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BRIEF COMMUNICATION

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New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study

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Abstract

Our aim was to clarify the incidence and risk of acute symptomatic seizures in people with coronavirus disease 2019 (COVID-19). This multicenter retrospective study enrolled people with COVID-19 from January 18 to February 18, 2020 at 42 government-designated hospitals in Hubei province, the epicenter of the epidemic in China; Sichuan province; and Chongqing municipality. Data were collected from medical records by 11 neurologists using a standard case report form. A total of 304 people were enrolled, of whom 108 had a severe condition. None in this cohort had a known history of epilepsy. Neither acute symptomatic seizures nor status epilepticus was observed. Two people had seizurelike symptoms during hospitalization due to acute stress reaction and hypocalcemia, and 84 (27%) had brain insults or metabolic imbalances during the disease course known to increase the risk of seizures. There was no evidence suggesting an additional risk of acute symptomatic seizures in people with COVID-19. Neither the virus nor potential risk factors for seizures seem to be significant risks for the occurrence of acute symptomatic seizures in COVID-19.

KEYWORDS

acute symptomatic seizures, COVID-19, epilepsy, SARS-CoV-2

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1 | INTRODUCTION

In December 2019, pneumonia caused by a novel coronavirus, later called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China. On March 12, 2020, the World Health Organization (WHO) declared the syndrome caused by SARS-CoV-2 infection, coronavirus disease 2019 (COVID-19), a pandemic. According to a WHO Situation Report of April 7, 2020,[1] there are >1,200,000 confirmed COVID-19 cases and >72,000 deaths globally. COVID-19 affects people of all ages,[2,3] and in severe cases, it may cause dyspnea, hypoxia, acute respiratory distress syndrome, and septic shock.[4,5]

The current situation has raised concerns regarding whether people with epilepsy have a higher risk to be infected with COVID-19 and whether people would develop acute seizures during the course of COVID-19. The objective of this study is to clarify the incidence and the risk of acute symptomatic seizures during acute COVID-19 infections.

2 | MATERIALS AND METHODS

2.1 | Study population

This retrospective multicenter study was approved by the ethics committee of West China Hospital, Sichuan University (approval 2020[100]). The study was conducted in 42 officially designed hospitals in Hubei province, the epicenter of the COVID-19 epidemic in China; Sichuan province; and Chongqing municipality. These hospitals included the East Branch of Renmin Hospital of Wuhan University (West China Ward), Chongqing Three Gorges Central Hospital, and hospitals in Sichuan province designated by the government to treat COVID-19 (see the list of hospitals in Appendix S1).

People with COVID-19 who were discharged from or died in the participating hospitals between January 18 and February 18, 2020 were consecutively enrolled. All cases were diagnosed according to the Diagnosis and Treatment Protocol for COVID-19 (trial version 6).[6] All those enrolled tested positive through nucleic acid detection. Disease severity was classified as mild, moderate, severe, or critical according to the national guidelines (see Box 1 for classification criteria).[6] For our study, we aggregated severe and critical cases into a single severe group, whereas mild and moderate cases were aggregated into a single milder group. The clinical outcome at discharge was either cured or death.

2.2 | Study data

Electronic medical records of all enrolled cases were reviewed by 11 neurologists using a standard case report form (Appendix S2). Data were extracted on demographic characteristics, medical history, complications, treatments, and presence of risk factors for seizures. These risk factors were considered to be the following: acute cerebrovascular disease, traumatic brain injury (TBI), central nervous system (CNS) infection, shock, hypoxia, severe metabolic disturbance (based on criteria from the International League Against Epilepsy[7]), multiple-organ dysfunction syndrome, sepsis, and exposure to drugs or toxic substances.

2.3 | Statistical analysis

Continuous variables were presented as median (interquartile range) and categorical variables as n (%).

3 | RESULTS

All of 304 people discharged from or who died at participating hospitals were consecutively identified and enrolled. Most were from Sichuan province (n = 174), followed by Chongqing (n = 81) and Hubei (n = 49).

BOX 1 Criteria for classification of COVID-19 severity (modified from the Diagnosis and Treatment Protocol for COVID-19, trial version 6)[6]

Group	Classification	Criteria
Mild	Mild	Light clinical symptoms and no sign of pneumonia on imaging
	Moderate	Fever, respiratory tract symptoms, and other symptoms; imaging suggests pneumonia
Severe	Severe	Any of the following: (1) respiratory distress, respiration rate ≥ 30 times/min; (2) oxygen saturation ≤ 93% in the resting state; or (3) PaO_2/FiO_2 ≤ 300 mm Hg (1 mm Hg = 0.133 kPa)
	Critical	As in severe plus any of the following: (1) respiratory failure occurs, and mechanical ventilation is required; (2) shock occurs; or (3) complicated with other organ failure and need of intensive care unit monitoring and treatment

Ten individuals died, giving case fatality rates of 6.1% (n = 3) in Hubei, 4.9% (n = 4) in Chongqing, and 1.7% (n = 3) in Sichuan. Of the 108 severe cases, 51 (47%) received mechanical ventilation, and 16 (19%) were given sedatives. Apart from the effect of sedatives, mental state was relatively normal in 296 people. Eight were encephalopathic (one was obtunded, one was delirious, and six were comatose). The diagnosis of nonconvulsive status epilepticus was not made in any of these cases based on clinical presentation, results of investigations, or response to therapy. No routine or long-term electroencephalogram (EEG) was recorded due to exposure concerns.

None in this cohort had a past history of epilepsy. None had any seizures, including febrile seizures, or status epilepticus during hospitalization. Seizurelike events were seen in two people; it was believed that this was the result of an acute stress reaction in one and hypocalcemia in the other.

The first was a 32-year-old woman who reported bilateral bodily spasms lasting for about 1 minute, with mouth deviation but no impairment of awareness. She was evaluated neurologically and psychiatrically and was diagnosed with an acute anxiety disorder, which was treated with olanzapine, paroxetine, and diazepam.

The second case was a 65-year-old woman who displayed bilateral myoclonus in the limbs with no impairment in consciousness 2 hours after admission. Although this was initially suspected to represent seizures, she was found to have an electrolyte disturbance including hyponatremia, hypokalemia, and hypocalcemia, and the myoclonus resolved with correction of the metabolic disturbances.

Eighty-four (27%) cases reported systemic or direct brain insults that increased their risk for acute symptomatic seizures (Table 1). The most common risk factor was hypoxia. No severe electrolyte disturbance was seen, but hypokalemia (n = 40, 13%), hyponatremia (n = 34, 11%) and hypocalcemia (n = 22, 7%), were frequently seen in the cohort. Urea, creatinine, and serum glucose levels were moderately altered in most of cases. In two cases who had chronic kidney dysfunction, substantial increases in creatinine levels were noted. Results of investigations are shown in Table 2. One case with TBI had an epidural hematoma, cerebral contusion, and skull base fracture. Five people with severe COVID-19 experienced septic shock. Three other cases of shock had hypovolemia or cardiac problems. Ninety-four (31%) were given antibiotics; moxifloxacin (n = 53, 17%), piperacillin sulbactam sodium (n = 30, 10%), and third-generation cephalosporins (n = 21, 7%) were most commonly used.

TABLE 1 Demographic characteristics and seizure risk factors in people with coronavirus disease 2019

Characteristic	All, N = 304	Disease severity	
		Mild, n = 196	Severe, n = 108
Age, y	44 (33-59.25)	39 (31-49)	61.5 (47-73.25)
0-14	2	2	0
15-49	180	147	33
50-64	66	39	27
≥65	56	8	48
Male sex	59.9%	59.2%	61.1%
Risk factors of seizure			
Acute cerebrovascular disease	3	0	3
Traumatic brain injury	1	1	0
CNS infection	0	0	0
Hypoxia	77	14	63
Shock	8	0	8
Sepsis	8	0	8
Imipenem use	13	0	13
Multiple organ dysfunction syndrome	8	0	8
Hyperglycemia, >25 $mmol \cdot L^{-1}$	1	0	1
Hypoglycemia, <2.0 $mmol \cdot L^{-1}$	0	0	0
Hyponatremia, <115 $mmol \cdot L^{-1}$	0	0	0
Hypocalcemia, <1.2 $mmol \cdot L^{-1}$	0	0	0
Hypomagnesemia, <0.3 $mmol \cdot L^{-1}$	0	0	0
Urea nitrogen, >35.7 $mmol \cdot L^{-1}$	0	0	0
Creatinine, >884 $\mu mol \cdot L^{-1}$	2	0	2
Exposure to drugs or toxic substances	0	0	0

Note: Values are n, %, or median (interquartile range).

Abbreviation: CNS, central nervous system.

4 | DISCUSSION

We found no new onset seizures or status epilepticus in a large cohort of people hospitalized during the acute phase of COVID 19 infection despite a substantial proportion having risk factors for acute symptomatic seizures. This is useful information, given the prior lack of knowledge about seizure risk during the acute phase of infection.

No individual in this cohort had a history of epilepsy prior to hospital admission. To date, there is not much information available on people with epilepsy during the COVID-19 crisis. There is one report of epilepsy in a case COVID-19 from Wuhan.[8] As information is limited, it is not possible to establish whether this was a patient who had a history of epilepsy or whether the patient presented acute seizures. There is at this time little if any evidence indicating that people with epilepsy are at an increased risk of COVID-19 infection. A major challenge for people with epilepsy in this outbreak is nonadherence with the prescribed antiseizure medication, which was seen during the in SARS endemic in 2003.[9]

TABLE 2 Chemical Pathology results in people with coronavirus disease 2019

	Median (IQR)		
	All, N = 304	**Mild, n = 196**	**Severe, n = 108**
Serum glucose, mmol·L^{-1}	5.8 (5.0-7.3)	5.6 (5.1-7.04)	6.1 (5.2-8.4)
Serum sodium, mmol·L^{-1}	140.1 (137.7-142.2)	140.1 (138.1-142.2)	139.3 (137.2-142.3)
Serum potassium, mmol·L^{-1}	4.0 (3.7-4.4)	4.0 (3.7-4.4)	4.0 (3.6-4.4)
Serum calcium, mmol·L^{-1}	2.2 (2.1-2.3)	2.3 (2.2-2.3)	2.1 (2.0-2.2)
Blood urea nitrogen, mmol·L^{-1}	3.9 (3.3-5.1)	3.8 (3.2-4.7)	4.7 (3.4-6.5)
Creatinine, μmol·L^{-1}	67.4 (55.0-78.1)	68.0 (56.0-77.9)	67.1 (54.9-80.2)

Abbreviation: IQR, interquartile range.

This indicates the need to ensure the availability of supplies of medications and to advocate patients' self-management. Possible strategies for coping could also include online consultations and telemedicine networks.

Although many neurological and systemic disorders regarded as potential triggers[7] of acute symptomatic seizures were identified in this cohort, seizures and status were not seen. Stroke is one such risk factor. The risk of developing acute symptomatic seizures after stroke ranges from 3.1% to 33%.[10] Acute cerebrovascular disease is considered a major cause of seizure and status epilepticus. An earlier study from Hubei[8,11] also reported six people with COVID-19 who had acute cerebrovascular disease without seizure. Infection of the CNS can also give rise to seizures. Although there is limited evidence of the presence of the SARS-CoV-2 in the cerebrospinal fluid (CSF), the co-occurrence of tubercular meningitis[12] had been reported, with no seizure or status observed. To determine whether COVID-19 can cause direct CNS insults requires further follow-up. In the earlier outbreaks of another coronavirus, a generalized convulsion with a positive reverse transcriptase polymerase chain reaction for SARS-CoV in CSF was reported, which could have been a coincidence.[13]

Disturbances of homeostasis may lead to acute symptomatic seizures. Hypoxia, the most common complication in our cohort, may trigger anoxic encephalopathy, particularly in refractory hypoxia. Electrolyte disturbances as seen in COVID-19 are considered to be potential causes of acute symptomatic seizure.[14] The severity and speed of such disturbances may affect onset of seizures, so these parameters should be carefully monitored.

The cytokine storm syndromes[15] behind severe infection may cause the production of inflammatory cytokines systemically, with the consequence of acute toxic encephalopathies. Although sepsis is a common cause of encephalopathy in intensive care medicine,[16] hypoxia appears far more often than sepsis in COVID-19. There was also a high rate of septic shock in the COVID-19 population, varying from 4%[17] to 20% in earlier studies in Hubei.[5,14]

Certain antibiotics have been associated with symptomatic seizure.[18] Antibiotics were used in a large number of people in our cohort without problems, but the most used antibiotics in the cohort were of low or moderate risk. Clinicians should keep this seizure risk in mind when prescribing antibiotics, especially for people with renal dysfunction.[18]

Our study has several limitations. First, as a cross-sectional study, we only have data from the acute phase of the disease. A follow-up study is underway to evaluate longitudinal seizure outcomes. Second, the retrospective study design meant that we could not collect data on all relevant variables; for example, EEG was not recorded, so subclinical seizures could have been missed. As all health care costs of COVID-19 treatment are covered by the government, all those suspected of infection are screened. This may assure the objectivity and reliability of study materials, and it will allow for a future follow-up study.

Our analysis suggests that COVID-19 poses minimal risk for seizures during the acute illness, although a significant proportion of severely ill individuals have risk factors that may increase the propensity to experience seizures. These risk factors should be promptly addressed to minimize the risk of developing seizures. Prospective long-term studies must be done to determine whether people who have suffered from COVID-19 have an increased risk for developing seizures or epilepsy in subsequent months or years as a consequence of their illness.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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