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# Epileptic seizures in patients with COVID-19: A systematic review of early evidences

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## ABSTRACT

### Background
Global emergence of SARS-CoV-2 surfaced neurological complications amongst the patients. COVID-19 resembles with other coronavirus strains follows a trend of neurological complication, damage and encephalopathy, which entails considerable risks, requires attention for the neurologists. This is, to our knowledge, the first systematic review of the literature to investigate solely to elucidate the seizure spectrum by unfolding epileptogenicity of the SARS CoV-2 and potential pathways of neuroinvasion.

### Methods
A systematic literature search was performed in PubMed and Embase database following standard guidelines, using specific keywords based on epileptic seizure onset described from December 01, 2019, to July 17, 2020

### Results
A total of 17 studies were included ranging from case reports, series of cases, multicentre cross-sectional study with the first-time onset of seizure associated with an epileptic origin. We excavated causes of complex COVID-19 related neurological manifestations, e.g., cerebrovascular diseases, encephalitis, demyelinating lesions, cytokine storm and proposed routes of SARS-CoV-2 entry into the nervous system to understand the mechanism of an epileptic seizure.

### Conclusion
COVID-19 is a potent neuropathogen which causes the new onset of epileptic seizures should get diagnostic recognition to evade possible deterioration of neurological conditions. However, more shreds of evidence from the future will further elucidate the epileptogenic potential of the pandemic.

### Keywords
Brain diseases, Coronavirus infections, Epilepsia Partialis Continua, Epilepsy, neurologic manifestations, SARS-CoV-2, Seizures

## Background

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is recently emerged human pandemic stormed the whole world. The virus was identified as a beta coronavirus is dissimilar with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), hence got a distinct identity. The clinical presentation of SARS-CoV-2 is acute respiratory distress syndrome (ARDS) and viral pneumonia [1,2]. The disease was first surfaced in Wuhan, Hubei Province, since December 12, 2019, in China, conceivably linked to the Huanan Seafood Wholesale Market located in Jianghan District [3]. The virus was named as Coronavirus disease 2019 "COVID-19" by the World Health Organization (WHO), affected 216 countries with 2,102,6758 confirmed cases and 75,5786 deaths as of August 16, 2020 [4]. The spread of this virus and ongoing devastation around the world shows no evidence of ending of this global pandemic and it impacted deadly on economic, financial, social, and mental wellbeing on the humanity.

Shortness of breath, fever, and cough reported since the beginning of the pandemic [1, 2], but clinical manifestations of SARS-CoV-2 are not limited to the respiratory system; it infects the nervous system too. Mao et al. published the first hospital-based report on the SARS-CoV-2 infected patients revealed that 36.4% of the patients had neurological complications: CNS (53 [24.8%]), PNS (19 [8.9%]). Dizziness, headache, taste and smell impairment was the most common symptoms reported [5]. Growing shreds of evidence of nausea, vomiting, myalgia, asthenia, dizziness, and reduced consciousness imply the viral neuroinvasive potential which increases with the severity of infection [5, 6]. SARS-CoV-1 outbreak in 2002-2003 documented numerous neurological manifestations ranging from moderate complications like seizures, status epilepticus, myopathy, to severe consequences stroke and polyneuropathy [7, 8].

This systematic review aims to outline a spectrum of the seizures and epileptic symptoms of SARS-CoV-2 infected patients and enlighten the viral invasion to CNS and mechanism of epileptogenicity.

## Material and methods

A systematic literature search was conducted from December 01, 2019, to July 17, 2020, in PubMed and Embase database. We followed the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocol [9]. The search strategy was developed by an expert panel of neurologists and neurophysiologists. Search terms included “COVID-19” OR “SARS-CoV-2” OR “2019-nCoV” OR “novel coronavirus” in conjunction with “epilepsy” OR “Seizure.” (Figure 1).

Articles written in the English language were included for this review. The authors carefully examined the list of references in the included studies to confirm the literature saturation. All authors scanned the titles and full-text reports independently against the standard search criteria for the systematic review to identify the eligibility and inclusion. Disagreement pertaining for the inclusion of articles were resolved through the discussions. The authors extracted the following data from all included studies: Author/year, age, gender, design, the interval of COVID-19 symptom onset and first seizure, clinical presentation, neurological manifestations, diagnostic findings, interventions, and limitations. The level of evidence and quality of the research was also carefully observed. Reference management was done by EndNote X5 software (Clarivate Analytics, Boston, MA, USA). This systematic review protocol was not registered earlier. We mostly followed the WHO recommended gold standard guidelines (epidemiological history, clinical symptoms, and laboratory or radiological findings) to consider the articles in our study. All cases included in this review were confirmed cases of SARS-CoV-2, which was diagnosed by SARS-CoV-2 PCR testing using a nasopharynx swab. We reviewed the clinical researches, including original articles, case series, and case reports, for neurological involvement by COVID-19 on the incidence of epilepsy and organized them into tables.

## Results

Through our search strategy, we have identified a total of 160 abstracts. After exclusion and eligibility of full text, 17 articles were selected for systematic review, involved seizures, or epilepsy as a new-onset due to SARS-CoV-2 infection. Among these articles, 12 were case reports; four were case series, and one study was a multicentre cross-sectional study. Table-1 and Table-2 shows the summary of the included studies [5, 10-25].

All studies were critically analyzed based on the standard diagnosis for epilepsy (e.g., EEG, head CT /MRI, CSF analysis). We also included CSF-PCR to obtain information for neuroinvasion of SARS-CoV-2 and the intervention strategy towards the administration of Anti-epileptic drugs. Besides, we rigorously reviewed a few relevant literature (26-30) to understand the mechanism of entry of SARS-CoV-2 in CNS summarized in Figure 2.

Figure 2: Explains the possible routes of SARS-CoV-2 entry in the nervous system.

2a. shows the hematologic route where viral particles cross the endothelial cells of the blood-brain barrier (BBB) either directly or enter by using the infected cells of the reticuloendothelial system (RE) or lymphocyte as a vehicle through the paracellular route.

2b. shows the neurologic route where virus enters in the olfactory epithelium, olfactory bulb and later enters in the olfactory tract. Retrograde axonal transport and CoVs clathrin-dependent endocytotic/exocytotic pathway may help in this process.

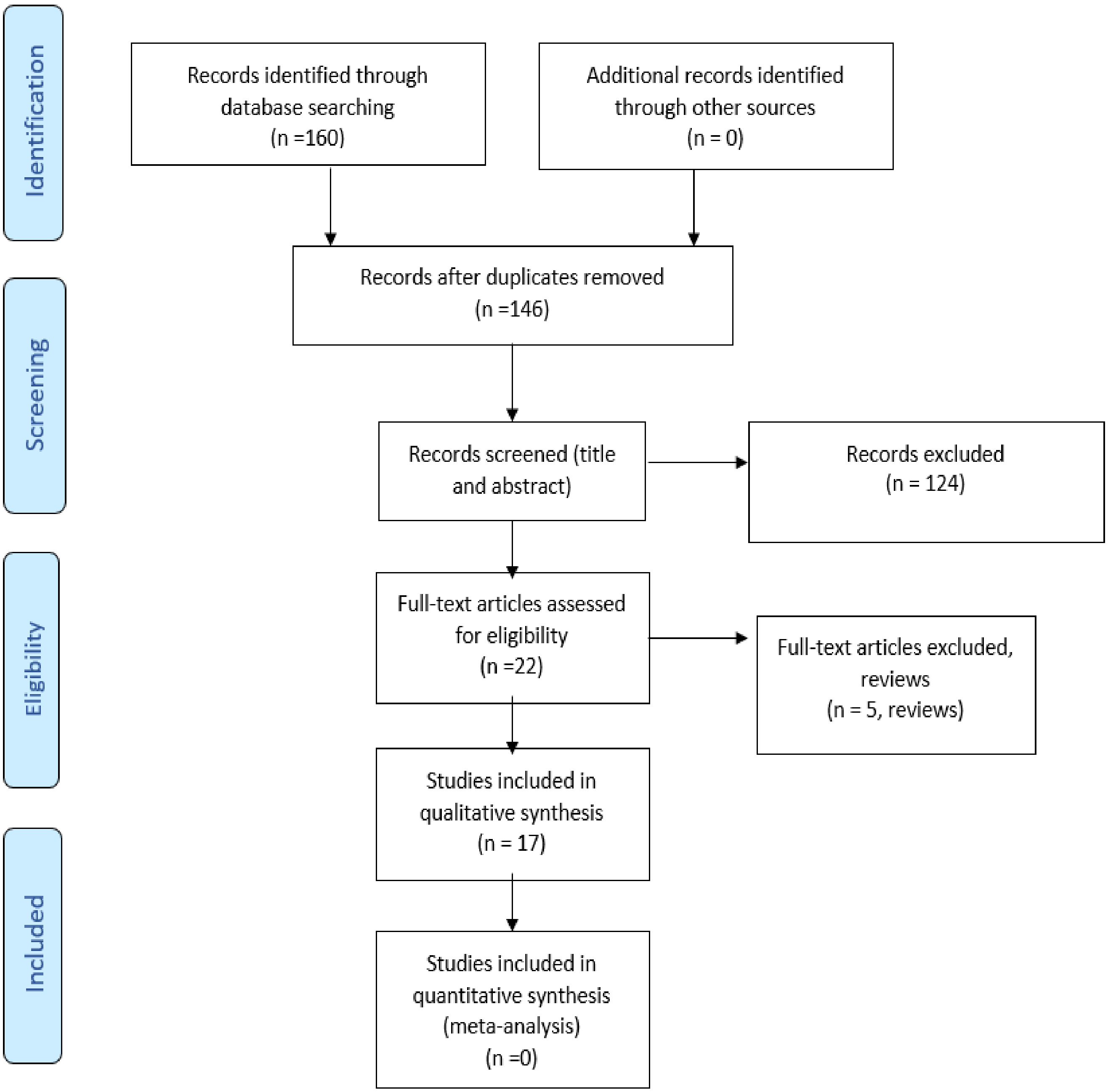


**Figure 1: Inclusion of articles by Preferred Reported Items for Systematic reviews**

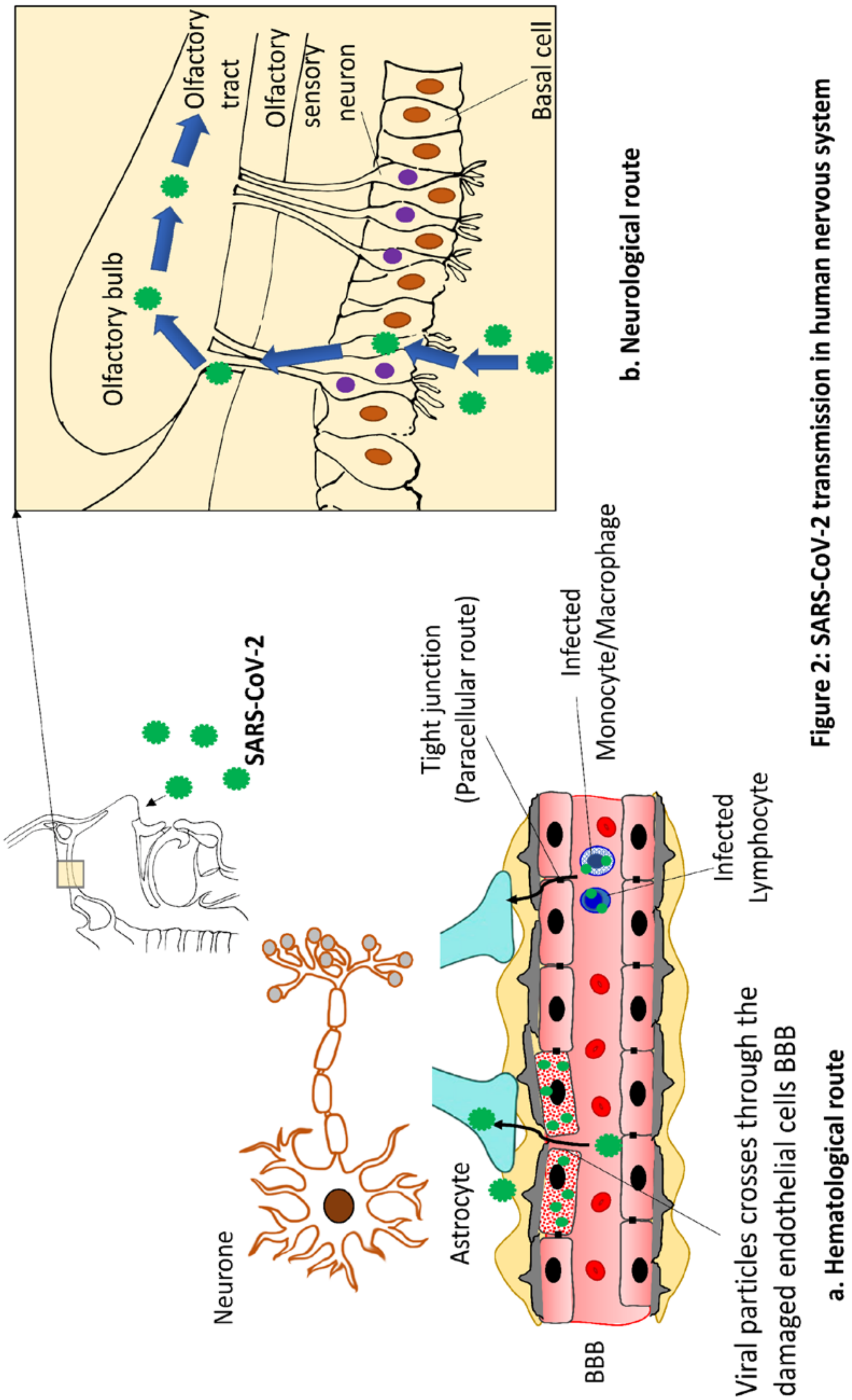


**Figure 2: SARS-CoV-2 transmission in human nervous system**

**Table 1: Summary of the studies, infection interval and clinical presentation**

| Author, year | Age(years)/mean/ mean [SD], Gender | Design | No (% in total participants) | Interval of COVID symptom onset and first seizure activity (days) | Clinical presentation towards epileptic manifestations /Seizure description/ characteristics |
|---|---|---|---|---|---|
| Lyons et al. 2020 | 20, M | Case report | 1 | +3 | Light-headedness with blurred and double vision, lower limb weakness, generalised tonic-clonic seizure |
| Moriguchi et al. 2020 | 24, M | Case report | 1 | +9 | consciousness disturbance, transient generalized seizures for about a minute |
| Atere et al. 2020 | 46, M | Case report | 1 | +3 | Episode of seizures, syncope; conscious after 30 seconds; an involuntary loss of feces |
| Somani et al. 2020 | 49, F | Case report | 1 | -3 | Case 1: altered mental status, seizure |
| | 73, F | Case report | 1 | +1 | Case 2: Persistent face and arm myoclonus with worsening altered mental status (status epilepticus) |
| Fasano et al. 2020 | 54, M | Case report | 1 | +7 | Single seizure characterized by clonic movements in the right arm and loss of consciousness. |
| Zanin et al. 2020 | 54, F | Case report | 1 | Not clear | Unconscious, later unrest |
| Stefano et al. 2020 | 56, F | Case report | 1 | +18 | Agitation |
| Dixon et al. 2020 | 59, M | Case report | 1 | +10 | Vacant staring, speech arrest, flexion of both shoulders and a brief witnessed generalized tonic-clonic seizure (GTCS), followed by postictal state |
| Sohal et al. 2020 | 72, M | Case report | 1 | +2 | Multiple episodes of persistent tonic colonic movements of upper and lower extremities |
| Elgamasy et al. 2020 | 73, F | Case report | 1 | +2 | Painful muscle stiffening and twitching in the left arm and leg |
| Hepburn et al. 2020 | 76, M | Case report | 1 | +2 | Multiple episodes of left upper extremity clonic activity and worsening encephalopathy |
| | 82, M | Case report | 1 | +15 | Right eyelid and facial twitching |
| Farhadian et al. 2020 | 78, F | Case report | 1 | +2 | Sudden-onset uncontrolled limb movements with ocular deviation followed by several minutes of unresponsiveness. |
| Galanopoulou et al. 2020 | Age: 63.23 ± 11.9 (30-83) | Case series (retrospective) | 11(64.7%) | NA | Motor seizure like events |
| Morassi et al. 2020 | 76, F | Case series | 1 | +10 | Transient loss of consciousness, followed by confusion |
| Garazzino et al. 2020 | 5, not mentioned | Multicentre cross-sectional (prospective) | 2(1.2) | 1.6 | Febrile seizure |
| Mao et al. 2020 | 58.2±15.0 | Case series (retrospective observational) | 1(0.5) | NA | Sudden onset of limb twitching, foaming in the mouth, and loss of consciousness, lasted for 3 minutes. |
| Pinna et al. 2020 | 59.6 | Case series (retrospective observational) | 13(26) | NA | Not available |

**Table 2: Diagnostic findings, interventions, and limitations**

| Author, year | EEG findings | Head CT /MRI findings | CSF analysis/ CSF PCR for SARS-CoV2 | Intervention (Anti epileptic drugs) | Main findings | Potential limitations | Outcome |
|---|---|---|---|---|---|---|---|
| Lyons et al., 2020 | Normal | CT: Normal; MRI: Mild mucosal thickening in the sphenoid sinus | Lymphocytic pleocystosis (21 cells/mm3, 99 % mononuclear, 1% polymorphs); PCR Negative | Levetiracetam | Meningoencephalitis | No known limitations | Survived |
| Moriguchi et al., 2020 | Not performed | CT: Normal; MRI: Hyperintensity along the wall of inferior horn of right lateral ventricle. Fluid-attenuated inversion recovery (FLAIR) images showed hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy. | Normal; PCR positive | Levetiraceta | Right lateral ventriculitis and encephalitis mainly on right mesial lobe and hippocampus | EEG not performed, no follow up information | Alive during reporting of the case |
| Atere et al., 2020 | Not performed | Normal | Not performed | Not administered | SARS-CoV-2 associated neurological symptoms | No EEG, SARS-CoV-2 PCR in CSF; CSF PCR for other viruses was done to rule out as DD | Survived |
| Somani et al., 2020 | Frequent (4-6/hour) cyclical seizures emanating from left fronto-central regions | Normal | Not performed | Lorazepam, Levetiracetam | De novo status epilepticus | No CSF investigations(analysis, PCR), CSF PCR was performed to rule out other viral infections as DD | Survived |
| | Frequent (5/hour) cyclical seizures emanating from left and right fronto-central regions | CT: Normal, MRI: Not performed | Not performed | Lorazepam, levetiracetam, lacosamide, phenytoin, midazolam | New-onset refractory status epilepticus (NORSE) | No CSF investigations(analysis, PCR), CSF PCR was performed to rule out other viral infections as DD | Passed away |
| Fasano et al., 2020 | Normal | CT: Normal; MRI: Not performed | Not performed | Not administered | First focal motor seizure | No CSF investigations(analysis, PCR); CSF PCR for other viruses was not performed to rule out as DD, Anti epileptic drug was not administered | Survived |
| Zanin et al., 2020 | Two seizures in frontotemporal region and diffusing in homologous contralateral hemisphere | CT: Normal, MRI: Alterations of the periventricular white matter. Lesions present in bulbo-medullary junction (cervical and dorsal spinal cord) | Normal; PCR negative | Lacosamide, levetiracetam, phenytoin | CNS involvement and demyelinating lesions associated with SARS-CoV-2 | No known limitations | Survived |
| Stefano et al., 2020 | Intermittent onset of 4 Hz rhythms over the bilateral parasagittal regions, lasting from 5 s to maximum 25 s. | CT: Not performed; MRI: numerous punctiform signal voids in bilateral juxtacortical white matter, corpus callosum, and internal capsule, compatible with cerebral microbleeds, without any ischemic or necrotizing lesion. | Increased protein level (1.31 g/l) and Immunoglobulins; PCR negative | Sedatives (not mentioned) | Focal injury in the absence of encephalopathy, critical illness–associated cerebral microbleeds (related to cytokine release syndrome) | CT not performed; standard CSF virology PCR was not done for other viruses to rule out as DD | Survived |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dixon et al., 2020 | Not performed | CT: Brain stem swelling, subtle intrinsic pontine hemorrhage, symmetrical hypodensities in the deep gray matter and amygdalae; MRI: Extensive, relatively symmetrical changes throughout the supratentorial and infratentorial compartments. | Increased protein concentration (2.3 g/L); PCR negative | Levetiracetam | Rapidly evolving encephalopathy involving brain stem; hemorrhagic ANE | Patient passed away, no follow up | Passed away |
| Sohal et al., 2020 | Six left temporal seizures and left temporal sharp waves which were epileptogenic. | CT: Chronic microvascular ischemic changes; MRI: Not performed | Not performed | Levetiracetam, valproate | Cytokine storm, encephalitis | No SARS-CoV-2 PCR in CSF; standard CSF virology PCR was not done for other viruses to rule out as DD patient passed away, no follow up | Passed away |
| Elgamasy et al., 2020 | Normal | CT: Mild dilatation of the lateral ventricles with prominent fissures and sulci. Scattered deep white matter hypodensities, MRI: dilated ventricular system with a patent and prominent aqueduct of Sylvius | Normal, slightly elevated leukocytes (0.5 per cubic millimeter); not performed | magnesium, levetiracetam lacosamide, clobazam | Focal epilepsy, chronic small vessel ischemia | No SARS-CoV-2 PCR in CSF; standard CSF virology PCR was not done for other viruses to rule out as DD | Survived |
| Hepburn et al., 2020 | Three focal seizures lasting approximately 30 s each arising from the right centroparietal region | Normal | Not performed | Levetiracetam | Focal seizure, co-morbidity | No SARS-CoV-2 PCR in CSF; CSF PCR for other viruses was not done to rule out as DD | Passed away |
| | EEG seizures mainly in left frontal–temporal regions eventually progressed to focal status epilepticus | CT: Hypodensities within the supratentorial white matter, consistent with mild microvascular disease but without acute intracranial lesion; MRI: Not performed | Not performed | Levetiracetam | Status epilepticus, brain damage | No SARS-CoV-2 PCR in CSF; CSF PCR for other viruses was not done to rule out as DD | Passed away |
| Farhadian et al.,2020 | Mild generalized slowing in ECG | No CT, MRI: atrophy and patchy periventricular and subcortical white matter hyperintensities | CSF inflammation; inflammatory cytokines present, 350 red cells/uL, protein 43 mg/dL; PCR negative | Not available | Sequelae of small vessel ischemic disease; encephalopathy | No treatment data was available towards seizure management | Survived |
| Galanopoulou et al., 2020 | Sporadic epileptiform discharges present 7(41.18%) | Not performed | Not performed | Sedatives, antiseizure medications (ASMs) | Myoclonic seizures, abnormal tremulous movements concerning for seizure, motor seizures, abnormal movements or shaking movements, concerning for seizures. | Scanty neurological/diagnostic work-up | Not applicable |
| Morassi et al., 2020 | Recurrent sharp slow waves over the left temporal region, with occasional observation on the right homologous regions | CT: hypodense area (5 mm) in the head of the right caudate nucleus referable to a lacunar infarction. MRI: a small rounded area of diffusion restriction on the left pre-rolandic gyrus | Normal; PCR not performed | Levetiracetam | encephalopathy, characterized by focal seizures | No SARS-CoV-2 PCR in CSF; CSF PCR for other viruses was not done to rule out as DD | Survived |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Garazzino et al., 2020 | Not performed | Not performed | Not performed | Not mentioned | Non-encephalopathic seizure | Scanty neurological/diagnostic work-up | Not applicable |
| Mao et al., 2020(a) | Not performed | Not performed | Not performed | Not clear | SARS-CoV-2 induced seizure | Scanty neurological/diagnostic work-up | Not applicable |
| Pinna et al., 2020 | Not available | Not available | Not available | Not applicable | Seizure was more prominent in patients with COVID-19 symptoms as first onset, other than neurological symptoms | Retrospective approach and patient selection bias, a full neurological evaluation was not done, no long-term follow-up and outcome data were unavailable | Not applicable |

NA-not applicable
SE-status epilepticus
ANE-acute necrotizing encephalopathy
NORSE-new-onset refractory status epilepticus
ASMs-antiseizure medications
DD-differential diagnosis

## Discussion

We are now passing through a tough time due to the SARS-CoV-2 pandemic affected almost all the countries [4]. Previous outbreaks of Coronaviruses showed potential for CNS invasion, neuronal infection, and cytokines' entry along with immune cells in brain tissue. Human coronavirus OC43, a single-stranded RNA virus, can affect neurons and cause pervasive destruction [31, 32]. In a study of 70 patients infected with MERS-CoV, showed epileptic seizures and altered mental state(33). SARS-CoV-2 possess high homology with other coronavirus strains, so in this current pandemic neurologists and medical practitioners face challenges to confront the central and peripheral nervous systems manifestations. An updated systematic review may enlighten the spectrum of epileptic seizure for the diagnosis of SARS-CoV-2 infection, helping clinicians understand the underlying mechanism to start intervention earlier.

**Prevalence and management of seizures associated clinical manifestations**

In this study, we observed that evidence of seizures and epilepsy is closely associated. However, articles are scarce. Moriguchi et al. documented the first reported case of seizures in COVID-19 patients [11]. Earlier instances of coronavirus infections showed the potential for seizure. A study by Saad M showed that six patients 8.6% have a seizure onset in the Middle East respiratory syndrome (MERS)-CoV infection [33]. On average, the interval of the infection and onset of symptoms is 3-5 days, but it may go up to 10 days (Table-1).

Seizure was less commonly observed in the study by Ling Mao, 2020, where 1(0.5%) case was reported. The authors acknowledged that clinical outcomes were unavailable during the time of analysis because of the patients' hospitalization [5]. Whereas others documented more number of cases [22, 25]. We observed that most common clinical presentations towards seizure amongst COVID-19 victims were status epilepticus, tonic colonic movements, and loss of consciousness. According to a series of COVID-19 patients from the USA, seizure events occurred in 11 (64.7%) of the patients. Authors reported gaze deviation, motor seizure-like events such as myoclonic seizures, abnormal tremulous movements concerning seizure, motor seizures, abnormal movements, and associated these events with new onset of encephalopathy. These symptoms may arise due to COVID-19 infection as a consequence of damage to the nervous system, alteration in metabolic activities, hypoxia, and organ failure. The presence of frontal sharp waves as epileptic discharge indicated frontal epileptogenic anomaly, which authors connected with the nasopharyngeal mucosal entry of SARS-CoV-2 or via the olfactory nerve [22] . Mao et al reported 14.8% patients with severe COVID-19 disease, displayed encephalopathy [5].

Lorazepam, Levetiracetam are the commonest seizure management drugs used [10, 11, 13, 15, 17-19, 23]. Other drugs namely lacosamide, phenytoin, midazolam [13, 15], valproate [18], magnesium, lacosamide, clobazam [19] also used.

**Probable mechanism of seizure in SARS-CoV-2 patients**

Infection in CNS is the origin of unprovoked seizure and epilepsy. Viral encephalitis is associated with the development of seizures may go up to 22% [34]. Encephalitis is observed in SARS-CoV-2 infection is associated with seizures in its acute phase [10, 11, 16, 18, 21, 23]. The toxins generated by SARS-CoV-2 and inflammatory cytokines by the brain [35] ignite a vicious cycle of inflammation resulting in a hyperexcitable state for neurons. This leads to the activation of the glutaminergic receptor via neurotransmitter glutamate, which heavily implicates anomalous signalling leading to acute epileptic seizures [35, 36]. Stephano et al reported focal injury in absence of encephalopathy and cerebral microbleeds – a result of cytokine release [16], whereas others reported cytokine storm [21] with encephalopathy [18]. Past researchers connected status epilepticus (SE) induced glutamate release and excessive stimulation of glutaminergic receptors and N-methyl-D-aspartate receptors (NMDARS) [37, 38], linked with seizure and neurological morbidity in SARS-CoV-2 outbreak [12, 13, 20].

Electrolyte imbalance was the less likely cause of new onset of seizures, observed in two of the reports, but a clear indication towards encephalitis and normocapnic hypoxia as a cause [12, 15]. Dixon et al reported acute necrotizing encephalopathy with rapid progression of seizures and reduced consciousness [17].

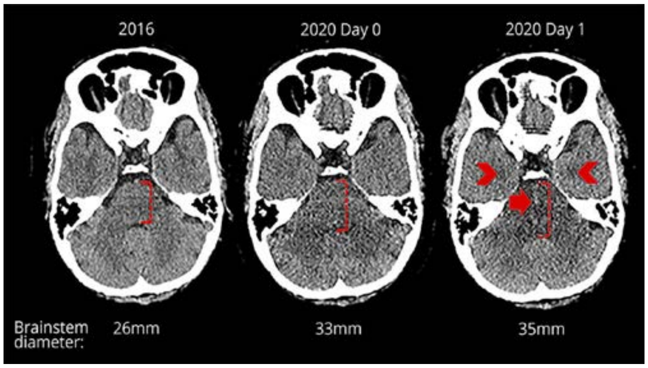


**Figure 3: Head CT findings from a SARS-CoV-2 infected patient with acute necrotizing encephalopathy** [17].

Axial CT head images on different dates (left to right) 2016, 2020 day 0, day 1 follow up. Early admission CT demonstrates subtle new swelling of the brain stem which progressed on follow-up. Fig 3c shows swelling with new central hemorrhagic foci (closed arrow) and symmetrical hypodensities in both amygdalae (chevrons) [17].

There may be a possible role of cytotoxic granules of CD8+ T cells that overexcites N-methyl-D-aspartate receptor (NMDA) in the process of immune reactions, substantially contributing to neuronal degenerations [39]. Most of the viral infections increase T cell populations in brains [40, 41]. Lyons reported Lymphocytic pleocystosis (21 cells/mm3, 99 % mononuclear, 1% polymorphs) is indicative of this [10]. Interleukin-12 (IL-12), secreted by macrophages and microglia [42, 43] involved in potential CNS damage in Kainic acid (KA) induced seizures [44].

**SARS-Cov-2 and neuroinvasion**

The underlying mechanisms of viral transmissions to CNS involves BBB and modulates functional ramifications. There are two possible routes – hematological and neurological are available for the SARS-CoV-2 entry to the CNS. In the hematologic route, the virus crosses the specialized brain microvascular endothelial cells (BMECs) of the BBB either directly or by using the infected cells of the reticuloendothelial system as a vehicle through the paracellular route(26). Circulating lymphocytes may be another possibility for the hematological invasion [11]. COVID virus is capable of direct BBB penetration and meningeal inflammation reported by Tohidpour et al., 2017 [27].

Structurally endfeet of the astrocytes covers intracranial blood vessels [45]. Astrocyte mediated endocytic route of Tick-borne encephalitis virus (TBEV) and Zika virus (ZIKV) is well documented [28,29]. TBEV enters via clathrin-dependent endocytosis, which resembles with entry pattern for other family members like West Nile virus, Dengue virus, Hepatitis C virus, and Bovine Viral Diarrhoea virus [29] and another coronavirus, porcine haemagglutinating encephalomyelitis (HEV67) [30].

In the neurologic route, retrograde axonal transport through the specific peripheral nerves is the key route of SARS-CoV-2 transmission to the CNS. Olfactory epithelium and nerve fibers play a vital role in this viral transmission [46]. The trans-synaptic viral transfer is reported for other CoVs clathrin-dependent endocytotic/exocytotic pathway. Although SARS-CoV-2 enters through BBB in Nervous system, interestingly except one case study [11] all tested SARS-CoV-2 PCR in CSF was negative in our review [5, 10, 12-25].

Diminished viral RNA in the brain in autopsy studies (7 out of 22) of SARS-CoV-2 related fatality is suggestive of it [47]. There is a possibility that early stages of infections may not allow viral entry in CNS but causes neuroinflammation. So COVID-19 treatment should be oriented towards host-inflammation. Farhadian et al. reported increased Monocyte Chemoattractant Protein-1(MCP-1), a key chemokine in CSF – a clear indication of deployment of inflammatory infiltrate into the nervous tissue [21].

## Conclusion

COVID-19 infects nervous system which causes the new onset of epileptic seizures is an important aspect of diagnosis. Cerebrovascular diseases, encephalitis, demyelinating lesions, cytokine storm are possible underlying pathology for epileptogenicity. Seizure amongst hospitalized patients varied from mild to life-threatening complications, such as hemorrhagic acute necrotizing encephalopathy (ANE). The neuroinflammatory potential unveils the viral entry through hematologic and neurogenic route and underpin existing knowledge. More evidence from cohort studies with complete diagnostic findings and differential diagnosis will strengthen the association of COVID-19 virus with an epileptic seizure.

We believe our work's novelty lies in the breadth of coverage, guiding neurologists by cumulative evidence of seizure associated with neurological damage from a practical point of view. However, we humbly acknowledge the shortfalls. First, we used mostly single case reports and relatively small case series which restrict to generalize our findings. Secondly, due to the patient's critical condition or morbidity, it was not possible to follow-up even to perform CT/MRI scan and CSF analysis in some studies we listed. Although number of studies are relatively less and predominance of suboptimal level of evidence, still sporadic epileptic seizure episodes indicates encephalopathy, brain damage in SARS-CoV-2 infection.

## Abbreviations

acute necrotizing encephalopathy (ANE), acute respiratory distress syndrome (ARDS), blood-brain barrier (BBB), brain microvascular endothelial cells (BMECs), CD8 (cluster of differentiation 8), Central nervous system (CNS) Cerebrospinal fluid (CSF), Computed Tomography (CT) Coronavirus disease 2019 (COVID-19), electroencephalogram (EEG), Interleukin (IL), Kainic acid (KA), Magnetic Resonance Imaging (MRI), Middle East respiratory syndrome coronavirus (MERS-CoV), monocyte Chemoattractant Protein-1(MCP-1), N-methyl-D-aspartate receptor (NMDA), novel coronavirus (2019-nCoV), polymerise chain reaction (PCR), porcine haemagglutinating encephalomyelitis (HEV67), Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA), reticuloendothelial system (RE), Ribonucleic Acid (RNA), Severe acute respiratory syndrome coronavirus-2(SARS-CoV-2), status epilepticus (SE), Tick-borne encephalitis virus (TBEV), Zika virus (ZIKV)

## Authors' contribution

a. Study planning: BR
b. Literature search: BR, IB
c. Manuscript writing: BR, IB
d. Manuscript revision: BR, IB
e. Final approval: BR, IB
f. Agreement to be accountable for all aspects of the work: BR, IB

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## Availability of data and materials

All data underlying the results are available as part of the article.

## Competing interests

None declared.

## Publisher's Note



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