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

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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,

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while for other coronaviruses (such as MERS-CoV), this occurrence had greater prevalence up to 8.6 percent in a report in Saudi Arabia.[1,2] 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-1β), IL-6, and tumor necrosis factor alpha (TNF-α) 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-α.[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 (GTCSs), 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.

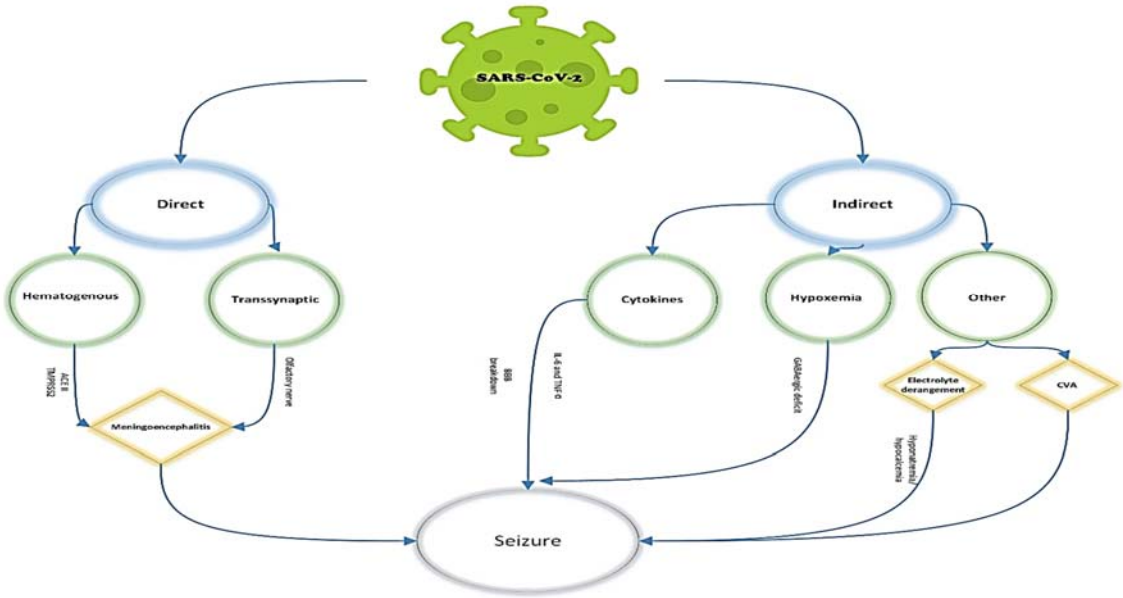

Figure 1. A summary of possible mechanisms of seizure in patients with coronavirus disease 2019 (COVID-19)
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; BBB: Blood-brain barrier; CVA: Cerebrovascular accident; IL-6: Interleukin 6; GABA: Gamma-aminobutyric acid; ACE-II: Angiotensin-converting 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 Mansur[24]	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
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
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

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.[29]	Kuwait	Male	32 years	-	-	GTCS	Diazepam, MDZ	-	Discharged with a stable condition
Garcia-Howard et al.[30]	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.[31]	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

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.

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