Electroencephalographic abnormalities in COVID-19-related encephalopathies: A systematic review

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Abstract

Background: *Acute encephalopathy is a common neurological manifestation in coronavirus disease 2019 (COVID-19) patients and presents with confusion, delirium, or poor responsiveness. Non-convulsive status epilepticus (NCSE) is an important differential diagnosis in this situation. The electroencephalography (EEG) patterns in COVID-19 patients remain largely unknown.*

Method: *A literature search was conducted on MEDLINE, EMBASE, and Cochrane database. Eligibility criteria included case series and case reports of COVID-19 patients with neurological complication who underwent EEG. Two authors screened all resulting studies and extracted the data independently.*

Results: *Four retrospective case control studies and eleven case reports were identified. Background diffuse slow activity were seen in most of the COVID-19 patients. Other EEG patterns reported included status epilepticus, focal slow activity, rhythmic periodic discharges, and interictal epileptiform discharges. Imaging and CSF studies were available in only a few patients.*

Conclusions: *Acute encephalopathy is common in the context of COVID-19. There is no specific EEG pattern found in these patients.*

Keywords: COVID-19, coronavirus, SAR-CoV-2, electroencephalogram, EEG

Introduction

The global pandemic of severe respiratory syndrome coronavirus 2 (SARS-CoV-2), known as COVID-19, presents a substantial public health challenge. The virus not only infects the respiratory system but can disseminate into other tissues and cause multi-organ failure.[1] Accumulating evidence has demonstrated that neurological symptoms can develop in COVID-19 patients.[2,3] Acute encephalopathy with impaired consciousness is a common neurological phenomenon in these patients, which may stem from several pathophysiological mechanisms. Electroencephalography (EEG) is often performed in patients with an altered mental status and to rule out subclinical seizure in hospitalized patients. The availability of EEG testing in COVID-19 patients has been limited due to the contagiousness of the virus, and information about EEG patterns in COVID-19 related encephalopathy is limited.

This study reviews and summarizes the literature on EEG studies performed in COVID-19 patients around the world. The purpose of this brief review is to better understand EEG patterns in COVID-19 related encephalopathy.

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Methods

Literature search strategy

Two investigators (J.P. and S.T.) independently searched for published articles indexed in MEDLINE, EMBASE, and Cochrane databases from inception to July 6, 2020. The search strategy included the terms for EEG and coronavirus and is available in

Supplementary Table 1. References of the included articles and the relevant links were also manually reviewed for additional eligible articles.

Selection criteria and data extraction

The inclusion criteria for the systematic review included case series or case reports of COVID-19 patients with encephalopathy who underwent EEG. Data extraction was independently performed by J.P. and S.K. using a standardized data collection form to collect the following information: demographic data, study design, neurological manifestation, neuroimaging findings, cerebrospinal fluid study, and EEG findings. Disagreements were resolved by consensus and with another author (S.T.) if needed.

Results

The literature review process is shown in Figure 1. The initial systematic search identified 49 studies; five additional articles were identified through the reference review and personal library. After removal of duplicates, 40 articles were screened through titles and abstracts for potential relevance. Nineteen selected articles underwent full-text review. Finally, four retrospective case series (Table 1)[4–7] and 11 case reports were identified (Table 2).[8–18]

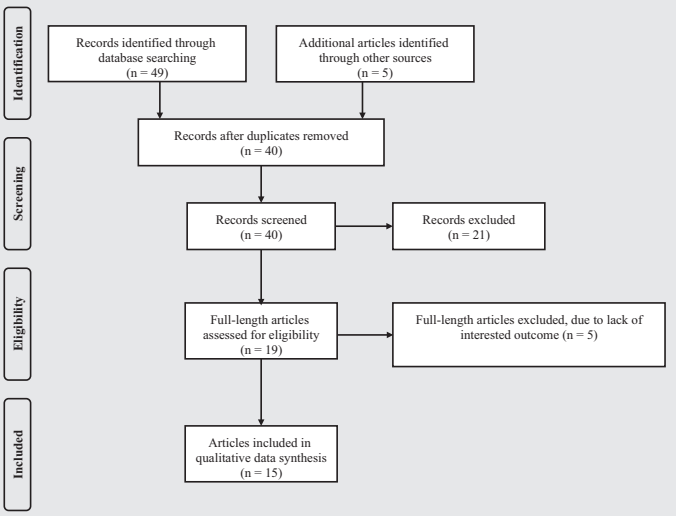

Figure 1. Flow diagram of literature search results, article screening, and article inclusion numbers.

The findings from the four case series are summarized in Table 1. In the 78 patients reported in these four studies, background diffuse slow activity was seen in 68 patients (87.1%). Interictal epileptiform discharges were seen in 11 patients (14.1%). Non-convulsive status epilepticus (NCSE) was seen in one patient (1.3%), but it was unclear if this patient had a prior history of seizures. Focal slow activity was seen in 12 patients (15.4%); seven of these patients have confirmed focal lesions, and five had inadequate information to identify an exact cause. Generalized periodic discharges were seen in eight patients (10.2%); four of these patients had been intubated, and one was known to be not intubated. One of these patients had anoxic injury due to cardiac arrest, and one was on ECMO. Information regarding the other patients was imcomplete. Burst-suppression or isoelectric EEGs were seen in three patients (3.8%) due to hypoxic brain injury.

There were 12 cases in 11 case report articles; 11 were adults and 1 was an infant (6 months) (Table 2). In the adult patients, background diffuse slow activity were reported in seven patients. Status epilepticus was reported in 5 patients: one patient had a known prior epileptogenic focal lesion, one had a known new focal lesion, and three had status epilepticus without a known focal lesion (one of the three patients did not have an MRI). Epileptiform discharges (but not status seizures) were seen in three patients; a known prior epileptogenic focal lesion was reported in one of the three patients.

Discussion

Neurological symptoms are becoming increasingly recognized in COVID-19 patients. An EEG is a common study used for evaluating altered mental status and seizures during routine clinical care. However, data show that the volume of EEG studies has decreased significantly during the pandemic to minimize unnecessary exposure for neurophysiology technicians.[19] From studies used in this review, common neurological manifestations prompting EEG evaluation included new encephalopathy (confusion, delirium), poor responsiveness after stopping sedation, and suspicion for clinical or subclinical seizures.

In general, there is no specific EEG pattern in COVID-19 related encephalopathy. Background abnormality of

Table 1. Summary of EEG Findings from Case Series

Author	Study type	Age	EEG type	Neurological symptoms	EEG pattern	Images	CSF study
Cecchetti[4]	Retrospective case series study N=18	62.4 ± 15.9 –70.5 ± 8 (mean ± SD)	Not mentioned	LOC, seizure, delirium and coma	16/18: generalized slow; 10/18: anterior (bifrontal) prevalence of slow. 7/18: focal slow; 2/18: Epileptiform discharges (unclear type, one with known glioblastoma, one with sever hypernatremia)	7 patients have focal lesions: PRES (1), remote IPH (1), glioblastoma (1), brain metastasis (1), traumatic SDH (1), remote ischemia (1), pontine demyelination (1)	Performed in 1 patient: normal
Galanopoulou[5]	Retrospective case series study N=22	30–83	Caribell rapid response EEG in 20; routine EEG in 4; continuous video EEG in 7	AMS, poor responsive ness after stopping sedation; new encephalopathy (confusion, delirium); seizure-like activity	22/22: bilateral slowing; 5/22: focal slowing; 18/22: PDR absent; 17/22: no AP gradient; 1/22: discontinuous or burst-suppression; 9/22: sporadic epileptiform discharges; 4/22: periodic rhythmic discharges (3 of 4 are GPDs, 1of 4 is LPDs)	MRI: 1 with periventricular white matter changes, 1 with subdural hemorrhage due to aneurysm, 1 with subdural hematoma. Unclear the correlation with EEG	Not mentioned
Vespignani[6]	Retrospective case series study N=26	n/a	30-min, 10–20 system using 9-electode placement; disposable needle electrodes	Mental status changes or poorly responsive	19/26: diffuse slow activity; 5/26: generalized periodic discharges; 2/26: isoelectric EEG consistent with brain death	CT or MRI done in 2 of the 5 GPDs pattern patients: no focal abnormality	Performed on 2 of the 5 GPDs pattern patients: normal
Scullen[7]	Retrospective case series study N=12	35–91	Not mentioned	Encephalopathy can not be explained by CT/MRI	11/12: diffuse slow (theta-delta activity); 1/12: NCSE	Done, but did not mention the correlation with EEG	Not done

Abbreviation: LOC: loss of consciousness; EEG: electroencephalography; PDR: posterior dominant rhythm; AP gradient: anterior-posterior gradient; IPH: intracranial parenchymal hemorrhage; PRES: posterior reversible encephalopathy; GPDs: generalized periodic discharges; LPDs: lateralized periodic discharges; NSCE: non-convulsive status epilepticus.

diffuse slow activity (theta-delta activity) and absence of posterior dominant rhythm (PDR) have been seen in a majority of patients. These EEG background patterns are nonspecific for encephalopathy caused by different etiologies, including hypoxic/hypercapnic encephalopathy, metabolic derangements, electrolytes disturbance, and inflammatory cascade following viral infection.[20,21] All these can occur in COVID-19 patients. These EEG background patterns in COVID-19 related encephalopathy range from diffuse slow activity to burst-suppression to even isoelectric EEGs.

Generalized periodic discharge is an unique EEG pattern, suggesting diffuse brain dysfunction, but it remains challenging to differentiate from NCSE in certain clinical situations.[22,23] This EEG pattern typically occurs in toxic-metabolic encephalopathy, such as hepatic and uremic encephalopathy, but can also occur in CNS viral infections, such as subacute sclerosing panencephalitis.[24] Similar to other coronaviruses, COVID-19 can cause direct CNS invasion.[25] However, lumbar punctures have been performed in very few patients during the COVID-19 pandemic. In addition, the value of a routine CSF panel without specific PCR study in the diagnosis of viral encephalitis is limited. Though there are case reports showing that COVID-19 has been detected in CSF PCR,[12,26] most of the studies did not report positive results.

A focal EEG pattern in COVID-19 patients has also been reported, including focal slowing, lateralized periodic discharges, or focal epileptiform discharges. Usually, the existence of focal abnormalities should lead to imaging studies to screen for intracranial lesions. Unfortunately, MRIs of the brain are not widely available in COVID-19 patients. Emerging evidence showed that different etiologies are involved in COVID-19 related focal brain lesions; these include necrotic encephalitis,

Table 2. Summary of Case Report of EEG in and COVID-19 Patients

Author	Age/ Gender	Neurological symptoms	History of seizures	EEG pattern	Images	CSF Study
Balloy[8]	59/M	NSCE	No	Epileptiform discharges from bifrontal lobes	MRI normal	Neg
Bernard-Valnet[9]	64/ F	Tonic-clinic seizure	No	Focal status epilepticus	MRI: Neg	Neg
De Stefano[10]	56/F	AMS	No	4Hz rhythms over bilateral parasagittal region	MRI: diffuse microbleed	Increased protein; PCR neg
Dugue[11]	0.5/M	An episode of sustained upward gaze with bolateral leg stiffening and decreased response.	No	Excess of temporal sharp transients for age and intermittent vertex delta slowing with normal sleep-wake cycling	MRI unremarkable	N/A
Duong[12]	41/F	Lethargic, meningeal irritation	No	Diffuse slow	CTH: neg	COVID PCR Pos
Filatov[13]	74/M	Headache, AMS	No	Left focal slow and sharp wave from left temporal lobe.	CTH: remote stroke with left temporal lobe encephalomalacia	Increased protein; PCR neg
Flamand[14]	80/F	Focal motor seizure	No	Diffuse slow and repetitive epileptiform discharges from bifrontal	CTH: unremarkable	
Le Guennec[15]	69/M	NCSE	No	Focal status epilepticus from right frontal lobe	MRI: right frontal lobe new lesion, resolved in 30 days	Neg
Pilotto[16]	50/M	Progressive irritability, confusion, akinitic mutism, suspected for immune-related encephalitis	No	Diffuse slow (theta activity)	MRI unremarkable	Mild lymphocytic pleocytosis and moderate increasd CSF protein; CSF PCR neg
Somani, (case1)[17]	49/F	Multiple seizure	No	Epileptiform discharges from midline and left fronto-central region	MRI unremakable	n/a
Somani (case2)[17]	73/F	New onset refractory status epilepticus (NORSE)	No	Bilateral independent periodic dhacharges (BIPDs).	CTH unremarkable	n/a
Vollono[18]	78/F	NCSE	Focal seizure due to prior HSV encephalitis	Focal status epilepticus (same region, left fronto-parietal)	MRI: encephalomalacia from left fronto-parietal	Not done

Abbreviation: NSCE: non-convulsive status epilepticus; AMS: altered mental status; HSV: herpes simplex virus; EEG: electroencephalography.

immune-mediated encephalitis, and cerebrovascular events caused by vasculopathy and a hypercoagulable state.[27] In a case report of a COVID-19 patient with acute encephalopathy, the EEG showed epileptiform discharges from the right frontal region. This EEG finding correlated with a new but temporary lesion in the right frontal lobe shown in an MRI; the CT of the head and the CSF study were unremarkable and the etiology remained unclear.[15] Unfortunately, focal intracranial lesions similar to those illustrated in the case may never be be confirmed in most of the COVID-19 cases.

One of the case series studies reported that sporadic epileptiform discharges (interictal changes) tend to happen more frequently in COVID-19 positive patients (40.9%) than in a COVID-19 negative control group (16.7%).[5] Even after excluding patients with a prior history of seizure, interictal changes are still more common in COVID-19 positive patients than in the control group. The COVID-19-negative group included ICU patients with a similar encephalopathy, therefore eliminating the explanation that the decreased seizure threshold is due to metabolic derangement or sepsis. Bilateral frontal symmetrical or asymmetrical sharp waves are the major patterns of sporadic epileptiform discharges in this study, which correlated with the hypothesis that COVID-19 enters CNS through the olfactory pathway.[28] This bifrontal epileptic origin was also reported in two independent case reports.[8,14] Although no statistical significance was achieved due to the limited sample size, this study offers the possibility of a unique mechanism of CNS involvement with this virus.

Conclusion

Acute encephalopathy is common in the context of COVID-19, and the etiology is usually multifactorial. EEG studies in COVID-19 patients are rarely done or reported. Limitations of all the studies are apparent and include small sample sizes and a lack of CSF studies and MRIs in most of the patients. Although helpful information can be obtained from EEG studies in COVID-19 patients, it is important to weigh the value of the study in diagnosis and management of the patient against the possible risk of virus transmission to the EEG technician.

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