



Is a First Epileptic Seizure a COVID-19 Finding?

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Abstract

Objective: It is known that coronavirus disease-2019 (COVID-19) can manifest with neurologic findings in addition to respiratory symptoms. This study aimed to investigate the rate of patients with COVID-19 who presented with a first epileptic seizure as a neurologic finding.

Methods: The study included patients who presented to our hospital's emergency department reporting a seizure between March 11 and May 30, 2020. Of 90 patients, 32 (35.5%) presented first seizures. The patients' demographic characteristics, medical history, complications, the presence of risk factors relating to their treatment and seizures, laboratory findings, clinical properties, and imaging findings were recorded.

Results: Of the patients with first seizures, 19 were men, and 13 were women. Their mean age was 49.5 (minimum: 18, maximum: 89) years. The percentage of patients with COVID-19 who presented with a first seizure was 31.2% (n=10). A risk factor was identified in 8 (80%) patients who presented with a first seizure, and no risk factor was found in 2 (20%) patients. In all patients, COVID-19 was diagnosed following a seizure presentation. The intensive care requirement rate was 30% (n=3), and 2 (20%) patients died.

Conclusion: The rate of COVID-19 among patients presenting with a first seizure is high. It would be appropriate to consider patients arriving with a seizure without any other respiratory or systemic issues as being related to COVID-19 and plan the necessary analyses and treatment.

Keywords: COVID-19, SARS-CoV-2, first seizure, epilepsy, neurologic symptom

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a novel infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which first emerged in Wuhan, China, in late 2019. It spread around the globe, causing the World Health Organization to announce a pandemic (1). In addition to systemic and respiratory symptoms, it has been documented that 36.4% (78/214) of patients with COVID-19 developed neurologic symptoms, including headaches, impaired consciousness, and paresthesia (2). Various studies demonstrated that coronaviruses were neurotrophic and neuroinvasive (3). The probability of developing neurologic symptoms is higher in severely affected patients than in those with mild or moderate diseases (2).

The reported symptoms of COVID-19 are primarily related to the respiratory or gastrointestinal systems, and seizures remain

in the background (4). As the pandemic developed, it has been found that the disease may manifest without respiratory problems through other systemic findings. Although it has not been reported that the ratio of neurologic comorbidity is greater for COVID-19 than other respiratory viral infectious diseases, prospective data will yield more definite results. In addition to causes such as high temperature being capable of giving rise to seizures in patients with epilepsy infected by COVID-19 or any other infectious disease, seizures may also be triggered by direct virus invasion or through cytokines (5). The effects of COVID-19 on patients with epilepsy or the prevalence of newly emerging epilepsy is still uncertain.

This study aimed to investigate the rate of COVID-19 diagnoses in patients presenting to the emergency department (ED) with primary symptoms of seizures and demonstrate whether seizures might be considered a first finding of COVID-19.



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Cite this article as: Üstün Özek S, Kalkan A, Ünal E, Üçler S. Is a First Epileptic Seizure a COVID-19 Finding? Eur Arch Med Res 2021;37(3):173-7

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European Archives of Medical Research published by Galenos Publishing House.

Received: 29.12.2020

Accepted: 18.03.2021

METHODS

This study is a single-center, retrospective, observational study. The University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital is a tertiary care multidisciplinary hospital where 500,000 to 550,000 patients are treated annually. In our hospital, around 400 patients present daily to our ED pandemic area with suspected COVID-19 infection, and about 40 patients are diagnosed with COVID-19. The study included 90 patients aged over 18 years who presented to our hospital's ED with symptoms of seizure between March 11 and May 30, 2020. For the study, approval was obtained from the University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital Ethics Board (no: 48670771-514.10) and the Ministry of Health. Informed consent was obtained from all patients. The study was compliant with the Helsinki Declaration.

Patients

Patients aged over 18 years who presented to the ED with symptoms of seizure were evaluated. Patients aged under 18 years and those who declined to participate in the study were excluded. The electronic medical records of all recorded cases were registered in the case reporting form. The patients' demographic properties, medical history, complications, and the presence of risk factors for treatments and seizures were obtained. Clinical, laboratory, and imaging findings were evaluated. The following risk factors were considered: Acute cerebrovascular disease, head trauma, central nervous system infection, and metabolic disorder.

Statistical Analysis

The Number Cruncher Statistical System Statistical Software (NCS Statistical Software Inc., Utah, USA) was used for statistical analysis. To evaluate the data from the study, descriptive statistical methods (mean, standard deviation, median, frequency, and ratio) were used.

RESULTS

The study included 90 patients who presented to the ED with a seizure. Of them, 5 (5.5%) who had an early seizure diagnosis were non-epileptic: 3 syncopes, 1 dystonic spasm related to the adverse effects of medication, and 1 seizure secondary to hypocalcemia. During this process, the rate of patients with known epilepsy who presented to the ED among all cases of epilepsy was 62.35% (n=53), and 35.5% (n=32) presented with a first seizure. Of the first seizure cases, there were 19 men and 13 women. Their mean age was 49.5 (minimum: 18, maximum: 89) years. Of the 32 patients, 14 had definitively

eliminated COVID-19, 8 had suspected COVID-19, and 10 were COVID-19-positive (Figure 1). Of the 10 patients diagnosed with COVID-19, 5 were women and 5 men, with a mean age of 56.6 ± 13.48 years.

Of the 10 patients with COVID-19, 6 had focal or secondary generalized and 4 generalized tonic-clonic (GTC). Three patients with focal seizures were sequela of cerebrovascular accidents. Table 1 shows the patients' demographic characteristics, computed tomography scans, and concomitant illnesses. Because the seizures of two patients with focal seizures and one with GTC seizures could not be controlled, they were transferred to the intensive care unit (ICU). All patients were started on levetiracetam as treatment.

Ten patients who presented with a first seizure were diagnosed with COVID-19. Among the first seizures, the rate of patients with COVID-19 from among all seizure symptoms presenting to the ED was 11.7% (n=10). Their rate among patients with first seizures was 31.25% (10/32). Of the patients evaluated with a first seizure and diagnosed with COVID-19, one was a healthy 34-year-old woman who had given birth 1 week ago, one was a 51-year-old man with no features other than a COVID-19 infection, and eight had a seizure-triggering risk factor. The most frequently encountered risk factor was a previous cerebrovascular disease. No severe electrolyte abnormality was observed in any of the patients. There were two patients with chronic kidney dysfunction, and significant increases were found in their creatinine levels.

All patients were diagnosed following the COVID-19 diagnosis and treatment protocol. A polymerase chain reaction (PCR) test was performed on each patient using a nasopharyngeal swab sample. Radiologic appearance compatible with viral pneumonia was found in all patients, and PCR positivity was found in 3 (30%). Lymphopenia was present in 3 (30%) patients,

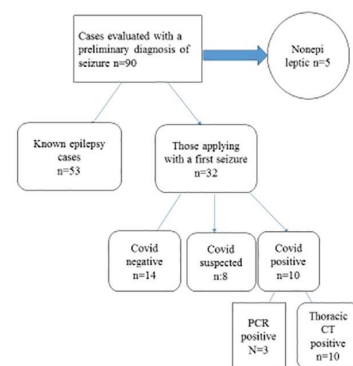


Figure 1. Study table

PCR: Polymerase chain reaction, CT: Computed tomography

high D-dimer levels in 6 (60%), and high C-reactive protein (CRP) levels in 9 (90%; Table 2). Only one patient reported shortness of breath and palpitations.

The mortality rate was also evaluated. A 78-year-old woman who presented with severe COVID-19 findings and had been transferred to the ICU died on the 22nd day. However, she had accompanying comorbid factors such as chronic renal insufficiency, congestive heart failure, diabetes mellitus, hypothyroid, and asthma. Her last CRP and D-dimer values were 262.51 and 1892, respectively. Another 57-year-old woman who had colon carcinoma also died after being discharged.

DISCUSSION

In our study, 10 patients were diagnosed with COVID-19 after

performing analyses following a first seizure presentation to the ED. We found that accompanying seizure-triggering comorbidities existed in eight patients, in which a combination of a first seizure and COVID-19 was present. In their study, Lu et al. (6) emphasized that there were seizure-triggering predisposing factors. In two patients with no risk factors, the seizures were considered symptomatic, and treatment was started. These seizures may be a finding brought about by the infection, but they may also be coincidental. There are insufficient data on whether COVID-19 per se is a risk factor. Although there were no risk factors that would lower the seizure threshold in most cases, no seizure was identified previously in any of these cases, who, accordingly, had not received any treatment. During the pandemic, it is important to follow up on patients who present with a first

Table 1. Demographic properties of cases arriving with COVID-19 and a first seizure

Case no.	Gender	Age (years)	Seizure type	History	PCR	Thoracic CT	Brain CT
1	Male	51	GTC	No	Negative	Yes	Normal
2	Female	89	Focal	Sequela CVA	Positive	Yes	Left frontoparietal ischemia
3	Female	64	Focal	Sequela CVA	Negative (3 times)	Yes	Left thalamic infarction
4	Male	37	Focal	Sequela CVA	Negative	Yes	Bilateral cerebral atrofia
5	Female	78	Focal	CHF, CRI, DM hypothyroidism	Negative	Yes	Normal
6	Male	57	GTC	Alcohol abuse	Negative	Yes	Normal
7	Male	37	GTC	HIV, CRI	Positive	Yes	Normal
8	Male	62	Focal	Subacute ischemia	Negative	Yes	Right frontal ischemia
9	Female	34	GTC	No	Negative	Yes	Normal
10	Female	57	Focal	Colon cancer	Positive	Yes	Normal

COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction, CHF: Chronic congestive heart failure, CRI: Chronic renal failure, DM: Diabetes mellitus, GTC: Generalized tonic-clonic, HIV: Human immunodeficiency virus, CVA: Cerebrovascular accident, CT: Computed tomography

Table 2. Hematological values

Case no.	WBC	Neutrophil	Lymphocyte	Hb	HCT	Plt	D-dimer	CRP
Normal values	3800-10,000/uL	1780-5380/uL	1320-3570/uL	130-175 g/L	40-52%	150.000-400.000/uL	80-500 ug/L	<5 mg/L
1	8100	6700	1520	121	36.2	310.000	420	5
2	10,630	8480	990	94	30.1	384.000	1320	96.43
3	6730	4370	2230	74	22.9	356.000	1970	26
4	6070	4000	1560	117	35.8	251.000	615	54.24
5	14,300	12,190	1840	87	27.4	280.000	892	218
6	11,430	8150	2120	114	34.2	304.000	495	23.24
7	8160	6990	920	82	24.5	6000	996	21
8	11,600	7500	2780	141	42.9	181.000	500	6.85
9	8320	6500	2100	118	37.4	302.000	430	15
10	2300	1930	230	84	24.7	89.000	548	71.45

WBC: White blood cell, Hb: Hemoglobin, HCT: Hematocrit, Plt: Platelet, CRP: C-reactive protein

seizure concerning COVID-19 and take early precautions (5-7).

Among human coronaviruses, HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are common and endemic in the world. They are the causative agents of seasonal upper respiratory tract infections such as rhinitis, pharyngitis, and otitis. Sometimes, they can cause bronchitis, bronchiolitis, and asthma attacks. SARS-CoV and the Middle East respiratory syndrome (MERS-CoV) cause more serious respiratory symptoms. In addition to the respiratory symptoms of endemic coronaviruses (MERS-CoV and SARS-CoV), neurologic clinical pictures such as meningitis, encephalitis, Guillain-Barre syndrome, necrotizing encephalopathy, and myelitis are reported. The agent was present in the cerebrospinal fluid (CSF) of patients, and histopathologically, cranial involvements such as viral particles, cerebral edema, ischemic pad, demyelination, and mononuclear cell infiltration were proven in the autopsies of some mortal cases (8,9). The pathobiology of these neuroinvasive viruses is not yet fully known. Accordingly, it is important to study the impacts of CoV infections on the nervous system (10).

Angiotensin-converting enzyme 2 is found on the surfaces of glial cells and neurons, and the CNS may be a potential target of SARS-CoV-2 through this receptor (11). The accumulation of inflammatory markers may cause local cortical damage related to the COVID-19 infection, which triggers seizures (12). Patients with COVID-19 may present with fever, hypoxia, multiple organ failure, and serious metabolic and electrolytic irregularities; therefore, subclinical acute symptomatic seizures are expected in such patients. In some patients, seizures develop as a result of hypoxia, metabolic disorders, organ failure, and even cerebral damage, which may also occur in COVID-19 patients. In addition to data indicating that COVID-19 increases cerebral thrombosis, there are also papers suggesting that it triggers cerebral edema, which, in turn, triggers seizures (13). A study indicated that the cumulative risks of COVID-19 were high in patients diagnosed with epilepsy. In hospitalizations, epilepsy was related to mortality, and these cases were accompanied by high blood pressure (14).

Mao et al. (2) evaluated the neurologic involvement of 214 inpatients and found a neurologic involvement rate of 25%. The rate of epilepsy was 0.5% among these neurologic findings. An electroencephalography (EEG) recording was not made in this study, and the virus was not isolated from the CSF (2). A COVID-19 diagnosis was verified in a patient who presented with meningoencephalitis findings, but the virus could not be isolated from the CSF (15). CSF PCR studies are important to

demonstrate neurologic involvement rates accurately. Also, there is a meningitis/encephalitis report relating to SARS-CoV-2. SARS-CoV-2 RNA was found in the CSF, but a nasopharyngeal swab yielded a PCR-negative result (16). In a case report, a 78-year-old female patient presented initially for focal seizures, and then, a SARS-CoV-2 infection was found (17).

CSF positive and negative cases are found in the literature. This, in turn, supports the thought that seizure-triggering mechanisms may be different. A limitation to our cases was that we were unable to take EEGs or perform PCR on the CSF due to the pandemic conditions. We could have presented more valuable data and stronger interpretations if we were able to perform isolations from the CSF of COVID-19 positive patients with no risk factors (18).

In the literature, a patient who presented to the ED reporting cough, fever, and headache was intubated 2 days afterward and was extubated in the ICU after 10 days. However, a non-convulsive status epilepticus (NCSE) diagnosis was given when mental fog continued, despite normal magnetic resonance and CSF examination results. The patient was diagnosed with NCSE and treated with levetiracetam and clobazam (19). In our clinical observation, we provided symptomatic treatment to changes in mental state and agitation, especially inpatients, but we were unable to verify the NCSE distinctive diagnosis in these patients. Even if we had such cases, we were unable to identify them; the cases we examined consisted of epileptic cases with a motor component.

When planning treatment, the interaction of medication used for COVID-19 with antiepileptic medication should be considered. In these patients, levetiracetam treatment was started by considering the drug's adverse effects and interactions. Provided that care is exercised on renal functions, levetiracetam is among the recommended drugs. It is necessary to perform dose adjustment in the event of renal insufficiency. Carbamazepine, lacosamide, phenytoin, and rufinamide may cause cardiac transmission abnormalities (20). It is logical to continue for approximately 6 weeks until the COVID-19 tests yield negative results and then to discontinue them quickly over 1-2 weeks. We will be able to determine the presence of seizures or lack thereof in patients in whom we started treatment only after a long-term follow-up, but for now, we have planned that they should receive antiepileptics for at least 6 months. ICU treatment was necessary for 3 of 10 patients because their seizures could not be controlled.

Study Limitations

The limitations of our study were the low number of patients, the extraordinary circumstances caused by the pandemic, and the fact that CSF examinations and EEG scans were not performed to protect the healthcare personnel on duty. We included only seizures with a motor component in the study. We were unable to diagnose any NCSE, and we probably overlooked it clinically.

CONCLUSION

In conclusion, COVID-19 may rarely present with a seizure, sometimes with no other underlying causes. Prospective long-term studies must be performed to identify the risk of patients with COVID-19 developing seizures or epilepsy in later months or years as a result of their disease. Also, post-mortem autopsy studies will be valuable to identify pathogenesis and involvement rates.

Ethics

Ethics Committee Approval: For the study, approval was obtained from the University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital Ethics Board (no: 48670771-514.10) and the Ministry of Health.

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ü.Ö., A.K., E.Ü., S.Ü., Concept: S.Ü.Ö., S.Ü., Design: S.Ü.Ö., Data Collection or Processing: S.Ü.Ö., A.K., E.Ü., Analysis or Interpretation: S.Ü.Ö., A.K., E.Ü., Literature Search: S.Ü.Ö., Writing: S.Ü.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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