Blepharospasm as a Tardive Manifestation of Covid-19 Disease

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Abstract

Purpose: to describe a new clinical manifestation caused by Covid-19.

Observations: We report two confirmed case of COVID-19 who showed blepharospasm as a tardive sequel of the infection.

Conclusions and Importance: blepharospasm could represent a tardive clinical sign of Covid-19 infection, responsible for the 2020 pandemia.

Introduction

A new virus belonging to Coronavirus strain, called SARS-CoV-2, was identified in Wuhan, China, in December 2019. The SARS-CoV-2 spread very rapidly, causing a global pandemic, confirmed by OMS in march 2020. COVID-19 had an high fatality among older patients, especially those with comorbidities, due to severe acute respiratory syndrome, cardiovascular accidents and neurological disorders.

Concerning the ophthalmological diseases, cases of kerato-conjunctivities caused to Covid-19 have been described as a typical manifestation related to a direct migration of the virus from the upper respiratory tract to the conjunctiva¹.

In this case report, we describe two cases of blepharospasms risen in two patients after Covid-19 infection.

Patient 1

A 43-year-old female. She had dyspnoea and cough about 6 months ago. No pneumonia. Medical history was negative. Her parents were healthy. Concerning ophthalmological examination, she presented a high myopia and a dry eye disease. Empiric anti-inflammatory therapy was administered. Blepharospasm appeared two weeks after Covid-19 infection. PCR test was positive for Covid-19. When she came to our attention, she was already negative.

Patient 2

A 43-year-old female. She had a cold about 4 months ago. No pneumonia. Medical, familial and ophthalmological history were negative. Blepharospasm appeared three weeks after Covid-19 infection. She underwent PCR test, which confirms Covid-19 disease; nevertheless, she was negative at the time of the ophthalmological visit.

Discussion

Concerning ocular infection by Covid-19, conjunctivitis caused by Covid-19 which have been described in previous studies² are attributable to the straightforward inoculation of the conjunctiva due to a droplet

transmission; the migration of upper respiratory tract infection through the nasolacrimal duct; the hematogenous infection of the lacrimal gland.

A study carried out by Loon et al. in 2004 demonstrated the presence of SARS-CoV RNA in tears³; however, no virus was detected in the tears or conjunctival secretions of patients without conjunctivitis.

Covid-19 has access to human tissue by attaching the ACE-2 receptors, which are very distributed in aqueous humor and in the ocular surface⁴; it indicates they could be represent a target in COVID-19 infection.

Given the crucial role of the ACE-2 receptors in the pathogenesis of SARS-CoV-2 neurotropism, Netland et al.⁵ studied mice transgenic for human ACE-2 and demonstrated that the virus enters the brain through the olfactory bulb and rapidly spread 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 parataenial nucleus of the thalamus, paraventricular nucleus of the hypothalamus, and the medial and basolateral amygdala, were also virus antigen positive. A feasible infection via oral uptake was demonstrated by the positivity of some regions such as the dorsal vagal complex, nucleus ambiguus, and hypoglossal nucleus.

Blepharospasm foresees three pathogenic hypothesis⁶:

1. an output from motor cortical regions to descending projections direct to the basal ganglia nuclei, the substantia nigra pars reticulata, and terminating in brainstem motor nuclei, (2) the embedded loops of the trigeminal blink reflex arc and the long sensorimotor circuit from trigeminal nucleus through thalamus to somatosensory cortex back through basal ganglia to the brainstem nuclei and (3) abnormalities in the basal ganglia dopamine 1 and 2 and serotonin system.

In our opinion, blepharospasm could represent a dystonia attributable to an abnormal functioning of the basal ganglia and diencephalic regions after Covid-19 transneuronal penetration, even in absence of olfactory or gustative symptoms.

We think that virus enters the olfactory filaments located in lamina papiracea, passing through the nasal ACE receptors, it arrives to the amigdala and cortico-medial nuclei, then to the amigdal baso-lateral nucleus, and lastly to the hypothalamus.

Thalamus plays a crucial role both in olfactive pathways than in orbicular muscles function.

Furthermore, we suggest that virus penetrates through the mouth, it gets through the taste filaments of the VII cranial nerve and it reaches the postero-medial nucleus of the thalamus.

We assume that VII cranial infection causes a bouncing dysregulation of the VII nerve somatic motor branch that belatedly manifests in a blepharospasm.

Based on the hypothesis formulated by Li et al⁷, Dopa Decarboxylase (DDC)

is a major enzyme of both the dopamine and the serotonin synthetic pathways as it converts L-3,4-dihydroxyphenylalanine (L-DOPA) into dopamine and L-5-hydroxytryptophan into serotonin. In addition, DDC also supports the conversion of histidine into histamine. That ACE-2 coregulates with DDC neurological circuits implicated in Covid-19 symptoms; that is due to a possible functional link between the ACE-2-mediated synthesis of angiotensin (AT) 1-7 and the DDC-mediated synthesis of dopamine and serotonin.

According to Nataf⁸, ACE-2 and DDC may coexpress and coregulate in non-neuronal cell types in patients affected by COVID-19, who suffer from of a central autonomic failure of respiratory functions.

AT 1–7 are primarily formed by the degradation of AT II by ACE-2, and they do not cross the blood-brain barrier. AT receptors (AT1, AT2, and AT4) have been described during the last decades as located in the circumventricular organs, in cerebrovascular endothelial cells, cerebral cortex, basal ganglia⁹, in dopaminergic neurons, and glial cells in rats, as well as mesencephalic primary cultures¹⁰. AT II receptors were also identified in neurons and glial cells inside the blood-brain barrier and they seem to be produced by astrocytes¹¹.

The effects mediated by AT 1–7 are in direct opposition to the actions of the Renin-Angiotensin axis. Moreover, AT 1-7-mediated NF-κB inhibition has been also documented in several animal models, including hypertensive kidney disease¹², pulmonary fibrosis¹³, and fatty liver disease¹⁴.

The neuroprotective effect of AT 1–7 was highlighted in an ischemic stroke model¹⁵.

Autoradiographic studies reported a high concentration of AT 1 receptors in dopaminergic neurons, both in cell bodies of the substantia nigra, and their terminal neurons in the striatum of different mammals, including humans^{16,17}. ACE receptors have been studied as crucial elements in Parkinson disease.

Nevertheless, the dopamine system is implicated as a potential factor in many different forms of dystonia (Augood et al.,¹⁸; Perlmutter and Mink¹⁹; Breakefield et al.²⁰, Wichmann²¹), in tardive dystonia due to neuroleptics whose initial presentation is commonly blepharospasm²².

In our hypothesis, the binding of COVID-19 to ACE receptors localized in basal ganglion, causes blepharospasm by altering the degradation of the L-DOPA to dopamine.

Patient Consent

Consent to publish this case report has been obtained from the patient(s) in writing.

Acknowledgements and Disclosures

Declarations

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Consent to publish this case report has been obtained from the patient(s) in writing.

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All authors attest that they meet the current ICMJE criteria for Authorship.

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