




Clinical Electroencephalography Findings and Considerations in Hospitalized Patients With Coronavirus SARS-CoV-2

The Neurohospitalist
2021, Vol. 11(3) 204-213
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1941874420972237
journals.sagepub.com/home/NHO


Neishay Ayub, MD¹, Joseph Cohen, BA¹, Jin Jing, PhD^{1,2},
Aayushee Jain, MSc^{1,2}, Ryan Tesh, BSc^{1,2},
Shibani S. Mukerji, MD, PhD¹ , Sahar F. Zafar, MD¹,
M. Brandon Westover, MD, PhD^{1,2}, and Eyal Y. Kimchi, MD, PhD¹ 

Abstract

Background and Purpose: Reports have suggested that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes neurologic manifestations including encephalopathy and seizures. However, there has been relatively limited electrophysiology data to contextualize these specific concerns and to understand their associated clinical factors. Our objective was to identify EEG abnormalities present in patients with SARS-CoV-2, and to determine whether they reflect new or preexisting brain pathology. **Methods:** We studied a consecutive series of hospitalized patients with SARS-CoV-2 who received an EEG, obtained using tailored safety protocols. Data from EEG reports and clinical records were analyzed to identify EEG abnormalities and possible clinical associations, including neurologic symptoms, new or preexisting brain pathology, and sedation practices. **Results:** We identified 37 patients with SARS-CoV-2 who underwent EEG, of whom 14 had epileptiform findings (38%). Patients with epileptiform findings were more likely to have preexisting brain pathology (6/14, 43%) than patients without epileptiform findings (2/23, 9%; $p = 0.042$). There were no clear differences in rates of acute brain pathology. One case of nonconvulsive status epilepticus was captured, but was not clearly a direct consequence of SARS-CoV-2. Abnormalities of background rhythms were common, as may be seen in systemic illness, and in part associated with recent sedation ($p = 0.022$). **Conclusions:** Epileptiform abnormalities were common in patients with SARS-CoV-2 referred for EEG, but particularly in the context of preexisting brain pathology and sedation. These findings suggest that neurologic manifestations during SARS-CoV-2 infection may not solely relate to the infection itself, but rather may also reflect patients' broader, preexisting neurologic vulnerabilities.

Keywords

coronavirus, SARS-CoV-2, electroencephalography, seizure, sedation

Introduction

As the coronavirus disease 2019 (COVID-19) pandemic has grown, there has been concern about its possible neurologic consequences.¹ COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, whose presentations range from asymptomatic to severe.² One early series of patients with severe infection described neurologic findings of impaired consciousness (14.8%) and seizure (1.1%),³ while another noted that 27% of patients had seizure risk factors, though clinical seizures appeared rare.⁴ However, routine EEG data to support or contextualize these concerns has been limited to smaller series,⁵⁻⁸ with some series abstaining from EEGs altogether due to safety concerns,⁴ including limited personal protective equipment (PPE), risks of technician exposure, and possible iatrogenic spread through

personnel or equipment contamination. A paucity of EEGs could underestimate the rate of seizures and epileptiform activity in SARS-CoV-2, given reports of seizures in other coronavirus outbreaks⁹ and reports of patients with SARS-CoV-2 with nonconvulsive or focal status

¹ Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

² Clinical Data Animation Center, Massachusetts General Hospital, Boston, MA, USA

Corresponding Author:

Eyal Y. Kimchi, MD, PhD, Department of Neurology, Massachusetts General Hospital, 55 Fruit St., MWEL 423, Boston, MA 02114, USA.
Email: ekimchi@partners.org

epilepticus.^{10,11} It is therefore imperative to understand what EEGs might reveal in a broader series of patients with SARS-CoV-2.

Concerns have also been raised about the neuroinvasive potential of SARS-CoV-2.¹² In some cases, the presence of neurologic symptoms has even been used to infer central nervous system (CNS) invasion,¹³ and there is at least 1 possible case of meningoencephalitis with a positive cerebrospinal fluid (CSF) reverse-transcriptase polymerase chain reaction (RT-PCR).¹⁴ Autopsy series, however, have been conflicting regarding rates of neuroinvasion,¹⁵ with the largest series suggesting that neuroinvasion is limited.¹⁶ It is therefore unclear whether seizures or encephalopathy in SARS-CoV-2 are due to new CNS injury, reflect increased sensitivity in patients with preexisting vulnerabilities, or are associated with aspects of clinical care such as sedation.

We may be able to disambiguate this etiologic complexity by determining the burden and clinical associations of EEG abnormalities in SARS-CoV-2. We therefore undertook a study of all patients at our institution with SARS-CoV-2 who received an EEG, to test the hypothesis that there is a moderate rate of epileptiform discharges in patients with SARS-CoV-2, but that they are most common in patients with preexisting, rather than new, brain pathology.

Methods

Patient Cohort

We retrospectively identified all inpatients who received an EEG at an academic medical center in Boston, Massachusetts, starting after identification of the second case of COVID-19 statewide (March 2, 2020 – May 6, 2020). Patients receiving EEGs were cross-referenced against a centralized hospital database of COVID-19 status and SARS-CoV-2 results, detected using RT-PCR from nasopharyngeal samples. All patients with at least 1 positive SARS-CoV-2 result and a clinically interpreted EEG were included. To minimize bias, there were no further inclusion or exclusion criteria. The sample size was determined by the number of cases during the review period.

Protocol Approvals and Patient Consents

This study of human subjects was approved by the Institutional Review Board (IRB) at Massachusetts General Hospital (Boston, MA), including review of EEG and other clinical data. The Partners Healthcare Human Research Committee provided a waiver of consent for this retrospective study.

EEG Recordings

Protocols were developed to perform EEGs in the context of institutional guidance on care for patients with COVID-19, consistent with the American Clinical Neurophysiology Society's recommendations.¹⁷ Given uncertainty about the prevalence of EEG abnormalities, there were no pre-specified triaging

restrictions to determine which patients could receive an EEG. EEGs were recorded using disposable Ag/AgCl scalp electrodes (Rhythmlink) using standard international 10-20 electrode placement. Care was taken with the angle of the head of the bed and manipulation of intubated patients was minimized. Although electrode placement in prone patients was anticipated, with a plan to use disposable printed electrodes and related supplies (Spes Medica TechSystem), no patient was prone at the time of electrode placement; though 2 were prone prior to removal. Single use bags were made for all items including skin prep (NuPrep) and conductive paste (Ten20). No air hoses or colloidion were used. Leftover supplies were kept in patient rooms for possible later use and to minimize cross-contamination. Activation procedures, such as photic stimulation and hyperventilation, were not performed. Following use, computers and devices were wiped down using germicidal disposable wipes (Sani-Cloth). Portable EEG equipment was kept in a separate room for at least 1 hour after cleaning, away from people and other EEG machines.

All EEGs for patients with SARS-CoV-2 were performed by a single, experienced EEG technician, who volunteered to lead the division's pandemic care. This technician sequestered at least 2 meters away from all other staff and had an exclusive computer. EEG technicians worked on a limited hour basis in the hospital depending on daily inpatient needs. All hospital employees were required to wear a surgical mask for their entire shift while on-site, except when working in private individual offices or in areas where employees were reliably separated by more than 2 meters. Additional precautions in rooms of patients with known or suspected COVID-19 included an N95 respirator, gloves, gown, and eye protection (goggles or face shield). All hospital employees had to attest daily to not having COVID-19 related symptoms, including fever, sore throat, new cough, new nasal congestion, muscle aches, new loss of smell, or shortness of breath.

EEG Interpretation

EEG recordings were reviewed by 2 clinical electroencephalographers (1 board-certified attending physician and 1 fellow) before reports were finalized in the electronic medical record. Electroencephalographers interpreted recordings remotely via secure Internet connections, which also allowed access to routine clinical data. Clinical disagreements were resolved through virtual discussion.

Medical Record Review

Clinical EEG reports were reviewed by 2 neurologists to identify various possible abnormalities (listed in Table 1), including Background/Rhythm abnormalities, Rhythmic and Periodic Patterns, Sporadic Discharges, and Seizure activity. The characteristics of sporadic and periodic discharges were recorded, including whether they were identified as focal, multifocal, or generalized, and with triphasic morphology

Table 1. Neurologic Context for EEG Studies in Patients With SARS-CoV-2.

Neurologic Characteristics	n/Subset (%)
Past Seizure History	1/37 (3%)
Past History of CNS Pathology	8/37 (22%)
Past Psychiatric History	16/37 (43%)
Altered Mental Status in the absence of sedation	28/37 (76%)
Anosmia	4/37 (11%)
New Focal Exam Finding	3/37 (8%)
Known Acute CNS Injury	9/37 (24%)
Empiric Anti-Epileptic Drug prior to EEG	11/37 (30%)
Neuroimaging Performed	35/37 (95%)
Computed Tomography (CT)	35/37 (95%)
Magnetic Resonance Imaging (MRI)	9/37 (24%)
MRIs performed with Gadolinium Contrast demonstrating Meningeal Enhancement	0/7 (0%)
Neuroimaging Acutely Abnormal	9/35 (26%)
Cerebrospinal Fluid (CSF) Testing	4/37 (11%)
CSF Studies with Abnormal WBC or Protein	3/4 (75%)
CSF Studies with Abnormal WBC (>5 cells/ μ L)	2/4 (50%)
CSF Studies with Abnormal Protein	1/4 (25%)
Reason for EEG	n/Subset (%)
Possible Seizure	11/37 (30%)
Altered Mental Status	24/37 (65%)
Cardiac Arrest	2/37 (5%)
Sedation Context	n/Subset (%)
Recent sedation	27/37 (73%)
Propofol	19/27 (70%)
Dexmedetomidine	13/27 (48%)
Midazolam or Lorazepam	8/27 (30%)
Ketamine	2/27 (7%)
Sedation targeted for ventilator dyssynchrony	13/27 (48%)
Sedation decreased during EEG	10/27 (37%)

present or absent. If more than 1 morphology was reported then all were extracted. Patients with epileptiform findings were those with status epilepticus or seizures, with burst suppression with epileptiform activity, and with focal, multifocal, or generalized discharges, without triphasic morphology present.

Medical records were reviewed to extract clinical information including age, dates of symptom onset and hospitalization, medications, epidemiological risk factors,¹⁸ bedside assessments of arousal and sedation (Richmond Agitation Sedation Scale, RASS),¹⁹ neurologic exams, chest and brain imaging, and initial COVID-19 related labs. We also noted the clinical questions prompting EEG. Any disagreements were resolved through virtual discussion.

Statistical Analysis

Proportions, medians, and inter-quartile ranges (IQR) were calculated for descriptive analyses. Quantitative data was compared using rank-sum tests, and proportions were compared using Pearson Chi-square (χ^2) tests with Yates' continuity correction. The significance level for all tests was $p <$

0.05. No corrections for multiple comparisons were performed given the exploratory nature of the study. Analyses were performed in MATLAB (R2018b, MathWorks).

Results

Patient Characteristics

We studied EEG findings in hospitalized patients with SARS-CoV-2. A total of 307 patients received an acute care EEG during the study period, of which 37 tested positive for SARS-CoV-2, all before EEG. From the date of the first EEG in a patient positive for SARS-CoV-2 (3/27/2020), 25% of subsequent EEGs were in patients with SARS-CoV-2 (37/149 patients). This sample of 37 patients was studied among a total of approximately 1,128 adults admitted with known or possible SARS-CoV-2.

The patients' clinical characteristics are displayed in Table 1. Most patients had chest imaging findings consistent with COVID-19 (32/37, 86%), and most were intubated (28/37, 76%). Most patients had at least 1 epidemiological risk factor for COVID-19 (Supplemental Table 1) and laboratory studies revealed elevated inflammatory markers (Supplemental Table 2). 81% of patients (30/37) had a neurologist involved in their care at the time of EEG. Of the remaining 7 patients, 4 were referred for EEG by psychiatry, and 3 by intensivists.

Neurologic Context for EEG Studies

Patients had diverse neurologic characteristics (Table 2). Only 1 patient had a history of epilepsy prior to presentation (1/37, 3%), secondary to prior intraparenchymal hemorrhage. Seven other patients had a history of central nervous system (CNS) disease. One patient had Dementia with Lewy Bodies, and 6 patients previously had ischemic strokes, including 1 in the context of cerebral aneurysm coiling and 1 in the context of metastatic small cell lung cancer. Acutely, most patients had altered mental status, even in the absence of sedation or persistently during sedation weans (28/37, 76%). Some patients were reported to have anosmia (4/37, 11%). New focal signs were relatively rare: 2 had patients had gaze preferences and 1 had hemiparesis (3/37, 8%).

Based on clinical evaluation, neuroimaging, and cerebrospinal fluid (CSF) studies, 9 patients were determined to have acute CNS pathology (9/37, 24%), including 3 with ischemic stroke, 3 with intracerebral hemorrhage, and 1 each with cryptococcal meningitis in the setting of virally unsuppressed HIV infection, paraneoplastic encephalitis in the setting of small cell lung cancer, and subacute combined degeneration in the setting of nitrous oxide abuse. The latter 3 non-vascular events were thought not to be direct results of SARS-CoV-2 per care teams.

Several concerns prompted EEG, including convulsions with unresponsiveness concerning for seizures (11/37, 30%), altered mental status (24/37, 65%), and monitoring during

Table 2 EEG Findings in Patients With SARS-CoV-2.

EEG Findings	Total (N = 37) n/Total (%)	No Recent Sedation (n = 10) n/Subset (%)	Receiving Recent Sedation (n = 27) n/Subset (%)	χ^2 p value
Any EEG Abnormality	37/37 (100%)	10/10 (100%)	27/27 (100%)	1.000
Background/Rhythm Abnormalities				
Absent Posterior Dominant Rhythm (PDR)	34/37 (92%)	7/10 (70%)	27/27 (100%)	*0.022
Asymmetry	4/37 (11%)	0/10 (0%)	4/27 (15%)	0.488
Generalized Delta Slowing	31/37 (84%)	7/10 (70%)	24/27 (89%)	0.378
Generalized Theta Slowing	31/37 (84%)	10/10 (100%)	21/27 (78%)	0.260
Excess, Diffuse Alpha	6/37 (16%)	1/10 (10%)	5/27 (19%)	0.903
Excess, Diffuse Beta	5/37 (14%)	1/10 (10%)	4/27 (15%)	0.872
Focal/Unilateral Delta Slowing	2/37 (5%)	0/10 (0%)	2/27 (7%)	0.947
Focal/Unilateral Theta Slowing	1/37 (3%)	0/10 (0%)	1/27 (4%)	0.600
Burst suppression with epileptiform activity	4/37 (11%)	0/10 (0%)	4/27 (15%)	0.488
Burst suppression without epileptiform activity	1/37 (3%)	0/10 (0%)	1/27 (4%)	0.600
EEG Unreactive	1/37 (3%)	0/10 (0%)	1/27 (4%)	0.600
Intermittent brief attenuation	8/37 (22%)	1/10 (10%)	7/27 (26%)	0.552
Moderately low voltage	1/37 (3%)	0/10 (0%)	1/27 (4%)	0.600
Rhythmic and Periodic Patterns				
Generalized Periodic Discharges (GPDs): Triphasic morphology absent	4/37 (11%)	1/10 (10%)	3/27 (11%)	0.617
Generalized Periodic Discharges (GPDs): Triphasic morphology present	8/37 (22%)	2/10 (20%)	6/27 (22%)	0.761
Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs)	3/37 (8%)	0/10 (0%)	3/27 (11%)	0.673
Lateralized Periodic Discharges (LPDs)	0/37 (0%)	0/10 (0%)	0/27 (0%)	n/a
Generalized Rhythmic Delta Activity (GRDA)	5/37 (14%)	1/10 (10%)	4/27 (15%)	0.872
Lateralized Rhythmic Delta Activity (LRDA)	1/37 (3%)	0/10 (0%)	1/27 (4%)	0.600
Sporadic Discharges				
Focal	1/37 (3%)	0/10 (0%)	1/27 (4%)	0.600
Multifocal	6/37 (16%)	2/10 (20%)	4/27 (15%)	0.903
Generalized: Triphasic morphology present	9/37 (24%)	1/10 (10%)	8/27 (30%)	0.421
Generalized: Triphasic morphology absent	8/37 (22%)	1/10 (10%)	7/27 (26%)	0.552
Seizure Activity				
Discrete Seizures: Generalized	0/37 (0%)	0/10 (0%)	0/27 (0%)	n/a
Discrete Seizures: Focal	0/37 (0%)	0/10 (0%)	0/27 (0%)	n/a
Nonconvulsive Status Epilepticus: Generalized	1/37 (3%)	0/10 (0%)	1/27 (4%)	0.600
Nonconvulsive Status Epilepticus: Focal	0/37 (0%)	0/10 (0%)	0/27 (0%)	n/a

post-cardiac arrest hypothermia (2/37, 5%). Most EEGs involved long-term monitoring (LTM; 23/37, 65%), with a median of 22.5 hours (IQR 0.4 – 43.4 hours). Most patients had received recent sedation, either on the day of EEG or the day prior (27/37, 73%), and patients had a median RASS of -3 (IQR -4 to -2). Only 10 patients could have sedation weaned during EEG. Sedation was often specifically targeted to deep levels due to ventilator dyssynchrony in the context of acute respiratory distress syndrome (ARDS) (13/27 deeply sedated for dyssynchrony, 48%).

EEG Results

EEG revealed findings in all patients (Table 3). The most common EEG findings were generalized abnormalities of background rhythms, including absent posterior dominant

rhythms (34/37, 92%) and generalized delta and theta slowing (Figure 1A). Due to the possible effects of sedation on background rhythms, we stratified patients according to whether they had recently received sedation. Patients who had recently received sedation were more likely to lack a posterior dominant rhythm (absent in 27/27, 100%), compared to 7/10 (70%), of patients who had not recently received sedation (χ^2 p = 0.022).

EEG studies in 7 patients included capture of convulsive or concerning events, but none had electrographic correlates of discrete seizures. Electrographic seizures were also uncommon, with only 1 case of nonconvulsive status epilepticus (2.7%; 95% confidence interval 0-7.9%). This patient was a woman in her 60s with a history 20 years prior of a left posterior communicating artery aneurysm, whose coiling was complicated by a left precentral gyrus infarct. She had no prior history of seizures. She presented acutely with syncope, and Chest CT

Table 2. Clinical Characteristics of Patients With SARS-CoV-2 Undergoing EEG.

Patient Characteristics	(N = 37 Patients)
Age in years, median (IQR)	66.0 (59.5 - 76.3)
Gender	n/Total (%)
Female	10/37 (27%)
Male	27/37 (73%)
Preferred Language	n/Total (%)
English	24/37 (65%)
Spanish	8/37 (22%)
Haitian-Creole	3/37 (8%)
Other	2/37 (5%)
Race/Ethnicity	n/Total (%)
Hispanic/Latinx	9/37 (24%)
Non-Hispanic Black	12/37 (32%)
Non-Hispanic White	14/37 (38%)
Non-Hispanic Asian	2/37 (5%)
Respiratory Considerations	n/Total (%)
COVID-19 Findings on Chest Imaging	32/37 (86%)
Intubated	28/37 (76%)
Timing of Care	Median (IQR)
Days from Symptoms to Admission	5.0 (0.0 - 9.0)
Days from Symptoms to EEG	17.5 (8.5 - 27.5)
Length of Hospital Admission (days)	26.5 (12.5 - 41.0)
Disposition	n/Total (%)
Death or Hospice	10/37 (27%)
Discharge to Facility	23/37 (62%)
Discharge to Home	3/37 (8%)
Continued inpatient care	1/37 (3%)

revealed an ascending aortic dissection with rupture and tamponade, but no signs of viral pneumonia. She tested positive for SARS-CoV-2. She underwent emergent repair, and aortic pathology revealed focal chronic inflammation composed primarily of CD3+CD4+ T-cells and CD68+CD163+ macrophages, but no diagnostic features of active aortitis. Post-operatively she developed left sided head and arm twitching while being weaned from propofol. CT did not reveal acute pathology. Her EEG demonstrated occasional right frontal sharp waves, but more so generalized periodic discharges, whose frequency increased to 3-4 Hz when propofol was held (Figure 1B; Supplemental Figure 1), which was determined to be consistent with non-convulsive status epilepticus according to the Salzburg criteria for epileptiform discharges >2.5 Hz.²⁰ After treatment of non-convulsive status epilepticus, an MRI revealed small acute infarcts in right middle frontal gyrus and left superior parietal lobule, consistent with emboli from her dissection. Following care, she was discharged to a rehabilitation facility.

Sporadic and periodic discharges were also observed in the EEG studies (Figure 1C). Discharges were morphologically classified by clinical EEG readers, and patients sometimes had more than 1 morphology. There was no definite frontal or temporal predominance. We identified patients with epileptiform findings as those with focal, multifocal, or generalized

discharges, excluding those with triphasic morphology, as well as patients with electrographic seizures, status epilepticus, or burst suppression with epileptiform activity. 38% of patients had epileptiform findings (14/37, Table 4). We evaluated what clinical characteristics were more common in patients with epileptiform findings. A history of CNS pathology was more common in patients with epileptiform findings (6/14 patients with epileptiform findings had a history of CNS pathology, compared to 2/23 patients without epileptiform findings, χ^2 $p = 0.042$). EEGs with epileptiform findings were also obtained earlier in patient's courses ($p = 0.044$).

Care was escalated in 4 patients with epileptiform findings. Two patients received increased antiepileptic therapy. Two additional patients received benzodiazepine trials for generalized periodic discharges, one of which improved clinically but was ultimately thought to be more consistent with catatonia than nonconvulsive status epilepticus.

EEG Safety

To date, none of our EEG staff has tested positive for SARS-CoV-2, including the technician performing the studies, other EEG technicians, and interpreting neurophysiologists. Additionally, there have been no known cases nor safety reports in our institution regarding cross-contamination of other patients as a result of EEG testing.

Discussion

SARS-CoV-2 and Epileptiform EEG Findings

All patients with SARS-CoV-2 in our study who received EEGs for clinical purposes had EEG abnormalities, including epileptiform findings in just over a third of the patients, despite only 1 patient having a history of epilepsy. These findings have been seen in other types of critical illness,^{21,22} suggesting that direct neuroinvasion need not occur to explain such findings. Epileptiform activity appeared to be associated with preexisting brain pathology, but not acute clinical or radiographic findings. Case reports of status epilepticus in SARS-CoV-2 have been described both with^{11,23} and without^{10,24} prior CNS pathology. Although several patients had acute CNS pathology, a direct effect of SARS-CoV-2 was sometimes hard to ascertain, even for our patient with non-convulsive status epilepticus.

Epileptiform abnormalities were relatively diverse including multifocal and generalized discharges, and other potentially epileptiform findings such as discharges with triphasic morphology. While there has been concern that intranasal infection may be a potential route for coronavirus neuroinvasion,²⁵ there was no clear association between epileptiform findings and anosmia, nor was there a fronto-temporal predominance to suggest specifically limbic involvement. Other groups have noted frontally predominant abnormalities in patients with SARS-CoV-2,^{7,8,26,27} but in at least 1 paper frontal slowing appeared similar to that seen in metabolic

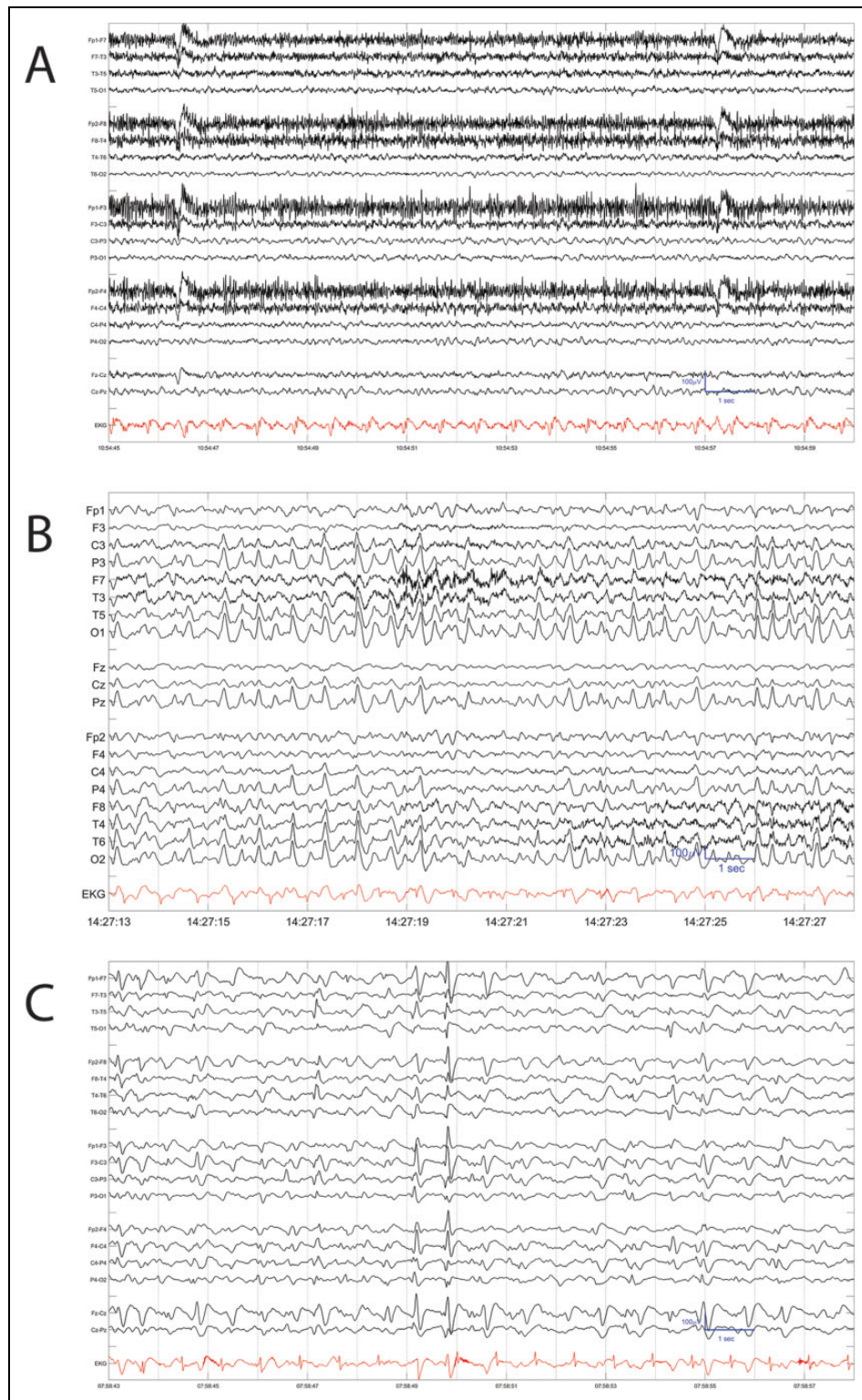


Figure I. Representative EEGs from Patients with SARS-CoV-2. A, Example EEG of a patient with SARS-CoV-2 who was not intubated and not receiving generalized sedation, with absent posterior dominant rhythm and the presence of generalized theta slowing. For all panels, data was filtered with a bandpass filter between 1-70 Hz and a notch filter at 60 Hz. EEG is shown in black in a longitudinal bipolar montage, EKG is shown in red. The sensitivity is indicated in blue for each panel. B, Example EEG of a patient with SARS-CoV-2 who had nonconvulsive status epilepticus as described in the Results, with generalized periodic discharges at a frequency of 3-4 Hz when propofol was held, displayed using a monopolar, physical referential montage. C, Example EEG of a patient with SARS-CoV-2 with multiple discharge morphologies, including both triphasic and otherwise generalized sharp wave morphologies, displayed in a longitudinal bipolar montage

Table 4. Clinical Associations With Epileptiform Findings in Patients With SARS-CoV-2.

Patient Characteristics	EEGs without Epileptiform Findings (N = 23)	EEG with Epileptiform Findings (N = 14)	Rank-sum p value
	Median (IQR)	Median (IQR)	
Age (years)	66.0 (57.0 - 78.0)	66.5 (63.0 - 73.0)	0.888
Days from Symptoms to EEG	20.0 (10.8 - 28.0)	4.0 (1.0 - 16.5)	*0.044
Patient Characteristics	n/Subset (%)	n/Subset (%)	χ^2 p value
COVID-19 Findings on Chest Imaging	21/23 (91%)	11/14 (79%)	0.547
Past History of CNS Pathology	2/23 (9%)	6/14 (43%)	*0.042
Anosmia	4/23 (17%)	0/14 (0%)	0.269
Altered Mental Status in the absence of sedation	17/23 (74%)	11/14 (79%)	0.940
Known Acute CNS Injury	6/23 (26%)	3/14 (21%)	0.940
Recent Sedation	14/23 (61%)	7/14 (50%)	0.760
Reason for EEG	n/Subset (%)	n/Subset (%)	χ^2 p value
Possible Seizure	5/23 (22%)	6/14 (43%)	0.321
Altered Mental Status	17/23 (74%)	7/14 (50%)	0.262
Cardiac Arrest	1/23 (4%)	1/14 (7%)	0.700
Impact of EEG	n/Subset (%)	n/Subset (%)	χ^2 p value
Antiepileptic Drug Started	0/23 (0%)	2/14 (14%)	0.265
Benzodiazepine Trial Initiated	0/23 (0%)	2/14 (14%)	0.265

encephalopathies and correlated with systemic lab findings.⁷ Although a few encephalitides are associated with suggestive EEG findings, such as very low frequency periodic complexes in measles-related subacute sclerosing panencephalitis²⁸ or lateralized periodic epileptiform discharges in HSV encephalitis,²⁹ neither finding is necessarily specific. Our study did not identify an EEG finding more specific to SARS-CoV-2 than other syndromes, similar to other recent systematic studies and reviews.³⁰⁻³²

Several EEGs included capture of convulsive or concerning events, but none had electrographic correlates. This suggests the need for care regarding the diagnosis of seizures solely based on convulsions in patients with SARS-CoV-2, which can also manifest with myoclonus.³³ More detail may be necessary when seizures are diagnosed or reported in COVID-19 without description of ancillary data.

SARS-CoV-2 and EEG Background Rhythms

In addition to epileptiform abnormalities, the most common EEG findings were background rhythms abnormalities, a non-specific finding that can be associated with poor prognosis.³⁴ Some abnormalities, for example generalized theta slowing, were frequent even in patients who had not recently received sedation, and this can be seen in non-encephalitic conditions such as toxic-metabolic encephalopathies.³⁵ However, the increased lack of a posterior dominant rhythm in patients recently receiving sedation suggests that some background rhythm abnormalities in SARS-CoV-2 may not simply reflect direct effects of SARS-CoV-2 infection, but may include contributions from its management, such as sedation.

A consideration that was unexpected at the outset of this study was how frequently patients were deeply sedated, beyond typical sedation goals (for example to a RASS of -3, rather than -1 to 0). While ICU sedation can unintentionally become deeper than intended, especially when the number of bedside evaluations are limited,³⁶ sedation was also intentionally deep and rarely lifted successfully due to ventilator dyssynchrony. The risks and benefits of deep sedation in Acute Respiratory Distress Syndrome (ARDS) are complex,³⁷ and the sedation strategy that most effectively balances patient-specific risks and benefits in SARS-CoV-2 remains unknown. Heavy sedation is likely to affect EEG sensitivity and specificity and has not been considered in all prior SARS-CoV-2 EEG reports. Given that several of our EEGs were prompted by convulsions in the setting of weaning sedation, we recommend anticipating whether and when attempts will be made to decrease sedation during long-term EEGs.

EEG and SARS-CoV-2 Safety Considerations

As the COVID-19 pandemic caused by SARS-CoV-2 continues, there will be increasing need to safely perform diagnostic tests that were previously routine.^{38,39} Early in the pandemic, dynamic institutional policies dictated overarching cessation of elective clinical work, minimization of onsite staff, and provision and limitation of PPE use. Protocols for specific procedures, however, were entrusted to specific divisions. Utilization of a single experienced technologist not only potentially minimized potential exposures, it also made it easier to adopt to evolving institutional requirements, to modify practices, to coordinate PPE, and to provide feedback.

To date there has been no clear transmission within or from our division and our protocol may be helpful to other institutions managing possible pandemic surges. However, there is limited data to guide safety protocols and limit iatrogenic spread, including among healthcare workers.⁴⁰ Protocols are likely to depend on local prevalence, PPE availability, and evolving understandings of COVID-19 spread. The benefits of masking patients remains uncertain, and exhalation airflow is redirected by masks, potentially flowing superiorly, with unclear consequences for EEG technicians who often stand above patients' heads.⁴¹ Tracking healthcare related cases of SARS-CoV-2 would be helpful to understand risks of transmission to and from specific provider roles.

Limitations

Our study has several imitations. This case series was drawn from a single center in order to evaluate data efficiently, albeit from a hospital with the largest caseload in a state considered one of the United States' early epicenters. The series was also relatively small, though to our knowledge, this is one of the largest known series to date of patients receiving standard EEGs for any coronavirus. All EEGs were ordered at the discretion of providers, which may introduce clinical biases that may limit generalizability to patients who do not prompt such studies. Our rate of electrographic seizures and estimated confidence interval, however, agrees with other, smaller series, suggesting a $\leq 8\%$ rate of seizures even in such selected populations.^{3,42-44} This series included a heterogeneous population, including some patients who appeared asymptomatic from a respiratory perspective. Asymptomatic patients will likely form an increasing portion of SARS-CoV-2 studies as both viral spread and testing increase. Additionally, while we have shared the specific safety protocols undertaken by our division at this time, we anticipate that protocols will evolve as more is learned.

Conclusion

EEG provides a dynamic window into the dramatic ways in which the brains of our patients are affected by the systemic and neurologic consequences of SARS-CoV-2. Epileptiform abnormalities were common in patients with SARS-CoV-2 referred for EEG and were associated with preexisting brain pathology. These findings suggest that the neurologic consequences of SARS-CoV-2, including seizures and encephalopathy, may not relate solely to infection itself, but also to how neurologically vulnerable patients are affected more broadly, including the ways in which we care for them.

Acknowledgments

The authors wish to acknowledge and express their appreciation to the patients who were a part of this study, as well as the EEG technicians and clinical neurophysiologists of the MGH Division of Clinical Neurophysiology who participated in their clinical care.

Declaration of Conflicting Interests

Dr. Ayub has nothing to disclose.

Mr. Cohen has nothing to disclose.

Dr. Jing has nothing to disclose.

Ms. Jain has nothing to disclose.

Mr. Tesh has nothing to disclose.

Dr. Mukerji reports grants from NIH/NIMH, grants from Harvard University, during the conduct of the study.

Dr. Zafar reports grants from NIH/NINDS, during the conduct of the study.


Dr. Westover reports grants from NIH/NINDS, from Massachusetts General Hospital, during the conduct of the study, and is a co-founder of Beacon Biosignals.


Dr. Kimchi reports grants from NIH/NIMH, during the conduct of the study.

Funding

The authors disclosed receipt of the following financial support: The authors were supported by the National Institutes of Health [grant number K08MH11613501, K23MH115812, K23NS114201, K23NS090900, R01NS102190, R01NS102574, R01NS107291], Harvard University [Eleanor and Miles Shore Fellowship Program], and the Massachusetts General Hospital [Department of Neurology funds].

ORCID iDs

Shibani S. Mukerji  <https://orcid.org/0000-0002-5677-6954>

Eyal Y. Kimchi  <https://orcid.org/0000-0003-4327-1102>

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Supplementary Material

Supplemental material for this article is available online.

References

1. Somani S, Agnihotri SP. Emerging Neurology of COVID-19. *Neurohospitalist*. 2020;10(4):281-286. Epub ahead of print July 10, 2020. doi:10.1177/1941874420936096
2. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *N Engl J Med*. 2020;382(22):2081-2090.
3. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690. Epub ahead of print 10 April 2020. doi:10.1001/jamaneurol.2020.1127
4. Lu L, Xiong W, Liu D, et al. New-onset acute symptomatic seizure and risk factors in corona virus disease 2019: a retrospective multicenter study. *Epilepsia*. 2020;61(6):e49-e53. Epub ahead of print April 18, 2020. doi:10.1111/epi.16524
5. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. 2020;382(23):2268-2270. Epub ahead of print April 15, 2020. doi:10.1056/NEJMc2008597

6. Pilato MS, Urban A, Alkawadri R, et al. EEG findings in coronavirus disease. *J Clin Neurophysiol*. 2020. Epub ahead of print July 1, 2020. doi:10.1097/WNP.0000000000000752
7. Cecchetti G, Vabanesi M, Chieffo R, et al. Cerebral involvement in COVID-19 is associated with metabolic and coagulation derangements: an EEG study. *J Neurol*. 2020;267(11):3130-3134. Epub ahead of print June 15, 2020. doi:10.1007/s00415-020-09958-2
8. Vespignani H, Colas D, Lavin BS, et al. Report on electroencephalographic findings in critically ill patients with COVID-19. *Ann Neurol*. 2020;88(3):626-630. Epub ahead of print June 13, 2020. doi:10.1002/ana.25814
9. Bohmwald K, Gálvez NMS, Ríos M, Kalergis AM. Neurologic Alterations Due to Respiratory Virus Infections. *Front Cell Neurosci*. 2018;12:386.
10. Balloy G, Mahé P-J, Leclair-Visonneau L, et al. Non-lesional status epilepticus in a patient with coronavirus disease 2019. *Clin Neurophysiol*. 2020;131(8):2059-2061. Epub ahead of print May 13, 2020. doi:10.1016/j.clinph.2020.05.005
11. Vollono C, Rollo E, Romozzi M, et al. Focal status epilepticus as unique clinical feature of COVID-19: A case report. *Seizure*. 2020;78:109-112.
12. Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92(6):552-555. Epub ahead of print February 27, 2020. doi:10.1002/jmv.25728
13. Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain Behav Immun*. 2020;88:945-946. Epub ahead of print April 10, 2020. doi:10.1016/j.bbi.2020.04.017
14. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-coronavirus-2. *Int J Infect Dis*. 2020;94:55-58. Epub ahead of print April 3, 2020. doi:10.1016/j.ijid.2020.03.062
15. Weyhern CH von, Kaufmann I, Neff F, Kremer M. Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. *Lancet*. 2020;395(10241):e109.
16. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological Features of Covid-19. *N Engl J Med*. 2020;383(10):989-992.
17. American Clinical Neurophysiology Society. *American Clinical Neurophysiology Society COVID-19 Resources*. American Clinical Neurophysiology Society COVID-19 Resources; 2020. Accessed April 17, 2020. <https://www.acns.org/practice/covid-19-resources>
18. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
19. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002;166(10):1338-1344.
20. Beniczky S, Hirsch LJ, Kaplan PW, et al. Unified EEG terminology and criteria for nonconvulsive status epilepticus. *Epilepsia*. 2013;54(Suppl 6):28-29.
21. Gilmore EJ, Gaspard N, Choi HA, et al. Acute brain failure in severe sepsis: a prospective study in the medical intensive care unit utilizing continuous EEG monitoring. *Intensive Care Med*. 2015;41(4):686-694.
22. Alvarez V, Rodriguez Ruiz AA, LaRoche S, et al. The use and yield of continuous EEG in critically ill patients: a comparative study of three centers. *Clin Neurophysiol*. 2017;128(4):570-578.
23. Kadono Y, Nakamura Y, Ogawa Y, et al. A case of COVID-19 infection presenting with a seizure following severe brain edema. *Seizure*. 2020;80:53-55.
24. Flamand M, Perron A, Buron Y, Szurhaj W. Pay more attention to EEG in COVID-19 pandemic. *Clin Neurophysiol*. 2020;131(8):2062-2064. Epub ahead of print May 22, 2020. doi:10.1016/j.clinph.2020.05.011
25. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol*. 2008;82(15):7264-7275.
26. Vellieux G, Rouvel-Talleg A, Jaquet P, Grinea A, Sonnevill R, d'Ortho MP. COVID-19 associated encephalopathy: is there a specific EEG pattern? *Clin Neurophysiol*. 2020;131(8):1928-1930.
27. Galanopoulou AS, Ferastraou V, Correa DJ, et al. EEG findings in acutely ill patients investigated for SARS-CoV-2/COVID-19: a small case series preliminary report. *Epilepsia Open*. 2020;5(2):314-324.
28. Gürses C, Oztürk A, Baykan B, et al. Correlation between clinical stages and EEG findings of subacute sclerosing panencephalitis. *Clin Electroencephalogr*. 2000;31(4):201-206.
29. Kim YS, Jung KH, Lee ST, et al. Prognostic value of initial standard EEG and MRI in patients with herpes simplex encephalitis. *J Clin Neurol*. 2016;12(2):224-229.
30. Sharifian-Dorche M, Huot P, Osharov M, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. *J Neurol Sci*. 2020;417:117085.
31. Petrescu A-M, Taussig D, Bouilleret V. Electroencephalogram (EEG) in COVID-19: a systematic retrospective study. *Neurophysiol Clin*. 2020;50(3):155-165.
32. Egbert AR, Cankurtaran S, Karpiak S. Brain abnormalities in COVID-19 acute/subacute phase: a rapid systematic review. *Brain Behav Immun*. 2020;89:543-554. Epub ahead of print July 17, 2020. doi:10.1016/j.bbi.2020.07.014
33. Rábano-Suárez P, Bermejo-Guerrero L, Méndez-Guerrero A, et al. Generalized myoclonus in COVID-19. *Neurology*. 2020;95(6):e767-e772. Epub ahead of print May 21, 2020. doi:10.1212/WNL.00000000000009829
34. Kimchi EY, Neelagiri A, Whitt W, et al. Clinical EEG slowing correlates with delirium severity and predicts poor clinical outcomes. *Neurology*. 2019;93:e1260-e1271.
35. Sutter R, Stevens RD, Kaplan PW. Clinical and imaging correlates of EEG patterns in hospitalized patients with encephalopathy. *J Neurol*. 2013;260(4):1087-1098.
36. Nassar AP, Zampieri FG, Salluh JJ, et al. Organizational factors associated with target sedation on the first 48 h of mechanical

- ventilation: an analysis of checklist-ICU database. *Crit Care*. 2019;23(1):34.
37. Shah FA, Girard TD, Yende S. Limiting sedation for patients with acute respiratory distress syndrome—time to wake up. *Curr Opin Crit Care*. 2017;23(1):45-51.
 38. Haines S, Caccamo A, Chan F, et al. Practical considerations when performing neurodiagnostic studies on patients with COVID-19 and other highly virulent diseases. *Neurodiagn J*. 2020;1-18.
 39. Géliste P, Rossetti AO, Genton P, Crespel A, Kaplan PW. How to carry out and interpret EEG recordings in COVID-19 patients in ICU? *Clin Neurophysiol*. 2020;131(8):2023-2031. Epub ahead of print May 13, 2020. doi:10.1016/j.clinph.2020.05.006
 40. CDCMMWR. Characteristics of health care personnel with COVID-19—United States, February 12–April 9, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(15):477-481. Epub ahead of print 2020. doi:10.15585/mmwr.mm6915e6
 41. Tang JW, Liebner TJ, Craven BA, Settles GS. A schlieren optical study of the human cough with and without wearing masks for aerosol infection control. *J R Soc Interface*. 2009;6(Suppl 6):S727-736.
 42. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA*. 2020;323(16):1612-1614.
 43. Romero-Sánchez CM, Díaz-Maroto I, Fernández-Díaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology*. 2020;95(8):e1060-e1070. Epub ahead of print June 1, 2020. doi:10.1212/WNL.00000000000009937
 44. Scullen T, Keen J, Mathkour M, et al. Coronavirus 2019 (COVID-19)–associated encephalopathies and cerebrovascular disease: the New Orleans experience. *World Neurosurg*. 2020;141:e437-e446. Epub ahead of print May 28, 2020. doi:10.1016/j.wneu.2020.05.192