

# Neurological and Neuro-Ophthalmological Involvement and Possible Mechanisms of Damage Due to Covid-19

Ali Küçüködük<sup>1</sup> , Şansal Gedik<sup>2</sup>

## ABSTRACT

Declared as a pandemic by the World Health Organization (WHO) on March 11, 2020, COVID-19 continues rapidly with the number of confirmed cases reaching 82.5 million and approximately 1.8 million deaths according to WHO data as of December 2020. All physicians in our country and around the world encounter this infection and its possible complications. SARS-CoV-2 is an enveloped RNA virus in the beta-coronavirus family. SARS-CoV-2 binds to the angiotensin converting enzyme (ACE2) protein and enters the host cell. ACE2 receptor has been detected on the surface of type 2 alveolar cells, enterocytes and intestinal epithelial cells, vascular endothelial cells, conjunctiva and corneal epithelial cells, and surface of some cells at the central nervous system (CNS) cortex and brainstem regions and retinal and visual pathway elements. The damage caused by the virus in these tissues constitutes the clinical picture of the disease. Neurological symptoms can be seen in a wide range including CNS involvement and peripheral nervous system (PSS) involvement. Viral neuro-invasion occurs through various ways such as the trans-synaptic pathway, olfactory nerve invasion, hematogenous pathway, leukocyte migration / inappropriate immune response, and trigeminal nerve trans-synaptic pathway or retinal ganglion cell involvement. Ocular involvement may show a wide range of manifestations such as conjunctivitis, anterior uveitis, retinal vasculitis, retinal degeneration and apoptosis, optic neuritis, and axonal damage. Although COVID-19 is prominent with respiratory system findings and complications, reports on neurological and neuro-ophthalmological findings are increasing. Therefore, physicians must take into account the neurological and neuro-ophthalmological relationships in patient examination and clinical study planning.

**Keywords:** SARS-CoV-2, COVID-19, neurology, neuro-ophthalmology.

## INTRODUCTION

A new coronavirus (SARS-CoV-2) causing severe acute respiratory tract infection was defined at December, 2019, and it was declared as a disease with human-to-human transmission in 20 January, 2020 by China National Health Institute and as pandemics in 11 March, 2020 by World Health Organization (WHO). As of December 2020, the number of confirmed cases reached up to 82.5 million with 1.8 million deaths according to data released by WHO. Regardless of their specialty, all clinicians have encountered with this infection and its potential complications in Turkey and worldwide. It is important to understand systemic presentations of the disease in order to improve awareness about the disease among clinicians. In this study, we aimed to present an overview about

neurological and neuro-ophthalmological involvement of the disease which affects many organ systems.

## OVERVIEW

The coronavirus family belongs to Nidoviridae order. The coronavirus family is classified into 4 genera including alpha, beta, gamma and delta viruses. All viruses in this family are enveloped, non-segmented, positive sense RNA viruses. They all contain very large genomic material for RNA viruses and some viruses have largest identified RNA genome containing up to 33.5 kilobase. This provides an unique replication strategy to coronaviruses. The SARS-CoV-2 is an enveloped virus having a positive sense RNA genome involving 29,881 nucleotides, which is classified in beta coronavirus family and gene sequencing was achieved in 10 January, 2020, revealing that SARS-CoV-2 shows

1- MD, Beyhekim Training and Research Hospital, Department of Ophthalmology, Konya, Turkey

2- Professor, Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Turkey

Received: 01.03.2021

Accepted: 01.03.2021

*Ret-Vit 2021; 30:312-320*

DOI: 10.37845/ret.vit.2021.30.55

**Correspondence Address:**

Ali Küçüködük

Beyhekim Training and Research Hospital, Department of Ophthalmology, Konya, Turkey

**Phone:** +90 312 212 68 68

**E-mail:** alikucukoduk@gmail.com

marked homology with SARS-CoV and MERS-CoV (80% and 50%, respectively). The SARS-CoV-2 has 4 major structural protein: envelope (E), membrane (M), spike (S1) and nucleocapsid (N3-5) proteins. The E protein is found in smallest quantity within in the virion and facilitates assembly and release of virus from host cell. It also accounts for structural polarity. The M protein is the most abundant structural protein within the virion. It is a small protein with 3 transmembrane domains and gives shape of virion. The S proteins are required for attachment to host cell and form structures that give characteristic corona-like appearance to virus. The N protein is the only protein in the nucleocapsid. A fifth structural protein, hemagglutinin esterase (HE), is only present in beta-coronaviruses. This protein binds to sialic acids in glycoproteins at cellular surfaces and enhances cell entry and virus spread through mucosa<sup>1</sup>.

The virion attachment to host cell is triggered by interaction between S protein and relevant receptor. The S protein-receptor interaction is the major determinant for host infection and tissue tropism. The SARS-CoV-2 enters to host cell via binding to angiotensin converting enzyme-2 (ACE2) protein. The tissue distribution of ACE2 receptors determine viral tropism. This protein is a type-1 transmembrane receptor that passes cell membrane for once and its enzymatic activity is observed in type 2 alveolar cells, enterocytes and intestinal epithelial cells, vascular endothelial cells, conjunctiva and corneal epithelial cells, renal tubule cells, immune system elements such as alveolar monocytes and macrophages and surface of some cells in central nervous system (CNS cortex and brainstem)<sup>2</sup>. In cells with ACE2 enzymatic domain on their surface, the S1 proteolysis is achieved by a transmembrane serine protease 2 (TMPRSS2) after S1 protein-receptor binding, leading fusion of viral and cellular membranes<sup>3</sup>. This results in endocytosis and both SARS-CoV-2 and ACE2 enter to cell by endosome.

The studies about inhibition of these mechanisms comprise the backbone of current pharmacological research. However, recently, it was shown that S protein binds to CD147 receptor (basigin) on cell surface, which was defined as a novel way for cell entry<sup>4</sup>. The CD147 receptor is highly expressed in tumoral tissues, inflamed tissues and infected tissue by a pathogen. The anti-CD147 antibody is also being investigated as a treatment modality. Another experimental treatment option studied is miRNA. The miRNA is a nanosize molecule that can suppress translocation by interacting with target genes of mRNA within the cell or accelerating mRNA degradation. It is thought that the above-mentioned physiological role of miRNA can be

useful since proteins produced during viral replication are synthesized within host cell.

## PHYSIOLOGICAL ROLE OF ACE2

ACE2 has a critical role in renin-angiotensin- aldosterone system (RAAS). It is involved in blood pressure regulation and electrolyte homeostasis. The angiotensin, produced in liver, is cleaved by renin, producing angiotensin (Ang I). Then, ACE2 enzyme catalyzes conversion of Ang I to angiotensin II (Ang II). The Ang II produced is the major active component of RAAS and acts via angiotensin II type 1 receptors (AT1R). The primary effects of Ang II include vasoconstriction, renal sodium reuptake and potassium excretion, aldosterone synthesis, elevation of blood pressure and activation of inflammatory and profibrotic pathways. ACE2 degrades Ang I to Ang1-9 and Ang II to Ang1-7, converting to angiotensin. Primary effects of angiotensin includes vasodilatation through Mas/G receptors and activation of anti-inflammatory and anti-fibrotic pathways; thus, physiologically, ACE2 exert effects opposite to ACE. The effects of RAAS on tissues is determined by ACE/ACE2 balance; thus activation of pro-/anti-inflammatory and pro-/anti-fibrotic pathways are dictated by tissue angiotensin peptide concentration. In SARS-CoV-2-infected cells, the event cascade is induced by virus-ACE2 interaction. The viral entry is facilitated by breakdown in ectodomain regions via trypsin/cathepsin G or ADAM17 and endodomain regions via TMPRSS2. As a result of breakdown, ACE2 receptor is dissolved, reducing its protective function. The loss of ACE2 function hampers production of Ang 1-9 and Ang 1-7. The lack of Ang 1-7 reduces protective activity of Mas/G receptor. In addition, it also up-regulates RAS/Ang II pathway by leading imbalance and loss of control in Ang II effects, which leads vasoconstriction, micro-thrombosis, alveolar epithelial injury and respiratory failure.

In addition to RAAS, the ACE2 has a regulatory role on vasodilatation and vascular permeability due to its effect on bradykinin metabolism in lung tissue. Moreover, it is also involved in the amino acid homeostasis, anti-microbial peptide expression, regional immunity and microbial ecology in the gastrointestinal system.

When tissue distribution of ACE2 is investigated, it is seen that ACE2 is highly expressed in surfaces with exposure to outer environment such as pulmonary alveolar epithelium or small intestine epithelium. In addition, it is widely distributed in vascular endothelial and smooth muscle cells. The renal ACE2 expression is seen at higher concentration in brush border of proximal tubule cells while at low-to-moderate concentration in parietal epithelial

cells and podocytes. In addition, ACE2 is also present in cutaneous basal epidermis, oral mucosa and nasal mucosa. It is also observed that ACE2 and TMPRSS2 protein are prominent at most superficial epithelial layers of cornea and conjunctiva<sup>5</sup>. The ACE2 mRNA level is found as 400 IU in testicular tissue, 200 IU in ileum and 100 IU in left ventricle whereas 20-28 IU in corneal epithelium. Moreover, it was found that ACE2 expression is high while CD147 expression is moderate-to high in retinal cells and visual pathway elements. The ACE2 receptor expression is affected by several factors including age, gender, ethnicity, medication, comorbid conditions and dementia. Based on these data, it is suggested that ACE2 is widely distributed in human tissues and important in the pathophysiology of end-organ injury and transmission pathways in SARS-CoV-2 infection.

### NEUROLOGICAL INVOLVEMENT

Neurological signs are seen in approximately 30% of COVID-19 cases<sup>6</sup>. The incidence of neurological signs is increased in cases with severe clinical course. In particular, comorbidity rate reaches up to 13.2% in the population aged >65 years; the loss of consciousness is seen in 22% of patients with fatal course and in 1% of survivors. Marked increases are observed in D-dimer, IL-2, IL-6, IL8, IL-10 and TNF-alpha levels, particularly in fatal cases with neurological involvement<sup>7</sup>.

The most neurological signs develop at early phase of disease. Nucleic acid components of SARS-CoV-2 were detected in CSF evaluations and postmortem brain tissue examinations in infected patients. The presence of viral particulars not only in neuronal cells but also in cerebral vascular endothelial cells suggests that hematogenous route may have role in the development of neurological symptoms. It is thought that ACE plays role in the pathogenesis of neuroinvasion. The ACE2 is expressed in neurons and glial cells, particularly at brainstem and cardiovascular regulatory centers (nucleus tract solitarius, paraventricular nucleus and rostral ventrolateral medulla etc.)<sup>8</sup>. The pons, medulla oblongata (respiratory systems) and amygdale are the areas with most concentrated ACE2 expression in CNS. The disrupted brain-lung crosstalk results in impaired respiratory rhythm, inspiration/expiration rate and complete interruption of spontaneous respiration. It is thought that invasion of cardiovascular and respiratory centers in brainstem is the most important cause of morbidity and mortality in SARS-CoV-2 infection<sup>9</sup>. The marked expression in hippocampus and temporal lobe may explain cognitive dysfunction in SARS-CoV-2 infection. Dense ACE2 expression is observed in substantia nigra,

ventricles, mid-temporal gyrus, posterior cingulate cortex and olfactory bulb<sup>10</sup>.

The neurological symptoms can be in a wide spectrum from involvement of CNS to peripheral nervous system (PNS) and musculoskeletal muscles. The signs suggestive of CNS involvement include altered mental status, vertigo, sleep disorder, loss of consciousness, ataxia, seizure, acute cerebrovascular disease, meningitis and encephalitis<sup>11</sup>. The findings such as taste and olfaction disorders, vision disorders and neuralgia indicate PNS involvement. The most common complaints are taste and olfaction disorders in this group. After initial assessment, these neurological manifestations can be categorized under three major groups:

1. Comorbid neurological disease seen with COVID-19: In this group, the complaints are already present before infection and even there is a predisposition to the infection due to suboptimal health status (cerebrovascular diseases, neural trauma, Alzheimer's disease and Parkinson's disease).
2. Non-specific neurological manifestations: This group of findings is, in part, secondary to neuro-invasive behavior of and systemic response to infection (e.g. headache, myalgia, nausea).
3. Specific neurological symptoms: This group of findings is directly associated to neurological involvement of COVID-19 disease (e.g. encephalitis, myelitis, cerebrovascular infarction, seizure).

Headache, myalgia, nausea, vomiting, confusion, anorexia, vertigo, fatigue and dyspnea/respiratory distress are among non-specific neurological symptoms. In a study on ICU patients, the patients reported that they need to perform active and conscious respiration in order to maintain normal respiratory rhythm<sup>12</sup>. As mentioned previously, the ACE2 expression in cardiorespiratory centers supports pathogenesis (disrupted brain-lung crosstalk).

The specific neurological symptoms include CNS- and PNS-related symptoms as well as musculoskeletal symptoms. Olfaction disorders and appetite-related disorders are very common specific neurological symptoms. Recently, it was shown that expression of ACE2 and SARS-CoV-2 entry genes were present in sustentacular cells at olfactory neuro-epithelium<sup>13</sup>. This suggests that virus directly invades olfactory neuro-epithelium, affecting olfactory function. IL-6-related olfactory bulb and vascular pericyte damage and decreased bradykinin release may be involved in impaired sense of taste. Again, ACE2 receptor blockade

on oral mucosa and tongue, sialic acid receptor blockade and enzymatic degradation of gustatory molecules can be effective in impaired sense of taste.

The gastrointestinal symptoms such as nausea, vomiting and loss of appetite may show disruption of central regulation of food intake and involvement of cerebral structures related to nausea and vomiting. Both structures indicate involvement of dorsal vagal complex (DVC) located at medulla oblongata. This region is responsible from regulation of autonomic activities related to heart, respiration and appetite. Thus, the damage in this region can disrupt homeostasis. The nucleus tract solitarius in DVC is one of the main regions that regulates food intake together with hypothalamus. Thus, decreased appetite indicates a pathology that impairs crosstalk between hypothalamus and DVC<sup>14</sup>. The density of ACE2 receptor in this region also seems as a data that supports pathogenesis.

Besides common neurological disorders, rare complications related to COVID-19 have also been reported. The Guillain-Barre syndrome (GBS) may develop with progressive extremity weakness within 5-10 days after disease onset in some COVID-19 cases<sup>15</sup>. Acute Disseminated Encephalomyelitis (ADEM), another rare condition, is a demyelinating entity that is characterized by encephalopathy and multi-focal neurological deficits<sup>16</sup>. In addition, chronic disease neuropathy and myopathy, viral myositis, Myasthenia gravis exacerbation, and GBS variants can also be seen<sup>17</sup>. In a their study, Efe et al. described a COVID-19-related encephalitis that progresses with neurological manifestations mimicking glial tumors<sup>18</sup>.

On the other hand, there are some important issues which must be taken into consideration in the management of COVID-19 cases with chronic neurological disorders. The epilepsy is one of the most common chronic neurological conditions. Although it is unclear whether epilepsy itself is a risk factor for COVID-19, the risk is increased in cases with epilepsy-related autoimmune disorders (such as tuberous sclerosis complex) or decreased pulmonary function. The COVID-19 may trigger fever-related epileptic seizures, particularly in severe cases. However, a COVID-19 case manifested with focal status epilepticus was also described<sup>19</sup>. No interaction was identified between antiepileptic agents and drugs used for treatment of COVID-19. The risk for COVID-19 may be increased with epileptics acting via immune system. The dementia and Parkinson's disease (PD) are common chronic conditions seen in the population affected severely by COVID-19. The comorbid conditions such as cardiovascular diseases and diabetes mellitus which are often present in cases with

Alzheimer's disease make these cases more vulnerable to COVID-19 infection. In Alzheimer's disease, the decreased ACE expression normally leads RAAS activity; which, in turn, results in increased tau protein (amyloid-beta protein). However, the patients harboring ApoE e4e4 allele is at higher risk<sup>20</sup>. No interaction has been reported between drugs used for Alzheimer's disease and COVID-19. It has been emphasized that vitamin D supplementation is important in these cases. Parkinson's disease is the second most common neurodegenerative disease following Alzheimer's disease. There is no available data suggesting that Parkinson's disease increases risk for infection; however, it is apparent to be careful given the age group affected and comorbid conditions. Moreover, the number of neurons where ACE2 binding occurs is lower due to loss of nigro-striatal cells in Parkinson's disease. Thus, Parkinson's disease may be protective against CNS infiltration. However, in Parkinson's disease, since the dopaminergic neurons, which is already decreased, also have ACE2 receptor, involvement of these cell may accelerate degenerative process<sup>21</sup>, warranting dose escalation. In advanced cases, pulmonary decompensation can be seen due to decreased lung capacity secondary to axial akinesia<sup>22</sup>. In addition, Parkinson's disease may also affect medullar respiration centers. No interaction has been reported between drugs used for management of COVID-19 and Parkinson's disease. The Multiple Sclerosis (MS) often affects young adults; however, the disease modifying therapies used comprise a risk factor for infection. When previous coronavirus pandemics were evaluated, it was seen that coronavirus or viral RNA was detected in brain tissue of MS cases. In addition, anti-CoV antibodies were detected in CSF of MS cases<sup>23</sup>. In COVID-19 disease, pro-inflammatory condition induced by cytokine storm can cause progression of MS finding by leading demyelination<sup>24</sup>. In addition, ACE2 receptors on oligodendrocytes may worsen demyelination process<sup>25</sup>. It is recommended to maintain MS treatment in milder infection while discontinue in severe and complicated infection.

Taken together, the question that how SARS-CoV-2 leads these clinical manifestations and which pathways does it use to access CNS.

## POSSIBLE MECHANISMS OF NEUROINVASION

Viral neuro-invasion occurs via several ways: transsynaptic pathway, olfactory nerve invasion, hematogenous pathway, leukocyte migration/inappropriate immune response and trigeminal nerve transsynaptic pathway or retinal ganglion cell involvement secondary to ocular epithelium invasion<sup>5</sup>.

1. **Transsynaptic pathway:** SARS-CoV-2 can access to CNS by retrograde spread after infecting peripheral nerve terminals<sup>26</sup>. Transsynaptic transfer has been proven for distinct coronavirus types (HCoV-OC43, HEV 67 and infectious bronchitis virus) in experimental studies. The virus can reach to brainstem via vagal nerve that connect CNS and lungs following invasion of respiratory tract as a result of substantial viral load.
2. **Olfactory nerve invasion:** The loss of sense of taste and olfaction, commonly seen in COVID-19, develops as a result of direct invasion of olfactory nerve by virus<sup>27</sup>. The virus can reach to CNS via trans-cribriform way. In experimental studies, CNS transmission was shown following nasal inoculation<sup>28</sup>. The olfactory nerve projects to olfactory bulb via olfactory foramen over lamina cribrosa of ethmoidal bone. The viruses passing to cerebrospinal fluid (CSF) via rupture of infected cells can spread via CSF circulation regardless of blood-brain barrier damage<sup>29</sup>.
3. **Hematogenous pathway:** The blood-brain barrier (BBB) consists of vascular endothelium, astrocytes, pericytes and extracellular matrix. The tight-junctions of vascular endothelial cells regulates BBB permeability. Two possible mechanism have been defined for passage of virus across BBB. First mechanism is transport of virus via infection in vascular endothelial cells. As mentioned previously, endothelial cells express ACE2. In postmortem electron microscopy studies, endocytosis and exocytosis findings were found for viral particles in endothelial cells<sup>30</sup>. After entry to vascular and neuronal tissue, virus produces cytopathic effects and cell rupture; the new viruses move to ACE2 receptors on neurons, glial cells and vessels<sup>31</sup>. It should be noted that the virus leads hypercoagulability states such as micro-thrombus and acute clotting in addition to neuropathic effect of endothelial injury<sup>32</sup>. In hematogenous route, another possibility is to access brain via systemic circulation. The virus that reaches to CNS via hematogenous route can either pass to brain tissue due to impaired blood-brain barrier or reach to DVC via periventricular structures such as area postrema and median eminence at base of fourth ventricle where blood-brain barrier is absent.
4. **Leukocyte migration/inappropriate immune response:** Another way to pass blood-brain barrier is defined as Trojan horse mechanism and it occurs via passage of infected leukocyte across blood-brain barrier<sup>33</sup>. It is known that SARS-Cov-1 infects cells expressing ACE2 such as lymphocytes, granulocyte or monocyte. It is

thought that SARS-CoV-2 also infects same cells. In addition, the systemic inflammation and cytokine storm triggered during COVID-19 also facilitate passage of cytokines and even viruses into CNS by increasing blood-brain barrier permeability<sup>34</sup>.

5. **Ocular epithelium:** In recent studies, it was shown that ACE2, CD147 and TMPRSS2 receptors are widely expressed to whole ocular surface including conjunctiva, limbus and corneal epithelium<sup>5</sup>, revealing that ocular surface is susceptible to SARS-CoV-2 infection. The factors influencing on ocular surface infection includes viral load, ocular cellular immunity and relevant lymphatic tissues. Conjunctival virus transmission, virus detection in eye water and ocular symptoms seen in COVID-19 cases indicate that ocular surface may be important for viral entry and viral transmission. Another mechanism for viral transmission is to access of viral particles to nasopharynx and upper respiratory tract via nasolacrimal canal<sup>35</sup>. It is thought that retrograde transport via trigeminal nerve may be another route for viral access to CNS<sup>36</sup>.

## OCULAR AND NEURO-OPHTHALMOLOGICAL INVOLVEMENT

In experimental studies, ocular involvement was shown in coronavirus infections. A wide spectrum of ocular manifestations including conjunctivitis, anterior uveitis, retinal vasculitis, retinal degeneration and apoptosis, optic neuritis and axonal injury can be seen.

In COVID-19 cases, chemosis, epiphora, conjunctival hyperemia and ocular secretion comprise 31.6% of all ocular manifestations<sup>37</sup>. Although SARS-CoV-2-related conjunctivitis have been reported in varying rates in different studies, it is rarely seen (0.08%) and it is not a presenting complaint in general<sup>38</sup>. It is thought that conjunctivitis might have been underreported as it has mild course without decreased vision<sup>39</sup>. However, in 2 distinct case reports, it was reported that conjunctivitis preceded other symptoms with respiratory symptoms later on course of disease<sup>40, 41</sup>. In a case reported from China, bilateral conjunctivitis developed on day 13 after onset of systemic symptoms and conjunctival smear was positive in a patient with positive nasopharyngeal smear<sup>42</sup>. In another case reported from France, the conjunctival smear was negative in an elder patient with bilateral hemorrhagic conjunctivitis developed at week 2 during treatment. In another study using tissue culture test, pterygium could be a predisposing factor for SARS-CoV-2 infection and it expressed TMPRSS2 gene at higher rate<sup>43</sup>. Taken together, it can be suggested that ocular surface transmission is not

high for the virus. It has been proposed that viral replication at ocular surface is vague and that conjunctivitis may also develop via viral exudation secondary to increased viremia by involvement of infected lacrimal gland. In addition, ocular cellular immunity, molecules such as lactoferrin in eye water and protective factors such as mucosal lymphatic tissue have protective effect against ocular involvement. However, eye glass and face shield are recommended as personal protective equipments; in addition, it should be kept in mind that non-contact tonometry can lead viral spread via droplet infection by leading micro-aerosol formation. Another anterior segment manifestation is anterior uveitis in COVID-19. Although it was confirmed by serology and other potential causes of anterior uveitis was not ruled out, anterior uveitis was considered to be secondary to COVID-19 in the case<sup>44</sup>.

The findings indicating posterior segment involvement were demonstrated in SARS-CoV-2. In a study evaluating optical coherence tomography (OCT) findings of 12 SARS-CoV-2 positive patients, hyper-reflective lesions were reported at inner plexiform layer and ganglion cell layer; in addition, OCT angiography found to be normal in same patients. In fundus examination, cotton wool spots and micro-hemorrhages along with retinal vessels were observed, indicating micro-vascular disease. The visual acuity and pupillary reflexes were found to be normal and no finding suggesting intraocular inflammation was detected<sup>45</sup>. In another study, viral RNA was detected in retinal biopsy in postmortem retinal tissue examination in 14 SARS-CoV-2 positive cases<sup>46</sup>. Again, acute macular neuroretinopathy may develop through involvement in retinal interdigitation zone.

Neuro-ophthalmological involvement is anticipated in SARS-CoV-2 infection since central and peripheral nervous system involvement is seen in SARS-CoV-2 infection. The most common neuro-ophthalmological symptoms are headache, ocular and periocular pain. The pathophysiology of the symptom hasn't been fully elucidated. It is though it may be due to increased pro-inflammatory cytokine or trigeminal nerve activation. Meningitis and encephalitis should be taken into consideration when it is seen with other neurological symptoms.

In a study from Wuhan, visual disturbance was reported in 19 (1.4%) of 214 COVID-19 cases. The characteristics and etiology of this finding hasn't been elucidated. It was suggested that it may be a component of peripheral nervous system involvement such as loss of olfaction and sense of taste or neuralgia<sup>47</sup>. Cyr et al. reported severe loss of vision in 2 cases positive for COVID-19<sup>48</sup>.

The first case was a 61-years old diabetic patient with visual acuity loss up to light perception in both eyes. On computerized tomography (CT) scan, cytotoxic edema was seen at bilateral occipital region, which was considered as ischemic infarct. Second case was a 34-years old woman with systemic lupus erythematosus, hypertension, end-stage renal disease and previous cerebral vascular disease. Bilateral acute loss of vision was developed at week 1 after admission. Visual acuity was found as light perception in both eyes and both optical disks were found to be faded. In CNS imaging studies, there was acute infarct at right frontal lobe, acute posterior temporo-occipital infarct at left and chronic infarct at right temporoparietal and bilateral medial occipital lobes. It should kept in mind that thrombotic events may be more common in such cases with systemic disease that may cause endothelial dysfunction.

Dinkin et al. reported 2 SARS-CoV-2 cases manifested with diplopia and ophthalmoparesis<sup>49</sup>. The first case was a 36-years old man with neurological symptoms accompanied to incomplete paralysis of left third cranial nerve with pupillary involvement and paralysis of bilateral sixth cranial nerve. Miller-Fischer syndrome was considered in the case. The second case was a 71-years old woman with paralysis of sixth cranial at right side, which gradually resolved within 2 weeks. Optic nerve and optic nerve sheath enlargement were striking on CNS imaging in both cases. Gutierrez-Ortiz et al. reported other cases with Miller-Fisher syndrome and cranial polyneuritis<sup>50</sup>. In cases with Miller-Fisher syndrome, diplopia, afferent pupil defect, inter-nuclear ophthalmoparesis and incomplete oculomotor paralysis were observed in addition to other neurological symptoms while esotropia and bilateral abducens paralysis was detected in the case with cranial polyneuritis. The involvement of third and fourth cranial nerves were reported in another case with COVID-19-related Guillain-Barre syndrome on MR imaging<sup>51</sup>. Taken together, it may be suggested that there is a relationship between SARS-CoV-2 and demyelinating disorders. Although cranial nerve involvement on CNS imaging studies indicates an inflammatory process, the etiology may be related to para-infectious factors, direct invasion or immune-related demyelination.

Progressive bilateral facial nerve paralysis and loss of blinking reflex were reported in a 61-years old case with COVID-19-related Guillain-Barre variant and facial diplegia<sup>52</sup>. Since it was failed to perform thorough ophthalmological examination in the case, data was lacking regarding other ophthalmological findings related to seventh cranial nerve involvement.

In a case reported by Gutierrez-Ortiz et al., nystagmus was reported, which accompanied to inter-nuclear ophthalmoparesis<sup>50</sup>. In another COVID-19 case, Pellitero et al reported horizontal nystagmus<sup>53</sup>. No abnormal finding was observed in CNS imaging studies in the case.

COVI-19-related pupil defects are seen secondary to oculomotor nerve involvement resulting from Miller-Fisher syndrome<sup>49</sup>. However, it was reported that pupil response was slower in a case with encephalitis<sup>54</sup>. In a 62-years old male patient, Ordas et al. found tonic pupil and trochlear nerve paralysis together with vertical diplopia and blurred vision in the left eye<sup>55</sup>.

In animal experiments, optic neuritis and CNS demyelination were shown in coronavirus. The coronavirus-related acute disseminated encephalomyelitis, Miller-Fisher syndrome and Guillain-Barre syndrome have been reported in human. In the literature, the relationship between human coronaviruses and multiple sclerosis have been suggested as an environmental factor<sup>56</sup>. Zhou et al. reported a case with bilateral severe optic neuritis and myelitis, which was positive for SARS-CoV-2 and myelin oligodendrocyte protein<sup>57</sup>. In a 26-years old man, loss of vision was initially developed in the right eye, followed by the left eye on day 3, and the patient described painful ocular movements, non-productive cough and pain at neck before onset of vision loss. In ophthalmological examination, it was found that both optic discs were edematous with retinal hemorrhage at right eye. On CNS imaging studies, bilateral thickening was detected in optic nerves. Recently, it was reported that Kawasaki disease was more commonly seen in SARS-CoV-2 infection<sup>58</sup>. Although findings seen in Kawasaki disease such as hyperemia, uveitis, vitreal opacities and papillary edema have not been observed so far, ophthalmologist should be careful in this context.

## CONCLUSIONS and RECOMMENDATIONS

Although COVID-19 is distinguished by respiratory system findings and complications, the reports of neurological and neuro-ophthalmological findings are increasing over time. Thus, the clinicians must be considered neurological and neuro-ophthalmological associations during examination and clinical plans. The patients with COVID-19 should be questioned regarding conjunctivitis, anterior segment findings, diplopia, painful ocular movements, changes in visual acuity or color vision and other neurological symptoms. Accordingly, the patient presenting with such complaints should be evaluated for COVID-19. The presence of concurrent respiratory symptoms strongly suggest COVID-19. Cranial neuropathy finding should

be assessed in patients undergoing neuroimaging studies. Since neurological symptom may often be non-specific at initial phased of the disease, the levels of suspicion and awareness in clinicians are important for early diagnosis and prevention of severe complications in cases with non-specific clinical presentation.

## REFERENCES

1. COVID NBA. The COVID-19 from neurological overview. *Turk J Neurol.* 2020; 26:58-108.
2. Li M-Y, Li L, Zhang Y, Wang X-S. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infectious Diseases of Poverty.* 2020; 9:45.
3. Lewis R, Yap A, Easter S et al. COVID-19 Vaccine Will Close in on the Spikes. *DNA Science Blog.* 2020.
4. Wang K, Chen W, Zhou Y-S et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. *BioRxiv.* 2020.
5. Zhou L, Xu Z, Castiglione GM et al. ACE2 and TMPRSS2 are expressed on the human ocular surface, suggesting susceptibility to SARS-CoV-2 infection. *bioRxiv.* 2020:2020.2005.2009.086165.
6. Öztürk Ş. COVID-19 and Neurology. *Turkish Journal of Neurology/Turk Noroloji Dergisi.* 2020; 26.
7. Halacli B, Kaya A, İskit AT. Critically ill COVID-19 patient. *Turkish Journal of medical sciences.* 2020; 50:585-591.
8. Xia H, Lazartigues E. Angiotensin-converting enzyme 2: central regulator for cardiovascular function. *Current hypertension reports.* 2010; 12:170-175.
9. Steardo L, Steardo Jr L, Zorec R et al. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiologica.* 2020:e13473.
10. Şimşekoğlu R, Tombul T. Covid-19 Pandemic and Neurological Manifestations. *Anadolu Kliniği Tıp Bilimleri Dergisi.* 25:246-251.
11. Acarlı ANÖ, Samancı B, Ekizoğlu E et al. Coronavirus Disease 2019 (COVID-19) From the Point of View of Neurologists: Observation of Neurological Findings and Symptoms During the Combat Against a Pandemic. *Noro-Psikiyatri Arsivi.* 2020; 57:154-159.
12. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *Journal of medical virology.* 2020; 92:552-555.
13. Fodoulian L, Tuberosa J, Rossier D et al. SARS-CoV-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium. *bioRxiv.* 2020:2020.2003.2031.013268.
14. Chigr F, Rachidi F, Tardivel C et al. Modulation of orexigenic and anorexigenic peptides gene expression in the rat DVC and hypothalamus by acute immobilization stress. *Frontiers in cellular neuroscience.* 2014; 8:198.
15. Zhao H, Shen D, Zhou H et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol.* 2020; 19:383-384.

16. Parsons T, Banks S, Bae C et al. COVID-19-associated acute disseminated encephalomyelitis (ADEM). *Journal of Neurology*. 2020;1.
17. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology*. 2020; 94:959-969.
18. Efe IE, Aydin OU, Alabulut A et al. COVID-19-associated encephalitis mimicking glial tumor: a case report. *World Neurosurgery*. 2020.
19. Asadi-Pooya AA. Seizures associated with coronavirus infections. *Seizure*. 2020.
20. Kuo C-L, Pilling LC, Atkins JL et al. APOE e4 genotype predicts severe COVID-19 in the UK Biobank community cohort. *medRxiv*. 2020.
21. Helmich RC, Bloem BR. The impact of the COVID-19 pandemic on Parkinson's disease: hidden sorrows and emerging opportunities. *Journal of Parkinson's disease*. 2020; 10:351.
22. Shill H, Stacy M. Respiratory complications of Parkinson's disease. *Seminars in respiratory and critical care medicine*. Vol 23: Copyright© 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New ; 2002: 261-266.
23. Matías-Guiu J, Gomez-Pinedo U, Montero-Escribano P et al. Should we expect neurological symptoms in the SARS-CoV-2 epidemic? *Neurología (English Edition)*. 2020.
24. DosSantos MF, Devalle S, Aran V et al. Neuromechanisms of SARS-CoV-2: a review. *Frontiers in neuroanatomy*. 2020; 14:37.
25. Chen R, Yu J, Wang K, Howard D et al. The spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in human and mouse brain. *BioRxiv*. 2020.
26. Arbour N, Day R, Newcombe J et al. Neuroinvasion by human respiratory coronaviruses. *Journal of virology*. 2000; 74:8913-8921.
27. Giacomelli A, Pezzati L, Conti F et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study [published online March 26, 2020]. *Clin Infect Dis*. 2020.
28. Pivot X, Raymond E, Laguerre B et al. Pemetrexed disodium in recurrent locally advanced or metastatic squamous cell carcinoma of the head and neck. *British journal of cancer*. 2001; 85:649-655.
29. Kehoe PG, Al Mulhim N, Zetterberg H et al. Cerebrospinal Fluid Changes in the Renin-Angiotensin System in Alzheimer's Disease. *Journal of Alzheimer's Disease*. 2019; 72:525-535.
30. Paniz-Mondolfi A, Bryce C, Grimes Z et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *Journal of medical virology*. 2020; 92:699-702.
31. Wu Y, Xu X, Chen Z, Duan J et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Brain, behavior, and immunity*. 2020.
32. Klok F, Kruijff M, Van der Meer N et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thrombosis research*. 2020.
33. Desforges M, Le Coupanec A, Brison É et al. Neuroinvasive and neurotropic human respiratory coronaviruses: potential neurovirulent agents in humans. *Infectious Diseases and Nanomedicine I*; Springer; 2014: 75-96.
34. Sankowski R, Mader S, Valdés-Ferrer SI. Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration. *Frontiers in cellular neuroscience*. 2015; 9:28.
35. Sun CB, Wang YY, Liu GH et al. Role of the Eye in Transmitting Human Coronavirus: What We Know and What We Do Not Know. *Front Public Health*. 2020; 8:155.
36. Driessen AK, Farrell MJ, Mazzone SB et al. Multiple neural circuits mediating airway sensations: Recent advances in the neurobiology of the urge-to-cough. *Respir Physiol Neurobiol*. 2016; 226:115-120.
37. Wu P, Duan F, Luo C et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. *JAMA ophthalmology*. 2020; 138:575-578.
38. Guan W-j, Ni Z-y, Hu Y et al. Clinical characteristics of coronavirus disease 2019 in China. *New England journal of medicine*. 2020; 382:1708-1720.
39. Şeker ED. Ocular Findings of COVID-19. *Eurasian Journal of Health Technology Assessment*. 4:1-8.
40. Daruich A, Martin D, Bremond-Gignac D. Unilateral conjunctivitis as first presentation of Coronavirus Disease 2019 (COVID-19): A telemedicine diagnosis. *Journal Français d'Ophthalmologie*. 2020.
41. Cheema M, Aghazadeh H, Nazarali S et al. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19). *Canadian journal of ophthalmology*. 2020; 55:e125-e129.
42. Chen L, Liu M, Zhang Z et al. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. *British Journal of Ophthalmology*. 2020; 104:748-751.
43. Ma D, Chen C-B, Jhanji V et al. Expression of SARS-CoV-2 receptor ACE2 and TMPRSS2 in human primary conjunctival and pterygium cell lines and in mouse cornea. *Eye*. 2020:1-8.
44. Bettach E, Zadok D, Weill Y et al. Bilateral anterior uveitis as a part of a multisystem inflammatory syndrome secondary to COVID-19 infection. *Journal of medical virology*. 2020.
45. Marinho PM, Marcos AA, Romano AC et al. Retinal findings in patients with COVID-19. *The Lancet*. 2020; 395:1610.
46. Casagrande M, Fitzek A, Püschel K et al. Detection of SARS-CoV-2 in Human Retinal Biopsies of Deceased COVID-19 Patients. *Ocular Immunology and Inflammation*. 2020:1-5.
47. Mao L, Jin H, Wang M et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA neurology*. 2020; 77:683-690.
48. Cyr DG, Vicidomini CM, Siu NY et al. Severe bilateral vision loss in 2 patients with coronavirus disease 2019. *Journal of Neuro-Ophthalmology*. 2020.
49. Dinkin M, Gao V, Kahan J et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology*. 2020.
50. Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S et al. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. *Neurology*. 2020.

51. Bigaut K, Mallaret M, Baloglu S et al. Guillain-Barré syndrome related to SARS-CoV-2 infection. *Neurology-Neuroimmunology Neuroinflammation*. 2020; 7.
52. Caamaño DSJ, Beato RA. Facial diplegia, a possible atypical variant of Guillain-Barré Syndrome as a rare neurological complication of SARS-CoV-2. *Journal of Clinical Neuroscience*. 2020.
53. Pellitero SE, Ferrer-Bergua LG. Paciente con clínica neurológica como única manifestación de infección por SARS-CoV-2. *Neurologia (Barcelona, Spain)*. 2020.
54. Xiang P, Xu X, Gao L, Wang H et al. First case of 2019 novel coronavirus disease with encephalitis. *ChinaXiv*. 2020; 202003:00015.
55. Ordás CM, Villaceros-Álvarez J, Pastor-Vivas A-I et al. Concurrent tonic pupil and trochlear nerve palsy in COVID-19. *Journal of Neurovirology*. 2020:1-3.
56. Stewart JN, Mounir S, Talbot PJ. Human coronavirus gene expression in the brains of multiple sclerosis patients. *Virology*. 1992; 191:502-505.
57. Zhou S, Jones-Lopez EC, Soneji DJ et al. Myelin Oligodendrocyte Glycoprotein Antibody-Associated Optic Neuritis and Myelitis in COVID-19. *Journal of Neuro-Ophthalmology*. 2020.
58. Verdoni L, Mazza A, Gervasoni A et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *The Lancet*. 2020.