Blepharospasm as a tardive manifestation of COVID-19 disease: A case report

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We report three cases of blepharospasms developed after a symptomatic COVID-19 infection, in order to describe a possible association between COVID-19 infection and essential blepharospasm. Blepharospasm could represent a late sign of COVID-19 infection (more than four weeks after the contagion) and may be triggered by the neurotropism of the coronavirus.

Key words: 2020 pandemic, blepharospasm, COVID-19, facial dystonia

A new virus belonging to the Coronavirus family, SARS-CoV-2, was identified in Wuhan, China, in December 2019. SARS-CoV-2 spread worldwide rapidly and caused a global pandemic, as was confirmed by the World Health Organization (WHO) in March 2020.

The most common ophthalmological manifestation of coronavirus disease 2019 (COVID-19) is keratoconjunctivitis, which occurs because of migration of the virus from the upper respiratory tract to the conjunctiva.[1]

Here we present three cases of blepharospasm after COVID-19 infection (more than four weeks after the contagion)[2].

Case Reports

Case 1

A 43-year-old woman experienced dyspnea and cough almost six months ago, for which she was empirically treated with anti-inflammatory therapy. Her medical history was unremarkable. She had high myopia and developed dry eyes.

Two weeks after the COVID-19 infection, she developed blepharospasm. Although her PCR test for COVID-19 was initially positive, it was negative when she presented to our hospital.

Discussion

Previous studies have reported that COVID-19 infection may cause conjunctivitis via droplet transmission and conjunctival inoculation, migration of the upper respiratory tract infection through the nasolacrimal duct, or hematogenous infection of the lacrimal glands.[1]

A study conducted by Loon et al.[3] in 2004 demonstrated the presence of SARS-CoV RNA in the tears of patients with conjunctivitis; however, the virus was not detected in the tears or conjunctival secretions of patients without conjunctivitis.

COVID-19 invades human tissues by binding to the angiotensin-converting enzyme (ACE) 2 receptor proteins; these receptors are highly distributed in the aqueous humor and on the ocular surface.[3]

Given the crucial role of ACE2 receptors in the pathogenesis of SARS-CoV-2 neurotropism,[4] Netland et al.[5] studied mice
transgenic for human ACE2 and demonstrated that the virus enters the brain through the olfactory bulbs and rapidly spreads to the connected regions of the cortex (piriform and infralimbic cortices), basal ganglia (ventral pallidum and lateral preoptic regions), and midbrain (dorsal raphe). Other areas, such as the paratenial nucleus of the thalamus, paraventricular nucleus of the hypothalamus, and the medial and basolateral amygdala also demonstrated the presence of viral antigens.

There are three pathways hypothesized to be involved in the pathogenesis of blepharospasm:[8]
(1) Motor cortical regions send descending projections through the basal ganglia nuclei and substantia nigra pars reticulata to the brain stem motor nuclei;
(2) Embedded loops of the trigeminal blink reflex arc and the long sensorimotor circuit, that is, from the trigeminal nucleus to the somatosensory cortex through the thalamus, and to the brainstem nuclei through the basal ganglia; and
(3) Abnormal dopaminergic (D1 and D2) and serotonergic transmission in the basal ganglia.

Blepharospasm is a dystonia that may be attributable to basal ganglia and diencephalic dysfunction as a result of transneuronal penetration of COVID-19, even in the absence of olfactory and gustative symptoms.

The virus may enter the olfactory filaments located in the lamina papyracea through nasal ACE receptors. Then the virus may spread to the corticomedial amygdala, followed by the basolateral amygdala, and finally to the hypothalamus.

The thalamus plays crucial roles in olfactory pathways and oribcular muscle function. We suggest that when the virus penetrates through the mouth, it invades the taste filaments of cranial nerve VII to reach the posteromedial nucleus of the thalamus. Cranial nerve VII infection may lead to dysregulation of its somatic motor branch and consequently blepharospasm.

Li et al.[7] suggested that the enzyme dopa decarboxylase (DDC) is crucial for dopamine and serotonin synthesis because it converts L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine and L-5-hydroxytryptophan to serotonin. Additionally, DDC converts histidine to histamine. ACE2 and DDC co-regulate the neurological circuits implicated in COVID-19 symptoms, which may explain the functional link between the ACE2-mediated synthesis of angiotensin (AT) 1–7 and DDC-mediated synthesis of dopamine and serotonin.

AT1–7 are primarily produced by the degradation of AT2 by ACE2; AT1–7 cannot cross the blood-brain barrier. The AT receptors AT1, AT2, and AT4 are present in the circumventricular organs, cerebrovascular endothelial cells, cerebral cortex, basal ganglia, dopaminergic neurons, and glial cells in rats, as well as in primary mesencephalic cultures.[9] AT2 receptors are also present on neurons and glial cells inside the blood-brain barrier, particularly on astrocytes. The actions of AT1–7 oppose those of the renin-AT axis.

Autoradiographic studies have reported a high concentration of AT1 receptors on dopaminergic neurons in the substantia nigra and their terminal neurons in the striatum of different mammals, including humans.[9] ACE receptors also play a crucial role in the pathogenesis of Parkinson’s disease.

The dopamine system is implicated in the pathogenesis of several types of dystonia,[10] including tardive dystonia caused by neuroleptics, which frequently presents with blepharospasm.

**Conclusion**

We hypothesize that the binding of SARS-CoV-2 to basal ganglia ACE receptors alters the degradation of L-DOPA to dopamine and causes blepharospasm.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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