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A study of Electroencephalography Findings and its Prognostic Value in Severe COVID-19 Patients Admitted at Intensive Care Unit

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ABSTRACT

Objective: To study electroencephalography patterns in COVID-19 patients admitted to intensive care unit and find the association of these patterns with outcome.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Intensive Care Unit, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Nov 2020 to Mar 2021.

Methodology: Eighteen electroencephalograms in COVID-19 patients with Encephalopathy were recorded using a 10-20 electrode system. The duration of each recording was 30 minutes. Traces were analysed by a neurologist for delta slowing, epileptiform discharges, and posterior dominant rhythm. Generalised slowing was classified as mild (background slowing), moderate (intermittent slowing) and severe (continuous slowing).

Results: A total of 18 COVID-19 patients, with a mean age of 63±16.02 years, underwent electroencephalography recording of 30 min duration. Diabetes mellitus and ischemic heart disease were the most common co-morbidity (7, 38.9%), followed by CKD. Non-specific generalised slowing was observed in all EEGs. No epileptiform discharges or focality were seen. Posterior Dominant Rhythm has been related to a good outcome. At the same time, severe Encephalopathy (Richmond Agitation-Sedation Scale of -3 to -5) was associated with poor outcomes (p-value<0.05).

Conclusion: Patients with Posterior Dominant Rhythm had more chances of having good outcomes, while patients with severe encephalopathy findings on EEG were more at risk of poor outcomes.

Keywords: COVID-19, Electroencephalography, Encephalopathy, Electroencephalogram, Richmond Agitation-Sedation Scale.

How to Cite This Article: *Ahmad F, Alamgir W, Ahmad I, Shafat S, Pervaiz A, Baig ZF. A study of Electroencephalography Findings and its Prognostic Value in Severe COVID-19 Patients Admitted at Intensive Care Unit. Pak Armed Forces Med J 2024; 74(2): 273-276.*
DOI: https://doi.org/10.51253/pafmj.v74i2.7446

INTRODUCTION

Encephalopathy refers to diffuse cerebral dysfunction, which usually manifests as altered mental status and psychomotor behavioural disturbances.[1] Encephalopathy is a very common finding in critical COVID-19 patients admitted to ICU, and the aetiology is multifactorial, including cytokine storm, and secondarily due to the consequence of severe respiratory/multi-organ failure, sepsis and metabolic derangements.[2]

In addition to Encephalopathy, seizures are also seen in COVID-19 patients. Not only does the frequency of seizures increase in patients who already have structural brain disease and epilepsy, but these patients are at significantly increased risk of going into status epilepticus.[3] This heightened risk is especially important in critically ill patients with reduced conscious levels where seizures are often subtle and may have little or no clinical correlate.[4,5] Early diagnosis and aggressive treatment of non-convulsive status epilepticus is crucial to improve the prognosis. Hence, EEG is important in the ICU, as it can guide the clinician in instituting anti-seizure medication on time. At the same time, the absence of seizure activity on EEG also guides the clinician in stopping unnecessary medication, which can have adverse neurological consequences.[6] It can also guide prognosis in patients with severe Encephalopathy and finally in deciding brain death as an ancillary test. Hence, critical care EEG monitoring is a very important investigation in critical patients in ICU.[7]

Surprisingly, EEG data in critical COVID-19 are very limited. Even the hallmark study by Mao *et al*. on the neurological manifestation of COVID-19 lacked this important point, and only a few studies have checked this correlation.[8] There has yet to be published data from Pakistan on this issue. The primary aim was to characterise Encephalopathy, exclude

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Received: 30 Sep 2021, revision received: 28 Feb 2022; accepted: 01 Mar 2022

non-convulsive seizures, and check the correlation between the patient's clinical condition, the severity of EEG abnormalities, and the outcome.

METHODOLOGY

The comparative cross-sectional study was conducted at the Medical Intensive Care Unit (ICU) of PEMH, Rawalpindi Pakistan, from November 2020 to March 2021 after approval from the Hospital Ethical Review Committee (Certificate number A/28/EC/343/2021). The sample size was calculated using Open-Epi 3.0 with the estimated prevalence of treatment of COVID-19 with Remdesivir at 24.6%.[9]

Inclusion Criteria: COVID-19 patients of either gender with Encephalopathy were included.

Exclusion Criteria: Patients with Encephalopathy due to other causes, including chronic kidney disease, chronic liver disease, septicemia, hypo/hypernatremia, hypoglycemia, hyperosmolar hyperglycemia, diabetic ketoacidosis, pre-existing epilepsy and EEG abnormalities, were excluded.

COVID-19 was diagnosed based on Reverse transcriptase polymerase chain reaction RT PCR from nasopharyngeal secretions and occasionally from throat swabs or bronchial secretions. All patients with hypoxia admitted to the ICU were treated by the consultant in critical care as per hospital policy. They were initially managed with standard care, including Remdesevir, steroids, general supportive care, non-invasive ventilation, and invasive ventilation. Patients with Richmond Agitation-Sedation Scale(RASS) of -1 to -2 had mild Encephalopathy, whereas those with -3 to -5 were classified as severe Encephalopathy. Neuroimaging with non-contrast CT/MRI Brain was done in all such patients. EEGs were recorded in COVID-19 patients with cerebral dysfunction, including confusion, encephalopathy, focal or generalised seizures or decreasing consciousness level.

Electroencephalogram (EEG) Recordings were performed for 30 minutes by a qualified EEG technician at the patient's bedside. Electrodes were placed using a 10-20 international system, and tracings were obtained using standard software. High and low pass filters were set at .5 Hz and 70 Hz, respectively. To check for responsiveness, our technicians were trained to apply pressure over the trapezius or supra-orbital notch or call out the patient's name or clapping or noxious stimuli in all limbs (at least twice per limb, each stimulus for 3 seconds to ensure temporal summation), Pertinent clinical information relevant to the case including neurological status, brain stem reflexes, Glasgow coma scale (GCS), sedation status, and other laboratory measurements of metabolic and immune function for cytokine release syndrome and finally information regarding any complications.

Electroencephalogram (EEG) traces were analysed by a qualified neurophysician blinded to the patient's laboratory findings and imaging results. Alpha, theta and delta rhythm were noted in the presence or absence of alpha coma, periodic discharges, non-convulsive status or reactivity. Encephalopathy was categorised as mild if there was background slowing, moderate if there was intermittent generalised slowing and severe if there was continuous generalised slowing.

Data was analysed using Statistical Package for the Social Sciences(SPSS) version 23.00. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. The *p*-value of ≤0.05 was set as the cut-off value for significance.

RESULTS

A total of eighteen COVID-19 patients, with a mean age of 63±16.02 years, underwent EEG recording of 30 min duration. There were 11(61.1%) males and 7(38.8%) females respectively (Table-I). Diabetes mellitus and ischemic heart disease were the most common co-morbidity (7, 38.9%), followed by CKD. All 18 patients had pneumonia and fever, and 13(72.2%) were on mechanical ventilation. Indication of the EEG was Encephalopathy in all patients, failure to regain consciousness after sedation withdrawal and seizure-like activity in 3 patients. 2(11.1%) patients had Cerebrovascular accident (CVA) and 1(5.5%) was a case of traumatic brain injury. The general EEG picture was consistent with non-specific Encephalopathy with polymorphic delta waves with a mild anterior emphasis. Posterior dominant rhythm was seen in 6(33.3%) patients. Mild Encephalopathy was seen in 7(38.8%) patients and severe Encephalopathy in 11(61.1%). 6(33.3%) of the patients who lacked PDR were on IV anaesthetics. No focal abnormalities or asymmetry was observed. Epileptiform abnormalities were not seen in any EEG recording. No clinical event was observed during the recording. The presence of PDR and severe Encephalopathy had a statistically significant relationship with poor outcome (*p*-value<0.05) (Table-II).

Table-I: Demographic and Clinical Characteristics of the Patients (n=18)

Characteristics	n(%)
Gender	
Female	7(38.8%)
Male	11(61.1%)
Age(years)	
Mean±(SD)	63±16.02 years
Neurological co morbidities:	
Chronic Obstructive Pulmonary Disease	1(5.6%)
Diabetes Mellitus	7(38.9%)
Hypertension	4(22.2%)
Ischemic Heart Disease	7(38.9%)
Chronic Kidney Disease	6(33.3%)
Chronic Liver Disease	1(5.6%)
History of neurological co-morbidities	
Epilepsy	3(16.7%)
Stroke	2(11.1%)
Traumatic Brain Injury	1(5.6%)
COVID-19 specific characteristics	
Median Length of Hospitalization	14 Days
Fever	18(100%)
Pneumonia	18(100%)
Mechanical Ventilation Required	13(72.2%)
Remdesivir Given as Treatment	18(100%)
Steroids	18(100%)
Use of Antiepileptic Drugs	18(100%)

discharge, focal abnormality or any specific pattern was observed in the EEG. Hence, the most common cause of failure to regain consciousness was Encephalopathy, and none of the patients had non-convulsive status epilepticus (NCSE).[12] We also found moderate to severe Encephalopathy had a bad prognostic significance compared to mild Encephalopathy. Canham *et al*. have reported similar results in their a study done in an intensive care unit in which they included a total of 10 patients with severe COVID-19 and Encephalopathy that showed only non-specific slowing, and no specific abnormality was noted.[13]

However, epileptiform discharges have been described in COVID-19 patients by different observers. Louis *et al*. reported a frequency of electrographic seizures in 10% of the encephalopathic patients with no previous history of epilepsy. There had been some twitching movement of the face or arm in these patients. Electrographic seizures improved with the administration of anti-seizure medication. The continuous generalised slowing was present in almost

Table-II: Electroencephalography Findings with Respect to Outcome (n=18)

	Alive (n=9)	Expired in Hospital (n=9)	*p*-value
EEG Indication			
Altered Mental Status (AMS)	9(50%)	9(50%)	-
Seizure-Like Event	2(11.1%)	1(5.6%)	0.527
Patients on Anesthesia During EEG	3(16.7%)	1(5.6%)	0.257
Presence of Clinical Seizure	0	0	-
Epileptic EEG	0	0	-
Presence of PDR	4(22.2%)	0	0.023
Mild Encephalopathy	5(2.8%)	2(11.1%)	0.147
Moderate Encephalopathy	4(22.2%)	7(38.9%)	0.629
Severe Encephalopathy	4(22.2%)	7(38.9%)	0.023

DISCUSSION

A total of 18 EEGs were carried out at the COVID-19 ICU, Pak Emirates Military Hospital. Among co-morbid Diabetes mellitus followed by IHD and CKD were the most commonly found as documented in the literature.[10] Generalised non-specific slowing of varying degrees was noted in all patients with a frontal predominance; this may suggest a frontal epileptogenic focus or dysfunction.

This finding has been reported before, and one proposed hypothesis of preferential frontal lobe involvement could be the unique entry into the brain via nasopharyngeal mucosa or olfactory nerves.[11] Whereas patients with impaired consciousness level due to critical illness of other etiologies only show non-specific slowing in EEG. No epileptiform all patients.[14,15]

Another small case series published by Chen *et al*. also demonstrated non-convulsive status epilepticus in 2 out of 5 patients in intensive care. Indication for EEG was unexplained altered mental status and seizure-like activity.[16] This study highlighted the importance of EEG recording in COVID-19 patients with severe Encephalopathy and the possible potential of SARS-COV-2 in triggering seizures and status epilepticus.[17]

One very important interpretation from this study was the routine use of antiepileptic drugs in all unconscious patients. However, we found no epileptic discharges, which could have further contributed to the sedation and side effect profile but without any clinical use when EEG has been non-epileptic. This will

guide the clinicians in their treatment protocol; only an AED unlife patient is clinically seizing.

The results were encouraging in patients with PDR and mild Encephalopathy, but in moderate and severe Encephalopathy with diffuse slowing, they carried a bad prognosis. Whether these EEG findings are specific for COVID-19 encephalopathy is unknown and needs further research.[18] This will guide clinicians in prognostication and cessation of ventilator support if required in resource-constrained settings. Continuous EEG monitoring would have better shown any abnormality, especially epileptiform discharges or non-convulsive seizures when they are occurring in a paroxysmal fashion.[19]

LIMITATION OF STUDY

This study has its limitation. One important limiting factor in replication was the non-availability of continuous EEG in different centres and experts' availability for EEG interpretation. As we were routinely doing only 30 minutes of recording, and this was insufficient in ICU.

CONCLUSION

Encephalopathy was the most common finding in COVID-19 patients admitted to the ICU. Patients with PDR had more chances of a good outcome, while patients with severe Encephalopathy and diffuse slowing on EEG were more at risk of a poor outcome.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

FA & WA: Data acquisition, data analysis, drafting the manuscript,

IA & SS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

AP & ZFB: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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