Neurophysiological findings and their prognostic value in critical COVID-19 patients: An observational study

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ARTICLE INFO

HIGHLIGHTS

- EEG is a simple way to evaluate outcome in patients with critical Coronavirus Disease 2019.
- Unreactive background activity was associated with poor outcome.
- Low-voltage activity and periodic delta waves could be unfavorable prognostic factors.

ABSTRACT

Objective: To describe EEG patterns of critical Coronavirus Disease 2019 (COVID-19) patients with suspicion of encephalopathy and test their association with clinical outcome.

Methods: EEG after discontinuation of sedation in all patients, and somesthesic evoked potentials and brainstem auditive evoked potentials when EEG did not show reactivity, were performed. Clinical outcome was assessed at day 7 and 14 after neurophysiological explorations.

Results: 33 patients were included for analysis. We found slowed background activity in 85% of cases, unreactive activity in 42% of cases, low-voltage activity in 21% of cases and rhythmic or periodic delta waves in 61% of cases. EEG epileptic events were never recorded. Clinical outcome at day 14 was associated with unreactive background activity and tended to be associated with rhythmic or periodic delta waves and with low-voltage activity. Results of multimodal evoked potentials were in favor of a preservation of central nervous system somatosensory and auditory functions.

Conclusions: Among critical COVID-19 patients with abnormal arousal at discontinuation of sedation, EEG patterns consistent with encephalopathy are found and are predictive for short term clinical outcome.

Significance: The abnormal EEG with presence of periodic discharges and lack of reactivity could be related to encephalopathy linked to COVID-19.

1. Introduction

Even if the most frequent symptoms are initially related to the respiratory tract (fever, cough, dyspnea), Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) patients with critical evolution experience a multisystemic dysfunction, which manifestations are driven by acute respiratory failure, but can also result in

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acute kidney injury, heart failure, acute liver failure, shock, etc (Huang et al., 2020; Yang et al., 2020). Among 72,314 Coronavirus Disease 2019 (COVID-19) patients in China, Wu and McGoogan determined that 5% were critical (Wu and McGoogan, 2020).

There is more and more evidence of neurologic manifestations: olfactory and gustatory dysfunctions have been well established as clinical presentations of COVID-19 (Lechien et al., 2020); Guillain-Barré syndrome and Miller-Fisher syndrome have been reported (Camdessanche et al., 2020; Gutiérrez-Ortiz et al., 2020; Padroni et al., 2020; Zhao et al., 2020). Central nervous system (CNS) may be concerned as well. Mao *et al.,* described 36.4 % patients with neurologic symptoms, such as acute cerebrovascular diseases, impaired consciousness, and skeletal muscle injury, with more severe patients being more likely to have neurologic symptoms (Mao et al., 2020). Several cases of encephalopathy (Filatov et al., 2020) or encephalitis (Moriguchi et al., 2020; Poyiadji et al., 2020; Ye et al., 2020) linked with COVID-19 have been reported.

Helms *et al.,* reported the neurologic features in 58 critical COVID-19 patients in 2 French intensive care units (ICU). From those, 69% presented agitation when neuromuscular blockade was discontinued, and from 40 patients for whom the evaluation was possible, 26 (65%) showed signs of confusion. Yet, only 8 patients underwent electroencephalography; 1 had diffuse bifrontal slowing consistent with encephalopathy (Helms et al., 2020).

Electroencephalography (EEG) is the most suited test to evaluate cerebral activity in patients hospitalized in ICU, as it allows to establish a functional state of encephalopathy, exclude differential diagnosis such as seizures or non-convulsive status epilepticus and has a recognized prognostic value for some etiologies (Rossetti et al., 2012; Sutter and Kaplan, 2013; Sutter et al., 2015). Evoked potentials (EP) also have a predictive value on the outcome of comatose or poorly responsive patients (André-Obadia et al., 2018).

EEG have been poorly studied in this population: by the time we started our study, there were no specific study about encephalopathy and EEG in COVID-19 patients; since then, attention was raised on its use (Flamand et al., 2020), and a preliminary report of 22 EEG conducted on acutely ill COVID-19 patients has been published since (Galanopoulou et al., 2020), yet with heterogenous recording method and clinical indication, since 64% were recorded under sedation. Two studies have reported EEG patterns of encephalopathy linked to COVID-19 (Petrescu et al., 2020; Vespignani et al., 2020). However there is still controversy about the significance of the EEG abnormalities which may be related to non-specific comorbidities seen in severe COVID-19 (such as hypoxemia, toxic or metabolic encephalopathy). And it is well known that the lack of reactivity and the presence of periodic discharges are predictors of unfavorable outcome in critically ill patients hospitalized in ICU (Oddo et al., 2009; Kurtz et al., 2014; Gilmore et al., 2015).

In these preliminary reports, there were very few clinical information and their evolution and the clinical relevance of an encephalopathy among those patients is still undetermined.

In severe COVID-19 patients hospitalized in our ICU for respiratory failure, an abnormal arousal (agitation, confusion or lack of arousal) was suspected after discontinuation of sedation drugs without any objective etiology (particularly metabolic or toxic). In the present study, we systematically conducted EEG in patients hospitalized in ICU for a severe COVID-19 who presented persisting neurological signs after the sedative drugs were stopped. Exploration of evoked potentials brainstem auditive evoked potentials (BAEP), and somatosensitive evoked potentials (SSEP) were performed when no reactivity to stimulations was detected during EEG.

The primary objective was to assess the predictive value of abnormal EEG on short term clinical prognosis.

2. Materials & methods

2.1. Patients

In this retrospective observational study, all consecutive EEG conducted on critical COVID-19 patients admitted in ICU of Lille University Hospital, France, from March 23rd, 2020 to April 28th, 2020, were analyzed. Patients had an EEG recording if there was an abnormal awakening after discontinuation of sedation drugs. EEG recording was required to look after signs of encephalopathy, seizures or non-convulsive status epilepticus.

For all patients, according to the World Health Organization guidance, laboratory confirmation for SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase–polymerase chain reaction assay of nasal and pharyngeal swabs.

Exclusion criteria were ongoing sedation during EEG, cardiac arrest with no flow, or low flow superior to 5 minutes, which could participate to abnormal electroencephalographic activity.

2.2. Data collection

A trained team of physicians reviewed and collected epidemiological data, past medical history, treatments, clinical data, and outcomes for all consecutive patients from their admission to May 12th, 2020, from medical records.

2.3. EEG & EP recording

EEG were recorded with Micromed BRAIN QUICK acquisition units, with 21 electrodes, for a minimal length of 20 consecutive minutes.

SSEPs and BAEPs were recorded following European guidelines (Guérit et al., 2009). They were recorded in the patients whose EEG was totally non-reactive to stimulations.

2.4. EEG interpretation

Each EEG and EP was interpreted on clinical routine by a senior neurophysiologist of Department of Clinical Neurophysiology, Lille University Hospital. To ensure reproducibility of the measure, all EEG have been reviewed by a second neurophysiologist. If there was any discordance, EEG was reviewed by a third expert neurophysiologist.

All neurophysiologists were aware of basic clinical information about the patient (age, reason of EEG, ongoing mechanical ventilation, level of consciousness, relevant active comorbidities) and any potential confounding factor (kidney failure, hepatic failure, history of cardiac arrest, ongoing antibiotherapy).

Collected variables were background activity, reactivity (present or not), presence of abnormal additional delta waves, and low-voltage activity. If background activity was fluctuant, the higher range was considered. Reactivity was defined as a clear and reproducible modification of baseline activity (frequency and/or amplitude) following arousal, call or nociceptive stimulation. Abnormal additional widespread delta waves were defined as: rhythmic or periodic. Non-reactive low-voltage activity was defined as incapacity to determine background activity on standard configuration (*i.e.* amplification of the signal was required) with no reactivity following repeated stimulations.

2.5. Follow-up and clinical outcomes

Patients have been followed-up for 14 days after inclusion. Status at day 7 and day 14 after EEG were chosen as clinical outcomes to assess its predictive value. Outcome was defined as favorable for patients still hospitalized in regular medical department, rehabilitation department or discharged at home, and unfavorable if they were deceased or still in ICU. Patients transferred at day 7 or day 14 were assigned status at the end of the day.

2.6. Statistics

Continuous variables were described with mean and standard deviation if they were normally distributed, with median and interquartile range (IQR) otherwise. Categorial variables were described with count and frequencies.

Bivariate associations between EEG characteristics and clinical outcomes were tested with Fisher's exact test.

Predictive value of EEG on clinical outcomes was determined by testing the area under curve (AUC) of the corresponding receiver operating characteristic (ROC) curve, with EEG classification used as a continuous variable.

Two-sided p-values of less than 0.05 were considered to indicate statistical significance.

All statistical work was performed using IBM SPSS Statistics version 22.

2.7. Ethics

This retrospective observational study was based on medical records, in strict compliance with the French reference methodology MR-004, established by French National Commission on Informatics and Liberties (CNIL), and approved by the Institutional data protection authority of Lille University Hospital. Patient confidentiality was protected by assigning an anonymous identification code, and the electronic data were stored in a locked, password-protected computer. The study was conducted according to the principles of the declaration of Helsinki.

3. Results

3.1. Socio-demographic characteristics

From March 23rd, 2020 to April 28th, 2020, we conducted 58 EEG on 44 consecutive critical COVID-19 patients, who required mechanical ventilation and sedation, and for whom encephalopathy was suspected by ICU physicians at discontinuation of sedations. Among those, 11 patients were excluded: 10 patients were still under sedation at the time of the EEG, and 1 had a prolonged cardiac arrest. We then analyzed 33 patients and their initial EEG. No patient was lost to follow-up (Fig. 1).

Reason for admission in ICU, sedation and mechanical ventilation was acute respiratory failure for 32 patients and severe Guillain-Barré syndrome for 1.

Median age was 69 years (IQR [57–72]). 28 patients were male (84.8%). There was no difference between groups on simplified acute physiology score (SAPS II) at admission and complications during intubation (oxygen desaturation and hypotension).

Most frequent comorbidities were arterial hypertension (20 patients, 60.6%), obesity (12 patients, 36.4%), diabetes mellitus (12 patients, 36.4%), dyslipidemia (11 patients, 33.3%) and heart disease (8 patients, 24.2%) (Table 1).

Median total length of sedation was 10 days (IQR [7–12]), with a median maximum dose of propofol of 160 mg/h (IQR [100–200]; no difference between patients with favorable and unfavorable

outcome at 14 days: p = 0.52, Mann-Whitney's U test), and median total length of invasive mechanical ventilation was 21 days (IQR [11–36]). Median ventilator-free days 28 days after intubation was 7 (IQR [0–17]).

Encephalopathy was suspected because agitation or confusion in 12 cases (36.4%), and delayed awakening in 21 cases (63.6%).

Patients with unfavorable outcome tended to have a greater urea blood level leading to a renal replacement therapy. 20 patients were treated by betalactam during EEG: antibiotic overdosing was found in only 4 patients, without difference between groups (Supplementary Table 1).

3.2. EEG characteristics

At the time of EEG, mean time from first day with COVID-19 symptoms was 24 days (SD 7.15), and median time from discontinuation of sedation was 2 days (IQR [1.5–3]).

Background activity was strictly into alpha range in 5 cases (15.2%), slowed to theta range in 17 cases (51.5%) and slowed to delta range in 11 cases (33.3%). 14 EEG (42.4%) were unreactive to arousing, call or nociceptive stimulation. 7 EEG (21.2%) showed low-voltage activity.

Rhythmic or periodic delta waves, which could be widespread or predominant over bilateral frontal region, were noted in 20 cases (60.6%).

No epileptiform anomalies or seizures were found. No EEG was suggestive of antibiotic-associated or uremic encephalopathy.

Only 2 EEG (6.1%) were considered as strictly normal.

3.3. Clinical outcomes

At day 7 after EEG, 8 patients (24.2%) were considered to have a favorable outcome, as 2 (6.1%) were discharged at home and 6 (18.2%) were still hospitalized in regular medical department or rehabilitation department, and 25 were considered to have an unfavorable outcome, as 23 (69.7%) were still in ICU and 2 (6.1%) were deceased.

At day 14 after EEG, 11 patients (33.3%) were considered to have a favorable outcome, as 4 (12.1%) were discharged at home and 7 (21.2%) were still hospitalized in regular medical department or rehabilitation department, and 22 were considered to have an unfavorable outcome, as 20 (60.6%) were still in ICU and 2 (6.1%) were deceased.

3.4. Relation between EEG characteristics and clinical outcomes

At day 7 after EEG, proportion of unfavorable outcome was higher in patients with unreactive activity than those with reactive one (100% vs 57.9%, p = 0.01). Proportion of unfavorable outcome was not different between patients with rhythmic or periodic delta waves and those without (85% vs 61.5%, p = 0.21), between patients with low-voltage activity and those without (100% vs 69.2%, p = 0.15) and with patient with slowed background activity and those with normal one (76.8% vs 60%, p = 0.57).

At day 14 after EEG, proportion of unfavorable outcome was higher in patients with unreactive activity than those with reactive one (100% vs 42.1%, p < 0.001), and tended to be higher in patients with rhythmic or periodic delta waves than those without (80% vs 46.2%, p = 0.065) and in patients with low-voltage activity than those without (100% vs 57.7%, p = 0.067). It was not different between patients with slowed background activity and those with normal one (67.9% vs 60%, p = 1) (Table 2).

There was no difference between the two groups concerning the delay between time of sedation withdrawal and EEG recording.
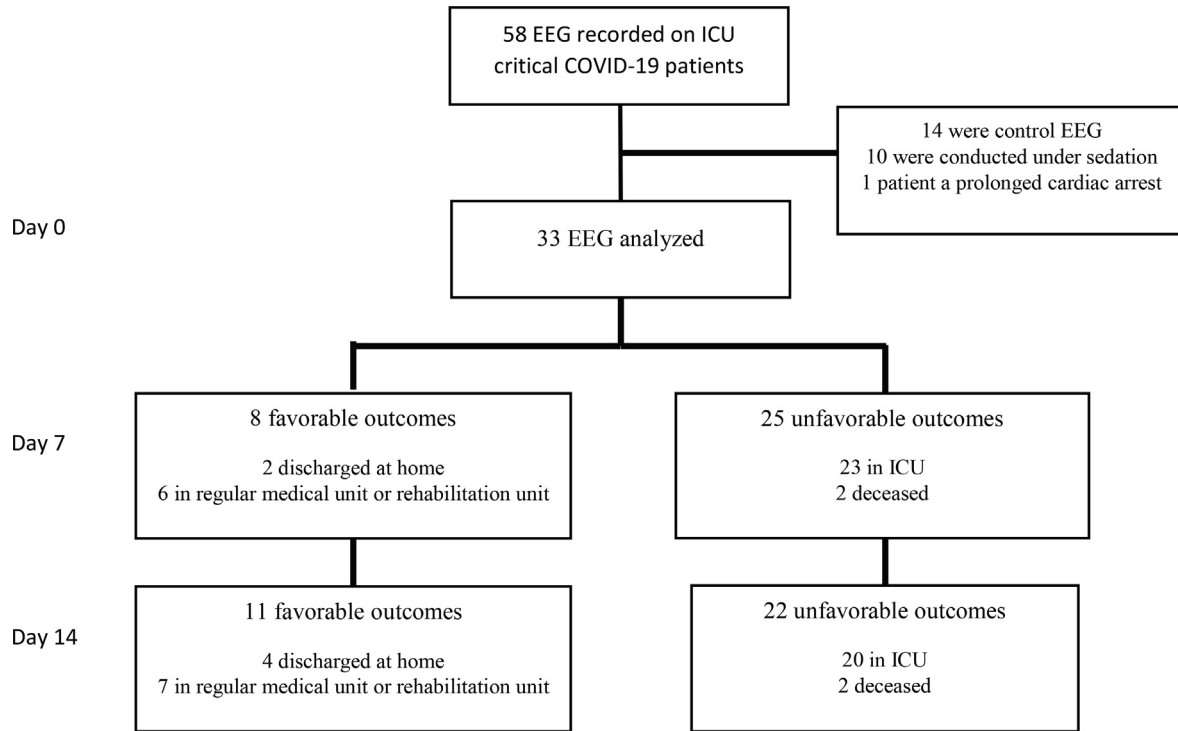
Fig. 1. EEG selection and clinical outcome at day 7 and 14 after EEG. Abbreviation: ICU, intensive care unit.

Table 1
Baseline information. Continuous variables were described with mean and standard deviation if normally distributed, with median and interquartile range otherwise. Categorial variables were described with count and frequencies.

Variables	All patients (n = 33)
Age (years)	69 [57–72]
Sex (male)	28 (84.8%)
Comorbidities	
Arterial hypertension	20 (60.6%)
Obesity	12 (36.4%)
Diabetes mellitus	12 (36.4%)
Dyslipidemia	11 (33.3%)
Heart disease	8 (24.2%)
Sleep apnea syndrome	5 (15.2%)
Renal insufficiency	3 (9.1%)
COPD	2 (6.1%)
Malignancy	1 (3.1%)
Immunosuppression	1 (3.1%)
ICU characteristics	
Maximum dose of propofol (mg/h) *	160 [100–200]
Total length of sedation (days) *	10 [7–14]
Total length of mechanical ventilation (days) *	21 [11–36]
Ventilator-free days at day 28 after intubation (days) *	7 [0–17]
Time to EEG	
Time from first day with symptoms to EEG (days)	23.84 (7.15)
Time from discontinuation of sedation to EEG (days)	2 [1.5–3]
Confounding factors	
Acute kidney injury, day of EEG	12 (30.3%)
requiring dialysis	6 (18.2%)
Hepatic cytolysis	3 (9.1%)
Ongoing antibiotherapy, day of EEG	24 (72.7%)
Cardiac arrest prior to EEG	4 (12.1%)
Cause of encephalopathy suspicion	
Delayed awakening	21 (63.6%)
Agitation / confusion	12 (36.4%)

Abbreviation: COPD, Chronic obstructive pulmonary disease.
* Data is missing for 4 patients for maximum dose of propofol, and for 2 patients for total length of sedation, total length of mechanical ventilation, ventilator-free days at day 28 after intubation.

3.5. EEG classification and predictive value on prognosis

Those findings brought us to categorize EEGs among 5 different patterns, depending on 3 characteristics: 8 patients (24.2%) had EEG with reactive background activity without additional periodic or rhythmic delta waves (type I); 9 patients (27.3%) had EEG with reactive background activity with additional periodic or rhythmic delta waves (type II); 3 patients (9.1%) had EEG with unreactive background activity without additional periodic or rhythmic delta waves (type III); 6 patients (18.2%) had EEG with unreactive background activity with additional periodic or rhythmic delta waves (type IV); 7 patients (21.2%) had EEG with diffuse low-voltage activity (type V) (Figs. 2 and 3).

Then, we determined the sensitivity and specificity of each rank of this new classification as a threshold for unfavorable outcome at days 7 and 14, and we drew the corresponding ROC curves. At both endpoints, this classification was significantly predictive of clinical outcome (at day 7: AUC = 0.873; p = 0.002; at day 14: AUC = 0.928; p < 0.001) (Fig. 4; Tables 3 and 4).

Moreover, an EEG with unreactive background activity and/or low-voltage activity (type III or higher) is pathognomonic for an unfavorable outcome at both days 7 and 14. Besides, 7 out of 8 patients with normal or subnormal EEG (type I) experienced a favorable outcome at day 14, corresponding to a negative predictive value of 87.5%.

3.6. EP characteristics

17 out of our 44 initial patients underwent SSEP and BEAP under clinical routine, because of a persistent lack of clinical and/or EEG reactivity.

Among SSEP, 2 were uninterpretable because of agitation, 2 showed peripheral abnormalities of N9 (generator: brachial plexus), either in latency or amplitude, 1 showed no response (corresponding to the patient with Guillain-Barré syndrome) and 12 were considered as normal with N20 latency within the normal ranges.

Table 2
Relationship between EEG characteristics & clinical outcome.

Variable	Outcome at day 7			Outcome at day 14		
	Favorable (n = 8)	Unfavorable (n = 25)	p	Favorable (n = 11)	Unfavorable (n = 22)	p
Slowed background activity * (n = 28)	6 (75%)	22 (88.0%)	0.574	9 (81.8%)	19 (86.4%)	1
Lack of reactivity (n = 14)	0 (0%)	14 (56%)	**0.01**	0 (0%)	14 (63.6%)	**<0.001**
Additional delta waves (n = 20)	3 (37.5%)	17 (68.0%)	0.21	4 (36.4%)	16 (72.7%)	0.065
Low-voltage activity(n = 7)	0 (0%)	7 (28,0%)	0.15	0 (0%)	7 (31.8%)	0.067

*Theta or delta background activity compared to alpha background activity.
Frequencies are given into the clinical outcome. Associations were tested with Fisher's exact test.
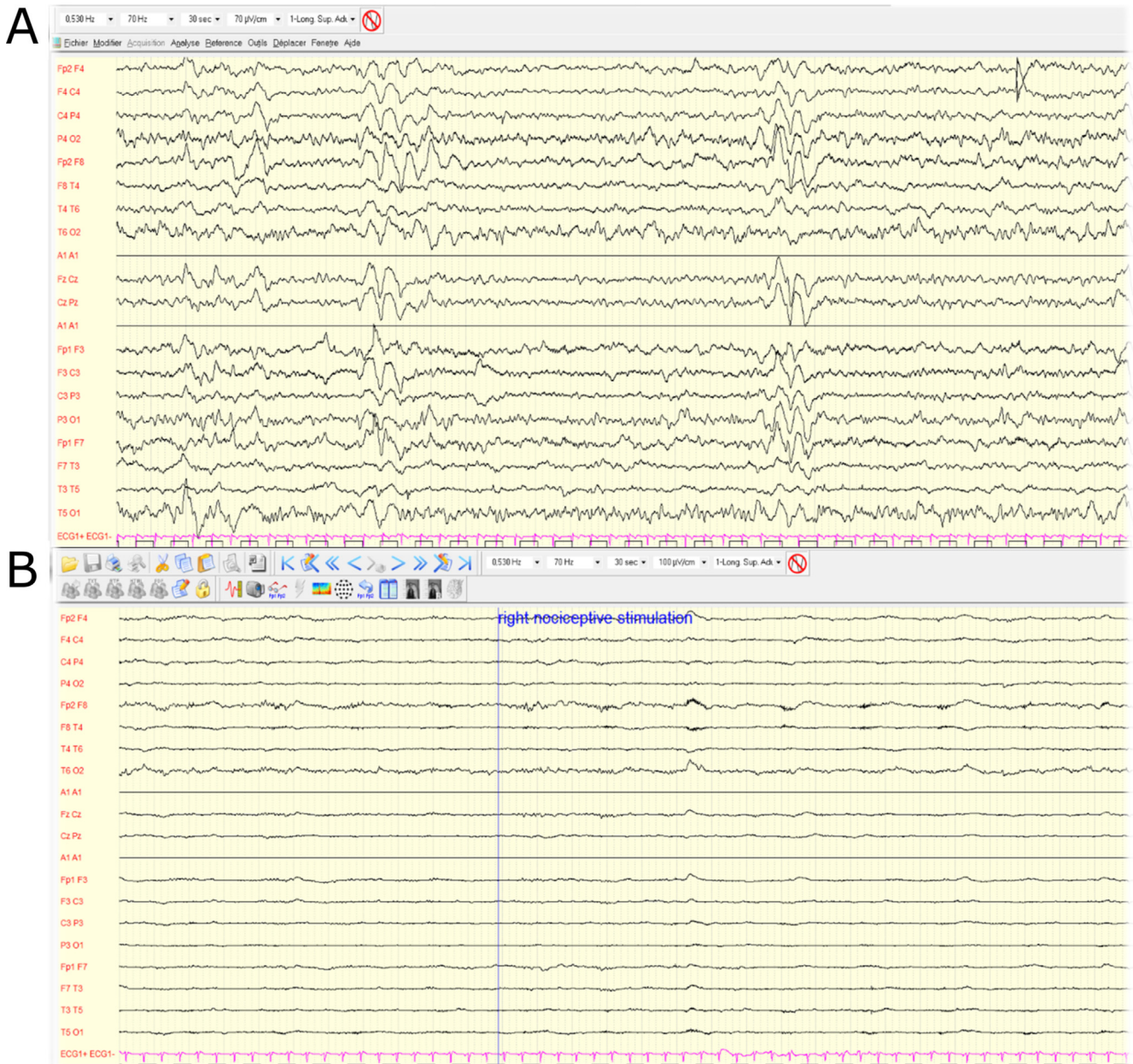

Fig. 2. EEG pattern from two different patients. EEG recording performed with 21 scalp electrodes, a bipolar montage and epochs of 30 seconds. A. EEG recording showing periodic delta waves (Filter settings 0.53–70 Hz, amplitude 70 µV/cm). B. Low-voltage activity, with no reactivity to nociceptive stimulation (Filter settings 0.53–70 Hz, amplitude 100 µV/cm).

Among BEAP, 2 were uninterpretable because of agitation, 6 were normal, and 9 (52,9%) showed peripheric disorganization of BEAP (decreased amplitude with difficulties to identify waves I, III, V; since wave I whose generator is peripheral was abnormal, VIIIth nerve was involved), which was unilateral in 4 cases. None showed specific brainstem dysfunction. These results were in favor of a preservation of central somatosensory and auditory systems.
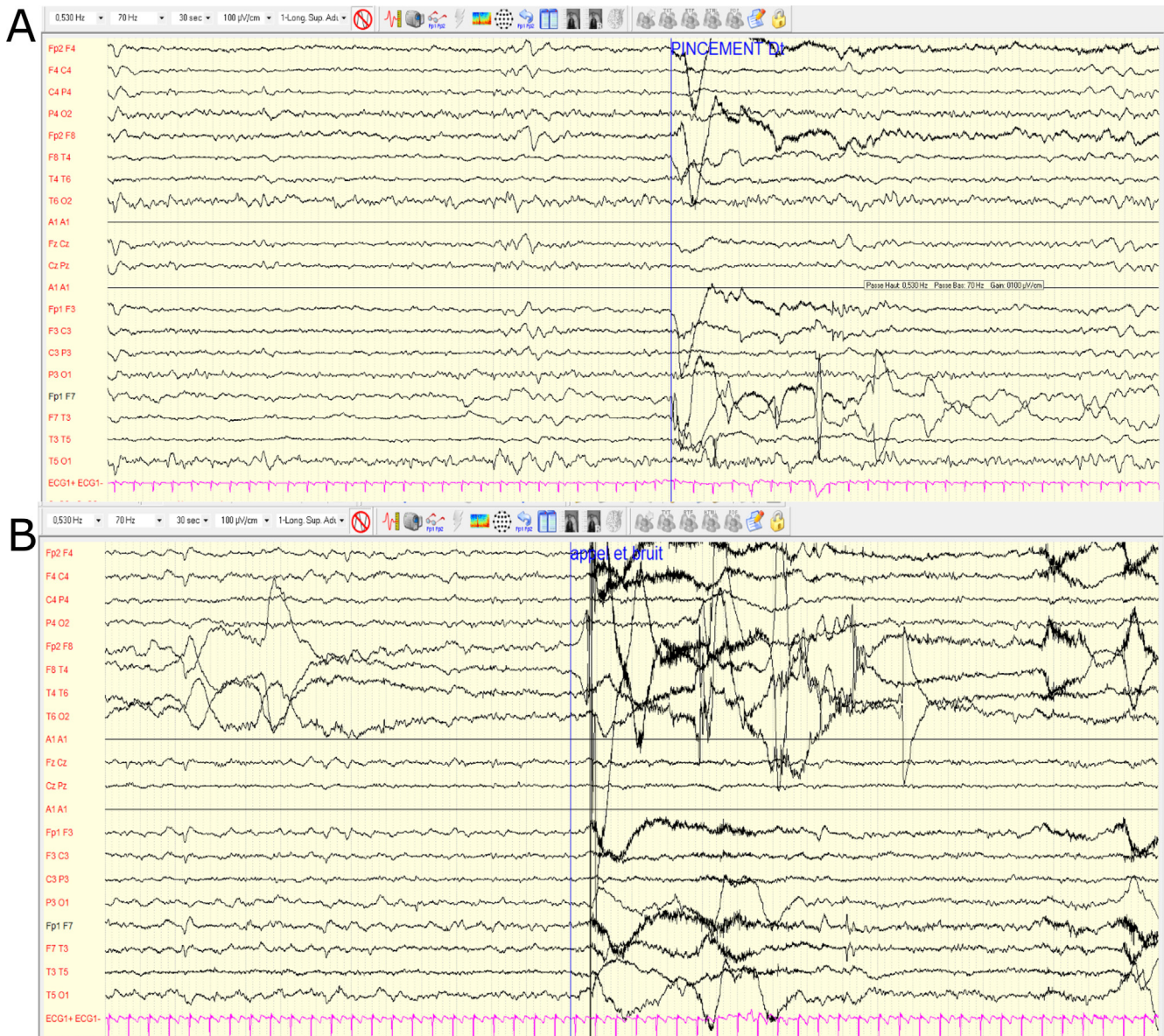
Fig. 3. Evaluation of EEG reactivity and relation to clinical outcome. A. EEG recording showing rhythmic delta-waves and no reactivity to nociceptive stimulation (Filter settings 0.53–70 Hz, amplitude 100 μV/cm): patient was still hospitalized in ICU 14 days after EEG. B. EEG recording showing rhythmic delta-waves and reactivity to auditive stimulation (Filter settings 0.53–70 Hz, amplitude 100 μV/cm): patient was hospitalized in regular medical department 14 days after EEG.

4. Discussion

In this retrospective monocentric cohort, we are reporting EEG characteristics among critical COVID-19 patients for whom encephalopathy was suspected at discontinuation of sedation. We determined that clinical outcome at day 7 and 14 after EEG were associated with reactivity of background activity and tended to be associated with presence of additional rhythmic or periodic delta waves and with low-voltage activity at day 14. We proposed a five-group EEG classification depending on those factors, which was predictive of clinical outcome at both endpoints: normal or subnormal EEG (type I) were highly predictive of favorable outcome and unreactive EEG and/or low-voltage activity (type III and higher) were all associated to unfavorable outcome.

Compared to Yang *et al.,* (Yang et al., 2020), our patients are older (69 vs 59.7 years), and have more frequent comorbidities as heart disease (24.2% vs 10%) or diabetes mellitus (36.4% vs

17%). One possible explanation is that Lille University Hospital is the tertiary referral center for 4.5 million inhabitants from 2 French departments, resulting in a recruitment of more comorbid patients. Mortality rate at 14 days after EEG is relatively low (6.1%), which is explained as we only included patients who lived long enough to have their sedations discontinued.

Several cases of encephalopathy on COVID-19 patients have been described (Filatov et al., 2020; Mao et al., 2020; Ye et al., 2020), and Helms *et al.,* focused on neurologic features in severe COVID-19 infection (Helms et al., 2020). Among 58 patients, 40 (69%) presented with agitation when neuromuscular blockade was discontinued, and 26 showed confusion. No case of delayed awakening is mentioned. 8 patients only underwent EEG: 1 had diffuse bifrontal slowing consistent with encephalopathy, others were reported to show "only nonspecific changes". Our cohort does not allow to estimate the incidence of encephalopathic features on severe COVID-19 patients for it was our inclusion criteria, but
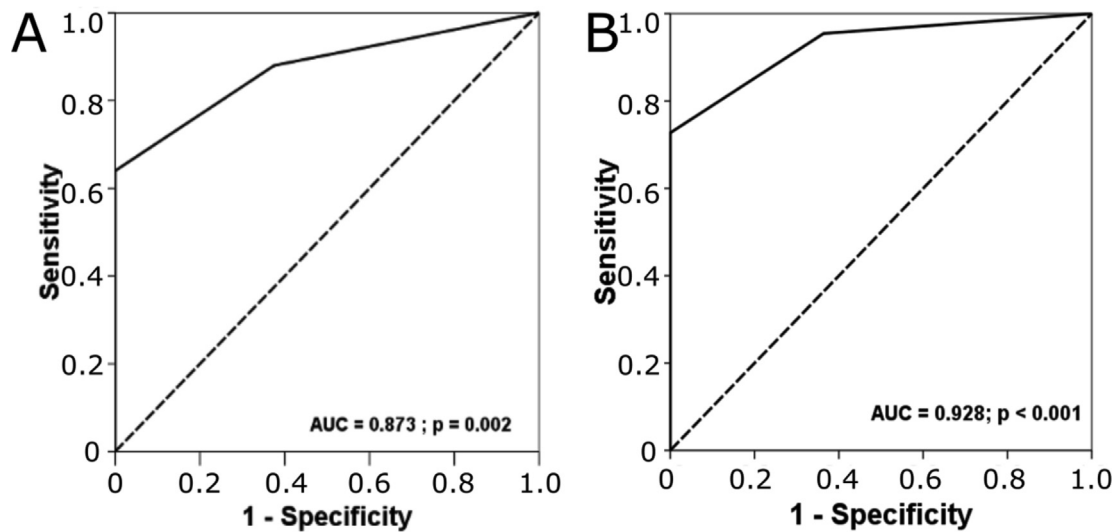
Fig. 4. ROC curve of EEG patterns for clinical outcome. A. at day 14 and B. at day 7. Abbreviations: AUC, area under curve; ROC, receiver operating characteristic.

Table 3
Clinical outcome at day 7 and 14 depending on EEG pattern.

EEG patterns	Day 7		Day 14	
	Favorable outcome	Unfavorable outcome	Favorable outcome	Unfavorable outcome
I	5	3	7	1
	2 at home	3 in ICU	2 at home	1 in ICU
	3 in med. or rehab.	0 deceased	5 in med. or rehab.	0 deceased
II	3	6	4	5
	0 at home	6 in ICU	2 at home	5 in ICU
	3 in med. or rehab.	0 deceased	2 in med. or rehab.	0 deceased
III	0	3	0	3
	0 at home	3 in ICU	0 at home	3 in ICU
	0 in med. or rehab.	0 deceased	0 in med. or rehab.	0 deceased
IV	0	6	0	6
	0 at home	6 in ICU	0 at home	6 in ICU
	0 in med. or rehab.	0 deceased	0 in med. or rehab.	0 deceased
V	0	7	0	7
	0 at home	5 in ICU	0 at home	5 in ICU
	0 in med. or rehab.	2 deceased	0 in med. or rehab.	2 deceased

EEG patterns: reactive background activity without additional periodic or rhythmic delta waves (type I); reactive background activity with additional periodic or rhythmic delta waves (type II); unreactive background activity without additional periodic or rhythmic delta waves (type III); unreactive background activity with additional periodic or rhythmic delta waves (type IV); diffuse low-voltage activity (type V).
Abbreviations: med., regular medical department; rehab., rehabilitation department; ICU, intensive care unit.

Table 4
Cumulative sensitivity and specificity of EEG patterns for unfavorable outcome.

EEG patterns	Day 7		Day 14	
	Sensitivity	Specificity	Sensitivity	Specificity
I	100%	0%	100%	0%
II	88%	62,5%	95.5%	63.6%
III	64%	100%	72.7%	100%
IV	52%	100%	59.1%	100%
V	28%	100%	31.8%	100%

EEG patterns: reactive background activity without additional periodic or rhythmic delta waves (type I); reactive background activity with additional periodic or rhythmic delta waves (type II); unreactive background activity without additional periodic or rhythmic delta waves (type III); unreactive background activity with additional periodic or rhythmic delta waves (type IV); diffuse low-voltage activity (type V).
EEG classification is used as a continuous variable, with worse patterns considered as positive results for unfavorable outcome.

among our patients, 21 (63.6%) were considered to have a delayed awakening. Only 2 of our patients had a completely normal or sub-normal EEG. Others showed either diffuse low-voltage activity, lack of reactivity, and/or diffuse or frontal rhythmic or periodic delta waves, which are all consistent with encephalopathy (Young et al., 1997; Young 1998; Kaplan 2004; Rossetti et al., 2012; Sutter and Kaplan 2013; Sutter et al., 2015).

These differences in clinical presentation and EEG findings could be explained by our unactive prospect of ICU physicians or patients to conduct electroencephalography. Rather, it was conducted on demand of ICU practicians, when they considered that the neurologic status was clearly unusual regarding the type and duration of sedation used and the time from discontinuation of sedation, resulting in a different selection of patients.

In this series of 33 patients with a lack of awakening, we found no seizures, non-convulsive status epilepticus or epileptiform anomalies (that is no spike or spike and wave) and no focalized periodic triphasic waves. That means that mental status was not altered because of an epileptic mechanism and this provides no argument that COVID-19 favors seizures. This is also an argument against encephalitis, especially that no unexplained focal anomalies were found (Venkatesan et al., 2013).

After the end of our study, Galanopoulou *et al.,* reported EEG findings in 22 acutely ill COVID-19 patients (Galanopoulou et al., 2020). All their patients shown bilateral slowing, versus 28/33 (85%) in our study. In both studies, none had electrographic seizures. They mention 9 patients (41%) with epileptiform discharges, mostly frontal sharp waves, when we report none. Those differences could have several explanations: first, 4 of their patients were known to have prior epilepsy (none in our study); second, the clinical indication of EEG was motor seizure-like events or seizures at presentation or confusion resembling prior seizure in 54.5% of cases, when we only included patients with confusion, agitation or delayed awakening. Finally, 86.4% of their EEG were conducted under sedation or anti-seizure medication.

The most frequent EEG pattern in our population was rhythmic or periodic delta waves, which could be widespread or predominant over bilateral frontal region, and reactive or not to stimulation. This pattern could correspond to frontal intermittent rhythmic delta activity (FIRDA) which has been described in comatose patients and is a nonspecific EEG sign of encephalopathy (Niedermeyer and Lopes da Silva, 1999).

Our pathological findings, yet non-specific for their etiology, attest the presence of a brain dysfunction in context of severe COVID-19. Neuro-invasive potential of respiratory virus, including Human Coronavirus (HCoV), has already been described (Hung et al., 2003; Lau et al., 2004; St-Jean et al., 2004; Bohmwald et al., 2018). Different pathogenic pathways are suggested for SARS-CoV-2: direct viral pathogenicity, immune-mediated pathogenicity targeting brain tissue, inflammatory involvement of brain blood vessels, and/or intravascular coagulation (Natoli et al., 2020; Wu et al., 2020). For direct viral pathogenicity, several mechanisms of neuro-invasiveness are suspected, either from a hematogenous route, with SARS-CoV-2 being able to pass the blood–brain barrier, either from a neuronal dissemination, in which it could enter CNS through the olfactory route or peripheric nerves (Bohmwald et al., 2018; Desforges et al., 2019; Wu et al., 2020). Hypothesis of an immune mediated pathogenicity could be supported by the development of a systemic inflammatory response syndrome in severe COVID-19 patients (Wu et al., 2020).

Wu *et al.,* suggest the possible occurrence of an infectious toxic encephalopathy among COVID-19 patients, referring to a reversible brain dysfunction syndrome caused by systemic factors such as toxemia, metabolic disorders, and hypoxia during the process of acute infection (Mizuguchi et al., 2007; Young 2013; Tauber et al., 2017; Wu et al., 2020). The most likely is that our pathological EEG findings are not referring to a specific COVID-19 encephalitis, but to a COVID-19-related encephalopathy included in a multisystemic dysfunction.

Among our initial 44 patients, 19 underwent cerebral imaging (which was an MRI in 16 cases). None showed signs of encephalitis. Ischemic and/or hemorrhagic stroke were found in 6 patients during follow-up. 3 of those patients had a cardiac arrest prior to EEG (no-flow 0 minute, low-flow 3, 4 and 40 minutes). This data supports a possible participation of neuro-vascular events in COVID-related encephalopathy.

At the time of EEG, 20 had on ongoing antibiotherapy with beta-lactam: 4 patients had a betelactam overdosing. When uremia was high, all patients underwent renal replacement. There were never biologic signs of hepato-cellular failure that could be responsible for a hepatic encephalopathy. Consequently, these factors must not be considered as the etiology of their encephalopathy but could be considered as part of the many systemic factors that favors infectious toxic encephalopathy.

Evoked potentials were recorded in the patients whose EEG was totally non-reactive to stimulations. We found no evidence to support a brainstem dysfunction as no patient had brainstem anomalies with BAEP. 9 (52.9%) had peripheral disorganization of auditory EP, which might correspond to a cochleo-vestibular nerve lesion, a neurologic manifestation that has not yet been described in COVID-19.

Our study has several limitations. First, all patients were included in one center only, in which were transferred the most severe patients from the region. Second, we only included severe COVID-19 patients, who were all hospitalized in ICU, sedated and under invasive mechanical ventilation. We also recorded EEG with similar encephalopathic patterns in COVID-19 patients who were not critical, or were not hospitalized in ICU, but we chose to restrict inclusions to ensure homogeneity in patient's severity and medical support.

Further studies will be needed: the predictive value of our EEG classification on clinical outcome should be confirmed on a validation sample; subclinical EEG modifications shall be investigated on control patients; finally, COVID-19 patients with abnormal EEG should have long term follow up and we must pay attention to a possible following neuro-degeneration and/or cognitive impairment, as some authors suggested (Desforges et al., 2019; Needham et al., 2020).

5. Conclusion

Among critical COVID-19 patients with suspicion of cerebral disorder at discontinuation of sedation, abnormal EEG patterns are found and are predictive for clinical outcome at 7 and 14 days after EEG, especially if EEG was not reactive.

Further studies will be needed to follow these patients, searching for long-term neurologic sequelae.

Author contributions

All authors contributed to study conception and design. Collection of clinical data was performed by Jean-Paul Niguet, Romain Tortuyaux, Bruno Garcia, Mercé Jourdain, Sébastien Préau, Julien Poissy, Raphael Favory, Saad Nseir and Daniel Mathieu. Collection of neurophysiological data was performed by Jean-Paul Niguet, Laurence Chaton, Arnaud Delval and Philippe Derambure. Laboratory samples were analyzed by Enagnon Kazali Alidjinou. Statistical analyses were performed by Jean-Paul Niguet and Arnaud Delval. The first draft of the manuscript was written by Jean-Paul

Niguet and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.02.007.

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