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Seizure and COVID-19: Association and review of potential mechanism

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ABSTRACT

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, this highly transmissible virus has since spread rapidly around the world. Though respiratory complication is the primarily reported manifestation though rare, yet serious neurological complications are being frequently reported in the literature. In selected coronavirus disease-2019 (COVID-19) cases neurologic complications may manifest as seizures. In this paper, we have reviewed current literature on seizures linked with SARS- COV 2 infection including published or pre-print original articles, review articles, and case reports. We have discussed the electroencephalogram (EEG), imaging, and Cerebrospinal fluid (CSF) findings in patients with COVID-19 presenting with seizure. We will be concluding the paper by briefly discussing the three mechanisms by which seizures can develop in patients infected with SARS- COV 2 - (a) Direct Mechanism (b) Indirect Mechanism and (c) Exacerbation of Seizure in Patients with Epilepsy (PWE). Our aim is to update the physicians working with COVID-19 patients about this potential complication and hope that understanding of these proposed mechanisms can provide an opportunity for the physicians for early diagnosis or even better, help prevent this complication.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is a novel coronavirus that causes Coronavirus Disease of 2019 (COVID-19), a disease that can present with a variety of symptoms (Naming the coronavirus disease (COVID-19) and the virus that causes it, 2020). COVID-19 was first reported in the Wuhan, Hubei province in China in December 2019 (Zhu et al., 2020) and has since been declared a global pandemic by the World Health Organization (WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020, 2020). The most common symptoms at the onset of COVID-19 illness are fever, cough, and fatigue; in severe cases, patients may develop severe pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure (Rothan & Byrareddy, 2020). Viral encephalitis was the first neurological complication linked to SARS-CoV2 (Wu et al., 2020) and since then cases have been reported linking COVID-19 to a spectrum of neurological associations. The neurologic symptoms can be seen in up to 36.4 % of patients and are being reported increasingly in patients with severe respiratory involvement. (Mao et al., 2020).

Coronaviruses, a family of large enveloped non-segmented positive-sense RNA viruses, have been associated with neurological manifestations in patients secondary to the neurotropic and neuro-invasive capabilities exhibited. In a study of 70 patients infected with the Middle East respiratory syndrome (MERS)-CoV infection, 8.6 % of enrolled patients manifested seizures. (Bohmwald, Galvez, Rios, & Kalergis, 2018; Saad et al., 2014).

Hung et al. reported the first case of status epilepticus associated with COVID19, with the presence of SARS-CoV RNA in both the CSF and serum (Hung et al., 2003) and since then over the last few months, there has been increased reportage of seizures associated with SARS- COV2. This article presents a review of the current literature on seizures linked with SARS- COV 2 infection and aims to describe underlying mechanisms associated with development of seizures.

2. Methods

We searched Medline, Google Scholar, and Pubmed using the keywords; "seizures", SARS COV2'', "COVID-19". Search was limited to the

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English language manuscript only. The literature search was last done on June 30, 2020. At the time of writing this article, we identified 478 research articles describing neurological complications in SARS-COV-2. Eleven of those articles described seizures associated with SARS-COV2. Table 1 highlights the demographic data, time to onset of neurological symptoms, diagnostic criteria, intervention, and outcomes from the eleven reports describing a total of 13 cases of seizures in patients with SARS- COV-2 infection.

3. Results

3.1. Demographics

Table 1 highlights the eleven reports that have described a total of 13 cases of seizures in patients with COVID-19. Of the 13 patients, 7 were male and 6 female.. The mean age was 61.3 yearswith a standard deviation (SD) of 16.73. The mean time for the onset of neurological symptoms from presentation was 4.69 days(SD of 4.51). Five patients presented with seizures as the initial presenting symptom; of these, three went on to develop respiratory symptoms while the other two only had further progression of the neurological symptoms. (Fasano, Cavallieri, Canali, & Valzania, 2020; Hepburn et al., 2020; Logmin, Karam, Schichel, Harmel, & Wojtecki, 2020; Sohal & Mansur, 2020).

3.2. Lumbar puncture

Of the thirteen patients, eight patients underwent lumbar puncture. CSF COVID-PCR was reporteded positive in one patient though the nasopharngeal swab was reported negative. (moriguchi et al 2020). Six patients had negative CSF PCRs or were in institutions which could not test the CSF for COVID PCR. Three patients had elevated lymphocytes, one had elevated protein with otherwise normal CSF findings, and the 3 patients had no specific CSF findings. (Bernard-Valnet et al., 2020; Duong, Xu, & Liu, 2020; Haddad et al., 2020). Lumbar puncture was not performed in 6 patients.

3.3. Imaging

Computed tomography (CT) head scan and magnetic resonance imaging (MRI) brain were obtained in all thirteen patients. One patient had MRI evidence of ventriculitis and encephalitiswhile one patient had MRI evidence of multiple, non-enhancing demyelinating lesions (Moriguchi et al., 2020; Zanin et al., 2020). In the remaining eleven patients, imaging studies showed no acute changes.

3.4. Electroencephalography (EEG)

Electroencephalography was obtained in eleven patients. Three patients had generalized slowing, and six patients showed focal areas of status epilepticus including the temporal lobe, frontotemporal regions and the centro-parietal regions (Duong et al., 2020; Filatov, Sharma, Hindi, & Espinosa, 2020; Haddad et al., 2020; Hepburn et al., 2020; Sohal & Mansur, 2020; Vollono et al., 2020; Zanin et al., 2020). Two patients had negative EEG.

3.5. Interventions

Two patientsdid not require treatment with AEDs. Eleven patients were treated with standard AEDs, including levetiracetam, diazepam, lacosamide, and valproic acid. No reports mentioned if the patients were discharged on AEDs.

3.6. Outcomes

Death was reported as an outcome in two out of thirteen patients. Final outcomes were unavailable or not reported for three patients. Poor outcome was reported in three patients with controlled seizures but critically ill due to other reasons. The remaining five patients were discharged with no neurological symptoms

4. Mechanisms of seizures in SARS-COV-2

4.1. Direct mechanism

As discussed earlier, CSF SARS- COV-2 PCR was reported positive in one patient with evidence of ventriculitis and encephalitis on the MRI. Another patient had multiple, non-enhancing demyelinating lesions. This demonstrates that SARS- COV-2 is able to directly enter and infect the central nervous system (CNS), causing meningitis and encephalitis, and thereby causing seizures (Desforges et al., 2020; Fotuhi, Mian, Meysami, & Cyrus, 2020).

There are several theorized pathways for SARS- COV-2 to enter the CNS.One of the chief targets of the SARS- COV-2 is the Angiotensin-converting-enzyme-2 (ACE-2) receptor cells (Kuba, Imai, Rao, Jiang, & Penninger, 2006). ACE-2 receptors are located on cells throughout the body, including the cardio-respiratory neurons of the brainstem, glial cells, basal ganglia, motor cortex, raphe, and endothelial cells of the brain (Doobay et al., 2007; Iroegbu, Ifenatuoha, & Ijomone, 2020; Xia & Lazartigues, 2008). Once in the bloodstream, SARS-COV-2 can travel to infect the endothelial cells of the blood-brain barrier and then accumulate in the various ACE 2 heavy brain regions causing direct infection with neurological sequelae (Desforges et al., 2013; Iroegbu et al., 2020).

A second route through which the SARS- COV-2 is theorized to enter the CNS is the olfactory nerve via the nasal cavity (Iroegbu et al., 2020; Koyuncu, Hogue, & Enquist, 2013). It has been demonstrated that within seven days of infection, SARS-COV-2 can reach the CSF and brain through the olfactory nerve causing inflammation and demyelinating reactions with potential subsequent seizures.Removal of the olfactory bulb in mice has shown to restrict invasion of SARS-COV-2 into the CNS (Wu et al., 2020).

4.2. Indirect mechanism

4.2.1. Down-regulation of ACE-2 expression, the role of cytokine storm and hypoxia/hypoperfusion

The overloading of ACE-2 receptors by SARS- COV-2 results in the down-regulation of ACE-2 expression (Kuba et al., 2006). This loss of ACE-2 receptors leads to dysfunction of the renin-angiotensin system and elevated production of angiotensin II. The overproduction of angiotensin II results in a cascade of interactions that eventually leads to severe acute lung injury, vasoconstriction, and oxidative processes that promote brain degeneration with the possibility of resulting in seizures (Iroegbu et al., 2020).

4.2.2. Cytokine storm

Infection with SARS- COV-2 has been shown to result in a cytokine storm, an immune-mediated life-threatening disease which is caused by impaired natural killer and cytotoxic T-cell function (Adult hemophagocytic syndrome, 2014; Fotuhi et al., 2020; Scott & Robb-Smith, 1939). This impaired function results in excessive secretion of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), and interleukins (IL) 1, 4, 6, 8, 10, and 18. Experimental studies infecting in vitro cultured glial cells with SARS-COV-2 noted enormous production of inflammatory cytokines such as IL-6, IL-12, IL-15, and TNF-α (Bohmwald et al., 2018; Wu et al., 2020). IL-6 in particular has been shown to positively correlate with the severity of COVID-19 symptoms. The overproduction of the cytokines result in an exaggerated inflammatory response and cause vascular permeability, edema, and widespread inflammation with consequent damage to multiple organs with the progression to multi-organ failure. (Adult hemophagocytic syndrome, 2014; Chiossone et al., 2012; Milner et al., 2010; Scott & Robb-Smith, 1939; Sumegi et al., 2011; Wan et al., 2020).

Table 1
Characteristics Associated In Patients With COVID-19 Associated Seizure.

No. of patients	Median age	Gender M/F	Symptoms on Initial presentation	Time of onset	Lumbar puncture	Radiological findings	EEG	On anticoagulation	intervention	Reference
1	24	M	Headache, encephalopathy, Seizure	9th day	CSF- Pressure >320 mmH2O CSF PCR COVID (+) (nasal Swab negative)	CT normal MRI right lateral ventriculitis and encephalitis mainly on right mesial lobe and hippocampus	ND	NA	Keppra Acyclovir/Steroids/ Keppra/Favipir avir	Moriguchi et al. (2020)
1	74	M	Confusion, nonverbal, encephalopathic	7th day	CSF- normal	CT head normal	Diffuse slowing, Slowing in left temporal with sharply countered waves	NA	Acyclovir Lopinavir/ritonavir Unstated antiseizure drugs	Filatov et al. (2020)
1	41	F	Headache,Seizure and Lethargy	1st day	CSF- WBC70 (lymphocytic predominant)	CT head normal	Generalized slowing	NA	Rocephin/Vancomycin/ Acyclovir	Duong et al. (2020)
1	41	M	Encephalopathy, Seizure, left ptosis	7th day	CSF-Elevated protein	MRI-Negative	Generalized slowing	N/A	Keppra Hydroxycholoroquine/ acyclovir	Haddad et al. (2020)
1	72	M	Seizures	3rd day	ND	CT head negative	Temporal lobe sharp waves	NA	Versed, Keppra, valproate	Sohal and Mansur (2020)
1	78	F	Seizures	1	ND	CT negative MRI-old gliosis and atrophy left temporoparietal lobe, nothing acute	irregular, high amplitude delta activity, predominantly lateralized over the left fronto-centro-temporal regions, consistent with focal status epilepticus	NA	Lopinavir/Ritonavir HCQ versed/valproic acid	Vollono et al. (2020)
2	64	F	Seizure, Psychosis	5th day	Both showed lymphocytic dominant pleocytosis with otherwise normal findings	MRI-normal	A: focal seizures	NA	Clonazepam, valproate No treatment	Bernard-Valnet et al. (2020)
	67	F	Headache,confused, likely seizures	17th day			B: ND			
1	54	F	Altered	First day	CSF-No pleocytosis, normal protein, negative PCR	CT-negative MRI-multiple periventricular white matter alterations-consistent with demyelinating lesions	seizures + in right frontotemporal region and diffusing in homologous contralateral hemisphere	NA	Dexamethasone lacosamide, levetiracetam, and phenytoin	Zanin et al. (2020)
2	79	male	Weakness, encephalopathy, dyspnea, seizures	Seizures on second day after admission	ND	A: CT negative. MRI chronic white matter hyperintensities, nothing acute B: CT mild microvascular disease but without acute lesion	EEG A:focal seizure right centroparietal region EEG B: left more than right frontal–temporal regions	N/A	Levetiracetam	Hepburn et al. (2020)
1	70	F	seizure	Day 1	No pleocytosis, normal protein, negative PCR	MRI non-acute	EEG negative	NA	NA	Logmin et al. (2020)
1	54	M	seizure	Day 1	ND	CT scan showed no acute changes	Negative EEG	NA	NA	Fasano et al. (2020)

Abbreviation/Footnotes- CSF- cerebrospinal fluid, ND- Not Determined, NA- Not Applicable, M- Male, F- Female, CT- Computed Tomography, EEG- Electroencephalography.

4.2.3. Hypoxia and hypoperfusion

It is well documented that COVID-19 can cause pneumonia and result in devastating hypoxia. Hypoxia can potentiate hypoxic encephalopathy, which can further contribute to the development of seizures. Ischemic brain injury also contributes to cerebral tissue hypoperfusion and may lead to seizures (Connors & Levy, 2020).

4.3. Exacerbation of seizure in patients with epilepsy (PWE)

The effects of COVID-19 on PWE still remain unclear. The importance of maintaining control of epilepsy with AEDs is important as mortality associated with epilepsy is higher in patients with uncontrollable seizures. Seizures can be provoked by sepsis, fever, sleep deprivation, electrolyte disturbances- the factors which are infrequently associated with COVID-19. A number of medications are being considered for for management of COVID-19 and therefore it is recommended to consider drug-drug interactions between AEDs and the anti-COVID therapy..(Huff & Seizure, 2020; Russo & Iannone, 2020; Sveinsson, Andersson, Mattsson, Carlsson, & Tomson, 2020)

5. Conclusion

Neurologic complications of patients with COVID-19 are common and may manifest as seizures.. However, the underlying mechanism for development of seizure in patients with COVID-19 still remains unclear. More studies are needed to examine these disease pathways in-depth as the world continues to monitor this pandemic. The clinician should always prioritize to determine any inciting factors frequently- hypoxia, fever, sepsis, electrolyte derangements)and aim to manage seizures in patients with COVID-19 with the application of general management principals of seizures and status epilepticus. When an AED)is initiated consideration should be given to the pharmokinetics of the drug, drug interactions, medication associated adverse effects.Patient factors such as the age of the patient alongwith any renal and/or hepatic impairment should also be taken into account.

Ethical statement

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation).
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

Declaration of Competing Interest

The authors report no declarations of interest.

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