

Peripheral Nervous System Manifestations Associated with COVID-19

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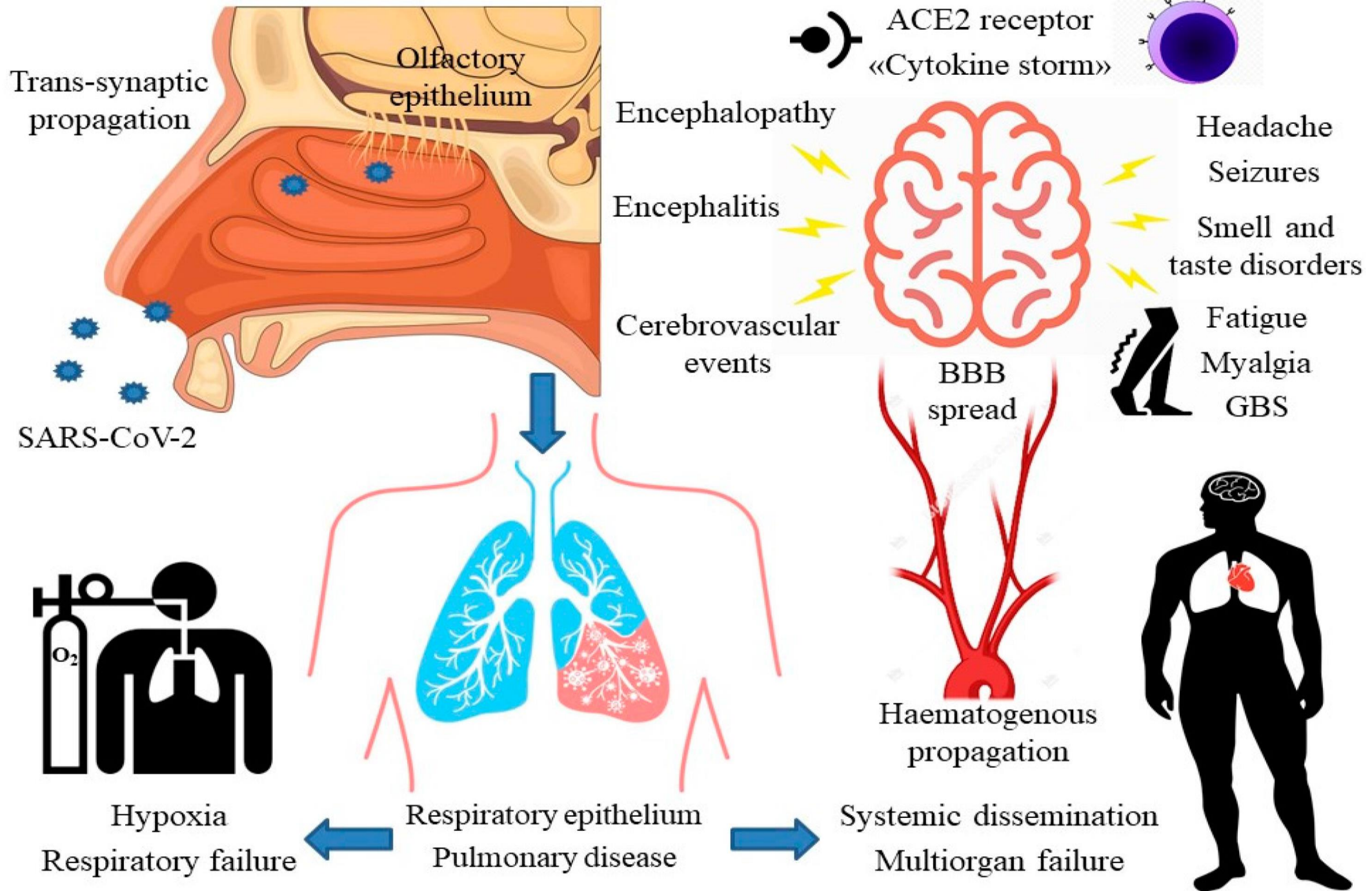
-SARS-CoV-2 is a beta-coronavirus that belongs to the family of SARS viruses, whose transition path is through person-to-person transmission.

-Structurally, SARS-CoV-2 has a well-defined composition comprising of 14 binding residues. Spike (S) glycoprotein receptor on the surface of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors expressed on various host tissues.

- Fever, cough, myalgia, arthralgia, fatigue, and dyspnea are the common symptoms.

Mechanisms of coronaviruses neuroinvasion

- ▶ The mechanism associated with COVID-19 neuroinvasion and the potential neurologic disorders in the infected patients remains largely unclear.
- ▶ Coronaviruses invade the CNS through two possible mechanisms: hematogenous dissemination or neuronal retrograde involvement.
- ▶ Hematogenous spread is caused by bloodstream travel of the virus (by infecting endothelial cells of the blood-brain barrier (BBB) or infecting leukocytes that become a viral reservoir) similar to enteroviruses (i.e. coxsackieviruses and polioviruses) and flaviviruses CNS involvement.
- ▶ Retrograde transmissions through transmission of the virus from periphery to the CNS (intranasal infection that infects nasal olfactory nerve system gets access to the CNS, consequently reaching the hippocampus, brainstem, and spinal cord, while almost always sparing the cerebellum).



Neurologic manifestations

- ▶ HCoV infections manifest as respiratory and extra respiratory, including CNS involvement.
- ▶ COVID-19 had neurologic manifestations in 36.4% of cases and thereby suggesting the neuroinvasive potential of this virus.
- ▶ Neurological presentations of COVID-19 infection are categorized into two groups: CNS symptoms and peripheral nervous system (PNS) symptoms.
- ▶ CNS symptoms include headache, dizziness, disorder of consciousness, ataxia, acute cerebrovascular disease and convulsion.
- ▶ It is interesting that laboratory data are not helpful in patients with PNS involvement.
- ▶ In patients with CNS engagement, severe cases are accompanied by lymphopenia and thrombocytopenia and higher blood urea nitrogen (BUN) levels compared with cases without CNS involvement.

PNS Manifestations of COVID-19

- ▶ Gustatory and olfactory disorders
- ▶ Guillain-Barré Syndrome Spectrums
- ▶ Nerve Pain, Myalgias, and Skeletal Muscle Injury
- ▶ Myopathy and Myositis
- ▶ Multiple Cranial Neuropathies
- ▶ Neuromuscular Junction Disorders
- ▶ Neuro-ophthalmological Disorders
- ▶ Sensorineural Hearing Loss
- ▶ Acute Care-Related Peripheral Nervous System Complications

Gustatory and olfactory disorders

- ▶ Hyposmia is a reduction in the sense of smell that occurs because of viruses with the ability to damage or affect the nervous system.
- ▶ Hyposmia can be an early and mild symptom for COVID-19 patients and could occur suddenly.
- ▶ The study by Bénézit et al. reported that of the 68 patients who were positive for COVID-19, 75% were hyposmic.
- ▶ Anosmia is thought to occur in COVID-19 via binding of the virus to the host receptors of the ACE2 and TMPRSS2 proteases that express themselves in the nonneural olfactory epithelium.
- ▶ Dysgeusia is the distortion of the sense of taste and may present with anosmia at the same time.
- ▶ Results showed a close link between partial or complete loss of smell and taste and a positive diagnosis of COVID-19.

Guillain-Barré Syndrome Spectrums

- ▶ Both GBS and acute motor axonal neuropathy (AMAN) have been reported after SARS-CoV and MERS-CoV infections.
- ▶ peripheral motor neuropathy has also been reported before the onset of the typical flu-like symptoms of COVID-19.
- ▶ Miller Fisher syndrome, a rare variant of GBS, has also been reported in COVID-19 patients
- ▶ A post-infectious dysregulation of the immune system arising from COVID-19 is presumably the cause of GBS.
- ▶ A molecular mimicry mechanism in which infecting viruses likely share epitopes similar to some peripheral nerve components is believed to occur and stimulate autoreactive T or B lymphocytes.

Nerve Pain, Myalgias, and Skeletal Muscle Injury

- ▶ Nerve pain was found in 4 (4.5%) and 1 (0.8%) of the patients with severe and non-severe COVID-19, respectively.
- ▶ Skeletal muscle injury was seen in 17 (19.3%) and 6 (4.8%) of the patients with severe and non-severe COVID-19, respectively.
- ▶ It is important to consider that reports of creatine kinase (CK) elevation, as the only marker of muscle injury, are non-specific and may be related to prolonged bed rest and medications in severe COVID-19 cases more than a direct muscle injury from COVID-19.
- ▶ Myositis can be a manifestation of COVID-19, although most literature only involves case reports.
- ▶ Regenerating fibers, perivascular inflammatory infiltration with endomysial extension, and upregulation of human leukocyte antigen class ABC expression on non-necrotic fibers was shown using muscle biopsy.

Multiple Cranial Neuropathies

- ▶ evidences indicates that COVID-19 may also lead to multiple cranial neuropathies, as well as the more recognized high incidence of anosmia with infection, with rates of up to 73% of those infected.
- ▶ Auditory complications have also been reported in COVID-19 patients.

Neuromuscular Junction Disorders

New-onset myasthenia gravis (MG) after COVID-19 infection can also occur and may also be due to molecular mimicry mechanisms as with other neurological manifestations.

A retrospective Brazilian study conducted among 15 adult MG patients with COVID-19, showed a 30% mortality rate. The most common presentation was dyspnea, followed by fever.

Acute Care-Related Peripheral Nervous System Complications

- ▶ ICU-acquired weakness, including critical illness polyneuropathy (CIN) and myopathy (CIM), have been identified in many patients recovering from prolonged mechanical ventilation due to severe COVID-19.
- ▶ There was a high incidence of CIN or CIM in COVID-19 patients compared with the general ICU patients during 2019.
- ▶ CIN was found to have a higher frequency in the COVID-19 ICU cases (50%) than in the non-COVID-19 ICU cases (0%).
- ▶ COVID-19 patients may present with nerve entrapment secondary to large hematomas or another fluid buildup during their hospital stay.

Vaccine-Related Peripheral Nerve Syndromes

- ▶ The incidence of serious adverse events was low, and no serious safety concerns were observed.
- ▶ Short-term mild-to-moderate pain at the injection site was the most commonly reported reaction.
- ▶ The anecdotal finding of a slight excess of Bell's palsy in this trial and in the BNT162b2 vaccine trial may be more than a chance event, but the incidence was extremely low. For example, in the Pfizer-BioNTech clinical trial, which included 44,000 participants, 4 people reported experiencing Bell's palsy, a total of 0.0091% of participants.
- ▶ In the Moderna trial, which included 30,400 participants, 3 people (0.099%) reported experiencing Bell's palsy.



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