Severe acute respiratory syndrome coronavirus 2 and seizure: An insight into the pathophysiologic mechanisms

Shima Zareh-Shahamati¹, Mahyar Noorbakhsh², Hadi Digaleh³, Behnam Safarpour-Lima¹

¹ Department of Neurology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
² Autoimmune Disease Research Center, Kashan University of Medical Sciences, Kashan, Iran
³ Department of Neurosurgery, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

Keywords
SARS-CoV-2; COVID-19; Seizures; Neurology

Abstract
Based on previous studies, seizure has been reported to accompany coronavirus disease 2019 (COVID-19). Underlying mechanisms are those leading to the direct central nervous system (CNS) invasion through hematogenous spread or trans-synaptic retrograde invasion, causing meningoencephalitis. On the other hand, there are pathophysiologic mechanisms that seizure would be one of their early consequences, such as cytokine storm, hypoxemia, metabolic derangement, and structural brain lesions. Herein, we focused on available evidence to provide an insight into the pathophysiologic mechanisms that link seizure and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, as a better understanding of pathophysiology would lead to better diagnosis and treatment.

Introduction
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel species from the beta-coronavirus genus, has led to the most recent outbreak of severe acute respiratory syndrome (SARS). The symptomatology and underlying signaling pathway of two previous highly-pathogenic coronaviruses species, known as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), was studied in 2002 and 2012, respectively. However, SARS-CoV-2 seems to possess the most malignant epidemic impact among Coronaviridae with many reported neurologic manifestations.

Seizure has been reported in numerous coronavirus disease 2019 (COVID-19) cases. Based on a retrospective study in China, one patient with severe COVID-19 out of 214 patients had seizure,
while for other coronaviruses (such as MERS-CoV), this occurrence had greater prevalence up to 8.6 percent in a report in Saudi Arabia.\(^2\) Accepting the similarities between coronaviruses would improve alertness about the expected complications among involved physicians.

Although the hypotheses for SARS-CoV-2 neuroinvasion are mainly based on previous evidence on the coronavirus family and shared similar characteristics, unique SARS-CoV-2 signaling pathways have to be clarified in future studies. Herein, we review possible mechanisms associated with COVID-19 infection that result in seizure as a presenting symptom. For this purpose, we categorize these mechanisms into direct and indirect pathways.

**Direct pathway**

Seizure is a well-described complication of meningitis and/or encephalitis. Accordingly, Moriguchi et al. reported a case of SARS-CoV-2 meningoencephalitis predominantly presented with generalized seizures.\(^3\)

Based on cellular, animal, and clinical studies on previous coronavirus infections, possible central nervous system (CNS) involvement of SARS-CoV-2 has been postulated. Previous studies showed the presence of sporadic epileptiform discharges (EDs) and frontal sharp waves in critically-ill patients with COVID-19, which confirm the involvement of the brain in these patients.\(^4\) Viral meningoencephalitis and acute necrotizing encephalitis (ANE) have been reported as histopathologic evidence of brain invasion in SARS-CoV-2.\(^5\) To unveil these findings, we have to explore the direct entry of the virus into the brain with two classic pathways, trans-synaptic and hematologic.

Trans-synaptic spread of the virus throughout the CNS is one of the possible direct pathways of SARS-CoV-2 neuroinvasion. Prospective epidemiologic studies reported that up to 80% of patients with COVID-19 had significant olfactory dysfunction.\(^6\) Moreover, studies on rats and humans have been carried out to describe the way viruses can enter the brain through the olfactory nerve to cause meningoencephalitis. Apart from the olfactory nerve pathway, there are studies suggesting neuroinvasion and retrograde trans-synaptic propagation of the virus to the brain after its inoculation to the cornea, retina, lung, and gut, making the neuroinvasion more possible.\(^7\)

Hematogenous spread is another pathway proposed as a mechanism of SARS-CoV-2 invasion to the brain. A post-mortem study by Paniz-Mondolfi et al. has shown the presence of SARS-CoV-2 in the endothelial cells and frontal lobe of an infected patient with encephalopathy who died of COVID-19 complications.\(^8\) SARS-CoV-2 seems to be present in blood circulation. In fact, the capillary endothelium of CNS microcirculation expresses angiotensin-converting enzyme 2 (ACE-2), which is the receptor for SARS-COV2. Thus, the interaction between the virus and cells is guaranteed, which then results in subsequent damage of endothelium and virus entry to the brain. Another proposed mechanism is the passage of leukocytes into the brain tissue. In other words, the virus uses them as its reservoir to enter the brain tissue.\(^9\) Besides, transmembrane serine protease II (TMPRSS2), as a host cell factor for spike protein priming, is crucial for the spread of several clinically-similar viruses, including influenza A viruses and coronaviruses.\(^10\) Hoffmann et al. indicated that SARS-CoV-2 spread also depended on TMPRSS2 activity.\(^11\)

**Indirect mechanisms**

Systemic complications of SARS-CoV-2 infection affect almost every organ, resulting in multi-organ failure in critically-ill patients. Here, we discuss current evidence on various possible mechanisms of COVID-19 systemic complications, presenting with seizure.

**Cytokine storm**

The overwhelming evidence proposes that seizure is associated with inflammation and elevated levels of cytokines. In this regard, neuronal hyperexcitability has been widely studied concerning elevated circulatory and cerebrospinal fluid (CSF) certain cytokines. Interleukin 1 beta (IL-1\(\beta\)), IL-6, and tumor necrosis factor alpha (TNF-\(\alpha\)) activities have extensively been investigated in the context of their pro-convulsive effects.\(^12\) Regarding COVID-19, cytokine release syndrome (CRS) includes elevated levels of inflammatory cytokines, such as IL-6 and TNF-\(\alpha\).\(^13\) Interestingly, Karimi et al. reported frequent compulsive seizures in a case of COVID-19, which have been attributed to pro-inflammatory cytokine storm.\(^14\) On the other hand, the blood-brain barrier (BBB) breakdown is another hypothesis that has been discussed regarding circulatory cytokine elevation and seizure provocation.\(^15\) It is worth mentioning that the cytokine storm has also been
reported in connection with ANE, which is mentioned as a complication of COVID-19.16

**Hypoxia and other mechanisms**

Respiratory failure in patients with COVID-19 may be justified by various rationales. First of all, extended lung involvement is present after being infected with SARS-COV-2 which is evident in lung imaging. This may cause decreased oxygen levels in the case of diffuse alveolar involvement. Furthermore, as explained in SARS, myopathy, neuropathy, and involvement of respiratory centers have been assumed which may lessen the respiratory function.17 Acquired acute porphyria due to viral hemoglobin (Hb) 1-beta chain invasion is another hypothesis for SARS-CoV-2-induced hypoxemia, although doubtful methodology precludes its widespread acceptance.18 Moreover, suggested mechanisms of hypoxic damages include astrocyte swelling and gamma-aminobutyric acid (GABA)ergic deficit in the synapses, which could explain the occurrence of post-hypoxic myoclonic jerks and seizures.19

Lippi et al. in a pooled analysis of 1415 patients with COVID-19 reported that sodium, calcium, and potassium were significantly lower in patients with severe COVID-19 compared to those with the non-severe disease.20 In addition, consequent changes in sodium and calcium level have been shown to bring about neuronal irritability which can potentially provoke seizure in these patients.21

Finally, hypercoagulable state and thrombotic microangiopathy (TMA) in patients with COVID-19 might be responsible for the significant rate of cerebrovascular accident (CVA) in these patients.22,23 Following CVA, there is a risk of acute symptomatic seizure that should be considered in SARS-CoV-2 infection presented with seizure.

Mechanisms of seizure in COVID-19 are summarized in figure 1.

**Reported COVID-19-associated seizures**

Numerous cases of COVID-19-associated seizures have been reported in the literature. These seizures were documented in a broad range of age groups, from infancy to elderly patients. Generalized tonic-clonic seizures (GTCs), focal motor seizures, and status epilepticus (SE) have been observed in subjects with COVID-19. Besides, several pathologies have been found in these patients justifying the occurrence of seizure, including encephalopathy, meningitis, ANE, and venous sinus thrombosis (VST). The outcome of these patients varied from complete resolution to death in severe cases. Some cases of COVID-19-associated seizures are summarized in table 1.

---

**Figure 1.** A summary of possible mechanisms of seizure in patients with coronavirus disease 2019 (COVID-19)

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; BBB: Blood-brain barrier; CVA: Cerebrovascular accident; IL-6: Interleukin 6; GABA: Gamma-aminobutyric acid; ACE-II: Angiotensin-converting enzyme II; TNF-α: Tumor necrosis factor alpha; TMPRSS2: Transmembrane serine protease II
Table 1. A summary of some coronavirus disease 2019 (COVID-19)-associated seizures and patients' characteristics

| Author            | Country | Gender | Age          | Medical history | Other findings                                                                 | Seizure type                                                                 | Treatment                                | EEG findings                                      | Outcome                                                                 |
|-------------------|---------|--------|--------------|-----------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------|---------------------------------------------------|-----------------------------------------------------------------------|
| Sohal and Mansur24| America | Male   | 72 years     | HTN, CAD, DM2, ESRD | Weakness and lightheadedness (after a hypoglycemic episode), then intubated   | Multiple episodes of tonic colonic movements                                   | MDZ, LEV, VPA                            | Six left temporal seizures and epileptogenic left temporal sharp waves | Deceased                                                                                            |
| Efe et al.25      | Turkey  | Female | 35 years     | -               | Headache, nausea, dizziness, imaging findings were suggestive of high-grade glioma | Drug-refractory seizures                                                      | Combined antiepileptic medication, left anterior temporal lobectomy | -                                                | Diagnosed with encephalitis, improvement of symptoms after surgery 1 deceased, 4 discharged with no recurrence, 1 extubated with no recurrence, 1 remaining ed intubated* |
| Anand et al.26     | America | 7 cases (5 female cases) | 37-88 years  | 3 patients: prior history of well-controlled epilepsy; 2 patients with remote stroke; 1 with PD; 1 with ESRD | -                                                                             | 5 patients with GTCS; 1 with focal, unawareness, leftward gaze deviation, and tonic right arm movement followed by postictal confusion; 1 with rightward gaze deviation, rightward head version, rhythmic left arm, and leg twitching | 1 MDZ, VPA; 1 LOR, LEV; 2 LEV; 1 MDZ, LEV, ZNS; 1 LEV, LCM, PPF, MDZ | 1 with moderate to severe encephalopathy, with frequent short runs of GRDA; 1 with moderately slow background, frequent sharp waves, focal EDs, occasional independent sharp waves, and frequent bifrontal generalized sharp waves with triphasic morphology, 5 not obtained | 1 deceased, 4 discharged with no recurrence, 1 extubated with no recurrence, 1 remaining ed intubated* |
| Moriguchi et al.3  | Japan   | Male   | 24 years     | -               | Unconsciousness, fatigue, fever, vomiting, neck stiffness                      | Transient generalized seizures                                               | Ceftriaxone, vancomycin, acyclovir, and steroids, LEV                       | -                                                | Meningitis, encephalitis, remains under treatment ANE with brain stem involvement, deceased |
| Dixon et al.27     | UK      | Female | 59 years     | Transfusion-dependent aplastic anemia | Fever, cough, headache, DLOC                                                  | Episodes of vacant staring and speech arrest associated with flexion of both shoulders, GTCS | Steroid therapy                         | -                                                | ANE with brain stem involvement, deceased                      |
| Bhatta et al.28    | America | Male   | 11 years     | -               | -                                                                             | Sudden shakiness of the whole body, associated with stretching and tightening of all four limbs, uprolling of eyes, frothing from the mouth, and tongue bite, GTCS | LEV                                       | -                                                | Discharged, no recurrence                                   |

References:
- Sohal and Mansur (2024)
- Efe et al. (2025)
- Anand et al. (2026)
- Moriguchi et al. (2023)
- Dixon et al. (2027)
- Bhatta et al. (2028)
Table 1. A summary of some coronavirus disease 2019 (COVID-19)-associated seizures and patients' characteristics (continue)

| Author | Country    | Gender | Age          | Medical history | Other findings | Seizure type                        | Treatment               | EEG findings | Outcome                                                                 |
|--------|------------|--------|--------------|-----------------|----------------|-------------------------------------|-------------------------|--------------|-------------------------------------------------------------------------|
| Abdulsalam et al. | Kuwait   | Male   | 32 years     | -               | -              | GTCS                                | Diazepam, MDZ           | -            | Discharged with a stable condition                                      |
| Garcia-Howard et al. | Spain   | Female | 3 months     | -               | Fever, cough   | Focal motor seizures with impaired consciousness and awareness | LEV, hydroxychloroquine | Normal       | A pathogenic frameshift mutation in the PRRT2 gene in both the mother and the infant, discharged, favorable response within 3 months of the follow-up |
| Bolaji et al. | UK        | Male   | 63 years     | -               | Shortness of breath, dry cough, fever, left-sided weakness, inability to stand | Focal seizures, CSE | LMWH and LEV, LOR and PHT | -            | Extensive VST with bilateral venous cortical infarcts and acute cortical hemorrhage, discharged and transferred to the rehabilitation center |

EEG: Electroencephalography; HTN: Hypertension; CAD: Coronary artery disease; PD: Parkinson's disease; ED: Epileptiform discharge; ANE: Acute necrotizing encephalopathy; DM2: Diabetes mellitus type 2; ESRD: End-stage renal disease; GTCS: Generalized tonic-clonic seizure; LEV: Levetiracetam; PHT: Phenytoin; LOR: Lorazepam; MDZ: Midazolam; VPA: Valproic acid; ZNS: Zonisamide; PPF: Propofol; LCM: Lacosamide; GRDA: Generalized rhythmic delta activity; DLOC: Decreased level of consciousness; CSE: Convulsive status epilepticus; UK: United Kingdom; PRRT2: Proline-rich transmembrane protein 2; VST: Venous sinus thrombosis; LMWH: Low-molecular-weight heparin

*1 remaining ed intubated
COVID-19 and seizure

Conclusion
Current evidence on SARS-CoV-2 along with previous studies from coronavirus infections indicates multifactorial causes for seizure as a COVID-19 manifestation. Although some authors concluded that new-onset seizure was unlikely in patients with COVID-19, other important evidence on seizure frequency in these patients underscores the fact that being aware of clinical signs of seizure may lead to better diagnosis and treatment of underlying source.

Conflict of Interests
The authors declare no conflict of interest in this study.

Acknowledgments
None.

References
1. Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: A single-center experience in Saudi Arabia. Int J Infect Dis 2014; 29: 301-6.
2. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77(6): 683-90.
3. Moriguchi T, Harri N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-CoV-2. Int J Infect Dis 2020; 94: 55-8.
4. Lee JW. COVID-19 EEG studies: The other coronavirus spikes we need to worry about. Epilepsiy Cure 2020; 20(6): 353-5.
5. Stoyanov GS, Lyutfi E, Dzenkov DL, Pekkova L. Acute necrotizing encephalitis in viral respiratory tract infection: An autopsy case report. Cureus 2020; 12(5): e8070.
6. Vavougios GD. Potentially irreversible olfactory and gustatory impairments in COVID-19: Indolent vs. fulminant SARS-CoV-2 neuroinfection. Brain Behav Immun 2020; 87: 301-6.
7. Ahmed MU, Hanif M, Ali MJ, Haider MA, Kherani D, Memon GM, et al. Neurological Manifestations of COVID-19 (SARS-CoV-2): A Review. Front Neurol 2020; 11: 518.
8. Paniz-Mondolfi A, Bryce C, Grimes Z, Gordon RE, Reidy J, Lednicky J, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol 2020; 92(7): 699-702.
9. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020; 87: 18-22.
10. Bertram S, Heuristic A, Lavender H, Gierer S, Danisch S, Perin P, et al. Influenza and SARS-coronavirus activating proteases TMPRSS2 and HAT are expressed at multiple sites in human respiratory and gastrointestinal tracts. PLoS One 2012; 7(4): e35876.
11. Hoffmann M, Klein-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and Is blocked by a clinically proven protease inhibitor. Cell 2020; 181(2): 271-80.
12. Vezzani A, Moneta D, Richichi C, Aliprandi M, Burrows SJ, Ravizza T, et al. Functional role of inflammatory cytokines and antinflammatory molecules in seizures and epileptogenesis. Epilepsia 2002; 43(Suppl 5): 30-5.
13. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020; 368(6490): 473-4.
14. Karimi N, Sharifi Razavi A, Rouhani N. Frequent convulsive seizures in an adult patient with COVID-19: Aa case report. Iran Red Crescent Med J 2020; 22(3): e102828.
15. Marchi N, Angelov L, Masaryk T, Fazio E1, Y C, Bai WZ, Hashikawa T. The neurological manifestations of the COVID-19: A retrospective case series. Epilepsia 2020; 61(5): e102828.
16. Jan YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020; 92(6): 552-5.
17. Majeed A, Shajar MA. Is hemoglobin the fifth risk factor for COVID-19 disease. BMJ Case Rep 2020; 13(8): e236820.
18. Tan CW, Low JGH, Wong WH, Chua YY, Goh SL, Ng HJ. Critically ill COVID-19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability. Am J Hematol 2020; 95(7): E156-E158.
19. Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy BJ, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: An autopsy series from New Orleans. Lancet Respir Med 2020; 8(7): 681-6.
20. Kohal S, Mansur M. COVID-19 Presenting with Seizures. IDCases 2020; 20: e00782.
21. Efe IE, Aydin OU, Alabula C, Celik O, Aydin K. COVID-19-associated encephalitis mimicking glial tumor. World Neurosurg 2020; 140: 46-8.
22. Anand P, Al-Faraj A, Sader E, Dashkoff J, Abdennadher M, Murugesan R, et al. Seizure as the presenting symptom of COVID-19: A retrospective case series. Epilepsie Behav 2020; 112: 107335.
23. Dixon L, Varley J, Gontsarova A, Mallon D, Tona F, Murr D, et al. COVID-19-related acute necrotizing encephalopathy with brain stem involvement in a patient with aplastic anemia. Neurol Neuroimmunol Neuroinflamm 2020; 7(5): e789.
24. Bhattacharjee S, Sanyal A, Ranabhat B, Bhattacharjee RK, Acharya Y. New-onset seizure as the only presentation in a child with COVID-19. Cureus 2020; 12(6): e8820.
25. Abdulsalam MA, Abdulsalam AJ, Shehab D. Generalized status epilepticus as a possible manifestation of COVID-19. Acta Neurol Scand 2020; 142(4): 297-8.
26. Garcia-Howard M, Herranz-Aguirre M, Moreno-Galarraga L, Ureñatizcaya-Martinez M, Alegria-Echaury J, Gorría-Redondo N, et al. Case report: Benign infantile seizures temporally associated with COVID-19. Front Pediatr 2020; 8: 507.
27. Bolaji P, Kukoyi B, Ahmad N, Wharton C. Extensive cerebral venous sinus thrombosis: A potential complication in a patient with COVID-19 disease. BMJ Case Rep 2020; 13(8): e236820.