

CHAPTER 5

COVID -19 AND OCULAR FINDINGS

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INTRODUCTION

The coronavirus outbreak, which spread from the Chinese city of Wuhan to the whole world in early January 2020, has gained a new aspect when WHO declared the disease as a pandemic. Unlike previous pandemics, failure to detect the initial transmission route of the causative virüs and due to its rapid spread, the Covid-19 pandemics affected millions of people all over the world and caused many deaths at the end of a year. Covid-19, defined as a new RNA β corona virüs, is transmitted from person to person by coughing and sneezing from an infected patient, and direct contact and droplets. The primary target is lung epithelial cells in Covid-19 and this target is associated with angiotensin-converting enzyme (ACE-2) receptors. Patients may develop symptoms ranging from mild symptoms to death with severe respiratory failure, due to both upper and lower respiratory tract affection. Upon the demonstration of ACE receptors in the conjunctiva and retina of the eye, ocular involvement may be caused by the disease or a source of transmission. While no ocular

symptoms or signs were found in the SARS-CoV and MERS-CoV outbreaks in the past, Covid-19 has been demonstrated by PCR in the conjunctiva of patients. Therefore, Covid 19 may cause clinical findings with involvement in ocular structures and the ocular surface is also considered as an entrance to the body for SARS-Cov2. It should also be remembered that ocular contamination is potential occupational exposure for ophthalmologists. In this section; ocular findings of Covid-19, the treatments used, and side effects related to drugs will be discussed.

COVID -19 AND ANTERIOR SEGMENT FINDINGS

Transmission and treatment focused on respiratory disease in Covid 19. However, the ocular surface is presumed to be an entrance, potentially through exposure to aerosol droplets or hand-eye contact. Conjunctivitis is the most common ocular finding in the anterior segment in patients with Covid 19. Cases have been reported suggesting that conjunctivitis may be the first manifestation of the disease and then systemic symptoms begin after a variable time. The pathogenetic mechanisms of conjunctival infections are still unknown. Some studies have shown the presence of ACE-2 receptors in the cornea and conjunctival limbus. This condition may be a cause of conjunctivitis. Another mechanism thought to be responsible for conjunctivitis is an autoimmune-mediated macrophage activation syndrome. Although the exact incidence of Covid 19 conjunctivitis is not known, it is thought to range from 0.8% to 31.6%. Symptoms such as photophobia, stinging, burning, itching and blurred vision develop in patients with Covid 19 conjunctivitis, which are similar to other signs of viral conjunctivitis.

Chemosis, conjunctival hyperemia, follicular reaction of the tarsal conjunctiva, epiphora, watery discharge, mild eyelid edema, eyelid margin hyperemia, blepharitis, and enlarged submaxillary and preauricular lymph nodes were observed on examination. Although conjunctivitis is seen in patients with Covid 19, its incidence is observed to be extremely low compared to the general population. One cause for the less frequent occurrence of viral conjunctivitis may be the protective effect of antimicrobial agents such as lactoferrin and secretory Ig A on tears and continuous cleaning of the ocular surface with tear flow.

Covid 19 can be seen with symptoms similar to Kawasaki Disease (KD) in infants and children. Kawasaki disease is a sudden onset and often self-limiting vasculitis that mostly affects young children and is characterized by

oropharyngeal and limb changes, fever, polymorph rash, and cervical lymphadenopathy. It is of particular importance for ophthalmologists because ocular involvement can be seen in KD. The most common ocular findings in KD are iridocyclitis, subconjunctival hemorrhage, punctate epitheliopathy, papilledema, vitreous opacities and conjunctival injection. It is estimated that the incidence of KD may increase with the spread of the outbreak, and ophthalmologists are recommended to act with awareness in terms of the signs and symptoms of the disease.

Although it is not directly related to the disease, care should be taken when using contact lenses in patients with Covid-19. Patients who wear contact lenses are recommended to suspend contact lenses as much as possible during this period, due to the possibility of more contact with their eyes and considering that one of the possible transmission routes of the disease is the conjunctiva. In case of mandatory use, it has been reported that the lens can be cleaned and used in its solution after providing hand hygiene.

Effects on the ocular surface have also been reported in Covid-19 disease other than conjunctivitis. However, this situation develops in intensive care units, depending on the environment itself or the treatment applied, rather than the direct effect of the disease. Ocular surface involvement can be seen in a broad spectrum, ranging from mild conjunctivitis to infectious keratitis. The absence of blinking and loosening of the orbicularis oculi muscle, which occurs due to the use of muscle relaxants and sedative agents in patients under mechanical ventilation, may lead to drying of the ocular surface and lagophthalmos. The usage of continuous positive airway pressure (CPAP) and oxygen masks in patients with Covid-19 may cause the ocular surface to dry and lead to infection development. Besides, symptoms such as conjunctival chemosis and subconjunctival hemorrhage were observed when the patients were placed in the prone position. Conjunctival chemosis may develop due to decreased venous pressure and increased hydrostatic pressure in the eye. Conjunctival hemorrhage may occur in case of increased central venous pressure. Both conditions have a good prognosis and do not require treatment as long as they do not develop an ocular surface problem. Although these conditions involving ocular surface problems are frequently observed in intensive care units, it has been shown that they can be prevented and their incidence can be reduced with appropriate protocols.

COVID -19 AND POSTERIOR SEGMENT FINDINGS

ACE receptors have been demonstrated in ocular tissues in the posterior segment such as the retina, retinal pigment epithelium, ciliary body and choroid. Since COVID-19 can target ACE-2 expressing vascular pericytes, viral infection can lead to complement-mediated, microvascular damage, endothelial cell dysfunction and thus ocular circulation involvement. Coagulopathy in Covid -19 may predispose to various thromboembolic events and this situation is mostly observed as pulmonary thromboembolism. Complement-mediated thrombotic microangiopathy is thought to be the leading factor in the pathogenesis of microcirculatory damage in patients with Covid-19. Adjunct system activation, which causes retinal artery and vein occlusions, was previously defined as directly responsible for vascular damage. It should also be noted that high serum C3 complement factor level is associated with an increased risk of developing microvascular complications in diabetic patients through endothelial dysfunction and thrombosis. Although there have been reports of retinal artery occlusion in patients with Covid-19, an increase in the incidence of retinal vein occlusion has not been noted. Similar to lung tissue, this situation may predispose to vascular events originating from an embolism in ocular tissues. There are few studies evaluating retinal findings in Covid-19 patients. In a study using optical coherence tomography (OCT) and color fundus photographs, hyperreflective foci were detected, especially in the papillomacular bundle, ganglion cell, and inner plexiform layers. However, OCT angiography findings and ganglion cell complexes of these patients were normal. Another finding was cotton wool spots and retinal microhemorrhages observed in the retinal passage, especially in red-free photographs, in the same study. However, no intraocular inflammation, decrease in visual acuity, and impairment in light reflexes were observed in the patients. Fundus photographs of 54 patients with Covid 19 were taken and the artery-vein diameters and possible retinal findings were evaluated in another study. It has been found that Covid 19 can affect the vascular structure of the retina, causing retinal findings such as retinal hemorrhages, cotton wool spots, and dilatation in the retinal veins. However, it has not been clarified whether this is a cause, or an immune response developed by the patient against the disease. Another patient group affected secondarily in the Covid -19 pandemic is vascular diseases of the retina such as age-related macular degeneration diabetic retinopathy and diabetic retinopathy. It is thought that the number of patients may increase in the future, especially in the diabetic retinopathy group, due to the restrictions in the pandemic, reduced physical

activity, additional problems brought by their diseases, and difficulties in accessing treatment.

COVID-19 AND NEUROOPHTHALMOLOGIC FINDINGS

Involvements of the cranial nerves have been reported in patients with Covid-19. This is due to direct invasion of the nerve or its inflammatory effects. Clinical findings such as diplopia and ophthalmoparesis may be seen in patients. Perineural changes could be demonstrated in some cases by magnetic resonance imaging. Although it has been experimentally demonstrated that Covid-19 can also affect the optic nerve, no cases of ischemic or inflammatory optic neuritis have been reported due to the pandemic.

POSSIBLE OCULAR COMPLICATIONS IN COVID-19 TREATMENT

The Covid-19 treatment has especially aimed at the treatment of lung findings and respiratory failure symptoms. With the increase in oxygen saturation in the blood with the prone position, treatment planning is made especially in this way. It is known that the prone position applied to the patient affects both the anterior surface and vascular structure of the eye. Ocular anterior surface problems of the intensive care patients were mentioned above. The effects of treatment on ocular perfusion will be discussed in this section. Ocular perfusion depends on intraocular pressure (IOP) and ocular blood flow. These are related to vascular resistance and arterial-venous pressure and vascular resistance. The prone position can significantly reduce ocular perfusion through on two mechanisms. While increasing venous pressure, it also increases IOP. Intraocular pressure is elevated in the prone position, besides, systemic conditions such as arterial hypertension, diabetes, and atherosclerosis can cause an increase in vascular resistance, further reducing ocular blood flow. Patients who are more likely to get Covid 19 and hospitalized in the intensive care unit due to their comorbidities also have a higher risk of developing ocular hypoperfusion. Publications are reporting that prone position ventilation applied in intensive care units before Covid-19 disease may uncommonly lead to acute ischemic optic neuropathy and develop permanent vision loss. Another rare complication of the prone position is angle-closure glaucoma. In the presence of underlying risk factors, besides prone position, acute angle-closure may also

develop due to anticholinergics, sympathomimetics, and other drugs (sulfonamide derivatives and topiramate). As a result, ocular complications can be observed rarely in intensive care units. However, vision-threatening complications can be recognized and prevented by expanding the awareness of intensive care staff.

OCULAR SIDE EFFECTS OF DRUGS USED IN THE TREATMENT OF COVID-19

There is no treatment with proven effectiveness in Covid-19 disease so far. However, antivirals, anti-malarial drugs, immune modulators, and steroids are used for the treatment of the symptoms and signs of the disease with partial efficiency. Antivirals are in the first place in the treatment planning of Covid-19. Antiviral drugs (lopinavir and ritonavir) commonly used in HIV treatment have been used in the early stages of the pandemic as a probable treatment in patients with Covid-19 infection. Signs of different types and degrees of toxicity in the retina due to these drugs have been described in the past.

The use of favipiravir, which was launched in Japan in 2014 and approved for the influenza pandemic, came up in the later stages of the Covid 19 pandemic. Favipiravir, which is strong in vitro efficiency against Covid 19 and has oral use, has been shown to have better disease cure rates than other antiviral drugs. Favipiravir has mostly gastrointestinal system side effects, and its ocular toxicity has not been reported yet.

Another group of drugs used in the treatment of Covid 19 is chloroquine and hydroxychloroquine which are known as anti-malarial drugs. In addition to their use in malaria, these drugs are also used in the treatment of many rheumatological diseases. Their efficacy in the treatment of Covid-19 has been determined in in-vitro and animal experiments and has been rapidly approved by the FDA for treatment. The mechanisms of action of these drugs are not fully known in the treatment of Covid-19 disease, but various hypotheses have been proposed. The first hypothesis is that they cause an increase in endosomal pH that inhibits viral fusion and replication. Another mechanism of action is that they affect terminal glycosylation of the ACE-2 receptor for cell entry targeted by the virus. It is also thought that these drugs provide immunomodulatory activity in patients with Covid-19. Studies have shown that chloroquine and hydroxychloroquine improve the clinical symptoms of the disease, reduce the exacerbation of pneumonia and encourage virus-negative seroconversion. Patients are treated for an average of 4-7 days with protocols

that vary according to clinics. The most common side effects related to treatment are hypoglycemia, cardiological problems due to prolongation of QT interval, anemia, extrapyramidal disorders, and ocular problems. Patients who used these drugs for rheumatological diseases were followed up in ophthalmology clinics for ocular side effects before the Covid-19 pandemic. Cumulative and dose-dependent side effects can be detected both in the anterior and posterior segments in the long term. Chloroquine and hydroxychloroquine may cause intraepithelial corneal lesions, posterior subcapsular cataracts, and ciliary body dysfunction at the anterior segment. They may accumulate in the retinal pigment epithelium and cause bilateral maculopathy, firstly parafoveal and then affecting the fovea at the posterior segment. The most serious risk factor for the development of chloroquine and hydroxychloroquine toxicity is excessive daily dosage. The American Academy of Ophthalmology recommends keeping the daily dosage of chloroquine less than 2.3 mg/kg and hydroxychloroquine 5.0 mg/kg to prevent the development of retinopathy. Duration of treatment is also an additional critical factor. The risk of ocular toxicity is below 2% after 10 years and increases to almost 20% after 20 years in long-term use of hydroxychloroquine at recommended doses. However, it has been reported that high doses of chloroquine and hydroxychloroquine can lead to retinopathy even in a shorter treatment period. The last two studies in patients receiving 800-1,000 mg of hydroxychloroquine per day over 1-2 years have shown an incidence of retinopathy from 25% to 40%. Retinal toxicity was not reported with 2 weeks of chloroquine or hydroxychloroquine administration. Therefore, it is thought that high doses of these drugs may increase retinal toxicity over weeks to years and drug-related effects can be detected after ophthalmological examinations to be performed in the post-covid period.

Interferons (IFN) have been proposed as a potential treatment for Covid-19 due to their antiviral, antiproliferative, and immunomodulatory activities. It has been observed that IFN- β , a subtype of IFNs, is particularly effective in the treatment of inflammatory symptoms of Covid-19. It is known that interferons affect especially the posterior segment of ocular tissues. They may cause changes in the optic nerve head and posterior pole, such as cotton wool spots and retinal hemorrhage. Findings can be seen at the late stages of treatment and improvement in symptoms is reported after discontinuation of treatment.

Interleukin-1 (IL-1) inhibitors (anakinra) and interleukin-6 inhibitors (sarilumab, siltuximab, and tocilizumab) are also immunomodulatory agents

used in the treatment of Covid-19. Increases in IL-1 and IL-6 levels have been observed in Covid 19 patients, but the effects of this situation on clinical outcomes have not been reported yet. A case thought to be associated with retinal toxicity of tocilizumab in the pre-Covid 19 pandemic has been shown in the literature. Multifocal cotton-wool spots and retinal bleeding and bilateral papilledema were described in this case. These ocular side effects, which are rarely seen during treatment, should be kept in mind.

Recently, steroids have been added to the treatment to suppress the inflammation that occurs in Covid 19. Systemic steroids are used in variable doses for a short time, depending on the severity of the disease. Although systemic steroids are frequently used in the treatment of ocular diseases (optic neuritis, uveitis, etc.), ocular side effects (glaucoma, cataract, etc.) may occur in patients receiving short-term and high-dose therapy. Besides, there may be an increase in the incidence of diabetic retinopathy due to high blood sugar levels during steroid use in patients with diabetes mellitus who also have increased risks against Covid 19.

CONCLUSION

As a result, apart from being a transmission route for the disease, ocular tissues may directly be affected and various clinical findings may be seen in Covid-19 disease. Also, various side effects may appear due to the drugs used during the treatment. Ophthalmologists should be aware of the clinical signs of the disease, the possibility of transmission during the examination, and the adverse situations that may occur during treatment. The long-term ocular effects of Covid 19 disease are still unclear. Future studies will be a guide to reveal the effects of the disease in both systemic and ocular tissues.

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