

# COVID-19 in the Brain and Nervous System

Subjects: [Immunology](#) | [Infectious Diseases](#)

Contributor: Aisha Sodagar , Rasab Javed , Hira Tahir , Saiful Izwan Abd Razak , Muhammad Shakir , Muhammad Naeem , Abdul Halim Abdul Yusof , Suresh Sagadevan , Abu Hazafa , Jalal Uddin , Ajmal Khan , Ahmed Al-Harrasi

COVID-19 can spread throughout the central nervous system, impacting the brain and spinal cord, and neurological symptoms could explain this in people infected with long-term infection.

COVID-19

brain

neurological manifestations

## 1. Neurological Effects of COVID-19

Coronavirus was initially observed as a pathogen responsible for respiratory illness with cough, shortness of breath, fever, muscle pain, headache, sore throat with loss of taste and smell. These symptoms were declared by the center for disease control (CDC). Still, this virus was later considered a pathogen that negatively impacted multiple organs. Its heterogeneity showed more neurological disorders, indicating its RNA in the cerebrospinal fluid of its infected patients in acute and long-term phases <sup>[1]</sup>. SARS-CoV-2 may directly impact the white and grey matter of the brain and spine with demyelinating lesions and symptoms of seizures, ataxia, dizziness, and cerebrovascular illness. French and Turkish scientists also reported neurological symptoms during coronavirus infection in patients with agitation, delirium, ischemic stroke, and encephalopathy, along with anosmia and dysgeusia, while headache is the most common manifestation <sup>[2]</sup>. This viral infection of the respiratory tract has the strength to cause psychiatric and neurological problems because COVID-19 is neurotropic in nature and has the strength to enter into the central nervous system, while antibodies of COVID-19 have been observed in deceased patient's cerebrospinal fluid. It is essential to consider COVID-19 as a neuropsychiatric manifestation of long-term complications <sup>[3]</sup>.

Another study observed that obscured monocular vision, dysphoria, vomiting, deliria, coma, brain herniation, loss of consciousness, up-rolling eyeballs, vomiting, four-limb twitching, confusion, and seizures are common in patients infected with the novel coronavirus <sup>[1]</sup>. However, the neurotropic and neuro-invasive symptoms were observed since the first case of coronavirus in human in 2003 <sup>[4]</sup>. A few neurological manifestations due to novel coronavirus are mentioned in **Table 1**.

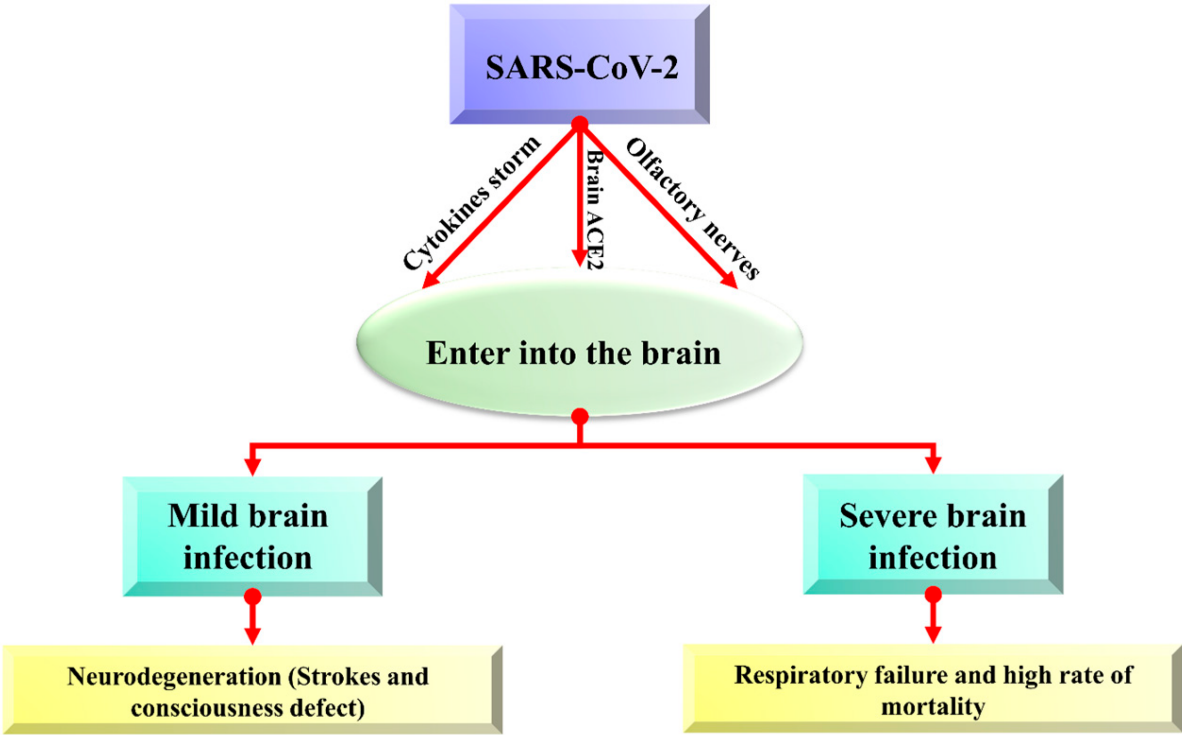
**Table 1.** List of neurological disorders caused by SARS-CoV-2 infection.

Disorder	Mean Age (Years)	Onset of Disease	Percentage of Infected Patients	Effect	Treatment/Drug	Reference
Dizziness	39	Shortly after COVID-19	16.8%	Inflammation of the inner ear nerve that connected to the brain	Betahistine, danshenchuandomazine, meclizine, benzodiazepine, steroids, vestibular rehabilitation	<a href="#">[1]</a> <a href="#">[5]</a> <a href="#">[6]</a> <a href="#">[7]</a>
Ischemic stroke and hemorrhage	67.4	In the first week of respiratory symptoms with moderate pulmonary involvement	83.7% stroke and 20.8% hemorrhage	Numbness or weakness in the face, arm, or leg on one side of the body, confusion, difficulty speaking, dizziness, loss of balance, and severe headache	Apixaban 5 mg twice daily, enoxaparin 1 mg/kg every 12 h	<a href="#">[8]</a> <a href="#">[9]</a> <a href="#">[10]</a> <a href="#">[11]</a>
Encephalopathy	66	At the time of documented COVID-19 infection	8.7% while 31.8% in the case study of 509 COVID-19 hospitalized patients	Confusion, non-oriented to time, person, or place, seizures, and sleepiness	High-dose IV steroids, IV immunoglobulin, and immunomodulators (e.g., rituximab)	<a href="#">[12]</a> <a href="#">[13]</a> <a href="#">[14]</a>
Delirium	77.7	As a sixth primary symptom of coronavirus	28%	Confusion, disorientation, inattention, and cognitive disturbances commonly affect older persons	Haloperidol, melatonin as prophylaxis	<a href="#">[15]</a> <a href="#">[16]</a>
Anosmia and Dysguesia	47	Initial symptoms for coronavirus infected patients	47% 54/114 patients and 5.1% anosmia while 5.6% dysgeusia in another study of 214 infected patients	Official symptoms for COVID-19	Caffeine in coffee	<a href="#">[17]</a> <a href="#">[18]</a> <a href="#">[19]</a> <a href="#">[20]</a>

Disorder	Mean Age (Years)	Onset of Disease	Percentage of Infected Patients	Effect	Treatment/Drug	Reference
Dysautonomia (also known as secondary COVID-19 infection)	48	Onset 6 weeks following initial COVID-19 symptoms, within the last week of the illness, also seen symptom onset occur within three months of recovery.	50%	Postural lightheadedness and near-syncope, fatigue, activity intolerance, hypertensive response, and orthostatic hypotension	Cefazolin and acebutolol (in case of significant hypertension)	<a href="#">[21]</a> <a href="#">[22]</a> <a href="#">[23]</a> <a href="#">[24]</a>
Microbleed	67.7	Fever, productive cough, myalgias, headache during coronavirus attack	24.4%	Confusion, agitation, and delayed recovery of consciousness	Co-amoxicillin, hydroxychloroquine, piperacillin, tazobactam, azithromycin, lopinavir, ritonavir, levofloxacin, tazobactam	<a href="#">[25]</a> <a href="#">[26]</a>
Coma	66	Severe illness due to viral attack	15%	Breathlessness, an erratic heart rate and fatigue, altered mental status, and inability to wakeup off leads to unconsciousness	Modafinil and carbidopa/levodopa, amantadine, aspirin, statin	<a href="#">[27]</a>
Brain herniation, cerebral edema	57	Positive for SARS-CoV 2, fatigue, and fever	3.9%	Hypertension, dyspnea, nausea, vomiting, diarrhea, and multiple juxtacortical hemorrhages (CT scan observation)	Midazolam, low dose norepinephrine	<a href="#">[27]</a>
Cerebral ataxia and myoclonus	59.6	Acute onset within one	40% ataxia and 46.7% Myoclonus	Spontaneous, action-induced, posture-induced,	Methylprednisolone daily for 5 days, clonazepam after 10 days of	<a href="#">[28]</a>

Disorder	Mean Age (Years)	Onset of Disease	Percentage of Infected Patients	Effect	Treatment/Drug	Reference
		month of COVID-19		and mild dysarthria	symptoms, levetiracetam started on day 14	
Seizures [31]	76- and 82-years old patient's case history	Patients suffering from coronavirus	23% detected by anti-CoV IgM	Convulsive activity and subtle twitching	Antiseizure medication (ASM) therapy, brivaracetam, lacosamide, carbamazepine, phenytoin, phenobarbital, benzodiazepines, valproic acid, vancomycin, meropenem, and Acyclovir for CSF coverage, all drugs should be prescribed cautiously by following doctor's advice in which patient's health history is essential	[4][29]

infects astrocytes over other cells, and neurological symptoms can be described in the brain [32]. About 0.04% of long-term severe acute respiratory syndrome (SARS) infected patients showed symptoms of the affected central nervous system, and this problem is becoming scarier, while only 0.2% of neurological symptoms were observed with MERS [33]. There are possibly three main ways (olfactory bulb, angiotensin-converting enzyme (ACE) pathway, and cytokine storm) that coronavirus follows to enter the brain, as shown in **Figure 1**.



**Figure 1.** The overview of possible entry routes of SARS-CoV-2 in the brain.

## 2.1. Coronavirus Enters the Brain via ACE2 Pathway

The COVID-19 virus enters the brain via angiotensin-converting enzyme (ACE)-2 receptors present in the CNS and is particularly expressed in the nasal mucosa [34]. A transmembrane protein ACE-2 (Angiotensin-converting enzyme-2) is typically recognized for its carboxypeptidase activity and its physiological role in the renin-angiotensin system (RAS) [35]. ACE-2 (Angiotensin-converting enzyme-2) has an ability to express in many tissues of the brain, and novel coronavirus can directly interact with this enzyme in the capillary endothelium due to which the blood–brain barrier is devastated, which enhances virus entry into the brain and affect the central nervous system, because ACE-2 can express throughout the brain. Viral mRNA also interacts with ACE-2 in COVID-19 infected patients. Increased neurological infections are due to a novel coronavirus that is promoted to enter the central nervous system because of the abundance of ACE-2 enzymes in the brain [36][37]. Viral spike protein interacts with the ACE-2 receptor, an important regulator of the renin-angiotensin system (RAS). Its expression has also been studied in the retina, cerebellum, cerebrum, and olfactory mucosa [38]. The virus enters the brain via other receptor cells, too, like neuropilin-1 (NRP1), basigin (BSG; CD147), cathepsin L (CTSL), and serine protease 2 and 4 (TMPRSS2/4) [38][39][40].

## 2.2. Coronavirus Entry into the Brain via Olfactory Pathway

The presence of a high amount of virus in the nasal epithelium suggests that novel coronavirus can travel to the brain through olfactory nerves. Such viruses that can invade neurons can bind with olfactory receptor neurons [41]. nCoV-19 migrates from the cribriform plate by following the trigeminal pathway and penetrating the olfactory mucosa, which causes smell loss and may enter the brain [42]. The virus attaches to olfactory receptors, enters the neuroepithelium, then spreads in the brain stem, thalamus, and medulla oblongata and causes serious disorders. Postmortem reports also provided evidence of its presence in neural endothelial cells in frontal lobe tissues [43].

## 2.3. Coronavirus Entry in the Brain via Cytokine Storm

Cerebrospinal fluid and the blood–brain barrier help in creating a balanced environment to protect the brain from viruses and other pathogens, but these can enter via peripheral nerves and olfactory sensory neurons. SARS-CoV-2 trigger pro-inflammatory microglia phenotype (M1 phenotype) that activate proinflammatory cytokines and enhance neurodegenerative disorders [44]. Activating proinflammatory cytokines enhances neutrophil activation, resulting in the characteristic cytokine storm. Interleukin (IL)-1, IL-6, IL-12, interferon (IFN)  $\gamma$ , and tumor necrosis factor (TNF)  $\alpha$ , which mainly targets the lung tissue, are also released along with proinflammatory cytokines. Damaged neuroepithelium cells cause inflammation and activate cytokine storms that damage neurons and neurological disorders. Cytokine storm is also associated with immune effector cell-associated neurotoxicity syndrome (ICANS) and other encephalopathies associated with cytokine storm [45].

Increased levels of cytokines, including Macrophage-Colony Stimulating Factor (M-CSF), interferon  $\gamma$ -induced protein (IP-10), and Macrophage Inflammatory Protein 1- $\alpha$  (MIP1- $\alpha$ ). The activated cytokine storm results in a hyperactive immune response that leads to inflammation and inflammatory cytokines, followed by a delayed

production of interferons (IFN). The released cytokines stimulate the neutrophils that triggers inflammation when the virus replicates within the macrophages resulting in apoptosis [\[46\]](#).

## References

1. Cheng, Q.; Yang, Y.; Gao, J. Infectivity of human coronavirus in the brain. *EBioMedicine* 2020, 56, 102799.
2. Bougakov, D.; Podell, K.; Goldberg, E. Multiple neuroinvasive pathways in COVID-19. *Mol. Neurobiol.* 2021, 58, 564–575.
3. Butler, M.; Pollak, T.A.; Rooney, A.G.; Michael, B.D.; Nicholson, T.R. Neuropsychiatric complications of COVID-19. *Br. Med. J. Publ.* 2020, 371, m3871.
4. Asadi-Pooya, A.A. Seizures associated with coronavirus infections. *Seizure* 2020, 79, 49–52.
5. Arabi, Y.; Harthi, A.; Hussein, J.; Bouchama, A.; Johani, S.; Hajeer, A.; Saeed, B.; Wahbi, A.; Saedy, A.; AlDabbagh, T. Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV). *Infection* 2015, 43, 495–501.
6. Saniasiaya, J.; Kulasegarah, J. Dizziness and COVID-19. *Ear Nose Throat J.* 2021, 100, 29–30.
7. Kong, Z.; Wang, J.; Li, T.; Zhang, Z.; Jian, J. 2019 novel coronavirus pneumonia with onset of dizziness: A case report. *Ann. Transl. Med.* 2020, 8, 506.
8. Katz, J.M.; Libman, R.B.; Wang, J.J.; Sanelli, P.; Filippi, C.G.; Gribko, M.; Pacia, S.V.; Kuzniecky, R.I.; Najjar, S.; Azhar, S. Cerebrovascular complications of COVID-19. *Stroke* 2020, 51, e227–e231.
9. Qureshi, A.I.; Baskett, W.I.; Huang, W.; Shyu, D.; Myers, D.; Raju, M.; Lobanova, I.; Suri, M.F.K.; Naqvi, S.H.; French, B.R. Acute ischemic stroke and COVID-19: An analysis of 27 676 patients. *Stroke* 2021, 52, 905–912.
10. Karvigh, S.A.; Vahabizad, F.; Banihashemi, G.; Sahraian, M.A.; Gheini, M.R.; Eslami, M.; Marhamati, H.; Mirhadi, M.S. Ischemic stroke in patients with COVID-19 disease: A report of 10 cases from Iran. *Cerebrovasc. Dis.* 2021, 50, 239–244.
11. Zakeri, A.; Jadhav, A.P.; Sullenger, B.A.; Nimjee, S.M. Ischemic stroke in COVID-19-positive patients: An overview of SARS-CoV-2 and thrombotic mechanisms for the neurointerventionalist. *J. NeuroInterventional Surg.* 2021, 13, 202–206.
12. Haider, A.; Siddiqa, A.; Ali, N.; Dhallu, M. COVID-19 and the brain: Acute encephalitis as a clinical manifestation. *Cureus* 2020, 12, e10784.

13. Umapathi, T.; Quek, W.M.J.; Yen, J.M.; Khin, H.S.W.; Mah, Y.Y.; Chan, C.Y.J.; Ling, L.M.; Yu, W.-Y. Encephalopathy in COVID-19 patients; viral, parainfectious, or both? *Eneurologicalsci* 2020, 21, 100275.
14. Elkind, M.S.; Cucchiara, B.L.; Koralnik, I.J.; Rabinstein, A.A.; Kasner, S.E. COVID-19: Neurologic Complications and Management of Neurologic Conditions. 2021. Available online: <https://www.medilib.ir/uptodate/show/128153> (accessed on 4 March 2022).
15. Kennedy, M.; Helfand, B.K.I.; Gou, R.Y.; Gartaganis, S.L.; Webb, M.; Moccia, J.M.; Bruursema, S.N.; Dokic, B.; McCulloch, B.; Ring, H.; et al. Delirium in Older Patients With COVID-19 Presenting to the Emergency Department. *JAMA Netw. Open* 2020, 3, e2029540.
16. Velásquez-Tirado, J.D.; Trzepacz, P.T.; Franco, J.G. Etiologies of Delirium in Consecutive COVID-19 Inpatients and the Relationship Between Severity of Delirium and COVID-19 in a Prospective Study With Follow-Up. *J. Neuropsychiatry Clin. Neurosci.* 2021, 33, 210–218.
17. Klopfenstein, T.; Kadiane-Oussou, N.J.; Toko, L.; Royer, P.Y.; Lepiller, Q.; Gendrin, V.; Zayet, S. Features of anosmia in COVID-19. *Médecine Mal. Infect.* 2020, 50, 436–439.
18. Vaira, L.A.; Deiana, G.; Fois, A.G.; Pirina, P.; Madeddu, G.; De Vito, A.; Babudieri, S.; Petrocelli, M.; Serra, A.; Bussu, F. Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. *Head Neck* 2020, 42, 1252–1258.
19. Zahra, S.A.; Iddawela, S.; Pillai, K.; Choudhury, R.Y.; Harky, A. Can symptoms of anosmia and dysgeusia be diagnostic for COVID-19? *Brain Behav.* 2020, 10, e01839.
20. Hosseini, A.; Mirmahdi, E.; Moghaddam, M.A. A new strategy for treatment of Anosmia and Ageusia in COVID-19 patients. *Integr. Respir. Med.* 2020, 1, 2.
21. Goodman, B.P.; Khoury, J.A.; Blair, J.E.; Grill, M.F. COVID-19 Dysautonomia. *Front. Neurol.* 2021, 12, 624968.
22. Eshak, N.; Abdelnabi, M.; Ball, S.; Elgwairi, E.; Creed, K.; Test, V.; Nugent, K. Dysautonomia: An Overlooked Neurological Manifestation in a Critically ill COVID-19 Patient. *Am. J. Med. Sci.* 2020, 360, 427–429.
23. Barizien, N.; Le Guen, M.; Russel, S.; Touche, P.; Huang, F.; Vallée, A. Clinical characterization of dysautonomia in long COVID-19 patients. *Sci. Rep.* 2021, 11, 14042.
24. Alyesh, D.; Mathew, J.; Jordan, R.; Choe, W.; Sundaram, S. COVID-19 Dysautonomia: An Important Component of “Long-Hauler Syndrome”. *EP Lab Dig.* 2021, 21, 36–37.
25. Fitsiori, A.; Pugin, D.; Thieffry, C.; Lalive, P.; Vargas, M.I. Unusual microbleeds in brain MRI of COVID-19 patients. *J. Neuroimaging* 2020, 30, 593–597.
26. Jegatheeswaran, V.; Chan, M.W.; Chakrabarti, S.; Fawcett, A.; Chen, Y.A. Neuroimaging Findings of Hospitalized COVID-19 Patients: A Canadian Retrospective Observational Study. *Can. Assoc.*

- Radiol. J. 2022, 73, 179–186.
27. Roy, D.; Song, J.; Awad, N.; Zamudio, P. Treatment of unexplained coma and hypokinetic-rigid syndrome in a patient with COVID-19. *BMJ Case Rep.* 2021, 14, e239781.
  28. Chan, J.L.; Murphy, K.A.; Sarna, J.R. Myoclonus and cerebellar ataxia associated with COVID-19: A case report and systematic review. *J. Neurol.* 2021, 268, 3517–3548.
  29. Hepburn, M.; Mullaguri, N.; George, P.; Hantus, S.; Punia, V.; Bhimraj, A.; Newey, C.R. Acute symptomatic seizures in critically ill patients with COVID-19: Is there an association? *Neurocritical Care* 2021, 34, 139–143.
  30. Alquisiras-Burgos, I.; Peralta-Arrieta, I.; Alonso-Palomares, L.A.; Zacapala-Gómez, A.E.; Salmerón-Bárcenas, E.G.; Aguilera, P. Neurological Complications Associated with the Blood-Brain Barrier Damage Induced by the Inflammatory Response During SARS-CoV-2 Infection. *Mol. Neurobiol.* 2021, 58, 520–535.
  31. Chen, Z.; Li, G. Immune response and blood–brain barrier dysfunction during viral neuroinvasion. *Innate Immun.* 2021, 27, 109–117.
  32. Marshall, M. COVID and the brain: Researchers zero in on how damage occurs. *Nature* 2021, 595, 484–485.
  33. Marshall, M. How COVID-19 can damage the brain. *Nature* 2020, 585, 342–343.
  34. Li, L.; Hill, J.; Spratt, J.C.; Jin, Z. Myocardial injury in severe COVID-19: Identification and management. *Resuscitation* 2021, 160, 16–17.
  35. El-Aziz, A.; Mohamed, T.; Al-Sabi, A.; Stockand, J.D. Human recombinant soluble ACE2 (hrsACE2) shows promise for treating severe COVID 19. *Signal Transduct. Target. Ther.* 2020, 5, 258.
  36. Mao, X.-Y.; Jin, W.-L. The COVID-19 Pandemic: Consideration for Brain Infection. *Neuroscience* 2020, 437, 130–131.
  37. Mahalakshmi, A.M.; Ray, B.; Tuladhar, S.; Bhat, A.; Paneyala, S.; Patteswari, D.; Sakharkar, M.K.; Hamdan, H.; Ojcius, D.M.; Bolla, S.R.; et al. Does COVID-19 contribute to development of neurological disease? *Immun. Inflamm. Dis.* 2021, 9, 48–58.
  38. Naik, G.O.A. COVID-19 and the Renin-Angiotensin-Aldosterone System. *Clin. Infect. Dis.* 2020, 72, 1105–1107.
  39. Lou, J.J.; Movassaghi, M.; Gordy, D.; Olson, M.G.; Zhang, T.; Khurana, M.S.; Chen, Z.; Perez-Rosendahl, M.; Thammachantha, S.; Singer, E.J.; et al. Neuropathology of COVID-19 (neuro-COVID): Clinicopathological update. *Free. Neuropathol.* 2021, 2, 2.



40. DeKosky, S.T.; Kochanek, P.M.; Valadka, A.B.; Clark, R.S.B.; Chou, S.H.; Au, A.K.; Horvat, C.; Jha, R.M.; Mannix, R.; Wisniewski, S.R.; et al. Blood Biomarkers for Detection of Brain Injury in COVID-19 Patients. *J. Neurotrauma* 2021, 38, 1–43.
41. Butowt, R.; Meunier, N.; Bryche, B.; von Bartheld, C.S. The olfactory nerve is not a likely route to brain infection in COVID-19: A critical review of data from humans and animal models. *Acta Neuropathol.* 2021, 141, 809–822.
42. Boldrini, M.; Canoll, P.D.; Klein, R.S. How COVID-19 Affects the Brain. *JAMA Psychiatry* 2021, 78, 682–683.
43. Desai, I.; Manchanda, R.; Kumar, N.; Tiwari, A.; Kumar, M. Neurological manifestations of coronavirus disease 2019: Exploring past to understand present. *Neurol. Sci.* 2021, 42, 773–785.
44. Mehta, O.P.; Bhandari, P.; Raut, A.; Kacimi, S.E.O.; Huy, N.T. Coronavirus Disease (COVID-19): Comprehensive Review of Clinical Presentation. *Front. Public Health* 2021, 8, 582932.
45. Pensato, U.; Muccioli, L.; Cani, I.; Janigro, D.; Zinzani, P.L.; Guarino, M.; Cortelli, P.; Bisulli, F. Brain dysfunction in COVID-19 and CAR-T therapy: Cytokine storm-associated encephalopathy. *Ann. Clin. Transl. Neurol.* 2021, 8, 968–979.
46. Hirawat, R.; Saifi, M.A.; Godugu, C. Targeting inflammatory cytokine storm to fight against COVID-19 associated severe complications. *Life Sci.* 2021, 267, 118923.

---

Retrieved from <https://www.encyclopedia.pub/entry/history/show/61987>