



COVID-19-Associated Neurological Manifestations: An Emerging Electroencephalographic Literature

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide since the end of year 2019 and is currently responsible for coronavirus infectious disease 2019 (COVID-19). The first reports considered COVID-19 as a respiratory tract disease responsible for pneumonia, but numerous studies rapidly emerged to warn the medical community of COVID-19-associated neurological manifestations, including encephalopathy at the acute phase and other postinfectious manifestations. Using standard visual analysis or spectral analysis, recent studies reported electroencephalographic (EEG) findings of COVID-19 patients with various neurological symptoms. Most EEG recordings were normal or revealed non-specific abnormalities, such as focal or generalized slowing, interictal epileptic figures, seizures, or status epilepticus. Interestingly, novel EEG abnormalities over frontal areas were also described at the acute phase. Underlying mechanisms leading to brain injury in COVID-19 are still unknown and matters of debate. These frontal EEG abnormalities could emphasize the hypothesis whereby SARS-CoV-2 enters the central nervous system (CNS) through olfactory structures and then spreads in CNS via frontal lobes. This hypothesis is reinforced by the presence of anosmia in a significant proportion of COVID-19 patients and by neuroimaging studies confirming orbitofrontal abnormalities. COVID-19 represents a new viral disease characterized by not only respiratory symptoms but also a systemic invasion associated with extra-respiratory signs. Neurological symptoms must be the focus of our attention, and functional brain evaluation with EEG is crucial, in combination with anatomical and functional brain imaging, to better understand its pathophysiology. Evolution of symptoms together with EEG patterns at the distance of the acute episode should also be scrutinized.

Keywords: SARS-CoV-2, coronavirus, COVID-19, encephalopathy, neurophysiology, EEG

INTRODUCTION

The coronavirus infectious disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, was initially recognized as a respiratory tract disease which could lead to an acute respiratory distress syndrome. However, there is growing evidence of a multi-organ involvement (Gupta et al., 2020). Several authors

reported central nervous system (CNS) manifestations, as anosmia referring to olfactory tract involvement. Other critical presentations, including meningoencephalitis, seizures, status epilepticus (SE), encephalopathy, and altered mental status were also described (Ellul et al., 2020). Neurological complications, such as encephalopathy and seizures/SE, and electroencephalographic (EEG) abnormalities, mainly diffuse slowing and epileptiform discharges, have already been described in past viral pandemics such as influenza A H1N1 (Ekstrand et al., 2010; Kedia et al., 2011; Ibrahim and Haddad, 2014). Results of EEG in patients with COVID-19 were increasingly reported. While the volume of COVID-19-related case studies is still growing, we present the spectrum of EEG findings published at the moment, allowing physicians to be cognizant of this new and emerging literature while dealing with COVID-19 patients.

METHODS

We considered all studies with EEG findings at the acute phase in COVID-19 patients with neurological manifestations. We performed an electronic research from December 1, 2019, to October 1, 2020, using the database PUBMED by Medline with the following terms (in all fields): (i) (“EEG” OR “electroencephalogram” OR “electroencephalography”) AND (“COVID” OR “coronavirus” OR “SARS-CoV-2”) and (ii) (“brain” OR “nervous system” OR “neurology”) AND (“COVID” OR “coronavirus” OR “SARS-CoV-2”). We also scanned the reference lists of all included articles or relevant reviews for studies to be included in our work. We did not include reviews, non-English articles, unavailable full-text articles, and animal studies. After exclusion of duplicates, we screened the title/abstract or full-text reports and decided whether these met the inclusion criteria.

EEG OBSERVATIONS IN COVID-19 PATIENTS

A total of 107 studies were included. Normal EEG findings were reported in adult series (Cecchetti et al., 2020; Helms et al., 2020b; Petrescu et al., 2020) and case reports of patients who displayed various neurological conditions such as focal or generalized seizures (Elgamasy et al., 2020; Fasano et al., 2020; García-Howard et al., 2020; Lyons et al., 2020), non-epileptic seizures (Logmin et al., 2020), myoclonus (Muccioli et al., 2020b; Rábano-Suárez et al., 2020), psychotic symptoms (Lim et al., 2020), encephalopathy (Andriuta et al., 2020; Chaumont et al., 2020; Delorme et al., 2020; Paterson et al., 2020; Perrin et al., 2020), encephalitis (Paterson et al., 2020), brainstem encephalitis (Khoo et al., 2020), and encephalomyelitis (Zoghi et al., 2020). Some studies also reported non-specific abnormalities without more precise EEG features specified by authors (Chougar et al., 2020; Farley and Zuberi, 2020; Freij et al., 2020; Helms et al., 2020a; Pugin et al., 2020).

Diffuse and Focal Slowing

Diffuse slowing of the background activity or focal slowing (sometimes associated with focal sharp waves or epileptiform discharges) was the most frequently published abnormality, especially in adult series (Ayub et al., 2020; Canham et al., 2020; Cecchetti et al., 2020; Chougar et al., 2020; Galanopoulou et al., 2020; Helms et al., 2020a,b; Louis et al., 2020; Pasini et al., 2020; Pellinen et al., 2020; Petrescu et al., 2020; Pilotto et al., 2020a; Scullen et al., 2020; Sethi, 2020; Vespignani et al., 2020) (**Figure 1A**). Main results of adult series including at least 10 patients with confirmed SARS-CoV-2 infection and EEG recordings are summarized in **Table 1**. Diffuse or focal slowing was also associated in many case reports with various neurological presentations, mainly of vascular or inflammatory origin. Main vascular complications included ischemic and hemorrhagic strokes (Chaumont et al., 2020; Díaz-Pérez et al., 2020; Morassi et al., 2020; Soldatelli et al., 2020; Zahid et al., 2020), intracranial hemorrhage with cerebral venous thrombosis (Roy-Gash et al., 2020), posterior reversible encephalopathy syndrome (PRES) (Llansó and Urrea, 2020; Princiotta Cariddi et al., 2020), intracranial vasculitis (Dixon et al., 2020), subarachnoid hemorrhage (Harrogate et al., 2020), acute hemorrhagic leukoencephalitis or leukoencephalomyelitis (Handa et al., 2020; Kihira et al., 2020; Svedung Wettervik et al., 2020), and acute necrotizing encephalopathy (Delamarre et al., 2020; Virhammar et al., 2020). Main inflammatory syndromes included acute disseminated encephalomyelitis (ADEM) (Parsons et al., 2020; Umapathi et al., 2020), acute leukoencephalopathy (Abenza-Abildúa et al., 2020; Anand et al., 2020; Brun et al., 2020; Huang H. et al., 2020; Kihira et al., 2020; Klironomos et al., 2020), acute leukoencephalitis (Perrin et al., 2020), meningoencephalitis without any acute lesions on brain imaging (Duong et al., 2020; El-Zein et al., 2020; Pilotto et al., 2020b), Bickerstaff encephalitis (Llorente Ayuso et al., 2020), and concomitant autoimmune encephalitis (Grimaldi et al., 2020; Panariello et al., 2020). In critically ill patients, other conditions were described including post-hypoxic injury (Fischer et al., 2020; Radmanesh et al., 2020; Radnis et al., 2020; Vellieux et al., 2020), unresponsiveness after sedation discontinuation (Espinosa et al., 2020; Vellieux et al., 2020), encephalopathy or altered mental status without any acute lesions on brain imaging (Chaumont et al., 2020; Delorme et al., 2020; Filatov et al., 2020; Gaughan et al., 2020; Jang et al., 2020; Manganelli et al., 2020; Muccioli et al., 2020a; Méndez-Guerrero et al., 2020; Romero-Sánchez et al., 2020; Shekhar et al., 2020), encephalopathy with seizures (Ashraf and Sajed, 2020; Benameur et al., 2020; Farhadian et al., 2020; Haddad et al., 2020), defined toxic/metabolic encephalopathy (Flamand et al., 2020; Radmard et al., 2020; Rasmussen et al., 2020), neuroleptic malignant syndrome (Kajani et al., 2020), after seizures or SE (Anand et al., 2020; Edén et al., 2020; Emami et al., 2020), and critical illness-associated cerebral microbleeds (De Stefano et al., 2020). EEG slowing was also observed in pediatric reports (Abdel-Mannan et al., 2020; Abel et al., 2020; Dugue et al., 2020; Panda et al., 2020).

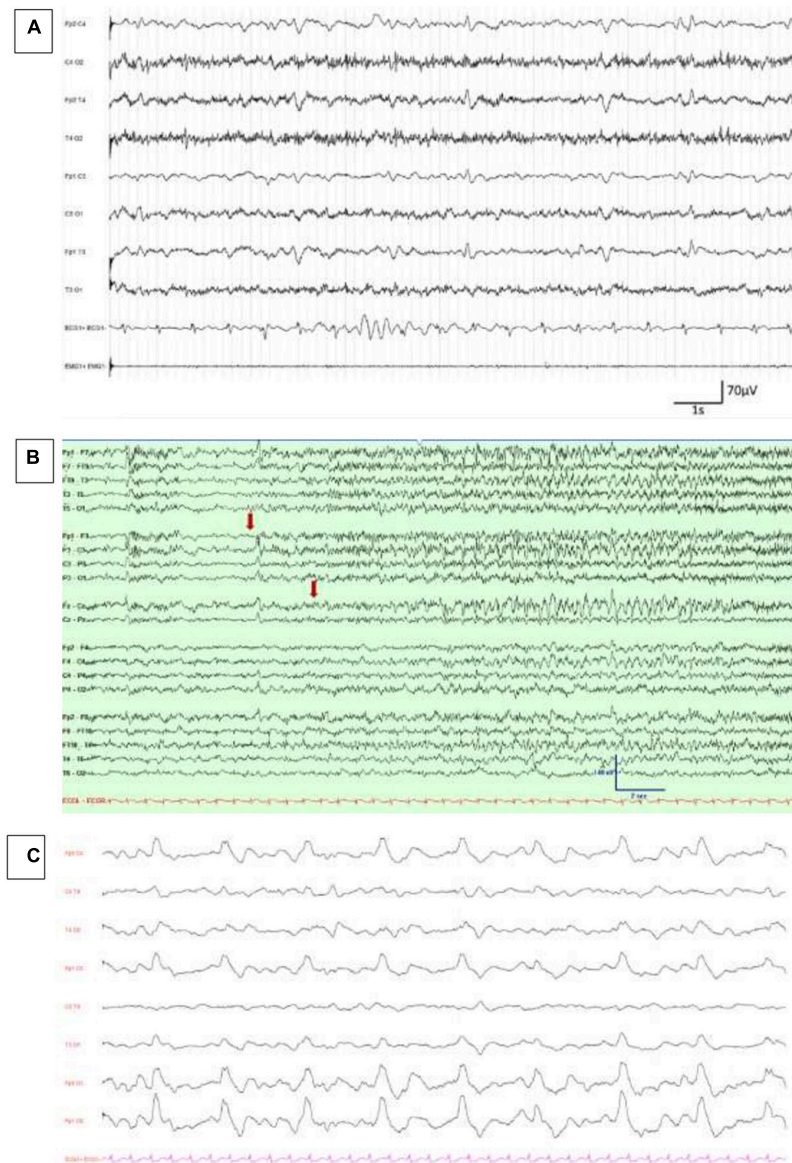


FIGURE 1 | EEG findings in COVID-19 patients. **(A)** Diffuse theta–delta slowing and continuous generalized periodic discharges, reproduced with authors' agreement from Petrescu et al. (2020). **(B)** Emergence of low-amplitude ictal fast rhythmic activity over left frontocentral and midline regions (marked with an arrow), reproduced with authors' agreement from Somani et al. (2020). **(C)** Continuous, periodic, monomorphic diphasic, delta slow waves over both frontal areas, published in Vellieux et al. (2020).

Seizures and SE

Seizures and/or SE were recorded in 10 patients out of 111 included in the series of Pellinen et al. (2020), in 2 out of 22 in the series of Louis et al. (2020), in 1 out of 37 in the series of Ayub et al. (2020), in 1 out of 15 in the series of Pasini et al. (2020), in 1 out of 27 in the series of Scullen et al. (2020), and in an unknown precise number of patients out of the 73 included in the series of Chougar et al. (2020) (Table 1).

Seizures and/or SE were recorded in reports of patients without any acute or chronic cortical lesions on brain imaging nor cerebrospinal fluid (CSF) abnormalities. The EEG of the

patient reported by Balloy et al. (2020) revealed two widespread, but predominantly in frontal localizations, seizures that were interrupted by a moderate interictal frontal activity. Sohal and Mansur (2020) reported a patient whose 24-h EEG revealed six left temporal seizures and left temporal sharp waves. One of the two patients reported by Somani et al. (2020) displayed, on a continuous EEG (cEEG) monitoring, multiple seizures emanating from the midline and left frontocentral regions (Figure 1B). Hepburn et al. (2020) reported the cases of two patients whose cEEG monitoring showed, for the first one, three focal seizures arising from the right frontocentral region and,

TABLE 1 | Main results of case series including at least 10 patients admitted for COVID-19 with EEG recordings.

Series	Patients' features	Brain imaging results	CSF results	EEG settings	Ongoing psychoactive drugs	Main EEG results
Ayub et al., 2020 USA Monocentric	> Included, <i>n</i> =37 M/F, <i>n</i> =27/10 Median age: 66 years Anosmia, <i>n</i> =4 Intubated, <i>n</i> =28 <i>Prior neurological history</i> Stroke, <i>n</i> =6 Cerebral aneurysm, <i>n</i> =1 Epilepsy, <i>n</i> =1 ICH, <i>n</i> =1 DLB, <i>n</i> =1	> CT-scan, <i>n</i> = 35 and MRI, <i>n</i> = 9 IS, <i>n</i> =3 ICH, <i>n</i> =3	> CSF examination, <i>n</i> =4 Abnormal WBC count, <i>n</i> =2 Abnormal protein level, <i>n</i> =1	> Total EEG recordings, <i>n</i> = 37 > Types of EEG Long-term monitoring EEG, <i>n</i> =23 > Period of recordings: NA > EEG indication Altered mental status, <i>n</i> =24 Possible seizures, <i>n</i> =11 Cardiac arrest, <i>n</i> =2	> At time of EEG or the day prior Propofol, <i>n</i> =19 Dexmedetomidine, <i>n</i> =13 Empiric AD, <i>n</i> =11 Midazolam or lorazepam, <i>n</i> =8 Ketamine, <i>n</i> =2	> Background activity Absent PDR, <i>n</i> =34 Asymmetry, <i>n</i> =4 Generalized delta and theta slowing, <i>n</i> =34 Burst suppression, <i>n</i> =5 Unreactive, <i>n</i> =1 > Rhythmic and periodic patterns GPDs without triphasic waves, <i>n</i> =4 GPDs with triphasic waves, <i>n</i> =8 SIRPIDs, <i>n</i> =3 GRDA, <i>n</i> =5 LRDA, <i>n</i> =1 > Epileptiform findings and seizures Burst suppression with epileptiform activity, <i>n</i> =4 Focal sporadic discharges, <i>n</i> =1 Multifocal sporadic discharges, <i>n</i> =6 Generalized sporadic discharges without triphasic waves, <i>n</i> =8 Generalized NCSE, <i>n</i> =1
Canham et al., 2020 United Kingdom Multicentric	> Included, <i>n</i> =10 M/F, <i>n</i> =8/2 Median age: 65 years Anosmia/agueusia: NA Intubated: NA <i>Prior neurological history</i> SAH, <i>n</i> =1 Stroke, <i>n</i> =1 Learning difficulties, <i>n</i> =1 Essential tremor, <i>n</i> =1 Epilepsy, <i>n</i> =1	> CT-scan, <i>n</i> =10 Normal, <i>n</i> =3 Small vessel disease, <i>n</i> =4 SAH, <i>n</i> =2 Atrophy, <i>n</i> =2 > MRI, <i>n</i> =4 Normal, <i>n</i> =1 Small vessel disease, <i>n</i> =2 IS, <i>n</i> =1 Atrophy, <i>n</i> =1	> CSF examination, <i>n</i> =6 Abnormal WBC count, <i>n</i> =3 Abnormal protein level, <i>n</i> =4 Negative HSV 1&2, VZV and enterovirus PCR, <i>n</i> =6 Negative SARS-CoV-2 PCR, <i>n</i> =2	> Total EEG recordings, <i>n</i> =11 > Types of EEG 9 electrodes 20-30 min EEG, <i>n</i> =11 > Period of recordings: NA > EEG indication Altered mental status, <i>n</i> =6 Seizure, <i>n</i> =6 Delirium, <i>n</i> =2	> At time of EEG Levetiracetam, <i>n</i> =6 Propofol, <i>n</i> =2 Alfentanil, <i>n</i> =2 Phenytoin, <i>n</i> =2 Valproate, <i>n</i> =2 Lamotrigine, <i>n</i> =1 Gabapentin, <i>n</i> =1 Carbamazepine, <i>n</i> =1 Lacosamide, <i>n</i> =1 Primidone, <i>n</i> =1 Amitriptyline, <i>n</i> =1 Lorazepam, <i>n</i> =1 Citalopram, <i>n</i> =1 Olanzapine, <i>n</i> =1 Clozapine, <i>n</i> =1 Paliperidone, <i>n</i> =1 Midazolam, <i>n</i> =1 Remifentanyl, <i>n</i> =1 Morphine, <i>n</i> =1	> Background activity Generalized symmetrical slowing, <i>n</i> =11 Anterior emphasis of slow activity, <i>n</i> =3 Asymmetry, <i>n</i> =1 > Rhythmic and periodic patterns FIRDA, <i>n</i> =1 > Epileptiform findings and seizures, <i>n</i>=0
Cecchetti et al., 2020 Italy Monocentric	> Included, <i>n</i> =18 M/F, <i>n</i> =11/7 Mean age: 67 years Anosmia/agueusia, <i>n</i> =0 Intubated: NA <i>Prior neurological history</i> NA	> CT-scan and/or MRI PRES, <i>n</i> =1 Remote ICH, <i>n</i> =1 Remote IS, <i>n</i> =1 Glioblastoma, <i>n</i> =1 Metastasis, <i>n</i> =1 Traumatic SDH, <i>n</i> =1 Anterior pontine demyelinating lesion, <i>n</i> =1	> CSF examination, <i>n</i> =1 Normal WBC count, <i>n</i> =1 Normal protein level, <i>n</i> =1 Negative bacteriologic and virologic assays (including SARS-CoV-2 RT-PCR), <i>n</i> =1	> Total EEG recordings, <i>n</i> =18 > Types of EEG Basal EEG, <i>n</i> =18 > Period of recordings: NA > EEG indication Transient loss of consciousness, <i>n</i> =5 Seizures/spasms, <i>n</i> =5 Coma, <i>n</i> =5 Delirium, <i>n</i> =3	NA	> Background activity Normal or with mild alteration, <i>n</i> =5 With moderate alteration, <i>n</i> =9 With severe alteration, <i>n</i> =4 Generalized slowing, <i>n</i> =16 Anterior (bifrontal) prevalence of slow waves, <i>n</i> =10 Focal slowing, <i>n</i> =7 > Rhythmic and periodic patterns, <i>n</i>=0 > Epileptiform findings and seizures Epileptiform discharges, <i>n</i> =2 Seizures, <i>n</i> =0

(Continued)

TABLE 1 | Continued

Series	Patients' features	Brain imaging results	CSF results	EEG settings	Ongoing psychoactive drugs	Main EEG results
Chougar et al., 2020 France Monocentric	>Included, <i>n</i> =73 M/F, <i>n</i> =48/25 Mean age: 56 years Anosmia/ageusia, <i>n</i> =4 Intubated: NA <i>Prior neurological history</i> Stroke, <i>n</i> =NA	>MRI, <i>n</i> =73 No significant abnormalities, <i>n</i> =30 Acute IS, <i>n</i> =17 Multiple microhemorrhages, <i>n</i> =8 Multifocal enhancing WM lesions, <i>n</i> =4 Basal ganglia lesions, <i>n</i> =4 Hypoxic-ischemic lesions, <i>n</i> =3 Cytotoxic lesions of the CC, <i>n</i> =3 Central pontine myelinolysis, <i>n</i> =3 PRES, <i>n</i> =2 Meningeal enhancement, <i>n</i> =2 Neuritis, <i>n</i> =2 Deep venous thrombosis, <i>n</i> =1 Corticospinal tracts FLAIR hyperintensity, <i>n</i> =1 >Perfusion MRI, <i>n</i> =46 Seizure-related perfusion abnormalities, <i>n</i> =9 Recent or old vascular lesions-related perfusion abnormalities, <i>n</i> =4 Perfusion abnormalities unrelated to seizures or ischemia, <i>n</i> =10	>CSF examination, <i>n</i> =39 Abnormal WBC count, <i>n</i> =8 Abnormal protein level, <i>n</i> =10 Oligoclonal bands, <i>n</i> =2 Negative bacteriologic and virologic assays (including HSV 1&2, VZV, CMV, EBV and SARS-CoV-2 RT-PCR), <i>n</i> =39	>Total EEG recordings, <i>n</i> =40 >Types of EEG: NA >Period of recordings: NA >EEG indication: NA	NA	>Background activity / Epileptiform findings and seizures Pathological findings related to seizure or encephalopathy, <i>n</i> =9 Non-specific findings, <i>n</i> =24 >Rhythmic and periodic patterns: NA
Galanopoulou et al., 2020 USA Multicentric	>Included, <i>n</i> =22 M/F, <i>n</i> =14/8 Mean age: 63 years Anosmia/ageusia: NA Intubated, <i>n</i> =14 <i>Prior neurological history</i> Epilepsy, <i>n</i> =4 Neurological disorders except epilepsy, <i>n</i> =7	>Modality: NA (at least 1 brain MRI) Subcortical and mild periventricular WM signal hyperintensity, <i>n</i> =1 SAH due to aneurysm, <i>n</i> =1 SDH, <i>n</i> =1	NA	>Total EEG recordings, <i>n</i> =31 >Types of EEG 10 electrodes/8-channel EEG, <i>n</i> =20 Routine EEG, <i>n</i> =4 cEEG, <i>n</i> =7 >Period of recordings: NA >EEG indication Altered mental status, <i>n</i> =20 Motor seizure-like event or seizure at presentation or confusion resembling prior seizures, <i>n</i> =12 Gaze deviation, <i>n</i> =2 Confusion at presentation and no prior seizures, <i>n</i> =1	>During hospital stay (at time of EEG: NA) Sedatives, <i>n</i> =14 AD, <i>n</i> =12	>Background activity Bilateral slowing, <i>n</i> =22 Focal slowing, <i>n</i> =5 Asymmetry, <i>n</i> =3 Absent PDR, <i>n</i> =18 Slow PDR, <i>n</i> =4 Discontinuous or burst suppression, <i>n</i> =1 >Rhythmic and periodic patterns Generalized or frontal RDA, <i>n</i> =3 Temporal LRDA, <i>n</i> =1 Bifrontal sharply contoured periodic waves, <i>n</i> =1 >Epileptiform findings and seizures Bilateral frontal sharp waves, <i>n</i> =6 Unilateral frontal sharp waves, <i>n</i> =2 Temporal or hemispheric sharp waves, <i>n</i> =2 Seizures, <i>n</i> =0
Helms et al., 2020a France Bicentric	>Included, <i>n</i> =58 M/F: NA Median age: 63 years Anosmia/ageusia: NA Intubated, <i>n</i> =58 <i>Prior neurological history</i> TIA, partial epilepsy, MCI, <i>n</i> =7	>MRI, <i>n</i> =13 Leptomeningeal enhancement, <i>n</i> =8 Acute IS, <i>n</i> =2 Subacute IS, <i>n</i> =1 >Perfusion MRI, <i>n</i> =11 Bilateral frontotemporal hypoperfusion, <i>n</i> =11	>CSF examination, <i>n</i> =7 Normal WBC count, <i>n</i> =7 Elevated protein level, <i>n</i> =1 Oligoclonal bands with mirror pattern, <i>n</i> =2 Negative SARS-CoV-2 RT-PCR, <i>n</i> =7	>Total EEG recordings, <i>n</i> =8 >Types of EEG: NA >Period of recordings: NA >EEG indication: NA	>During hospital stay (at time of EEG: NA) Sufentanil, <i>n</i> =58 Midazolam, <i>n</i> =50 Propofol, <i>n</i> =27	>Background activity Nonspecific changes, <i>n</i> =8 Diffuse bifrontal slowing, <i>n</i> =1 >Rhythmic and periodic patterns: NA >Epileptiform findings and seizures: NA

(Continued)

TABLE 1 | Continued

Series	Patients' features	Brain imaging results	CSF results	EEG settings	Ongoing psychoactive drugs	Main EEG results
Helms et al., 2020b France Bicentric	>Included, n=140 M/F, n=100/40 Median age: 62 years Anosmia/ageusia: NA Intubated, n=140 <i>Prior neurological history</i> Stroke/TIA, n = 9 Migraine, n = 5 Mild cognitive alteration, n=4 Partial epilepsy, n=2 Trauma brain injury, n=2 Aneurysm, n=1	>MRI, n=28 Subarachnoid spaces FLAIR and T1 contrast enhancement, n=17 WM microhemorrhages, n=7 WM FLAIR hyperintensities, n=4, with small foci of contrast enhancement, n=2 and diffusion hyperintensities, n=2 Acute IS, n=2 Intraparenchymal hematoma, n=1 Preexisting IS, n=1 >Perfusion MRI, n=26 Perfusion abnormalities, n=17	>CSF examination, n=25 Elevated WBC count, n=3 Elevated protein level, n=8 Elevated IgG levels, n=9 Oligoclonal bands with mirror pattern, n=13 Positive SARS-CoV-2 RT-PCR (negative result in blood), n=1 Negative bacterial cultures and viral research (HSV 1&2, enterovirus), n = 25	>Total EEG recordings, n=42 >Types of EEG: NA >Period of recordings: NA > EEG indication Unexplained and persistent altered consciousness after prolonged sedation discontinuation (> 3 days) Multimodality neurological screening in combination with brain MRI and/or CSF examination	>During hospital stay (at time of EEG: NA) Midazolam, n=121 Sufentanil, n=138 Propofol, n=83	>Background activity Normal, n=5 Unspecific abnormalities, with low voltage, rapid rhythm, and lack of asymmetry, n=26 Diffuse, especially bifrontal, slow activity n=11 >Rhythmic and periodic patterns: NA > Epileptiform findings and seizures: NA
Louis et al., 2020 USA Monocentric	>Included, n=22 M/F, n=14/8 Mean age: 67 years Anosmia/ageusia: NA Intubated, n=18 <i>Prior neurological history</i> Epilepsy, n=2 Stroke, n=1 Headache, n=1 Traumatic brain injury, n=1 Spinal stenosis, n=1	>CT-scan, n=18 Possible IS, n=2 Acute IS, n=1 ICH, n=1 >MRI, n=1 Acute IS, n=1	NA	>Total EEG recordings, n=22 >Types of EEG cEEG, n=19 Routine EEG, n=3 >Period of recordings: NA >EEG indication Altered mental status, n=17 Seizure-like event, n=5	>At time of EEG Sedative drugs (including fentanyl, propofol and/or midazolam), n=14	>Background activity Continuous generalized polymorphic delta slowing, n=19 Slow PDR, n=9 Absent PDR, n=11 Normal PDR, n=2 >Rhythmic and periodic patterns GPDs, n=7 GPDs with triphasic morphology, n=5 GPDs with sharply contoured morphology, n=2 Intermittent GRDA, n=11 Hemispheric LRDA, n=1 >Epileptiform findings and seizures Epileptic abnormalities, n=5 Seizures, n=2
Pasini et al., 2020 Italy Monocentric	>Included, n=15 M/F, n=6/9 Mean age: 65 years Anosmia/ageusia: NA Intubated: NA <i>Prior neurological history</i> Cognitive decline, n=2 Limbic encephalitis, n=1 Frontal metastasis, n=1	>CT-scan, n=8 Normal, n=8 >MRI, n=6 Mild WM T2 hyperintensity, n=2	>CSF examination, n=5 Elevated protein level, n=1 Negative SARS-CoV-2 detection, n=5	>Total EEG recordings, n=15 >Types of EEG 18 electrodes EEG, n=15 >Period of recordings: NA >EEG indication Confusion, n=11 Impairment of consciousness, n=4 with post-anoxic coma, n=2 Aphasia, n=1	NA	<i>Subset of non post-anoxic patients, n=13</i> >Background activity Generalized slowing with theta prevalence, n=5 Generalized slowing with intrusions of theta/delta activity, n=4 Focal slowing predominantly over the frontal or central regions n=3 Unreactive, n=10 >Rhythmic and periodic patterns FIRDA, n=1 >Epileptiform findings and seizures Epileptiform abnormalities, n=0 <i>Subset of post-anoxic comas, n=2</i> Severely suppressed activity, n=1 Discontinued activity compatible with post-anoxic SE, n=1 Unreactive, n=2

(Continued)

TABLE 1 | Continued

Series	Patients' features	Brain imaging results	CSF results	EEG settings	Ongoing psychoactive drugs	Main EEG results
Pellinen et al., 2020 USA Multicentric	>Included, <i>n</i> =111 M/F, <i>n</i> =79/32 Median age: 64 years Anosmia/ageusia: NA Intubated, <i>n</i> =79 <i>Prior neurological history</i> Stroke, <i>n</i> =23 Epilepsy, <i>n</i> =13 ICH, <i>n</i> =4 Dementia, <i>n</i> =4 Developmental delay/intellectual disability, <i>n</i> =3 Brain tumor, <i>n</i> =3 Traumatic brain injury, <i>n</i> =2 Parkinson disease, <i>n</i> =2 Vascular malformation, <i>n</i> =1 Tuberous sclerosis complex, <i>n</i> =1 Herpes encephalitis, <i>n</i> =1	>Brain imaging, <i>n</i> =90 (with CT-scan only, <i>n</i> =75) Acute IS, <i>n</i> =18 Acute ICH, <i>n</i> =15 Cerebral edema, <i>n</i> =6 Diffuse leukoencephalopathy with microhemorrhages, <i>n</i> =4 Mixed acute ischemic and hemorrhagic lesions, <i>n</i> =3	NA	>Total EEG recordings, <i>n</i> =118 >Types of EEG 21-channel cEEG for a target of at least 24 hours, <i>n</i> =111 Rapid EEG system with 8-bipolar channel montage 0.5-12 hours, <i>n</i> =7 >Period of recordings: NA >EEG indication Persistent encephalopathy, <i>n</i> =72 Paroxysmal activity of unclear cause, <i>n</i> =25 Seizure exacerbation, <i>n</i> =10 Cardiac arrest <i>n</i> =11	>During EEG Sedative drugs (including propofol, midazolam, pentobarbital, dexmedetomidine and/or fentanyl) <i>n</i> =67 >Prior to EEG AD, <i>n</i> =57	>Background activity Normal, <i>n</i> =5 Mild generalized slowing, <i>n</i> =17 Moderate generalized slowing, <i>n</i> =60 Severe generalized slowing/discontinuous/ECL, <i>n</i> =29 Focal slowing, <i>n</i> =27 >Rhythmic and periodic patterns GRDA, <i>n</i> =4 LRDA, <i>n</i> =7 LRDA and GRDA, <i>n</i> =2 GPDs, <i>n</i> =11 LPDs, <i>n</i> =3 >Epileptiform findings and seizures Focal epileptiform discharges, <i>n</i> =12 Multifocal epileptiform discharges, <i>n</i> =6 Generalized epileptiform discharges, <i>n</i> =5 Seizures, <i>n</i> =8 NCSE, <i>n</i> =2
Petrescu et al., 2020 France Monocentric	>Included, <i>n</i> =36 M/F, <i>n</i> =26/10 Mean age: 70 years Anosmia/ageusia: NA Intubated, <i>n</i> =11 <i>Prior neurological history</i> Dementia, <i>n</i> =10 Stroke, <i>n</i> =3 SDH, <i>n</i> =2 Memory impairment, <i>n</i> =1 Hydrocephalus, <i>n</i> =1 Epilepsy, <i>n</i> =1 Parkinson disease, <i>n</i> =1	>CT-scan, <i>n</i> =14 Normal, <i>n</i> =4 Atrophy, <i>n</i> =9 IS, <i>n</i> =2 Calcification, <i>n</i> =2 SDH, <i>n</i> =1 Leukoaraiosis, <i>n</i> =1 Meningioma, <i>n</i> =1 Postoperative lesion, <i>n</i> =1 >MRI, <i>n</i> =11 Atrophy, <i>n</i> =4 IS, <i>n</i> =2 SDH, <i>n</i> =2 Gliosis of CC, <i>n</i> =1 Leukoaraiosis, <i>n</i> =1 Leptomeningeal enhancement, <i>n</i> =1 Probable septic lesions (multiple ischemic and hemorrhagic lesions) related to endocarditis, <i>n</i> =1 Multiple FLAIR hyperintense lesions, <i>n</i> =1	>CSF examination, <i>n</i> =4 Normal, <i>n</i> =4	>Total EEG recordings, <i>n</i> =40 >Types of EEG Routine 20 min EEG, <i>n</i> =40 >Period of recordings: NA >EEG indication Fluctuating alertness, <i>n</i> =13 Confusion, <i>n</i> =9 Delayed awakening after stopping sedation or inadequate emerge of sedation, <i>n</i> =8 Focal neurologic symptoms, <i>n</i> =6 Seizures, <i>n</i> =3 Abnormal movements, <i>n</i> =3 Cardiac arrest, <i>n</i> =1 Encephalopathy, <i>n</i> =1 Control follow-up, <i>n</i> =1	>At time of EEG Levetiracetam, <i>n</i> =6 Sedations, <i>n</i> =5 Risperidone, <i>n</i> =4 Clobazam, <i>n</i> =2 Dexmedetomidine, <i>n</i> =2 Citalopram or escitalopram, <i>n</i> =2 Midazolam, <i>n</i> =2 Oxazepam, <i>n</i> =2 Morphine, <i>n</i> =2 Oxazepine, <i>n</i> =1 Haloperidol, <i>n</i> =1 Doxylamine succinate, <i>n</i> =1 Lacosamide, <i>n</i> =1 Diazepam, <i>n</i> =1 Valproate, <i>n</i> =1 Bromazepam, <i>n</i> =1 Gabapentin, <i>n</i> =1 Paroxetine, <i>n</i> =1 Alprazolam, <i>n</i> =1 Hydroxyzine, <i>n</i> =1 Mianserine, <i>n</i> =1	>Background activity Normal, <i>n</i> =4 Mildly altered, <i>n</i> =19 Moderately altered, <i>n</i> =4 Severely altered, <i>n</i> =8 Critically altered, <i>n</i> =5 Focal bioccipital slowing, <i>n</i> =1 Sporadic triphasic waves, <i>n</i> =1 >Rhythmic and periodic patterns RDA, <i>n</i> =7 with frontal predominant, <i>n</i> =1 GPDs, <i>n</i> =6 Multifocal PDs, <i>n</i> =2 >Epileptiform findings and seizures Epileptiform discharges, <i>n</i> =0 Seizures, <i>n</i> =0

(Continued)

TABLE 1 | Continued

Series	Patients' features	Brain imaging results	CSF results	EEG settings	Ongoing psychoactive drugs	Main EEG results
Pilotto et al., 2020a Italy Multicentric	> Included patients, <i>n</i> =25 M/F, <i>n</i> =15/10 Mean age: 66 years Anosmia/ageusia: NA Intubated, <i>n</i> =4 <i>Prior neurological history</i> Stroke, <i>n</i> =2 Mental retardation, <i>n</i> =1 Possible encephalitis and Behçet disease, <i>n</i> =1	> MRI, <i>n</i> =25 Normal, <i>n</i> =13 Multiple subcortical T2-hyperintensities, <i>n</i> =4 Focal cortical T2 and DWI hyperintensities, <i>n</i> =3 Acute necrotizing encephalopathy, <i>n</i> =2 Limbic encephalitis, <i>n</i> =2 ADEM, <i>n</i> =1 Leptomeningeal enhancement, <i>n</i> =1	> CSF examination, <i>n</i> =25 Normal, <i>n</i> =8 Elevated WBC count, <i>n</i> =9 Elevated protein level, <i>n</i> =15 Negative bacteriological and virological screening, <i>n</i> =25 Negative SARS-CoV-2 RT-PCR, <i>n</i> =14	> Total EEG recordings, <i>n</i> =25 > Types of EEG: NA > Period of recordings: NA > EEG indication Delirium/altered mental status, <i>n</i> =17 Aphasia/dysarthria, <i>n</i> =6 Seizures, <i>n</i> =6	NA	> Background activity Generalized slowing especially localized to frontal derivations, <i>n</i> =16 > Rhythmic and periodic patterns: NA > Epileptiform findings and seizures Focal epileptic alterations, <i>n</i> =6
Scullen et al., 2020 USA Monocentric	> Included patients, <i>n</i> =27 M/F, <i>n</i> =14/13 Mean age: 60 years Anosmia/ageusia, <i>n</i> =1 Intubated: NA <i>Prior neurological history</i> Stroke, <i>n</i> =3 Pseudotumor cerebri, <i>n</i> =1	> CT-scan, <i>n</i> =27 Focal hypodensities in deep structures, <i>n</i> =14 Diffuse hypoaattenuation, <i>n</i> =6 Subacute IS, <i>n</i> =4 Subcortical parenchymal hematoma, <i>n</i> =3 > MRI, <i>n</i> =8 Viral encephalitis with diffuse involvement of the deep WM, CC and basal ganglia, <i>n</i> =NA	NA	> Total EEG recordings, <i>n</i> =13 > Types of EEG cEEG, <i>n</i> =13 > Period of recordings: NA > EEG indication Pronounced encephalopathy not explained by previous CT alone, <i>n</i> =9 Pronounced encephalopathy not explained by previous combined CT and MRI, <i>n</i> =4	NA	> Background activity Generalized encephalopathy (i.e. irregular slowing with delta and theta frequency oscillations), <i>n</i> =11 > Rhythmic and periodic patterns: NA > Epileptiform findings and seizures NCSE, <i>n</i> =1
Sethi, 2020 USA Monocentric	NA	NA	NA	> Total EEG recordings, <i>n</i> =20 > Types of EEG: NA > Period of recordings: NA > EEG indication Altered mental status	NA	> Background activity Diffuse theta and delta slowing > Rhythmic and periodic patterns: NA > Epileptiform findings and seizures: NA
Vespignani et al., 2020 France Multicentric	> Included patients, <i>n</i> =26 <i>Subset of patients with PDs, n=5</i> M/F, <i>n</i> =4/1 Mean age: 67 years Anosmia/ageusia: NA Intubated, <i>n</i> =4 Prior neurological history: NA	> CT-scan, <i>n</i> =1 Occipital cyst, <i>n</i> =1 > MRI, <i>n</i> =1 Diffuse WM hyperintensities, <i>n</i> =1	> CSF examination, <i>n</i> =2 Normal, <i>n</i> =2	> Total EEG recordings, <i>n</i> =26 > Types of EEG 9 electrodes 30 min EEG, <i>n</i> =26 > Period of recordings: NA > EEG indication Mental status changes Poor responsiveness Determine the presence of SE in non-arousable patients <i>Subset of the 5 patients with PDs</i> Poor or absent responsiveness, <i>n</i> =4 Cardiac arrest, <i>n</i> =1 Confusion and lethargy, <i>n</i> =1	<i>Subset of the 5 patients with PDs</i> > At time of EEG Propofol, <i>n</i> =2 Fentanyl, <i>n</i> =2 Midazolam, <i>n</i> =1	> Background activity Diffuse slowing without PDs, <i>n</i> =19 Isoelectric, <i>n</i> =2 > Rhythmic and periodic patterns GPDs with frontal involvement, <i>n</i> =4 LPDs with frontal involvement, <i>n</i> =1 > Epileptiform findings and seizures, n=0

AD: antiepileptic drug, ADEM: acute disseminated encephalomyelitis, CC: corpus callosum, cEEG: continuous EEG, CMV: cytomegalovirus, CSF: cerebrospinal fluid, CT: computed tomography, DLB: dementia with Lewy bodies, DWI: diffusion weighted imaging, EBV: Epstein-Barr virus, ECI: electrocerebral inactivity, EEG: electroencephalogram, FIRDA: frontal intermittent rhythmic delta activity, FLAIR: fluid-attenuated inversion recovery, GPDs: generalized periodic discharges, GRDA: generalized rhythmic delta activity, HSV: herpes simplex virus, ICH: intracranial hemorrhage, IS: ischemic stroke, LRDA: lateralized rhythmic delta activity, MCI: mild cognitive impairment, M/F: male/female, n: number, MRI: magnetic resonance imaging, NA: not available, NCSE: non convulsive SE, PCR: polymerase chain reaction, PDR: posterior dominant rhythm, PDs: periodic discharges, PRES: posterior reversible encephalopathy syndrome, RDA: rhythmic delta activity, RT-PCR: reverse transcriptase PCR, SAH: subarachnoid hemorrhage, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, SDH: subdural hematoma, SE: status epilepticus, SJRPIDs: stimulus-induced rhythmic, periodic or ictal discharges, TIA: transient ischemic attack, VZV: varicella-zoster virus, WBC: white blood cells, WM: white matter.

for the second one, left more than right frontotemporal seizures which progressed to focal SE. The EEG of the patient reported by Le Guennec et al. (2020) revealed a non-convulsive SE (NCSE) over the right frontal region. The brain MRI of this patient only showed peri-ictal diffusion abnormalities over the right orbital and mesial prefrontal cortex and right caudate nucleus. Flamand et al. (2020) reported the case of a patient who benefited from several EEG. The first two EEG findings were consistent with a bilateral frontal SE. One EEG in the series of five patients reported by Chen et al. (2020) showed a bifrontal SE, and another one revealed a generalized NCSE. Finally, the EEG of the patient reported by Rodrigo-Armenteros et al. (2020) showed a bilateral frontotemporal NCSE.

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. Among the four patients with a PRES reported by Parauda et al. (2020), two had seizures or SE emanating from posterior regions: for the first one, a focal NCSE arising from the left posterior quadrant and, for the second one, focal seizures arising from the right posterior quadrant. The history of a 2-month-old boy was published by Schupper et al. (2020). His brain imaging revealed multiple infarctions with hemorrhagic transformations, and his cEEG showed NCSE. Zanin et al. (2020) published the case of a patient with diffuse CNS demyelinating lesions on brain and spine imaging whose EEG revealed two seizures starting from the right frontotemporal region and diffusing in the homologous contralateral hemisphere. Hussein et al. (2020) reported the case of a patient with an ADEM whose EEG revealed left hemispheric seizures and, 3 days later, brief focal right posterior seizures. Finally, Bernard-Valnet et al. (2020) reported the history of a patient with a lymphocytic meningitis on CSF analysis with normal brain MRI whose EEG showed a focal anterior NCSE.

Seizures and/or SE were recorded in patients with a prior neurological history and radiological sequelae but without any acute lesions. The EEG of the second patient, who had a prior history of skull base surgery, reported by Somani et al. (2020) showed recurrent seizures emanating from either right or left frontocentroparietal regions. Vollono et al. (2020) reported the case of a left frontocentrotemporal SE in a patient with a remote *herpes simplex virus 1* encephalitis.

Seizures were reported on cEEG in the series of 33 patients published by Radmard et al. (2020), as frontotemporal and parasagittal seizures in two patients, but without precise imaging or CSF results available for these two patients.

Rhythmic and Periodic Discharges

Rhythmic discharges were mentioned in series, as generalized rhythmic delta activity (GRDA) (Ayub et al., 2020; Galanopoulou et al., 2020; Louis et al., 2020; Pellinen et al., 2020; Petrescu et al., 2020), lateralized rhythmic delta activity (LRDA) (Ayub et al., 2020; Galanopoulou et al., 2020; Louis et al., 2020; Pellinen et al., 2020), and frontal intermittent rhythmic delta activity (Canham et al., 2020; Pasini et al., 2020) (Table 1). Rhythmic patterns were also reported in a few case reports. Vandervorst et al. (2020) published the EEG of a patient with a clinical and radiological picture of encephalitis with temporal bilateral more left than

right imaging abnormalities. The EEG showed short-lasting left temporal LRDA. In the series of Beach et al. (2020), one patient, with a previous history of dementia with Lewy bodies and remote traumatic brain injury, displayed GRDA with sharp contouring and bifrontal predominance, without any acute lesions on brain imaging. The EEG of the three other patients reported in the series of Chen et al. (2020) previously mentioned revealed GRDA, with unremarkable CSF analysis for the three and no acute lesions on brain imaging for one of them (unavailable for the two others). One EEG recorded among the seven patients reported by Anand et al. (2020) showed GRDA in a patient with extensive leukoencephalopathy on brain MRI and normal CSF sample.

Periodic discharges were noted in series, as generalized periodic discharges (GPDs) (Ayub et al., 2020; Galanopoulou et al., 2020; Louis et al., 2020; Pellinen et al., 2020; Petrescu et al., 2020; Vespignani et al., 2020) and lateralized periodic discharges (LPDs) (Pellinen et al., 2020; Petrescu et al., 2020; Vespignani et al., 2020) (Table 1). Especially, in the series of Vespignani et al. (2020), five EEGs out of 26 showed periodic discharges. Four of these five patients were under mechanical ventilation (MV), and three were sedated. One patient suffered from a cardiac arrest. EEG showed periodic (with a < 4 s interval), monomorphic biphasic, delta activity, which was diffuse with frontal predominance for four and lateralized over right frontal area for one. The second patient reported in the work of Beach et al. previously mentioned presented with a left-sided acute-on-chronic subdural hematoma (SDH) due to a fall with head trauma. The EEG showed frequent runs of epileptiform GPDs (Beach et al., 2020). Young et al. (2020) reported 1–1.5 Hz LPDs and diffuse delta–theta slowing in a patient who displayed Creutzfeldt–Jakob disease in tandem with symptomatic onset of COVID-19. Conte et al. (2020) published the history of a patient who presented a severe COVID-19 pneumonia and then a PRES-like encephalopathy. She displayed focal seizures, and after seizure treatment, EEG revealed LPDs in the right posterior regions. Vellieux et al. (2020) published the EEG of two critically ill patients who displayed a severe COVID-19 pneumonia requiring MV. For the first one, the brain MRI was consistent with a hypoxic encephalopathy, and the EEG was recorded while he was sedated and under extracorporeal membrane oxygenation. For the second one, the EEG was recorded 24 h after sedation discontinuation. EEG revealed continuous, symmetric, non-reactive, generalized but mainly bifrontal, monomorphic diphasic or even triphasic, periodic (with a short interval of 1–2 s) delta slow waves (Figure 1C). One patient, without any acute abnormalities on brain MRI and with normal CSF analysis, reported by Delorme et al. (2020) showed GPDs. In the previously mentioned case reported by Le Guennec et al. (2020), a control follow-up EEG was recorded the day after the first EEG. It showed persistent right frontal LPDs with a short interval (0.7–1.2 s). The brain MRI performed 1 month later was normal. Finally, the previously mentioned patient reported by Flamand et al. (2020) who benefited from iterative EEG showed, on the last two recordings, a generalized periodic triphasic activity with short periods (1–1.5 s) over a worsened background activity, without concomitant metabolic disorders.

Spectral Analysis

Two studies reported quantitative analysis of EEG (qEEG) in COVID-19 patients. The study of Pastor et al. (2020) reported 20 patients with COVID-19 encephalopathy for whom standard visual analysis of EEG showed scarce abnormalities. However, compared to 31 infectious toxic encephalopathy patients and 21 post-cardiorespiratory arrest encephalopathy patients, some qEEG features were specific in COVID-19 patients, such as the distribution of EEG bands, the structure of Shannon's spectral entropy, and the hemispheric connectivity. Finally, the study of Pati et al. (2020) showed that some qEEG markers, especially an increase in both the theta power and its temporal variance during EEG reactivity, can predict a good neurological outcome in 10 critically ill COVID-19 patients.

DISCUSSION

The vast majority of these studies emphasized the absence of specificity of EEG abnormalities reported in COVID-19 patients, as generalized slowing of the background activity, focal slowing sometimes associated with sharp waves, seizures, SE, and predictable pattern of metabolic/toxic or postanoxic encephalopathy in ICU patients. Numerous EEGs in the context of COVID-19 were recorded in elderly patients and mainly in male patients, with multiple comorbidities especially chronic brain disorders, under various psychotropic drugs or in critically ill conditions. Confounding factors such as infections, metabolic disturbances, severe hypoxemia, hyperthermia, and psychotropic drugs (such as antiepileptic or sedative drugs) were frequent at the time of EEG recordings. All these confounding factors may contribute to the modification of brain activity and therefore EEG findings. Thus, based on the current literature, it seems not possible to identify a specific EEG pattern due to the suspected neuroinvasion of SARS-CoV-2 in patients who displayed neurological manifestations of COVID-19.

Most current studies with available EEG data are case reports or retrospective single-center series. All reported patients are very heterogeneous concerning prior neurological histories, illness severity, and use of psychotropic drugs. Moreover, some studies reported EEG recorded with limited montage and number of electrodes that may limit the detection of EEG abnormalities. EEG is not a systematic exam in the diagnostic workup of COVID-19 patients. All patients reported in the current literature had an EEG for an urgent clinical indication due to concerning neurological symptoms. A wider neurological multimodality screening, including EEG, of COVID-19 patients may be suggested to grow the body of knowledge on the SARS-CoV-2 infection. However, it will face many logistic difficulties and ethical and safety concerns regarding the availability of trained personnel to EEG recordings and the risk of contamination with the SARS-CoV-2.

It should be pointed out that many EEG abnormalities reported were recorded over anterior or frontal regions. Regardless of EEG montage used by clinicians and neurophysiologists, it thus seems essential to include frontal electrodes. Periodicity, morphology, and reactivity of these frontal abnormalities were not mentioned in all studies.

Moreover, a few reported periodic patterns, as GPDs (Ayub et al., 2020; Beach et al., 2020; Delorme et al., 2020; Louis et al., 2020; Pellinen et al., 2020; Petrescu et al., 2020), GPDs with bifrontal predominance (Galanopoulou et al., 2020; Vellieux et al., 2020; Vespignani et al., 2020), and LPDs (Conte et al., 2020; Le Guennec et al., 2020; Pellinen et al., 2020; Petrescu et al., 2020; Vespignani et al., 2020; Young et al., 2020). In particular, these frontal periodic discharges were monomorphic and displayed a short interval, and the absence of reactivity was noted (Vellieux et al., 2020; Vespignani et al., 2020). These frontal periodic discharges may indicate an acute neurological process linked to the brain SARS-CoV-2 infection. In COVID-19 patients, the combination of the frontal localization of these EEG discharges, the frequently reported anosmia (Yazdanpanah et al., 2020), the olfactory bulb abnormalities found on brain imaging (Lin et al., 2020), and the hypometabolism within the orbitofrontal cortex on functional brain imaging (Karimi-Galougahi et al., 2020) may support the hypothesis whereby SARS-CoV-2 could invade the brain through the olfactory pathway. Then, it could spread transneuronally to other related brain areas particularly to frontal lobes, especially the orbital prefrontal cortex, which are adjacent to olfactory structures (Huang J. et al., 2020).

CONCLUSION

In the context of the SARS-CoV-2 infection, increasing EEG results were published along with clinical reports describing various neurological symptoms in patients with COVID-19. Due to the suspected neuroinvasion of SARS-CoV-2, the major issue when interpreting EEG is to determine whether the observed abnormalities reflect this viral neuroinvasion, a severe encephalopathy with systemic and brain inflammation, hypoxemia and hyperthermia, and/or many confounding factors especially due to critical illness. At this time, no study had described specific EEG abnormalities of the SARS-CoV-2 infection. The majority of currently reported EEGs showed generalized slowing, focal slowing, epileptiform discharges with seizures, and SE. However, frontal discharges, for some periodic, may integrate in the olfactory hypothesis of the CNS invasion of SARS-CoV-2. It reinforces the need to accumulate precise neurophysiological observations of COVID-19 patients worldwide and to aggregate multimodality screening of these patients also with clinical, radiological, biological, and neuropathological data.

AUTHOR CONTRIBUTIONS

GV collected the data and wrote the manuscript. RS, SV, PJ, and AR-T revised the manuscript. M-PO suggested and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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