

BILATERAL ACUTE MACULAR NEURORETINOPATHY IN ACUTE COVID-19 INFECTION: A CASE STUDY

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SUMMARY

Introduction: Acute macular neuroretinopathy (AMN) is a rare disease of uncertain etiology that mostly affects young women.

Aim: The aim of the present paper is to describe the case study of a female patient with bilateral AMN, suffering from active acute infection with COVID-19.

Methods: A 32-year-old female patient with impaired vision bilaterally persisting for 2 days reported to the emergency Department of Ophthalmology at the Central Military Hospital in Ružomberok, Slovakia. The patient manifested symptoms of COVID-19 infection persisting for 3 days before the onset of visual complaints.

Results: At the primary examination, initial uncorrected central visual acuity was 20/40 bilaterally, paracentral scotomas were present more in the right eye. Upon examination of the ocular fundus, the edges of the optic nerve disc were out of focus more in the left eye; brownish-red petaloid lesions were present around the fovea, the periphery was without pathological findings. OCT and OCTA were performed, with a conclusion of bilateral AMN upon a background of COVID-19 infection. Low molecular weight heparin (LMWH) was administered in a preventive dose.

Conclusion: The number of documented ocular complications of COVID-19 infection, including microvascular events, is currently increasing.

Key words: acute macular neuroretinopathy, COVID-19, OCT, OCTA

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INTRODUCTION

Acute macular neuroretinopathy (AMN) is a rare microvascular pathology of the retina. This disease was first recorded and described by Bosom and Deutman in 1975 [1].

AMN is characterized by an acute onset of deterioration of vision with paracentral scotomas. The symptoms may be either unilateral or bilateral, and may be either temporary or permanent [2]. In the majority of cases, progression or recurrence of the disease does not take place. Scotomas are relative, and can be identified with the aid of perimeter or an Amsler grid.

Upon ophthalmoscopic examination, we identify brownish-red petaloid (or cuneiform) perifoveal lesions on the ocular fundus. It is these lesions that cause relative paracentral scotomas. The size and shape of the lesions can be documented by means of red-free fundus photography, or with the aid of optical coherence to-

mography (OCT). With the development of OCT, Sarraf et al. [3] categorized the lesions into two types on the basis of the afflicted retinal layer, which is located above or beneath the outer plexiform layer (OPL). AMN of the first type, known as paracentral acute middle maculopathy (PAMM) is characterized by hyperreflexive bands in the inner nuclear layer (INL). AMN of the second type, classic AMN type 2, is characterized by hyperreflexive bands in the outer nuclear layer (ONL), with impairment of the ellipsoid zone. It was only recently proposed that we start to consider these two types of lesions to constitute different entities [3].

PAMM lesions reflect superficial or intermediate occlusion of the capillary plexus, whereas lesions of classic AMN are caused by deep ischemia of the capillary plexus [5]. The ONL contains rods and cones, the OPL contains synapses between the horizontal or bipolar cells from the INL and nerve fibers of the photore-

ceptors from the ONL. The ellipsoid zone is frequently impaired, but during the development of the pathology it is slowly reconstituted, whereas the ONL remains thinner [6].

Fluorescein angiography is often normal, but may manifest minor abnormalities of the parafoveal capillaries.

The etiology of AMN is manifold, and at present it has not yet been entirely clarified. The incidence of AMN correlates with viral pathologies similar to influenza and vaccines against influenza, as well as with the use of oral contraceptives and with various causes of vasospasm such as systemic shock, or the use of vasoconstrictive pharmaceuticals such as adrenaline [7,8]. However, risk factors are not always present, and AMN frequently occurs in young patients (more than 80% of whom are women, and more than half of whom are in the third decade of life). Other than this, AMN may also occur following non-specific infection or vaccination, or in association with an autoimmune disorder. AMN is bilateral in 50% of affected patients, and in rare cases is associated with edema of the optic nerve [8]. The prevalence of AMN is estimated at less than 1 patient per million [9]. This prevalence may be distorted, since the disease may not be correctly diagnosed. At present no options for therapy exist. It is not known whether or not the discontinuation of oral contraception has an influence on the course of the pathology.

Ocular complications in the case of infection with COVID-19 were anticipated, based on prior experiences with other coronaviruses [10]. Conjunctivitis may be the first sign or symptom, and its presence correlates with the severity of the course of infection with COVID-19. Cotton-wool exudates and micro-hemorrhages have also been recorded on the retina. An increased number of cases of AMN has been recorded in connection with the COVID-19 pandemic [11].

MATERIAL AND METHODS

A 32-year-old female patient reported to the Institutional Emergency Service of the Department of Ophthalmology at the SNP Central Military Hospital in Ružomberok in February 2022. The patient had been COVID-19 positive for 3 days, she had previously been vaccinated by means of two doses of the Pfizer vaccine. She was symptomatic, suffering from body temperatures of above 38°C for 3 days and muscle pains, a cold and cough. Since the previous evening, i.e. the second day of the symptomatic course of the infection, she had subjectively perceived a deterioration of vision in the sense of reduced visual acuity. Since the previous evening she had noticed spots in front of both eyes; initially she assumed that they would disappear by the next day, but this did not take place, and as a result she reported to the emergency service. Her pharmaceutical medical history showed that she has been taking oral contraceptives, otherwise her anamnesis was without any remarkable features. Objectively the patient's uncorrected

visual acuity bilaterally was on the level of 20/40.

A positive Amsler grid showed scotomas more in the right eye. An examination of the anterior segment was without noteworthy features. An examination of the ocular fundus detected bilateral brownish-red lesions in the parafoveal region, which were more pronounced in the left eye. In the left eye the edges of the optic nerve papilla were also out of focus. OCT and OCTA examinations were subsequently performed.

RESULTS

OCT examination displays a hyperreflexive band with parafoveal location on the level of the ONL (Fig. 1). AMN was diagnosed according to the characteristics of the OCT findings.

Although no form of therapy is known to date, we administered low molecular weight heparin (LMWH) to the patient in a therapeutic dose, which she received for one week, before transferring to oral antithrombotic agents following the alleviation of the symptoms of COVID-19 infection. Despite the fact that no evidence exists to date regarding whether or not the discontinuation of oral contraception has an influence on improving the course of AMN, we recommended to our patient that she did not use them during the course of the pathology.

At a follow-up examination the next day, best corrected central visual acuity (BCCVA) was unchanged at 20/40 bilaterally, scotomas were still present, and on the ocular fundus there were formed, bordered brownish-red petaloid lesions characteristic of AMN. OCT and OCTA examinations were performed repeatedly (Fig. 2).

One week later, the patient's central visual acuity had improved. BCCVA was 20/20 bilaterally, though the scotomas persisted, even if they were now less pronounced. The hyperreflexive band on OCT was also now less pronounced (Fig. 3).

One month later, the patient's BCCVA was 20/20 bilaterally, scotomas persisted, but the patient perceived them only in front of her right eye. No hyperreflexive band was now visible on the OCT examination, but the outer layer was thinned and the structure of the layers in the place of the defects was irregular (Fig. 4). This condition persisted also in the subsequent observation period.

DISCUSSION

AMN is a rare retinal pathology which occurs in association with several other diseases. Predisposing or potential triggering factors include viral pathologies or fever (48%), use of oral contraception (36%), use of vasoconstrictive or sympathomimetic agents (8%), and less frequent causes such as hypovolemic shock and bodily trauma [9].

At present, during the COVID-19 pandemic we have recorded an increased incidence of this disease, not only in connection with the viral infection itself, but also with vaccination. The SARS-CoV-2 virus, which

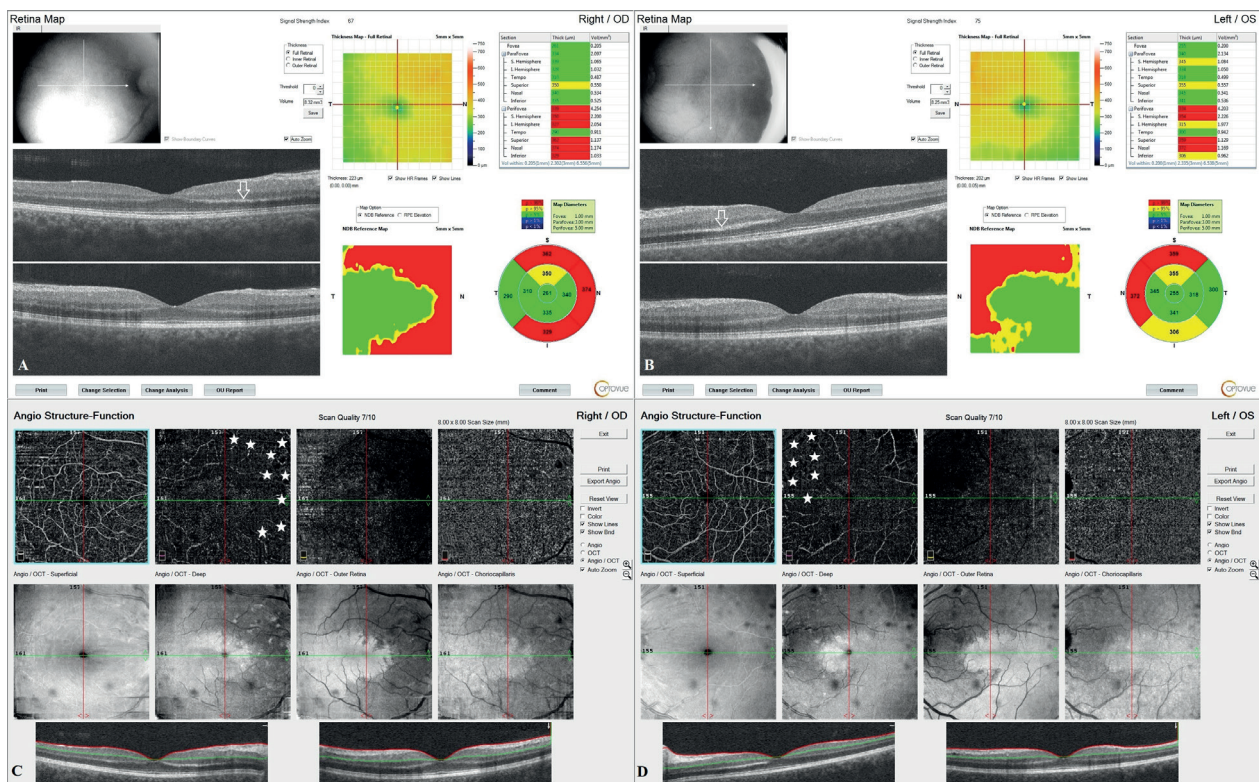


Figure 1. OCT examination of the macula with a hyperreflective band in the outer nuclear layer (white arrows) and nasal macular edema (A, B). OCTA showing retinal ischemia of the superficial and deep (white stars) capillary plexus (C, D)

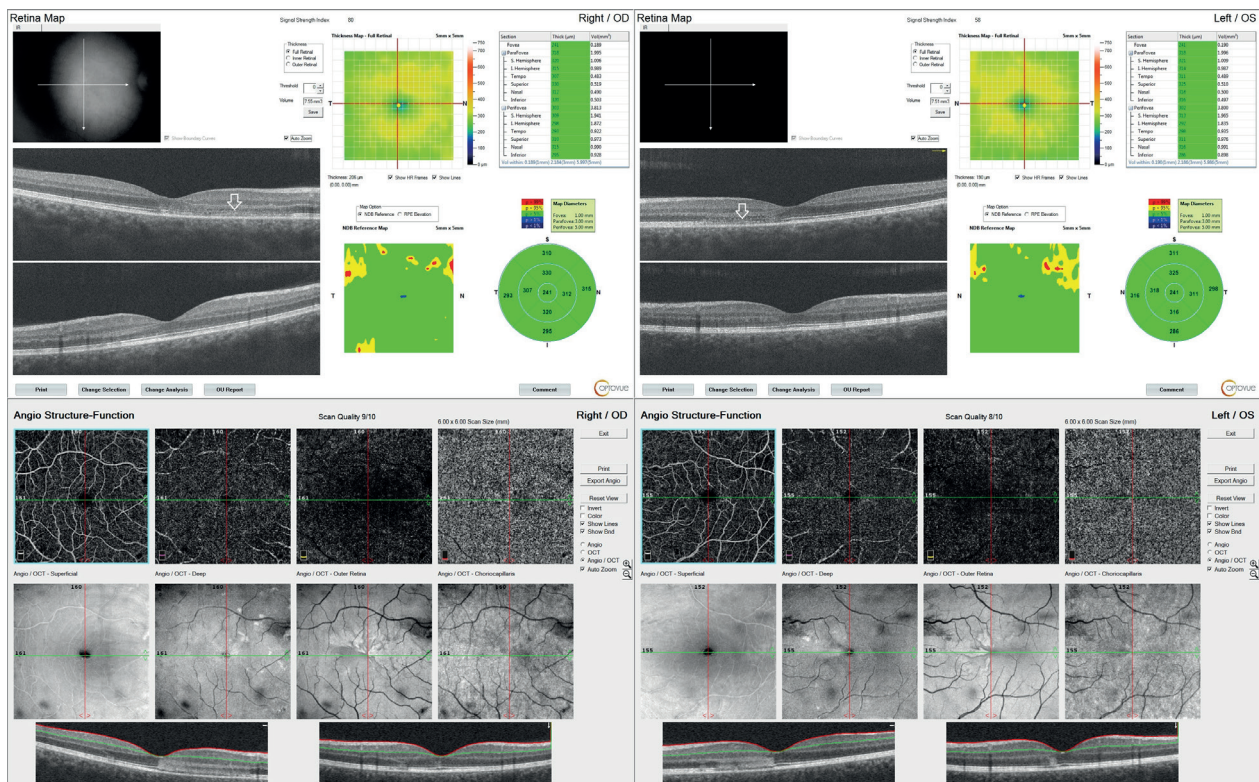


Figure 2. OCT examination shows a wide hyperreflective band (white arrows) in the outer nuclear layer and the outer plexiform layer characteristic of acute macular neuroretinopathy (A, B); OCTA shows typical petaloid lesions with a hyperreflective band in the corresponding parafoveolar lesion site (C, D)

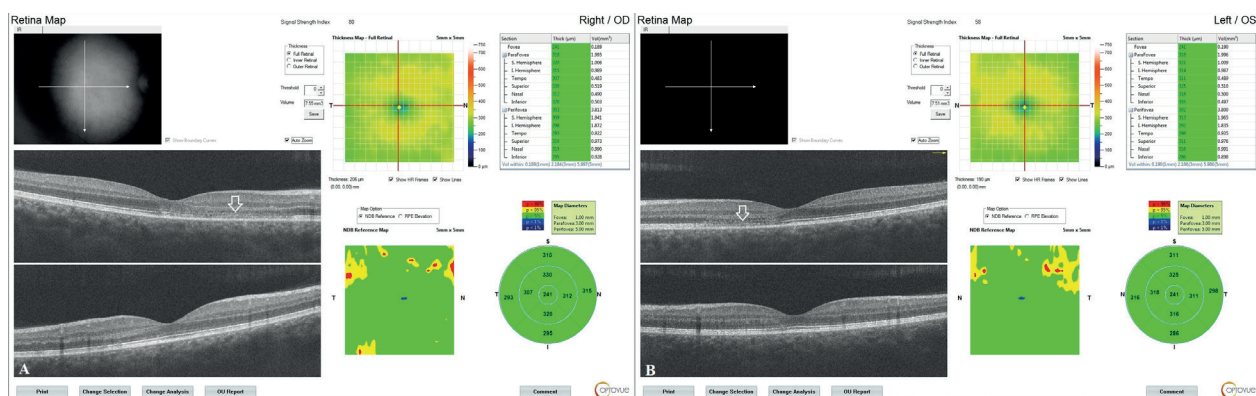


Figure 3. On the OCT examination, we can see reduced hyperreflectivity at the site of the lesions in the outer nuclear layer and the outer plexiform layer (white arrows) (A, B)

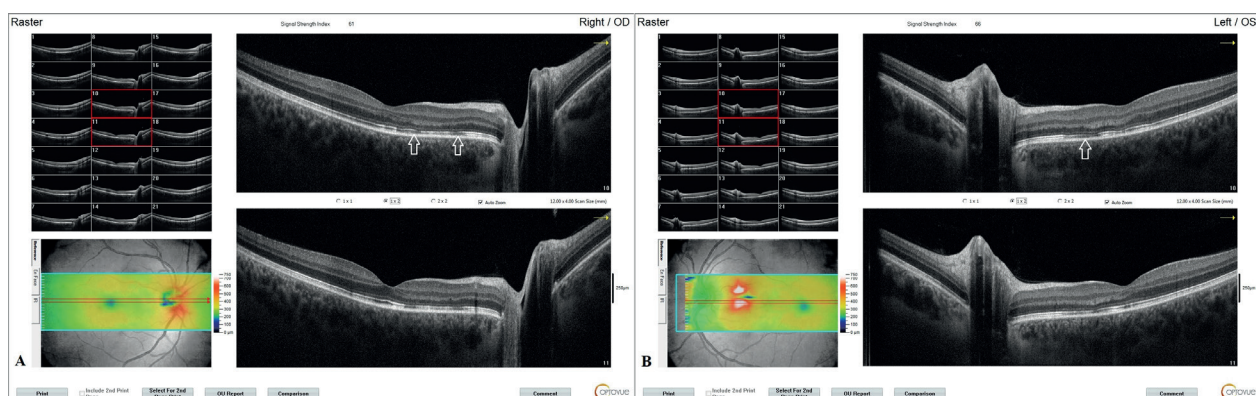


Figure 4. On the OCT examination, we observe thinning in the outer nuclear and plexiform layers of the retina with disruption of the ellipsoid zone (white arrows) (A, B)

triggers the disease coronavirus 2019 (COVID-19) has been the cause of millions of deaths worldwide. A remarkable characteristic of COVID-19 is its capacity to induce a hypercoagulable state, which leads to micro- and macro-thrombotic complications. The presumption is that the use of oral contraception predisposes individuals to such an event, and this is the reason why AMN occurs more frequently in young women [12]. The precise etiology of coagulopathy triggered by COVID-19 has not yet been entirely clarified, but a key element appears to be the connection between the endothelium, the immune system and the coagulation system generated by pathogens [13]. AMN occurs upon a background of a pathology on the level of the microvasculature of the retina, with possible ischemia of the deep capillary plexus. As a result, we may presume that it is associated with hypoperfusion of the retinal circulation. Viral infections and vaccinations generally cause AMN, but during the COVID-19 pandemic we recorded a rapid increase of new cases of AMN. It is only with difficulty that we can evaluate whether AMN occurs more frequently following the COVID-19 infection and its vaccinating substances, or whether this is the consequence of a sharp increase in the number of infected and vaccinated in-

dividuals [14]. However, evidence exists that COVID-19 primarily affects the human retina by means of direct infection. In a series of 14 autopsies on patients who were COVID-19 positive at the time of death, in three cases (21%) it was determined that mRNA COVID-19 was found in the retina [15]. COVID-19 also attacks the retina secondarily by means of its thromboembolic and inflammatory systemic effects.

In this case study we documented the case of a young 32-year-old woman with bilateral symptoms of this pathology upon a background of acute infection with COVID-19. Our patient is a healthy woman of Caucasian race who was using oral contraceptives, which is the most characteristic demographic group for AMN. A positive PCR test for COVID-19, fever, headache and subsequent bilateral scotoma were present at the same time, which makes COVID-19 infection the most probable triggering etiology of AMN. Of course, we must not forget that oral contraception probably also heightened the hypercoagulable state caused by the COVID-19 infection. Although initially the lesions were not of the typical petaloid form, their brownish-red color and OCT finding were characteristic of AMN. OCTA was also of fundamental significance for visualizing the de-

fects of the vascular content and ischemia in the deep retinal capillary plexus.

A case study of a 22-year-old woman by the authors David and Fivgas in 2021 [16] documented a very similar case of bilateral AMN in connection with acute infection with COVID-19, as well as with the use of oral contraceptives. In this case study also, the authors recorded ischemia on OCTA, mainly in the deep retinal capillary plexus. Another study by Chen and Chen in 2019 [17] documented a case of bilateral AMN in a 27-year-old woman with preeclampsia, in which they performed OCTA one month after the onset of AMN with presence of ischemia also in the superficial retinal capillary plexus. This finding may indicate a progression of ischemia in certain cases of AMN. No treatment for AMN exists in general, or in association with COVID-19 infection.

In addition to anticoagulative properties, heparins or low molecular weight heparins (LMWH) have further anti-inflammatory and antiviral effects. Heparin binds cytokines, chemokines, cytotoxic peptides and complement proteins, and reduces the expression of P-selectin, which leads to a reduction of the adhesion of leukocytes to the endothelial cells [18]. Recent experimental studies have determined that human coronaviruses use heparin sulphate in order to bind to the target cells, in which after binding the virus is subject to structural modulation which prevents further infection. On the basis of this evidence, we may presume that heparin provides a valuable therapeutic agent in the battle against COVID-19 induced immunothrombosis [19]. We administered LMWH to our patient in a preventive dose in order to alleviate the progression of ischemia, though further data and research is required in order to establish whether or not this treatment was justified. At minimum, on the basis of the above-stated findings we may state that the treatment was not unjustified, since the patient had active infection with COVID-19 at the time of AMN. A great deal more knowledge is still required concerning potential preventive and therapeutic interventions aimed at alleviating the long-term consequences of upon COVID-19 infection. In our patient we also discontinued the use of oral contraceptives as a potential risk factor of AMN. In the case of this approach also, there is not sufficient evidence or a unified consensus as to whether the discontinuation of oral contraceptives indeed leads to a reduction of retinal ischemia.

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CONCLUSION

Our case study supplements the previous findings concerning the fact that a hypercoagulable state in association with the COVID-19 disease may cause vascular pathologies of the retina such as AMN. As a result, it is necessary to ensure examination of the retina, including OCT and OCTA in the macular region, in patients with defects of vision that occur upon a background of COVID-19 infection or vaccination.

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