines MG, Hiscott J. Interferon activation and innate immunity. *Reviews in Immunogenetics*. 2000; 2: 374–386.
- [130] Chan JFW, Yao Y, Yeung ML, Deng W, Bao L, Jia L, *et al.* Treatment With Lopinavir/Ritonavir or Interferon-β1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. *The Journal of Infectious Diseases*. 2015; 212: 1904–1913. <https://doi.org/10.1093/infdis/jiv392>.
- [131] Shah SU, Kaliki S, Kim HJ, Lally SE, Shields JA, Shields CL. Topical interferon alfa-2b for management of ocular surface squamous neoplasia in 23 cases: outcomes based on American Joint Committee on Cancer classification. *Archives of Ophthalmology (Chicago, Ill.: 1960)*. 2012; 130: 159–164. <https://doi.org/10.1001/archophthalmol.2011.385>.
- [132] Deuter CME, Koetter I, Guenaydin I, Stuebiger N, Zierhut M. Interferon alfa-2a: a new treatment option for long lasting refractory cystoid macular edema in uveitis? A pilot study. *Retina (Philadelphia, Pa.)*. 2006; 26: 786–791. <https://doi.org/10.1097/01.iae.0000244265.75771.71>.
- [133] Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, *et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature Communications*. 2020; 11: 222. <https://doi.org/10.1038/s41467-019-13940-6>.
- [134] Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. *Antiviral Research*. 2020; 178: 104791. <https://doi.org/10.1016/j.antiviral.2020.104791>.
- [135] Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. *Proceedings of the National Academy of Sciences of the United States of America*. 2017; 114: 206–214. <https://doi.org/10.1073/pnas.1617020114>.
- [136] Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases With Coronavirus Disease 2019 in Wuhan, China. *Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America*. 2020; 71: 769–777. <https://doi.org/10.1093/cid/ciaa272>.
- [137] Wang X, Cao R, Zhang H, Liu J, Xu M, Hu H, *et al.* The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. *Cell Discovery*. 2020; 6: 28. <https://doi.org/10.1038/s41421-020-0169-8>.
- [138] Breining P, Frølund AL, Hojen JF, Gunst JD, Staerke NB, Saedder E, *et al.* Camostat mesylate against SARS-CoV-2 and COVID-19-Rationale, dosing and safety. *Basic & Clinical Pharmacology & Toxicology*. 2021; 128: 204–212. <https://doi.org/10.1111/bcpt.13533>.
- [139] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, *et al.* SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020; 181: 271–280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>.
- [140] Kang S, Kishimoto T. Interplay between interleukin-6 signaling and the vascular endothelium in cytokine storms. *Experimental & Molecular Medicine*. 2021; 53: 1116–1123. <https://doi.org/10.1038/s12276-021-00649-0>.
- [141] Sy A, Eliasieh K, Silkiss RZ. Clinical Response to Tocilizumab in Severe Thyroid Eye Disease. *Ophthalmic Plastic and Reconstructive Surgery*. 2017; 33: e55–e57. <https://doi.org/10.1097/IOP.0000000000000730>.
- [142] Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, *et al.* Trial of Tocilizumab in Giant-Cell Arteritis. *The New England Journal of Medicine*. 2017; 377: 317–328. <https://doi.org/10.1056/NEJMoa1613849>.
- [143] Sheth JU, Narayanan R, Goyal J, Goyal V. Retinal vein occlusion in COVID-19: A novel entity. *Indian Journal of Ophthalmology*. 2020; 68: 2291–2293. https://doi.org/10.4103/ijo.IJO_2380_20.