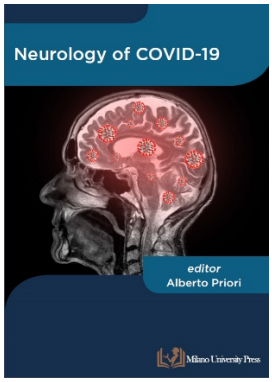

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Chapter 9. **Seizures and EEG**

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Chapter 9. Seizures and EEG

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Introduction

Many neurological symptoms, such as encephalopathy, seizures and status epilepticus, have been reported in patients with COVID-19[1-4]. Even if the acquisition of an Electroencephalogram (EEG) in SARS-CoV-2 positive patients presents some particular limitations, mainly due to the risk of infection, many papers describing electroencephalographic patterns of those patients have been published in the last year.

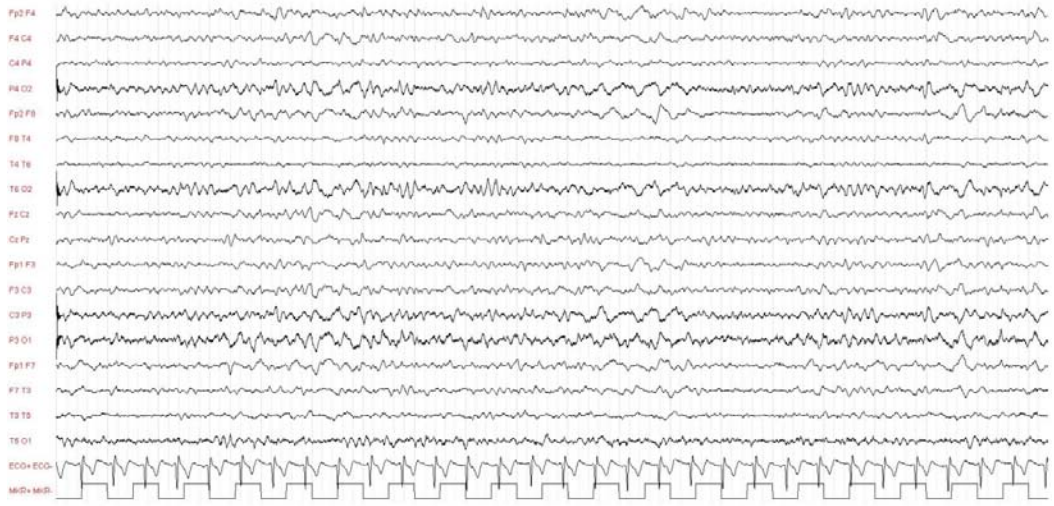
EEG findings

Although changes in mental status have been frequently reported in patients with COVID-19[5-11] together with other neurological symptoms, including clinical and subclinical seizures and status epilepticus[12-16], EEG studies have been significantly underused in these patients due to the risk of infection. Three studies showed that EEG services have been widely disrupted by the COVID-19 pandemic[17-19]. On the other hand, studies conducted using the scarce EEG data available showed that many of the patients with COVID-19 and encephalopathy/seizures had epileptiform discharges/seizures in their EEG examinations[7,20,21]. In a review of 617 patients from 84 reports, Antony and Haneef[22] found that EEG abnormalities in COVID-19 patients were common, comprising a wide variety of findings such as background abnormalities, periodic and rhythmic activity, and other epileptiform abnormalities[7,23,24]. Diffuse background slowing was the most frequent EEG finding, reported in two-thirds of patients, indicating that a diffuse, non-specific encephalopathy is the most constant brain abnormality in this condition (Figure 9.1).

These findings are in line with those of Roberto et al.[25] and those of Kubota et al.[26] who found that the proportion of abnormal background activity was even higher. These results confirm that patients infected with COVID-19 who required EEG may likely have encephalopathy. In fact, also in the meta-analysis

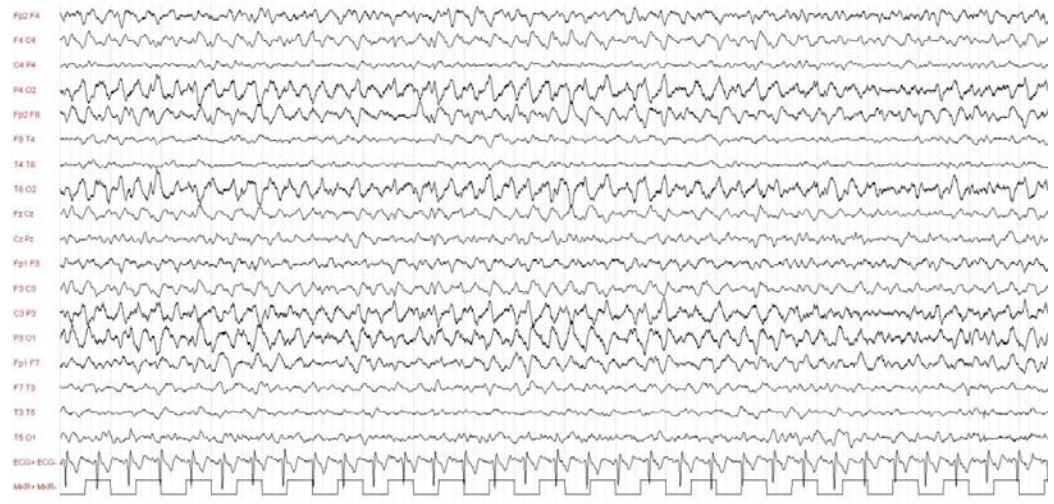
of Kubota et al.[26], the most common indication for EEG was altered mental status (68.4% of cases).

Figure 9.1



Male patient, aged 58, admitted for an episode of loss of consciousness; detection of COVID-19 at swab test at admission. EEG showed diffuse background slowing and sporadic sharp waves. 20 sec/page, 100 μm amplitude.

Figure 9.2



Female patient, aged 55, admitted for confusion and altered mental status appeared 24 hours after onset of low-grade fever and malaise in COVID-19 infection. EEG showed sub-continuous rhythmic delta activity. 20 sec/page, 100 μm amplitude.

Other EEG features suggesting diffuse encephalopathy included generalized rhythmic delta activity (GRDA)[7,9], generalized periodic discharges (GPD) with triphasic morphology[9,27], and discontinuous/burst suppression/background suppression. Kubota and colleagues found discontinuous / burst suppression / background suppression and GPDs in 5.33% and 16.5% of the patients, respectively[26].

Lateralized periodic and rhythmic abnormalities have also been reported, suggesting a co-existent focal dysfunction in some patients. Epileptiform discharges were common, indicating underlying cortical irritability predisposing to seizures[22].

Several studies reported abnormalities in the frontal region[7,22,27-29] including focal slowing, periodic discharges and rhythmic delta activity (Figure 9.2).

In the systematic review conducted by Antony and Henef[22], half of all status epilepticus and focal slowing originated in the frontal lobe. Most of the authors considered these frontal findings to be aspecific[25]. Others have described a specific EEG pattern characterized by continuous, slightly asymmetric, monomorphic, diphasic, delta slow waves with greater amplitude over both frontal areas and with a periodic organization[22,29] proposing this pattern as a potential biomarker. Some authors hypothesize that the common frontal location of focal abnormalities in COVID-19 patients correlates with the purported entry of the virus into the brain[7,27,28,30]. Early clinical manifestations of COVID-19 like anosmia and ageusia are thought to be due to viral entry in the nasal and oral mucosa facilitated by ACE-2 receptors[31]. Subsequent spread to the orbitofrontal region[31,32] via afferent nerves leads to preferential involvement of the olfactory bulb and orbitofrontal/frontal regions and can explain the preponderance of frontal EEG findings. This theory is also corroborated by frontal hypometabolism seen in PET scans in these patients[33].

Technical recommendations for EEG

Although much information may be gained from an EEG, the value of this information in the diagnosis and management of the patient must be weighed against the risks of infection from COVID-19 for the technologist. In this setting, reduced EEG montages using single-use subdermal EEG needle electrodes may be used in comatose patients. A full 10-20 EEG complement of electrodes with an ECG derivation remains the standard in all other cases. Under COVID-19 conditions, an expedited study that adequately screens for generalized status epilepticus, most types of regional status epilepticus, encephalopathy or sleep, may serve for most clinical questions, and using simplified montages may limit the risk of infection to EEG technologists[34]. Carrying out an EEG should be assessed in accordance with clinical urgency, setting, status of SARS-CoV-2 infection, and phase of governmental restrictions. In the most

critical phases of the pandemic, EEGs should be limited to patients with acute / subacute neurological symptoms, and outpatient examinations should be suspended. Risk of infection could be reduced by limiting contact between staff through rescheduling work shifts, and the use of disposable electrodes and of dedicated EEG devices for COVID-19-positive patients[35]. (International League Against Epilepsy [ILAE]'s Guidance for EEG investigation is available online at https://www.ilae.org/patient-care/covid-19-and-epilepsy/for-clinicians.)

Mechanisms of seizures in SARS-CoV-2

Many case series report an association between seizures and SARS-CoV-2 infection[15,24,36-38]. Three different mechanisms have been theorized by which seizures can develop in patients infected with SARS-CoV-2: a direct mechanism, am indirect mechanism, and an exacerbation of seizure in patients with epilepsy[39].

Direct mechanism

SARS-CoV-2 is capable of entering directly and infecting the central nervous system, leading to meningitis and encephalitis, and consequent seizures[39-41] through different ways. One of them involves Angiotensin converting-enzyme-2 (ACE-2) receptors[42], which are located on cells throughout the body, including the cardio-respiratory neurons of the brainstem, glial cells, basal ganglia, motor cortex, raphe, and endothelial cells of the brain. SARS-CoV-2 can infect the endothelial cells of the blood-brain barrier and then accumulate in the various previously mentioned brain regions causing direct infection with neurological complications[40,43]. Another pathway through which SARS-CoV-2 is thought to enter the central nervous system (CNS) is the olfactory nerve via the nasal cavity. In fact, it has been shown that, within seven days of infection, SARS-CoV-2 is able to reach the cerebrospinal fluid (CSF) and brain through the olfactory nerve causing inflammation and demyelinating reactions with potential subsequent seizures[43,44].

Indirect mechanism

Downregulation of ACE-2 expression - ACE-2 receptors may play a role also in an indirect mechanism. The overloading of these receptors by SARS-CoV-2 infection leads to a downregulation of ACE-2 expression, dysfunction of the renin-angiotensin system with overproduction of angiotensin II resulting in a cascade of biochemical events that eventually cause severe acute lung injury, vasoconstriction, and oxidative processes that promote brain damage with the possible occurrence of seizures[42,43].

Cytokine storm - Another possible indirect mechanism derives from the impairment of natural killer and cytotoxic T-cell function which results in excessive secretion of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), and interleukins (IL) 1, 4, 6, 8, 10, and 18. This cytokine storm results in an exaggerated inflammatory response leading to vascular permeability, edema, and widespread inflammation with consequent damage to multiple organs with progression to multi-organ failure[41,45].

Hypoxia and hypoperfusion - Also, hypoxia can potentiate encephalopathy, which can further play a role in the development of seizures. Ischemic brain injury also contributes to cerebral tissue hypoperfusion and may lead to seizures[46].

Exacerbation of seizure in patients with epilepsy

The effects of COVID-19 on patients with epilepsy (PWE) are still not clear. The ILAE has issued a declaration that PWE are not likely to be more susceptible to getting COVID-19 nor are they inclined to suffer through severe manifestations of SARS-CoV-2 infection[47]. Even if PWE are exposed to SARS-CoV-2, it is unlikely that the frequency of seizures increases. Nevertheless, management of COVID-19 in PWE requires certain precautions, and guidelines need to be followed in order to avoid a worsening of the condition; maintaining control of epilepsy with anti-seizure medication (ASM) is crucial as mortality associated with epilepsy is higher in patients with uncontrollable seizures. In particular, potential drug-drug interaction that may occur on concomitant administration of ASM along with the drugs used to treat COVID-19 need to be taken into account[48,49], since an increasing number of medications are being considered for the management of COVID-19[50-52]. Information about drug-drug interactions is also of particular relevance for intensive care unit management of critically ill COVID-19 patients who may develop acute seizures during a severe disease course.

Some drugs currently used as anti-COVID-19 medications may increase the risk of seizures, although this is rare. The mechanisms of seizure facilitation can be manifold: effects of anti-COVID-19 drugs on seizure threshold, effects of infection on ASM pharmacokinetics, and drug-drug interaction. Furthermore, common adverse effects of anti-COVID-19 drugs (such as diarrhea) could lower plasma ASM concentration. Lastly, immunomodulation by ASMs has also been hypothesized[53].

Moreover, COVID-19 infection could be related to impaired hepatic and renal function. This means that critically ill patients in particular may require ASM plasma concentrations to be monitored and possible dose adjustment. Major interactions relate to strong hepatic enzyme-inducing ASMs (phenobarbital, primidone, phenytoin and carbamazepine), but other mechanisms of drug-drug interaction have also been reported (i.e., P-glycoprotein way)[54].

Possible drug interactions between more common anti-COVID-19 medications and ASMs are summarized in Table 9.1.

Table 9.1: Possible interactions between anti-COVID-19 drugs (some of them not currently used) and most the commonly used ASMs, and recommendations for their combinations

	Drug interaction	Cardiac side effects	Recommendations
Chloroquine/ Hydroxychloroquine	BRV, CBZ, ESL, FBM, OXC, PHT, PB, PRM	Possible dysrhythmias if associated to FBM	Avoid co-administration with CBZ, PHT, PB, PRM
Lopinavir/Ritonavir	BRV, CBZ, CLN, CLB, DZP, ESL, FBM, LTG, MDZ, OXC, PER, PHT, PB, PRM, VPA	Possible dysrhythmias if associated to ESL or LCS	Avoid co-administration with MDZ. If in combination with CBZ, administer twice daily instead of once daily. If co-administered with LTG, therapeutic monitoring of LTG is required.
Tocilizumab	CBZ, CLB, CLN, DZP, LZP, MDZ, PHT, PRM, VPA		
Remdesivir	CBZ, ESL, OXC, PHT, PB, PRM		Avoid co-administration with CBZ, PHT, PB, PRM
Azithromycin	PHT	Possible dysrhythmias if associated to PRG	Dose adjustment and monitoring may be required if administered with PHT
Prednisone/dexamethasone	PB		Monitor plasma concentrations of PB if co-administered; dose of corticosteroids may have to be increased if administered with PB
DOACs	CBZ, ESL, LEV, FBM, OXC, PB, PHT, PRM, TPM, VPA		If associated with CBZ, PB, PHT or PRM caution and surveillance are needed, in addition to possible increases in DOAC dose; low molecular weight heparin or unfractionated heparin may be used in these cases.
	Drug interaction	Cardiac side effects	Recommendations
Chloroquine/ Hydroxychloroquine	BRV, CBZ, ESL, FBM, OXC, PHT, PB, PRM	Possible dysrhythmias if associated to FBM	Avoid co-administration with CBZ, PHT, PB, PRM
Lopinavir/Ritonavir	BRV, CBZ, CLN, CLB, DZP, ESL, FBM, LTG, MDZ, OXC, PER, PHT, PB, PRM, VPA	Possible dysrhythmias if associated to ESL or LCS	Avoid co-administration with MDZ. If in combination with CBZ, administer twice daily instead of once daily. If co-administered with LTG, therapeutic monitoring of LTG is required.
Tocilizumab	CBZ, CLB, CLN, DZP, LZP, MDZ, PHT, PRM, VPA		

Remdesivir	CBZ, ESL, OXC, PHT, PB, PRM		Avoid co-administration with CBZ, PHT, PB, PRM
Azithromycin	PHT	Possible dysrhythmias if associated to PRG	Dose adjustment and monitoring may be required if administered with PHT
Prednisone/dexamethasone	PB		Monitor plasma concentrations of PB if co-administered; dose of corticosteroids may have to be increased if administered with PB
DOACs	CBZ, ESL, LEV, FBM, OXC, PB, PHT, PRM, TPM, VPA		If associated with CBZ, PB, PHT or PRM caution and surveillance are needed, in addition to possible increases in DOAC dose; low molecular weight heparin or unfractionated heparin may be used in these cases.

AMSs - BRV: brivaracetam; CBZ: carbamazepine; CLB: clobazam; CLN: clonazepam; DZP: diazepam; ESL: eslicarbaz: epine; FBM: felbamate; LEV: levetiracetam; LTG: lamotrigine; LZP: lorazepam; MDZ: midazolam; OXC: oxcarbazepine; PER: perampanel; PHT: phenytoin; PB: phenobarbital; PRG: pregabalin; PRM: primidone; TPM: topiramate; VPA: valproic acid.

Seizures and SARS-CoV-2

Seizures and/or status epilepticus (SE) were often recorded in patients without any evidence of acute or chronic brain injury on imaging and without any alteration in CSF; in those patients, seizures have been recorded mainly in the frontal lobe[55] or in the fronto-central region[15,56]. Moreover, non-convulsive SE (NCSE) has been reported in the frontal region, unilaterally[30,57], or bilaterally[38] or in the fronto-temporal region[58].

Seizures and/or SE were recorded more rarely in patients with acute CNS lesions on brain imaging and/or significant CSF abnormalities, of either vascular or inflammatory origin, and in those cases, seizures or SE were often described as arising from the posterior regions. Occipital focal seizures or NCSE were described by Parauda et al.[59] in patients with posterior reversible encephalopathy syndrome (PRES). In other cases, seizures starting from the right fronto-temporal region were recorded in a patient with diffuse CNS demyelinating lesions on brain and spine imaging[60] or multifocal and bilateral seizures were detected in a patient with an acute disseminated encephalomyelitis[61]. Finally, Bernard-Valnet et al.[62] reported the case of a patient with lymphocytic meningitis diagnosed by CSF analysis, with normal brain Magnetic Resonance Imaging (MRI), whose EEG showed a focal anterior NCSE.

Seizures and/or SE were also reported in patients with neurological and radiological sequelae but without any acute lesions, arising from an area of previous cerebral insult, for example, due to prior surgery or to remote herpes simplex virus1 encephalitis[16,56].

Status epilepticus and SARS-CoV-2

Hung et al. reported the first case of status epilepticus associated with SARS, with the evidence of SARS-CoV RNA in both the CSF and serum[63]. Since then, over the last few months, there has been an increased reporting of seizures associated with SARS-CoV-2.

A review which analyzed published data of SE in COVID-19 infection[64] found that only a small proportion (6.4%) of patients who develop SE had prior history of epilepsy. Time of onset of SE may vary. Most of the patients developed SE after COVID-19 respiratory / gastrointestinal symptoms; in a minority of cases (14.9%), SE appeared before other systemic symptoms. The cause of SE was unknown in the majority of cases; acute symptomatic and multifactorial etiologies have been reported. Although motor symptoms represented the most frequent manifestation of SE, about one-third of the reported SE were non-convulsive SE. EEG abnormalities were mostly localized in the frontal lobe, followed by the temporal lobe. Most frequent EEG abnormalities consisted of continuous epileptiform activity, recorded in about half the patients; EEG slow-wave continuous activity was also reported in some patients. Cerebral imaging (CT or MRI) detected abnormal findings in 29-42% of patients reported having SE in the context of COVID-19 syndrome, including inflammatory lesions (17%), PRES (8.5%), brain atrophy or cerebral hemorrhage in two patients respectively (4.3%), brain tumor and cerebral hemorrhage in one patient (2.1%). Acute seizures and SE can arise from febrile status, hypoxia, or metabolic derangements. Nevertheless, according to the available data, such etiologies are infrequent, and are generally associated with a milder form of SE, with a good response to treatment and a favorable outcome. In SE, the most frequently used medication was levetiracetam, probably for its favorable tolerance profile, few drug-drug interactions and on the whole, an absence of respiratory depression, making it preferable to benzodiazepine in patients with COVID-19 pneumonia. Outcome was positive in the majority of cases reported (96%) (Table 9.2)[64].

A recent epidemiological study[65] has shown that the incidence of SE during the pandemic was no different from the general SE incidence recorded in the previous five years, even if it is probable that the real frequency of SE, and in particular of NCSE in SARS-CoV-2 infection, has been underestimated due to problems in using adequate diagnostic tools and in having prompt access to EEG recording during the pandemic.

Table 9.2: Status epilepticus features

Onset	Intra-hospital	30	63.8%
	Extra-hospital	12	25.5%
	NA	5	10.6%
Etiology	Acute	19	
	-Vascular	7	14.9%
	-Septic	5	10.6%
	-Inflammatory	4	8.6%
	-Multifactorial	3	6.4%
	Unknown	26	55.3%
	NA	2	4.3%
Semiology	Motor onset		
	-GCSE	11	23.4%
	-GCSE evolving to NCSE	2	4.3%
	-FMSE	2	4.3%
	-FMSE evolving to NCSE	6	12.8%
	-MSE evolving to NCSE	1	2.1%
	Non-motor onset		
	-NCSE	8	17%
	Unknown	17	36.2%
EEG Pattern	GPDs	5	10.6%
	LPDs	2	4.3%
	LPDs PLUS	2	4.3%
	BILPD	2	4.3%
	GRDA	2	4.3%
	NA	34	72.3%

Modified from Dono et al.[64]. BILPDs: bilateral independent periodic discharges; FMSE: focal motor status epilepticus; GCSE: generalized convulsive status epilepticus; GPDs: generalized periodic discharges; GRDA: generalized rhythmic delta activity; MSE: motor status epilepticus; NCSE: non-convulsive status epilepticus; LPDs: lateralized periodic discharges; NA: not available.

Treatment suggestions

In relation to the complexity of COVID-19 disease, to the variety of neurological symptoms, and to the possible interactions between ASMs and anti-COVID-19 drugs, the decision as to the best treatment for seizures should take into account the specific characteristics, the comorbidity, and the current clinical condition of the patient. As a general rule, it would be reasonable to choose ASMs with less known interactions (i.e., avoiding strong hepatic

enzyme-inducing ASMs), and giving preference to those with an intravenous formulation.

Conclusions

Neurological complications in patients with COVID-19 are common and may manifest as seizures. However, the underlying mechanism for development of seizure in patients with COVID-19 is still unclear.

EEG remains a crucial tool in the management of patients with neurological manifestations of COVID-19, especially encephalopathy, seizures, and status epilepticus. Abnormalities, when present, include slowing, periodic discharges, epileptiform discharges, seizures and status epilepticus, indicating the presence of a localized dysfunction, non-specific encephalopathy and cortical irritability in this condition. Several EEG patterns have been reported in seizures and SE associated with COVID-19, including periodic (LPDs, LPDs "plus", BiLPDs, and GPDs) and rhythmic (GRDA) patterns. However, based on the available evidence, no single EEG pattern appears to be specific in relation to this viral infection, even though a prevalent frontal lobe localization has been described.

Seizure or SE during SARS-CoV-2 infection can occur before any other symptom of respiratory and systemic involvement of COVID-19, although more frequently they occur within the context of a clinically overt respiratory infection. The lack of prompt access to EEG recordings may lead to an underestimation of the incidence of epileptic complications, particularly for NCSE. The etiology of SARS-CoV-2-related SE remains mostly unknown. A direct role of SARS-CoV-2 invasion in the CNS or the systemic inflammatory syndrome due to cytokine release has been proposed as a possible explanation.

The clinician should always prioritize identification of any inciting factors (hypoxia, fever, sepsis, electrolyte derangements) and aim to manage seizures in patients with COVID-19 with the application of principles of general management of seizures and status epilepticus. When an AED is initiated, consideration should be given to the pharmacokinetics of the drug, drug interactions, and medication-associated adverse effects. Patient factors such as age, along with any renal and/or hepatic impairment, should also be taken into account.

Further research into the relation of the EEG findings to the clinical status and short- or long-term prognosis of COVID-19 patients may be conducted to help clinicians identify which patients require an EEG procedure and would eventually require treatment, with the ultimate aim of improving their clinical outcomes.

Take-home message

- No specific EEG pattern has been described in COVID-19 patients: diffuse background slowing is the most frequent EEG finding.
- COVID-19 infection does not seem to increase seizure frequency in patients with epilepsy.
- Seizures and/or status epilepticus are often recorded in patients without any evidence of acute or chronic brain injury on imaging and without any alteration in CSF.
- There is no specific anti-seizure medication for COVID-19 patients. ASMs with no/few interactions and with available intravenous formulation should be preferred.

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