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EEG findings and clinical prognostic factors associated with mortality in a prospective cohort of inpatients with COVID-19

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ARTICLE INFO

Keywords:

COVID-19

Electroencephalogram

Mortality

ABSTRACT

Purpose: Our objective is to describe the most prevalent electroencephalographic findings in COVID-19 hospitalized patients, and to determine possible predictors of mortality including EEG and clinical variables.

Methods: A multicentric prospective observational study in patients with COVID-19 requiring EEG during hospitalization.

Results: We found 94 EEG from 62 patients (55 % men, mean age 59.7 ± 17.8 years) were analyzed. Most frequent comorbidity was cardiac (52 %), followed by metabolic (45 %) and CNS disease (39 %). Patients required ICU management by 60 %, with a mortality of 27 % in the whole cohort. The most frequent EEG finding was generalized continuous slow-wave activity (66 %). Epileptic activity was observed in 19 % including non-convulsive status epilepticus, seizures and interictal epileptiform discharges. Periodic patterns were observed in 3 patients (3.2 %). Multivariate analysis found that cancer comorbidity and requiring an EEG during the third week of evolution portended a higher risk of mortality

Conclusion: We observed that the most prevalent EEG finding in this cohort was generalized continuous slow-wave activity, while epileptic activity was observed in less than 20 % of the cases. Mortality risk factors were comorbidity with cancer and requiring an EEG during the third week of evolution, possibly related to the hyperinflammatory state.

1. Introduction

Coronavirus (COVID-19) is a novel severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2). Mortality is associated with risk factors such as older age, male gender, cancer, pulmonary and cardiovascular comorbidities [1].

Neurological involvement in COVID-19 has been described before and includes dizziness, headache, anosmia and ageusia [2]. Severe involvement of the central nervous system presents itself as encephalopathy, stroke, seizures [3], encephalitis and meningitis [4]. The last two affecting also young patients [5].

The electroencephalogram (EEG) is crucial when assessing patients with seizures and encephalopathy in COVID-19 disease. To date, small series show that epileptiform discharges or severe/critical EEG

abnormalities occur in 30–40 % of patients with COVID-19 [6,7]. However, it is still unknown whether specific EEG findings could predict patients' outcomes.

The aim of our study is to describe the most prevalent electroencephalographic findings during COVID-19 and to analyze whether these findings, together with other clinical variables, are predictors of mortality in this inpatient cohort.

2. Material and methods

2.1. Patients

Demographic, clinical and paraclinical data from patients were prospectively registered in a database from May 1st to June 15th, 2020

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<https://doi.org/10.1016/j.seizure.2020.10.007>

Received 29 July 2020; Received in revised form 7 October 2020; Accepted 9 October 2020

Available online 13 October 2020

1059-1311/© 2020 British Epilepsy Association.

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at the Pontificia Universidad Católica de Chile Clinical Hospital (UC, private health system) and the Hospital Dr. Sótero del Río (HSR, public health system). Adults (>18 years old) with COVID-19 were confirmed with positive detection by nucleic acid-based polymerase chain reaction (PCR), amplifying a specific genetic sequence of SARS-CoV-2, from nasopharyngeal swab (CDC qPCR Integrated DNA Technologies). All patients were studied with at least one portable EEG or EEG monitoring within four weeks from the onset of symptoms. Database collection for research was approved by the local Ethics Committee.

2.2. EEG

For portable EEG (duration of recording from 30 min to 1 h) and EEG monitoring (recording over 12 h) a Cadwell's Easy II EEG system at UC and a Natus NeuroWorks at HSR with 21 electrodes using 10–20 montage at 200 Hz sampling rate plus electrocardiogram were used. EEGs were indicated in patients with unexplained loss of consciousness without major abnormalities on blood tests and/or neuroimaging. Seizures or suspicious events were also indication. We used the standardized terminology of the American Clinical Neurophysiology Society. Recordings were examined by two trained clinical neurophysiologists (I. S. and R.U-S-M) to define the main EEG findings using bipolar and monopolar montage.

2.3. Statistical analysis

Results were reported using mean \pm standard deviation and percentages. Two groups, UC and HSR Centers were compared. Differences in qualitative variables between the groups were established using Fisher exact test. For quantitative variables, Mann–Whitney *U* test was used. Potential risk factors for mortality among recognized prognostic clinical variables and EEG findings were assessed. Binomial logistic regression was performed to analyze the probability of death using Relative Risk (RR) and 95 % confidence interval (95 % CI). First, we performed a univariate analysis and then selected for the multivariable analysis, all variables that had $p < 0.1$. Differences were considered significant at $p < 0.05$. For statistical analysis, IBM SPSS Statistics 21 was used.

3. Results

3.1. Clinical characteristics

Ninety-four EEGs from 62 patients were included in the study. Mean age was 59.7 ± 17.8 years and males represented 55 %. Cardiac comorbidity was the most frequent (51.6 %) including coronary heart disease, hypertension, and arrhythmias. These were followed by metabolic comorbidities (45.2 %, diabetes mellitus 2, hypothyroidism and obesity), and central nervous system (CNS) disease (38.7 %, brain tumours, stroke, traumatic brain injury, encephalitis and epilepsy) (Table 1).

Most of the patients (93.5 %) were studied with neuroimaging and 41.9 % (26 patients) had pathological findings. Acute findings were found in 12 patients (UC: 5 and HSR:7) including stroke $n = 3$, parenchymal hematomas $n = 2$, acute/chronic subdural hematomas $n = 2$, subarachnoid haemorrhage $n = 2$, cerebral venous thrombosis $n = 2$, brain oedema $n = 2$ and reversible posterior encephalopathy syndrome $n = 1$. Chronic findings were found in 16 patients (UC: 12 and HSR: 4) with non-specific white matter hyperintensities $n = 10$, stroke $n = 7$, parenchymal hematomas $n = 1$ and other $n = 2$.

In patients who required antiepileptic drugs ($n = 12$), the most frequent treatment was levetiracetam (58 %), followed by phenytoin (40 %), clobazam (25 %), valproic acid (8%) and lacosamide (8%). Sixty percent of the patients required management in critical care units (ICU) and 43.5 % required invasive ventilation. The mortality in this cohort reached 27.4 % (Table 1).

Table 1
Demographic, clinical and paraclinical variables.

	Total (EEG: 94)	UC (EEG: 72)	HSR (EEG: 22)	<i>p</i> -Value
Patients	62	44	18	
Gender* (F/M)	28 / 34 (45 % / 55 %)	17 / 27 (39 % / 61 %)	11 / 7 (61 % / 39 %)	0.160
Age* (years, $X \pm SD$)	59.7 ± 17.8	60.5 ± 19.2	57.8 ± 14.2	0.438
Comorbidities*				
- Respiratory	10 (16.1 %)	5 (11.4 %)	5 (27.8 %)	0.137
- Cardiac	32 (51.6 %)	22 (50 %)	10 (55.6 %)	0.786
- Hepatic	4 (6.5 %)	2 (4.5 %)	2 (11.1 %)	0.573
- Renal	14 (22.6 %)	8 (18.2 %)	6 (33.3 %)	0.315
- Metabolic	28 (45.2 %)	18 (40.9 %)	10 (55.6 %)	0.400
- Autoimmune systemic	2 (3.2 %)	1 (2.3 %)	1 (5.6 %)	0.500
- CNS	24 (38.7 %)	11 (25 %)	13 (72.2 %)	0.001
- Cancer	4 (6.5 %)	3 (6.8 %)	1 (5.6 %)	1.000
- Others	21 (33.9 %)	11 (25 %)	10 (55.6 %)	0.038
Type EEG [#]				
- Portable EEG	87 (92.6 %)	70 (97.2 %)	17 (77.3 %)	0.007
- EEG Monitoring	7 (7.4 %)	2 (2.8 %)	5 (22.7 %)	
EEG duration [#] (min, $X \pm SD$)	89.3 ± 189.7	48.9 ± 113.5	221.4 ± 303.1	<0.001
N° EEG per patients [#] ($X \pm SD$)	1.5 ± 1.1	1.6 ± 1.3	1.2 ± 0.4	0.422
COVID-19 disease duration at EEG [#]				
- Time to EEG (days, $X \pm SD$)	11.9 ± 9.2	13.5 ± 8.6	6.7 ± 9.3	<0.001
- 1 st week	35 (37.2 %)	21 (29.2 %)	14 (63.6 %)	0.005
- 2 nd week	27 (28.7 %)	24 (33.3 %)	3 (13.6 %)	0.106
- 3 rd week	16 (17.0 %)	13 (18.1 %)	3 (13.6 %)	0.755
- 4 th week	18 (19.1 %)	16 (22.2 %)	2 (9.1 %)	0.225
EEG Findings [#]				
- Non-convulsive status epilepticus	2 (2.1 %)	1 (1.4 %)	1 (4.5 %)	0.415
- Seizures	2 (2.1 %)	1 (1.4 %)	1 (4.5 %)	0.415
- Interictal epileptiform discharges	14 (14.9 %)	9 (12.5 %)	5 (22.7 %)	0.304
- Focal intermittent slow waves	13 (13.8 %)	10 (13.9 %)	3 (13.6 %)	1.000
- Generalized intermittent slow waves	34 (36.2 %)	29 (40.3 %)	5 (22.7 %)	0.204
- Continuous focal slowness	3 (3.2 %)	3 (4.2 %)	0 (0%)	1.000
- Slow theta background with reactivity	17 (18.1 %)	14 (19.4 %)	3 (13.6 %)	0.754
- Generalized continuous slow-wave (delta)	62 (66.0 %)	44 (61.1 %)	18 (81.8 %)	0.121
- Generalized low voltage	10 (10.6 %)	7 (9.7 %)	3 (9.7 %)	0.555
- Periodic pattern	3 (3.2 %)	2 (2.8 %)	1 (4.5 %)	0.694
- Normal	9 (9.6 %)	8 (11.1 %)	1 (4.5 %)	0.680
Neuroimaging*				
- No	8 (12.9 %)	7 (15.9 %)	1 (5.6 %)	0.418
- CT	42 (67.7 %)	27 (61.4 %)	15 (83.3 %)	0.136
- MRI	16 (25.8 %)	13 (29.5 %)	3 (16.7 %)	0.355
- Neuroimaging injury	26 (41.9 %)	15 (34.1 %)	11 (61.1 %)	0.087
Concordant lateralization of abnormalities between EEG and MRI [#]	28 (29.8 %)	17 (23.6 %)	11 (50 %)	<0.001
Sedation during EEG [#]	38 (40.4 %)	22 (30.6 %)	16 (72.7 %)	0.001

(continued on next page)

Table 1 (continued)

	Total (EEG: 94)	UC (EEG: 72)	HSR (EEG: 22)	<i>p</i> -Value
Requirements*				
- ICU	37 (59.7 %)	22 (50 %)	15 (83.3 %)	0.022
- IMV	27 (43.5 %)	16 (36.4 %)	11 (61.1 %)	0.095
Hospital stay* (days, X ± SD)	23.8 ± 18.3	23.4 ± 20.9	23.8 ± 18.4	0.520
- Discharge	32 (51.6 %)	21 (47.7 %)	11 (61.1 %)	0.408
- Transfer	2 (3.2 %)	1 (2.3 %)	1 (5.6 %)	0.500
Mortality*	17 (27.4 %)	8 (18.2 %)	9 (50 %)	0.025

*analysis performed with all patients (n: 62). #analysis performed with all EEG (n: 94). UC: Clinical Hospital of the Pontificia Universidad Católica de Chile. HSR: Hospital Dr. Sótero del Río. F: Female. M: Male. X: mean. SD: standard deviation. Respiratory (asthma, COPD, smoking, pulmonary fibrosis). Cardiac (coronary heart disease, hypertension, arrhythmias). Hepatic (chronic liver disease, acute hepatic failure). Renal (chronic renal disease, acute renal disease). Metabolic (type 2 diabetes, hypothyroidism, Obesity). Autoimmune systemic (systemic lupus erythematosus, rheumatoid arthritis). Central nervous system, CNS (tumours, stroke, brain traumatic brain injury, encephalitis, epilepsy). Cancer (solid and haematological). CT: computed tomography. MRI: magnetic resonance imaging. ICU: intensive care unit. IMV: invasive mechanical ventilation.

Some differences were found between the two centers (UC and HSR). CNS comorbidities were more frequent in HSR, 72.2 % versus 25 % in UC, *p*: 0.001. In HSR, a higher percentage of patients were in ICU, 83.3 % versus 50 %, *p*: 0.022 and mortality was also higher, 50 % versus 18.2 %, *p*: 0.025 (Table 1).

3.2. EEG findings

Most recordings were portable EEGs (92.6 %) with a mean duration of 89.3 ± 189.7 min corresponding to 1.5 ± 1.1 EEG per patient. Most EEG (65.9 %) were performed during the first 2 weeks of COVID-19 with a mean of 11.9 ± 9.2 days from symptoms onset (Table 1).

The most frequent EEG finding was the generalized continuous slow-wave delta activity (66 %) followed by generalized intermittent slow waves (36.2 %). Epileptic activity corresponded to 19.1 % and included non-convulsive status epilepticus, seizures and interictal epileptiform discharges. Periodic patterns were observed in 3 patients (3.2 %) (Table 1). The localization of the interictal activity (from 14 EEG) was generalized in 21 %. The rest was focal and corresponded to the frontal lobe 86 %, temporal lobe 36 %, parietal lobe 21 % and occipital lobe 21 %. The ictal onset zone of the two patients who had seizures was focal. Bifrontal and right temporoparietal lobes respectively. Non-convulsive status epilepticus was bifrontal in one patient, and right frontal in other patient (Supplementary figure 1). When correlating the EEG findings, 28 EEGs (30 %) were spatially concordant with the abnormalities visible in the neuroimaging.

There were differences between both centers. A higher percentage of EEG monitoring was performed at HSR, 22.7 % versus 2.8 % at UC, *p*: 0.007, presenting a longer duration of recordings 221.4 ± 303.1 min versus 48.9 ± 113.5 min at UC, *p* < 0.001. EEGs were performed earlier at HSR compared to UC, 6.7 ± 9.3 days versus 13.5 ± 8.6 days, *p* < 0.001, the majority at HSR during the first week (63.3 %). The concordant lateralization of the abnormalities between EEG and neuroimaging was greater at HSR, 50 % vs. 23.6 % in UC, *p* < 0.001. EEGs were more frequently performed under sedation at HSR compared to UC, 72.7 % versus 30.6 %, *p*: 0.001 (Table 1).

3.3. Risk factors for mortality

In the univariate analysis, we found 4 risk factors for mortality: The

HSR center, respiratory and cancer comorbidities and requiring an EEG during the third week of COVID-19 evolution. One variable presented to elicit a more favorable outcome: the presence of generalized intermittent slow waves in EEG (Table 2). Multivariate analysis found that cancer and requiring an EEG during the third week of evolution had a higher risk of mortality (Table 2).

4. Discussion

The main findings in this study showed that the most frequent EEG abnormality was generalized continuous slow-wave activity and that epileptic activity occurred in almost 20 % of cases. We found on multivariate analysis that cancer as a comorbidity and an EEG required during the third week of COVID-19 infection were independent risk factors for mortality in this specific cohort including mainly critical ill patients.

Our prevalence of non-convulsive status epilepticus and seizures on EEG was 4.2 %, below that observed in other infectious pathologies that directly affect the CNS with prevalence near to 30 % [8] and also below the 10–15 % found in patients hospitalized for medical conditions without CNS involvement [9]. The same occurred in terms of epileptic activity, we found a prevalence of 19 % compared to 30–40 % in recent reports of COVID-19 [6,7]. Although a small case series (10 patients with COVID-19) found interictal discharges in only one patient [10]. In our case, one patient with non-convulsive status epilepticus and one patient with seizures were managed in ICU, the other 2 patients were managed in intermediate care units.

The finding of requiring an EEG at the third week of COVID-19 as an independent risk factor is interesting. It is known that this period can be related to a hyperinflammatory phase with a cytokine storm, which accompanies the acute respiratory distress syndrome, alterations of consciousness and multiple organ failure [11]. Requiring an EEG study during that time might be a marker of altered consciousness, which might be multifactorial, especially in the more severe patients, leading to worse prognosis associated to mortality.

In the univariate analysis, we found that HSR center had a higher risk of mortality, which could be explained by a greater number of seriously ill patients, who had more comorbidities affecting the CNS and required ICU management and sedation, although this variable was not statistically significant in the multivariate analysis. Comorbidities were similar to those published in previous reports (respiratory and cancer) [1] which supports the external validity of our findings.

Other variables have been described as prognostic in patients with

Table 2

Univariate and multivariate analysis of factors associated with mortality.

Variables	Univariate analysis (<i>p</i> < 0.1)			Multivariate analysis		
	RR	95 %CI	<i>p</i> -value	RR	95 %CI	<i>p</i> -value
HSR Center	5.0	1.8–14	0.002	4.8	0.46–49	0.190
Respiratory comorbidity	7.3	1.9–28	0.004	2.9	0.37–23	0.313
Cancer comorbidity	12.2	2.3–65	0.004	56	3.5–903	0.004
EEG at 3 rd week	4.2	1.4–13	0.013	11	1.3–93	0.027
Generalized intermittent slow waves	0.3	0.09–0.9	0.038	0.12	0.01–1.5	0.102
EEG monitoring	4.8	0.9–23	0.053	3.1	0.13–74	0.488
Generalized low voltage	3.7	0.96–14	0.058	3.8	0.53–27	0.185
Sedation during EEG	2.4	0.92–6.2	0.074	2.3	0.37–14	0.376
Concordant lateralization of abnormalities between EEG and MRI	2.4	0.88–6.7	0.087	5.3	0.58–49	0.138

other brain or systemic conditions that have required EEG studies [12], such as requiring EEG monitoring, sedation with a lower voltage EEG and concordant lateralization of abnormalities between EEG and neuroimaging, although we did not observe statistical significance results in the multivariate analysis. Also, we did not find that age or gender were prognostic factors as in other reports [1], probably due to our smaller number of patients.

There are several limitations to our study. The most important is the small sample size and the lack of inclusion of some recognized prognostic variables in critically ill patients such as the high fraction of inspired oxygen (FiO₂), high positive end-expiratory pressure or low PaO₂:FiO₂ ratio and patients admitted to hospitals with fewer ICU beds [1]. Prospective studies including some of these variables or others from ICU would provide more information for the recognition of portended mortality outcomes and to validate the importance and reliability of our results for its use in clinical practice.

5. Conclusion

Our results show a lower prevalence of epileptic activity than previously reported in patients with COVID-19, and we found that the presence of cancer and the need of an electroencephalographic study during the third week of COVID-19 evolution were independent risk factors for mortality.

Ethical publication statement

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.

Disclosure

All authors have nothing to disclose.

Acknowledgements

We thank the staff of electroencephalography readers and the electroencephalography laboratory team for their permanent dedication to

patients in these difficult times. We also thank Ethel Ciampi and Christian Cantillano for helping with the manuscript editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.seizure.2020.10.007>.

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