EEG characteristics of mechanically ventilated critically ill patients at high risk of delirium

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Research

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Abstract

Background

Neurophysiological exploration of ICU delirium is limited. Here, we examined EEG characteristics of medical-surgical critically ill patients with new onset altered consciousness state at high risk for ICU delirium.

Methods

Pre-planned analysis of non-neurological mechanically ventilated medical-surgical ICU subjects, who underwent a prospective multicenter randomized, controlled EEG study (NCT03129438, April 2017–November 2018). EEG characteristics, according to the 2012 ACNS nomenclature, included background activity, rhythmic periodic patterns/epileptic activity, amplitude, frequency, stimulus-induced discharges, triphasic waves, reactivity and NREM sleep. We explored EEG findings in delirious vs. non-delirious patients, specifically focusing on presence of burst-suppression and rhythmic periodic patterns (ictal-interictal continuum), and epileptiform activity (ictal EEG).

Results

We analyzed 91 patients (median age, 66 years) who underwent EEG because of new onset altered consciousness state at a median 5 days from admission; 42 patients developed delirium (46%). Burst-suppression (10 vs. 0%, $p = 0.02$), rhythmic/periodic patterns (43% vs. 22%, $p = 0.03$) and epileptiform activity (7 vs. 0%, $p = 0.05$) were more frequent in delirious vs. non-delirious patients. The presence of at least one of these abnormal EEG findings (32/91 patients; 35%) was associated with a significant increase in the likelihood of delirium (42 vs. 15%, $p = 0.006$). Cumulative dose of sedatives and analgesics, as well as all other EEG characteristics, did not differ significantly between the two groups.

Conclusion

In mechanically ventilated non-neurological critically ill patients with new onset alteration of consciousness, EEG showing burst-suppression and/or ictal-interictal continuum findings indicates a higher risk of ICU delirium, independently of sedation and analgesia.

Background

Electroencephalography is part of standard diagnostic procedures in critically ill patients with new onset altered state of consciousness. In these patients, ICU delirium is frequent and may often go undetected, in particular because of hypo-active forms and the confounding effect of sedative-analgesia (1). The pathophysiology of delirium remains unclear, and is associated with neurotransmitter deficiency, pro-

inflammatory cytokines, acute stress responses and neuronal injury (2). Delirium is related to functional outcome and mortality (3, 4); nevertheless, a tool that can predict delirium development especially in ICU has not yet been widely established. The use of screening scales is valuable and the Confusion Assessment Method for the ICU (CAM-ICU) has the highest sensitivity in patients in the ICU (64%-100%), but still may miss up to 50% of delirious patients (5, 6).

EEG is part of standard diagnostic procedures of acute alteration of consciousness in the ICU, and may therefore prove useful to contribute to delirium diagnosis (7-9). Yet, clinical data on EEG in ICU delirium is limited (10, 11), and to our knowledge, a comprehensive analysis of EEG characteristics in mechanically ventilated critically ill patients at high delirium risk has not been explored so far, especially in adults without known acute brain injury.

Objectives

We aimed at examining EEG characteristics of mechanically ventilated ICU patients with new onset altered consciousness state, and to evaluate whether in this high-risk population the presence of any abnormal EEG findings, based on the 2012 American Clinical Neurophysiology Society (ACNS) nomenclature (12), may be indicative of a higher delirium rate.

Methods

Patients

In this pre-planned analysis of a multicenter randomized controlled EEG study (Continuous EEG Randomized Trial in Adults, CERTA) performed in four Swiss hospitals between April 2017 and November 2018(13, 14), adult inpatients presenting with consciousness disorders of any etiology were randomized to receive continuous EEG (30–48 hours) or routine EEG (20 minutes repeated once within 48 hours); 368 patients have been included.

Since our aim was to study the relationship between delirium and EEG in ICU patients without brain injury or cardiac arrest, we retrospectively identified patients in whom the primary cause for ICU admission was sepsis or cardio-respiratory failure; patients with a cerebral lesion such as a tumor that were admitted in ICU for a non-neurological reason were also kept included. Only patients from Lausanne University Hospital (CHUV) were included, since comprehensive data concerning delirium were not all recorded in the CERTA trial (n = 287). We collected data concerning delirium mainly via the CAM-ICU score, which is part of the local routine assessment in the ICU and is performed daily by an experienced ICU nurse. Patient's medical records and drug administration such as haloperidol or quetiapine were also examined to help with diagnosis of delirium when CAM-ICU score was missing. Delirium diagnosis was made according to the DSM-5 criteria (15). Patients without an ICU stay were also excluded (n = 10).

EEG and clinical data

For the purpose of this study, we considered only the first EEG for each patient, whether continuous or routine. Digital video-EEG were recorded using scalp electrodes placed according to the international 10–20 system. Type of sedation and dosages, duration of hospital stay, duration of mechanical ventilation, reason for EEG request, and main ICU admission diagnosis were prospectively collected. Occurrence of delirium was defined and assessed by means of the CAM- ICU scale for 45 patients, and via medical records and drug administration for the others ($n = 46$) (16). We also assessed retrospectively the timing of EEG in relationship with delirium diagnosis. EEG interpretation followed the 2012 American Clinical Neurophysiology Society (ACNS) nomenclature (12). It prospectively assessed background activity (frequency, amplitude, reactivity) and continuity: continuous or nearly continuous (suppression $< 10\%$), discontinuous (suppression $10–49\%$), burst suppression (suppression $\geq 50\%$) and suppressed ($< 10 \mu\text{V}$). Further, sporadic epileptiform activity, lateralized rhythmic (LRDA), lateralized or generalized periodic discharges (LPD, GPD) (ictal-interictal continuum), sporadic epileptiform activity, presence of triphasic waves, and occurrence of NREM 2 sleep features (spindles, K complexes) (12). A uniform operational definition of electrographic seizures (≥ 10 seconds) and SE (≥ 5 minutes) was used for the CERTA study: repetitive, rhythmic, or periodic discharges or spike-waves at greater than 3 Hz or at less than 3 Hz with evolution in amplitude, frequency, location, or with electroclinical response to antiseizure drugs (ASD) (12, 17, 18). EEG reactivity was tested by auditory and nociceptive stimuli (19). Background reactivity was considered present if a clearly reproducible change in amplitude or frequency was seen immediately after stimulation, excluding stimulus-induced discharges (SIRPIDS) and muscle artifacts. Amplitude was divided into three categories according to voltage: 1 = suppressed $< 10\mu\text{V}$, 2 = low $10–20 \mu\text{V}$, 3 = normal $> 20 \mu\text{V}$.

Statistical analysis

We explored EEG characteristics among delirious vs. non-delirious patients, focusing on specific EEG patterns, including presence of burst-suppression, rhythmic or periodic patterns or ictal activity. Continuous, not normally distributed variables were presented using the median and first to third quartile and compared using a Wilcoxon-Mann-Whitney test. Categorical variables were compared using a chi square test. Statistical analysis of patients' characteristics was conducted with JMP statistics (20). In explorative analyses, all possible combinations of EEG characteristics were compared between patients who were delirious and those who were not. Associations were considered statistically significant at $p\text{-value} \leq 0.05$ (21). Given the exploratory nature of the study, we did not apply corrections for multiple comparisons.

Results

Patient demographics.

The study flow chart is shown in Fig. 1. A total of 91 patients were included in the present analysis, of which 42 were diagnosed with ICU delirium (46%). Median age was 66 years and male gender was predominant (66%) (Table 1). The main primary ICU admission diagnosis was sepsis (42%). EEG was performed when the diagnosis of consciousness disorder was made (within four hours after clinician

request according to the study protocol), which occurred at a median 5 days (2–10) from hospital admission. Median EEG duration was 0.5 hours (0.3–30). The majority of patients (64%) were under continuous sedation during EEG, with propofol and/or midazolam; their median duration of mechanical ventilation was 8 days (4–14) and the median ICU stay was 11 days (6–20).

Table 1
Characteristics of the 91 analyzed patients. Data are expressed as median and quartile 25–75% or number (%).

Age (years)	66 (57–73)
Female gender	31 (34%)
Medical ICU primary diagnosis	35%
Sepsis	9%
Metabolic dysfunction	24%
Cardiopulmonary dysfunction	32%
Other*	
SAPS II score	39 (33–54)
Delirium	42 (46%)
EEG after hospital admission (latency in days)	5 (2–10)
Median EEG duration (hours)	0.45 (0.3–30)
Any sedation during EEG	58 (64%)
Mechanical ventilation (days)	8 (4–14)
ICU length of stay (days)	11 (6–20)
Hospital length of stay (days)	33 (16–60)
Poor outcome (mRs 4–6)	39 (43%)
*Trauma (without brain lesion), digestive hemorrhage, drug intoxication, brain tumor, etc.	

EEG findings

Delirium median duration in ICU was 7 days. EEG was performed during delirium in the majority of patients (81/91; 89%), and before its onset in 10 (Fig. 2).

EEG findings according to the ACNS nomenclature were compared between delirious and non-delirious patients (Table 2). While EEG duration and sedation rate and doses/kg (propofol, midazolam) were similar for patients with and without delirium, mechanical ventilation and ICU stay were significantly longer for the delirium group.

Table 2

Characteristics compared between delirium patients and mortality. Data are expressed as median, first and third quartile, or numbers (%). Bold values are significant.

EEG characteristics	Patients with delirium (n = 42)	Patients without delirium (n = 49)	P value
Age	65 (58–74)	66 (51–73)	0.43
ICU primary diagnosis:	43%	27%	0.23
Sepsis	5%	13%	
Metabolic dysfunction	26%	23%	
Cardiopulmonary dysfunction	26%	37%	
Other			
SAPS II score	43 (34–57)	37 (30–53)	0.11
Dominant background activity:	90%	100%	0.02
Continuous/discontinuous	10%	0%	
Burst suppression	0%	0%	
Suppressed			
Amplitude	33%	20%	0.16
Low	67%	80%	
Normal			
Best frequency	7%	6%	0.83
delta	74%	67%	
theta	17%	25%	
alpha	2%	2%	
beta			
Lack of background reactivity	7%	6%	0.84
NREM sleep EEG features	21%	22%	0.9
Sporadic epileptiform discharges	31%	32%	0.86
Rhythmic or periodic EEG patterns not classifying as seizures	43%	22%	0.03
Seizure or status epilepticus	7%	0%	0.05

EEG characteristics	Patients with delirium (n = 42)	Patients without delirium (n = 49)	P value
Stimulus induced rhythmic, periodic or ictal discharges	17%	18%	0.91
Triphasic morphology	33%	27%	0.73
EEG duration (hours)	21.5 (0.33-40)	0.35 (0.33-30)	0.07
Mechanical ventilation (days)	10 (5–16)	6 (2–13)	0.02
ICU length of stay (days)	15 (10–22)	8 (5–17)	0.002
Sedation during EEG	62%	65%	0.73
Propofol total dose mg/kg first 5 days of hospitalization	858 (161–2508)	497 (50-1243)	0.11
Midazolam total dose mg/kg first 5 days of hospitalization	13 (0.2–34)	3 (0–59)	0.37
Fentanyl total dose mg/kg first 5 days of hospitalization	520 (309–1176)	348 (0-1002)	0.09

Regarding background activity, we found that the majority of the patients had a continuous or discontinuous EEG; however, only in the delirium group a burst-suppression pattern was observed (10% vs 0%, $p = 0.02$). Out of these patients ($n = 4$), 2 were not sedated during EEG and 2 were receiving propofol. All were diagnosed with sepsis, and 2 of them died during hospital stay. Regarding the best frequency observed, in both groups, theta was dominant; followed by alpha and delta. Reactivity to stimuli (noise, pain, name call) was present in the majority of patients in both groups.

In the delirium group, significantly more patients (43% vs 22.5%) presented rhythmic or periodic patterns not classifying as seizures ($p = 0.037$). Only in delirious patients we found seizures or status epilepticus (7 vs. 0%, $p = 0.05$). The presence of triphasic waves was similar in both groups (33 vs 27%). All other EEG variables (amplitude, background activity, best frequency, NREM sleep, rhythmic or periodic patterns, seizures, stimulus induced epileptiform discharges and triphasic morphology) did not differ between delirious and non-delirious patients.

Specific EEG findings are associated with high delirium risk

The presence of at least one abnormal EEG findings, among burst-suppression, rhythmic or periodic patterns, or seizures/status epilepticus, was associated with a higher rate of ICU delirium (42 vs. 15%, $p = 0.006$). Percentages of specific EEG findings are illustrated in Fig. 3.

Discussion

Delirium in ICU is frequent with harmful consequences for patients (22). EEG is a noninvasive, broadly available tool that can provide important information for delirium detection and management (23). According to our findings, presence of burst-suppression, rhythmic or periodic patterns, or epileptic activity, seem associated with a higher likelihood of delirium. Our data suggest that identification of these particular EEG patterns in patients with severe critical illness with altered consciousness state may be indicative of delirium. They support the concept that EEG monitoring is helpful in this setting, and if done at the early phase may prompt preventive or therapeutic anti-delirium strategies.

In our study, a small proportion of patients with delirium had burst-suppression during EEG. Sedation rates were similar in both groups before and during EEG, minimizing sedative drugs influence over EEG between both groups. Burst-suppression in ICU may be an independent predictor of delirium as previously suggested by another study using processed EEG (24), could primarily attributable to critical illness itself (25), and may be associated with increased mortality (26). We observed seizures and status epilepticus in 7% of our patients with delirium compared to none in the group without delirium. Seizures are known to be associated with a poor outcome in patients in ICU (27) and can be found in patients with delirium of any cause and in patients with sepsis like the majority of our patients (2, 28). The co-occurrence of seizures in septic patients may be seen as a potential marker of brain dysfunction with prognostic significance (2, 28, 29). On the other hand, presence of epileptiform activity may worsen and/or may even trigger delirium in some patients(30). Periodic discharges without seizures were also more prominent in delirium patients; studies in neurologic ICU patients suggest that periodic discharges are independent predictors of poor outcome (31, 32). Rhythmic or periodic patterns without seizure activity were significantly more prevalent in patients with delirium and are part of the ictal-interictal continuum (33). Individual management according to each pattern and close monitoring is advised for early detection and treatment of epileptiform activity if present (33, 34).

Generalized EEG slowing (increased delta and theta frequency) is frequently found in patients with delirium (9, 29). However slowing is also common in ICU patients and related with various causes of altered mental status, decreased arousal, including coma, sleep, and sedation(35). In our study, we did not find any significant differences in slowing when patients were compared for delirium. Triphasic waves evolve from an interplay of pathological neurostructural, metabolic, and toxic conditions, and are significantly associated with white matter disease, infections, and metabolic derangements (36). In our study, these were not increased in frequency in patients with delirium, as reported in previous studies (9, 37). NREM stage 1–2 sleep was not differently prevalent between the two groups It has been hypothesized that presence of sleep elements, especially K-complexes is associated with good outcome in encephalopathic adults (38) (39).

This study has limitations. The sample size is relatively limited and consisted of a selected population of non-neurological ICU patients, without acute brain injury. Data generalization is therefore limited. CAM-ICU scores were not available in all patients. EEG timing was not uniform across patients in relationship with their delirium development, but this reflects real clinical practice. Importantly however, clinical

variables and EEG interpretation were completed prior to this analysis, and blinded to the development of delirium.

Conclusions

In mechanically ventilated medical-surgical critically ill patients with new onset alteration of consciousness, EEG showing burst-suppression state and/or ictal-interictal continuum findings indicates a higher risk of ICU delirium, independently of sedation and analgesia.

Abbreviations

ICU: Intensive care unit

CAM-ICU: Confusion Assessment Method for the ICU

EEG: Electroencephalography

ACNS: American Clinical Neurophysiology Society

CERTA: Continuous EEG Randomized Trial in Adults

LPD: lateralized periodic discharges

GPD: generalized periodic discharges

SIRPIDS: stimulus-induced discharges

Declarations

Ethical approval:

This study was approved by the Ethic's Commission of each participating hospital. Informed consent was obtained from all individual participants included in the study.

Consent for publication

Consent for publication in a scientific journal was obtained from all study participants and/or their legal guardians.

Availability of data and materials

The clinical datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Mauro Oddo is supported by research grants from the Swiss National Science Foundation; he receives speaker fees and is member of the Scientific Advisory Board of Neuroptics, USA, all unrelated to the present study. All other authors have nothing to disclose.

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Authors Contributions:

EE contributed to acquisition and data analysis, statistical analysis, and drafted the manuscript; CI contributed to acquisition and data analysis, and revised the manuscript; VA, SR, KS contributed to acquisition and data analysis, and revised the manuscript; AOR contributed to acquisition and data analysis, study conception, and critically revised the manuscript. MO conceived the study, supervised acquisition and data analysis, statistical analysis, and critically revised the manuscript.

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Figures

Flowchart of patient's inclusion

Figure 1

Study flow chart

Figure 2

EEG chronologic relationship between delirium duration. In blue: number of days with delirium before EEG; in orange, number of days with delirium after EEG.

Figure 3

EEG characteristics between two groups.