



Seizure in patients with COVID-19

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Abstract

Objective The purpose of the current study was to collect the data on the occurrence of seizures in patients with COVID-19 and to clarify the circumstances of the occurrence of seizures in these patients.

Methods All consecutive patients who referred to healthcare facilities anywhere in Fars province (located in South Iran with a population of 4.851 million people) from February 19 until June 2, 2020, and had confirmed COVID-19 by positive result on polymerase chain reaction testing and seizure were included.

Results During the study period, 6,147 people had confirmed COVID-19 in Fars province, Iran; 110 people died from the illness (case fatality rate 1.79%). During this time period, five people had seizures (seizure rate 0.08%). In four patients, seizure was one of the presenting manifestations, and in one person, it happened during the course of hospital admission. Two patients had status epilepticus. All patients experienced hypoxemia and four of them needed respirator. Two patients had related metabolic derangements and one had cerebrospinal fluid (CSF) lymphocytic pleocytosis. Brain imaging was abnormal in three patients. Four patients died.

Conclusion New-onset seizures in critically ill patients with COVID-19 should be considered as acute symptomatic seizures and the treating physician should try to determine the etiology of the seizure and manage the cause immediately and appropriately. Detailed clinical, neurological, imaging, and electrophysiological investigations and attempts to isolate SARS-CoV-2 from CSF may clarify the role played by this virus in causing seizures in these patients.

Keywords Coronavirus · COVID · Epilepsy · Seizure

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Introduction

Since the beginning of the year 2020, the world has been experiencing a catastrophic pandemic of coronavirus disease (COVID-19) that is caused by SARS-CoV-2 [1]. As this is a newly emerged viral infection, we have been learning a lot about the presentations of COVID-19 with the passage of time [2]. While seizures had not been widely reported in the first few months of COVID-19 pandemic [3–5], there has been increasing numbers of reports of seizures in patients with COVID-19 recently [6–8]. Patients with COVID-19 may have hypoxia, multiorgan failure, and severe metabolic and electrolyte disarrangements [9]; therefore, it is plausible to expect acute symptomatic seizures to occur in these patients. Furthermore, a growing body of evidence indicates that neurotropism is one common feature of coronaviruses [10, 11]. Seizures had been reported in outbreaks of coronavirus infections (severe acute respiratory syndrome (SARS) in 2002 and the Middle East respiratory syndrome (MERS) in 2012) before [12–14].

The purpose of the current study was to collect the data on the occurrence of seizures in patients with COVID-19 and to clarify the circumstances of the occurrence of seizures in people who are infected with this virus.

Methods

Iran reported its first confirmed cases of SARS-CoV-2 infection on 19 February 2020. As of 24 June 2020, there have been 9,863 COVID-19 deaths with 209,970 confirmed infections in Iran [15]. In this study, all consecutive patients who referred to healthcare facilities anywhere in Fars province (located in South Iran with a population of 4.851 million people) from February 19 until June 2, 2020, and had confirmed COVID-19 by positive result on real-time polymerase chain reaction (qRT-PCR) testing of nasopharyngeal and oropharyngeal (NP/OP swabs) samples, which were inserted in the same tube, were included. The denominator was the total number of the people with confirmed COVID-19 in Fars province during that time period. The numerator was the number of people with seizures. The clinical manifestations and paraclinical findings of patients with seizure were collected retrospectively and after reviewing their medical records.

Standard protocol approvals, registrations, and patient consents

Shiraz University of Medical Sciences Review Board approved this study as a minimal-risk research using the data that were collected for routine clinical practice and waived the requirement for informed consent. Information was

collected and entered into the electronic registry of Shiraz University of Medical Sciences (Ethics code: IR.SUMS.REC.1399.022).

Results

From February 19 until June 2, 2020, 6,147 people had confirmed COVID-19 in Fars province, Iran; 110 people died from the illness (case fatality rate 1.79%). During this time period, five people had tonic-clonic seizures (seizure rate 0.08%). In four patients, seizure was one of the presenting manifestations, and in one person, it happened during the course of the hospital admission. Table 1 describes demographics and clinical manifestations of the patients with COVID-19 and seizures. Adults and children, women, and men with COVID-19 had seizures in our series. Two patients had additional neurological manifestations, other than seizure and altered mental status (Table 1). While two patients had comorbid human immune deficiency virus (HIV) infection, none had pre-existing epilepsy. Two patients had status epilepticus (one adult person with comorbid HIV infection and one child with febrile status epilepticus). All patients experienced hypoxemia and four of them needed ventilators. Two patients had related (to seizures) metabolic derangements (increased BUN and creatinine in one (BUN 49 mg/dL, creatinine 2.8 mg/dL) and hyponatremia (blood sodium level = 126 mEq/L) in another). Lumbar puncture was performed in two patients; one had lymphocytic pleocytosis and one had normal results; PCR test on cerebrospinal fluid (CSF) for SARS-CoV-2 was not done in any patient. Brain imaging was done in four patients; three had abnormal findings (see Table 1). Electroencephalography was performed in two patients; both had diffuse slowing. Two patients received hydroxychloroquine and three people did not. Four patients died and one child was discharged in a healthy condition with no further seizures.

Discussion

In this study, we observed that seizure could be seen in both sexes and all ages and patients with COVID-19 may have *de novo* seizures without a history of epilepsy. Patients with COVID-19 may develop seizures as a consequence of hypoxia, metabolic derangements, organ failure, or even neuroinvasion or cerebral damage that may happen in these patients [9]. The specific SARS-CoV-2 RNA was detected in the CSF in a patient with meningoencephalitis in a previous study [4]. While one of our patients had CSF lymphocytic pleocytosis, we cannot confirm a COVID-related meningoencephalitis (we did not have PCR test on the CSF for SARS-CoV-2).

Table 1 Characteristics of patients with COVID-19 and seizure

	Patient # 1	Patient # 2	Patient # 3	Patient # 4	Patient # 5
Age	54 years	42 years	35 years	2.9 years	2 days (term)
Sex	Female	Male	Male	Male	Female
Chief complaint	Seizure (status epilepticus)	Fever, cough	Altered mental status	Fever, status epilepticus	Respiratory distress
Time of seizure from the onset	1st day	15th day	1st day	1st day	1st day
Fever	No	Yes	Yes	Yes	No
Cough	Yes	Yes	Yes	No	No
Respiratory distress	Yes	Yes	Yes	No	Yes
Headache	No	No	No	-	-
Altered mental status	Yes	No	Yes	Yes	Yes
Other neurological symptoms/- signs	No	No	Left pupil 2 mm non-reactive (right 3 mm reactive)	Dysarthria, bilateral upward plantar reflexes	No
Other signs/- symptoms	No	No	Increased secretions, bilateral rales	Nausea, vomiting, abdominal pain	No
Comorbidity	HIV infection	No	HIV infection	Allergy to cow milk	Low birth weight
PaO ₂	68–90	22–88	58–100	52–91	37
Admitted	ICU	ICU	ICU	ICU	ICU
Ventilator	Yes	No	Yes	Yes	Yes
Abnormal blood works	BUN 49 mg/dL, creatinine 2.8 mg/dL, platelet 55,000 per microliter	D-Dimer 6396 ng/mL, PTT 56 s, LDH 1398 U/L	CRP 91 mg/L, ESR 98 mm/h	Troponin I 154 ng/ml, CPK 482 U/L, CRP 105 mg/L, LDH1019 U/L	Total bilirubin 6 mg/dL, bicytopenia (RBC 1.93×10^6 and WBC 2000 per microliter), blood sodium level = 126 mEq/L
CSF	6 PMN, 14 lymphocytes, normal protein and glucose	Not done	Not done	1st: 1 PMN, normal protein and glucose 2nd: No cell, normal protein and glucose	Not done
Chest X-ray	Bilateral diffuse infiltration	Not done	Not done	Bilateral diffuse infiltration	Bilateral diffuse infiltration
Chest CT scan	Bilateral diffuse infiltration	Bilateral ground-glass opacity	Multiple nodule and cavity in favor of septic emboli	Not done	Not done
Brain imaging	Brain CT: Basal frontal hypodensity	Not done	Brain CT: right ischemic stroke	Brain CT: Right occipital mass and intracerebral hemorrhage. Brain MRI: Right occipital mass (ganglioglioma?) + intracerebral hemorrhage intracerebral hemorrhage [®]	Brain sonography: Normal
EEG	Generalized slowing	Not done	Not done	Generalized slowing	Not done
Treatment (ASM)	Levetiracetam, midazolam	Midazolam	Midazolam, fentanyl, levetiracetam	Phenobarbital, levetiracetam, valproate, phenytoin, midazolam, thiopental, fentanyl	Phenobarbital
Other medications	Famotidine, ciprofloxacin, clindamycin, heparin, pantoprazol,	Ranitidine, ondansetron, oseltamivir, levofloxacin, vancomycin, lopinavir/ritonavir,	Dexamethasone, vancomycin, atorvastatin, morphine, acetazolamide, dextromethorphan, acetaminophen,	Colistin, pantoprazole, acetaminophen, meropenem, hydroxychloroquine, vancomycin,	Ampicillin, amikacin, vitamin K, ceftriaxone, pantoprazole

Table 1 (continued)

	Patient # 1	Patient # 2	Patient # 3	Patient # 4	Patient # 5
	propranolol, acyclovir, etomidate	hydroxychloroquine, ribavirin, meropenem, vancomycin, ipratropium, salbutamol, salmeterol/fluticasone	meropenem, N-acetylcysteine, magnesium hydroxide, amikacin, enoxaparin, clonidine, lopinavir/ritonavir	domperidone, acyclovir, dexamethasone, N-acetylcysteine, enoxaparin, vitamin B-complex, norepinephrine, furosemide, potassium chloride, packed cell	
Outcome	Expired in ICU	Expired in ICU	Expired in ICU	Discharged	Expired in ICU
Duration of admission (days)	7	3	31	21	3
Follow-up	-	-	-	4 days after being discharged: No problem, no seizures	-

HIV human immune deficiency virus, *ICU* intensive care unit, *BUN* blood urea nitrogen, *PTT* partial thrombin time, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *CPK* creatine phosphokinase, *PRL* prolactin, *RBC* red blood cell, *WBC* white blood cell, *PMN* polymorphonuclear leukocytes

@pathology: normal brain tissue with dilated vessels and hemorrhage

Cerebrovascular events have been reported in patients with COVID-19 in multiple studies [2, 16]. Two of our patients had such findings in their brain imaging studies. There is a case with COVID-19-associated encephalitis mimicking a glial tumor in the literature [17]. One of our patients had a similar finding in his brain imaging/pathology studies. Other scenarios for acute symptomatic seizures in critically ill patients with COVID-19 have also been reported before [18–21]. All of our patients were admitted to intensive care unit (ICU) and had hypoxemia, two patients had metabolic derangements, and one child suffered from febrile status epilepticus.

Unfortunately, four of our patients died at the hospital. While total case fatality rate was 1.79%, this rate of 80% mortality among patients with seizures seems to be very high. However, we cannot establish a cause and effect relationship between seizure and mortality in patients with COVID-19 based on this study, because of the small number of patients with seizures.

While the rate of convulsive seizures was small in our study and most previous studies [2–6], in previous studies, change in mental status have been reported in about 10% of patients with severe COVID-19 [2]. However, EEG has not been done in most previous studies to investigate the possibility of non-convulsive status epilepticus (NCSE) in patients with altered responsiveness and COVID-19. One small study of 22 patients with confirmed COVID-19 showed that the most common indications for EEG were new-onset encephalopathy and seizure-like events. Sporadic epileptiform discharges were present in 41% of the patients [8]. It is recommended to perform a continuous EEG monitoring in a patient who is in a critical medical condition, including those with

COVID-19, and has a change in mental status to make sure that NCSE is not a part of the clinical scenario [9].

New-onset seizures in critically ill patients with COVID-19 should be considered as acute symptomatic seizures, and therefore, long-term antiseizure medication (ASM) therapy is often not needed, unless a subsequent seizure happens [9]. However, the treating physician should try to determine the etiology of the seizure and manage the cause immediately and appropriately. Detailed clinical, neurological, imaging, and electrophysiological investigations and attempts to isolate SARS-CoV-2 from CSF may clarify the role played by this virus in causing seizures in these patients.

Limitations

This study was cross-sectional in design and the data were collected retrospectively. Furthermore, we did not have access to the whole database and information on all 6,147 patients to compare these patients with those without seizures. This study should be replicated in other populations. Finally, in most patients, EEG and CSF analyses were not done and PCR test on the CSF for SARS-CoV-2 was not done in any patient.

Authors' contributions Ali A. Asadi-Pooya, M.D.: Design and conceptualized the study, analyzed the data, and drafted and revised the manuscript. Others: Data collection and revision of the manuscript.

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Data availability The data use in this study is confidential and will not be shared.

Compliance with ethical standards

Shiraz University of Medical Sciences Review Board approved this study.
Conflict of interest Ali A. Asadi-Pooya, M.D.: Honoraria from Cobel Daruo, RaymandRad, Sanofi, and Tekaje; Royalty: Oxford University Press (Book publication). Others: none.

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