SHORT COMMUNICATION

This Short communication is accompanied by Invited Editorial, see page 8

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LEADING TOPIC

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High prevalence of electroencephalographic frontal intermittent rhythmic delta activity in patients with moderately severe COVID-19

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ABSTRACT

Introduction. The aim of our study was to analyse EEG findings in patients with COVID-19 not requiring respiratory support.

Material and methods. We reviewed EEGs performed in patients with COVID-19 between April 2020 and May 2021 at the University Hospital in Kraków, Poland. Demographic and clinical data, including comorbid conditions, discharge disposition, survival, neuroimaging findings, laboratory results, and treatment was collected.

Results. The study included 44 EEGs performed in 35 patients (51.4% females), aged 65.5 ± 13.9 years. Almost all patients had at least one comorbidity, and one-third had one or more preexisting neurological conditions. Three quarters of EEGs were abnormal. The most frequent EEG finding was background slowing (16 patients; 45.7%). Frontal findings included frontally predominant rhythmic delta (FIRDA) in 10 (28.6%) patients and focal slowing in the left frontal lobe. Patients with abnormal EEG significantly more often required oxygen supplementation ($p = 0.003$) and were less likely to recover ($p = 0.048$).

Conclusions and clinical implications. Patients with COVID-19 infection may frequently manifest with an abnormal EEG. FIRDA seems to be a frequent EEG pattern in less severe cases of COVID-19 infection. Future studies are needed to establish whether COVID-19 infection increases the risk for FIRDA, and to investigate its pathogenesis.

Key words: FIRDA, COVID-19, EEG abnormalities, prevalence, prognosis

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Introduction

Neurological symptoms and signs have been reported in the majority of patients with COVID-19 [1]. While clinical seizures affect only a small proportion of patients, electroencephalographic (EEG) abnormalities have been reported in 88–96% of cases, with generalised background slowing being the most frequent finding [2–4]. No clear and specific EEG pattern, however, has reliably been found in this population. EEG abnormalities in frontal lobes have been recently proposed as a biomarker of COVID-19-related encephalopathy [2, 6–8]. The majority of studies on EEG abnormalities in COVID-19 have focused on critically ill patients. Less is known about EEG findings in patients with a less severe course of infection.

The main goal of our study was to analyse the EEG findings in hospitalised patients with COVID-19 not requiring respiratory support, with a special focus on frontal lobe-related abnormalities.

Material and methods

We retrospectively reviewed consecutive EEGs of patients with COVID-19 hospitalised from April 2020 to May 2021 in the Department of Neurology of the University Hospital in Krakow.

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Patients were included if they were ≥ 18 years old and had a positive SARS-CoV-2 nasopharyngeal RT-PCR swab. The following patient data was recorded: age, sex, medical history, neuroimaging findings, laboratory results, treatment, and outcome (i.e. recovered, discharged with disability, or deceased). All patients underwent 21-channel EEG (video-EEG) recordings using 19 silver/silver chloride electrodes affixed to the scalp according to the international 10–20 system with additional ground and reference electrodes (DigiTrack, Elmiko). A single channel ECG was recorded simultaneously. EEGs were performed for a short duration (routine for approximately 20–30 min). EEG recordings were performed with an Elmiko DigiTrack device. Additional precautions for EEG technicians included an N95 respirator, gloves, gown, and eye protection (goggles or face shield). EEGs were reviewed using bipolar and monopolar montages by two neurophysiologists (MB, DW-K) according to the American Clinical Neurophysiology Society (ACNS) terminology. During readings, high pass and low pass filters were usually at 1 Hz (range 0.05–5 Hz) and 70 Hz (range 5–100 Hz), respectively [9]. The following EEG features were assessed: dominant background activity, focal/generalised slowing, generalised/lateralised rhythmic delta activity, periodic discharges, and epileptiform discharges/electrographic seizures/non-convulsive status epilepticus (NCSE). Frontal intermittent rhythmic delta activity (FIRDA) was defined as predominantly frontal rhythmic delta activity (1–4 Hz) [10].

Respiratory status, presence of metabolic abnormalities, medication, and level of consciousness during EEG were also noted. No patient required mechanical ventilation.

We additionally reviewed all reports from EEG studies performed in our centre between June 2016 and December 2020 for the presence of FIRDA.

Our study protocol was approved by the local bioethics committee. Informed consent was waived due to the retrospective nature of this study.

Discrete variable was expressed as a mean ± standard deviation (SD) and qualitative data was characterised with percentages. The significance of the differences between groups were analysed using the $\chi 2$ test or Fisher exact test (qualitative data) or with Student t-test. Analysis of potential independent predictors of poor outcome (death or disability at discharge as a dependent variable) was performed by logistic regression modelling. The initial model involved all the variables that differed between patients with poor or good outcomes at the level of $p < 0.2$ in univariate analysis. Subsequent models were built using the backward selection method.

Results

Patients

This study included 35 patients with the mean age of 65.5 ± 13.9 years. Neurological manifestations comorbid with COVID-19 were the reason for admission in the great majority of patients (31/35; 88.6%) and included: altered mental status (18 patients), seizures (eight patients), stroke (3), headache (1), subarachnoid haemorrhage (1), and posterior reversible encephalopathy syndrome (1). Almost all patients (32/35; 91.4%) had at leastone comorbidity. One-third of patients (12, 34.3%) had preexisting neurological conditions, including a prior history of epilepsy (5, 14.3%), ischaemic stroke (4), surgical treatment of brain metastasis (1), or brain tumour (2). All patients underwent at least one neuroimaging procedure. Various abnormalities in those studies were found in 21 patients (60%). One-third of the cohort underwent lumbar puncture which revealed abnormalities of cerebrospinal fluid in all but one patient. Most patients (27/35; 81.8%) required oxygen supplementation and had metabolic abnormalities other than decreased oxygen (26/35; 74.3%). Two thirds of patients (24/35; 68.6%) received neuroactive medication during EEG. Decreased awareness during EEG was seen in 37.1% (13/35) of patients. Twenty patients (57.1%) recovered, 10 patients (28.6%) were discharged with disability, and five patients died (14.3%).

EEG findings

Forty four EEG recordings were obtained. Indications for EEG studies were as follows: altered mental status (33), seizures (8), and follow-up (3). Three quarters of recordings were abnormal, and three quarters of patients had at least one abnormal EEG. The most frequent EEG finding was background slowing (16 patients; 45.7%). Frontal findings included FIRDA in 10 (28.6%) patients, and focal slowing in the left frontal lobe in one patient. Epileptiform discharges were noted in five patients. EEG findings and clinical characteristics of patients during EEG recording are set out in Table 1.

We compared patients with abnormal and normal first EEG recording in terms of their demographic and clinical variables (Table 1). Patients with abnormal EEG significantly more often required oxygen supplementation ($p = 0.003$) and were less likely to recover ($p = 0.048$). In the second univariate analysis, patients with and without FIRDA were compared. Subjects with FIRDA more frequently underwent MRI ($p = 0.05$). There was also a trend towards more frequent use of oxygen supplementation in patients with FIRDA ($p = 0.054$).

Multivariate analysis revealed the need for oxygen supplementation as the only independent predictor of a poor outcome ($p = 0.008$).

Between June 2016 and December 2019, a total of 6,431 EEG recordings were carried out in our centre. The presence of FIRDA was reported in 112 (1.7%) studies, comprising 108 inpatients (3.2%) and four outpatients (0.1%).

Discussion

Here, we report EEG findings in patients with a moderately severe COVID-19 infection. The most frequent EEG findings were diffuse background slowing, focal slowing, and frontal intermittent rhythmic delta activity, found in one third of patients.

Table 1. Comparison of clinical characteristics between patients with abnormal and normal first EEG and between patients with and without frontal intermittent rhythmic delta activity (FIRDA)

Variable	Patients with abnormal first EEG (N = 26) n, (%)	Patients with normal first EEG (N = 9) n, (%)	p-value*	Patients with FIRDA (N = 1) n, (%)	Patients without FIRDA (N = 25) n, (%)	p-value*
Age, years [mean ± SD]	67.1 (12.2)	60.7 (18.0)	0.23**	67.3 (10.6)	64.8 (15.2)	0.63**
Women	13 (50.0)	5 (55.5)	1.0	5 (50.0)	13 (52.0)	1.0
Neurological symptoms upon admission	23 (88.5)	8 (88.9)	1.0	9 (90.0)	22 (88.0)	1.0
Comorbidities	25 (96.1)	7 (77.8)	0.16	10 (100.0)	22 (88.0)	0.54
History of epilepsy	5 (19.3)	0	0.30	1 (10.0)	4 (16.0)	1.0
CT	23 (88.5)	9 (100)	0.55	8 (80.0)	24 (96.0)	0.19
MRI	16 (61.5)	6 (66.7)	1.0	9 (90.0)	13 (52.0)	0.05
CT angiography	10 (38.5)	5 (55.5)	0.45	3 (30.0)	12 (48.0)	0.46
Abnormal neuroimaging	17 (65.4)	4 (44.4)	0.43	6 (60.0)	15 (60.0)	1.0
Lumbar puncture	9 (34.6)	3 (33.3)	1.0	4 (40.0)	8 (32.0)	0.71
Abnormal CSF	9 (34.6)	2 (22.2)	0.69	4 (40.0)	7 (28.0)	0.69
EEG on neuroactive drugs	20 (76.9)	4 (44.4)	0.10	7 (70.0)	17 (68.0)	1.0
Epileptiform discharges	5 (19.2)	–	0.11	0	5 (20.0)	0.29
Other EEG abnormalities	24 (92.3)	–	0.003	–	14 (56.0)	0.45
EEG slowing	16 (61.5)	–	0.19	6 (60%)	10 (40.0)	1.0
FIRDA	10 (38.5)	–	0.048	–	–	1.0
Focal EEG abnormalities	8 (30.8)	–	0.23	2 (20%)	6 (24.0)	0.054
Decreased awareness during EEG	12 (46.2)	1 (11.1)	0.30	4 (40.0)	11 (44.0)	1.0
Oxygen supplementation	20 (76.9)	2 (22.2)	1.0	9 (90.0)	13 (52.0)	0.49
Metabolic abnormalities other than decreased oxygen saturation	21 (80.8)	5 (55.5)	0.69	8 (80.0)	18 (72.0)	1.0
Outcome	12 (46.2)	8 (88.9)		7 (70.0)	13 (52.0)	0.29
Recovery	9 (34.6)	1 (11.1)		3 (30.0)	7 (28.0)	1.0
Disability	5 (19.2)	0		0	5 (20.0)	1.0
Death	8 (30.8)	3 (33.3)		3 (30.0)	8 (32.0)	
Seizures during hospitalisation	8 (30.8)	4 (44.4)		3 (30.0)	9 (36.0)	
Final diagnosis: COVID only						

CSF — cerebrospinal fluid; CT — computed tomography; EEG — electroencephalography; FIRDA — frontal intermittent rhythmic delta activity; MRI — magnetic resonance imaging
*Fisher exact test; ** Student's t-test

Previous systematic reviews of COVID-19 patients [2–4] have reported that EEG findings were nonspecific, with the majority of cases having generalised background slowing. Likewise, the most common EEG abnormality in our cohort was diffuse background slowing, found in half of the patients. Unlike most studies [2–4, 11] a quarter of our patients had normal EEG. However, most previously studied patients were specified as being critically ill, intubated, or having multiorgan failure [4–6, 13]. The lower percentage of background slowing and the high proportion of subjects with normal EEGs were probably related to the less severe course of COVID-19 infection in our patients.

The high frequency of background slowing (45.7%) and generalised rhythmic delta activity (28.4%) in our cohort suggest the presence of a nonspecific diffuse encephalopathy in COVID-19 patients not requiring ICU treatment.

Patients with normal and abnormal EEG did not differ in terms of any demographic and clinical characteristics, except for the need for oxygen supplementation. The frequency of any EEG abnormalities was higher in patients requiring oxygen supplementation ($p = 0.003$). This might suggest that preexisting lower values of oxygen saturation leading to oxygen therapy may contribute to EEG abnormalities. Patients with a normal first EEG were more likely to recover ($p = 0.048$). Electroencephalographic abnormalities were previously found to be associated with a worse outcome in COVID-19 patients [5].

We could not confirm this finding in our cohort, for at least three reasons. The sample could be too small to establish a significant impact of EEG abnormalities. The population studied consisted of less severely affected patients, in whom factors other than EEG abnormalities could play a more important role. And finally, the need for oxygen supplementation was closely related to the presence of EEG abnormalities, and the predictive role of the former supplanted the value of the latter variable.

The most interesting finding in our study was the high prevalence of FIRDA, which was recorded in almost one third of patients. On the contrary, FIRDA was seen in only 1.7% out of 6,431 EEG studies (3.2% of inpatient studies) performed in our hospital between June 2016 and December 2019. The latter frequency was similar to previously published studies on the prevalence of FIRDA [10, 14].

To the best of our knowledge, the prevalence of FIRDA in patients with COVID-19 has never been specifically studied. Previous systematic reviews of COVID-19 patients [2–4] did not reveal consistent EEG findings specific to a COVID-19 infection. In several studies [6, 15–18], frequent frontal abnormalities were found and suggested as a potential EEG biomarker of COVID-19 encephalopathy related to the concept of entry of the SARS-CoV-2 virus to the brain through the olfactory nerves and subsequent spread to the orbitofrontal regions. Galanopoulos et al. found frontal sharp waves in nearly all patients with epileptiform discharges. In a small study from Italy, frontal prevalence of slow waves was noted in more than half of cases [15]. Vellieux et al. reported non-reactive bifrontal monomorphic diphasic periodic delta slow waves in two patients with COVID-19 [17].

FIRDA is a nonspecific EEG pattern and has been reported in a wide variety of cerebral lesions and different metabolic disturbances [10, 14]. The neurophysiological mechanisms underlying the high frequency of FIRDA in our cohort are unclear. This may reflect subclinical encephalopathy related to cerebral involvement with frontal predominance in COVID-19, or mild hypoxic encephalopathy, as most patients required oxygen supplementation. One third of patients had a preexisting neurological condition, which may also cause FIRDA abnormalities.

The majority of studies published so far have focused on EEG changes during an acute phase of COVID-19 infection. Cognitive decline after COVID-19 along with EEG signal alterations have also been reported [19]. Further studies are needed to explain this correlation.

This study has several limitations. Firstly, the sample was small. EEG studies have been significantly underused due to exposure concerns and limited resources. Secondly, this was a retrospective study, and all data was extracted from electronic medical records. Thirdly, we utilised only routine EEG without continuous monitoring, and a substantial percentage of electrographic seizures could have been missed. However, unlike many other studies [6, 11] we used a full set of electrodes in all cases.

Conclusion

Patients with a COVID-19 infection may frequently manifest with an abnormal EEG, mainly with background slowing. FIRDA seems to be a frequent EEG pattern in less severe cases of COVID-19 infection.

Clinical implications/future directions

Background slowing and FIRDA may reflect subclinical COVID-19 related encephalopathy or mild hypoxic encephalopathy. The neurophysiological mechanisms underlying the high frequency of FIRDA in less severe cases of COVID-19 are unclear. Future studies are needed to establish whether COVID-19 infection increases the risk for FIRDA, and to investigate the pathogenesis of this EEG pattern.

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