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Letter to the Editor

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SARS-CoV-2 infection and sleep disturbances: nitric oxide involvement and therapeutic opportunity

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During the first week early phase of COVID-19, some patients exhibit symptoms that are mainly due to SARS-CoV-2 replication and the important pulmonary cytolysis that takes place. Thereafter, a progressive decrease in upper airway viral shedding ensues, which may result from the emergence of a cytokine storm [1]. Meanwhile, data regarding the involvement of the nervous system in relation to SARS-CoV-2 infection become progressively available [2]. Here, we consider sleep impairment potentially provoked by virus brain penetration and the nitric oxide (NO)-induced deleterious mechanisms that may emerge.

One century ago, H1N1 influenza, another neurotropic virus, provoked sleep disorders related to von Economo's encephalitis lethargica [3]. In the initial phase, von Economo observed hypersomnia, insomnia associated with "choreatic" dysfunction, parasomnias described as "dissociation of cerebral and body sleep," "akinetic cases" (sleep paralysis), and "somnambulism." He related these symptoms to the anterior ("center for regulation of sleep") and posterior hypothalamus ("wake center"). During this influenza pandemic, sporadic cases of Kleine-Levin syndrome were also reported.

An epidemic of narcoleptic-like syndromes was also observed in Chinese children during the 2009–2010 H1N1 influenza pandemic. In intranasally infected mice, 4 weeks after infection, the virus targeted sleep-wake regulatory neurons in lateral hypothalamus (orexin and melanin-concentrating hormone), pontine raphe, and locus cœruleus nuclei [4].

Considering the high prevalence of neurological impairments in COVID-19 patients, as well as the concomitant or subsequent anosmia, ageusia, headache, myalgia, paresthesia, dizziness, and fatigue, one may expect the emergence of sleep problems. Rapid eye movement (REM) sleep behavior disorders (RBD) may occur in Guillain-Barré syndrome, which has been also described in COVID-19 patients [5]. A systematic literature review suggests that a third of COVID-19 patients experience sleep disturbances (reported symptoms: sleep-wake schedule disorders, stress-related sleeplessness associated with anxiety and depression, sleepiness) [6]. However, published data on specific sleep disorders in COVID-19 highly medicalized patients are still lacking.

SARS-CoV-2 can be detected in the brain by quantitative RT-PCR. In about half of reported cases, the virus was found

in basal ganglia, pyriform and infra-limbic cortices, and brainstem, notably the dorsal vagal complex and the dorsal raphe nucleus [7, 8]. SARS-CoV-2 may penetrate the brain in regions that lack a blood-brain barrier (BBB), such as the area postrema. SARS-CoV-2 binds to angiotensin-converting enzyme (ACE-2) receptors expressed in brain capillary endothelium and vascular smooth muscle cells. Disruption of BBB would allow the virus to enter the brain and bind to ACE-2 receptors on neurons and glial cells [7, 8]. SARS-CoV-2 may enter the brain via cranial nerves (CN), including terminals of olfactory, trigeminal, and gustatory nerves. Anosmia designates the olfactory (CN I), while ageusia reports to lingual (CN VII), cheek (CN V), glossopharyngeal (CN IX), and laryngeal vagal influx (CN X). SARS-CoV-2 may also trigger cerebral processes indirectly in relaying messages through a cytokine storm, and from thoracic and abdominal organs, using the vagal nerve (CN X) route [7, 8]. As a result, the presence of SARS-CoV-2 in the brain may trigger neurological impairments, including sleep disturbances.

In healthy conditions, NO is produced by constitutive forms of NO-synthase (NOS), endothelial eNOS, and neuronal nNOS. It is released at a picomolar concentration and plays various regulatory roles for the maintenance of physiological homeostasis. With pathogen invasion (parasites, bacteria, and viruses), the brain reacts by activating microglial cells (the brain's resident macrophages), and astrocytes. Both cell types belong to the innate immune system and produce cytokines such as interleukins (IL-6, IL-17A), tumor necrosis factor alpha, interferon gamma, and NO. In African trypanosomiasis, for example, inducible NOS (iNOS) is activated in microglial cells and astrocytes, which release high concentrations of parasiticidal NO (above nanomolar concentration); this constitutes the first response to pathogen invasion [9]. Similarly, in COVID-19 and throughout the cytokine storm, iNOS may be expressed in a wide variety of inflammatory and residential cells to release probably large quantities of NO (above nanomolar concentration) in various tissues [9]. For example, in the lungs, marked NO production might then be responsible for the decreased viral replication that takes place during the second phase of the infection [10]. In the brain, such a scenario of pronounced iNOS-dependent NO release may occur, since activated astrocytes and microglial cells were observed together with SARS-CoV-2 viral proteins in lower brainstem cranial nerve nuclei [7, 8]. To our knowledge, such a cerebral NO-dependent mechanism has never been investigated in COVID-19 patients. Since brain pathogens can initiate a surge in iNOS-dependent NO production [9], this may attenuate viral replication but result in deleterious side effects. Nitric oxide reacts avidly with oxygen and superoxide radicals to form NO derivatives, including long half-life peroxynitrite ($ONOO^-$). This highly reactive free radical and powerful oxidant provokes systemic and CNS damage, including protein deterioration, cell membrane destruction, DNA/RNA lesions, and cell death [10].

In parallel, in the peripheral compartment, during the COVID-19 early phase marked by highest viral pressure, a deficit in NO production occurs, especially in the lungs. The induced increase in pulmonary resistance can be reduced by inhaled NO [11]. However, during the COVID-19 second phase, the cytokine storm may be accompanied by iNOS-dependent NO production. In such a situation, the inhalation of NO may prove to be dangerous for COVID-19 patients.

Interestingly also, throughout the healthy aging process, the iNOS enzyme becomes permanently expressed in the brain, especially in neurons, where it is required for sleep maintenance [12]. In old rats, neuronal iNOS-dependent NO production ensures an adequate maintenance of REM sleep (Stage R) and, to a lesser extent, slow-wave-sleep (Stage N3) [12]. Since the virus-induced iNOS-dependent NO production would add to basal iNOS expression, sleep disturbances would be expected, among other brain dysfunction. This deleterious situation may improve with the administration of harmless specific iNOS inhibitors and antioxidants (vitamins C, E, and melatonin) [9, 13].

In conclusion, we hypothesize that the neurotropic virus SARS-CoV-2 activates brain iNOS expression leading to the overproduction of NO-related free radicals that compromise neurocellular integrity. As with certain other neurotropic pathogens, limiting or suppressing free radical-induced damage may attenuate brain damage and neurological manifestations of COVID-19, including sleep abnormalities.

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