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Research Article

A Review on Pathophysiology and Prognosis of Seizures in Covid-19

Philip Oreoluwa[1], Abdul Habib Eimal Latif[2], Zainab Mehkari[3], Abdirahman Hassan Shafad[4], Sidra Shahid Mubasher[5], Muhammad Adil Aftab khan[6], Varsha Nandwana[7], Noor Ul Huda Nabeel[8*], Usman Tariq[8], Rana Inamullah Zafar[9], Sadaf Rifaz[10], Mireille Nkongho[11], Anita Kengel Sangong[12], Yamini Kahlon[13], Amarachi Abara[14]

[1]University of Lagos, Nigeria

[2]Kabul University of Medical Sciences, Afghanistan

[3]Ziauddin Medical University, Pakistan

[4]Cairo University School of Medicine, Egypt

[5]University Medical and Dental College, Pakistan

[6]Shifa College of Medicine, Pakistan

[7]Lady Hardinge Medical College, India

[8]Bahria University Medical and Dental College, Pakistan

[9]Army Medical College, Pakistan

[10]Jinnah Medical and Dental College, Pakistan

[11]Saint James School of Medicine, Saint Vincent

[12]Washington University of Health and Science, US

[13]American University of Antigua College of Medicine, Antigua & Barbuda

[14]Abia State University College of Medicine and Health Sciences, Nigeria

[*]Corresponding author: Noor Ul Huda Nabeel, Department of Internal Medicine, Bahria University Medicine and Dental College, Pakistan

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Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) is a novel infectious disease. It has caused one of the most destructive pandemics in human history with symptoms ranging from mild to severe. In severe cases, patients can develop pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure. Among the neurological manifestations, seizures have been most commonly reported. Different mechanisms have been proposed for the occurrence of seizures in COVID-19 patients. Hypoxia and severe metabolic and electrolyte derangements may theoretically lower seizure thresholds. Furthermore, cytokine storm and the involvement of ACE receptors are also being considered as possible etiologies for these seizures. We performed a detailed literature review and included 15 case reports of seizures in COVID patients. The majority of the patients had past conditions ranging from diabetes and hypertension to as severe as fahr syndrome, AF (Atrial Fibrillation), and MM (Multiple Myeloma). Most of the patients with fits had moderate to severe COVID-19. Most patients were treated with levetiracetam, a very effective anti-epileptic. For COVID-19 patients with seizures, a multidisciplinary approach should be considered to enhance the care of the patients. It is very important to do a long-term follow-up of these patients to fully understand if these patients tend to develop epilepsy.

Keywords: COVID-19, Seizures

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) is a novel infectious disease. It has caused one of the most destructive pandemics in human history [1]. On average, it takes 5 days for covid-19 symptoms to appear. Fever, cough, and fatigue are among the most common symptoms. In severe cases, patients may develop acute respiratory distress syndrome (ARDS), acute cardiac injury, neurological complications, or multi-organ failure [2]. Mao *et al*. investigated the neurological involvement of COVID-19 in Wuhan, China, and found that 25% of the patients with COVID-19 had neurological issues [3]. Among the neurological manifestations, seizures have been most commonly reported. The incidence of seizures due to covid-19, as reported by several studies, is about 1%. The cause of seizures in coronavirus patients may be due to metabolic abnormalities, hypoxia, or even encephalitis [3]. Also, it is well documented that coronavirus targets angiotensin-converting enzyme 2 (ACE-2) receptors, which are not only present in the blood vessels and lower respiratory tract but also in the brain. Furthermore, coronavirus induces recruitment of inflammatory cytokines, mainly interleukin-8 and monocyte chemoattractant protein-1 (MCP1). MCP1 is present on the cells of CNS and helps in the degradation of the blood-brain barrier and recruits more inflammatory markers, causing a cytokine storm in the brain resulting in cortical irritation and seizures [4, 5].

Other respiratory viruses including the human respiratory syncytial virus, the influenza A virus, the Nipah virus, and the human metapneumovirus also affect CNS [6] and can cause clinical manifestations in subgroups of patients. These include acute encephalitis with febrile or afebrile seizures as well as status epilepticus and even long-term complications like chronic encephalopathies [7]. Seizures have been reported in case series and in isolated case reports in COVID-19 patients. It is paramount that we understand the association between COVID-19 and seizures.

In this review article, we discussed new-onset seizures reported in COVID-19 patients and attempted to understand the probable mechanisms and possible CNS

invasion linking SARS-CoV-2 and seizures. We have also discussed the possibility of triggers like fever, hypoxia, cytokine storm, or cerebrovascular events causing seizures.

2. Methods and Results

A review of the PubMed database was conducted using the search terms "Covid-19," and "Seizures". Filters for human studies, case reports, age 19+ years, and articles written in the English language were applied. The total number of articles initially retrieved was 29. After screening, a total of 15 articles were included in our review.

3. Discussion

3.1 Probable mechanisms linking SARS-CoV-2 and seizures

Among the severe neurological symptoms mentioned in the various articles, seizures reached the highest prevalence in COVID-19 cases [7]. COVID-19 patients, especially those with severe disease course, are at an increased risk for seizures, and the underlying etiology of these seizures is probably multifactorial. Different mechanisms have been proposed to understand the link between SARS-CoV-2 and seizures. Some of them are summarized below. SARS-CoV-2 binds to ACE2 receptors, which mediate virus entry into the host cells. Argañaraz GA et al. proposed that upregulation of the components of renin-angiotensin system can occur in the hippocampus of patients with temporal lobe epilepsy [8].

This study provides evidence that seizures are linked with the upregulation of the renin-angiotensin system. Another study demonstrated that a decrease in the severity of seizures occurred after ACE inhibitor enalapril was administered [7]. Further studies are necessary to explore a possible infection-associated upregulation of ACE2 receptors, its effects on the balance in the renin-angiotensin system in different tissues, and its functional consequences.

IL-6 is a pro-inflammatory cytokine that contributes to the fever response during infections. Previous clinical reports have associated the occurrence of febrile seizures with high levels of IL-6. IL-6 can also play a role in CNS inflammation by increasing the levels of acute-phase proteins like CRP. Various clinical reports have linked elevated levels of IL-6 with new-onset seizures. Keeping in mind that viral infections such as SARS-CoV-2 are usually associated with fever and elevated cytokine levels, there is the risk that seizure thresholds are lowered in affected patients [7]. Hypoxic encephalopathy has been reported in 20% of the 113 deceased patients with COVID-19 [9]. Therefore, hypoxia should be contemplated as another factor that may cause seizures in COVID-19 cases with severe disease. Other risk factors like, electrolyte derangements, hypo- or hyperglycemia, acute kidney injury, shock, systemic infections, medications, and stroke could result in seizures in these populations [10].

Furthermore, anxiety in acute COVID-19 patients can cause seizure mimics [10]. A similar situation has been described in influenza patients, who were otherwise healthy adults but developed seizures during Influenza A and B. There is a possibility that an associated encephalopathy resembling that of our patients was present, with neuroimaging being normal and seizures tending to disappear after a few weeks [11]. Thus, in conclusion, there are several possible mechanisms by which COVID-19 may hypothetically, increase seizure susceptibility.

3.2 Data set in our study

The total number of patients in our data set was 15 (13 males, 2 females). The majority of the patients had past conditions ranging from diabetes and hypertension to as

severe as fahr syndrome, AF (Atrial Fibrillation), and MM (Multiple Myeloma). Most of the patients with fits had moderate to severe COVID-19 disease. Table 1 summarizes the demographic details as well as past conditions, vitals, and severity of the COVID-19 in patients presenting with seizures associated with covid-19.

3.3 Seizures presentation, treatment, and outcomes in COVID-19 patients

Most cases of seizures in COVID-19 patients occurred in individuals with no history of epilepsy. These seizures were sudden in onset with no aura. In most cases, they were reported 7 to 21 days after covid onset, but there was an exception to this as one patient presented with clonic movements in the right arm and loss of consciousness; developing symptoms of cough, high fever, and shortness of breath after 4 days and was later diagnosed with COVID-19 infection [17].

In our data set, levetiracetam was used frequently in all types of seizures. Phenytoin and benzodiazepines were also administered in few cases. All patients had a normal follow-up course with no seizure, except for patients with refractory status epilepticus (RSE) [10]. Most patients in our dataset had generalized tonic-clonic seizures except for three patients. Of whom, two patients developed non-convulsive status epilepticus and one patient a focal seizure. In most of the patients, one episode of seizure was observed except for 2 patients; one was diagnosed with refractory status epilepticus (RSE) and the other with posterior leukoencephalopathy syndrome (PRES). Table 2 discusses in detail the neurological symptoms, their onset, and treatment given to every individual patient.

3.4 Epilepsy as a neurological complication of COVID-19

Epilepsy is a chronic condition involving recurrent seizures. It is different from acute symptomatic seizures as observed in patients with COVID-19 infection. The incidence of epilepsy after a seizure triggered by COVID-19 infection is not yet known, however, most patients in our data set had a normal follow-up course. It is very important to do a long-term follow-up of these patients to fully understand the future risk of epilepsy [20].

Reference	Gender	Age	Past condition	Vitals at presentations	COVID presentation at admission	Severity of symptoms
Jalil BA et al. [3]	Male	29-year-old	Partially resected choroidal fissure arachnoid cyst at age 19 months.	Hypoxic to 89% on room air, and mildly tachypneic; respiratory rate between 28 and 36 per minute.	Fever for the preceding 3 days.	Moderate
Bhagat R et al. [12]	Male	54-year-old	Paroxysmal atrial fibrillation (PAF), hypertension, glucose-6-phosphate dehyd-rogenase deficiency, and hepatosteatosis.	An irregularly irregular pulse rate of 110 beats per minute.	Fever, hypoxia, respiratory acidosis.	Moderate
Mithani F et al. [13]	3 male patients	-	-		Critically ill	-
Demir G et al. [14]	Female	68-year-old	Fahr's syndrome	--	COVID-19 pneum-onia with extreme fatigue	Moderate
Carroll E et al. [10]	Female	69-year-old	Diabetes, renal transplant.		Confusion, diarrh-ea, and cough. Int-ubated for hypoxia	Severe
Rodrigo-Armenteros P et al. [11]	Male	62-year-old	Left eye amblyopia	Oxygen saturation (SaO2) of 89% at room air	Upper respiratory tract symptoms and fever for eight days.	Moderate
Lyons S et al. [15]	Male	20-year old	--	Febrile (101.3 F) with heart rate 85bpm, respiratory rate 12, and sO2 97 % on room air.	Myalgia, lethargy, and fever for three days.	Moderate
Gómez-Enju to S et al. [16]	Male	74-year-old	IgG kappa multiple myeloma		Asthenia, dry cough, and fever.	Severe
Kadono Y et al. [17]	Male	44-year-old	Nephrosis. A week before admission, he felt bulging of a scalp flap. (the patient was on warfarin)	Normal	Presented with fits initially and then developed sympto-ms of COVID-19 after 4 days that included fever, cough, lethargy.	Moderate
Hepburn M	Two male	advanced-	--	--	Severe disease.	Severe

et al.[4]	patients	age				
Fasano A et al. [18]	Male	54-year-old	--		Cough, high fever, and shortness of breath.	Moderate
Balloy G et al. [19]	Male	59-year-old	Atrial fibrillation		fever, dry cough, dyspnea, and headache.	Severe

Table 1: Illustrates demographic details and COVID presentation in patients with seizures after COVID-19 infection.

Reference	**Neurological symptoms**	**Onset**	**Treatment**	**Follow-up**
Jalil BA, et al. [3]	Visual and auditory hallucinations, intermittent confusion, and confabulation. witnessed generalized tonic-clonic seizure.	12 hours after admission to ICU	Propofol, intravenous levetiracetam, Phenytoin.	No further seizure was reported.
Bhagat R, et al. [12]	Nonradiating pressure type holocranial headache along with diaphoresis, palpitation. A 5-minute episode of loss of consciousness without convulsion. Fifteen minutes later a generalized convulsion lasting 1 minute. 15 minutes of post-ictal confusion.		He was treated with lorazepam and levetiracetam in the ED.	Normal follow-up course.
Mithani F, et al. [13]	seizure	three-and-a-half weeks after symptoms.		
Demir G, et al. [14]	The patient had a tonic-clonic convulsion starting from the left arm and spreading to the whole body.		* intravenous midazolam. *Calcium replacement *calcitriol twice a day. *Levetiracetam. *Midazolam and fentanyl infusions for sedation.	The patient died on the 8th day.
Carroll E, et al. [10]	A 2-minute episode of spontaneous, symmetric, tonic movements of her arms and left gaze deviation without a reported head turn	On hospital day (HD) #2,	HD 2. The episode resolved with lorazepam 2 mg.	Patient was re-admitted and developed refractory status epilepticus (RSE)

Rodrigo-Armenteros P, et al. [11]	became confused and disorientated, with bradyphrenia, ideomotor apraxia, and bilateral Babinski signs.	8th day of admission	levetiracetam (1500 mg every 12 h) and valproic acid (400 mg every six hours)	Recovered.
Lyons S, et al. [15]	lightheadedness with blurred and double vision. He then had a 1 min generalized tonic-clonic seizure. In the wake of the seizure, he was confused and aggressive,		He was isolated and treated with levetiracetam, aciclovir, ceftriaxone, and vancomycin.	No further seizure was reported. EEG, performed on outpatient follow-up was normal.
Gómez-Enjuto S, et al. [16]	suffered two focal aware motor seizures 1)left oculocephalic deviation and clonic movements of the upper left limb, that ceased spontaneously. 2)A new focal motor onset seizure with impaired awareness.	15th day of hospitalization	progressive doses of antiepileptic drugs were administered, (diazepam, levetiracetam, lacosamide, and valproate) without ceasing. Later, 2.5 mg of verapamil was administered, which controlled the seizure.	--
Kadono Y, et al. [17]	Numbness in left hand and face….then intermittent twitch on the left hand and face. This followed by a seizure, starting from jerking of his left hand and then the entire body lasted for few minutes.		administration of 7.5 mg diazepam initially.	the brain swelling improved after 2 weeks, as was shown by CT brain.
Hepburn M. et al.[4]	Tonic-clonic seizures	Few days after hospitalization	levetiracetam	
Fasano A, et al.[18]	single seizure characterized by clonic movements in the right arm and loss of consciousness.	Before admission to the hospital		Remained seizure-free.
Balloy G, et al. [19]	short episodes of impaired consciousness together with confusion and behavioral disturbances. The first seizure lasted 6 minutes and the second seizure lasted at least 5 minutes.	On the 15th day,	Clobazam (30 mg/day) and levetiracetam (1.5 g/day)	improved

Table 2: Summarizes neurological symptoms, their onset, and treatment given to each patient.

4. Conclusion and Recommendations

Covid-19 binds to ACE receptors in brain which might be responsible for the susceptibility of fits in COVID patients. Moreover, patients with COVID-19 may have hypoxia, multiorgan failure, and severe metabolic and electrolyte disarrangements and that might be the reason for acute symptomatic seizures in these patients. Detailed clinical, neurological, and electrophysiological investigations of the patients should be performed. Most patient were treated with levetiracetam, a very effective anti-epileptic. For COVID-19 patients with seizures, a multidisciplinary approach should be considered to enhance the care of the patients. It is very important to do a long-term follow-up of these patients to fully understand if these patients tend to develop epilepsy.

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