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COVID-19

EEG changes in intensive care patients diagnosed with COVID-19: a prospective clinical study

Omer Karadas[1] · Bilgin Ozturk[1] · Ali Rıza Sonkaya[1] · Ulkuhan Duzgun[1] · Javid Shafiyev[1] · Mehmet Burak Eskin[2] · Tehlil Bostan[1] · Akcay Ovunc Ozon[3]

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Abstract

Introduction Coronavirus disease (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was declared a pandemic on March 11th, 2020, by the World Health Organization (WHO). There has been a substantial increase in the epileptic seizures and status epilepticus reported in the pandemic period. In this context, it is aimed with this study to identify the electroencephalography (EEG) features of patients admitted to the intensive care unit with the diagnosis of COVID-19 and to look for any specific patterns in these features.

Material and method The material of this study primarily comprised the neurological evaluations and continuous EEG recordings of 87 intensive care patients who were diagnosed with COVID-19. In addition, demographic and clinical features and comorbid conditions of these patients were also analyzed, and any correlation thereof was investigated.

Results The EEG data of 87 patients who were diagnosed with COVID-19 and were followed up in the intensive care unit were recorded and then analyzed. Abnormal EEG findings were detected in 93.1% ($n = 81$) of the patients, which were found to increase significantly with age ($p < 0.001$). The mean age of patients with specific epileptiform abnormalities on EEG was found to be significantly higher than those with non-specific abnormalities. Epileptiform discharges were seen in 37.9% ($n = 33$) of the patients. Nonconvulsive status epilepticus (NCSE) was detected in 5.7% of the patients, and antiepileptic drugs were started in 25 (28.7%) of the patients.

Discussion Statistically significant EEG changes were observed in the continuous EEGs of the patients followed up in the intensive care unit due to COVID-19 infection. However, further studies are needed to associate the EEG changes observed in the COVID-19 patients with the epileptogenesis of COVID-19 infection.

Keywords Coronavirus · Electroencephalography · Epileptic seizures · Status epilepticus

Introduction

COVID-19 mainly involves the respiratory system; nevertheless, it has been observed that it involves other systems as well. There have been increasing evidences for the effect of COVID-19 on one of these systems that is the central nervous system. Disorders of consciousness which affect different levels of consciousness have been reported in COVID-19 patients [1, 2], including epileptic seizures. Hence, it is necessary to better understand the neurological symptoms of COVID-19 and the related disorders of consciousness [1–3]. The effect of COVID-19 infection on the central nervous system can take place at very different levels. Accordingly, COVID-19 patients were observed to develop encephalopathy, slow cognitive activity, impaired concentration, memory impairment, sleep disorders, and personality changes. Additionally, encephalopathy, clinical seizures, and subclinical seizures have also been reported in COVID-19 patients. Electroencephalography (EEG) is an important neurological diagnostic test that is widely used to diagnose such conditions and guide the relevant treatment decisions [1–4].

✉ Javid Shafiyev
shafiyevjavid13@gmail.com

1 Department of Neurology, Gülhane School of Medicine, University of Health Science, Ankara 06010, Turkey

2 Department of Anesthesia, Gülhane School of Medicine, University of Health Science, Ankara, Turkey

3 Department of Neurology, Liv Hospital, Ankara, Turkey

Detection of nonconvulsive seizures and nonconvulsive status epilepticus (NCSE) in COVID-19 patients, especially in patients treated in intensive care, and particularly in the absence of other symptoms but presence of encephalopathy and nonspecific clinical findings as well as in case of coma is of critical importance, since the said conditions worsen the prognosis [4, 5]. EEG can be used to evaluate encephalopathy, clinical seizures, subclinical seizures, and epileptogenicity in the presence of nonspecific findings in COVID-19 patients. EEG, which is used to predict the changes in consciousness, may provide a window of opportunity for effective intervention in the early period in cases with poor prognosis [4–7]. In this context, it is important to provide continuous EEG monitoring during the COVID-19 pandemic, as it provides detection of subclinical seizures and reveals the patients that are at risk within the epilepsy spectrum.

The mechanisms that cause seizures are not yet fully understood. Nevertheless, development of certain disturbances in the membrane potentials and firing patterns of cortical neurons have been suggested as possible mechanisms. Acute metabolic disorders such as hypoglycemia, hyperglycemia, electrolyte imbalance, infections, acute neuronal damage, stroke, head injury, mitochondrial dysfunction, hypoxia, and fever may also cause seizures by affecting the nervous system [7, 8].

COVID-19 can affect the central nervous system both directly and indirectly. Seizures, stroke, electrolyte imbalance, increased oxidative stress, and mitochondrial dysfunction may occur following the entry of pro-inflammatory cytokines into the central nervous system [8]. In parallel, in a retrospective study conducted by Pellinen et al., the analysis of the continuous EEG findings of the 111 COVID-19 patients indicated a high rate of nonspecific EEG abnormalities, whereas the seizures and epileptiform activities were less frequent in EEG [4]. In another study, in which both continuous and routine EEG of 22 patients were examined retrospectively, a higher frequency of epileptiform anomalies was found on EEG of COVID-19 patients with encephalopathy as compared to the control subjects, and electroencephalographic seizures were observed in the COVID-19 patients [9]. Studies on EEG findings of COVID-19 patients are generally based on retrospective data analysis.

To the best of knowledge of the authors of this study, this study is the first study to date, in which prospective clinical data were collected by a neurology team serving in a routine pandemic clinic. The primary objective of the study is to investigate the continuous EEG changes arising from the disorders of consciousness that occur in combination with COVID-19 infection and to determine the specific EEG findings in COVID-19 patients receiving intensive care treatment, whereas the secondary objective of the study is to assess the relation between the COVID-19-related EEG changes with the clinical status.

Material and method

The study group included 87 COVID-19 patients, who were admitted to the COVID-19 intensive care unit, a neurology clinic managed by an epileptologist converted to a routine COVID-19 clinic during the pandemic period, and diagnosed with a change in consciousness therein. Adult patients, that is, patients over 18 years of age, who tested positive for COVID-19 based on the SARS-CoV-2 real-time reverse transcription polymerase chain reaction (rRT-PCR) test in accordance with the World Health Organization (WHO) guidelines were included in the study, whereas patients with a malignancy, severe metabolic syndrome, uncontrolled hypertension, uncontrolled diabetes, chronic liver failure, chronic renal failure, decompensated congestive heart failure, current alcohol/drug use, and major psychiatric disorders were excluded from the study. The 87 COVID-19 patients, who met the above criteria, were performed continuous EEG and followed up in the intensive care unit.

This prospective randomized clinical study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Local Ethics Committee (Protocol No: 2020–197). All COVID-19 patients were diagnosed and managed with the same treatment protocol approved by the Ministry of Health in accordance with the WHO Guidelines. Neurologists and epileptologists examined all the COVID-19 patients included in the study as to whether they had altered consciousness. Subsequently, comorbid conditions of the patients, who were determined to have altered consciousness, were recorded. Nasopharyngeal and nasal swab samples of the patients were tested using the rRT-PCR test for COVID-19. All patients were performed thoracic computed tomography (CT) and routine laboratory tests (complete blood cell count, blood chemical analysis) as standard procedure.

Data collection

Patients over the age of 18, who were transferred to the intensive care unit with the diagnosis of COVID-19 and had a change in consciousness, were included in the study. Continuous EEG of patients who had altered consciousness was taken during the first period of admission to the intensive care unit and before they needed mechanical ventilation. A 24-h continuous EEG was administered to all patients, while they had their personal protective equipment on. EEG recordings were made using 21 electrodes in all patients. EEGs were performed by the same experienced epileptologist and technician for all patients.

EEG findings were evaluated according to the International League Against Epilepsy (ILAE) criteria. Patients, whose EEGs were without any abnormalities, were coded as normal, whereas patients with abnormal EEG findings were further categorized into 2 groups as the group of patients with specific epileptiform activities and the group of patients with nonspecific EEG abnormalities.

Salzburg Consensus criteria were used to define nonconvulsive seizures. Patients who met the diagnostic criteria were treated accordingly, and the treatment methods administered were recorded. The demographic and clinical variables of all patients were analyzed. In this context, patients were assessed in terms of metabolic disorders, neurological complications such as epilepsy stroke, and risk factors such as hypertension, diabetes, coronary artery disease, liver failure, and renal failure. The relationships between continuous EEG changes detected in COVID-19 intensive care patients and age, gender, comorbidities, and neurological complications were investigated.

Patients with abnormal EEG findings were further categorized into 2 groups as the group of patients with specific epileptiform abnormalities and the group of patients with nonspecific EEG abnormalities. Specific epileptiform abnormalities featured sharp, spike, multi-spike, and ictal discharges (with sharp, spike, and rhythmic theta/delta activities), whereas nonspecific EEG abnormalities featured focal and generalized slow waves and contained several activities arising from various etiologies. Consequentially, specific EEG abnormalities were found to be more frequent in older patients with chronic disease. In cases where the potential risks were high in terms of recurrence of epileptic seizures, such as in patients diagnosed with epilepsy, patients who had epileptiform activity as detected in EEG, and patients with findings compatible with NCSE in EEG and intracranial lesion, anti-epileptic medication was started in such patients who had epileptic seizures.

Statistical analysis

In the analysis of descriptive statistical data, continuous data were expressed as mean ± standard deviation values, and discrete data were expressed in numbers (n) and percentages (%). Chi-squared test, a non-parametric test, was used to compare the categorical data between the groups, and student's *t* test, a parametric test, was used to compare the data that were found to conform to normal distribution. Pearson's correlation coefficient was used to analyze the correlation of the data. Probabilty (p) values of < 0.05 were deemed to indicate statistical significance. SPSS 22.0 (Statistical Package for Social Sciences for Windows, version 22.0. Armonk, NY: IBM Corp.) software package was used to conduct the statistical analyses of the research data.

Results

The mean age of the 87 patients included in the study, of whom 48 (55.2%) were male, was calculated as 62.57 ± 14.15 (min.: 29, max.: 89) years. There was no statistically significant difference between the gender groups in terms of age ($p = 0.921$) (Table 1). Fifty-eight (66.7%) patients were found to have one or more comorbid chronic diseases. The most commonly observed comorbidity in the patients included in the study was hypertension, which was observed in 51 (58.6%) of the patients, followed by diabetes, which was observed in 23 (26.4%) of the patients and coronary artery disease, which was observed in 17 (19.5%) of the patients (Fig. 1). Abnormal EEG findings were detected in 93.1% ($n = 81$) of the

Table 1 Demographic characteristics of the patients

		Mean ± SD*	Median	Overall range	*p*
Age (years)	Female	62.74 ± 13. 50	65.00	35–89	**0.921****
	Male	62.44 ± 14. 79	65.50	29–87	
	Total	62.57 ± 14. 15	66.00	29–89	
		n (%)			
Gender	Female	39 (44.8)			
	Male	48 (55.2)			
EEG	Normal	6 (6.9)			
	Abnormal	81 (93.1)			
EEG abnormality	Specific	33 (37.9)			
	Nonspecific	48 (55.2)			
Clinical seizure		13 (14.9)			
Antiepileptic use		25 (28.7)			

*Standard deviation, ***p* (probability) values obtained from the Student's *t* test, ****EEG* electroencephalography

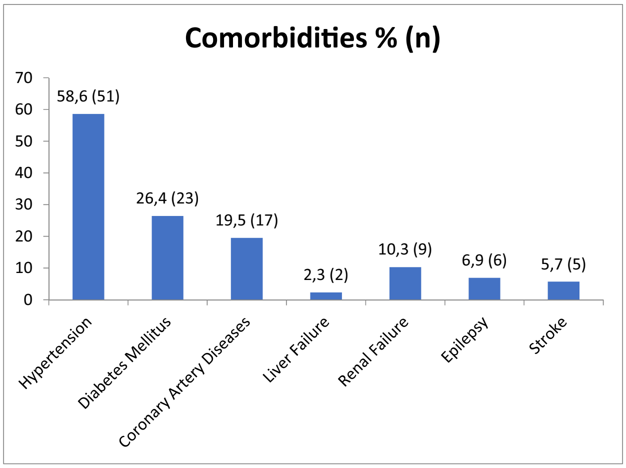

Fig. 1 Comorbidities

patients, which were found to increase significantly with age ($p < 0.001$). Abnormal EEG findings were found in all 58 patients with chronic disease, who accounted for 66.7% of all patients included in the study ($p < 0.001$). On the other hand, as for the abnormal EEG findings in the 29 patients without chronic disease, who accounted for 33.3% of all patients included in the study, abnormal EEG findings were observed in 23 of these patients ($p < 0.001$). Thirteen (14.9%) of the patients had a history of clinical seizures.

No statistically significant difference was found between the groups in terms of clinical seizure history, epilepsy history, presence of stroke, and EEG involvement (Table 2).

The distribution of the abnormal EEG findings revealed that the most common abnormal EEG finding observed in patients was the generalized slow wave, which was observed in 76 (87.4%) of the patients, followed by specific EEG abnormalities, which were observed in 33 (37.9%) of the patients. Additionally, NCSE was detected in 5.7% of the patients. Antiepileptic drug treatments were started in 25 (28.7%) of the patients. The distribution of abnormal EEG findings of the patients is shown in Fig. 2.

Of the 33 patients, who had specific EEG abnormalities, 29 (87.9%) were determined to have a chronic disease was present, as compared to 60.4% of those with nonspecific EEG abnormalities ($p = 0.007$). The presence of specific EEG abnormalities was statistically significantly higher in those with a history of epilepsy ($p < 0.002$), a history of stroke ($p = 0.005$), and a history of clinical seizures ($p < 0.001$) (Table 3).

Mean age of the patients with specific EEG abnormalities was calculated as 68.12 ± 10.65 years, indicating a statistically significant increase as compared to 61.94 ± 13.45 years, that is the mean age of the patients with nonspecific EEG abnormalities ($p = 0.030$).

Table 2 Difference between the groups in terms of different parameters

Parameters		EEG involvement		p^*
		Normal (*n*, %)	Abnormal (*n*, %)	
Gender	Female	3 3.4%	36 41.4%	0.792
	Male	3 3.4%	45 51.7%	
Chronic disease(s)	No	6 6.9%	23 26.4%	**< 0.001**
	Yes	0 0.0%	58 66.7%	
Epilepsy	No	6 6.9%	75 86.2%	0.490
	Yes	0 0.0%	6 6.9%	
Stroke	No	6 6.9%	76 87.4%	0.531
	Yes	0 0.0%	5 5.7%	
Clinical seizure	No	6 6.9%	68 78.2%	0.287
	Yes	0 0.0%	13 14.9%	

[*] *p* (probability) values obtained from the Pearson's chi-squared test

The results of the correlation analysis, which was performed to determine the level and direction of the relationship between the variables, indicated moderately significant relationships in the positive direction between age and the presence of chronic disease ($r = 0.394$, $p < 0.001$), between age and EEG involvement ($r = 0.385$, $p < 0.001$), and between the presence of chronic disease and EEG involvement ($r = 0.299$, $p = 0.007$). The results of the correlation analysis in respect of other variables are shown in Table 4.

Discussion

This prospective study marks one of the very few studies, in which continuous EEG findings of 87 COVID-19 patients, who needed intensive care due to a disorder of consciousness, were evaluated. It was determined as a result of this study that 93.1% of the patients included in the study had abnormal EEG findings and that these abnormal EEG findings increased significantly with age. The most commonly observed EEG abnormality was the generalized slow wave. Specific epileptiform abnormalities were observed in 37.9% of the patients. The number of patients with clinical seizures and a history of

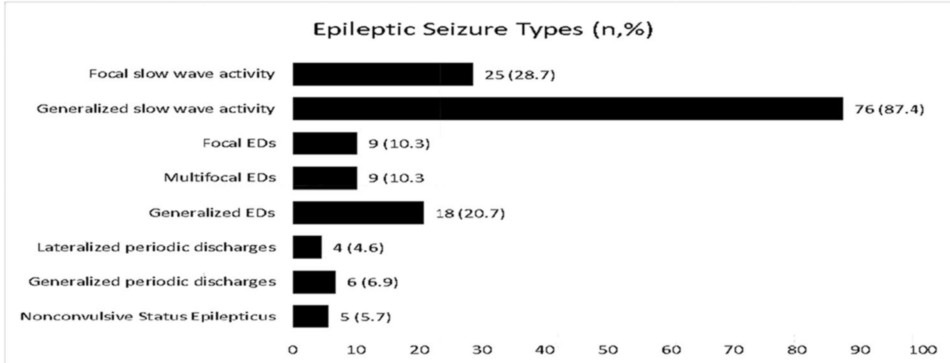

Fig. 2 Continuous EEG findings. EDs: epileptiform discharges

Table 3 Distribution of specific and nonspecific EEG findings by neurological symptoms

EEG* abnormality		No *n* (%)	Yes *n* (%)	*p***
Clinical seizure	Specific (*n* = 33)	20 (60.6)	13 (39,4)	**< 0.001**
	Nonspecific (*n* = 48)	48 (100.0)	-	
Epilepsy	Specific (*n* = 33)	27 (81.8)	6 (18,2)	**0.002**
	Nonspecific (*n* = 48)	48 (100.0)	-	
Stroke	Specific (*n* = 33)	28 (84.8)	5 (15,2)	**0.005**
	Nonspecific (*n* = 48)	48 (100.0)	-	
Chronic disease(s)	Specific (*n* = 33)	4 (4.9)	29 (35,8)	**0.007**
	Nonspecific (*n* = 48)	19 (23.5)	29 (35,8)	

**EEG* electroencephalography, ***p* (probability) values obtained from the Pearson's chi-squared test

Table 4 Correlation data

Correlations		*r*	*p***
EEG* abnormality (specific and nonspecific)	Gender	0.067	0.550
	Age	− 0.241	**0.030**
	Chronic disease(s)	− 0,299	**0.007**
	Clinical seizure	− 0,527	**< 0.001**
	Epilepsy	− 0,341**	**0.002**
	Stroke	− 0,309	**0.005**

**EEG* electroencephalography, ***p* (probability) values obtained from the Pearson's chi-squared test

epilepsy, who were found to have specific epileptiform abnormalities, was significantly higher than those without clinical seizures and/or a history of epilepsy. Four of the 13 (14.9%) patients who had clinical seizures also had a history of epilepsy. 87.9% of the patients with a specific epileptiform abnormality in EEG had a chronic disease. The mean age of these patients was significantly higher than those with non-specific EEG abnormalities. 5.7% of the patients was diagnosed with NCSE by EEG. The presence of chronic comorbidities was more prominent in patients with epileptiform activity, and the mean age of these patients was higher than those of the patients with nonspecific EEG abnormalities.

COVID-19 is primarily a respiratory tract infection. However, it was demonstrated in recently held studies that it is a disease also with neuroinvasive features, affecting the central nervous system [1]. Taking into consideration that COVID-19 is a new disease, the long-term effects of COVID-19 on the central nervous system could not be elucidated just yet. Nevertheless, it is known that COVID-19 can affect the central nervous system both directly and indirectly. The most common neurological symptoms associated with COVID-19 are headache, muscle pain, changes in consciousness, dizziness, cerebrovascular diseases, sleep disturbance, smell, and taste disorders [1, 2]. The changes in consciousness are among the most important neurological symptoms associated with COVID-19. Whether these changes in consciousness are related to epileptic seizures is yet to be clarified. In the relevant studies available in the literature, changes in consciousness were reported in 9.6% of the COVID-19 patients [1, 7]. In a study, in which 304 patients were evaluated retrospectively, EEG recordings were deemed unnecessary, since there was no case with clinical seizures and no risk factor for epilepsy [10].

Additionally, in a study conducted in New York, USA, the continuous EEGs of 111 COVID-19 patients, also including the patients receiving treatment in the intensive care unit neurology service and emergency service unit, were examined retrospectively [4]. In the said study, the clinical conditions and laboratory data of the patients were reported to be very different from one another. EEG revealed epileptiform findings in 30% of the patients, with the most common finding being encephalopathy. On the other hand, NCSE was detected in 2% of the patients. Clinical or electroencephalographic seizures were detected in 15% of the patients without a history of epilepsy, which was interpreted as that COVID-19 may have a potential epileptogenic effect. Nine (10.3%) patients without a previous history of epilepsy were found to have had seizures in presence of COVID-19 comorbidity, which was interpreted as that COVID-19 may in fact have an epileptogenic effect. Consequentially, it was concluded that EEG has proven beneficial in detecting NCSE. It was reported in the same study that the detection of NCSE early by means of EEG allowed the treatment of the patients in the early period preventing poor prognosis in these patients [4]. In comparison, in this study, specific EEG abnormalities were detected in 33 (37.9%) patients, and NCSE was detected in 5.7% of the patients, which indicate slightly higher rates than the respective rates reported in the literature. This difference in results has been attributed to the prospective nature of this study and to the fact that the patients included in this study were evaluated by an experienced epileptologist.

In a retrospective study conducted by Louis, 22 patients with suspected epileptic seizures were evaluated [9]. Epileptiform anomaly was detected in 5 of these patients. Electrographic seizures were observed in 2 patients without a history of epilepsy. Periodic discharges were observed in one third of the patients. The sample size of the said study was relatively small, yet continuous EEGs were not performed in all the patients. Routine EEGs were performed only in 3 patients, and all the assessments were made using the information available in the database [9]. In comparison, in this study, all patients were evaluated prospectively, and continuous EEGs were performed on all patients and by an experienced epileptologist and technician. The sample size of this study was approximately 4 times higher than the said study. A higher percentage of patients in this study, also including in patients without a previous diagnosis of epilepsy, were found to have epileptiform abnormalities and epileptic seizures. NCSE was detected in 5 patients who underwent continuous EEG due to clinical suspicion. The difference between the EEG findings of the said study and those of this study may be attributed to the fact that continuous EEGs were performed prospectively on all patients included in this study using a standard method [9].

In another study by Galanopoulou, the EEGs of 28 patients, which were performed using 8-channel EEG to a large extent, were evaluated retrospectively [5]. In the said study, there was no detailed information on whether the patients included in the study were clinical patients or intensive care patients. EEGs were performed in patients due to new-onset encephalopathy and seizure-like events, also including patients without COVID-19. It was reported that 63.6% and 40.9% of the COVID-19 patients had seizure-like conditions and epileptiform discharges, respectively, and that 16.7% of the patients without COVID-19 had epileptiform discharges as well. No seizure was reported to have been detected electrographically. Additionally, it was stated that some patients had already been started on antiepileptic drugs prior to the EEG recording. No significant difference was found between patients with kidney and liver dysfunctions and those without, in terms of the presence of epileptiform discharges [5].

Strengths and weaknesses of the study

This prospective study marks one of the very few studies, in which continuous EEG findings of 87 COVID-19 patients, who needed intensive care due to a disorder of consciousness, were evaluated using a structured method. In comparison, most of the relevant literature work available on the EEG findings of COVID-19 patients are case reports, apart from several retrospective studies or studies conducted with a smaller sample size as compared to the sample size of this study. The use of 21-channel continuous EEG in this study gave researchers the opportunity to analyze waveforms better. The fact that all continuous EEG recordings were made by the same epileptologist as well as using the same method and same device was another strength of the study.

Apart from its strengths, there were also several limitations to this study. First, the study did not include COVID-19 negative patients, in accordance with the main objective of this study, which was to characterize the continuous EEG findings of COVID-19 patients. Secondly, patients hospitalized in the intensive care unit, yet not the ones in the COVID-19 clinic, were included in the study. Thirdly, the cases, in whom a change in consciousness could not be detected, were excluded from the study. Accordingly, evaluation of continuous EEGs of patients in whom a change in consciousness was detected reflects upward bias. Lastly, the follow-up period was limited, which was expected, given the clinical course of the COVID-19.

Declarations

Ethical approval None.

Conflict of interest None.

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