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EEG spindles integrity in critical care adults. Analysis of a randomized trial

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Objectives: Occurrence of EEG spindles has been recently associated with favorable outcome in ICU patients. Available data mostly rely on relatively small patients' samples, particular etiologies, and limited variables ascertainment. We aimed to expand previous findings on a larger dataset, to identify clinical and EEG patterns correlated with spindle occurrence, and explore its prognostic implications.

Methods: Retrospective observational study of prospectively collected data from a randomized trial (CERTA, NCT03129438) assessing the relationship of continuous (cEEG) versus repeated routine EEG (rEEG) with outcome in adults with acute consciousness impairment. Spindles were prospectively assessed visually as 12-16Hz activity on fronto-central midline regions, at any time during EEG interventions. Uni- and multivariable analyses explored correlations between spindles occurrence, clinical and EEG variables, and outcome (modified Rankin Scale, mRS; mortality) at 6 months.

Results: Among the analyzed 364 patients, spindles were independently associated with EEG background reactivity (OR 13.2, 95% CI: 3.11–56.26), and cEEG recording (OR 4.35, 95% CI: 2.5 – 7.69). In the cEEG subgroup (n=182), 33.5% had spindles. They had better FOUR scores (p=0.004), fewer seizures or status epilepticus (p=0.02), and lower mRS (p=0.02). Mortality was reduced (p=0.002), and independently inversely associated with spindle occurrence (OR 0.50, CI 95% 0.25–0.99) and increased EEG background continuity (OR 0.16, 95% CI: 0.07 – 0.41).

Conclusions: Besides confirming that spindle activity occurs in up to one third of acutely ill patients and is associated with better outcome, this study shows that cEEG has a higher yield than rEEG in identifying them. Furthermore, it unravels associations with several clinical and EEG features in this clinical setting.

KEYWORDS
coma, critical care, outcome, spindles

Trial Registration: CERTA, NCT03129438, registered 25 April 2017.

1 | INTRODUCTION

Dysfunction of cerebral activity (encephalopathy) can affect up to 70–80% of critically ill patients and represents a major source of morbidity and mortality.[1] Early identification of prognosis has crucial implications in daily practice to allow informing families and caregivers, and targeting complementary work-up.

EEG is a broadly used, noninvasive tool to assess encephalopathy severity in this setting,[2] through evaluation of background activity, amplitude, reactivity, and, more recently, sleep patterns.[3,4] It has been postulated that normal cyclic EEG variations reflect the integrity of the brainstem reticular activating system and its projections.[5] Underlying mechanisms of sleep alteration may be multifactorial: environmental (light, noises, nursing care), toxic (general anesthetics, benzodiazepines), metabolic (eg, sepsis, hypercapnia), or secondary to neurological lesions.[6]

Findings from previous studies show that preserved NREM2 sleep EEG features (spindles, K-complexes) are related to better prognosis in patients with disorders of consciousness of multiple etiologies,[7-9] including trauma,[8,10-14] stroke,[15] hypoxic and non-hypoxic encephalopathy,[15-17] status epilepticus,[18,19] mechanical ventilation, or cardiogenic shock.[20-23] Limitations of these studies include relatively small sample sizes, mostly retrospective assessments, heterogeneity of populations and of duration and timing of EEG recordings, and, often, restriction of analysis to sleep features, discarding other EEG and clinical prognostic variables.

The aim of this study was to assess the occurrence of spindles at any time during EEG recordings in a well characterized, relatively large cohort of adult patients with acute consciousness impairment of various etiologies using a standardized EEG terminology, and to define their prognostic value in relationship with other EEG features.

2 | METHODS

2.1 | Study design

We performed a retrospective analysis of prospectively collected data from the CERTA study (NCT03129438),[24] a multicenter randomized clinical trial evaluating the prognostic yield of continuous versus routine EEG in critically ill adults with altered consciousness and no recent seizure. Patients older than 18 years admitted in intensive or intermediate care units having impaired consciousness of any etiology (defined as GCS ≤11 or FOUR ≤12) and undergoing EEG for clinical reasons were included. Exclusion criteria were: documented seizures within 36 h or status epilepticus within 96 h preceding randomization, palliative situation, or invasive procedures scheduled in the following 36 hours. Patients were randomized 1:1 to continuous video-EEG recordings (cEEG) for 30–48 h, or two routine video-EEGs (rEEG, 20–30 min).[25] EEG were prospectively interpreted by board-certified electroencephalographers, with experience in sleep EEG and additional certification in ACNS Standard Critical Care Terminology.[26]

2.2 | Standard Protocol Approvals, Registrations, and Patient Consents

The trial, including this analysis, was approved by local ethic commissions (Project-ID 2017–00268) foreseeing informed consents and waivers in specific situations (such as early death); its protocol is freely accessible.[24]

2.3 | Variables and Outcomes

Following variables were prospectively collected[25]: demographics, admission diagnoses, underlying etiologies, degree of consciousness impairment (GCS and FOUR scores), SAPS II (ICU severity score), time and duration of EEG, drug administrations (anti-seizure medications (ASM), benzodiazepines (BZD), general anesthetics); EEG background continuity (continuous: <10% of attenuation or suppression, discontinuous <50%, burst-suppression 50–99%, suppressed), best background frequency (alpha or beta; theta; delta; none; if two bands were equally present, the best one was chosen for the present analysis); presence of electro-(clinical) seizures and status epilepticus, generalized rhythmic delta activity (GRDA), epileptiform discharges and interictal continuum features -lateralized rhythmic delta activity (LRDA), generalized (GPD) or lateralized periodic discharges (LPD). Spindles were prospectively identified by visual analysis according to current scoring criteria,[27] as the repetitive occurrence of 12–16 Hz oscillations lasting >0.5 seconds on fronto-central midline regions, occurring at any time during the EEG intervention. Of note, different EEG features (eg, alpha background and spindles) did not need to occur at the same time of a given EEG (but in the same recording). Outcome at six months was prospectively assessed by collaborators blinded to the EEG intervention (mortality, CPC score, and evolution of modified Rankin Scales before the index hospital admission).

2.4 | Statistical analysis

Comparisons of proportions were performed through chi-square, Fisher's, Student's t tests, or Mann-Whitney U tests, as appropriated. Stepwise multivariable logistic regressions were used to explore the associations between spindles occurrence and other clinical EEG variables, and between mortality and spindles occurrence, including those having $p<0.1$ in univariable assessments. Goodness of fit was assessed with Hosmer-Lemeshow tests. Statistical significance was set at $p=0.05$, with 2-sided approaches. Statistical analyses were performed with Stata, version 16 (Stata Corp., College Station, TX, USA).

3 | RESULTS

A total of 364 patients were analyzed[24]; spindles were observed in 22.8% of them at any time during their EEG recording. Table 1 illustrates clinical and EEG characteristics according to spindle occurrence or absence. Patients with spindles had higher FOUR scores on enrollment, a higher prevalence of a continuous, reactive EEG background, and were clearly more frequently recorded with cEEG. Demographics, site of recruitment, etiologies, ICU severity, latency of EEG recording since admission, concomitant medication (ASM and sedation), EEG background frequency, GRDA, features of the ictal-interictal continuum, seizures/status epilepticus, and clinical outcome were comparable across the two groups (Tables 1,2). Spindles were identified in 61/182 cEEG (33.5%) versus 22/182 (12.1%) rEEG patients, with an absolute difference of 21.4% ("number to miss" of nearly 5 or, in other words, nearly 2/3 of patients having spindles were probably missed by performing rEEG). In the rEEG group, we observed spindles in the first rEEG in 17/182 (9.3%) patients. The logistic regression revealed that spindles occurrence was independently associated with EEG background reactivity (OR 13.2, 95% CI: 3.11–56.26) and cEEG (OR 4.35, 95% CI: 2.5–7.69), with an excellent goodness of fit (p=0.602).

To eliminate the selection bias (under-ascertainment) of spindles in patients undergoing rEEG, we limited subsequent analyses to the cEEG group (n=182, mean duration 32.1 ± 13.2 hours), see Table 2. Additionally to the overall population, cEEG subjects with spindles had significantly better GCS scores on enrollment, fewer seizures or status epilepticus, lower mortality, and better functional outcomes compared to the pre-admission estimation. The logistic regression showed that mortality (the trial primary outcome) was independently and inversely associated with spindles occurrence (OR 0.50, CI 95% 0.25–0.99), and increasing continuity of background activity (OR 0.16, 95% CI: 0.07–0.41), with an excellent goodness of fit (p=0.823); underlying etiology did not play an independent role. For survival, the positive predictive value (PPV) of continuous background was 0.62 (95%CI: 0.53–0.70), and of spindles it was 0.67 (CI: 0.59–0.79).

In a further exploratory analysis of the cEEG subgroup focusing on the most frequent etiologies, lack of spindles was associated with mortality particularly in patients with anoxic-ischemic etiology (p=0.019, chi-square), but not brain trauma (p=1.000, Fisher), or brain hemorrhage (p=0.526, Fisher).

4 | DISCUSSION

In this analysis of adults with acutely reduced consciousness participating in an EEG clinical trial, we found that EEG spindles occurred more frequently in subjects undergoing cEEG recordings than rEEG, and who exhibit EEG background reactivity. Within the subgroup with cEEG, spindles were found in one third of patients; they were additionally associated with a lesser degree of consciousness impairment, increasingly continuous EEG background, reduced prevalence of seizures/status epilepticus, and improved long-term outcome; importantly, spindles were independently related to reduced mortality additionally to increasing background frequency.

Spindles are elicited by GABA-ergic neurons of the thalamic reticular nucleus and reflect intact thalamocortical and corticothalamic networks responsible of their synchronization.[5] Functional MRI and magnetoencephalography studies show the activation of limbic system and sensory cortices in the presence of spindles.[12,28,29]

To our knowledge, concomitant clinical and EEG findings in acutely critically ill patients with spindles have not yet been described in detail. Outcome differences between patients with and without spindles were identified in the subgroup undergoing cEEG, but not in the overall population. This aspect has received limited attention previously and appears highly relevant in clinical practice. In an automated EEG analysis of the same dataset but considering the whole cohort,[30] the prognostic relevance of spindles was low, since rEEG and cEEG were lumped together. Routine EEG may indeed miss these specific features in a relevant proportion of cases (almost 2 in 3 patients with spindles, possibly also in part because virtually all rEEG were recorded during the day, missing night-time brain activity), with an obvious impact on prognostic assessment. The prevalence of spindles in cEEG patients was 33.5%, similar to previous studies (28–50%[11,18,21,31]), reinforcing the generalizability of our findings (as did the similar prevalence across participating centers).

We did not identify significant differences across patients with and without spindles in terms of EEG latency since hospital admission, ASM, or sedation (type and dose), suggesting that these variables do not play a prominent role in this clinical setting regarding spindles identification. This probably reflects the end result of a balance between suppression of physiologic sleep by high dose sedation and enhancement of spindles activity by GABA-ergic compounds at lower doses.[32] Of note, our patients had relatively low amount of sedation.

Patients showing spindles had higher FOUR (and GCS) scores, reflecting lower degrees of brain dysfunction and better prognosis.[33] They also had a more continuous background activity. An explanation may be that spindles have been suggested to represent a measure of cortical synaptic recovery in post-cardiac arrest patients, and are associated with favorable outcome.[34] Since stroke patients had acute spindles loss ipsilaterally to the lesion, but progressively recovering during recovery, it was speculated that spindles are markers of neuronal plasticity.[15,35]

The patients' group with spindles also showed a higher prevalence of EEG reactivity, reflecting its association with good outcome after cardiac arrest,[36] and in disorders of consciousness of different etiologies.[37] Since stimulus modality seems crucial to optimize reactivity detection, a standardized protocol, as applied in the CERTA study, is recommended.[38]

Subjects with spindles had a lower prevalence of seizures and status epilepticus despite similar use of ASM and sedation. This could again reflect a less widespread functional or structural brain damage. While status epilpeticus outcome depends on the underlying etiology,[39] seizure density has been linked to worse outcome.[40] In any case, seizures/status epilepticus (but also etiology) were not independently related to mortality after introduction of spindles in the multivariable model.

TABLE 1 Patients characteristics: all participants (n= 364).

	Present spindles	Absent spindles	p	test
Patients (% of 364 total patients)	83 (22.8%)	281 (77.2%)		
Age, y (mean ±SD)	63.8 (±15.9)	63.8 (±14.6)	0.983	t
Female gender	30 (36.1%)	93 (33.1%)	0.606	χ^2
CHUV site	66 (79.5%)	221 (78.7%)	0.865	χ^2
Admission diagnostic group			0.581	Fisher
Primary brain injury	40 (57.1%)	151 (63.5%)		
Medical	19 (27.1%)	57 (24.0%)		
Surgical	10(14.3%)	23 (9.7%)		
Other	1 (1.4%)	7 (2.9%)		
Etiology			0.805	χ^2
anoxic-ischemic	20 (24.1%)	92 (32.7%)		
brain trauma	11 (13.1%)	37 (13.2%)		
intracranial hemorrhage	19 (22.9%)	66 (23.5%)		
ischemic stroke	8 (9.6%)	20 (7.1%)		
toxic-metabolic	6 (7.2%)	17 (6.0%)		
other	19 (22.9%)	59 (21.0%)		
SAPS II before EEG (mean ±SD)	45.7 (±18.6)	49.8 (±19.0)	0.123	t
GCS before EEG (median, IQR)	3 (3–7)	3 (3–6)	0.082	U
FOUR score before EEG (median, IQR)	5 (3–8)	4 (1–7)	**0.005**	U
Delay of 1st EEG after admission (h; median, IQR)	63.2 (25.8–150.9)	57.5 (22.3–135.7)	0.341	U
Continuous EEG recording	61 (73.5%)	121 (43.1%)	**<0.001**	χ^2
ASM at EEG start	25 (30.1%)	98 (34.9%)	0.421	χ^2
Benzodiazepines (incl. MDZ) during EEG	44 (53.0%)	146 (50.9%)	0.866	χ^2
IV propofol at EEG start	40 (48.2%)	154 (54.8%)	0.289	χ^2
dose, mg/kg/h (median, IQR)	0.94 (0.18–1.92)	0.87 (0.16–1.87)	0.823	U
IV MDZ at EEG start	34 (41.0%)	113 (40.2%)	0.903	χ^2
dose, mg/kg/h (median, IQR)	0.09 (0.03–1.17)	0.08 (0.01–1.19)	0.920	U
Best EEG background continuity			**0.002**	χ^2
continuous	75 (90.4%)	208 (74.0%)		
discontinuous	7 (8.4%)	32 (11.4%)		
burst-suppressed	1 (1.2%)	24 (8.5%)		
suppressed	0	17 (6.1%)		
Best EEG background frequency			0.086	Fisher
alpha or beta	32 (38.6%)	78 (27.8%)		
theta	50 (60.2%)	185 (65.8%)		
delta	1 (1.2%)	7 (2.5%)		
none	0	11 (3.9%)		
EEG background reactivity	81 (97.6%)	227 (80.8%)	**<0.001**	χ^2
GRDA	24 (28.9%)	58 (20.6%)	0.113	χ^2
Ictal-interictal continuum (LRDA, LPD, GPD)	17 (20.4%)	68 (24.2%)	0.482	χ^2
Seizures / Status epilepticus	5(6.0%)	32 (11.4%)	0.155	χ^2
Sporadic epileptiform transients	38 (45.8%)	108 (38.4%)	0.230	χ^2

TABLE 1 (Continued)

	Present spindles	Absent spindles	p	test
Outcome at 6 months				
Mortality	33 (39.8%)	144 (51.3%)	0.066	χ^2
CPC in survivors (median, IQR)	2 (1–3)	2 (1–3)	0.521	U
ΔmRS in survivors	1 (0–2)	1 (0–2.5)	0.204	U

Abbreviations: ASM, Anti-Seizure Medication; CPC, Cerebral Performance Category; FOUR, Full Outline of UnResponsiveness; GCS, Glasgow Coma Score; GPD, generalized periodic discharges; GRDA, generalized rhythmic delta activity; IQR, interquartile range; LPD, lateralized periodic discharges; LRDA, lateralized rhythmic delta activity; MDZ, midazolam; SAPS, Simplified Acute Physiology Score; SD, standard deviation; ΔmRS, difference of modified Rankin Scale between 6 months and before admission.

Bold values are significant (univariable analyses).

While we observed that patients with spindles tended to have a somewhat higher occurrence of GRDA (often observed in the context of metabolic impairment and not associated with epileptic activity), and fewer ictal-interictal continuum features and epileptiform discharges (commonly associated with seizures[41]), these associations were not significant, probably because of the limited sample size in the cEEG subgroup.

The favorable prognostic implication of EEG features looking similar to those occurring in physiologic sleep is in line with previous studies. Absence of structured sleep was a sensible but not specific predictor of poor outcome, defined as mRS >3, in subjects with subarachnoid hemorrhage.[9] In a large cohort of critically ill patients with encephalopathy without acute brain injury, lack of spindles was associated with lower functional outcome scores.[7] Other reported that even if sleep elements were associated with good outcome, only K-complexes were independent predictors in patients without brain lesions (excluding comatose patients or subjects receiving general anesthetics).[16]

Mortality was significantly and independently associated with absence of spindles and increasing discontinuity of background activity, strengthening their specific and additional prognostic value. Since clinical practice, as illustrated for anoxic-ischemic encephalopathy, is still dominated by prognostic factors forecasting poor outcome,[4,42] a good outcome predictor may prove extremely useful. This novel finding may be valuable for clinicians, since the presence of these features already in the early stage of acute illness may reflect a subcortical (for spindles) and cortical (for continuity of background activity) functional integrity crucial to survival. Another interesting observation is the higher mortality rate particularly in post-cardiac arrest patients without spindles. While this etiological association should be confirmed in further studies, anoxic-ischemic brain lesions in thalamus, periventricular, frontal, and occipital subcortical white matter are often reported.[42,43] On the contrary, consciousness-impaired patients from other causes may have lesions rather in juxtacortical or corpus callosum white matter, sparing deep structures or brain cortex,[44] and traumatic injury may generate a varied pattern of lesions. Such distributions could partially explain the impairment of thalamocortical networks implied in spindles generation in severely damaged post-cardiac arrest patients.

To the best of our knowledge, this represents the largest cohort study on prognostic value of spindles in adult critically ill patients with acute encephalopathy. The prospective assessment made by readers experienced with sleep EEG reinforces the internal validity of the study, while the similar prevalence of spindles compared to previous assessments,[11,18,21,31] and the population characteristics with diverse underlying etiologies supports generalizability of our findings. Furthermore, we adjusted analyses for potential confounding factors.

The results should, however, be interpreted in view of some limitations, such as a potential selection bias represented by the inclusion of patients needing EEG per clinical judgment (which appears common to virtually all other existing studies on the subject), and exclusion of subjects with recent seizures or status epilepticus. Despite providing quantitative data on functional outcome, detailed burden of residual neuropsychological deficit was not explored, nor the development of epilepsy. Another relevant limitation is sleep transients' assessment: K-complexes or POSTS were not prospectively identified (only "NREM 2 sleep features": spindles, not K complexes, define this stage); moreover, there is no consensus about sleep scoring in patients with disorder of consciousness, so the definition of spindles may include activity induced from sedative drugs. Even if NREM2 sleep spindles and GABA-ergic induced spindle-like activity are formally not identical in quantitative EEG analysis,[45] they seem to belong to similar states[46] and look almost identical on a EEG recording; in our experience, in clinical practice, they are often referred to as "spindles," or "spindle-like," or again "activity reminiscent of spindles." By analogy, spindle-like EEG pattern of spindle coma is associated with good prognosis, especially if associated with reactivity.[47] In any case, sleep assessment in critically ill patients may be challenged by sleep absence during overnight recordings in subjects with shifted sleep-wake cycle, occurrence of elements mimicking sleep transients (eg, delta slowing for K-complexes, sedation-induced fast activity for spindles), and effects of mechanical ventilation.[17,18,48,49]

5 | CONCLUSION

This study identifies novel correlations of EEG spindle activity with clinical and electroencephalographic variables, such as reduced consciousness impairment, EEG reactivity and continuity of the background, and fewer ictal activity. In light of our findings, pursuing cEEG seems reasonable when a more complete picture of prognosis is required after rEEG. Further studies should investigate the

TABLE 2 Participants with continuous EEG (182).

	Present spindles	Absent Spindles	p	test
Patients (% of 182 total patients)	61 (33.5%)	121 (66.5%)		
Age, y (mean ±SD)	63.5 (±15.7)	64.2 (±13.9)	0.740	t
Female gender	19 (31.2%)	43 (35.5%)	0.555	χ^2
Etiology			0.128	χ^2
anoxic-ischemic	15 (24.6%)	45 (37.2%)		
brain trauma	10 (16.4%)	21 (17.4%)		
intracranial hemorrhage	15 (24.6%)	30 (24.8%)		
ischemic stroke	4 (6.6%)	6 (5.0%)		
toxic-metabolic	2 (3.3%)	7 (5.8%)		
other	15 (24.6%)	12 (9.9%)		
SAPS II before EEG (mean ±SD)	45.4 (±18.5)	51.5 (±19.0)	0.057	t
GCS before EEG (median, IQR)	3 (3–7)	3 (3–6)	**0.042**	U
FOUR score before EEG (median, IQR)	5 (3–8)	3 (1–6)	**0.004**	U
Best EEG background continuity			**0.007**	χ^2
continuous	54 (88.5%)	88 (72.7%)		
discontinuous	7 (11.5%)	12 (9.9%)		
burst-suppressed	0	10 (8.3%)		
suppressed	0	11 (9.1%)		
Best EEG background frequency			0.103	Fisher
alpha or beta	24 (39.3%)	32 (26.4%)		
theta	36 (59.0%)	78 (64.5%)		
delta	1 (1.6%)	5 (4.1%)		
none	0	6 (5.0%)		
EEG background reactivity	59 (96.7%)	87 (71.9%)	**<0.001**	χ^2
GRDA	20 (32.8%)	33 (27.3%)	0.440	χ^2
Ictal-interictal continuum (LRDA, LPD, GPD)	12 (19.7%)	34 (28.1%)	0.217	χ^2
Seizures / Status epilepticus	5 (8.2%)	24 (19.8%)	**0.043**	χ^2
Sporadic epileptiform transients	26 (42.6%)	50 (41.3%)	0.867	χ^2
Outcome at 6 months				
Mortality	20 (32.8%)	69 (57.0%)	**0.002**	χ^2
CPC in survivors (median, IQR)	2 (1–2)	2 (1.5–3)	0.094	U
ΔmRS in survivors	1 (0–2)	2 (1–3)	**0.029**	U

Abbreviations: CPC, Cerebral Performance Category; FOUR, Full Outline of UnResponsiveness; GCS, Glasgow Coma Score; GPD, generalized periodic discharges; GRDA, generalized rhythmic delta activity; IQR, interquartile range; LPD, lateralized periodic discharges; LRDA, lateralized rhythmic delta activity; MDZ, midazolam; SAPS, Simplified Acute Physiology Score; SD, standard deviation; ΔmRS, difference of Modified Rankin Scale between 6 months and before admission.

Bold values are significant (univariable analyses).

long-term outcome after hospital discharge with particular attention on neuropsychological and epilepsy burden and, pending a significantly larger cohort, association with epileptiform discharges and rhythmic or periodic EEG patterns.

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CONFLICT OF INTEREST

None.

AUTHORS' CONTRIBUTIONS

Vassallo, Paola involved in conception and design of the study, acquisition and analysis of data, drafting a significant portion of the manuscript or figures. Novy, Jan and Zubler, Frédéric involved in acquisition and analysis of data, revision of the manuscript for intellectual content. Schindler, Kaspar and Rüegg Stephan involved in conception and design of the study, revision of the manuscript for intellectual content. Alvarez, Vincent involved in acquisition and analysis of data, Conception and design of the study, revision of the manuscript for intellectual content. Rossetti Andrea O. involved in conception and design of the study, acquisition and analysis of data, drafting a significant portion of the manuscript or figures, revision of the manuscript for intellectual content.

DATA AVAILABILITY STATEMENT

The dataset of the study is not publicly available, because of local ethic committees' policies, but is accessible from the corresponding author on request.

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